Guidance title: Disability, dementia and frailty in later life – mid-life approaches to prevent or delay the onset of these conditions.
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APPENDIX A – Evidence tables of included primary studies

**Study Details:** authors, year, citations, country of study, aim of study, study design, quality score [++, +, or -], applicability [++, +, or -]

**Source Population**
- Country of study
- Number of people who participated in original study (or who were initially contacted to participate or selected from register) with sex breakdown, if available (provide study name)

**Study (eligible and selected) population**
- Number of people who participated in this particular study/wave
- Location (city and country)
- Recruitment strategies (e.g. media advertisement, birth register, class list, area)
- Study time period/length of follow-up
- Sex breakdown (if available, include SES and ethnicity-breakdown)
- Mean age, or age at midlife and late-life examinations, if reported
- Response rate and loss to follow-up (% and number)
- State if the eligible population is considered by the study authors as representative of the source population.

**Excluded populations:** Who and how many were excluded

**Attrition:** Details on attrition (n lost to follow-up and why; was loss to follow-up higher in specific sub-groups [e.g. SES], as indicated by study authors)

**Exposures at midlife**
- Relevant exposures reported at midlife (with units) e.g. PA, diet, alcohol, smoking at baseline
- Time period during which the exposures were ascertained
- Report how exposures were measured – objective/subjective e.g. self-reported questionnaire or independent objective assessment

**Outcomes at 55 years or over**
- State all outcomes assessed
- Details on outcome measurement/ascertainment
- Report how outcomes were measured – objective/subjective e.g. self-reported questionnaire or independent objective assessment
- Time period during which cases were ascertained
- Note: indicate that measures have been validated only if this has been explicitly reported by the author

**Analysis**
- Analysis strategy used for multivariate model, e.g. logistic regression
- Report all confounders

**Results, limitations, source of funding**
- Include number of people who developed relevant outcome (with sex breakdown)
* Include statistically significant relevant effect estimates adjusted for all or as many covariates as possible (e.g. report OR, RR, HR with CI)
* Mention highly significant trends (do not need to report effect estimates for each level; however, state p-value of trend test)
* Include relevant and statistically significant interactions (report effect estimates with CI)

**Limitations:**
* Include limitations identified by study authors
* State additional study limitations not reported by study authors (only if significant and obvious biases have been omitted)

**Source of funding:**

**Authors:** Agahi N, Shaw BA  
**Year:** 2013  
**Citation:** Preventive Medicine 57(2): 107-112  
**Country of study:** Sweden  
**Aim of study:** To assess smoking trajectories from midlife to old age and the development of non-life-threatening health problems in a 34-year time span  
**Study design:** Longitudinal  
**Quality score:** (++, + or -): -

**Source population**
Data for this study originated from the Swedish Level of Living Survey, a nationally representative study of Swedish people ages 18-75 years, and the Swedish Panel Study of Living Conditions of the Oldest Old, which comprised participants from the first study over the age of 75 years.

**Study (eligible and selected) population**
- Data from the 1968, 1981, 1991 and 2000 phases of first study merged with data from 2002 phase of second study  
- Up to 34 years follow-up of individuals that were 30-50 years of age at baseline in 1968  
- Final sample: 1060 people (52% of original sample)  
**Follow-up:** Of the people meeting the inclusion criteria, 655 (32%) died during follow-up. Those who died during follow-up were older, less well educated, more likely to smoke, had more mobility impairment and psychological distress at baseline compared with those included in study  
**Exclusion:** -  
**Attrition:** Of 2051 people meeting the inclusion criteria, 336 (16%) people did not participate in study phases or had missing variable values (and 655 or 32% died)

**Exposures at midlife**
>Smoking was assessed using structured participant interviews  
Smoking categories: current non-smoking, light smoking (< 10 cigarettes/day), heavy smoking (10+ cigarettes/day)  
Persistent heavy smokers (n=81): those who smoked throughout the period, with heavy smoking reported for at least 3 study waves  
Persistent light smokers (n=63): those who smoked throughout the follow-up period, but with two or fewer episodes of heavy smoking
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>Former smokers: smoking in the first and/or second study waves</th>
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<tbody>
<tr>
<td>Former heavy smokers (n=107): those who reported mostly heavy smoking</td>
</tr>
<tr>
<td>Former light smokers (n=176): light smokers</td>
</tr>
<tr>
<td>Persistent non-smokers (n=633): never smoked</td>
</tr>
</tbody>
</table>

**Outcomes at 55 years or over**

- Three outcomes assessed using structured interviews: mobility impairment, musculoskeletal pain, psychological distress
- Mobility impairment: index measuring ability to walk, run, go up and downstairs without difficulties (0=no mobility problems; 3=moi in all 3 domains)
- Index of musculoskeletal pain and index of psychological distress based on summary score of health problems in past 12 months ranging from 0 (no pain) to 6 points (severe pain) and from 0 (no symptoms) to 8 points (severe problems in all domains assessed), respectively
- Musculoskeletal pain index: assessed perceived pain in hands, elbows, legs or knees, shoulders, back, hips, sciatica
- Psychological distress index: assessed anxiety, nervousness, anguish, general fatigue, sleeping problems, depression

**Analysis**

**Analysis strategy:** Multivariate, multinomial regression analysis was used to assess smoking trajectories from midlife to old age and the development of non-life-threatening health problems

**Confounders:** Age, education, sex

**Results, limitations, source of funding**

- Rate of increase in mobility impairment was steepest among persistent heavy smokers (coeff.=0.01, SE=0.004), and former heavy smokers (coeff.=0.01, SE=0.003) in comparison with non-smokers over 34 years of follow-up
- Compared to non-smokers, former light smokers had statistically significantly steep progression of mobility problems over 34 years of follow-up (coeff.=0.006, SE=0.003)
- Compared to the persistent non-smoking group, faster increases in mobility impairment were observed for all smoking trajectory groups
- Heavy smokers had higher levels of psychological distress at baseline compared to persistent non-smokers, and this difference did not change over the follow-up period

**Limitations:**

1. Selective survival, leaving healthier individuals in sample
2. Shorter period for observing the development of health problems for younger segments (follow-up until 2000) than for older segments (until 2002) in study; thus number of health problems may be underestimated in younger participants

**Source of Funding:** none reported

**Authors:** Agrigoroaei S, Lachman ME

**Year:** 2011

**Citation:** Journals of Gerontology Series B-Psychological Sciences & Social Sciences 66 Suppl 1: i130-140

**Country of study:** United States

**Aim of study:** To examine combined effect of psychological, social, and physical factors on cognitive...
functioning (above and beyond the effects of sodiodemographics, risk factors, cognitive activities

**Study design:** Longitudinal

**Quality score:** (++, + or -): +

**Source population**

Data used from 1995-96 and 2004-05 national survey called Midlife in the United States (MIDUS), as well as a survey subsample, the Boston Longitudinal Study (BOLOS). BOLOS measurements taken one year after MIDUS measurements.

Overall purpose: are behavioral, social, psychological, biological, neurological factors assessed in MIDUS associated with cognitive performance measured in MIDUS, as well as with subsequent cognitive functioning measured over 10-year-period in BOLOS

**Study (eligible and selected) population**

**Specific study aims:**

2. Influence of changes in the number of factors from Time 1 (1995-96) to Time 2 (2004-05) on cognition at Time 2
3. National probability sample of 4,238 non-institutionalised adults from 48 states selected through random-digit dialing
> included 949 siblings of main respondents
1,913 twins selected from national sample of 50,000 households
Time 1: **7,100** participants ages 24-75 years (mean=46.40, SD=13.00)
Time 2: **4,900** participants ages 32-84 years (mean=55.45, SD=12.44) remaining (75% of people from Time 1)

**Overall response rate:** 70%

1 year after MIDUS Time 1, **302** people ages 24-74 years (mean=47.89, SD=13.74), living in Boston recruited for BOLOS
1 year after MIDUS Time 2, **151** people who participated in first BOLOS wave participated in second BOLOS wave (68% participation rate); participants ages 34-84 years (mean=59.99, SD=12.81)

**Exclusion:** -

**Attrition:**

i) Participants at Time 2 indicated positive selection on variables compared to those who dropped out.

ii) Participants of BOLOS T2 were more education compared to non-participants of this wave

**Exposures at midlife**

**Control beliefs:** Perceived control over life outcomes assessed using MIDUS sense of control scale, with scores ranging from 1-7 (higher values = higher sense of control)

**Quality of social support:** 12 items assessed social strain in relationships, with scores ranging from 1-4 (higher values = higher quality of social support)

**Physical exercise:** Frequency of engaging in vigorous physical activities, with scores ranging from 1-6 (higher values = more frequent physical exercise)

Psychosocial and behavioural protective composite score of above variables created (scores of aforementioned variables summed and higher values represent greater number of factors present at higher level)

**Exposures assessed:**
## Influence of MIDUS protective composite

### Interaction of MIDUS composite with age and education

### Influence of Time 1 MIDUS protective composite score and difference in MIDUS protective composite scores between Time 2 and Time 1

### Outcomes at 55 years or over

Seven cognitive domains assessed over telephone at Time 2 in MIDUS using the Brief Test of Adult Cognition by Telephone; cognitive factors grouped into episodic memory and executive functioning. Cognitive factors, such as short-term memory, speed of processing, reasoning, and vocabulary, assessed in person at Time 1 and Time 2 in BOLOS.

### Analysis

#### Analysis strategy: Hierarchical multiple regression

#### Confounders:

1. Frequency of engaging in cognitive activities
2. Age, sex, level of education, race, waist circumference, smoking, alcohol or drug problems
3. Health status including history of diabetes, stroke, lupus, HIV or AIDS, MS, epilepsy or other neurological disorders, cancer, heart disease

### Results, limitations, source of funding

#### MIDUS

- The number of behavioural protective factors were positively associated with memory (b = 0.03, p = 0.032) and executive functioning, (b = 0.06, p < 0.001), and a significant percent of model variance was explained by these factors over and above the confounders assessed (R² change = 0.001, R² change = 0.003, respectively)
- The association between education and cognition was reduced by the number of protective factors for episodic memory (b = −0.04, p = 0.015)

#### BOLUS

- Time 1 protective composite positively associated with change in reasoning (b = .10, p = .045)
- The number of protective factors reduced the association between education and reasoning abilities when the interactions of the protective composite with age and education were entered in the model (b = −.09, p = .045)

#### Limitations:

1. Small sample size of BOLUS
2. Approach used to compute protective composite cannot provide universal guidelines (method of dividing participants into high and low categories may not be clinically meaningful)
3. Optimization of self-reported measures through use of multiple indicators
4. Residual confounding from unexplored variables such as level of stress, personality profiles, nutrition

#### Source of funding: National Institute on Aging and the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development

### Authors: Akbaraly T, Sabia S, Hagger-Johnson G, Tabak AG, Shipley MJ, Jokela M… Kivimaki M

### Year: 2013

### Citation: American Journal of Medicine 126(5): 411-419

### Country of study: England
**Aim of study:** The association between diet at midlife assessed using dietary patterns and adherence to the Alternative Healthy Eating Index (AHEI) and overall health at older ages

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**

**Study (eligible and selected) population**
Baseline: Phase 3 of study took place 1991-1996 and 8815 people included
Study comprised 5350 people at least 60 years of age at end of follow-up in phase 9 (2007-2009)
3775 (70.6%) men and 1575 (29.4%) women included

**Follow-up:** 16-years

**Exclusion:**
1. Participants with no history of stroke, myocardial infarction, or cancer (n=7032) in 1991-1996 at phase 3
2. For this particular study, 1682 excluded (more likely to be women, younger, less likely to have a higher AHEI score)

**Attrition:** Included participants were less likely to be younger, to have a higher AHEI score, and better health outcomes compared to excluded participants

**Exposures at midlife**
>At phase 3, participants completed a semi-quantitative food-frequency questionnaire (hence, self-report):

Nutrient intakes of food items were computed by multiplying the consumption frequency for each food by its nutrient content and then summing the nutrient contributions from all foods

Validity and reliability of questionnaire has been established

Dietary variables (exposure) for each participant included:
1. Dietary patterns: “healthy-foods” diet versus “Western-type” diet (see analysis)
2. AHEI score based on intake of vegetables, fruits, nuts and soy, ratio of white meat (seafood and poultry) to red meat, total fibre, trans fat, ratio of polyunsaturated fat to saturated fat, long-term multivitamin use, alcohol consumption; higher AHEI scores represent healthier diet

**Outcomes at 55 years or over**
>Five outcomes ascertained from three follow-up screenings in 1997-99, 2002-04, 2008-09: ideal aging, nonfatal cardiovascular disease at follow-up, cardiovascular death, noncardiovascular death, natural or normal aging

Records from national health registers (e.g. national cancer registry), self-reported questionnaires and medical records used for case ascertainment

Deaths identified through National Health Services Central Registry

>Ideal aging at age 60 and older defined as:

Being alive
Absence of chronic diseases, such as CHD, stroke, cancer (identified through cancer registry), diabetes (identified through self-reported doctor diagnosis, use of anti-diabetic medication, oral
glucose tolerance test)
Absence of mental health problems (>42 in mental health scale of the Short Form General Health Survey)
Good cardiometabolic functioning (based on systolic blood pressure and fasting glucose), respiratory functioning (forced expiratory volume at phase 9), musculoskeletal (walking speed), and cognitive functioning (5 cognitive tests at phase 9)

Analysis

Analysis strategy: Principal component analysis of the 127 food-frequency questionnaire items was performed and two dietary patterns were derived: 'healthy foods patterns' (had high loadings for intake of vegetables, fruit, fish) and the 'Western-type diet' (high loadings for items such as fried food, processed and red meat, pies, etc.); for each dietary pattern: factor scores were divided into tertiles and participants were categorised into the appropriate tertile based on their score. Logistic regression was used to assess the association between dietary variables and each dichotomous aging outcome

Confounders: Age, sex, total energy intake, smoking, physical activity

Results, limitations, source of funding

- 4% of participants met ideal aging definition, 12.7% developed a nonfatal cardiovascular disease, 2.8% died from cardiovascular disease, 7.3% died from noncardiovascular causes over 16 year follow-up; 73.2% showed natural aging
- The odds for ideal aging were lower for participants in the top tertile of the Western-type diet (OR=0.58, [0.36, 0.93]) compared to the bottom tertile
- High adherence to the AEHI recommendations was associated with lower odds of CVD and non-CVD deaths (OR=0.60, [0.39, 0.92]; OR=0.75, [0.57, 0.98], respectively)

Limitations:
1. Possibly lack of statistical power
2. Generalizability issues as participants are mainly white, office-based civil servants
3. Somewhat imprecise method of assessing dietary intake using semi-quantitative food-frequency questionnaire
4. Residual confounding

Source of funding: None reported

Authors: Alonso A, Mosley TH Jr, Gottesman RF, Catellier D, Sharrett AR, Coresh J
Year: 2009
Citation: Journal of Neurology, Neurosurgery & Psychiatry 80(11): 1194-1201
Country of study: USA
Aim of study: To study the association between cardiovascular risk factors and incidence for dementia among Caucasians and African American people
Study design: Longitudinal
Quality score: (+++, + or -): +

Source population
Population-based cohort of 15,792 participants ages 45-64 recruited in 1987-9 from Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; suburbs of Minneapolis, Minnesota in United States for Atherosclerosis Risk in Communities (ARIC) study. Participants were examined at baseline in 1987-9 and every three years until 1996-1998.
### Study (eligible and selected) population

Analysis restricted to white individuals from Minnesota, Washington County and Forsyth County communities and African Americans from Jackson and Forsyth County (n=11,151)

**Response rate:** 86%

**Follow-up:** From 1990-92 to occurrence of hospitalisation with dementia, death, loss to follow-up, or 31 December 2004, whichever occurred earlier

**Exclusion:** -

**Attrition:** No details provided

### Exposures at midlife

Lifestyles (e.g. smoking) assessed in 1990-92

### Outcomes at 55 years or over

Incident dementia identified through participant or proxy report and chart abstraction of hospital discharge codes between 1990-92 and Dec. 31 2004

Dementia cases ascertained at annual follow-up of participants

Cognitive function assessed via interviews using three neuropsychological tests measuring memory, sustained attention and psychomotor speed, flexibility of verbal thought processes

### Analysis

**Analysis strategy:** Cox proportional hazard models to estimate hazard ratios of dementia by presence of cardiovascular risk factors at baseline

**Confounders:** Sex, race, educational level, occupation, study centre, scores in cognitive assessment at baseline, presence of cardiovascular factors (hypercholesterolemia, BMI, hypertension, diabetes), APOE 4

-age assessed as confounder and as effect modifier

### Results, limitations, source of funding

- 203 dementia cases identified during 142,625 person-years of follow-up
- Current smokers were more likely to develop dementia compared to those who had never smoked [HR=1.7, (1.2, 2.5)]; no differences by race, sex, or APOE4 genotype categories (when baseline cognitive scores were not controlled for)
- Stratification by age at examination: among those <60 years of age, current smokers were more likely to develop dementia than those who had never smoked [HR=2.2, (1.2, 4.1)]

### Limitations:

1. Hospital discharge diagnoses used to ascertain dementia cases likely underestimate disease burden; dementia may be undetected in subgroups with high prevalence of comorbidities (e.g. smokers)
2. Subgroups (e.g. smokers) have higher risk of hospitalisation, therefore dementia more likely to be detected in these groups

### Source of funding:

National Heart, Lung and Blood Institute

### Authors:

Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M

### Year:

2008

### Citation:

### Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Country of study:** Sweden

**Aim of study:** Explored the association between physical exercise at midlife and subsequent risk of dementia

**Study design:** Case-control analysis and co-twin control analysis

**Quality score:** (+++, + or -): +

### Source population

**Number of people:** 4506

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 3224

**Characteristics**

**Case control:**
- %Women 61
- Age at cognitive screening, mean (SD) 79.5 (5.0)
- Age at baseline, mean (SD) 48.1 (5.0)
- Education, % more than basic 37
- smoke, % yes 30
- Drink alcohol, % yes 70
- Fruits and vegetables in diet, % small or no part 21
- BMI 11
- Angina pectoris, % yes 25

**Twin study Controls:**
- Age at cognitive screening 82.2 (4.9)
- Age at baseline 50.8 (5.3)
- Education, 11 more than basic 30
- Smoke, n yes 15
- Drink yes 56
- Fruits and vegetables in diet, small or no part 16
- BMI, 15
- Angina pectoris, 11 yes 22
- Leisure time physical activity, 11

**Location:** Sweden

**Recruitment strategy:** Swedish Twin Registry

**Length of follow-up:**
- Case-control: Hardly Any 31.3 (1.0); Light 31.5 (1.0); Regular 31.6 (0.9); Hard 31.4 (1.1)
- Twin Controls: 31.3 (1.4); case 31.2 (1.4)

**Response rate and loss to follow-up:** 70% combined

**Eligible population:** Swedish Twin Registry

**Excluded populations:** 730 refused to participate, 173 could not be reached, 155 could not be interviewed due to physical problems and an informant was not available, and 82 died before they could be interviewed. An additional 232 persons were screened as suspect for cognitive impairment but were not worked up.

### Exposures at midlife

**Relevant exposures:** Physical exercise

**Time:** 1967 or 1970

**Measurement of exposure:** Swedish Twin Registry

### Outcomes at 55 years or over

**Outcomes:** Dementia

**Outcome measurement:** Screened for cognitive impairment followed by full clinical evaluation

**Time:** Not reported
## Analysis

**Analysis strategy:** Logistic regression and conditional logistic regression

**Confounders:** -

**Case control:** Age at cognitive screening, gender, education, smoking, alcohol consumption, portion of fruits and vegetables in diet, BMI and angina pectoris

**Twin study:** Education, portion of fruit/vegetables in diet, current smoking status, alcohol consumption, BMI and angina pectoris

## Results, limitations, source of funding

**Number:** 264 cases with dementia (176 had Alzheimer’s disease). 90 twin pairs discordant for dementia

**Effect estimates:**

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<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Hardly Any</td>
<td>1.00 (ref.)</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>0.63 (0.43-0.91)</td>
<td>0.014</td>
</tr>
<tr>
<td>Regular</td>
<td>0.34 (0.16-0.72)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hard</td>
<td>0.70 (0.40-1.24)</td>
<td>0.215</td>
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<tr>
<td>p for Trend</td>
<td>.178</td>
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**Dementia**

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<tr>
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</tr>
<tr>
<td>Light</td>
<td>0.64 (0.41-1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Regular</td>
<td>0.34 (0.14-0.86)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hard</td>
<td>0.65 (0.33-1.29)</td>
<td>0.217</td>
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<tr>
<td>p for Trend</td>
<td>.339</td>
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**AD**

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<tr>
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<th>OR (95% CI)</th>
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<tr>
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<td>p for Trend</td>
<td>.339</td>
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</table>

**Significant trends:** Exercise at midlife may reduce the odds of dementia in older adulthood

**Limitations:**

1. Self-report data; used prevalent cases of dementia; could not control for
2. Specific physical conditions; only able to identify a small number of twin pairs discordant for dementia

**Source of funding:** National Institute on Aging (NIA) grants ROI AG08724 and P30 AG17265, and by an Alzheimer’s Association/Zenith Fellows Award

## Authors:

Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B… Kivipelto M

## Year:

2004

## Citation:

BMJ 329(7465): 539

## Country of study:

Finland

## Aim of study:

Association between midlife alcohol consumption and subsequent mild cognitive impairment and dementia in old age

## Study design:

Longitudinal
### Quality score: (+++ + or -): +

### Source population

Participants selected from eastern Finland during 1971-1987 as part of Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study. Study response rates between 82% and 90%

### Study (eligible and selected) population

1018 out of 1464 people (70%) ages 65-79 years invited for re-examination in 1998 participated. 632 women and 386 men with mean age of 48.3 years at midlife examination in 1972/1977, and 71.7 years at follow-up examination in 1998.

**Follow-up:** From 1972-77 to 1998

**Exclusion:** Non-participants at the follow up visit in 1998 were, at the midlife assessment, older than the participants; had spent less time in education, and had dementia in old age more often than the participants. 40 cases of dementia did not participate.

### Exposures at midlife

Frequency of alcohol consumption assessed using self-administered questionnaire administered at midlife in 1972 and 1977, as well as in the follow-up examination in 1998.

Frequency of alcohol consumption categorized as: never drank, drank infrequently (less than once a month), drank frequently (several times a month)

### Outcomes at 55 years or over

Cognitive function assessed in 1998 using MMSE, with scores <=24 on MMSE selected for further examination.

Mild cognitive impairment diagnosed according to Mayo Clinic Alzheimer Disease Research Center; diagnostic criteria; dementia diagnosis based on DSM-IV, Alzheimer’s disease diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.

### Analysis

**Analysis strategy:** Logistic regression used to investigate association between midlife alcohol consumption and subsequent mild cognitive impairment and dementia. Effect modification by APOE4 assessed.

**Confounders:** Age, sex, education, midlife BMI, total cholesterol concentration, smoking status, follow up time, midlife systolic and diastolic blood pressure, history of myocardial infarction and stroke at follow-up.

### Results, limitations, source of funding

- 61 (5.8%) participants had mild cognitive impairment, 48 (4.6%) had dementia of whom 37 (77%) had Alzheimer’s disease
- The odds for mild cognitive impairment were higher for those who never drank and those who drank frequently compared to infrequent drinkers (OR=2.15 [1.01, 4.59] and OR=2.57 [1.19, 5.52], respectively)
- Among carriers of the APOE4, the risk of dementia was greater for frequent drinkers compared to non-drinkers (OR=7.07, [1.37, 36.60])
- E4 carriers who drank infrequently and e4 carriers who drank frequently were 2.3 and 3.6 times more likely to develop dementia, respectively, in comparison with participants who never drank and did not carry e4; similar results were observed when dementia and mild cognitive impairment were assessed together as one outcome
- Sex stratification: an increased risk of mild cognitive impairment was observed for frequent male drinkers compared to infrequent male drinkers [OR=5.03, p=0.02]

**Limitations:**
1. Recall bias with respect to self-reported alcohol consumption
2. Selective survival related to APOE4 (heavy drinkers may be more likely to develop vascular morbidity, and presence of APOE4 can increase mortality) – this can underestimate relationship between alcohol drinking and dementia

**Source of funding:** Aging Program of the Academy of Finland, EVO-grants of Kuopio University Hospital and Academy of Finland grants (Insamlingsstiftelsen för Alzheimer- och Demensforskning), and the Gamla Tjänarinnor Foundation

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**Authors:** Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE, Willett WC

**Year:** 2001

**Citation:** Annals of Neurology 50: 56–63

**Country of study:** USA

**Aim of study:** To examine the relationship of coffee and caffeine consumption to the risk of Parkinson’s disease among health professionals and nurses

**Study design:** Longitudinal

**Quality score:** (+++, + or -): ++

**Source population**

51,529 male health professionals (mostly white, of European ancestry), ages 40-75 years, were recruited in 1986 to participate in HPFS study. 121,700 female nurses ages 30-55 years, living in 11 states (mostly white, of European ancestry), recruited in 1976 to participate in NHS study. Follow-up every two years.

**Study (eligible and selected) population**

Average follow-up of 9.2 years for 47,351 men and 15.5 years for 88,565 women

**Follow-up:**

< 3% loss to follow-up for men and < 2% for women

Follow-up for deaths more than 98% complete

Follow-up: from 1986 (for men part of the HPFS) or 1980 (for women part of the NHS) to the occurrence of Parkinson’s, death, or end of follow-up in June 1996

**Exclusion:**

i) Participants diagnosed with Parkinson’s disease, stroke, or cancer before they answered baseline questionnaire

ii) Men and women with extreme daily caloric intakes or incomplete food-frequency questionnaires at baseline

**Attrition:** -

**Exposures at midlife**

Caffeine intake and dietary information assessed every 2-4 years using semi-quantitative food-
frequency questionnaire (SFFQ); first administered in 1980 (NHS); assesses consumption of coffee, tea, chocolate, decaffeinated coffee, soft drinks with or without caffeine

Questionnaires assessed consumption (of 1 cup of coffee, 1 cup of tea, 1 glass of soft drink, 1 ounce of chocolate) during previous 12 months and allowed for 9 response categories ranging from never to 6 or more per day

Intakes of nutrients and caffeine calculated based on US Department of Agriculture assuming that caffeine content was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola, 7 mg per serving of chocolate candy

Reproducibility and validity of SFFQ evaluated within the NHS and HPFS; has good validity and reproducibility (when self-reported coffee intake was compared with dietary records, correlation coefficient was 0.78-0.93)

For women, 1980 SFFQ and slightly more refined 1984 version was used to calculate caffeine consumption as well as cumulative average of caffeine consumption from all the available questionnaires prior to the beginning of each 2-year period

### Outcomes at 55 years or over

**Parkinson’s disease cases**

**Measurement of outcomes:**

Lifetime occurrence of Parkinson’s disease included in 1988 (HPFS) and 1994 (NHS) questionnaires; Parkinson’s disease diagnosis within last 2 years assessed in subsequent questionnaires

Medical records and/or neurologist/internist/GP confirmed new patient self-reported diagnoses of Parkinson’s and certainty of diagnosis (definite, probable, possible)

Deaths were reported by next of kin, co-workers, postal authorities, or the National Death Index

When Parkinson’s listed as cause of death on death certificate, same process of outcome ascertainment was followed as for non-fatal cases

### Analysis

**Analysis strategy:** Pooled logistic regression with two-year intervals to assess the relationship between caffeine intake from different sources and the risk of Parkinson’s disease in men and women, separately

**Confounders:** Age, smoking, BMI, alcohol consumption, physical activity, niacin intake, use of HRT

### Results, limitations, source of funding

- 157 cases of Parkinson's disease in men and 131 in women
- (in men and women, coffee consumption was strongly associated with smoking and weakly associated with alcohol use)
- Among men, after adjustment for age and smoking, the relative risk of Parkinson’s disease was 0.42 (95% CI: 0.23–0.78; p for trend < 0.001) for participants consuming >6 cups/day compared to those consuming 0 cups/day
- Men: significant inverse association observed between: coffee consumption and risk of Parkinson's (p for trend= 0.004), caffeine from non-coffee sources and risk of Parkinson's (p for trend < 0.001), as well as, tea and Parkinson's (p for trend= 0.02)
- Women: the relationship between caffeine intake and risk of Parkinson’s disease was U-shaped, with the lowest risk observed for those reporting one–three cups of coffee/day compared to those reporting zero cups/day

**Limitations:**

1. Possible non-differential misclassification of caffeine
2. Chance or interaction with other factors could be plausible explanations for associations observed
### Source of funding: National Institutes of Health

### Authors: Baba S, Iso H, Mannami T, Sasaki S, Okada K, Konishi M; Shoichiro Tsugane; JPHC Study Group

### Year: 2006

**Citation:** European Journal of Cardiovascular Prevention & Rehabilitation 13(2): 207-213

**Country of study:** Japan

**Aim of study:** To determine the sex-specific relationships of smoking with the risk of CHD

**Study design:** Longitudinal

**Quality score:** (+, -, or +) ++

### Source population

- 27,063 men and 27,435 women, ages 40-59 years, and born between 1930-1949, and registered in 14 administrative districts supervised by public health centre areas on Jan 01, 1990

### Study (eligible and selected) population

- 19,794 men and 21,513 women (registered, non-institutional residents)

**Follow-up:** 88% follow-up. 11 years follow-up from 1990 to 2001 (from collection of baseline questionnaire to first endpoint, death, or Jan. 1 2002)

**Exclusion:** Participants with history of MI, angina pectoris, stroke, cancer

**Attrition:** -

### Exposures at midlife

- Self-administered lifestyle questionnaire distributed in 1990 and completed between Jan. 1990 and May 1992
- Smoking and drinking habits, diet and other lifestyles, including leisure time sports and sleeping hours
- Smoking categorised as: never, ex, and current smoker (additional sub-categories for male ‘current smokers’: 1-14, 15-34, 35 per day or more)
- Drinking categorised as: never, ex, current drinkers who drink more than once a month (frequency and kinds of alcoholic beverages, as well as average quantity per day)
- Daily food intake: frequency of weekly intake asked for 27 food items and categorized as: rarely, 1-2 days per week, 3-4 days per week, almost every day; food items assessed included rice, miso soup, fruit, vegetables, fish

### Outcomes at 55 years or over

- Acute coronary events [MI, sudden cardiac death, other fatal coronary events] that occurred between 1990 and Jan 01, 2002
- Medical records reviewed from hospitals with cardiology departments
- MI confirmed according to criteria of the MONICA project (electrocardiograms, cardiac enzymes, autopsy – if this work-up was not performed, probably diagnosis was made)
- Deaths occurring within 1 hour of symptom onset labelled as sudden cardiac deaths
- Death certificate also reviewed for evidence of CHD and acute heart failure [ICD-10]
- Other fatal coronary events were those in which medical records could not be found for cases
identified through death certificates, or coronary events identified through death certificates did not match study criteria for MI or sudden cardiac death
Total MI includes both definite and probable cases

Analysis

Analysis strategy: Cox proportional hazards model to assess the sex-specific relationships of smoking with the risk of CHD
Confounders: Age, alcohol intake, history of hypertension and diabetes, treated hyperlipidemia, food intake (fruit, vegetable, fish servings), education years, public health centre

Results, limitations, source of funding

- 461,761 person-years of follow-up:
- Men: 260 CHD cases of which 174 were MI, 63 were sudden cardiac deaths, 23 were other fatal coronary events
- Women: 66 CHD cases of which 43 were MI, 16 were sudden cardiac deaths, 7 were other fatal coronary events
- Risk of (total) coronary heart disease and (total) myocardial infarction significantly higher in male current smokers compared to those who never smoked (RR=2.85, [1.98, 4.12] and RR=3.64, [2.27, 5.83], respectively)
- Males: the risk of total coronary heart disease and total myocardial infarction increased with the number of cigarettes smoked per day (trend test p-values: <0.001 and <0.001, respectively)
- Women: the risk of (total) coronary heart disease and (total) myocardial infarction greater for current smokers compared to never smokers (RR=3.07, [1.48, 6.40], RR=2.90, (1.18, 7.18), respectively); the risk of (total) myocardial infarction was also greater for past smokers compared to never smokers (RR=3.72, [1.10, 12.6])
- Population-attributable risk percent (95% CI) of CHD was 46% (34, 55) in men and 9% (0, 18) in women

Limitations: None reported
Source of funding: None reported

Authors: Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT
Year: 2007
Citation: Journal of the American College of Cardiology 50(1): 14-21
Country of study: Netherlands

Aim of study: Explore the association between dietary glycemic load and glycemic index with CVD; assess whether this association is modified by BMI
Study design: Longitudinal
Quality score: (+++, + or -): ++

Source population
17,357 women (breast cancer screening participants part of the Prospect-European Prospective Investigation into Cancer and Nutrition [EPIC] cohort) ages 49-70 recruited between 1993-1997

Study (eligible and selected) population
10% random sample drawn from 15,714 women of original study, exclusion criteria applied to yield final cohort of 1,417 Dutch women
### Time period
1993-1997 to Jan. 1, 2005

### Follow-up
Follow-up from date of return of exposure assessment questionnaire until date of outcome of interest (CHD or CVA), participant date of death, or Jan. 1 2005

### Exclusion:
1. Women who did not consent to linkage with vital status registries
2. Women with missing questionnaires, who reported an energy intake of <500 kcal/day or >6000 kcal/day
3. Women with history of CHD or cerebrovascular disease before baseline, or with established diabetes
4. Study censoring: mortality due to non-cardiovascular causes (n=549), loss to follow-up due to emigration (n=60) and withdrawn alive (14,306)

### Attrition:
- 

### Exposures at midlife
Average exposure to glycemic index and glycemic load in the previous year (before completing questionnaire)

Food frequency questionnaire (validated – Spearman correlations between 0.56-0.78) used to assess average daily consumption of 178 foods; food glycemic index obtained

Glycemic load obtained by multiplication of glycemic index with carbohydrate content of food item and with frequency of consumption of food item – values over all food items summed

Unit of dietary glycemic load is 1g carbohydrate from glucose

Glycemic index (per gram of carbohydrate): glycemic load divided by total carbohydrate consumed

### Outcomes at 55 years or over
Outcomes of interest: cardiovascular disease (coronary heart disease (CHD), cerebrovascular accidents (CVA), cardiovascular disease (CVD))

Hospital discharge diagnoses (ICD-9 codes) obtained from the Dutch Centre for Health Care Information register

Follow-up until Jan 01, 2005

Vital status information obtained from municipal administration registries; cause of death obtained from GPs

### Analysis
**Analysis strategy:** Cox regression to estimate hazard ratios

**Confounders:** Age, hypertension, cholesterolemia, smoking, BMI, mean systolic blood pressure, total physical activity, menopausal status, HRT, oral contraceptive use, alcohol intake, total energy intake, energy-adjusted intake of vitamin E, protein, dietary fibre, folate, energy-adjusted intake of saturated fat, poly- and monounsaturated fat

### Results, limitations, source of funding
- During 141,633 person-years of follow-up: 556 incident cases of fatal or nonfatal CHD and 243 incident cases of fatal or nonfatal CVA
- The HR between the highest and lowest quartile of glycemic load was 1.47 (HR=1.47 [1.04, 2.09])
- The higher the quartile of energy-adjusted glycemic load, the greater the risk for cardiovascular disease (p-value for trend: 0.033)
- The HR between the highest and lowest quartile of glycemic index was 1.33 (HR=1.33 [1.07, 1.67])
The higher the quartile of energy-adjusted glycemic index, the greater the risk for cardiovascular disease (p-value for trend: 0.02)

Among women with high BMI (>25 kg/m2), there was an increased risk of CHD for both higher levels of glycemic load and glycemic index (p-values for trend: 0.04, 0.06, respectively)

Limitations:
1. Residual confounding by unknown risk factors
2. Misclassification of dietary exposure

Source of funding: None reported

Authors: Beulens JW, Rimm EB, Hu FB, Hendriks HF, Mukamal KJ
Year: 2008
Citation: Diabetes Care 31(10): 2050-55
Country of study: US
Aim of study: To determine whether the association between alcohol consumption and diabetes development is mediated by adiponectin concentrations and biomarkers of inflammation, endothelial dysfunction, and insulin resistance
Study design: Nested case-control study
Quality score: (+++, + or -): +

Source population
121,700 female nurses aged 30-55 years initially took part in Nurses’ Health Study in 1976

Study (eligible and selected) population
705 women free of diabetes in 1989-90 and with a confirmed diagnosis of type 2 diabetes by year 2000 constituted the cases
Cases matched to two controls on the basis of year of birth, date of blood draw, race, and fasting status at blood draw (one of the two controls was additionally matched to the case on the basis of BMI)
787 controls matched to 705 cases
Follow-up: 1990-2000
Exclusion:
   i) Women with missing information for alcohol consumption and markers of inflammation and endothelial dysfunction
   ii) Women providing blood in 1989-90 were free of diagnosed diabetes, coronary heart disease, stroke, or cancer at baseline

Attrition: Participants had a higher prevalence of obesity and family history of diabetes and a lower prevalence of current smoking than non-participants (those who did not provide blood)

Exposures at midlife
Self-reported alcohol intake
>1990 semi-quantitative food frequency questionnaire used to assess alcohol intake (among women who provided blood in 1989-90)
Standard portion defined as a glass, bottle, or can of beer; 4-ounce glass of wine; shot of liquor
Participant's average consumption over past year multiplied by alcohol content of portion size (12.8g for beer, 11g for wine, and 14g for liquor) and then summing across beverages
High validity of alcohol consumption (Spearman correlation coefficient: 0.90)

> Biennial self-administered questionnaire

### Outcomes at 55 years or over

Type 2 diabetes
Diabetes self-reported and confirmed through validated supplementary questionnaire detailing symptoms, diagnostic laboratory test results, and treatment
Validity of self-reported diabetes confirmed through medical record review in 62 participants

### Analysis

**Analysis strategy:** Logistic regression was used to determine if adiponectin concentrations and biomarkers of inflammation, endothelial dysfunction, and insulin resistance mediate the association between alcohol consumption and diabetes

**Confounders:** BMI, physical activity, smoking, family history of diabetes, postmenopausal HRT, energy intake, energy-adjusted intake of saturated fat, trans fatty acids, polyunsaturated fat, dietary fibre, glycemic load, coffee consumption

### Results, limitations, source of funding

- By year 2000, 714 women had type 2 diabetes diagnosis
- The odds for type 2 diabetes were significantly lower for those who consumed alcohol with an OR of 0.67 (OR=0.67, [0.56-0.79]) per 12.5 g increment of alcohol intake (p<0.001)
- 25% of the association between alcohol intake and type 2 diabetes development was explained by adiponectin

**Limitations:**
1. Possible selection bias through use of slightly different subgroups for each group of biomarkers
2. Only included women who provided blood samples (these women had higher prevalence of obesity and family history of diabetes in comparison with women who did not provide blood) – may limit generalizability to women with lower diabetes risk
3. More robust markers of insulin sensitivity may be needed

**Source of funding:** National Institutes of Health grants, a travel grant from the Dutch Heart Association, and a research exchange award from European Research Advisory Board

### Authors
Bielak AA, Anstey KJ, Christensen H, Windsor TD.

### Year
2012

### Citation
Psychology and Aging 27(1):219-28

### Country of study
Australia

### Aim of study
Relationship between activity engagement and cognitive ability

### Study design
Cohort-sequential design

### Quality score
(++, + or -): +

### Source population

**Number of people:** 7,485

**Demographics:** Not reported

### Study (eligible and selected) population
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Number of people:** 2,530 in the 40s; 2,551 in the 60s

**Characteristics:** Not reported

**Location:** Canberra or Queanbeyan, Australia

**Recruitment strategy:** Electoral rolls

**Length of follow-up:** 7.00 years (SD 2.43)

**Response rate and loss to follow-up:** Not reported

**Eligible population:** Only participants with available baseline data for all outcome variables were included. Those aged 40–44 years on January 01, 2000; and those aged 60–64 years on January 01, 2001

**Excluded populations:** Not reported

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### Exposures at midlife

**Relevant exposures:** Activity participation

**Time:** 2000-2001

**Measurement of exposure:** RIASEC (Realistic, Investigative, Artistic, Social, Enterprising, and Conventional) Activity List

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### Outcomes at 55 years or over

**Outcomes:** Perceptual speed, Short-term memory, Working memory, Episodic memory and vocabulary

**Outcome measurement:** Symbol Digit Modalities Test, California Verbal Learning Test, digit span backward from the Wechsler Memory Scale, CVLT-Delayed and Spot-the-Word Test

**Time:** 2009-2010

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### Analysis

**Analysis strategy:** Custom equations

**Confounders:** sex, employment status, physical and mental health, and education

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### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

**Activity-between X Age Group Estimate (SE)**

60 vs. 40

Symbol Digit -0.06 (.02); CVLT-Immediate -0.07 (.03); Digit Backwards -0.002 (.03); CVLT-Delayed -0.02 (.03); Spot-the-word -0.03 (.03)

**Change in model fit df=△=6**

Symbol Digit 372; CVLT-Immediate 735; Digit Backwards 222; CVLT-Delayed 722; Spot-the-word 683

**Significant trends:** There was significant change across the eight years in each cognitive measure, and significant random variance within- and between-individuals remaining to be explained. Older adults showed a greater effect of activity participation than the middle-aged adults. The direction of the association was positive, with greater average activity participation linked to a higher cognitive score.

**Limitations:**

**Author:**
1. Did not assess the frequency of activity engagement
2. The number of activity questions contributing to the overall measure was relatively small; limited statistical power

Reviewer: Model 3 (activity between-person effects) was mentioned but data not presented

**Source of funding:** A. A. M. Bielak was supported by a postdoctoral research fellowship from the Canadian Institute of Health Research. K. J. Anstey and H. Christensen were supported by National Health and Medical Research Council (NHMRC) Fellowships (366756 and 525411, respectively). T. D. Windsor is the recipient of an Australian Research Council Future Fellowship (FT100100228). The PATH Through Life Study was funded by NHMRC Grants (229936 and 179839). We thank the study participants, PATH interviewers, Trish Jacomb, Karen Maxwell, Tony Jorm, Bryan Rodgers, Peter Butterworth, and Simon Eastal for their contribution to the research.

**Authors:** Blanco-Cedres L, Daviglus ML, Garside DB, Liu K, Pirzada A, Stamler J, Greenland P

**Year:** 2002

**Citation:** American Journal of Epidemiology 155(4): 354-360

**Country of study:** United States

**Aim of study:** To determine the association between smoking and cardiovascular disease (CVD), coronary heart disease (CHD), and all-cause mortality among men with various levels of serum total cholesterol

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**
39,572 out of 70,000 men and women ages 18 years and older, employed by 84 Chicago-area companies agreed to participate in Chicago Heart Association Detection Project in Industry (CHA) study (55% response rate)

**Study (eligible and selected) population**
This study included 8,816 men aged 40-59 years at baseline

**Sociodemographics:** Study sample of men had mean age of 48.5 years, 5.3% were African Americans

**Follow-up:** 25 years follow-up with screening of men between 1967-1973

**Exclusion:**
1. Men and women 18-39 years and women 40-59 years at baseline
2. Of the men aged 40-59 years screened at baseline: excluded if they had missing data at baseline or follow-up (n=451), baseline evidence of prior myocardial infarction (n=62), previous diagnosis of diabetes mellitus (n=169)

**Attrition:** -

**Exposures at midlife**
Past and present smoking status ascertained by self-reported questionnaire

**Outcomes at 55 years or over**
CHD death, CVD death, all-cause mortality
Deaths ascertained from Social Security Administration and National Death Index records
## Analysis

**Analysis strategy:** Cox multivariate proportional hazards regression used to assess influence of baseline current smoking on cause-specific and all-cause mortality for men within four strata of serum cholesterol: <180, 180-199, 200-239, >=240

**Confounders:** Age, race, education, BMI, systolic blood pressure, presence of ECG abnormalities

## Results, limitations, source of funding

- Of 8,816 men, 32% and 45.7% of men died of CHD and CVD, respectively
- The relative risk for CHD death was greater for smokers compared to non-smokers and ranged from 1.50 (RR=1.50; [1.17, 1.88]) to 2.18 (RR=2.18, [1.54, 3.08]) across cholesterol levels
- The relative risk for CVD death was greater for smokers than non-smokers and ranged from 1.58 (RR=1.58, [1.17, 2.14]) to 1.95 (RR=1.95, [1.48, 2.57]) across cholesterol levels
- The relative risk for all-cause mortality greater for smokers compared to non-smokers and ranged from 1.78 (RR=1.78, [1.54, 2.07]) to 2.19 (RR=2.19, [1.84, 2.61]) across cholesterol levels
- Interactions between current smoking and cholesterol level were not significant for CHD, CVD, and all-cause mortality

**Limitations:** Regression dilution bias (potentially underestimated results due to misclassification of cholesterol measurement)

**Source of funding:** American Heart Association and its Chicago and Illinois affiliates; the Illinois Regional Medical Program; the National Heart, Lung, and Blood Institute; the Chicago Health Research Foundation; and private donors

## Authors

Boudík F, Reissigová J, Hrach K, Tomecková M, Bultas J, Anger Z... Zvárová J

**Year:** 2006

**Citation:** Atherosclerosis 184(1): 86-93

**Country of study:** Czech Republic

**Aim of study:** To evaluate the relationship between health risk factors and atherosclerotic CVD death

**Study design:** Longitudinal

**Quality score:** (+++, + or -): -

## Source population

50% of 2370 middle-aged men living in Prague identified through electoral register

## Study (eligible and selected) population

1390 out of 2370 men responded to and underwent screening examination in 1975-78
Mean age at study entry was 46.1 years
Analysis restricted to **926** men

**Follow-up:** 1979 to 1999-01

**Exclusion:** Diabetic patients at baseline

**Attrition:** -

## Exposures at midlife

Smoking was assessed through self-administered questionnaire in 1975-79
Outcomes at 55 years or over

Atherosclerotic cardiovascular disease (CVD) mortality ascertained in 1999-2001

Data on atherosclerotic CVD mortality and survival ascertained from outpatient departments, postal questionnaires, and registry offices (Institute of Health Information and Statistics of the Czech Republic)

Analysis

Analysis strategy: Cox proportional hazards model used to assess influence of smoking on CVD mortality among 'risk group men'. Risk group men defined as those with one or more atherosclerosis risk factors and without apparent atherosclerotic CVD, diabetes mellitus, and other serious disease at baseline

Confounders: Age, education, blood pressure, total cholesterol

Results, limitations, source of funding

- The hazard rate of death from atherosclerotic CVD was 3 for participants reporting >=15 cigarettes daily compared to those reporting <15 cigarettes daily (HR=3, [2.0, 4.6])

Limitations: Lack of a true control group (ethical reasons) and risk factor profile of participants may have varied from that of general population

Source of funding: Ministry of Education of the Czech Republic

Authors: Britton A, Shipley M, Singh-Manoux A, Marmot MG

Year: 2008

Citation: Journal of the American Geriatrics Society 56(6): 1098-1105

Country of study: England

Aim of study: The influence of early- and midlife predictors on successful aging

Study design: Longitudinal

Quality score: (+++, + or -): +

Source population


73% response rate

Study (eligible and selected) population

Analysis restricted to 5,823 participants (4,140 men and 1,683 women) ages 35-55, free of disease at Phase 1 and who had attended at least 5 phases of follow-up/data collection until Phase 7 (2002-2004), and with measures of functioning at Phase 7

Follow-up: From Phase 1 to Phase 7, 535 people died during follow-up

Mortality was greater in those of lower social position

Exclusion:

i) Those with prevalent disease at Phase 1, attended fewer than 5 phases of follow-up, did not
attend Phase 7, had missing data on functioning at Phase 7, had unknown metabolic syndrome during study period

ii) 4,485 people excluded from the analyses; they tended to be older (mean age at Phase 1 45.1 vs 43.9 years), were more often female (39% vs 29%), and were from the lowest socio-economic position groups (33% vs 15%) than those included

<table>
<thead>
<tr>
<th>Exposures at midlife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking: never-smoker, ex-smoker, current smoker</td>
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<tr>
<td>Alcohol: 0, 1-14, 15 units/week with 1 unit=8g ethanol</td>
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<tr>
<td>Poor diet (yes/no): summary index of poor diet was defined if two or three of the following applied: most frequently used bread was white, consumption of whole milk, fruit or vegetables eaten less often than daily</td>
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<tr>
<td>Physical activity: frequency and number of hours per week spent on activities: grouped as vigorous or moderate (performed 1 or more hours per week of these); none or mild</td>
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<tr>
<td>Self-reported questionnaire used to ascertain exposures</td>
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<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome) from Phase 1 up to Phase 7 and with good physical and mental functioning at Phase 7</td>
</tr>
<tr>
<td>Physical and mental functioning based on walking speed, lung function, Alice Heim 4-I cognitive test, physical component score of the 36-item Short Form General Health Survey</td>
</tr>
<tr>
<td>Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals used to ascertain outcome</td>
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<tr>
<th>Analysis</th>
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<tbody>
<tr>
<td>Analysis strategy: Logistic regression used to assess association between health behaviours (smoking, alcohol, diet, exercise) at Phase 1 and successful aging at Phase 7 for men and women, separately</td>
</tr>
<tr>
<td>Confounders: Age at Phase 1, number of phases attended, SES, early-life factors (father’s social class, education, height), psychosocial factors, job demands, work support, network index</td>
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<table>
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<tr>
<th>Results, limitations, source of funding</th>
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<tbody>
<tr>
<td>548/4,140 men and 246/1,683 women were aging successfully by Phase 7</td>
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<tr>
<td>The odds of successful aging were higher in:</td>
</tr>
<tr>
<td>Non-smokers compared to current smokers for men and women [OR= 2.7, (1.8, 4.1), OR=2.2 (1.3, 3.7), respectively];</td>
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<tr>
<td>Men who did not have a poor diet compared to those who did [OR=1.4, (1.1,1.7)];</td>
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<tr>
<td>Men and women with higher levels of physical activity [OR=1.9, (1.2, 3.1); OR=1.7 (1.1, 2.6), respectively];</td>
</tr>
<tr>
<td>The odds of successful aging were lower for women who did not drink alcohol versus those who had 15 units/week [OR=0.5 (0.3, 0.9)];</td>
</tr>
<tr>
<td>An increasing trend in the odds of successful aging occurred with:</td>
</tr>
<tr>
<td>Less exposure to cigarette smoking for men (p&lt;0.001) and women (p=0.006);</td>
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<tr>
<td>Greater levels of physical activity for men (p&lt;0.001) and women (p=0.03);</td>
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<tr>
<td>Fewer units of alcohol consumed per week for women (p=0.01)</td>
</tr>
</tbody>
</table>

Limitations:
1. Potentially imprecise definition of successful aging
2. Limited generalizability as study consisted of relatively homogeneous group (London-based office workers)
3. Ethnicity not examined

**Source of funding:** British Medical Research Council; British Economic and Social Research Council; British Heart Foundation; UK Health and Safety Executive; UK Department of Health; National Heart Lung and Blood Institute, US National Institute of Health, National Institute on Aging, US National Institutes of Health, Agency for Health Care Policy Research; and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

**Authors:** Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL

**Year:** 2008

**Citation:** Alzheimer’s & Dementia 4: 324–331

**Country of study:** US

**Aim of study:** To determine whether midlife cognitive and physical leisure activities are associated with delayed onset or reduced risk of dementia within older male twin pairs (World War II veterans)

**Study design:** Longitudinal

**Quality score:** (++, + or -): ++

**Source population**

15,942 white male twin pairs born 1917-1927 in 42 US states made up the NAS-NRC Twin registry of male World War II veterans. Registry created through linkage of birth certificates with files of Department of Veterans Affairs

**Study (eligible and selected) population**

Exposure assessment questionnaire administered to twins at around 45 years of age (84% response rate [n=7400 twin pairs])

Analysis restricted to 147 twin pairs (at least one twin received a dementia diagnosis and the other twin remained non-demented for at least 3 years after the onset of dementia in the first twin)

Participants more educated than non-participants

**Follow-up:** 1967 to 1990-2005

**Exclusion:** -

**Attrition:** -

**Exposures at midlife**

Four physical exercise and leisure activities assessed using 1967 self-reported questionnaire that focused on: outdoor activities; sports; gardening and home improvement; physical exercise after age 35

For each participant, the number of activities was tallied to yield maximum activity score of four

**Outcomes at 55 years or over**

Dementia assessment and cognitive screening conducted from 1990 to 2005

50-point Telephone Interview for Cognitive Status-modified (TICS-m) used for cognitive screening

When participants could not complete phone interview, proxy was interviewed using Informant
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

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**Questionnaire on Cognitive Decline in the Elderly** or another interview whereby a physician or psychologist reviewed participant’s answers

If suspected impairment on TICS-m or proxy instruments, Dementia Questionnaire (DQ) administered

If possible dementia identified through DQ, participant underwent neurologic examination, neuropsychological testing, blood or buccal DNA collection, history of cognitive symptoms and medical history assessed

**Analysis**

**Analysis strategy:** Dependent proportional hazard Cox ratios used to model the elapsed time from date of leisure activity assessment to either dementia diagnosis or censoring age

**Confounders:** Occupational history, age at date of activity assessment, education, natural matching (e.g., genes)

**Effect modification:** APOE4 allele

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**Results, limitations, source of funding**

- Dementia mean age of onset: 72.7 years
- Physical activity did not predict dementia risk reduction
- Risk for dementia by physical activity scores in discordant twin-pairs: OR=0.99 (0.73-1.33)
- Risk for dementia among monozygotic twin pairs with and without APOE 4 allele [OR=0.82, (0.48-1.41) and OR=0.94 (0.48-1.87), respectively]

**Limitations:** Possibly underpowered study and restricted measurement sensitivity

**Source of Funding:** National Institute on Aging

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**Authors:** Chang M, Jonsson PV, Snaedal J, Bjornsson S, Saczynski JS, Aspelund T… Launer LJ

**Year:** 2010

**Citation:** Journals of Gerontology Series A-Biological Sciences & Medical Sciences 65(12): 1369-1374

**Country of study:** Iceland

**Aim of study:** To evaluate the association between mid-life physical activity and late-life cognitive performance and dementia

**Study design:** Longitudinal

**Quality score:** (+++, + or -): -

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**Source population**

Men and women born in 1907-1935 and living in Reykjavik, Iceland part of Reykjavik Study that was initiated in 1967

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**Study (eligible and selected) population**

In 2002, cohort members re-invited to participate

4,761 participants (2,006 women and 2,755 men)

**Sociodemographics:** Mean age of 51 years of participants at midlife examination and 76 years at life-life

**Follow-up:** On average, 26 years elapsed between mid-life and late-life examinations

**Exclusion:**

i) Participants with APOE e2/4 (n=32)
ii) People with missing data from cognitive performance tests (n=819)
iii) 184 people with prevalent dementia at baseline

Attrition: -

Exposures at midlife

-Midlife physical activity assessed through interview

Participants who had ever participated in sports or exercise during adults life then reported the number of hours per week of exercise during winter and summer time and were subsequently categorised as follows: none (0 hours/week); <=5 hours/week; >5 hours/week

Outcomes at 55 years or over

Cognitive function assessed using cognitive tests measuring speed of processing, memory, executive function
DSM-IV dementia diagnosed according to 3 step protocol; those with low scores on MMSE or digit symbol substitution test were administered second diagnostic cognitive test battery; last step involved neurological test and a proxy interview regarding medical history, social, cognitive and daily functioning changes of participant

Analysis

Analysis strategy: Logistic regression used to assess midlife physical activity on late-life dementia

Confounders: Demographic and health factors, including age at time of examination, blood pressure, BMI, serum cholesterol, smoking status, resting heart rate, depressive symptoms

Stratification by APOE: APOE allele genotyping on subsample of 2,113; participants categorized as carriers vs. non-carriers

Results, limitations, source of funding

- Those who exercised <=5 hours/week and >5 hours/week at midlife had significantly faster speed of processing (p<0.0001), better memory (p<0.0001), and higher executive function (p<0.0001) compared to those who never exercised at midlife
- The odds of dementia were lower among those who exercised <=5 hours/week compared to those who never exercised (OR=0.59, [0.40, 0.88])

Stratification by APOE4:
- APOE e4 non-carriers who reported midlife physical activity had very low risk for late-life dementia compared to those who reported no midlife physical activity and were APOE e4 carriers (OR=0.18, [0.07, 0.45])
- APOE e4 non-carriers who reported no midlife activity also had reduced risk for dementia (OR=0.59, [0.36, 0.98])

Limitations: Limited detail by which physical activity is characterised

Source of funding: National Institutes of Health contract N01-AG-12100, the National Institute on Aging Intramural Research Program, the Icelandic Heart Association, the Icelandic Parliament, and the Icelandic Center for Research

Authors: Chang M, Saczynski JS, Snaedal J, Bjornsson S, Einarsson B, Garcia M... Jonsson PV
Year: 2013
Citation: Journal of the American Geriatrics Society 61(2): 237-242
Country of study: Iceland
**Aim of study:** To evaluate the association between mid-life physical activity and late-life lower extremity function (LEF) in older adults  

**Study design:** Longitudinal  

**Quality score:** (++, + or -): -

**Source population**

Men and women born in 1907-1935 and living in Reykjavik, Iceland part of Reykjavik Study that was initiated in 1967

**Study (eligible and selected) population**

> In 2002, cohort members re-invited to participate  
4,753 participants included in primary analysis of physical activity (PA) on LEF  
4,359 participants with complete cognitive data selected for secondary analysis of PA on LEF, adjusting for cognitive function

**Follow-up:** Average of 25 years

**Sociodemographics:** 2,011 men and 2,742 women included in primary analysis

**Exclusion:** > out of 5,764, people excluded from primary analysis because of:  
i) Missing data on LEF tests (n=797)  
ii) Had diagnosed dementia (n=214)  
Those excluded were older, more sick than participants

**Attrition:** -

**Exposures at midlife**

> Midlife physical activity was assessed through interviews on the number of hours per week that people participated in sports or exercise in the summer and winter; participants were categorised as:  
Active: if they reported any physical activity hours in summer or winter  
Inactive: if they reported no physical activity

**Outcomes at 55 years or over**

Lower extremity function (LEF) was measured in late life using reliable gait speed test, walk test (TUG test for assessing balance problems in older people and ADL decline), and knee extension strength (KES)

**Analysis**

**Analysis strategy:** Primary analysis: linear regression used to assess influence of midlife PA on gait speed, TUG, and KES tests while adjusting for all confounders, except cognitive function.  

**Secondary analysis:** Same as above, with additional adjustment for cognitive function

**Confounders:** Mid-life variables including education, blood pressure, height, weight, serum cholesterol, smoking, serum cholesterol. Late-life variables including diabetes mellitus, coronary events (history of myocardial infarction, coronary bypass surgery, heart bypass surgery, angioplasty, or others), stroke, depression, MMSE (only in primary analysis) or cognitive function (only in secondary analysis)

**Results, limitations, source of funding**
- Those who were active at midlife had significantly better LEF
- Primary analysis: the active group had 0.049-m/s faster gait speed (95% CI = 0.038, 0.059, P < .001), completed the TUG test 0.53 seconds faster (95% CI = 0.71, 0.36, P < .001), and had 1.34-kg greater KES (95% CI = 0.83, 1.86, P < 0.001) than the inactive group
- Secondary analysis: the active group had 0.037-m/s faster gait speed (95% CI = 0.026, 0.048, P < .001), completed the TUG test 0.34 seconds faster (95% CI = 0.52, 0.16, P < .001), and had 0.87-kg greater KES (95% CI = 0.34, 1.42, P < .001) than the inactive group

Limitations: None reported by the study authors

Source of funding: Intramural Research Program of the National Institutes of Health, the National Institute on Aging, the Icelandic Heart Association, Landspitali University Hospital, and the Icelandic Parliament

Authors: Christensen U, Støvring N, Schultz-Larsen K, Schroll M, Avlund K
Year: 2006
Citation: Scandinavian Journal of Medicine & Science in Sports 16(4): 245-251
Country of study: Denmark
Aim of study: Determine the influence of physical inactivity from middle-age to early old-age on disability at age 75
Study design: Longitudinal
Quality score: (+++, + or -): -

Source population
Cohort follow-up of 802 people selected for baseline study in 1964 from Copenhagen, Denmark (participation rate 84%)

Study (eligible and selected) population
387 people born in 1914 who participated in at least one of the three study phases in 1964, 1974, or 1984 and at the 25-year follow-up in 1989

Sociodemographics: Study had more women (54%) than men, 76% of participants had 7 years of school education and 84% were married or cohabiting
Follow-up: 25 years
Exclusion:
  i) People who died, moved, or refused to participate (75% participation rate, n=666; and 74% participation rate, n=537 at 10-year and 20-year follow-up, respectively)
  ii) At 20- and 25-year follow-up, non-participants were more likely to be men, have 7 years of basic school education, to be cohabiting and smoke in comparison with participants
Attrition: -

Exposures at midlife
>Self-reported physical activity in leisure time assessed in 1964, 1974, and 1984
Participants grouped as ‘mainly sedentary’ or ‘mainly active’ (e.g. light physical activity 1-4 h/week or moderate activity 1-3 h/week or vigorous activity more than 4h/week or in competitive sports several times/week)

Outcomes at 55 years or over
>Functional ability assessed by interviewer-administered Mob-T scale that measures tiredness after performing mobility activities with scores ranging from 0 to 6
Categorised participants into those with good function (score=6) and those with poorer function (score<6)
Cumulative physical activity measures formed for ages of 50+60, 60+70, and 50+60+70 – indicates average physical activity value during that time period
Construct validity, criterion-related validity and reliability of Mob-T scale described in different study

Analysis

Analysis strategy: Logistic regression used to assess influence of physical inactivity (accumulated and separately at each point in time) on disability
Confounders: Smoking, household composition at baseline
Stratification: By education

Results, limitations, source of funding

- Physical inactivity at age 60 to 70 was related to disability for the sub-group with more than 7 years of education (OR=8.62, [1.08, 68.54])

Limitations:
1. “Healthy participant effect”
2. If people who dropped out of study were more likely to be physically inactive, then effects of inactivity on functional ability may have been underestimated
3. Reporting bias and social desirability bias when participants self-reported sedentary lifestyle
4. Small sample size

Source of funding: None reported

Authors: Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C… DeCarli C
Year: 2011
Citation: Neurology 77(5): 461-468
Country of study: USA
Aim of study: To test the association of vascular risk factor exposure in midlife with progression of MRI markers of brain aging and measures of cognitive decline
Study design: Longitudinal
Quality score: (+++, + or -): +

Source population

Number of people: 5,124
Demographics: Only report on includes at baseline:
Age, y, mean±SD 54±9
Women, n (%) 718 (53.1)
High school graduate, n (%) 1,319 (97.6)

Study (eligible and selected) population

Number of people: 1,352
Characteristics:
Age 61 ± 9
Women, n (%) 718 (53.1)
High school graduate, n (%) 1,319 (97.6)

Location: Framingham

Recruitment strategy: The present study includes participants from the offspring cohort of Framingham HS

Exposures at midlife

Relevant exposures: Smoking habits, educational achievement, BMI


Measurement of exposure: Body mass index (BMI) was defined as weight (kg) divided by the square of height (m). Standing waist circumference was measured at the level of the umbilicus; hip circumference at the level of the trochanter major. Waist-to-hip ratio was calculated as the ratio of waist to hip circumferences. Educational achievement was studied as a 4-class variable (no high school degree; high school degree, no college; some college; college degree).

Outcomes at 55 years or over

Outcomes: White matter hyperintensity volume, total brain volume, and temporal horn volume of the lateral ventricles, verbal memory, visuospatial memory, and executive function.

Outcome measurement: Brain MRI techniques. The delayed recall component of the Logical Memory subtest from the Wechsler Memory Scale provides a savings measure of retention for verbal memory. The delayed recall component of the Visual Reproductions test assesses visuospatial memory. The difference between the score on Trail-Making Tests B and A is a marker of executive function.

Time: Not reported

Analysis

Analysis strategy: Used multivariable linear regression to relate each vascular risk factor to continuous measures of change and multivariable logistic regression for dichotomous measures of change.

Secondary analysis: Tested whether the associations were similar when additionally adjusting for the baseline measure of the examined outcome variable. The association of hypertension and systolic blood pressure with WMHV progression was also adjusted for interim stroke. Also tested for interaction with APOE 4 carrier status.

Confounders: All analyses were adjusted for sex, age at the first NP/MRI assessment, time interval between the risk factor assessment and the first NP/MRI assessment, and education for cognitive outcomes. For the dichotomous measure of white matter hyperintensity volume change, we also adjusted for the time interval between the first and last NP/MRI evaluation.

Source of funding: Framingham Heart Study’s National Heart, Lung, and Blood Institute contract (N01-HC-25195) and by grants from the National Institute of Neurological Disorders and Stroke (R01 NS17950) and from the National Institute on Aging (R01 AG16495; AG08122; AG033193; AG031287). Dr. Debette was supported by a Fulbright grant and received an award from the Bettencourt-Schueller Foundation

Results, limitations, source of funding

Number: 1,352

Effect estimates:

Smoking
Estimates ± SE p.
White matter hyperintensity volume -0.03±0.07 p.0.694
Total brain volume -0.15±0.07 p.0.025
Temporal horn volume -0.19±0.07 p.0.008
Logical Memory, delayed recall -0.08±0.08 p.0.316
Delayed recall component of the Visual Reproductions test -0.14±0.08 p.0.070
Trail-Making Test -0.04± 0.08 p.0.563

Significant trends: Vascular risk factors and structural brain aging.
Current smoking in midlife was associated with: greater annual increase in temporal horn volume and decrease in total brain volume and also predicted an increased risk of prominent change in temporal horn volume, Total Brain volume, and white matter hyperintensity volume.

Limitations:
1. Persons included are not representative of the general population
2. Vascular risk factors are highly correlated with each other, making it difficult to tease out the individual effects of each did not perform any correction for multiple testing as we considered our study as exploratory
3. Community sample of relatively young subjects, excluding persons with clinical dementia, thus leading to limited variability in cognitive performance longitudinal differences in brain structure may reflect an earlier effect of exposure to vascular risk than changes in cognition
4. Measures of change in brain structure are assessed using automated procedures. lack of a direct measure for longitudinal change in hippocampal volume
5. Measures of cognitive decline are subject to a learning effect

Authors: Dudas KA, Wilhelmsen L, Rosengren A
Year: 2007
Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(1): 122-127
Country of study: Sweden
Aim of study: Assess risk factors for future coronary bypass grafting as a first coronary event, and to compare them with risk factors for a first acute myocardial infarction
Study design: Prospective cohort study
Quality score: (+++, + or -): ++

Source population
Number of people: 7434
Demographics: Not reported

Study (eligible and selected) population
Number of people: 7388
Characteristics:
No CHD. n=5578: Age, mean; SD (years) 51.4;2.3: BMI, mean; SD (kg/m2) 25.4;3.2: Family history, 1013 (18%): Diabetes, n 73 (1%): Current smoker, n 2653 (47%): Sedentary physical activity, n 1379 (25%): Permanent stress, n 1112 (20%) 375
All MI. n=1664: Age, mean; SD (years) 52.1;2.2: BMI, mean; SD (kg/m2)  26.0;3.4: Family history, 401 (24%): Diabetes, n 68 (4%): Current smoker, n 969 (58%): Sedentary physical activity, n 487 (29%): Permanent stress, n 375 (23%)
Cases CABG. without previous MI n=146: Age, mean; SD (years) 51.0;2.2: BMI, mean; SD (kg/m2) 25.8;3.2: Family history, n 48 (33%): Diabetes, n 6 (4%): Current smoker, n 60 (41%): Sedentary physical activity, n 28 (19%): Permanent stress, n 33 (23%)
**Location:** Goteborg

**Recruitment strategy:** All men in the city who were born between 1915 and 1925 (n=30,000), except those born in 1923, were randomised into three groups of 10,000 men each

**Length of follow-up:** 28 years

**Response rate and loss to follow-up:** Not reported

**Eligible population:** All men in the city who were born between 1915 and 1925

**Excluded populations:** Women excluded. Forty-six men undergoing CABG in connection with an operation for aortic stenosis were excluded

## Exposures at midlife

**Relevant exposures:** Smoking habits, physical activity during leisure time, psychological stress

**Time:** 1970-1998

**Measurement of exposure:**

- **Smoking habits** coded as never smoked, former smoker of more than 1 month's duration, smoking 1–14 g of tobacco per day, smoking 15–24 g and smoking 25 g or more per day. One cigarette was considered to contain 1 g of tobacco, a cigarillo 2 g and a cigar 5 g of tobacco.

- **Physical activity** during leisure time was categorised into four levels with 1 representing sedentary activity, 2 moderate activity such as walking or light gardening during at least 4 h per week, and 3 regular, strenuous, or 4 very strenuous activities. Because there were few men in category 4, the two highest categories were combined.

- **Psychological stress** was assessed by way of one single question in the postal questionnaire and rated from 1 to 6, with 5 and 6 defined as permanent stress during the last year, or the last 5 years, before the examination

## Outcomes at 55 years or over

**Outcomes:** Coronary bypass

**Outcome measurement:** AMI was defined as a discharge, or death with International Classification of Diseases. To identify cases of aorto-coronary bypass operations classification codes 3066, 3067 and 3091 were used prior to 1997 and FNA and FNC during 1997 and 1998. Codes for coronary angioplasty were not registered for the purpose of the present study

**Time:** Not reported

## Analysis

**Analysis strategy:** A multiple logistic regression analysis for the two diagnoses, AMI and CABG, was used in a generalized logit model. According to this we modelled the logits of three category’s response variables (no risk, AMI and CABG) against the risk factors. In this model, age-adjusted odds ratios are obtained for the two separate outcomes, and then compared to see difference.

**Confounders:** Age, family history of AMI, BMI, cholesterol, systolic blood pressure, treatment for hypertension, diabetes, smoking, physical activity, stress

**Source of funding:** This study was supported by the Heart and Lung Foundation, the Swedish Research Council and FoU-radet in Goteborg and Sodra Bohuslan, Vastra Gotalandsregionen

## Results, limitations, source of funding

**Number:** 128 men

**Effect estimates:**

- All AMI
### Hazard ratio (95% CI)

**age adjusted**

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoking</td>
<td>1.00</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.19 (1.02–1.38)</td>
</tr>
<tr>
<td>1–14 g/day</td>
<td>1.70 (1.50–1.94)</td>
</tr>
<tr>
<td>15–24 g/day</td>
<td>1.90 (1.64–2.21)</td>
</tr>
<tr>
<td>25 g/day or more</td>
<td>1.89 (1.45–2.46)</td>
</tr>
</tbody>
</table>

**Physiological activity**

<table>
<thead>
<tr>
<th>Level</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.86 (0.76–0.96)</td>
</tr>
<tr>
<td>3</td>
<td>0.80 (0.68–0.95)</td>
</tr>
</tbody>
</table>

**Stress**

| Yes | 1.16 (1.04–1.31)      |

### Odds ratio age-adjusted

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.31 1.24–1.39</td>
</tr>
<tr>
<td>Smoking (1–5)</td>
<td>1.51 1.43–1.60</td>
</tr>
<tr>
<td>Physical activity (1–3)</td>
<td>0.83 0.76–0.90</td>
</tr>
<tr>
<td>Stress (yes/no)</td>
<td>1.16 0.99–1.35</td>
</tr>
</tbody>
</table>

### CABG without prior AMI

**Hazard ratio (95% CI)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoking</td>
<td>1.00</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.29 (0.84–1.98)</td>
</tr>
<tr>
<td>1–14 g/day</td>
<td>0.96 (0.62–1.51)</td>
</tr>
<tr>
<td>15–24 g/day</td>
<td>1.11 (0.65–1.90)</td>
</tr>
<tr>
<td>25 g/day or more</td>
<td>2.19 (1.02–4.66)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity (1–3)</td>
<td>1.27 0.98–1.64</td>
</tr>
<tr>
<td>Stress (yes/no)</td>
<td>1.03 0.64–1.65</td>
</tr>
</tbody>
</table>

**Significant trends:** High BMI, low physical activity and psychological stress were significantly associated only with AMI. Even light to moderate smoking (1–14 g/day) was associated with increased risk of AMI, hazard ratio 1.70 (1.50–1.94); whereas only very heavy smokers were more likely to undergo CABG, hazard ratio for 25 g/day or more 2.19 (1.02–4.66). Moderate smoking was not associated with coronary bypass grafting.

**Limitations:**

1. Only men of a comparatively limited age span were studied.
2. Did not have angiographic data in any patient group.
3. Patients with mild angina who did not undergo CABG were not studied.

**Authors:** Ekelund U, Brage S, Franks PW, Hennings S, Emms S, Wareham NJ

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
**Year:** 2005  
**Citation:** Diabetes Care 28(5): 1195-120  
**Country of study:** UK  
**Aim of study:** Examine the prospective associations between physical activity energy expenditure, aerobic fitness, obesity, and the progression toward the metabolic syndrome  
**Study design:** Population-based cohort  
**Quality score:** (++, + or -): +  

### Source population

**Number of people:** Not reported  
**Demographics:**  
- **Men** (n = 246)  
  - Baseline  
    - Age (years) 53.3 ± 10.5  
    - Height (cm) 175.3 ± 6.8  
    - Weight (kg) 80.6 ± 10.6  
    - BMI (kg/m²) 26.2 ± 2.9  
- **Women** (n = 359)  
  - Baseline  
    - Age (years) 53.1 ± 10.1  
    - Height (cm) 162.3 ± 6.1  
    - Weight (kg) 68.0 ± 12.6  
    - BMI (kg/m²) 25.8 ± 4.4

### Study (eligible and selected) population

**Number of people:**  
- **Men** (n = 246)  
- **Women** (n = 359)  
**Characteristics:**  
- **Men**  
  - Age (years) 58.9 ± 10.6  
  - Height (cm) 175.0 ± 6.7  
  - Weight (kg) 81.2 ± 12.2  
  - BMI (kg/m²) 26.5 ± 3.5  
- **Women**  
  - Age (years) 58.7 ± 10.2  
  - Height (cm) 162.0 ± 6.2  
  - Weight (kg) 69.5 ± 14.7  
  - BMI (kg/m²) 26.4 ± 6.2  
**Location:** Ely, UK  
**Recruitment strategy:** Randomly selected  
**Length of follow-up:** Median ± SD follow-up period of 5.6±0.30 years  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Not reported  
**Excluded populations:** Not reported  

**Exposures at midlife**
**Relevant exposures:** Physical activity

**Time:** Not reported

**Measurement of exposure:** Height and weight were measured using a rigid stadiometer and calibrated scales in light clothing. Body circumference was measured in duplicate using a metal tape. Resistance was assessed using a standard bioimpedance technique. Physical activity energy expenditure measured using the flex heart rate method. Total body water and fat-free mass were calculated using the impedance index. Fat mass was calculated as body weight minus fat-free mass. Percentage of body fat was calculated as fat mass/body weight x 100.

Blood pressure was measured in seated position using an Accutorr automatic sphygmomanometer. Systolic and diastolic blood pressures were measured in triplicate at minute intervals, and the mean of these measurements was used in analyses.

**Outcomes at 55 years or over**

**Outcomes:** Metabolic syndrome

**Outcome measurement:** Blood samples

**Time:** 2001–2003

**Analysis**

**Analysis strategy:** Generalized linear models

**Confounders:** Included all subcomponents of the metabolic syndrome and was adjusted for baseline zMS, sex, age, smoking, SES, and follow-up time.

**Results, limitations, source of funding**

**Number:** 84 subjects (46 male)

**Effect estimates:**

<table>
<thead>
<tr>
<th>Outcome (SD)</th>
<th>PAEE -coefficients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>0.002 (0.0037 to 0.00053)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.00004 (0.00076 to 0.00084)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.00058 (0.0006 to 0.0017)</td>
</tr>
<tr>
<td>2-h glucose</td>
<td>0.00008 (0.0016 to 0.0015)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.00086 (0.0024 to 0.0007)</td>
</tr>
<tr>
<td>SBP</td>
<td>0.002 (0.0037 to 0.00064)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.000088 (0.0015 to 0.0015)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.00074 (0.0005 to 0.002)</td>
</tr>
<tr>
<td>zMS</td>
<td>0.00085 (0.0017 to 0.00068)</td>
</tr>
<tr>
<td>zMS-Ob</td>
<td>0.0011 (0.0021 to 0.0006974)</td>
</tr>
</tbody>
</table>

**Significant trends:** Baseline PAEE significantly predicted fasting insulin at follow-up after adjustment for baseline age, sex, smoking, SES, fasting insulin, aerobic fitness, and duration of follow-up (standardized β 0.0012, P 0.01). This association was not affected by further adjustment for baseline BMI (standardized β 0.0013, P 0.005), baseline WHR (standardized β 0.0012, P 0.007), or baseline percentage body fat (standardized β 0.0012, P 0.006).

**Limitations:**

1. Not powered to explore the possibility of nonlinearity
2. Measure of aerobic fitness is less precise than a true maximal test

**Source of funding:** The Medical Research Council
**Authors:** Elwood P, Galante J, Pickering J, Palmer S, Bayer A, Ben-Shlomo Y... Gallacher J  
**Year:** 2013  
**Citation:** PLoS One 9;8(12): e81877  
**Country of study:** South Wales (Caerphilly)  
**Aim of study:** To assess influence of lifestyle on cognitive function  
**Study design:** Longitudinal  
**Quality score:** (+++, + or -): +

**Source population**
Cohort of men ages 45-59 years in small South Wales UK town. After 1979 baseline survey, men were re-examined every five years.

**Study (eligible and selected) population**

**Study population:** Analysis restricted to 2,235 men (89% of defined population) examined at baseline  
**Exclusion:**  
1. Men with evidence of disease at baseline (diabetes, a history of angina, chest pain, clinical or ECG evidence of infarction, stroke, high blood pressure)  
2. Men with evidence of cognitive impairment at baseline omitted  
**Attrition:** -

**Exposures at midlife**
Self-reported smoking history, physical activity and alcohol consumption captured through food frequency questionnaire at baseline in 1979  
**Uptake of health behaviours assessed:**
Health behaviour:  
> Not smoking including ex-smokers;  
> Diet: 3+ portions of fruit and/or vegetables a day and 30% less calories from fat;  
> Physical activity: walking 2+ miles or cycling 10+ miles each day, or vigorous exercise;  
> Alcohol: 3 or fewer units per day

**Outcomes at 55 years or over**
Incidence of diabetes, vascular disease, cancer, all-cause mortality, cognitive impairment and dementia ascertained through self-report, primary care and hospital records, CT scans and ECG, Office of National Statistics (for deaths and cancer registrations)  
In 2004, cognitive impairment and dementia assessed in late-life in participants ages 70-85 years using CAMDEX, CAMCOG, Frontal Assessment Battery, the Clinical Dementia Rating, and the Informant Questionnaire on Cognitive Decline in the Elderly

**Analysis**

**Analysis strategy:** Logistic regression used to assess influence of lifestyle (number of healthy behaviours practiced) on cognitive function  
**Confounders:** Age, social class
Results, limitations, source of funding

- The odds of diabetes were lower among those who regularly exercised (OR=0.63, [0.46, 0.85])
- The odds of vascular disease were lower among those who were classified as non-smoking (OR=0.70, [0.58, 0.84]); similar findings reported for cancer (OR=0.65, [0.54, 0.79])
- The odds of cognitive impairment were lower for those who regularly exercised (OR=0.62, [0.41, 0.92]); similar findings reported for dementia
- The odds of death were lower among those who did not smoke (OR=0.42, [0.35, 0.51])
- Generally, the greater the number of healthy lifestyle behaviours the participants adopted, the lower the odds of diabetes, vascular disease, cognitive impairment, dementia, all-cause mortality

Limitations:
1. Impact of healthy lifestyles underestimated due to small number of men adhering to all healthy behaviours (small cell sizes)
2. residual confounding

Source of funding: None reported

Authors: Emberson JR, Shaper AG, Wannamethee SG, Morris RW, Whincup PH
Year: 2005
Citation: American Journal of Epidemiology 161(9): 856-863
Country of study: UK
Aim of study: Examine associations between alcohol intake and the 20-year risk of coronary heart disease, stroke, and all-cause mortality
Study design: Cohort
Quality score: (+++, + or -): ++

Source population
Number of people: 7,735 men aged 40–59 years
Demographics: Not reported

Study (eligible and selected) population
Number of people: 6,544
Characteristics: Middle-aged British men
Location: Throughout Britain
Recruitment strategy: General practice
Response rate and loss to follow-up: 77%
Eligible population: One general practice in each of 24 British towns
Excluded populations: Women and men with evidence of cardiovascular disease. 1,186 men with baseline evidence of CVD; five had incomplete baseline data

Exposures at midlife
Relevant exposures: Alcohol
Time: Between 1998 and 2000. Time until censoring or first cardiovascular event, whichever is lowest
Measurement of exposure: A five-point scale from zero (none) to four (heavy) was used to denote the alcohol intake level at the baseline assessment and at each of the follow-up assessments.
Categorised as:

1) Non-drinkers
2) Occasional drinkers (1–2 times/month or on special occasions)
3) Light drinkers (1–2 drinks/day or “weekend only” drinkers (1–6 drinks/day))
4) Moderate drinkers (3–6 drinks/day or weekend only drinkers (>6 drinks/day))
5) Heavy drinkers (>6 drinks every day)

From these average exposure levels, each individual was reclassified on the original scale (an average exposure of <0.5 was defined as “none” 0.5–1.49 was defined as “occasional” 1.5–2.49 was defined as “light” 2.5–3.49 was defined as “moderate” and 3.5 was defined as “heavy”).

Outcomes at 55 years or over

Outcomes: Cardiovascular morbidity and all-cause mortality
Outcome measurement: Information on incident mortality was collected through the established “tagging” procedures provided by the National Health Service central registers.
Time: Between 1998 and 2000

Analysis

Analysis strategy: Cox proportional hazards regression. Hazard ratios were calculated as “floating absolute risks” and inverse variance-weighted quadratic curves were fitted through the values. The “relative informativeness” of baseline versus average alcohol intake was evaluated by examining the contributions made by each measure to the $X^2$ likelihood ratio statistic in the Cox regression model.
Confounders: Adjustment for cigarette smoking, physical activity, and body mass index. Adjustment for intake variation

Limitations:

1. Misclassification of consumption
2. Misclassification of outcome

Source of funding: Not reported

Results, limitations, source of funding

Number: 6,544 men

Effect estimates:
Major coronary heart disease
Baseline exposure
Hazard ratio (95% CI)
None 1.00 (0.75, 1.34)
Occasional 1.00
Light 0.81 (0.68, 0.96)
Moderate 0.94 (0.78, 1.12)
Heavy 1.08 (0.86, 1.35)
Usual exposure
Hazard ratio 95% CI
None 0.91 (0.72, 1.15)
Occasional 1.00
Light 0.74 (0.63, 0.87)
Moderate 1.01 (0.84, 1.21)
Heavy 1.74 (1.31, 2.33)

Stroke
Baseline exposure
Hazard ratio 95% CI
| None 1.58 (1.02, 2.44) | Occasional 1.00 |
| Light 0.97 (0.72, 1.31) | Moderate 1.19 (0.88, 1.61) |
| Heavy 1.54 (1.06, 2.22) | |

**Usual exposure**

<table>
<thead>
<tr>
<th>Hazard ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None 1.08 (0.73, 1.60)</td>
</tr>
<tr>
<td>Occasional 1.00</td>
</tr>
<tr>
<td>Light 0.93 (0.71, 1.22)</td>
</tr>
<tr>
<td>Moderate 1.45 (1.08, 1.96)</td>
</tr>
<tr>
<td>Heavy 2.33 (1.46, 3.71)</td>
</tr>
</tbody>
</table>

**All-cause mortality**

<table>
<thead>
<tr>
<th>Baseline exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>None 1.22 (0.98, 1.52)</td>
</tr>
<tr>
<td>Occasional 1.00</td>
</tr>
<tr>
<td>Light 0.88 (0.77, 1.01)</td>
</tr>
<tr>
<td>Moderate 1.12 (0.98, 1.29)</td>
</tr>
<tr>
<td>Heavy 1.44 (1.21, 1.72)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>None 0.93 (0.77, 1.12)</td>
</tr>
<tr>
<td>Occasional 1.00</td>
</tr>
<tr>
<td>Light 0.82 (0.72, 0.93)</td>
</tr>
<tr>
<td>Moderate 1.32 (1.15, 1.52)</td>
</tr>
<tr>
<td>Heavy 2.27 (1.84, 2.81)</td>
</tr>
</tbody>
</table>

**Significant trends:** After adjustment for variation in alcohol intake risks among heavy drinkers were respectively, 32%, 86% and 70% higher than for occasional drinkers. After adjustment for intake, regular light alcohol consumption was associated with a statistically significant 26% reduced risk of CHD and 18% reduced risk of all-cause mortality, as well as a statistically insignificant 7% reduced risk of stroke. Moderate drinking and heavy drinking associated with substantially increased risks of stroke, all-cause mortality, and (to a lesser degree) major CHD.

**Limitations:** No limitations reported by author.

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**Authors:** Englund U, Nordström P, Nilsson J, Hallmans G, Svensson O, Bergström U, Pettersson-Kymmer U

**Year:** 2013

**Citation:** Osteoporosis International 24(2): 533-540

**Country of study:** Sweden

**Aim of study:** Investigate whether a physically active lifestyle in middle-aged women was associated with a reduced risk of later sustaining a low-trauma wrist fracture

**Study design:** Population-based nested case–control study

**Quality score:** (+++, + or -): +

**Source population**

**Number of people:** 35,000 subjects

**Demographics:** Mean age at baseline was 54.3±5.8 years, and mean age at fracture was 60.3±5.8 years
<table>
<thead>
<tr>
<th>Study (eligible and selected) population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people:</strong> 778</td>
</tr>
<tr>
<td><strong>Characteristics:</strong></td>
</tr>
<tr>
<td>Means (±SD)</td>
</tr>
<tr>
<td><strong>Cases (n=376).</strong></td>
</tr>
<tr>
<td>Age (year) 54.3±5.9: Height (cm) 164.2±5.7: Weight (kg) 67.4±10.5: BMI 24.8±3.7: Follow-up time (year) 11.2±2.6: Distance to work (km) 12.5±15.2: Low active 18.1±16.1: Moderate active 6.9±11.4: High active 2.9±6.9: Current smokers 21.1: Never smokers 53.4: Alcohol users 79.3</td>
</tr>
<tr>
<td><strong>Controls (n=402).</strong></td>
</tr>
<tr>
<td>Age (year) 54.3±5.8: Height (cm) 164.0±5.8: Weight (kg) 69.0±12.0: BMI 25.6±4.3: Follow-up time (year) 11.1±2.5: Distance to work (km) 11.9±17.3: Low active 21.5±20.2: Moderate active 6.5±12.6: High active 2.7±5.4: Current smokers 25.0: Never smokers 50.2: Alcohol users 76.5</td>
</tr>
<tr>
<td><strong>Location:</strong> Sweden, county of Västerbotten</td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong> All inhabitants 40, 50, or 60 years old are invited to a health survey and are also asked to donate a blood sample</td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong></td>
</tr>
<tr>
<td>Cases: Follow-up time (year) 11.2±2.6</td>
</tr>
<tr>
<td>Controls: Follow-up time (year) 11.1±2.5</td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong></td>
</tr>
<tr>
<td><strong>Eligible population:</strong> Inclusion in contains three population-based subcohorts. Fracture case was compared with at least one control drawn from the same cohort and matched for age and week of reporting data</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong> Subjects who had a wrist fracture before they were recruited into the VIP cohort were subsequently excluded. Another exclusion criterion was if the fracture had occurred before the age of 45 years or was the result of a major trauma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposures at midlife</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relevant exposures:</strong> Commuting activities, occupational physical activity, exercise, leisure time activities, walking and bicycling activities, smoking habits, alcohol habits</td>
</tr>
<tr>
<td><strong>Time:</strong> 1985</td>
</tr>
<tr>
<td><strong>Measurement of exposure:</strong> Self-assessment questionnaire includes questions relating to the subject’s level of occupational activity, commuting activity (type of traveling to and from work), and different leisure time activities, if subject has performed any exercise wearing training clothes in the last 3 months and to training habits in youth</td>
</tr>
<tr>
<td>Commuting activities for each of the four seasons were defined in three categories: car-bus, bicycling, and walking.</td>
</tr>
<tr>
<td>Occupational physical activity divided into three categories: low, moderate, and high physically demanding work.</td>
</tr>
<tr>
<td>Exercise in training clothes two groups: performed or not performed.</td>
</tr>
<tr>
<td>Physical activity in youth was defined in three groups: physical training at school only (low activity), training and/or competing at an amateur level (moderate activity), and competing at an elite level (high activity).</td>
</tr>
<tr>
<td>Frequency of leisure time activities was based on seven different regular activities: walking and/or bicycling (besides the commuting activity), dancing, snow shovelling, gardening, hunting/fishing, and berry/mushroom picking.</td>
</tr>
</tbody>
</table>
| The frequencies of walking and bicycling activities defined as low (<one to two times/month) moderate (three to four times/month), and high (two - three times/week or more). The remaining leisure time activities were categorized as not performed or performed (if performed at least every month during...
Smoking habits were coded as “never smoker”, “former smoker” and “current smoker”. Alcohol habits coded as “teetotaller” or “alcohol user”.

### Outcomes at 55 years or over

**Outcomes**: Wrist fracture  
**Outcome measurement**: Identified from a prospective injury-fracture database at the Umeå University Hospital  
**Time**: 31 December 2008

### Analysis

**Analysis strategy**: Conditional logistic regression analysis. Subgroup analyses performed in women with data on HRT, alcohol use, calcium and vitamin D intake.  
**Confounders**: Adjustments for height, body mass index, smoking, and menopausal status, dietary habits and other physical activity variables  
Subgroup analyses were also performed in women with available data on HRT and alcohol use and also on women with data on calcium and vitamin D intake

### Results, limitations, source of funding

**Number**: 376  
**Effect estimates**:  
- **Risk factor Odds ratio (95% CI)**  
  - Height: 1.00 (0.96–1.030)  
  - BMI: 0.94 (0.89–0.99)  
  - Smoking  
    - Never smoker: 1.00  
    - Former smoker: 1.10 (0.66–1.83)  
    - Current smoker: 0.84 (0.51–1.38)  
  - Commuting activity  
    - Low: 1.00  
    - Moderate: 0.98 (0.60–1.59)  
    - High: 0.48 (0.27–0.88)  
  - Occupational activity  
    - Low: 1.00  
    - Moderate: 0.80 (0.53–1.19)  
    - High: 0.96 (0.39–2.38)  
  - Training activity: 1.14 (0.75–1.74)  
  - Bicycling  
    - Low: 1.00  
    - Moderate: 1.01 (0.54–1.92)  
    - High: 1.13 (0.70–1.82)  
  - Dancing: 0.42 (0.22–0.81)  
  - Snow shovelling: 0.50 (0.32–0.79)  

**Significant trends**: Subjects with active commuting (especially walking) were at significantly lower risk of sustaining a wrist fracture (OR 0.48; 95% CI 0.27–0.88) compared with those who commuted by car or bus, in middle-aged women  
**Reported limitations**: No data on bone mineral density, neuromuscular functions or Vitamin D or increased muscle strength or balance. No estimation on the intensity or duration of the different activities or the loading characteristics. Differences in the level of outdoor activities and exposure to sunlight. All information about physical activity, health, and other lifestyle variables were self-
estimated. Questionnaire was not validated. Assessments of the different physical variables were crude. Physical activity and other variables were only assessed at baseline. **Limitations:** Case-control

**Source of funding:** Swedish Research Council (K2006-72X-20155013), Swedish Sports Research Council (87/06), Swedish Society of Medicine, Medical Faculty of Umeå, and by project grants from the Erik and Anne-Marie Detlof Foundation and the J C Kempe Foundation

| Year: | 2011 |
| Citation: | Osteoporosis International 22(2): 499-505 |
| Country of study: | Sweden |
| Aim of study: | Investigate whether physical activity is associated with a decreased risk of later sustaining a hip fracture |
| Study design: | Population-based case-control study |
| Quality score: (++, + or -): | + |

**Source population**

| Number of people: | 70,000 |
| Demographics: | Not reported |

**Study (eligible and selected) population**

| Number of people: | 237 |
| Characteristics: | Means (±SD) |
| **Cases (n=81).** Age (year) 57.2±5.0: Height (cm) 165.6±6.2: Weight (kg) 68.2±12.9: BMI 24.8±4.2: Percent (%) Smokers 33.8, Former smokers 6.8, Never smokers 59.5, Alcohol users 78.3 |
| **Controls(n=156).** Age (year) 57.2±5.0: Height (cm) 162.1±6.9: Weight (kg) 68.8±11.9: BMI 26.2±4.8: Percent (%) Smokers 20.4, Former smokers 16.3, Never smokers 63.3, Alcohol users 72.7 |
| Location: | Sweden |
| Recruitment strategy: | All inhabitants 40-60 years old were invited to a health survey and asked to donate a blood sample |
| Length of follow-up: | Case follow up time (year) 11.0±3.2 Control follow up time (year) 11.0±3.2 |
| Response rate and loss to follow-up: | Not reported |
| Eligible population: | Involved in Västerbotten Intervention Programme |
| Excluded populations: | Subjects who had a hip fracture or another fragility fracture before they were recruited into the VIP cohort. Women taking other medications known to affect bone metabolism were excluded from the study cohort |

**Exposures at midlife**

| Relevant exposures: | Physical activity |
| Time: | Not reported |
| Measurement of exposure: | Self-assessment questionnaire includes questions relating to the subject’s level of occupational activity, commuting activity (type of traveling to and from work), and |
different leisure time activities, if subject has performed any exercise wearing training clothes in the last 3 months and to training habits in youth

Commuting activities for each of the four seasons were defined in three categories (Car-bus, bicycling, and walking).

Occupational physical activity divided into three categories: low, moderate, and high physically demanding work.

Exercise in training clothes two groups: performed or not performed

Frequency of leisure time activities was based on seven different regular activities: walking and/or bicycling (besides the commuting activity), dancing, snow shoveling, gardening, hunting/fishing, and berry/mushroom picking

The frequencies of walking and bicycling activities defined as low (<one to two times/month) moderate (three to four times/month), and high (two - three times/week or more). The remaining leisure time activities were categorized as not performed or performed (if performed at least every month during the season)

Smoking habits were coded as “never smoker”, “former smoker” and “current smoker”

Alcohol habits coded as “teetotaller” or “alcohol user”

### Outcomes at 55 years or over

**Outcomes:** Hip fracture

**Outcome measurement:** Fracture cases were identified from a prospective injury fracture database at the Umeå University Hospital

**Time:** Time from baseline to when the hip fracture occurred was 8.4±3.8 years and the mean age at fracture was 65.4±6.4 years

### Analysis

**Analysis strategy:** Conditional logistic regression analysis. Multiple-adjusted associations were calculated with adjustments made for height, weight, smoking habits, and menopausal status. Subgroup analyses were also performed using HRT or alcohol habits as potential confounding variables.

**Confounders:** Adjustments for height, weight, smoking, and menopausal status

### Results, limitations, source of funding

**Number:** 202

**Effect estimates:**
Independent predictors of hip fracture risk

- **Adjusted odds ratio (95% CI):**
  - Height: 1.26 (1.14–1.40)
  - Weight: 0.94 (0.91–0.98)
  - Smoking:
    - Never smoker: 1
    - Former smoker: 0.34 (0.08–1.50)
    - Smoker: 2.37 (0.81–6.92)
  - Menopause: 0.57 (0.03–11.4)
  - Walking:
    - Never: 1
    - 1 time/week: 0.14 (0.04–0.53)
    - ≥2 times/week: 0.33 (0.10–1.01)
  - Spare time activity
    - Low: 1
    - Moderate: 0.19 (0.08–0.46)
High 0.17 (0.05–0.64)

**Significant trends:** Walking and seasonal-dependent physical spare time activities were associated with a significant hip fracture risk reduction in middle-aged women. Significantly reduced hip fracture risk in women walking once a week only. Lower odds ratio for women with higher frequency of walking.

**Limitations:**
1. No data on bone mineral density, neuromuscular functions or Vitamin D. Information about lifestyle variables were self-reported.
2. Questionnaire was not validated.
3. Assessments of the different physical variables were crude.
4. Physical activity and other variables were only assessed at baseline.
5. Number of hip fracture cases in this cohort was also rather low.

**Authors:** Eskelinen MH, Ngandu T, Hellkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M.

**Year:** 2008

**Citation:** International Journal of Geriatric Psychiatry 23(7): 741-747

**Country of study:** Finland

**Aim of study:** Investigate the association of midlife dietary fat intake to cognitive performance, and to the occurrence of clinical mild cognitive impairment

**Study design:** Longitudinal population-based study

**Quality score:** (+, + or -): +

**Source population**

**Number of people:** 2000

**Demographics:** 835 women (62.3%) and 506 men (37.7%) had a mean age at midlife of 50.2 (6.0) years

**Study (eligible and selected) population**

**Number of people:** 1449

**Characteristics:** Mean age at midlife of 71.1 (4.0) years at the follow-up.

**Location:** Kuopio and Joensuu, Eastern Finland

**Recruitment strategy:** Random sample

**Length of follow-up:** 21 (SD 4.9) years

**Response rate and loss to follow-up:** 72%

**Eligible population:** Study came from four separate, independent population-based random samples studied within the North Karelia Project and the FINMONICA study in 1972, 1977, 1982 or 1987

**Excluded populations:** Individuals who had dementia (n=68) were excluded. Those individuals who had dementia (n=68) were excluded, and 40 individuals did not complete all evaluations

**Exposures at midlife**

**Relevant exposures:** Diet

**Time:** 1998

**Measurement of exposure:** Dietary habits investigated using a semi-quantitative food frequency questionnaire consisting of mostly qualitative or frequency-based questions. Consumption of milk, sour milk and spreads assessed quantitatively
Outcomes at 55 years or over

**Outcomes:** MCI, global cognitive and executive functions, episodic, semantic and prospective memory and psychomotor speed

**Outcome measurement:** Mayo Clinic AD Research Center criteria; Mini Mental State Examination; Category Fluency Test; Purdue Peg Board task; letter digit substitution test; the Stroop test; memory task by Einstein

**Time:** 1998

**Analysis**

**Analysis strategy:** Logistic regression analyses were used to calculate Odds Ratios with 95% Confidence Intervals. Two models reported but third model undertaken controlling additionally for midlife leisure-time physical activity, alcohol consumption, or vascular disorders at late-life including myocardial infarction, stroke, and diabetes, the results remained unchanged or virtually the same

**Confounders:** Adjusted for midlife age, sex, education, follow-up time and other subtypes of fats, ApoE e4 carrier status, smoking, systolic blood pressure, cholesterol, and BMI

**Results, limitations, source of funding**

**Number:** 1,341

**Effect estimates:**

Association of midlife fat intake with clinical MCI in late-life

<table>
<thead>
<tr>
<th>Total fat (from milk products and spreads)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–38.0 g)</td>
<td>1</td>
</tr>
<tr>
<td>High (&gt;38.0 g)</td>
<td>1.69 (1.00–2.87)</td>
</tr>
</tbody>
</table>

saturated fatty acids (from milk products and spreads)

| Low (0–21.6 g)                           | 1                   |
| High (>21.6 g)                           | 2.36 (1.17–4.74)    |

polyunsaturated fatty acids (from milk products and spreads)

| Low (0–2.1 g)                           | 1                   |
| High (>2.1 g)                           | 0.94 (0.45–1.96)    |

PUFA-SFA ratio (milk products and spreads)

| Low (0–0.05)                            | 1                   |
| High (>0.05)                            | 0.91 (0.53–1.56)    |

monounsaturated fatty acids (from milk products and spreads)

| Low (0–11.3 g)                           | 1                   |
| High (>11.3 g)                           | 1.81 (0.87–3.80)    |

Association of midlife fat intake with Global cognitive function (MMSE)

<table>
<thead>
<tr>
<th>Total fat from milk and spreads</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–38.0 g)</td>
<td>26.2 (0.1)</td>
</tr>
<tr>
<td>High (&gt;38.0 g)</td>
<td>25.9 (0.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.05</td>
</tr>
</tbody>
</table>

SFA from milk and spreads

| Low (0–21.6 g)                | 26.2 (0.1)          |
| High (>21.6 g)                | 25.8 (0.1)          |
| p-value                      | 0.03                |

PUFA from milk and spreads

| Low (0–2.1 g)                | 26.0 (0.1)          |
| High (>2.1 g)                | 26.1 (0.1)          |
| PUF-A–SFA ratio (milk and spreads) | Low (0–0.05) 26.0 (0.1) |
|                             | High (>0.05) 26.1 (0.1) |

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
### MUFA from milk and spreads
- **Low** (0–11.3 g): 26.1 (0.1)
- **High** (>11.3 g): 26.0 (0.1)

### Association of midlife fat intake with Episodic memory

<table>
<thead>
<tr>
<th>Total fat from milk and spreads</th>
<th>SFA from milk and spreads</th>
<th>MUFA from milk and spreads</th>
<th>PUFA from milk and spreads</th>
<th>PUFA–SFA ratio (milk and spreads)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong> (0–38.0 g): 5.0 (0.04)</td>
<td><strong>Low</strong> (0–21.6 g): 5.0 (0.05)</td>
<td><strong>Low</strong> (0–11.3 g): 5.0 (0.05)</td>
<td><strong>Low</strong> (0–0.05): 5.0 (0.04)</td>
<td><strong>Low</strong> (0–11.3 g): 5.0 (0.05)</td>
</tr>
<tr>
<td><strong>High</strong> (&gt;38.0 g): 4.9 (0.1)</td>
<td><strong>High</strong> (&gt;21.6 g): 4.9 (0.1)</td>
<td><strong>High</strong> (&gt;11.3 g): 4.9 (0.1)</td>
<td><strong>High</strong> (&gt;0.05): 4.9 (0.1)</td>
<td><strong>High</strong> (&gt;11.3 g): 4.9 (0.1)</td>
</tr>
</tbody>
</table>

### Association of midlife fat intake with Semantic memory

<table>
<thead>
<tr>
<th>Total fat from milk and spreads</th>
<th>SFA from milk and spreads</th>
<th>MUFA from milk and spreads</th>
<th>PUFA from milk and spreads</th>
<th>PUFA–SFA ratio (milk and spreads)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong> (0–38.0 g): 20.3 (0.2)</td>
<td><strong>Low</strong> (0–21.6 g): 20.4 (0.2)</td>
<td><strong>Low</strong> (0–11.3 g): 19.7 (0.4)</td>
<td><strong>Low</strong> (0–0.05): 20.1 (0.2)</td>
<td><strong>Low</strong> (0–11.3 g): 19.9 (0.2)</td>
</tr>
<tr>
<td><strong>High</strong> (&gt;38.0 g): 20.0 (0.3)</td>
<td><strong>High</strong> (&gt;21.6 g): 19.7 (0.4)</td>
<td><strong>High</strong> (&gt;11.3 g): 20.8 (0.3)</td>
<td><strong>High</strong> (&gt;0.05): 20.3 (0.3)</td>
<td><strong>High</strong> (&gt;11.3 g): 20.8 (0.3)</td>
</tr>
</tbody>
</table>

### Association of midlife fat intake with Psychomotor speed

<table>
<thead>
<tr>
<th>Total fat from milk and spreads</th>
<th>SFA from milk and spreads</th>
<th>MUFA from milk and spreads</th>
<th>PUFA from milk and spreads</th>
<th>PUFA–SFA ratio (milk and spreads)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong> (0–38.0 g): 0.10 (0.03)</td>
<td><strong>Low</strong> (0–21.6 g): 0.08 (0.03)</td>
<td><strong>Low</strong> (0–11.3 g): 0.09 (0.03)</td>
<td><strong>Low</strong> (0–0.05): 0.04 (0.03)</td>
<td><strong>Low</strong> (0–11.3 g): 0.01 (0.05)</td>
</tr>
<tr>
<td><strong>High</strong> (&gt;38.0 g): -0.02 (0.04)</td>
<td><strong>High</strong> (&gt;21.6 g): 0.02 (0.05)</td>
<td><strong>High</strong> (&gt;11.3 g): 0.01 (0.04)</td>
<td><strong>High</strong> (&gt;0.05): 0.1 (0.04)</td>
<td><strong>High</strong> (&gt;11.3 g): 0.01 (0.04)</td>
</tr>
</tbody>
</table>

### Association of midlife fat intake with Executive function (Stroop)

<table>
<thead>
<tr>
<th>Total fat from milk and spreads</th>
<th>SFA from milk and spreads</th>
<th>MUFA from milk and spreads</th>
<th>PUFA from milk and spreads</th>
<th>PUFA–SFA ratio (milk and spreads)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong> (0–38.0 g): 39.8 (0.8)</td>
<td><strong>Low</strong> (0–21.6 g): 0.1 (0.04)</td>
<td><strong>Low</strong> (0–11.3 g): 0.09 (0.03)</td>
<td><strong>Low</strong> (0–0.05): 0.04 (0.03)</td>
<td><strong>Low</strong> (0–11.3 g): 0.01 (0.05)</td>
</tr>
<tr>
<td><strong>High</strong> (&gt;38.0 g): 41.0 (1.1)</td>
<td><strong>High</strong> (&gt;21.6 g): 0.1 (0.04)</td>
<td><strong>High</strong> (&gt;11.3 g): 0.01 (0.04)</td>
<td><strong>High</strong> (&gt;0.05): 0.1 (0.04)</td>
<td><strong>High</strong> (&gt;11.3 g): 0.01 (0.04)</td>
</tr>
</tbody>
</table>
Association of midlife fat intake with Prospective memory

**Total fat from milk and spreads**
- Low (0–38.0 g) 2.7 (0.03)
- High (>38.0 g) 2.6 (0.04)

**SFA from milk and spreads**
- Low (0–21.6 g) 2.7 (0.04)
- High (>21.6 g) 2.6 (0.1)

**p-value 0.05**

**PUFA from milk and spreads**
- Low (0–2.1 g) 2.7 (0.04)
- High (>2.1 g) 2.7 (0.05)

**PUFA–SFA ratio (milk and spreads)**
- Low (0–0.05) 2.7 (0.03)
- High (>0.05) 2.7 (0.04)

**MUFA from milk and spreads**
- Low (0–11.3 g) 2.7 (0.04)
- High (>11.3 g) 2.7 (0.1)

**Significant trends:** Midlife dietary fat intake was related to cognitive performance, especially in domains of global cognitive function, semantic memory and psychomotor speed, and to the occurrence of MCI later in life.

**Limitations:**

**Author**
1. Dietary data was available from limited sources
2. Results of stratified analyses may be inconclusive due to insufficient power

**Reviewer**
1. Authors undertake three models but show results from two. In conclusion refer to the three models.
2. Selective reporting bias. Revisit when we have time to go through thoroughly.

**Source of funding:** The study was supported by EVO-grants of Kuopio University Hospital (5772708, 5772720), Academy of Finland grants 103334, 120676 and 206951, EU grant QLK-2002-172, The Swedish Council for Working Life and Social Research, the Finnish Cultural Foundation, The Foundation of Juho Vainio, the Gamla Tjanarinnor Foundation, and Uulo Arhio foundation

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**Authors:** Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M

**Year:** 2009

**Citation:** Journal of Alzheimer’s Disease 16: 85-91

**Country of study:** Finland

**Aim of study:** To evaluate the association between mid-life coffee and tea drinking and the risk of late-life dementia

**Study design:** Longitudinal
Quality score: (+++, + or -): +

Source population
A population-based random sample of 2000 people aged 65-79 years and living in Joensuu or Kuopio, Eastern Finland in 1997 were invited to participate in 1998. Response rate of 71% (1409), of which 875 (62%) were women and 534 (38%) were men.

Study (eligible and selected) population
See: ‘Source population’

Sociodemographics: At midlife examination, 875 women and 534 men had mean age of 50.4 years, while at late-life examination, mean age was 71.3 years

Follow-up: Mean follow-up time of 21 years. Response rate of 71%

Exclusion: -

Attrition: -

Exposures at midlife
Coffee and tea consumption examined at midlife using validated semi-quantitative food-frequency questionnaire
Coffee drinking categorised as: 0-2 cups/day (low), 3-5 cups/day (moderate), >5 cups/day (high)
Tea consumption categorised as: none (0 cups/day), drinking tea (>=1 cups/day)

Outcomes at 55 years or over
Cognitive status assessing through screening, clinical and differential diagnosis
Participants with score <=24 on MMSE addressed for further examination where dementia diagnosis may have been made

Analysis
Analysis strategy: Logistic regression was used to determine the influence of coffee or tea on the risk of developing dementia and AD

Confounders: Midlife age, education, follow-up time and community of residence, midlife smoking, SBP, serum total cholesterol, BMI, physical activity, myocardial infarction, stroke, diabetes mellitus, depression; sex and APOE 4 assessed as effect modifiers

Results, limitations, source of funding

- 61 people had dementia, of which 48 had AD;
- Moderate coffee drinkers had a 65-70% decreased risk of dementia and a 62-64% decreased risk of AD compared with low coffee consumers
- Odds of developing dementia were lower for those consuming moderate amounts of coffee (3-5 cups) compared to low amounts (0-2 cups) [OR=0.30, (0.10, 0.93)]
- APOE4 stratification: for APOE4 carriers, odds of developing dementia were lower among moderate coffee consumers compared to low coffee consumers [OR=0.32, (0.11, 0.92)]
- Sex stratification: for males: lower odds for dementia were reported among moderate and high coffee consumers compared to low coffee consumers [OR=0.27, (0.08, 0.89); OR=0.36, (0.13, 0.97)]

Limitations:
1. Residual confounding due to measurement error
2. Sample may have been too small to detect significant differences in interaction analyses and dose-response effects
3. Bias: self-reported data, residual confounding due to measurement error in the assessment of confounding factors

**Source of funding:** EVO-grant of Kuopio University Hospital, Academy of Finland grants, EU grant, the Swedish Council for Working Life and Social Research, the Finnish Cultural Foundation, the Foundation of Juho Vainio, the Gamla Tjanarinnor Foundation, the Helsingin Sanomain 100-vuotissaatio, and the Yrjo

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**Authors:** Field AE, Malspeis S, Willett WC.

**Year:** 2009

**Citation:** Archives of Internal Medicine 169(9): 881-886

**Country of study:** USA

**Aim of study:** Assess the independent association of weight cycling with mortality

**Study design:** Prospective study

**Quality score:** (+, + or -): +

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**Source population**

**Number of people:** 121,701

**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 44,882

**Characteristics**

**Non-cyclers:** Age in 1992, mean (SD), y 57.7 (7.1); BMI in 1992, mean (SD) 25.0 (4.3); BMI categories in 1992 17.0-20.9 1.0, 21.0-24.9 53.4, 25.0-29.9 28.6, >30.0 11.4; Smoking status Never 45.4, Past 38.7, Current 15.8; Alcohol intake g/day, mean (SD), 5.4 (9.8); Quintiles of MET hours of activity per week, % 1 (0.2-3.1 METs) 18.0, 2 (3.2-8.3 METs) 20.3, 3 (8.4-11.1 METs) 20.6, 4 (16.0-21.9 METs) 20.0, 5 (30.0-53.1 METs) 20.8

**Mild Cyclers:** Age in 1992, mean (SD), y 55.6 (6.7); BMI in 1992, mean (SD) 28.7 (4.8); BMI categories in 1992 17.0-20.9 0.1, 21.0-24.9 20.1, 25.0-29.4 2.1, >30.0 31.9; Smoking status Never 44.1, Past 45.1, Current 10.5; Alcohol intake g/day, mean (SD), 4.3 (8.4); Quintiles of MET hours of activity per week, % 1 (0.2-3.1 METs) 18.4, 2 (3.2-8.3 METs) 20.5, 3 (8.4-11.1 METs) 19.8, 4 (16.0-21.9 METs) 21.6, 5 (30.0-53.1 METs) 19.3

**Severe Cyclers:** Age in 1992, mean (SD), y 55.2 (6.5); BMI in 1992, mean (SD) 32.6 (6.2); BMI categories in 1992 17.0-20.9 0.0, 21.0-24.9 7.8, 25.0-29.9 28.0, >30.0 58.7; Smoking status Never 41.6, Past 47.4; Current 10.7; Alcohol intake g/day, mean (SD), 3.1 (7.4); Quintiles of MET hours of activity per week, % 1 (0.2-3.1 METs) 23.6, 2 (3.2-8.3 METs) 21.7, 3 (8.4-11.1 METs) 18.3, 4 (16.0-21.9 METs) 18.2, 5 (30.0-53.1 METs) 18.0

**Location:** USA

**Recruitment strategy:** Postal questionnaire

**Length of follow-up:** Variable - from 1976 to 1992 or 2004

**Exposures at midlife**

**Relevant exposures:** Height and weight
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Time:** Height and weight were ascertained in 1976, and current weight was assessed on each follow-up questionnaire.

**Measurement of exposure:** Body mass index was calculated from self-reported information on weight and height.

Net weight change, irrespective of intentionality, was assessed by calculating the difference in weight reported at two time points:

“Within the last 20 years, how many times did you lose each of the following amounts of weight on purpose (excluding illness or pregnancy)?” and “Within the last four years, how many times did you lose each of the following amounts of weight on purpose (excluding illness or pregnancy)?” The responses were 0, 1 to 2, 3 to 4, 5 to 6, or 7 or more times for each of the magnitudes of weight loss (2.3-4.1 kg, 4.5-8.6 kg, 9.1-22.2 kg, and 22.7 kg).

**Response rate and loss to follow-up:** Women who did not answer the 1988 or 1992 questionnaire (n=23,914), were diagnosed as having cancer (other than non-melanoma skin cancer) or heart disease (n=9,557), did not complete all of the intentional weight loss questions (n=34,560), reported no losses in the past 20 years but reported losses in the past four years (n=19), did not report their weight at age 18 years (n=5,807).

**Eligible population:** Female registered nurses aged 30 to 55 years.

**Excluded populations:** Women who had a body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, of less than 17 (n=286), reported bypass surgery (in 1992) (n=108), or died in the period of 1988 to 1994 (n=551) were excluded from the analysis.

### Eligible population

<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes:</strong> Deaths</td>
</tr>
<tr>
<td><strong>Outcome measurement:</strong> Deaths were reported by next of kin, the postal service, or ascertained by the National Death Index</td>
</tr>
<tr>
<td><strong>Time:</strong> 1992 or 2004</td>
</tr>
</tbody>
</table>

### Analysis

**Analysis strategy:** Multivariate Cox proportional hazards models, stratified by age in months and calendar time and that controlled for other potential confounders.

**Confounders:** Age, body mass index at age 18 years, weight change from age 18 years to start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years), smoking status with number of cigarettes currently smoked per day (never; past; current, 1-4; current, 5-24; current, 25-34; current, 35-45; current, number unknown), menopausal status, postmenopausal hormone therapy (premenopausal, never, past, or current), alcohol, activity level, and change in activity level, net weight change from the start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years) until 1992 (ie, end of the cycling period), net weight change from the start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years) until 2004 or the end of the follow-up period, instead of net weight change during the cycling period.

### Results, limitations, source of funding

<table>
<thead>
<tr>
<th>Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycling Between 1972 and 1992</td>
</tr>
<tr>
<td>Non-cycler (n=32,836)</td>
</tr>
<tr>
<td>Mild Cycler (n=8,452)</td>
</tr>
<tr>
<td>Severe Cycler (n=3,594)</td>
</tr>
<tr>
<td>Cycling Between 1988 and 1992</td>
</tr>
</tbody>
</table>
Non-cycler (n=41 045)
Mild Cycler (n=3142)
Severe Cycler (n=695)

Effect estimates:

Cycling Between 1972 and 1992

Non-cycler
Deaths, No. 319
Person-years 315 836
HR (95% CI) 1 [Reference]

Mild Cycler
Deaths, No. 65
Person-years 81 874
HR (95% CI) 0.89 (0.67-1.18)

Severe Cycler
Deaths, No. 41
Person-years 34 663
HR (95% CI) 1.08 (0.75-1.56)

Cycling Between 1988 and 1992

Non-cycler
Deaths, No. 384
Person-years 395 312
HR (95% CI) 1 [Reference]

Mild Cycler
Deaths, No. 29
Person-years 12
HR (95% CI) 1.11 (0.75-1.64)

Severe Cycler
Deaths, No. 12
Person-years 6641
HR (95% CI) 1.65 (0.89-3.05)

Significant trends: Women who were severe cyclers from 1988 to 1992 were almost three times more likely than non-cyclers to die from cardiovascular events during the follow-up period

Limitations: Self-reported information

Source of funding: Not reported

Authors: Fogelholm M, Kujala U, Kaprio J, Sarna S
Year: 2000
Citation: Obesity Research 8(5): 367-373
Country of study: Finland
Aim of study: To assess influence of lifestyle on 10-year weight change
Study design: Longitudinal
Quality score: (++, + or -): +

Source population
Large cohort originally comprising former top male athletes (n=2675) and untrained referents. 2062 out of 2535 (81%) surviving subjects completed baseline questionnaire in 1985 and 1670 out of 2114 completed follow-up questionnaire in 1995.

Study (eligible and selected) population
Analysis restricted to 1143 Finnish participants who completed baseline and follow-up questionnaires and with complete data
Participants were ages 36-88 years at baseline
**Follow-up:** 10 years (1985-95)
**Exclusion:** Analysis restricted to subjects without malignant cancer or diabetes
**Attrition:** -

**Exposures at midlife**
- Self-reported smoking, alcohol use
- Dietary habits, leisure physical activity
- Smoking categories: smoking, non-smoking, quit or started smoking
- Alcohol consumption frequencies assessed; alcohol content of beer, wine, and spirits assumed to be 4, 9.5, and 32g/litre, respectively (subjects classified into intake quartiles ranging from low to high alcohol use)
- Frequency of fruit and vegetable consumption assessed (healthy diet defined by presence of at least 2 of the following: fruit and vegetables intake at least 3 times/day; use of margarine; use of skimmed milk)
- Frequency, duration, intensity of physical activity assessed, ranging from low to high

**Outcomes at 55 years or over**
- Self-administered questionnaire captured 10-year weight change

**Analysis**

**Analysis strategy:** Step-wise linear regression was used to assess influence of lifestyle on 10-year weight change

**Confounders:** Age, chronic diseases, occupation, present occupational activity, living conditions, former athletic status

**Results, limitations, source of funding**
- Being a smoker (beta=-1.59, SE=0.48), and increased physical activity (beta=-1.27, SE=0.54) were significantly (p<0.05) associated with weight loss

**Limitations:**
1. Residual confounding
2. Self-reported body weight (may be underestimated) and physician-diagnosed diseases
3. Cohort was not a random, representative population sample

**Source of funding:** Academy of Finland

**Authors:** Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH... Debanne SM

**Year:** 2001

**Citation:** Proceedings of the National Academy of Sciences of the United States of America 98(6): 3440-3445

**Country of study:** USA

**Aim of study:** Examine if development of Alzheimer’s disease later in life is reflective of environmental factors operating over the course of a lifetime
### Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

#### Study design: Case-control study

**Quality score:** (+++, + or -): +

#### Source population

**Number of people:** Not reported

**Demographics:** Not reported

#### Study (eligible and selected) population

**Number of people:** 551

**Characteristics:**

**Case-group members (n=193)**

- Age [mean (SD)] 72.5 (8.0); Male 72.2 (7.3); Female 72.7 (8.5); Year of birth–median (range) 1919 (1898–1944); Male 1919 (1898–1940) Female 1918 (1901–1944); Gender–% (no.) Male 43.5% (84) Female 56.5% (109); Education–[mean (SD)] 13.0 (2.8); Income adequacy, lifetime average– [mean (SD)] 1.7 (0.4); MMSE–[mean (SD)] 17.8 (6.0); Number of activities ever performed 12.9 (4.1)

**Control-group members (n=358)**

- Age [mean (SD)] 71.3 (6.0); Male 71.7 (5.2); Female 71.0 (6.4); Year of birth–median (range) 1923 (1899–1936); Male 1923 (1909–1934); Female 1924 (1899–1936); Gender–% (no.) Male 39.7% (142) Female 60.3% (216); Education [mean (SD)] 15.3 (2.8); Income adequacy, lifetime average [mean (SD)] 1.7 (0.4); MMSE–[mean (SD)] 28.8 (1.0); Number of activities ever performed 16.0 (3.4)

**Location:** Cleveland, USA

**Recruitment strategy:** Recruited from clinical settings and the community

**Length of follow-up:** Not reported

**Response rate and loss to follow-up:** Refusal rates for participation as control-group members were 65/346 (19%) for males and 106/537 (20%) for females

**Eligible population:** Enrolled in the Research Registry of the University Alzheimer Center, University Hospitals of Cleveland. The control-group members (N=358) were the friends or neighbours of the case-group members or were members of the same organisations to which the case-group members belonged

**Excluded populations:** Not reported

### Exposures at midlife

**Relevant exposures:** Activities

**Time:** 1991

**Measurement of exposure:** 26 different types of activities (not reported), asking three questions about each one:

1. Did subjects participate in the activity at least once per month? If yes,
2. How many hours per month in their 20s and 30s; and
3. How many hours per month in their 40s and 50s

Data from the 26 activities were grouped into three general activity categories (passive, intellectual, and physical)

### Outcomes at 55 years or over

**Outcomes:** Alzheimer's Disease

**Outcome measurement:** Neuropsychological, laboratory, and neurological exams and all had X-ray
computed tomography or MRI scans of the brain.
Time: Not reported

Analysis

Analysis strategy: ANCOVA
Confounders: Year of birth, education, gender, and income adequacy

Results, limitations, source of funding

Number: 193
Effect estimates:
Comparisons between case- and control-group members on diversity scores (adjusted means)
Case: Passive diversity 0.84; Intellectual diversity 0.44; Physical diversity 0.42
Control: Passive diversity 0.91; Intellectual diversity 0.54; Physical diversity 0.53
ANCOVA: Passive diversity F(1, 544) = 19.25; Intellectual diversity F(1, 544) = 33.33; Physical diversity F(1, 544) = 29.24

Comparisons between case- and control-group members on “intensity” scores (adjusted means)
Case: Passive diversity 99.33; Intellectual diversity 68.15; Physical diversity 37.74
Control: Passive diversity 101.84; Intellectual diversity 79.21; Physical diversity 41.09
ANCOVA: Passive diversity F(1, 544) = 0.16; Intellectual diversity F(1, 544) = 3.82; Physical diversity F(1, 544) = 0.96

Significant trends: Diversity of activities and intensity of intellectual activities were reduced in patients with AD as compared with the control group

Limitations:
Author:
1. Not population-based.
2. Recruitment likely to produce overmatching.
3. Activity participation does not necessarily reflect quality of participation.
4. Did not include confounders such as apoE genotype

Reviewer: Case-control

Source of funding: This work was supported in part by grants from the National Institute on Aging (PO 263-MO-818915 and VO1 AG1713-01A1), the Alzheimer’s Disease Research Center Program (P50 AG 08012), the Mandel Foundation, the Nickman family, the Institute for the Study of Aging (New York), and Philip Morris USA.

Authors: Gerber Y, Myers V, Goldbourt U
Year: 2012
Citation: American Journal of Epidemiology 175(10): 1006-1012
Country of study: Israel
Aim of study: Assessed survival and life expectancy according to changes in smoking intensity
Study design: Prospective cohort study
Quality score: (++ , + or -): ++

Source population
Number of people: 10,059
Demographics: Not reported

Study (eligible and selected) population

Number of people: 4,633

Characteristics:

No.% Mean (SD)

**Increased Smoking Intensity.** Age, years 50.1 (6.5); Lowest SES category 126 35; Systolic blood pressure, mm Hg 134 (20); Diastolic blood pressure, mm Hg 85 (12); Cholesterol, mg/dL 207 (42); Body mass index 25.2 (3.4); Leisure-time physical activity; None 235 67%; Light 48 14%; Light daily 45 13%; Heavy 22 6%; Diabetes 23 6%; Known coronary heart disease 20 6%; Intermittent claudication 8 2%

**Maintained Smoking Intensity.** Age, years 50.6 (6.7); Lowest SES category 780 26; Systolic blood pressure, mm Hg 136 (21); Diastolic blood pressure, mm Hg 86 (12); Cholesterol, mg/dL 209 (39); Body mass index 25.6 (3.5); Leisure-time physical activity; None 1,876 63; Light 417 14; Light daily 487 16; Heavy 204 7; Diabetes 178 6; Known coronary heart disease 249 8; Intermittent claudication 117 4

**Reduced Smoking Intensity.** Age, years 50.2 (6.4); Lowest SES category 255 33; Systolic blood pressure, mm Hg 136 (21); Diastolic blood pressure, mm Hg 85 (12); Cholesterol, mg/dL 210 (38); Body mass index 25.3 (3.4); Leisure-time physical activity; None 490 63; Light 120 15; Light daily 115 15; Heavy 57 7; Diabetes 52 7; Known coronary heart disease 68 9; Intermittent claudication 45 6

**Quit.** Age, years 51.9 (7.2); Lowest SES category 104 23; Systolic blood pressure, mm Hg 139 (22); Diastolic blood pressure, mm Hg 87 (12); Cholesterol, mg/dL 210 (40); Body mass index 26.4 (3.2); Leisure-time physical activity; None 287 62; Light 75 16; Light daily 74 16; Heavy 26 6; Diabetes 36 8; Known coronary heart disease 71 15; Intermittent claudication 26 6

**P Value.** Age, years <0.001; Lowest SES category <0.001; Systolic blood pressure, mm Hg 0.02; Diastolic blood pressure, mm Hg 0.004; Cholesterol, mg/dL 0.63; Body mass index <0.001; Leisure-time physical activity 0.59; Diabetes 0.50; Known coronary heart disease <0.001; Intermittent claudication 0.01

Exposures at midlife

**Relevant exposures:** Smoking behaviour, physical activity

**Time:** 1963

**Measurement of exposure:** Smoking behaviour was self-reported. Participants were asked to choose one of 5 smoking status groups: never smoker, past smoker, 1–10, 11–20, or more than 20 cigarettes per day.

Physical activity during leisure time was determined via personal interview, with subjects reporting their physical activity outside working hours.

**Location:** Tel Aviv, Haifa, and Jerusalem, Israel

**Recruitment strategy:** Stratified sampling

**Length of follow-up:** Median follow-up of 26 (quartiles 1–3: 16–35) years

**Response rate and loss to follow-up:** 87% of participants died

**Eligible population:** Israeli working men; civil servants and municipal employees

**Excluded populations:** Excluding 96 participants who stopped cigarette smoking and switched to cigar or pipe smoking. 87% of participants died

Outcomes at 55 years or over
### Outcomes
Outcomes were timed to 1) all-cause death and 2) cause-specific death, dichotomised into CVD and non-CVD.

### Outcome measurement
Information on death was derived from the Israeli Mortality Registry

### Time

### Analysis

**Analysis strategy:** Cox proportional hazards regression models

**Confounders:** Age, socioeconomic status, and smoking intensity in 1963, systolic blood pressure, blood cholesterol, body mass index, leisure-time physical activity, diabetes, known coronary heart disease, and intermittent claudication

### Results, limitations, source of funding

**Number**
- Increased (n=358; %=8)
- Maintained (n=3,061; %=65)
- Reduced (n=787; %=17)
- Quit (n=472; %=10)

**Effect estimates:**

#### All-cause mortality
- HR 95% CI
  - Increased 1.14 0.99, 1.32
  - Maintained 1 Referent
  - Reduced 0.85 0.77, 0.95
  - Quit 0.78 0.69, 0.89
- Ptrend <0.001

#### CVD mortality
- Increased 1.14 0.92, 1.41
- Maintained 1 Referent
- Reduced 0.77 0.66, 0.94
- Quit 0.84 0.70, 1.05
- Ptrend 0.01

#### Non-CVD mortality
- Increased 1.05 0.88, 1.25
- Maintained 1 Referent
- Reduced 0.98 0.87, 1.10
- Quit 0.90 0.77, 1.05
- Ptrend 0.19

**Significant trends:** Survival benefit associated with smoking reduction was mostly evident among heavy smokers and for cardiovascular disease mortality

### Limitations:

1. No information is available on smoking habits throughout follow-up.
2. Smoking was self-reported.
3. Couldn’t control for dietary and physical activity patterns.
4. Male-only cohort

**Reviewer:** Difference in time for outcome

**Source of funding:** Supported by PL 480 counterpart funds, research agreement no. 375106. The Fund for Basic Research from the Israeli Academy of Sciences supported the mortality follow-up from 1970 to 1978.
**Authors:** Guallar-Castillón P, Rodríguez-Artalejo F, Tormo MJ, Sánchez MJ, Rodríguez L, Quirós JR... Moreno-Iribas C

**Year:** 2012

**Citation:** Nutrition Metabolism & Cardiovascular Diseases 22(3): 192-199

**Country of study:** Spain

**Aim of study:** Assess the association between major dietary patterns and the risk of coronary heart disease

**Study design:** Multi-centre prospective cohort study

**Quality score:** (++, + or -): +

### Source population

<table>
<thead>
<tr>
<th>Number of people:</th>
<th>519,978 (366,521 women and 153,457 men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### Study (eligible and selected) population

<table>
<thead>
<tr>
<th>Number of people:</th>
<th>40,757 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics:</td>
<td></td>
</tr>
</tbody>
</table>

#### Westernised pattern

**Quintile 1 (lowest).** Age (years) 50.9; Body mass index (kg/m²) 28.6; Waist circumference (cm) 92.3; No formal education (%) 38.3; Current smokers (%) 18.2; Sedentary at work (%) 24.2; Physical activity at home (METs h/wk) 68.2; Physical activity in leisure time (METs h/wk) 31.1

**Quintile 3.** Age (years) 48.6; Body mass index (kg/m²) 28.2; Waist circumference (cm) 91.6; No formal education (%) 33.9; Current smokers (%) 22.7; Sedentary at work (%) 20.9 17.5; Physical activity at home (METs h/wk) 69.9; Physical activity in leisure time (METs h/wk) 28.3

**Quintile 5 (highest).** Age (years) 47.0; Body mass index (kg/m²) 28.1; Waist circumference (cm) 92.1; No formal education (%) 31.9; Current smokers (%) 28.5; Sedentary at work (%) 17.5; Physical activity at home (METs h/wk) 69.9; Physical activity in leisure time (METs h/wk) 25.9

#### Evolved Mediterranean pattern

**Quintile 1 (lowest).** Age (years) 48.0; Body mass index (kg/m²) 28.0; Waist circumference (cm) 91.0; No formal education (%) 33.6; Current smokers (%) 28.8; Sedentary at work (%) 19.4; Physical activity at home (METs h/wk) 69.2; Physical activity in leisure time (METs h/wk) 26.7

**Quintile 3.** Age (years) 48.7; Body mass index (kg/m²) 28.3; Waist circumference (cm) 91.8; No formal education (%) 34.7; Current smokers (%) 23.1; Sedentary at work (%) 22.0; Physical activity at home (METs h/wk) 69.4; Physical activity in leisure time (METs h/wk) 28.7

**Quintile 5 (highest).** Age (years) 49.6; Body mass index (kg/m²) 28.4; Waist circumference (cm) 92.6; No formal education (%) 34.3; Current smokers (%) 18.1; Sedentary at work (%) 21.0; Physical activity at home (METs h/wk) 68.0; Physical activity in leisure time (METs h/wk) 30.6

**Location:** Spain. Five regions: Asturias, Gipuzkoa, Navarra, Granada and Murcia

**Recruitment strategy:** Invited to participate either by mail or in person

**Length of follow-up:** Median follow-up of 11 years

### Exposures at midlife

**Relevant exposures:** Dietary pattern, educational level, smoking, and physical activity

**Time:** Subject’s age at recruitment and exit time as the age at the occurrence of a CHD event, death,
Measurement of exposure: Self-administrated questionnaires and interview


Eligible population: Participant eligibility within each cohort was based on geographic or administrative boundaries. Used only the data from the Spanish cohort of the EPIC study

Excluded populations: 193 for having CHD at baseline; 167 for an implausibly high or low dietary consumption, defined as 3 standard deviations from the mean of the cohort (<788 kcal/day or >5710 kcal/day); and 321 for lack of information on important variables such as date of CHD event (12), hypercholesterolemia (197), diabetes (71), hypertension (60) and smoking (22).

Outcomes at 55 years or over

Outcomes: Myocardial infarction and mortality

Outcome measurement: Hospital discharge registers. CHD events were classified on the basis of symptoms, signs, biomarkers, and electrocardiogram

Time: Between 1992 and 1996

Analysis

Analysis strategy: Cox regression models

Confounders: Age, sex, BMI, waist circumference, educational level, smoking, physical activity at work, physical activity at home, physical activity in leisure time, diabetes, hypertension, hypercholesterolemia, cancer, oral contraceptives, menopausal status, hormone replacement therapy, and total energy intake

Results, limitations, source of funding

Number: 606 definite CHD events (466 myocardial infarctions and 140 anginas requiring revascularisation).

Effect estimates:

Definite CHD events

Westernized Pattern
Quintile 1) 1 Ref. Quintile 2) 0.96 (0.75-1.24) Quintile 3) 0.81 (0.61-1.09) Quintile 4) 0.98 (0.72-1.34) Quintile 5) 0.86 (0.60-1.24) P for trend 0.51

Evolved Mediterranean Pattern
Quintile 1) 1 Ref. Quintile 2) 0.77 (0.61-0.98) Quintile 3) 0.64 (0.50-0.83) Quintile 4) 0.56 (0.43-0.73) Quintile 5) 0.73 (0.57-0.94) P for trend 0.0013

Definite, possible and probable CHD events

Westernized Pattern
Quintile 1) 1 Ref. Quintile 2) 1.02 (0.81-1.29) Quintile 3) 0.88 (0.67-1.15) Quintile 4) 1.04 (0.78-1.38) Quintile 5) 0.87 (0.62-1.22) P for trend 0.55

Evolved Mediterranean Pattern
Quintile 1) 1 Ref. Quintile 2) 0.76 (0.61-0.95) Quintile 3) 0.64 (0.51-0.81) Quintile 4) 0.58 (0.46-0.74) Quintile 5) 0.72 (0.57-0.91) P for trend <0.001

Significant trends: No association was found between the Westernized dietary pattern and CHD risk. A Mediterranean diet, as consumed in this study population, was associated with a lower risk of CHD.
Limitations:
1. Interpretation of the dietary patterns obtained by factor analysis is subjective.
2. Patterns derived depend on the number of foods included in the diet measurement instrument.
3. Percentage of the variance explained by the two major dietary patterns was only modest.
4. Diet was measured only at baseline.
5. Residual confounding may persist

Source of funding: Spanish Ministry of Health PI04-0257, PI06-0366, PI04-2342, PI04-1822, PI04-1821 and PI04-2188 from the "Instituto de Salud Carlos III"; RETIC (RD06/0020) of ISCIII Spanish Regional Governments of Andalusia, Asturias, Basque Country, Murcia and Navarra and the Catalan Institute of Oncology; EL-G has a “Ramo´n y Cajal” contract from the Ministry of Education.

Authors: Haapanen-Niemi N, Miilunpalo S, Pasanen M, Vuori I, Oja P, Malmberg J

Year: 2000

Citation: International Journal of Obesity Related Metabolic Disorders 24(11): 1465-74

Country of study: Finland

Aim of study: To investigate the independent associations and the possible interaction of BMI, leisure time physical activity and perceived physical fitness and functional capability with the risk of mortality.

Study design: Prospective 16-year follow-up study

Quality score: (+, + or -): +

Source population

Number of people: 6787

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1090 men and 1122 women

Characteristics

Men
Alive (n.882) %
Age (y)
35-44 48.1
45-54 37.0
55-63 15.0
Socioeconomic status
Upper-level employee 19.7
Lower-level employee 13.2
Manual worker 54.2
Farmer or other own-account worker 11.6
Other 0.8
Housewife -
Missing data 0.6
Employment status
Participant in work life 83.3
Not participant in work life 15.6
Housewife -
Missing data 1.0
Marital status
Married 82.2
Single 12.8
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Housewife 18.4
Missing data 2.3
Marital status
Married 63.2
Single 13.8
Widowed 17.2
Divorced, separated 5.7
Missing data -
Perceived health
Good or fairly good 23.0
Average 37.9
Poor or rather poor 39.1
Missing data -
Smoking status
Never smoked 63.2
Past smoker 10.3
Current smoker 23.0
Missing data 3.4
Alcohol consumption (g=day)
0 69.0
0.1-12 24.1
>12 5.7
Missing data 1.1

Location: Medium-size industrial town and two rural municipalities in north-eastern Finland
Recruitment strategy: Census data
Length of follow-up: 16 years
Response rate and loss to follow-up:
77.5% (n=5259)
1y 88%
5y 84%
10y 85%
16y 85%

Eligible population: Subjects aged 35y and older (men, n=1340; women, n=1500), who were 51-79y of age at the end of the follow-up
Excluded populations: Those having an initial BMI of less than 20.0 and those suffering from a disease or symptoms that totally prevented participation in LTPA

Exposures at midlife

Relevant exposures: Living habits, health behaviour, health status, functional capacity and sociodemographic background
Time: 1980
Measurement of exposure: Self-administered questionnaire
LTPA was assessed with 23 questions concerning conditioning exercise, sports, physical recreation, different leisure time and household chores and active commuting to and from work.
Subjects were divided into high, moderate and low physical activity groups according to the index of total physical activity. For the men, the classes were designated as 0-1000, 1000.1-1900 and>1900 kcal per week, and for the women the respective categories were 0-800, 800.1-1500 and>1500 kcal per week.
Physical fitness was assessed by three measures indicating perceived fitness and functional status.
Outcomes at 55 years or over

Outcomes: Mortality
Outcome measurement: National census data
Time: September 1996

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age, marital and employment status, perceived health status, smoking and alcohol consumption

Results, limitations, source of funding

Number: 208 men and 87 women
Effect estimates:

Relative risks for all-cause-, CVD and CHD mortality for the men in 1980-1996
All causes
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.64 - 1.19 0.379
>30.0 1.06 0.67 - 1.69 0.796
LRa.1.1, df.2, P.0.577
Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.82 0.55 - 1.24 0.350
Low 1.20 0.82 - 1.76 0.349
LR.4.2, df.2, P.0.120
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.26 0.89 - 1.77 0.193
LR.1.7, df.1, P.0.187
Perceived physical fitness compared with age-mates
Better 1.00
Similar 1.93 1.15 - 3.24 0.013
Worse 3.29 1.80 - 6.02 <0.001
LR.16.9, df.2, P<0.001
2 km walking ability
No difficulties 1.00
At least some difficulties 1.62 1.05 - 2.50 0.028
LR.4.7, df.1, P.0.030
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.47 0.97 - 2.23 0.070
LR.3.3, df.1, P.0.070
CVD
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.56 - 1.35 0.541
>30.0 1.44 0.80 - 2.56 0.223
LR.2.6, df.2, P.0.274
Total LTPA energy expenditure index (kcal=week)
High 1.00
Relative risks for all-cause- and CVD mortality for the women in 1980-1996

All causes
RR 95% CI  P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.52 - 1.46 0.599
>30.0 1.35 0.76 - 2.41 0.310
LR.2.2, df.2, P.0.341

2 km walking ability
No difficulties 1.00
At least some difficulties 1.03 0.51 - 2.05 0.941
LR.0.005, df.1, P.0.941
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.61 0.82 - 3.16 0.167
LR.1.9, df.1, P.0.164

CHD
RR 95% CI  P
BMI
20.0-24.9 1.00
25.0-29.9 0.94 0.57 - 1.56 0.813
>30.0 1.23 0.61 - 2.50 0.564
LR.0.5, df.2, P.0.767

Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.88 0.44 - 1.76 0.709
Low 1.70 0.90 - 3.21 0.105
LR.5.8, df.2, P.0.056

Perceived physical fitness compared with age-mates
Better 1.00
Similar 2.82 1.06 - 7.46 0.037
Worse 4.64 1.56 - 13.84 0.006
LR.9.1, df.2, P.0.011

2 km walking ability
No difficulties 1.00
At least some difficulties 1.25 0.71 - 2.22 0.438
LR.0.6, df.1, P.0.441
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.85 1.04 - 3.30 0.036
LR.4.5, df.1, P.0.034

Perceived physical fitness compared with age-mates
Better 1.00
Similar 2.39 1.09 - 5.22 0.029
Worse 34.37 1.80 - 10.62 0.001
LR.12.5, df.2, P.0.002

Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.88 0.44 - 1.76 0.709
Low 1.70 0.90 - 3.21 0.105
LR.5.8, df.2, P.0.056

Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.61 0.98 - 2.64 0.058
LR.3.8, df.1, P.0.050

Perceived physical fitness compared with age-mates
Better 1.00
Similar 2.39 1.09 - 5.22 0.029
Worse 34.37 1.80 - 10.62 0.001
LR.12.5, df.2, P.0.002

2 km walking ability
No difficulties 1.00
At least some difficulties 1.03 0.51 - 2.05 0.941
LR.0.005, df.1, P.0.941
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.61 0.82 - 3.16 0.167
LR.1.9, df.1, P.0.164

Relative risks for all-cause- and CVD mortality for the women in 1980-1996

All causes
RR 95% CI  P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.52 - 1.46 0.599
>30.0 1.35 0.76 - 2.41 0.310
LR.2.2, df.2, P.0.341

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.59 0.30 - 1.18 0.136
Low 1.27 0.69 - 2.34 0.440
LR.6.8, df.2, P.0.033

Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.61 0.89 - 2.92 0.114
LR.2.7, df.1, P.0.101

Perceived physical fitness compared with age-mates
Better 1.00
Similar 0.82 0.41 - 1.65 0.582
Worse 1.71 0.72 - 4.05 0.221
LR.5.9, df.2, P.0.054

2 km walking ability
No difficulties 1.00
At least some difficulties 1.45 0.78 - 2.70 0.237
LR.1.4, df.1, P.0.243

Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 2.39 1.25 - 4.60 0.009
LR.7.2, df.1, P.0.007

CVD
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.85 0.42 - 1.74 0.664
>30.0 1.36 0.60 - 3.07 0.459
LR.1.3, df.2, P.0.527

Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.43 0.16 - 1.16 0.093
Low 1.17 0.51 - 2.68 0.717
LR.6.2, df.2, P.0.046

Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 4.68 1.41 - 15.57 0.012
LR.9.4, df.1, P.0.002

Perceived physical fitness compared with age-mates
Better 1.00
Similar 0.82 0.32 - 2.16 0.693
Worse 1.89 0.57 - 6.27 0.299
LR.3.7, df.2, P.0.154

2 km walking ability
No difficulties 1.00
At least some difficulties 1.25 0.53 - 2.90 0.611
LR.0.3, df.1, P.0.614

Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 3.38 1.22 - 9.41 0.020
LR.6.2, df.1, P.0.013

**Significant trends:** BMI was not associated with the risk of death among men or women

**Limitations:** Self-reported information about physical fitness and functional capability, LTPA and BMI

**Source of funding:** Juho Vainio Foundation, The Yrjo Jahnsson Foundation, the Finnish Ministry of Education and partially from the Emil Aaltonen Foundation
<table>
<thead>
<tr>
<th><strong>Authors:</strong></th>
<th>Halperin RO, Gaziano JM, Sesso HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year:</strong></td>
<td>2008</td>
</tr>
<tr>
<td><strong>Citation:</strong></td>
<td>American Journal of Hypertension 21(2): 148-52</td>
</tr>
<tr>
<td><strong>Country of study:</strong></td>
<td>USA</td>
</tr>
<tr>
<td><strong>Aim of study:</strong></td>
<td>Evaluate the relationship between smoking status and incident hypertension</td>
</tr>
<tr>
<td><strong>Study design:</strong></td>
<td>Randomized, double blind, placebo-controlled trial</td>
</tr>
<tr>
<td><strong>Quality score:</strong></td>
<td>(++, + or -): +</td>
</tr>
</tbody>
</table>

### Source population

<table>
<thead>
<tr>
<th><strong>Number of people:</strong></th>
<th>22,071</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics:</strong></td>
<td>52.4 years (s.d. 8.9). 51.9% never smoked, 37.6% as past smokers, 6.6% as current smokers of &lt;20 cigarettes/day, and 3.9% as current smokers of ≥20 cigarettes/day.</td>
</tr>
</tbody>
</table>

### Study (eligible and selected) population

<table>
<thead>
<tr>
<th><strong>Number of people:</strong></th>
<th>13,529</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Location:</strong></td>
<td>USA</td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong></td>
<td>Median follow-up was 14.5 years, with a maximum follow-up of 20.5 years.</td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong></td>
<td>&gt;99%</td>
</tr>
<tr>
<td><strong>Eligible population:</strong></td>
<td>Male physicians</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong></td>
<td>Excluded participants who reported any past or current history of hypertension, or a SBP of ≥140 mm Hg, or a DBP of ≥90 mm Hg. Excluded all participants with missing information on either baseline hypertension status or smoking status</td>
</tr>
</tbody>
</table>

### Exposures at midlife

<table>
<thead>
<tr>
<th><strong>Relevant exposures:</strong></th>
<th>Age, body mass index, alcohol consumption, exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time:</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Measurement of exposure:</strong></td>
<td>Categorised as never smoker, past smoker, or current smoker, and those currently smoking were also asked to provide the number of cigarettes smoked per day Alcohol consumption (rarely/never, monthly, weekly, daily) Exercise to sweat ≥ once per week (yes, no)</td>
</tr>
</tbody>
</table>

### Outcomes at 55 years or over

<table>
<thead>
<tr>
<th><strong>Outcomes:</strong></th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome measurement:</strong></td>
<td>The diagnosis of hypertension was based on self-reported BP and/or the initiation of antihypertensive treatment.</td>
</tr>
<tr>
<td><strong>Time:</strong></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### Analysis

<table>
<thead>
<tr>
<th><strong>Analysis strategy:</strong></th>
<th>Cox proportional hazards models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confounders:</strong></td>
<td>Adjusted for age, BMI, diabetes, any history of total cholesterol ≥240 mg/dl, alcohol</td>
</tr>
</tbody>
</table>
Results, limitations, source of funding

Number: 4,904

Effect estimates:

Relative risks (RR) and 95% confidence intervals (CIs) of developing hypertension according to smoking status in 13,529 men

- Never 1.00 (ref)
- Past 1.08 (1.01, 1.15)
- <20 cigarettes/day 1.18 (1.01, 1.38)
- ≥20 cigarettes/day 1.12 (0.99, 1.27)
- All current smokers 1.15 (1.03, 1.27)

P value 0.006

Significant trends: The multivariate models that considered changes in smoking status showed increased RR (95% CI) of developing hypertension for current and past smokers of 1.14 (1.00, 1.25) and 1.08 (1.01, 1.15) respectively, and an increased RR of developing hypertension for new smokers at 2 years and new quitters at 2 years of 1.21 (0.96, 1.52) and 1.35 (1.08, 1.68), respectively.

Limitations: Not reported

Source of funding: Supported by research grants CA 34944, CA 40360, and CA 97193 from the National Cancer Institute, and grants HL 26490 and HL 34595 from the National Heart Lung, and Blood Institute, National Institutes of Health, Bethesda, MD. Dr Halperin supported in part by a VA Special Ambulatory Fellowship award.

Authors: Hamer M, Lavoie KL, Bacon SL

Year: 2013

Citation: British Journal of Sports Medicine 48(3): 239-43

Country of study: England

Aim of study: Examine the association between physical activity and healthy ageing

Study design: Prospective study

Quality score: (+++, + or -): ++

Source population

Number of people: 11,391

Demographics: Aged 63.7±8.9 years at baseline. Other details not reported

Study (eligible and selected) population

Number of people: 1,953

Characteristics:

Healthy ageing: Age (years) 67.0±4.2; Men 300 (45.1); Smoking Never 307 (46.2), Previous 301 (45.3), Current 57 (8.6); Alcohol intake Daily 217 (32.6), At least once per week (but not daily) 220 (33.1), Rarely 186 (28.0), ever 42 (6.3); Physical activity Inactive 55 (8.3), Moderate (at least once per week) 345 (51.9), Vigorous (at least once per week) 265 (39.8); Marital status Married 479 (72.0), Single, never married 25 (3.8), Separated/divorced 56 (8.4), Widowed 105 (15.8); Wealth quintile 1 (lowest) 45 (6.8), 2 103 (15.5), 3 135 (20.3), 4 172 (25.9), 5 (highest) 210 (31.6)

Unhealthy ageing: Age (years) 62.9±9.5; Men 1169 (41.9); Smoking Never 1010 (36.2), Previous 1264 (45.3), Current 515 (18.5), Alcohol intake daily 804 (28.8), At least once per week (but not daily) 891 (31.9), Rarely 822 (29.5), Never 272 (9.8); physical activity Inactive 598 (21.4), Moderate (at least 31.6)
<table>
<thead>
<tr>
<th>Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location:</strong> England</td>
<td></td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong> Multistage-stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage</td>
<td></td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong> Eight years of follow-up</td>
<td></td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong> 70% at the household level and 67% at the individual level</td>
<td></td>
</tr>
<tr>
<td><strong>Eligible population:</strong> Not reported</td>
<td></td>
</tr>
<tr>
<td><strong>Excluded populations:</strong> Any participants with existing chronic disease at baseline and wave 2 were excluded. Between wave 1 and 5 2,158 died, 142 moved from UK, 109 institutionalised, 2809 non-response at wave 5. After wave 5 1586 had missing data and 1,133 had disease at baseline</td>
<td></td>
</tr>
</tbody>
</table>

### Exposures at midlife

**Relevant exposures:** Baseline demographics, cigarette smoking, current frequency of alcohol intake, marital status, wealth, physical activity  
**Time:** 2010-2011  
**Measurement of exposure:** Self-reported physical activity, participants wore a GeneActiv device on their wrist for seven consecutive days

### Outcomes at 55 years or over

**Outcomes:** Healthy aging  
**Outcome measurement:** Defined as those participants who survived without developing major chronic disease, depressive symptoms, physical or cognitive impairment. Disease status was measured using self-reported physician diagnosis of major chronic diseases  
Cognitive function was assessed objectively using a battery of widely used neuropsychological tests  
Depressive symptoms were assessed using the eight-item Centre of Epidemiological Studies Depression scale  
Disability based on participants' responses to questions on perceived difficulties in basic and instrumental activities of daily living  
Physical functioning was objectively assessed using walking speed measured over an eight-foot long course  
**Time:** 2010-2011

### Analysis

**Analysis strategy:** Multiple logistic regressions  
**Confounders:** Adjustment for age, sex, smoking (never; previous; current), alcohol (daily; at least weekly; rarely; never), marital status (married; always single; separated; widowed), wealth quintile.

### Results, limitations, source of funding

**Number:** 19.3% of the sample.  
38.4% of the sample had developed a chronic illness, 17.6% reported depressive symptoms, 32% reported disability, 19.2% had cognitive impairment and 17.7% had inadequate gait speed  
**Effect estimates:** OR (95% CI) for the association of physical activity and different components of healthy ageing over
eight years follow-up

Chronic disease
Inactive 1.00
Moderate physical activity 0.78 (0.64 to 0.95)
Vigorous physical activity 0.67 (0.54 to 0.84)
p-trend 0.001

Depressive symptoms (CES-D>3)
Inactive 1.00
Moderate physical activity 0.67 (0.53 to 0.85)
Vigorous physical activity 0.51 (0.39 to 0.67)
p-trend 0.001

Cognitive impairment
Inactive 1.00
Moderate physical activity 0.88 (0.69 to 1.13)
Vigorous physical activity 0.64 (0.48 to 0.85)
p-trend 0.005

ADL/IADL
Inactive 1.00
Moderate physical activity 0.57 (0.46 to 0.70)
Vigorous physical activity 0.41 (0.33 to 0.52)
p-trend <0.001

Impaired gait speed (<0.6 m/s)
Inactive 1.00
Moderate physical activity 0.54 (0.40 to 0.72)
Vigorous physical activity 0.41 (0.29 to 0.58)
p-trend <0.001

OR (95% CI) for the association of baseline physical activity and healthy ageing over 8 years follow-up (N=3454)
Inactive 1.00
Moderate physical activity 2.67 (1.95 to 3.64)
Vigorous physical activity 3.53 (2.54 to 4.89)
p-trend <0.001

OR (95% CI) for the association of physical activity change over wave 1–3 and healthy ageing at follow-up (N=3051)
Remained inactive 12/273 1.00
Became inactive 37/363 2.36 (1.19 to 4.68)
Became active 34/275 3.37 (1.67 to 6.78)
Remained active 521/2140 7.68 (4.18 to 14.09)
p-trend <0.001

Odds ratio (95% confidence interval) for the association of baseline physical activity and healthy ageing over 8 years follow up in clinical sub-sample.

OR (95% CI)
Inactive 1.00
Moderate physical activity 2.13 (1.45 – 3.13)
Vigorous physical activity 2.85 (1.91 – 4.23)

Significant trends: Becoming active (multivariate adjusted 3.37, 1.67 to 6.78) or remaining active (7.68, 4.18 to 14.09) was associated with healthy ageing in comparison with remaining inactive over follow-up. Among the covariates, wealth and smoking predicted healthy ageing; compared with participants in the poorest quintile, those in the richest were more likely to be healthy agers (multivariate adjusted OR=2.81, 95% CI 1.93 to 4.10)

Limitations:
1. Assessment of physical activity change was crude.
2. Chronic disease was based on self-report of physician diagnosis

**Source of funding:** The funding is provided by the National Institute on Aging in the USA (grants 2RO1AG7644-01A1 and 2RO1AG017644) and a consortium of UK government departments coordinated by the Office for National Statistics.

**Authors:** Happonen P, Voutilainen S, Salonen JT

**Year:** 2004

**Citation:** Journal of Nutrition 134(9): 2381-6

**Country of study:** Finland

**Aim of study:** Study the effect of coffee consumption on the incidence of nonfatal acute myocardial infarction or coronary death

**Study design:** Population-based cohort study

**Quality score:** (+, + or -): +

**Source population**

**Number of people:** 2682

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 1971

**Characteristics:** Median coffee consumption, mL 556; Age, y 52.5 ± 5.3; Current smoker, % 30; Packyears among smokers, y 28.4±18.3; Physical activity, kJ/d 581±707; Ischemia in exercise electrocardiogram, %18; Family history of CHD, % 46; Diabetes, % 5.2; Income, thousand Finnish Marks 130±74; Alcohol intake, g/wk 73±115; Total fat intake, % energy 39.7±5.9; Saturated fat intake, % energy 19.4±4.1; Daily total energy intake, MJ 10.8±2.7; Daily tea consumption, mL 110±194; Daily total water intake, L 2.35±0.60; BMI, kg/m2 26.7±3.5

**Location:** Finland

**Recruitment strategy:** Not reported

**Length of follow-up:** Mean follow-up of 14 years

**Response rate and loss to follow-up:** There were no losses to follow-up

**Eligible population:** Not reported

**Excluded populations:** 677 men with prevalent CHD at baseline

**Exposures at midlife**

**Relevant exposures:** Coffee and diet, smoking and alcohol

**Time:** Not reported

**Measurement of exposure:** Consumption of foods and beverages was assessed with an instructed and interview-checked 4-d food recording by household measures

Participant defined as a current smoker if he had ever smoked on a regular basis and had smoked within the past 30 days

Alcohol intake was measured with a recall of the frequency and usual amounts of alcoholic beverages consumed in the past 12 months

Mean daily coffee intake was divided into 4 categories: 0 (nondrinkers), 1 to 375 mL (light drinkers), 376 to 813 mL (moderate drinkers), and 814 mL and over (heavy drinkers).
Outcomes at 55 years or over

Outcomes: Acute coronary events

Outcome measurement: Obtained by computer linkage to the national hospital discharge registry; diagnostic information was collected from the hospitals and classified using identical diagnostic criteria

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards regression

Confounders: Age, smoking, exercise, ischemia, diabetes, income, serum insulin concentration, time, serum HDL and LDL cholesterol concentration, diastolic blood pressure, maximal oxygen uptake, and waist-hip ratio

Results, limitations, source of funding

Number: 269

Effect estimates:

Coffee intake category

None (n = 77)
Number of events 1
Person-time, y 379
RR (95% CI) 0.66 (0.09–4.91)

Light (n = 456)
Number of events 24
Person-time, y 2187
RR (95% CI) 1.93 (1.12–3.32)

Moderate (n = 1087)
Number of events 29
Person-time, y 5316
RR (95% CI) 1.00

Heavy (n = 351)
Number of events 21
Person-time, y 1672
RR (95% CI) 2.15 (1.20–3.83)

Significant trends: Heavy coffee consumption increases the short-term risk of acute myocardial infarction or coronary death, independent of the brewing method or currently recognized risk factors for CHD. The hazard rate of acute coronary events was 43% (95% CI, 5 to 94%) higher in heavy coffee drinkers compared with moderate drinkers.

Limitations: In Finland the consumption of decaffeinated coffee is minimal and our findings are confined to caffeine-containing coffee

Source of funding: Academy of Finland (201688 and 80185, S.V.), the Ministry of Education of Finland, the city of Kuopio, and the National Heart, Lung, and Blood Institute of the United States. Additional support was provided by the Juho Vainio Foundation, the Finnish Cultural Fund/North Savo Fund, the Yrjo Jahnsson Foundation, and the Finnish Foundation for Medical Science

Authors: Hara M, Sobue T, Sasaki S, Tsugane S

Year: 2002

Citation: Japanese Journal of Cancer Research 93(1): 6-14.
**Country of study:** Japan

**Aim of study:** Update the evidence on the association between smoking and mortality

**Study design:** Population-based prospective study

**Quality score:** (+++, + or -): +

### Source population

**Number of people:** 54,498 subjects (27,063 men and 27,435 women)

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 41,484 (19,950 men and 21,534 women)

**Characteristics:**

**Men never smokers:** Age (SD) 49.6 (5.6); Alcohol drinking, at least once per week (%) 59.1; Education, College or more (%) 15.2; Past history of Hypertension 15.1; Any drug for medication 20.9; Physical activity, 1+/week (%) 19.3; Body mass index (SD) 23.9 (2.9); Diet (daily, %) Fruit 30.0; Green vegetables 31.0; Yellow vegetables 16.6; White vegetables 34.0; Pickled vegetables 39.2; Soy products 37.1; Fresh fish 15.5; Red meat 26.2

**Men past smokers:** Age (SD) 50.2 (6.0); Alcohol drinking, at least once per week (%) 69.9; Education, College or more (%) 17.1; Past history of Hypertension 18.6; Any drug for medication 27.2; Physical activity, 1+/week (%) 21.3; Body mass index (SD) 23.9 (2.9); Diet (daily, %) Fruit 27.3; Green vegetables 30.3; Yellow vegetables 16.7; White vegetables 35.5; Pickled vegetables 41.7; Soy products 36.3; Fresh fish 14.7; Red meat 26.7

**Men current smokers:** Age (SD) 49.0 (6.0); Alcohol drinking, at least once per week (%) 71.7; Education, College or more (%) 13.4; Past history of Hypertension 13.1; Any drug for medication 19.8; Physical activity, 1+/week (%) 15.2; Body mass index (SD) 23.2 (2.9); Diet (daily, %) Fruit 20.8; Green vegetables 26.2; Yellow vegetables 12.3; White vegetables 32.4; Pickled vegetables 46.9; Soy products 34.5; Fresh fish 19.5; Red meat 32.3

**Women never smokers:** Age (SD) 49.6 (5.8); Alcohol drinking, at least once per week (%) 20.8; Education, College or more (%) 11.9; Past history of Hypertension 13.4; Any drug for medication 24.2; Physical activity, 1+/week (%) 14.5; Body mass index (SD) 23.6 (3.2); Diet (daily, %) Fruit 45.7; Green vegetables 36.7; Yellow vegetables 24.3; White vegetables 45.4; Pickled vegetables 53.1; Soy products 46.3; Fresh fish 19.8; Red meat 26.7

**Women past smokers:** Age (SD) 49.0 (6.3); Alcohol drinking, at least once per week (%) 41.3; Education, College or more (%) 19.5; Past history of Hypertension 19.3; Any drug for medication 33.8; Physical activity, 1+/week (%) 18.2; Body mass index (SD) 24.0 (3.4); Diet (daily, %); fruit 41.7; Green vegetables 30.3; Yellow vegetables 19.3; White vegetables 35.9; Pickled vegetables 46.4; Soy products 35.6; Fresh fish 15.4; Red meat 30.6

**Women current smokers:** Age (SD) 48.6 (5.9); Alcohol drinking, at least once per week (%) 44.6; Education, College or more (%) 11.7; Past history of Hypertension 12.2; Any drug for medication 24.7; Physical activity, 1+/week (%) 13.1; Body mass index (SD) 23.2 (2.9); Diet (daily, %) Fruit 30.1; Green vegetables 36.9; Yellow vegetables 18.4; White vegetables 35.5; Pickled vegetables 46.3; Soy products 36.8; Fresh fish 14.9; Red meat 30.7

**Location:** Five Public Health Center areas (Ninohe PHC in Iwate Prefecture, Yokote PHC in Akita Prefecture, Saku PHC in Nagano Prefecture, Ishikawa PHC in Okinawa Prefecture and Katsushika PHC in Tokyo Metropolitan area).

**Recruitment strategy:** Population registries

**Length of follow-up:** Until the date of death of the deceased, the last date when the survival status had been confirmed for censored cases, and the end of the study period (December 31, 1999)

**Response rate and loss to follow-up:** Men (76.5%) and women (82.1%)
Eligible population: Not reported
Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Smoking and alcohol
Time: Not reported
Measurement of exposure: Smoking status was initially classified as current, past, or never smoker
Usual alcohol intake was first reported as frequency of consumption in six categories: <1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, and every day.

Outcomes at 55 years or over

Outcomes: Death
Outcome measurement: Death certificates
Time: Not reported

Analysis

Analysis strategy: Cox’s proportional hazard model
Confounders: Adjusted for age and area, educational background, medication, past history of hypertension, sports in leisure time, dietary habits, alcohol habit and quintiled BMI
Significant trends: 22% of death from all causes, 25% of all cancer, and 17% of all circulatory system disease deaths, could be attributed to cigarette smoking in males, and 5%, 4%, and 11% in females, respectively.
Limitations: Smoking status was determined only once at baseline

Results, limitations, source of funding

Number: 1014 men and 500 women died
Effect estimates:
Risk Ratios According to Status of Cigarette Smoking for Selected Causes of Death
Men
Past
All causes 1.02 (0.82 – 1.28)
All Cancer 1.09 (0.77 – 1.54)
All circulatory system disease 0.99 (0.67 – 1.43)
Noncancer-noncirculatory system disease 0.97 (0.67 – 1.43)
Current
All causes1.55 (1.29 – 1.86)
All Cancer 1.61 (1.20 – 2.15)
All circulatory system disease 1.41 (0.97 – 2.03)
Noncancer-noncirculatory system disease 1.61 (1.17 – 2.19)
Women
Past
### Effect from Cumulative Dose as Indicated by Pack-years among Current Smokers Compared with Never Smokers

**RR (95%CI)**

#### Men

<table>
<thead>
<tr>
<th>Pack-year</th>
<th>All causes</th>
<th>All cancer</th>
<th>All circulatory system disease</th>
<th>Noncancer-noncirculatory system disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>10 – 19</td>
<td>1.44 (1.12–1.84)</td>
<td>1.33 (0.88–2.00)</td>
<td>1.02 (0.60–1.73)</td>
<td>1.89 (1.28–2.79)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>1.56 (1.23–1.99)</td>
<td>1.41 (0.94–2.10)</td>
<td>1.44 (0.90–2.31)</td>
<td>1.82 (1.23–2.68)</td>
</tr>
<tr>
<td>30 +</td>
<td>1.57 (1.28–1.93)</td>
<td>1.83 (1.34–2.51)</td>
<td>1.41 (0.95–2.12)</td>
<td>1.37 (0.96–1.95)</td>
</tr>
</tbody>
</table>

#### Women

<table>
<thead>
<tr>
<th>Pack-year</th>
<th>All causes</th>
<th>All cancer</th>
<th>All circulatory system disease</th>
<th>Noncancer-noncirculatory system disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>1.64 (0.98–2.72)</td>
<td>1.03 (0.42–2.52)</td>
<td>3.37 (1.52–7.47)</td>
<td>1.30 (0.47–3.57)</td>
</tr>
<tr>
<td>10 – 19</td>
<td>1.52 (0.80–2.88)</td>
<td>0.64 (0.16–2.61)</td>
<td>2.12 (0.65–6.95)</td>
<td>2.58 (1.10–6.02)</td>
</tr>
<tr>
<td>20 +</td>
<td>2.61 (1.52–4.47)</td>
<td>4.51 (2.45–8.30)</td>
<td>1.51 (0.35–6.57)</td>
<td>0.00 (0.00–0.00)</td>
</tr>
</tbody>
</table>

### Effect from Dose for Number of Cigarettes and Age at Start of Smoking in Current Smokers

#### Number of cigarettes

<table>
<thead>
<tr>
<th>Number of cigarettes</th>
<th>All causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>1.00</td>
</tr>
<tr>
<td>1 – 19</td>
<td>1.00</td>
</tr>
<tr>
<td>Gender</td>
<td>Number of cigarettes</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>1–19</td>
</tr>
<tr>
<td></td>
<td>20–29</td>
</tr>
<tr>
<td></td>
<td>30+</td>
</tr>
<tr>
<td>Women</td>
<td>Number of cigarettes</td>
</tr>
<tr>
<td></td>
<td>1–19</td>
</tr>
<tr>
<td></td>
<td>20–29</td>
</tr>
<tr>
<td></td>
<td>30+</td>
</tr>
</tbody>
</table>

**Age at start of smoking**

<table>
<thead>
<tr>
<th>Gender</th>
<th>All causes</th>
<th>All cancer</th>
<th>All circulatory system disease</th>
<th>Noncancer-noncirculatory system disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1–19</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>20–24</td>
<td>0.81 (0.67–0.98)</td>
<td>0.86 (0.63–1.17)</td>
<td>0.80 (0.54–1.16)</td>
</tr>
<tr>
<td></td>
<td>25+</td>
<td>0.69 (0.52–0.92)</td>
<td>0.77 (0.49–1.19)</td>
<td>0.51 (0.27–0.97)</td>
</tr>
<tr>
<td>Women</td>
<td>1–24</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td></td>
<td>25+</td>
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</tr>
</tbody>
</table>
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

| All causes | 1.00 (0.50–2.02) |
| All cancer | 0.63 (0.20–1.92) |
| All circulatory system disease | 1.00 (0.21–4.66) |
| Noncancer-noncirculatory system disease | 1.62 (0.23–11.61) |

**Authors:** Harmsen P, Lappas G, Rosengren A, Wilhelmsen L  
**Year:** 2006  
**Citation:** Stroke 37(7): 1663-7  
**Country of study:** Sweden  
**Aim of study:** To estimate the predictive value of risk factors for stroke measured in midlife  
**Study design:** Intervention trial  
**Quality score:** (+++, + or -): +

**Source population**  
**Number of people:** 7494 men  
**Demographics:** Not reported

**Study (eligible and selected) population**  
**Number of people:** 7457  
**Characteristics:** Not reported  
**Location:** Göteborg, Sweden  
**Recruitment strategy:** Responders to a postal questionnaire  
**Length of follow-up:** 28 years  
**Response rate and loss to follow-up:** 75% of the sample  
**Eligible population:** Middle-aged men  
**Excluded populations:** Women

**Exposures at midlife**  
**Relevant exposures:** Psychological stress, smoking, high body mass, physical activity  
**Time:** 1970 to 1973.  
**Measurement of exposure:** Psychological stress was assessed by using 1 question on self-perceived stress and rated from 1 through 6.  
Physical leisure time activity was coded as: (1) sedentary, (2) moderate, or (3) strenuous and regular.  
Socioeconomic class was coded according to the Swedish socioeconomic classification system: (1) unskilled and semiskilled workers, (2) skilled workers, (3) foremen in industrial production and assistant nonmanual employees, (4) intermediate nonmanual employees, and (5) employed and self-employed professionals, higher civil servants, and executives

**Outcomes at 55 years or over**  
**Outcomes:** Stroke  
**Outcome measurement:** End points of first-ever stroke in participants free of previous stroke were registered from several sources.  
**Time:** 1998
### Analysis

**Analysis strategy:** Multiple Cox regression analyses

**Covariates:** Not reported. Paper says model adjusted for all other factors

**Reported limitations:** Not reported

**Source of funding:** Bank of Sweden Tercentenary Fund, the Swedish Research Council, and the Swedish Heart Lung Foundation

### Results, limitations, source of funding

**Number:** 1019

**Effect estimates:**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure quintile 5 vs quintile 2</td>
</tr>
<tr>
<td>HypMed</td>
</tr>
<tr>
<td>Previous transient ischemic attacks</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Stroke in either parent</td>
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<tr>
<td>History of diabetes</td>
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<tr>
<td>Coronary events in parent</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>History of chest pain</td>
</tr>
<tr>
<td>Psychological stress</td>
</tr>
<tr>
<td>BMI quintile 5 vs quintile 1.26</td>
</tr>
<tr>
<td>Low physical activity</td>
</tr>
<tr>
<td>S-Chol quintile 5 vs quintile 1.08</td>
</tr>
<tr>
<td>Social class low, 5 vs 1.02</td>
</tr>
<tr>
<td>Age</td>
</tr>
</tbody>
</table>

**Significant trends:** Age, diabetes, and high blood pressure were independently associated with increased risk of stroke

### Authors

He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S

**Year:** 2004

**Citation:** Journal of Obesity and Related Metabolic Disorders 28(12): 1569-74

**Country of study:** USA

**Aim of study:** To determine the association between intake of fruit and vegetables and the risk of obesity and long-term weight gain among middle-aged women

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

### Source population

121,700 female registered nurses ages 30-55 years from 11 US states responded to a questionnaire in 1976

### Study (eligible and selected) population

**Study population:** Analysis restricted to 74,063 women

**Follow-up:** 12 years
Exclusion: Women with:

i) History of cardiovascular disease, cancer, diabetes
ii) Incomplete or implausible information

Attrition: -

Exposures at midlife

A semi-quantitative food frequency questionnaire (FFQ) was used to assess the intake of standard units of *fruit and vegetable* items in the previous year (responses ranging from ‘never’ to ‘six or more times per day’); these were subsequently converted to average daily intake of food items for each participant.

Changes in fruit and vegetable intake between 1984 (baseline) and 1994 were also computed.

Certain vegetables were grouped as cruciferous vegetables; dark and yellow vegetables; green leafy vegetables; other vegetables.

Validity of FFQ established with correlation coefficients ranging from 0.69-0.8.

Vegetable/fruit consumption was divided into quintiles with the first quintile indicating the largest decrease in intake and the fifth quintile the largest increase in intake during follow-up.

Median values of quintiles of changes in fruit and vegetable intake were used in linear trend tests.

Outcomes at 55 years or over

Self-reported body weight captured through questionnaire every other year; when self-reported weight was compared with measured weight, correlation was 0.96.

Obesity defined as BMI $\geq 30$ kg/m$^2$ and major weight gain as weight gain of 25 kg or more during follow-up.

Analysis

Analysis strategy: Logistic regression was used to assess the association between changes in fruit and vegetable intake (divided into quintiles) during follow-up. General linear models with least-square means were used to estimate the mean difference of changes in BMI during follow-up.

Confounders: Age, year of follow-up, change in physical activity, change in cigarette smoking status, changes in alcohol consumption and caffeine intake, change in use of HRT, changes in energy-adjusted intake of saturated fat, polyunsaturated fat, monounsaturated fat, trans-unsaturated fatty acid, protein, and total energy and baseline BMI.

Limitations:

1. If participants perceive themselves to be overweight, eating habits may change in accordance with dietary recommendations of past decades; this may result in an underestimation of association between intake of fruits and vegetables and weight gain.
2. Issues of reliability due to self-reported weight information.
3. Residual confounding.

Source of funding: National Institutes of Health.

Results, limitations, source of funding

- Of 65,294 non-obese participants at baseline, 6,530 became obese during follow-up.
- 669 women reported major weight gain during follow-up.
- Women with the largest increase in intake of fruits (median change=+1.86 servings/day) had the lowest risk for obesity compared to women with the largest decrease in intake of fruits (OR=0.76, [0.68, 0.84]; trend test p-value: 0.0007).
- Women with the largest increase in intake of vegetables (median change=+2.80 servings/day) had...
the lowest risk for obesity compared to women with the largest decrease in intake of vegetables (OR=0.84, [0.75, 0.93]; trend test p-value= 0.0002)
- Women with the largest increase in intake of fruits and vegetables combined had the lowest risk for obesity and major weight gain compared to women with the largest decrease in intake of fruits and vegetables combined (OR=0.76, [0.69, 0.86], trend test p-value<0.0001; and OR=0.72, [0.55, 0.93], trend test – value=0.01, respectively)
- There appeared to be a decreasing trend in risk for obesity with increasing intake of vegetables (trend test p-value: 0.0002); same observation noted for major weight gain in relation to fruits and vegetables combined (trend test p-value: 0.01)
- Baseline BMI stratification: Among overweight women, those reporting the greatest change in fruit and vegetable intake gained 0.76 kg less weight than women reporting the largest decrease in fruit and vegetable intake (among normal weight women at baseline, a change of 0.52 kg was observed)
- Stratification by chronic disease presence: Among women with incident chronic disease (e.g. cancer, CVD, diabetes), those reporting the largest increase in intake of fruits and vegetables gained 0.77 kg less weight than did women with the largest decrease in intake (among women without chronic diseases, a difference of 0.57 kg was observed)

Authors: Hodge A, Almeida OP, English DR, Giles GG, Flicker L
Year: 2013
Citation: International Psychogeriatrics 25(3): 456-466
Country of study: Australia
Aim of study: Investigate association between diet and psychological distress as a marker for depression
Study design: Cohort study
Quality score: (+++, + or -): +

Source population
Number of people: 41,51
Demographics: Not reported

Study (eligible and selected) population
Number of people: 8,660
Characteristics:
K10 at follow-up
<20: Age at baseline (years) 59.1 (5.4); Age at follow-up (years) 70.5 (5.7); Dietary energy (mJ) 9.4 (3.0); Female 61.8; At least some tertiary education 30.2; Top SEIFA quintile 32.9; Physically active 37.8; Current smoker 6.4
≥20: Age at baseline (years) 59.1 (5.6); Age at follow-up (years) 70.8 (6.0); Dietary energy (mJ) 9.5 (3.2); Female 72.1; At least some tertiary education 21.3; Top SEIFA quintile 28.4; Physically active 35.2; Current smoker 10.1
Location: Melbourne, Australia
Recruitment strategy: Electoral rolls, advertisements, and community announcements in local media
Length of follow-up: <20 Period of follow-up (years) 11.4 (1.3), ≥20 Period of follow-up (years) 11.6 (1.3)
Response rate and loss to follow-up: Italian-born <60%; Greek born <50%; Australian born 80%
**Eligible population:** Healthy men and women born in Australia and aged 50–69 years

**Excluded populations:** Those who were taking medication for anxiety or depression, did have extreme dietary energy intakes (i.e. in the upper or lower 1% of the sex-specific distribution), and who did have health conditions, such as angina, diabetes, cancer, coronary artery disease, or stroke at baseline

**Exposures at midlife**

**Relevant exposures:** Diet (alcohol was included in the dietary indices)

**Time:** 1990 and 1994

**Measurement of exposure:** 121-item food frequency questionnaire

**Outcomes at 55 years or over**

**Outcomes:** Psychological distress

**Outcome measurement:** The K10 has 10 questions regarding symptoms experienced during the last 30 days; each item has 5 possible responses from “all the time” to “never,” scored from 5 to 1, so the total score has a minimum of 10 and maximum of 50, with 50 implying severe psychological distress

**Time:** 2003–2007

**Analysis**

**Analysis strategy:** Logistic regression

**Confounders:** Physical activity, smoking status, alcohol use, education, history of arthritis, asthma, kidney stones or gallstones, dietary energy intake, and Socio-Economic Indexes for Areas

**Results, limitations, source of funding**

**Number:** Not reported

**Effect estimates:**

Associations OR (95%CI) between quintiles of the modified Mediterranean-style pattern and ADP at baseline and psychological distress according to K10 score at follow-up

**Modified Mediterranean-style pattern** 0.98 (0.92–1.04)

1 1.00
2 0.96 (0.78–1.20)
3 0.92 (0.73–1.16)
4 0.90 (0.70–1.16)
5 0.92 (0.69–1.24)

**Australian Dietary Pattern** 0.94 (0.87–1.01)

1 1.00
2 0.64 (0.43–0.95)
3 0.60 (0.41–0.88)
4 0.51 (0.34–0.75)
5 0.61 (0.40–0.91)

**Significant trends:** Observed an inverse association between the Mediterranean-style diet at baseline and psychological distress at follow-up. A Mediterranean-style diet was associated with less psychological distress, possibly through provision of a healthy nutrient profile.
**Limitations:**

**Author:**
1. Did not assess psychological distress at baseline.
2. Participants who completed the K10 at follow-up were generally healthier than those who did not.
3. Diet relying on self-report.
4. Dietary change over time.
5. K10 does not necessarily yield specific psychiatric diagnoses.

**Reviewer:** Low response rates from non-Australia born.

**Source of funding:** A. Hodge was funded by the National Health and Medical Research Council (NHMRC) (grant 520316). This work was funded by VicHealth, the Cancer Council Victoria, and the National Health and Medical Research Council (grant 209057).

| **Authors:** Holmberg AH, Johnell O, Nilsson PM, Nilsson J, Berglund G, Akesson K |
| **Year:** 2006 |
| **Citation:** Osteoporosis International 17(7): 1065-77 |
| **Country of study:** Sweden |
| **Aim of study:** To investigate the risk factors for fractures among men and women in middle age |
| **Study design:** Longitudinal |
| **Quality score:** (+, + or -): + |

**Source population**

- 72% of invited population recruited for Malmo Preventive Project
- 22,444 men ages 27-61 years and 10,902 women ages 28-58 years recruited during 1974-84 and 1977-92, respectively
- Mean response rate to core questions of baseline questionnaire was 98% for women and 72% for men, and approximately 100% for questions added during recruitment period

**Study (eligible and selected) population**

- Regression analysis restricted to 11 women and 10 men. Women and men had 11-year and 16-year follow-up, respectively.

**Sociodemographics:** Baseline mean age of 44 years for men and 48 years for women

**Follow-up:** Men and women followed up for average of 19 and 15 years, respectively (men: 1974-1984 until 1999; women: 1977-1992 until 1999)

**Exclusion:**
- i) Missing data for 6,368 men
- ii) High-energy fractures and fractures caused by cancer or other bone diseases

**Attrition:** -

**Exposures at midlife**

Self-reported smoking behaviour

**Outcomes at 55 years or over**

*Incident low-energy fractures and mortality* data was obtained through data linkage with hospital medical and radiological files using personal identification numbers.
Fractures were categorised as those of the forearm, vertebral, proximal humerus, or ankle. Outcomes restricted to fractures that were classified as low-energy or those resulting from falling from standing height or less (high-energy fractures or those caused by high-energy trauma were included in the non-fracture population). Individuals were still classified under low-energy fracture even if they had previous or subsequent high-energy fractures. The first fracture of each fracture type was assessed.

**Analysis**

**Analysis strategy:** Cox proportional hazard regression was used to assess risk factors for fragility fracture in middle age.

**Confounders:** Age, height, weight, >10 kg weight gain since age 30, skinfold, forced vital capacity, SBP, DBP, resting pulse, diabetes, triglycerides, cholesterol, y-glutamyl transferase, serum phosphate, serum creatinine, serum uric acid, blood haemoglobin, sedimentation rate, sick leave at present, chest pressure, poor self-rated health, poor appetite, premature awakening, hospitalization for mental disorder, physical activity, HRT, history of previous fracture.

**Results, limitations, source of funding**

- 1,257 out of 1,292 women and 1,262 out of 1,505 men were affected by incident low-energy fractures.
- Among women and men, the total number of low-energy fracture were: 622 and 330 for forearm, 155 and 123 for proximal humerus, 160 and 168 were vertebral, 233 and 259 ankle, and 141 and 174 hip.
- Smoking was more common among men with vertebral, proximal humerus, and hip fractures.
- Among women, smokers had a higher risk for vertebral fractures (RR=1.96, [1.47, 2.64]) than non-smokers.
- Among men, smokers had a greater risk for low-energy fractures (RR=1.25, [1.11, 1.39]), vertebral fractures (RR=1.85, [1.41, 2.42]), proximal humerus fractures (RR=1.58, [1.08, 2.33]), and hip fractures (RR=2.14, [1.51, 3.01]) than non-smokers.

**Limitations:**
1. Healthy volunteer effect: participants may have fewer fractures than non-participants.
2. Incomplete data sets.
3. Residual confounding.

**Source of funding:** The Swedish Research Council Project, The Kock Foundation, The Herman Järnhardt Foundation, Malmö University Hospital Funds, and regional research grants supported this study.

**Authors:** Holme I, Tonstad S, Sogaard AJ, Larsen PG, Haheim LL

**Year:** 2007

**Citation:** BMC Public Health 12(7): 154

**Country of study:** Norway

**Aim of study:** To assess association between smoking or physical activity and metabolic syndrome.

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population:** 16,209 men ages 40-49 years, born in 1923-32 and living in Oslo were invited and attended screening.
### Study (eligible and selected) population

Men living in Oslo in 2000-01 were surveyed and men originally invited to participate in study in 1972-73 and also living in Oslo or Akershus were invited for re-examination.

Of 10,328 eligible participants, 6410 (62%) men attended the baseline and follow-up.

Analysis restricted to **6382** men without baseline diabetes and with blood pressure measurements at baseline and follow-up.

**Follow-up:** 28 years

**Exclusion:** Men who:
- Were dead or had emigrated (**n=1655**)
- Lived outside Oslo and Akershus (**n=1278**)
- Had unknown addresses (**n=2944**)

**Attrition:** Participants who answered question on LTPA smoked less and had a greater level of education. Plus participants who attended in 2000 had lower body weight, height, systolic and diastolic blood pressure, total cholesterol, triglycerides and glucose values, and smoked less at baseline than non-participants.

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### Exposures at midlife

Self-reported physical activity at work and leisure, and smoking habits measured in 1972-73.

Leisure-time physical activity (LTPA) categorized as light (e.g., reading, watching TV); moderate (e.g., walking, bicycling – totally at least 4 hours/week); moderately vigorous (e.g., exercise, sports, heavy gardening – totalling at least 4 hours/week); vigorous (e.g., hard training several times/week).

Reliability and validity of LTPA question has been established.

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### Outcomes at 55 years or over

At baseline, physical measurements, blood pressure, and a blood sample were taken. Metabolic syndrome was defined as presence of at least three out of the following five criteria:

- **Triglycerides >=1.7 mmol/l** adjusted for the last meal
- **Glucose >= 6.1 mmol/l** adjusted for the last meal
- **BMI >=30 kg/m2**
- **Blood pressure >= 135/85 mmHg**, and
- **HDL cholesterol <1.03 mmol/l**

Smoking was categorised into ‘never’, ‘previous’, and ‘current’ smoker groups.

Diabetes definition included self-reported diabetes, antidiabetic medication, insulin use or non-fasting glucose **>=11.1 mmol/l**.

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### Analysis

**Analysis strategy:** Logistic regression was used to assess association between smoking or physical activity and metabolic syndrome or diabetes.

**Confounders:** Age, education

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### Results, limitations, source of funding

- The odds of metabolic syndrome were higher for current smokers compared to those who never smoked (OR=1.29, [1.11, 1.51])
- The odds of metabolic syndrome were lower for those who reported vigorous, moderately...
vigorou, or moderate levels of LTPA in comparison with those who reported sedentary/light levels (OR=0.46, [0.28, 0.74]; OR=0.65, [0.54, 0.80]; OR=0.83, [0.71, 0.98])

- The odds of diabetes were lower for those who reported vigorous, moderately vigorous, or moderate levels of LTPA in comparison with those who reported sedentary/light levels (OR=0.28, [0.11, 0.71]; OR=0.68, [0.52, 0.91]; OR=0.75, [0.60, 0.94])

**Limitations:**
1. If diseases started before year 2000, then biological, anthropometric indices and lifestyle factors may have been affected
2. Imperfect measurement/definition of metabolic syndrome leading to possible underestimation of its prevalence
3. Participants with metabolic syndrome at baseline were not excluded
4. Residual confounding, such as, dietary habits and alcohol consumption

**Source of Funding:** Norwegian Council for Cardiovascular Diseases of the Norwegian National Association for Public Health

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**Authors:** Holtermann A, Mortensen OS, Burr H, Søgaard K, Gyntelberg F, Suadicani P

**Year:** 2009

**Citation:** Scandinavian Journal of Work, Environment and Health 35(6): 466-74

**Country of study:** Denmark

**Aim of study:** To determine the association between physical activity and risk of ischemic heart disease and all-cause mortality

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

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**Source population**

5249 Copenhagen male employees ages 40-59 years were invited and agreed to participate (87% response rate) and undergo an interview, a clinical examination, and complete a questionnaire in 1970-71

**Study (eligible and selected) population**

Analysis restricted to 4952 men

**Follow-up:** From 1970-71 to 2001

**Exclusion:** Men with:

i) History of myocardial infarction (n=74), angina pectoris (n=165), intermittent claudication (n=105) at baseline

ii) Missing answers (n=9)

iii) Men who had emigrated during follow-up (n=14)

**Attrition:** -

**Exposures at midlife**

Physical activity at work: Was assessed using questionnaire and participants were classified as: a) 'low': mainly sedentary/not walking around much at workplace, b) 'moderate': walking around quite a bit but not having to carry heavy items, c) 'high': walking around most of the time or undertaking heavy/strenuous physical work

Strenuous work was assessed with answer options of 'seldom or never', 'occasionally', and 'often'

A dichotomous variable was created to assess presence of physically demanding work

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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
Another variable combined information on physical activity and strenuous work to assess physical work demands, with possible scores ranging from 2-6 (higher scores representing higher demands).

**Physical activity during leisure time:** Self-reported physical activity level during leisure time categorized as ‘low’ (mainly sedentary), ‘moderate’ (light activities for at least 4 hours/week), ‘high’ (active for at least 3 hours/week or taking part in high intensity activities several times/week).

**Outcomes at 55 years or over**

IHD mortality diagnoses between 1970-71 and 2001 obtained from national registers.

**Analysis**

**Analysis strategy:** Cox proportional hazard regression used to assess influence of physical activity on ischemic heart disease (IHD) and all-cause mortality.

**Confounders:** Age, BMI, SBP, DBP, treatment of diabetes or hypertension, alcohol use, smoking, social class.

**Results, limitations, source of funding**

- 591 died from IHD during study period.

Among men with moderate physical work demands:

- The risk of IHD mortality was significantly lower for those with a high level of physical activity during leisure time (HR=0.37, [0.19, 0.70]) compared to those with a low level of physical activity during leisure.
- The risk for all-cause mortality was significantly lower for those with a moderate and high level of physical activity during leisure time (HR=0.82, [0.71, 0.94]; and HR=0.64, [0.50, 0.81], respectively) compared to those with a low level of physical activity during leisure.
- The risk for all-cause mortality was significantly lower for those with moderate and high (combined) physical activity during leisure time (HR=0.80, [0.70, 0.92]) compared to those with low levels of physical activity reported during leisure time.

**Limitations:**

1. Self-reported information resulting in possible misclassification.
2. Misclassification of exposure due to lack of continuous exposure data and repeated measures of exposure during follow-up.
3. Unknown if results also apply to women, people of different races, ages, with varying levels of physical fitness, or from rural areas (generalizability issues).

**Source of funding:** None reported.

**Authors:** Holtzman RE, Rebok GW, Saczynski JS, Kouzis AC, Wilcox Doyle K, Eaton WW

**Year:** 2004

**Citation:** The Journals of Gerontology Series B Psychological Sciences and Social Sciences 59(6):278-84

**Country of study:** USA

**Aim of study:** To determine the influence of social networks on cognitive change.

**Study design:** Longitudinal

**Quality score:** (+++, + or -): ++

**Source population**
4,238 participants were recruited for wave 1 in 1981 using probability sampling methods. Of 4,238 people, 3,481 were interviewed at wave 1 and 1,920 (73% of survivors) were re-interviewed in 1993-96 at wave 3

### Study (eligible and selected) population
Analysis restricted to 354 out of 881 participants with age >= 50 years and MMSE >=28 at wave 1

**Exclusion:**
- i) 107 with missing longitudinal data
- ii) 88 had missing MMSE data at wave 3
- iii) 5.4% of 354 people with missing cross-sectional data at wave 3
- iv) People with MMSE <28

**Attrition:** 420 lost to follow-up.
Non-assessed participants were older, had fewer years of formal education, were less likely to be female, and had lower baseline MMSE scores compared to assessed participants

### Exposures at midlife
Social network included network size, frequency of contact, and emotional support
Network size at waves 1 and 3: The number of relatives, family members, friends and neighbours with whom the respondent kept in touch with via phone or visits, with corresponding scores assigned that were subsequently summed (range of possible scores of 0-10)
Frequency of contact at wave 3: Frequency of contact by phone or getting together with relatives or family and friends or neighbours with the range of possible scores of 0-10
Emotional support at wave 3: Support from partners, relatives, and friends was assessed; scores were subsequently assigned and summed with a possible range of 0-27

### Outcomes at 55 years or over
Cognitive change between wave 3 and wave 1 was assessed using MMSE

### Analysis

**Analysis strategy:** Simultaneous linear or logistic regression was used to determine whether interactions in larger networks at wave 1 are associated with MMSE change between wave 1 and wave 3

**Confounders:** Cerebrovascular disease or risk, age, education, depression, race, gender, physical disability, alcohol use disorder

### Results, limitations, source of funding
- Mean MMSE at wave 3 was 26.5
- A linear effect was observed for baseline network size (p=0.006, effect size=0.06); also, less increase - more decrease in network size is associated with decreased wave 3 MMSE (p=0.03, effect size=-0.06)
- Top tertiles of interpersonal activity and emotional support (paired as categorical variables) were significantly related to MMSE scores (activity betas=0.13 and 0.12, p <=0.04; support betas 0.16 and 0.17, p<=0.01)
- More frequent contact in larger networks and higher levels of emotional support positively influence cognitive change

**Limitations:**
1. Cannot assess whether decline in MMSE is due to regression to the mean
2. If follow-up period is too short, directionality confound may exist (particularly given the long prodromal period before clinical symptoms in Alzheimer’s begin to manifest)
3. Generalizability may be restricted as assessed participants were healthier, better educated, younger, and with larger networks than non-assessed individuals

Source of funding: National Institutes of Mental Health

Authors: Hu G, Qiao Q, Silventoinen K, Eriksson JG, Jousilahti P, Lindström J… Tuomilehto J
Year: 2003
Citation: Diabetologia 46(3): 322-9
Country of study: Finland
Aim of study: Examine the relationship of occupational, commuting and leisure-time physical activity with the incidence of Type 2 diabetes
Study design: Prospective cohort
Quality score: (+++, + or -): +

Source population
Number of people: 21,630
Demographics: Not reported

Study (eligible and selected) population
Number of people: 6898 men and 7392 women
Characteristics:
Men
Physical activity
Light
Participants n 2688
Age at baseline 50.9±8.8
BMI 27.0±3.9
Education 10.2±4.5
Obesity 20.3
Smoking 31.8
Moderate
Participants n 1563
Age at baseline 46.5±7.9
BMI 26.9±3.7
Education 10.1±3.7
Obesity 18.1
Smoking 23.6
Active
Participants n 2647
Age at baseline 47.5±8.0
BMI 26.9±3.6
Education 7.8±2.2
Obesity 17.8
Smoking 33.6
p value for trend
Age at baseline <0.001
### BMI >0.2
- Education <0.001
- Obesity 0.056
- Smoking <0.001

### Women
- Physical activity
- Light
  - Participants n 3255
  - Age at baseline 51.0±9.2
  - BMI 26.5±5.1
  - Education 9.8±3.9
  - Obesity 21.6
  - Smoking 13.6

- Moderate
  - Participants n 2357
  - Age at baseline 47.2±8.0
  - BMI 26.1±4.2
  - Education 10.1±3.8
  - Obesity 16.0
  - Smoking 12.9

- Active
  - Participants n 1780
  - Age at baseline 47.9±7.9
  - BMI 27.0±4.7
  - Education 8.4±2.6
  - Obesity 24.2
  - Smoking 12.9

*p value for trend
- Age at baseline <0.001
- BMI <0.001
- Education <0.001
- Obesity <0.001
- Smoking >0.2

### Location:
North Karelia and Kuopio, and the Turku-Loimaa region in south-western Finland

### Recruitment strategy:
Not reported

### Length of follow-up:
Mean follow-up of 12 years

### Response rate and loss to follow-up:
The participation rate varied by year from 74% to 88%

### Eligible population:
General population 25 to 64 years of age

### Excluded populations:
Subjects diagnosed with coronary heart disease or stroke (n=590), subjects with known diabetes (n=435) at baseline, and subjects with incomplete data on all required factors or on physical activity (n=1355)

### Exposures at midlife

#### Relevant exposures:
Physical activity and smoking habits

#### Time:
Through the end of 1998 or until death

#### Measurement of exposure:
Occupational physical activity according to the following three categories: (i) 'light' was physically very easy, sitting office work, e.g. secretary; (ii) 'moderate' was work including standing and walking, e.g. store assistant; (iii) 'active' was work including walking and lifting, or heavy manual labour. Subjects asked whether they walked, rode a bicycle, or used motorized transportation to and from work as well as the daily duration of this activity.
Outcomes at 55 years or over

Outcomes: Type 2 diabetes
Outcome measurement: From the National Hospital Discharge Register and the National Social Insurance Institution’s Register
Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age, study year, education, systolic blood pressure, smoking, the other two types of physical activity, BMI, and sex

Results, limitations, source of funding

Number: 373

Effect estimates:

Occupational physical activity
No. of new cases Person-years Adjusted hazards ratios (95% confidence intervals)

Men
Light 97 29216 1.00
Moderate 32 18874 0.67 (0.44–1.01)
Active 71 32955 0.73 (0.52–1.02)
p value for trend 0.075

Women
Light 102 38034 1.00
Moderate 31 29310 0.72 (0.46–1.12)
Active 40 22740 0.78 (0.52–1.18)
p value for trend 0.267

Men and women combined
Light 199 67250 1.00
Moderate 63 48184 0.70 (0.52–0.96)
Active 111 55695 0.74 (0.57–0.95)
p value for trend 0.020

Commuting physical activity
Adjusted hazards ratios (95% confidence intervals)

Men
0 min 1.00
1–29 min 1.00 (0.71–1.42)
≥30 min 0.75 (0.46–1.23)
p value for trend 0.501

Women
0 min 1.00
1–29 min 0.94 (0.63–1.42)
≥30 min 0.57 (0.34–0.96)
p value for trend 0.105

Men and women combined
0 min 1.00
1–29 min 0.96 (0.74–1.25)
≥30 min 0.64 (0.45–0.92)
p value for trend 0.048
Leisure-time physical activity
Adjusted hazards ratios (95% confidence intervals)

Men
Low 1.00
Moderate 0.78 (0.57–1.06)
High 0.84 (0.52–1.37)
p value for trend 0.282

Women
Low 1.00
Moderate 0.81 (0.58–1.15)
High 0.85 (0.43–1.66)
p value for trend 0.49

Men and women combined
Low 1.00
Moderate 0.81 (0.64–1.02)
High 0.84 (0.57–1.25)
p value for trend 0.186

Significant trends: The multivariate-adjusted hazards ratios of diabetes with none, 1 to 29, and more than 30 min of walking or cycling to and from work were 1.00, 0.96, and 0.64 (p=0.048 for trend). The multivariate-adjusted hazards ratios of diabetes for low, moderate, high levels of leisure-time physical activity were 1.00, 0.67, and 0.61 (p=0.001 for trend); after additional adjustment for BMI, the hazards ratio was no longer significant

Limitations:
1. Self-report of physical activity.
2. Did not carry out a glucose tolerance test in the baseline and follow-up

Source of funding: Finnish Academy (grants 38387, 46558, 52342, 53585, 76502, 77618)

Year: 2007
Citation: Movement Disorders 22(15): 2242-2248
Country of study: Finland
Aim of study: Examine the association of coffee and tea consumption with the risk of incident Parkinson’s disease
Study design: Independent cross-sectional population surveys
Quality score: (+++, + or -): +

Source population
Number of people: 29,890
Demographics: Not reported

Study (eligible and selected) population
Number of people: 29,335
Characteristics:
Coffee consumption
Men
0
Participants (n) 891
<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Age (yr)</th>
<th>Body mass index (kg/m²)</th>
<th>Education (yr)</th>
<th>Low leisure time physical activity (%)</th>
<th>Tea drinker (%)</th>
<th>Current smoker (%)</th>
<th>Alcohol drinker (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>5,583</td>
<td>44.8 (13.0)</td>
<td>10.9 (4.4)</td>
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<td>7,819</td>
<td>47.6 (12.8)</td>
<td>10.6 (4.1)</td>
<td>23.2</td>
<td>50.3</td>
<td>26.9</td>
<td>67.5</td>
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<tr>
<td></td>
<td></td>
<td>P-trend</td>
<td></td>
<td>Age (yr) &lt;:0.001</td>
<td>Body mass index (kg/m²) &lt;:0.001</td>
<td>Education (yr) &lt;:0.001</td>
<td>Low leisure time physical activity (%) &lt;:0.001</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1,022</td>
<td>40.4 (12.8)</td>
<td>11.1 (4.1)</td>
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<td>70.8</td>
<td>11.2</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>7,439</td>
<td>46.4 (12.4)</td>
<td>11.0 (4.0)</td>
<td>29.0</td>
<td>50.3</td>
<td>14.7</td>
<td>44.7</td>
</tr>
<tr>
<td></td>
<td>6,581</td>
<td>45.4 (10.8)</td>
<td></td>
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</tr>
</tbody>
</table>
Body mass index (kg/m²) 26.3 (4.9)
Education (yr) 10.1 (3.6)
Low leisure time physical activity (%) 34.6
Tea drinker (%) 22.5
Current smoker (%) 27.3
Alcohol drinker (%) 39.4

P trend
Age (yr) <0.001
Body mass index (kg/m²) <0.001
Education (yr) <0.001
Low leisure time physical activity (%) <0.001
Tea drinker (%) <0.001
Current smoker (%) <0.001
Alcohol drinker (%) <0.001

Exposures at midlife

Relevant exposures: Physical activity, smoking habits, and alcohol, coffee and tea consumption, leisure-time physical activity


Measurement of exposure: Self-administered questionnaire.

Leisure-time physical activity was classified into three categories: low, moderate, or high
Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily

Participants were asked, “How many cups of coffee or tea do you drink per day?” Coffee consumption categorised: none, 1 to 4 cups, and 5 cups per day. Tea consumption was categorised: none, 1 to 2 cups, and 3 cups per day

Alcohol consumption was categorised: none, 1 to 100, >100 g per week.

Location: North Karelia and Kuopio, and the Turku-Loimaa region in south-western Finland

Recruitment strategy: Not reported

Length of follow-up: Mean follow-up of 12.9 years

Response rate and loss to follow-up: Participation rate varied by year from 74% to 88%

Eligible population: 25 to 74 years

Excluded populations: 91 subjects due to prevalent PD at the baseline and 464 subjects due to incomplete data. Exclusion of subjects with stroke or those who used neuroleptic drugs

Outcomes at 55 years or over

Outcomes: Parkinson’s disease

Outcome measurement: National Social Insurance Institution’s Register on special reimbursement for drug costs

Time: 1964 through December 31, 2002

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, body mass index, systolic blood pressure, total cholesterol, education, leisure-time physical activity, smoking, alcohol and tea consumption, and history of diabetes
Results, limitations, source of funding

**Number:** 102 men and 98 women

**Effect estimates:**

HR (CI 95%)

**Volume of coffee consumption**

**Men**

负担

0 1.00

1–4 0.55 (0.26–1.15)

5 0.41 (0.19–0.88)

P-trend 0.063

**Women**

负担

0 1.00

1–4 0.50 (0.22–1.12)

5 0.39 (0.17–0.89)

P trend 0.073

**Men and Women**

负担

0 1.00

1–4 0.53 (0.31–0.92)

5 0.40 (0.23–0.71)

P trend 0.005

**Volume of tea consumption**

**Men**

负担

0 1.00

1–4 1.06 (0.67–1.69)

5 0.55 (0.24–1.25)

P-trend 0.31

**Women**

负担

0 1.00

1–4 0.97 (0.62–1.52)

5 0.21 (0.05–0.90)

P trend 0.11

**Men and Women**

负担

0 1.00

1–4 1.02 (0.74–1.41)

5 0.41 (0.20–0.83)

P trend 0.038

**Significant trends:** Coffee drinking is associated with a lower risk of PD. More tea drinking is associated with a lower risk of PD

**Limitations:**

1. Self-report for data on coffee drinking
2. No data on possible changes of coffee drinking during the follow-up.
3. Lack of information about other caffeine sources in participants’ diet

**Source of funding:** The Finnish Parkinson Foundation and Special Research Funds of the Social Welfare and Health Board, City of Oulu

**Authors:** Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P

**Year:** 2005

**Citation:** International Journal of Obesity 29: 894-902

**Country of study:** Finland
**Aim of study:** Examine the association of physical activity and body mass index, and their combined effect, with the risk of total, cardiovascular disease and cancer mortality

**Study design:** Prospective follow-up study

**Quality score:** (+++, + or -): +

### Source population

**Number of people:** 52,058

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 47,212

**Characteristics:**

#### Physical activity (men)

**Low**
- Number of participants: 2132
- Age (y): 45.6
- BMI (kg/m²): 26.9
- Total cholesterol (mmol/l): 6.3
- Education level (y): 9.5
- Current smoking (%): 52.3
- BMI (%):
  - <18.5: 9.0
  - 18.5–24.9: 35.5
  - 25–29.9: 40.6
  - >30.0: 23.0

**Moderate**
- Number of participants: 9659
- Age (y): 44.3
- BMI (kg/m²): 26.3
- Total cholesterol (mmol/l): 6.2
- Education level (y): 9.5
- Current smoking (%): 43.4
- BMI (%):
  - <18.5: 0.3
  - 18.5–24.9: 39.2
  - 25–29.9: 45.9
  - >30.0: 14.6

**High**
- Number of participants: 10,737
- Age (y): 41.3
- BMI (kg/m²): 25.9
- Total cholesterol (mmol/l): 6.2
- Education level (y): 9.2
- Current smoking (%): 41.2
- BMI (%):
  - <18.5: 0.2
  - 18.5–24.9: 42.7
  - 25–29.9: 46.1
  - >30.0: 11.0

#### Physical activity (women)
### Exposures at midlife

**Relevant exposures:** Physical activity and smoking


**Measurement of exposure:** Self-administered questionnaire. Questions on physical activity included both occupational and leisure time physical activity

Occupational physical activity three categories: ‘light’; ‘moderate’; and ‘active’

Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily

**Location:** Kuopio and North Karelia provinces, Turku-Loimaa, Oulu

**Recruitment strategy:** Random selection

**Length of follow-up:** Mean follow-up of 17.7 y

**Response rate and loss to follow-up:** Participation rate varied by year from 74 to 88%

**Eligible population:** Born between 1913 and 1947

**Excluded populations:** Subjects previously diagnosed with coronary heart disease (n=1252), stroke

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### Participant Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of participants</th>
<th>Age (y)</th>
<th>BMI (kg/m²)</th>
<th>Total cholesterol (mmol/l)</th>
<th>Education level (y)</th>
<th>Current smoking (%)</th>
<th>BMI (%)</th>
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<tbody>
<tr>
<td>Low</td>
<td>3613</td>
<td>45.7</td>
<td>27.1</td>
<td>6.2</td>
<td>9.3</td>
<td>21.5</td>
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<td>&lt;18.5</td>
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<td>18.5–24.9</td>
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<td>&gt;30.0</td>
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<tr>
<td>Moderate</td>
<td>11782</td>
<td>44.2</td>
<td>25.9</td>
<td>6.1</td>
<td>9.5</td>
<td>17.9</td>
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<td></td>
<td>&lt;18.5</td>
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<td>18.5–24.9</td>
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<td>25–29.9</td>
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<td>&gt;30.0</td>
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<tr>
<td>High</td>
<td>9289</td>
<td>42.4</td>
<td>25.3</td>
<td>6.0</td>
<td>10.0</td>
<td>16.1</td>
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<td>&lt;18.5</td>
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<td>18.5–24.9</td>
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<td>25–29.9</td>
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<td>&gt;30.0</td>
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</tbody>
</table>
Outcomes at 55 years or over

Outcomes: Cardiovascular disease and cancer mortality
Outcome measurement: Computerised register linkage. Mortality data was obtained from Statistics Finland.
Time: Until the end of 2001

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age, study year, education, smoking, systolic blood pressure, total cholesterol, diabetes and physical activity or BMI

Results, limitations, source of funding

Number: 7394 deaths

Effect estimates:
Hazard ratios for total, cardiovascular and cancer mortality according to different levels of physical activity among Finnish men and women

Men
Total mortality
Low 1.00
Moderate 0.74 (0.68–0.81)
High 0.63 (0.58–0.70)
P-value for trend <0.001
Cardiovascular mortality
Low 1.00
Moderate 0.82 (0.72–0.93)
High 0.71 (0.62–0.82)
P-value for trend <0.001
Cancer mortality
Low 1.00
Moderate 0.83 (0.69–1.00)
High 0.79 (0.65–0.96)
P-value for trend 0.05

Women
Total mortality
Low 1.00
Moderate 0.64 (0.58–0.70)
High 0.58 (0.52–0.64)
P-value for trend <0.001
Cardiovascular mortality
Low 1.00
Moderate 0.62 (0.54–0.71)
High 0.55 (0.47–0.65)
P-value for trend <0.001
Cancer mortality
Low 1.00
Moderate 0.85 (0.71–1.01)
High 0.73 (0.60–0.88)
P-value for trend 0.005
Hazard ratios for total mortality according to different levels of BMI and smoking status among Finnish men and women

<table>
<thead>
<tr>
<th>Level of Smoking</th>
<th>BMI</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1.39 (0.34–5.62)</td>
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</tr>
<tr>
<td>18.5–24.9</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>1.03 (0.88–1.20)</td>
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<tr>
<td>&gt;30.0</td>
<td>1.78 (1.47–2.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Ex-smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1.87 (0.59–5.92)</td>
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<tr>
<td>18.5–24.9</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>1.03 (0.88–1.21)</td>
<td></td>
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<tr>
<td>&gt;30.0</td>
<td>1.48 (1.23–1.78)</td>
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</tr>
<tr>
<td><strong>Current smoker</strong></td>
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<tr>
<td>&lt;18.5</td>
<td>3.17 (1.99–5.06)</td>
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<tr>
<td>18.5–24.9</td>
<td>1.00</td>
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<tr>
<td>25–29.9</td>
<td>0.98 (0.90–1.06)</td>
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<tr>
<td>&gt;30.0</td>
<td>1.14 (1.01–1.28)</td>
<td></td>
</tr>
</tbody>
</table>

*P*-value for trend <0.001

**Significant trends:** Total mortality was increased both among lean and obese subjects. Statistically significant increased total mortality was observed among the obese men in all smoking categories. Regular physical activity and normal weight are both important indicators for a decreased risk of mortality from all causes, CVD and cancer.

**Limitations:**
1. Self-report of physical activity.
2. Changes to physical activity behaviours among the cohort members over time causes misclassification.
3. Standardised alcohol drinking data was not available across the survey.

**Source of funding:** Finnish Academy (grant numbers 46 558, 53 585, 204 274 and 205 657).

**Authors:** Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P

**Year:** 2004

**Citation:** European Heart Journal 25(24): 2212-9

**Country of study:** Finland

**Aim of study:** Assess joint associations of physical activity and different indicators of obesity with the risk of cardiovascular disease

**Study design:** Prospective follow-up study

**Quality score: (+++, + or -): +**

**Source population**

**Number of people:** 20,547

**Demographics:** Not reported

**Study (eligible and selected) population**
Number of people: 18,892

Characteristics:
Baseline characteristics according to physical activity levels among the Finnish population by sex

| Physical activity (men) | | | |
|------------------------|------------------|------------------|------------------|------------------|------------------|
| **Low**                | **Moderate**     | **High**         |
| Age (year)             | 47.9             | 48.0             | 42.9             |
| Body mass index        | 27.3             | 26.6             | 26.6             |
| Total cholesterol (mmol/l) | 5.8          | 5.7              | 5.7              |
| Education (year)       | 11.3             | 11.3             | 10.3             |
| Current smoking (%)    | 44.6             | 33.5             | 34.3             |
| Obesity (%)            | 26.7             | 17.9             | 14.1             |

<table>
<thead>
<tr>
<th>p-Value</th>
<th>Age (year)</th>
<th>Body mass index</th>
<th>Total cholesterol (mmol/l)</th>
<th>Education (year)</th>
<th>Current smoking (%)</th>
<th>Obesity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Physical activity (women)

| Physical activity (women) | | | |
|---------------------------|------------------|------------------|------------------|------------------|------------------|
| **Low**                   | **Moderate**     | **High**         |
| Age (year)                | 46.7             | 46.4             | 43.3             |
| Body mass index           | 27.0             | 25.9             | 25.7             |
| Total cholesterol (mmol/l) | 5.6          | 5.6              | 5.6              |
| Education (year)          | 11.3             | 11.3             | 11.3             |
| Current smoking (%)       | 25.4             | 20.3             | 20.3             |
| Obesity (%)               | 28.5             | 18.8             | 18.8             |

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
Education (year) 11.2
Current smoking (%) 19.6
Obesity (%) 13.8

p-Value
Age (year) <0.001
Body mass index <0.001
Total cholesterol (mmol/l) 0.4
Education (year) 0.04
Current smoking (%) <0.001
Obesity (%) <0.001

Exposures at midlife

Relevant exposures: Physical activity and smoking
Measurement of exposure: Self-administered questionnaire. Questions on physical activity included both occupational and leisure time physical activity
Occupational physical activity, three categories: ‘light’; ‘moderate’; and ‘active’
Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily
Location: Kuopio and North Karelia provinces, Turku-Loimaa, Oulu
Recruitment strategy: Random sample, stratified by area, gender and 10-year age group
Length of follow-up: Median follow-up time was 9.8 years
Response rate and loss to follow-up: Participation rate varied by year from 74 to 88%
Eligible population: Born between 1913 and 1947s
Excluded populations: Previously diagnosed with coronary heart disease (CHD) (n = 672), stroke (n = 390) and heart failure (n = 408), incomplete data on any required factors (n=185)

Outcomes at 55 years or over

Outcomes: Cardiovascular disease and cancer mortality
Outcome measurement: Finnish hospital discharge register for non-fatal outcomes (hospitalised myocardial infarction and stroke) and the mortality register by the Statistics Finland for fatal outcomes (cardiovascular death)
Time: Until the end of 2001

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age, study year, education, smoking, systolic blood pressure, total and HDL cholesterol, diabetes at baseline, and body mass index

Results, limitations, source of funding

Number: 818
Effect estimates:
Hazard ratios for risk of cardiovascular disease according to different levels of physical activity by sex
Men
Physical activity
Low 1.00
Moderate 0.72 (0.57–0.91)  
High 0.68 (0.52–0.88)  
P trend 0.007

**Women**  
Physical activity  
Low 1.00  
Moderate 0.73 (0.55–0.97)  
High 0.64 (0.45–0.89)  
P trend 0.02

**Significant trends:** Both regular physical activity and normal weight can reduce the risk of CVD

**Limitations:**  
1. Self-report of physical activity.  
2. Residual confounding.  
3. Data on several risk factors, such as triglycerides and apolipoprotein B, are not available.

**Source of funding:** Finnish Academy (Grants 46558, 53585, 204274, and 205657).

---

**Authors:** Hughes TF, Andel R, Small BJ, Borenstein AR, Mortimer JA, Wolk A... Gatz M  
**Year:** 2010  
**Citation:** American Journal of Geriatric Psychiatry 18(5): 413-20  
**Country of study:** Sweden  
**Aim of study:** Examine the association between fruit and vegetable consumption in midlife and risk for all types of dementia and AD  
**Study design:** Three population-based cohorts of like-sexed twin pairs  
**Quality score:** (+++, + or -): +

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**Source population**

**Number of people:** 5,692  
**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 3052  
**Characteristics:**  
No CHD event  
(n=2122)  
Age (years) 55.7 (3.2)  
Body-mass index (kg/m2) 26.2 (3.4)  
Current smokers (number [%]) 573 (27%)  
CHD event  
(n=136)  
Age (years) 56.34 (3.4)  
Body-mass index (kg/m2) 27.0 (3.4)  
Current smokers (number [%]) 52 (38%)  
**Location:** UK  
**Recruitment strategy:** Not reported. Parts registered with nine general medical practices  
**Length of follow-up:** 11 years  
**Response rate and loss to follow-up:** RR (77%)
**Eligible population:** Middle-aged men  
**Excluded populations:** Women

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### Exposures at midlife

**Relevant exposures:** Smoking  
**Time:** Not reported  
**Measurement of exposure:** Smoking habit divided into groups: smokers (any man who had smoked at least one cigarette daily on average for a year or more), ex-smokers (those who had smoked less than one cigarette a day), and never-smokers

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### Outcomes at 55 years or over

**Outcomes:** Coronary heart disease  
**Outcome measurement:** ECG  
**Time:** Not reported

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### Analysis

**Analysis strategy:** Cox's proportional hazards model  
**Confounders:** Practice and conventional risk factors by including age, BMI, cholesterol, triglyceride, fibrinogen, and systolic blood pressure

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### Results, limitations, source of funding

**Number:** 96 men had an acute myocardial infarction, 26 needed coronary artery surgery, and 14 had silent myocardial infarctions  
**Effect estimates:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td></td>
</tr>
<tr>
<td>E3/E3</td>
<td>1.49 (0.93–2.37)</td>
</tr>
<tr>
<td>E2+</td>
<td>0.47 (0.11–1.94)</td>
</tr>
<tr>
<td>E4+</td>
<td>0.74 (0.35–1.55)</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
</tr>
<tr>
<td>E3/E3</td>
<td>1.47 (0.87–2.51)</td>
</tr>
<tr>
<td>E2+</td>
<td>0.85 (0.30–2.43)</td>
</tr>
<tr>
<td>E4+</td>
<td>2.79 (1.59–4.91)</td>
</tr>
</tbody>
</table>

**Significant trends:** Smoking increases the risk of coronary heart disease in men of all genotypes but particularly in men carrying the E4 allele  
**Limitations:** CIs for the risk estimates are large  
**Source of funding:** British Medical Research Council, the US National Institute of Health (NHLBI 33014), and DuPont Pharma, Wilmington, USA. SEH, PJT, MB, and DMW are supported by the British Heart Foundation, and INMD is a Lister Institute fellow

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**Authors:** Humphries SE, Talmud PJ, Hawe E, Bolla M, Day IN, Miller GJ  
**Year:** 2001  
**Citation:** Lancet 358: 115-19  
**Country of study:** UK
**Aim of study:** Investigated whether the effect of smoking on coronary heart disease risk is affected by APOE genotype

**Study design:**

**Quality score:** (+, + or -): +

**Source population**

- **Number of people:** 3984
- **Demographics:** Not reported

**Study (eligible and selected) population**

- **Number of people:** 3052

**Characteristics**

- **No CHD event**
  - (n=2122)
  - Age (years) 55.7 (3.2)
  - Body-mass index (kg/m2) 26.2 (3.4)
  - Current smokers (number [%]) 573 (27%)

- **CHD event**
  - (n=136)
  - Age (years) 56.34 (3.4)
  - Body-mass index (kg/m2) 27.0 (3.4)
  - Current smokers (number [%]) 52 (38%)

**Location:** UK

**Recruitment strategy:** Not reported. Patients registered with nine general medical practices

**Length of follow-up:** 11 years

**Response rate and loss to follow-up:** RR (77%)

**Eligible population:** Middle-aged men

**Excluded populations:** Women

**Exposures at midlife**

- **Relevant exposures:** Smoking
- **Time:** Not reported
- **Measurement of exposure:** Smoking habit divided into groups: smokers (any man who had smoked at least one cigarette daily on average for a year or more), ex-smokers (those who had smoked less than one cigarette a day), and never-smokers

**Outcomes at 55 years or over**

- **Outcomes:** Coronary heart disease
- **Outcome measurement:** ECG
- **Time:** Not reported

**Analysis**

- **Analysis strategy:** Cox proportional hazards model
- **Confounders:** Practice and conventional risk factors by including age, BMI, cholesterol, triglyceride,
fibrinogen, and systolic blood pressure

Results, limitations, source of funding

Number: 96 men had an acute myocardial infarction, 26 needed coronary artery surgery, and 14 had silent myocardial infarctions

Effect estimates:
Adjusted hazard ratio (95% CI)
Never-smokers 1.00

Ex-smokers
E3/E3 1.49 (0.93–2.37)
E2+ 0.47 (0.11–1.94)
E4+ 0.74 (0.35–1.55)

Smokers
E3/E3 1.47 (0.87–2.51)
E2+ 0.85 (0.30–2.43)
E4+ 2.79 (1.59–4.91)

Significant trends: Smoking increases the risk of coronary heart disease in men of all genotypes but particularly in men carrying the E4 allele

Limitations:
Reviewer: CIs for the risk estimates are large

Source of funding: British Medical Research Council, the US National Institute of Health (NHLBI 33014), and DuPont Pharma, Wilmington, USA. SEH, PJT, MB, and DMW are supported by the British Heart Foundation, and INMD is a Lister Institute fellow

Authors: Inoue M, Hanaoka T, Sasazuki S, Sobue T, Tsugane S; JPHC Study Group
Year: 2004
Citation: Preventive Medicine 38(5): 516-22

Country of study: Japan
Aim of study: Obtain a relevant epidemiological index of the impact of tobacco smoking on the subsequent risk of cancer in Japan
Study design: Population-based prospective study
Quality score: (+++, + or -): +

Source population
Number of people: 116,896
Demographics: Not reported

Study (eligible and selected) population
Number of people: 92,792 subjects (44,521 men and 48,271 women)

Characteristics:
Men
Number of subjects 44,521
Proportion (%) Age (years) ± SD Alcohol drinking status (%)
none 52.9 ± 7.9 23.1

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

### Exposures at midlife

#### Relevant exposures: Alcohol

**Time:** 2001
Measurement of exposure: Alcohol consumption was represented in the questionnaire by the frequency of consumption during the past month and categorised into six classes: 1 day/month, 1 to 3 days/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, and every day.

Outcomes at 55 years or over

Outcomes: Cancer

Outcome measurement: Occurrence of cancer was identified by active patients’ notification from local major hospitals in the study area and data linkage with population-based cancer registries with permission. Death certificate information was used as a supplementary information source.

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age at baseline, study area, weekly ethanol intake, body mass index and green vegetable intake

Results, limitations, source of funding

Number: 4,922 newly diagnosed cancer cases (2,969 men and 1,953 women) and 2,132 cases of cancer deaths (1,411 men and 721 women)

Effect estimates:

Hazard ratios of cancer incidence and death according to smoking status in men

Total cancer incidence (n = 2,969)

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Number of cases</th>
<th>Hazard ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>488</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Former</td>
<td>777</td>
<td>1.37 (1.22 – 1.54)</td>
</tr>
<tr>
<td>Current</td>
<td>1704</td>
<td>1.64 (1.48 – 1.82)</td>
</tr>
<tr>
<td>Daily cigarette consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;19</td>
<td>483</td>
<td>1.48 (1.29 – 1.68)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>796</td>
<td>1.71 (1.52 – 1.93)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>425</td>
<td>1.72 (1.51 – 1.98)</td>
</tr>
<tr>
<td>trend</td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Pack-years

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>Number of cases</th>
<th>Hazard ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>190</td>
<td>1.26 (1.06 – 1.49)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>307</td>
<td>1.54 (1.33 – 1.79)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>474</td>
<td>1.76 (1.54 – 2.08)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>732</td>
<td>1.76 (1.56 – 1.98)</td>
</tr>
<tr>
<td>trend</td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Age started smoking

<table>
<thead>
<tr>
<th>Age started smoking</th>
<th>Number of cases</th>
<th>Hazard ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25</td>
<td>283</td>
<td>1.50 (1.28 – 1.74)</td>
</tr>
<tr>
<td>20 – 24</td>
<td>1001</td>
<td>1.62 (1.45 – 1.82)</td>
</tr>
<tr>
<td>&lt;19</td>
<td>420</td>
<td>1.81 (1.58 – 2.08)</td>
</tr>
<tr>
<td>trend</td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Total cancer death (n = 1,411)

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Number of cases</th>
<th>Hazard ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>223</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Former</td>
<td>351</td>
<td>1.35 (1.13 – 1.53)</td>
</tr>
<tr>
<td>Current</td>
<td>837</td>
<td>1.78 (1.53 – 2.09)</td>
</tr>
</tbody>
</table>

Daily cigarette consumption
<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1779</td>
<td>1.00</td>
<td>(reference)</td>
</tr>
<tr>
<td>Former</td>
<td>37</td>
<td>1.47</td>
<td>(1.05 – 2.05)</td>
</tr>
<tr>
<td>Current</td>
<td>137</td>
<td>1.46</td>
<td>(1.21 – 1.75)</td>
</tr>
</tbody>
</table>

Daily cigarette consumption

<table>
<thead>
<tr>
<th>Age started smoking</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>90</td>
<td>1.45</td>
<td>(1.16 – 1.81)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>32</td>
<td>1.42</td>
<td>(0.99 – 2.03)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>15</td>
<td>1.63</td>
<td>(0.98 – 2.72)</td>
</tr>
</tbody>
</table>

Pack-years

<table>
<thead>
<tr>
<th>Age started smoking</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>80</td>
<td>1.34</td>
<td>(1.06 – 1.69)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>30</td>
<td>1.78</td>
<td>(1.20 – 2.63)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>10</td>
<td>1.32</td>
<td>(0.71 – 2.47)</td>
</tr>
</tbody>
</table>

Trend n.s.

Total cancer death (n = 721)

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>656</td>
<td>1.00</td>
<td>(reference)</td>
</tr>
<tr>
<td>Former</td>
<td>10</td>
<td>1.03</td>
<td>(0.53 – 1.99)</td>
</tr>
<tr>
<td>Current</td>
<td>55</td>
<td>1.58</td>
<td>(1.18 – 2.12)</td>
</tr>
</tbody>
</table>

Daily cigarette consumption

<table>
<thead>
<tr>
<th>Age started smoking</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>32</td>
<td>1.36</td>
<td>(0.93 – 2.00)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>16</td>
<td>1.99</td>
<td>(1.20 – 3.31)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>7</td>
<td>1.96</td>
<td>(0.93 – 4.15)</td>
</tr>
</tbody>
</table>

Trend n.s.

Pack-years

<table>
<thead>
<tr>
<th>Age started smoking</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>23</td>
<td>1.08</td>
<td>(0.69 – 1.67)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>20</td>
<td>3.37</td>
<td>(2.09 – 5.44)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>7</td>
<td>2.18</td>
<td>(1.03 – 4.62)</td>
</tr>
</tbody>
</table>

Trend n.s.

Age started smoking

**Hazard ratios and of cancer incidence and death according to smoking status in women**
Significant trends: From the baseline questionnaire, 52.2% of men were current smokers and they presented a significantly increased HR of subsequent cancer occurrence compared with never-smokers [HR 1.64, 95% confidence interval (95% CI) 1.48–1.82]. Only 5.6% of women were current smokers and their HR also represented a significant increase (HR 1.46, 95% CI 1.21–1.75).

Limitations:
1. Could not fully evaluate the effect of passive smoking due to the lack of detailed information.
2. The proportion of female current smokers was 12–20% in two metropolitan areas.
3. This is very high compared with the 4–10% proportion included in the analysis


Authors: Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, Tsugane S; JPHC Study Group
Year: 2004
Citation: Stroke 35(5): 1124-9
Country of study: Japan
Aim of study: Examine impact of light-to-moderate alcohol consumption on risk of stroke
Study design: Prospective study
Quality score: (+++, ++ or -): +

Source population
Number of people: 27,063 men and 27,435 women
Demographics: Not reported

Study (eligible and selected) population
Number of people: 19 54
Characteristics:
Nondrinker
At risk 4063
Age, year 50.0
Smoking history, %
Never 30
Past 22
Current 48
Mean body mass index, kg/m2 23.5
History of hypertension, % 11
History of diabetes, % 6
College or higher education, % 13
Sport at leisure time 2:1 d/wk, % 15
Diet, n of frequencies
Fruit, d/wk 3.2
Green vegetables, d/wk 3.5
Yellow vegetables, d/wk 2.8
Other vegetables, d/wk 3.7
Fresh fish, d/wk 2.5
Dried fish, d/wk 1.7
Occasional Drinker

N at risk 2133
Age, year 48.9
Smoking history, %
Never 33
Past 20
Current 46
Mean body mass index, kg/m2 24.0
History of hypertension, % 11
History of diabetes, % 5
College or higher education, % 17
Sport at leisure time 2:1 d/wk, % 19
Diet, n of frequencies
Fruit, d/wk 3.1
Green vegetables, d/wk 3.6
Yellow vegetables, d/wk 2.8
Other vegetables, d/wk 3.5
Fresh fish, d/wk 2.4
Dried fish, d/wk 1.4

Location: Ninohe City and Karumai Town in the Ninohe PHC area of Iwate Prefecture, Yokote City and Omonogawa town in the Yokote PHC area of Akita, 8 districts of Minami-Saku County in the Saku PHC area of Nagano, Gushikawa City and Onna Village in the Ishikawa PHC area of Okinawa

Recruitment strategy: Self-administered questionnaire was distributed to all registered non-institutional residents in 1990

Length of follow-up: 10-year follow-up questionnaire (88% followed-up)

Response rate and loss to follow-up: 20,665 men (76%) initially. 11.0 years of follow-up from 1990 to the end of 2001. 10-year follow-up questionnaire (88% followed-up)

Eligible population: Men aged 40-59

Excluded populations: Data for women are not presented because of the small number of moderate-to-heavy drinkers in this group. Excluded men who reported stroke, myocardial infarction, angina pectoris, or cancer at baseline

Exposures at midlife

Relevant exposures: Alcohol consumption, diet

Time: 1990

Measurement of exposure: Alcohol consumption was represented in the questionnaire by the frequency of consumption during the past month and categorized into 6 classes: 1 day/month, 1 to 3 days/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, and every day

Frequency of weekly intake of 27 food items was reported under 4 categories: rarely, 1 to 2 days/week, 3 to 4 days/week, and almost every day

Outcomes at 55 years or over

Outcomes: Stroke

Outcome measurement: Registered a total of 25 hospitals facilitated by computer tomographic scan and/or magnetic resonance images in the 4 PHC areas. Medical records were reviewed by registered hospital workers or PHC physicians, blinded to the lifestyle data. Systematic search for death certificates was also undertaken.

Time: Stroke events were registered if they occurred after the date of return of the baseline questionnaire and before January 01, 2002.
## Analysis

**Analysis strategy:** Cox proportional hazards models

**Confounders:** Age, smoking status, body mass index, history of diabetes, education level, sports at leisure time, and dietary intake categories of fruits, total vegetables, and fish. History of hypertension as well as the confounding variables to examine the residual or independent effect of alcohol consumption on risk of stroke.

## Results, limitations, source of funding

**Number:** 694

**Effect estimates:**

### Non-drinker

- **Person-years 44 379**
- **Total stroke**
- **N of cases 133**
- **RR (95% CI)**
  - Further adjusted for hypertension: 1.09 (0.80–1.48)
  - Definite total stroke: N of cases 106
  - Further adjusted for hypertension: 0.95 (0.68–1.33)
  - Hemorrhagic stroke: N of cases 48
  - Further adjusted for hypertension: 1.48 (0.84–2.62)
  - Intraparenchymal hemorrhage: N of cases 38
  - Further adjusted for hypertension: 1.35 (0.73–2.51)
  - Subarachnoid hemorrhage: N of cases 10
  - Further adjusted for hypertension: 2.40 (0.52–11.0)
  - Ischemic stroke: N of cases 58
  - Further adjusted for hypertension: 0.72 (0.47–1.08)
  - Lacunar infarction: N of cases 27
  - Further adjusted for hypertension: 0.64 (0.36–1.16)
  - Large-artery occlusive infarction: N of cases 11
  - Further adjusted for hypertension: 0.73 (0.28–1.89)
  - Embolic infarction: N of cases 10
  - Further adjusted for hypertension: 0.58 (0.23–1.47)

### Occasional drinker

- **Person-years 23,532**
- **Total stroke**
- **N of cases 59**
- **Further adjusted for hypertension: 1.0**
- **Definite total stroke**
- **N of cases 53**
- **Further adjusted for hypertension: 1.0**
- **Hemorrhagic stroke**
- **N of cases 16**
- **Further adjusted for hypertension: 1.0**
- **Intraparenchymal hemorrhage**
- **N of cases 14**
Further adjusted for hypertension 1.0
Subarachnoid hemorrhage
N of cases 2
Further adjusted for hypertension 1.0
Ischemic stroke
N of cases 37
Further adjusted for hypertension 1.0
Lacunar infarction
N of cases 19
Further adjusted for hypertension 1.0
Large-artery occlusive infarction
N of cases 7
Further adjusted for hypertension 1.0
Embolic infarction
N of cases 8
Further adjusted for hypertension 1.0

Significant trends: There was a lower risk of ischemic stroke, more specifically lacunar infarction, a higher risk of hemorrhagic stroke, and no excess risk of total stroke among drinkers of 1 to 149 g ethanol per week compared with occasional drinkers; the respective multivariate RR (95% CI) was 0.59 (0.37 to 0.93), 0.43 (0.22 to 0.87), 1.73 (0.98 to 3.07), and 0.98 (0.71 to 1.36).

Limitations:
1. Residual uncontrolled confounding of the association between alcohol consumption and risk of stroke.
2. Data on hypertension and diabetes were self-reported.
3. Generalizability of findings to women

Source of funding: Cancer Research and for the Second Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor, and Welfare of Japan

Authors: Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE… Ascherio A
Year: 2009
Citation: American Journal of Clinical Nutrition 89(5): 1425-32
Country of study: Various
Aim of study: Associations between energy intake and risk of coronary heart disease
Study design: Follow-up study in which data from 11 American and European cohort studies were pooled
Quality score: (+++, + or -): +

Source population
Number of people: Not reported
Demographics: Not reported

Study (eligible and selected) population
Number of people: 344,696
Baseline cohort n by study: AHS F 13,430; M 9212; ARIC F 6481 M 5240; ATBC M 21,141; FMC F 2481 M 2712; GPS F 1666 M 1658; HPFS M 41,754; IIHD M 8272; IWHS F 30,180; NHSa F 81,415; NHSb F 61,706; VIP F 10,555, M 9521; WHS F 37,272
Characteristics:
Median age at baseline by study: AHS F 57 (39–76) M 55 (39–74); ARIC F 53 (47–62) M 54 (47–62)
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>Location: America and Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment strategy: Various</td>
</tr>
<tr>
<td>Length of follow-up: Various</td>
</tr>
<tr>
<td>Response rate and loss to follow-up: Various</td>
</tr>
<tr>
<td>Eligible population: Various</td>
</tr>
<tr>
<td>Excluded populations: Age &lt;35 y; history of cardiovascular disease, diabetes, or cancer (other than non-melanoma skin cancer); and extreme energy intake (i.e., &gt; or &lt; 3 SDs from the study-specific log-transformed mean energy intake of the population)</td>
</tr>
</tbody>
</table>

### Exposures at midlife

**Relevant exposures:** Dietary intake


**Measurement of exposure:** Food frequency questionnaire or a dietary history interview

### Outcomes at 55 years or over

**Outcomes:** Fatal coronary heart disease (including sudden death) and nonfatal myocardial infarction

**Outcome measurement:** Various

**Time:** Various

### Analysis

**Analysis strategy:** Cox proportional hazards regression

**Confounders:** Intakes of MUFAs, PUFAs, trans fatty acids, carbohydrates, and protein expressed as percentages of total energy intake and total energy intake, smoking, body mass index, physical activity, highest attained educational level, alcohol intake, history of hypertension, and energy-adjusted quintiles of fiber intake and cholesterol intake

### Results, limitations, source of funding

**Number:** 5249 coronary events and 2155 coronary deaths occurred

**Effect estimates:**

**Coronary events HR (95% CI) P-trend**
- MUFAs for SFAs 1.19 (1.00, 1.42) 0.32
- PUFAs for SFAs 0.87 (0.77, 0.97) 0.70
- CHs for SFAs 1.07 (1.01, 1.14) 0.51

**Coronary deaths HR (95% CI) P-trend**
- MUFAs for SFAs 1.01 (0.73, 1.41) 0.18
- PUFAs for SFAs 0.74 (0.61, 0.89) 0.40
- CHs for SFAs 0.96 (0.82, 1.13) 0.05

**Significant trends:** Replacing saturated fatty acid with polyunsaturated fatty acids rather than monounsaturated fatty acids or carbohydrates prevents CHD over a wide range of intakes

**Limitations:**
**Author:** None reported

**Reviewer:**
1. Diet relying on self-report.
2. Dietary change over time

**Source of funding:** Supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (grant R01 HL58904) and the Danish Heart Foundation (grants 02-1-9F-7-22961 and 02-2-9-8-22010). The establishment of the Research Unit for Dietary Studies was financed by the Female Researchers in Joint Action program from the Danish Medical Research Council.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Janzon E, Hedblad B, Berglund G, Engström G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year:</strong></td>
<td>2004</td>
</tr>
<tr>
<td><strong>Citation:</strong></td>
<td>Journal of Internal Medicine 256(2): 111-8</td>
</tr>
<tr>
<td><strong>Country of study:</strong></td>
<td>Sweden</td>
</tr>
<tr>
<td><strong>Aim of study:</strong></td>
<td>Explored how the risk of myocardial infarction in current and former smokers is modified by other cardiovascular risk factors</td>
</tr>
<tr>
<td><strong>Study design:</strong></td>
<td>Cohort study</td>
</tr>
<tr>
<td><strong>Quality score:</strong></td>
<td>(+)</td>
</tr>
</tbody>
</table>

**Source population**

**Number of people:** 10902

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 10,619

**Characteristics:**
**Never-smokers (n = 4848)**
- Age (year) 50.5 ± 6.6 (28.3–57.6)
- BMI (kg m$^2$) 25 ± 4
- Occupation, low (%) 77.5
- Civil status, married (%) 77.4

**Ex-smokers (n = 2035)**
- Age (year) 49.8 ± 7.3 (28.2–57.2)
- BMI (kg m$^2$) 24 ± 4
- Occupation, low (%) 72.1
- Civil status, married (%) 73.2

**Current smokers (n = 3738)**
- Age (year) 48.3 ± 8.2 (28.2–56.9)
- BMI (kg m$^2$) 23 ± 4
- Occupation, low (%) 81.4
- Civil status, married (%) 64.6

**Location:** Malmo, Sweden

**Recruitment strategy:** Not reported

**Length of follow-up:** Mean follow-up was 14.0 ± 4.5 years (range 0.5–21.9 years)

**Response rate and loss to follow-up:** Overall attendance rate was 71%

**Eligible population:** Women 28–58 years old

**Excluded populations:** Exclude women with a history of MI or stroke (n=176)
### Exposures at midlife

**Relevant exposures:** Smoking  
**Time:** Not reported  
**Measurement of exposure:** Self-administered questionnaire. Women asked ‘Are you a smoker?’ or ‘Are you a daily smoker?’ Women who reported that they had stopped smoking were considered to be ex-smokers. Women who did not report any history of smoking were never-smokers.  
Tobacco consumption amongst daily smokers was classified as low consumption (<10 cigarettes day), medium consumption (>10, <20 cigarettes day) and high consumption (>20 cigarettes day).

### Outcomes at 55 years or over

**Outcomes:** Myocardial infarction  
**Outcome measurement:** Cases of nonfatal MI were retrieved from the Malmo Myocardial Infarction register and from the Swedish Myocardial Infarction register  
**Time:** All subjects were followed from the baseline examination until death, cardiac event, emigration out of Sweden, or to 31 December 1998

### Analysis

**Analysis strategy:** Cox proportional hazards model  
**Confounders:** Systolic blood pressure, age, BMI, cholesterol, diabetes, occupation, marital status and HRT

### Results, limitations, source of funding

**Number:** 228  
**Effect estimates:**  
*RR (CI 95%)*  
- **Never-smoker**  
  - Normotension 1.0  
  - Hypertension 2.4 (1.4–4.3)  
  - Normal cholesterol 1.0  
  - High cholesterol 1.8 (1.02–3.2)  
  - No diabetes 1.0  
  - Diabetes 8.8 (4.4–17.4)  
- **Ex-smoker**  
  - Normotension 1.8 (0.99–3.2)  
  - Hypertension 2.7 (1.1–6.0)  
  - Normal cholesterol 1.6 (0.9–2.9)  
  - High cholesterol 2.4 (1.2–5.0)  
  - No diabetes 1.7 (1.01–2.8)  
  - Diabetes 7.8 (2.4–25.6)  
- **Current smoker**  
  - Normotension 5.3 (3.3–8.1)  
  - Hypertension 12.2 (7.5–19.8)  
  - Normal cholesterol 5.6 (3.6–8.6)  
  - High cholesterol 8.2 (5.2–12.9)  
  - No diabetes 6.0 (4.1–8.6)  
  - Diabetes 19.0 (10.2–35.4)  

**Significant trends:** Smoking is a major risk factor for MI, however the risk varies widely between...
women with similar tobacco consumption. There was a statistically significant interaction between smoking and hypertension for the risk of cardiac events.

**Limitations:**

**Author:**

1. Crude categorisation of occupation.
2. No question about occasional smoking.
3. Misclassification of occasional smokers as never-smokers.
4. No information on age of initiation of smoking.
5. No information on smoking cessation during follow-up.

**Reviewer:** Self-reported exposure

**Source of funding:** Swedish Council for Work Life and Social Research

---

**Authors:** Johnsen NF, Christensen J, Thomsen BL, Olsen A, Loft S, Overvad K, Tjønneland A

**Year:** 2006

**Citation:** European Journal of Epidemiology 21(12): 877-84

**Country of study:** Denmark

**Aim of study:** Investigate the effects of occupational activity and leisure time activity on incident colon cancer risk

**Study design:** Prospective cohort

**Quality score:** (+++, + or -): -

### Source population

**Number of people:** 160,725

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 57,053

**Characteristics:**

**Women**

- Age (years) 56 (50–64)
- BMI 25 (20–34)
- Education (years)
- < 7 8751 (31)
- 8–10 14,296 (50)
- >10 5309
- Smoking
- Never 12,460 (44)
- Former 6716 (24)
- Present 9180 (32)
- Alcohol (g/day) 27,764 (97)
- Total number of Leisure time physical activity 28,356 (100)
- Occupational physical activity
- Sitting 9248 (33)
- Standing 4964 (18)
- Manual 6219 (22)
- Not working 7925 (28)

**Men**

- Age (years) 56 (50–64)
<table>
<thead>
<tr>
<th>BMI 26 (21–33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 9000 (34)</td>
</tr>
<tr>
<td>8–10 10,894 (42)</td>
</tr>
<tr>
<td>&gt;10 6228 (24)</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Never 6764 (26)</td>
</tr>
<tr>
<td>Former 9104 (35)</td>
</tr>
<tr>
<td>Present 10,254 (39)</td>
</tr>
<tr>
<td>Alcohol (g/day) 25,787 (98)</td>
</tr>
<tr>
<td>Total number of Leisure time physical activity 26,064 (100)</td>
</tr>
<tr>
<td>Occupational physical activity</td>
</tr>
<tr>
<td>Sitting 10,369 (40)</td>
</tr>
<tr>
<td>Standing 4417 (17)</td>
</tr>
<tr>
<td>Manual) 7282 (28)</td>
</tr>
<tr>
<td>Not working 4054 (16)</td>
</tr>
</tbody>
</table>

**Location:** Copenhagen and Aarhus, Denmark

**Recruitment strategy:** Not reported

**Length of follow-up:** Mean follow-up of 7.6 years

**Response rate and loss to follow-up:** Less than 0.8% of the participants were completely lost to follow-up

**Eligible population:** Danish middle-aged population

**Excluded populations:** -

### Exposures at midlife

**Relevant exposures:** Smoking, daily intake of dietary fibre, red meat, alcohol and dietary fat

**Time:** 1993-1997

**Measurement of exposure:** Self-report questionnaire

### Outcomes at 55 years or over

**Outcomes:** Colon cancer

**Outcome measurement:** Danish Cancer Registry

**Time:** Date of diagnosis of any cancer (except for non-melanoma skin cancer), date of death or emigration, or December 31, 2003, whichever came first

### Analysis

**Analysis strategy:** Cox proportional hazards model

**Confounders:** Model 1) participation in each of the six activities, occupational physical activity (four categories), BMI, education, NSAID, present use of HRT, smoking and intake of total energy, fat, dietary fibre, red meat and alcohol.

Model 2) occupational activity, BMI, education, NSAID, present use of HRT, smoking and intake of total energy, fat, dietary fibre, red meat and alcohol

### Results, limitations, source of funding

**Number:** 140 women and 157 men were diagnosed with colon cancer

**Effect estimates:**

Incidence rate ratios for colon cancer per additional hour/week of six types of leisure time physical activity
**Incidence rate ratios for colon cancer for active compared to non-active for six types of leisure time physical activity**

<table>
<thead>
<tr>
<th>Activity</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>MET-score (per 10 units)</td>
<td>1.00 (0.96–1.04)</td>
</tr>
<tr>
<td>Sports (per one hour)</td>
<td>1.03 (0.93–1.14)</td>
</tr>
<tr>
<td>Cycling (per one hour)</td>
<td>1.00 (0.94–1.06)</td>
</tr>
<tr>
<td>Walking (per one hour)</td>
<td>0.99 (0.95–1.03)</td>
</tr>
<tr>
<td>Gardening (per one hour)</td>
<td>0.95 (0.87–1.03)</td>
</tr>
<tr>
<td>Housework (per one hour)</td>
<td>1.01 (0.98–1.03)</td>
</tr>
<tr>
<td>Do-it-yourself (per one hour)</td>
<td>1.00 (0.91–1.11)</td>
</tr>
<tr>
<td><strong>Men (cases = 157)</strong></td>
<td></td>
</tr>
<tr>
<td>MET-score (per 10 units)</td>
<td>0.97 (0.93–1.01)</td>
</tr>
<tr>
<td>Sports (per one hour)</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>Cycling (per one hour)</td>
<td>1.00 (0.94–1.07)</td>
</tr>
<tr>
<td>Walking (per one hour)</td>
<td>1.01 (0.98–1.04)</td>
</tr>
<tr>
<td>Gardening (per one hour)</td>
<td>0.98 (0.92–1.04)</td>
</tr>
<tr>
<td>Housework (per one hour)</td>
<td>0.95 (0.89–1.02)</td>
</tr>
<tr>
<td>Do-it-yourself (per one hour)</td>
<td>0.97 (0.92–1.02)</td>
</tr>
</tbody>
</table>

Significant trends: No associations were found between risk of colon cancer and occupational activity, MET-hours per week of total leisure time activity, residuals from a regression of each activity on the total MET-hours or the time spent on any of the six types of leisure time activities.

Limitations:
1. Not all the aspects of activity (type, frequency, duration and intensity) were measured.
2. Self-administered questionnaires.
3. Study is based on persons of a relatively high age.
4. Adding random variation by applying an assumed intensity to the included activities.

Source of funding: Danish Medical Research Council and the Danish Cancer Society.

---

Authors: Kåreholt I, Lennartsson C, Gatz M, Parker MG
Year: 2011
Citation: International Journal of Geriatric Psychiatry 26(1): 65–74
Country of study: Sweden
### Aim of study
Examine the relationship between leisure time activity and cognition over two decades.

### Study design
Longitudinal

### Quality score
(+++, + or -): +

## Source population

<table>
<thead>
<tr>
<th>Number of people</th>
<th>7483</th>
</tr>
</thead>
</table>

### Demographics
Not reported

## Study (eligible and selected) population

<table>
<thead>
<tr>
<th>Number of people</th>
<th>1,643</th>
</tr>
</thead>
</table>

### Characteristics:

#### Age
- Range 46–75 years
- Mean 57.4

#### Age at FU
- Range 69–98
- Mean 80.2

#### Sex
- % Women 58.7
- Men 41.3

#### Mobility problems
- 0 70.8
- 1 13.8
- 2 8.8
- 3 6.6

#### Employment status
- Employed 70.1
- Unemployed 29.9

#### Years of education
- Range 0–29
- Mean 8.4

#### Adult socioeconomic status
- % Blue-collar (unskilled) 33.4
- Blue-collar (skilled) 21.1
- Lower white-collar 19.5
- Intermediate and upper white-collar 26.0

#### Childhood socioeconomic status
- % Blue-collar (unskilled) 24.7
- Blue-collar (skilled) 35.1
- Lower white-collar 28.4
- Intermediate and upper white-collar 11.0
- Missing and unclassifiable 0.9

#### Smoking
- %
- No 74.6
- Yes, 1–10 cigarettes 12.8
- Yes >10 cigarettes 12.5

#### Alcohol drinking
- %
- No 24.4
- Moderate 44.9
- >Moderate 30.7

### Location
Sweden
<table>
<thead>
<tr>
<th>Recruitment strategy:</th>
<th>Randomised recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of follow-up:</td>
<td>From 1968 to 1992 was 24 years, from 1981 to 2002 was 21 years, and from 1981 to 2004 was 23 years (average 22.8 years)</td>
</tr>
<tr>
<td>Response rate and loss to follow-up:</td>
<td>‘Has a low nonresponse rate’. Number not provided</td>
</tr>
<tr>
<td>Eligible population:</td>
<td>Not reported</td>
</tr>
<tr>
<td>Excluded populations:</td>
<td>1871 persons aged 56–75 were interviewed in 1968. Of these, 534 were still alive in 1992 and cognitive data could be collected for 430 individuals. From the 1981 baseline survey, cognitive data could be collected for 416 individuals in 2002 and for 797 individuals in 2004.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposures at midlife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant exposures:</td>
</tr>
<tr>
<td>Time:</td>
</tr>
<tr>
<td>Measurement of exposure:</td>
</tr>
<tr>
<td>Alcohol drinking:</td>
</tr>
<tr>
<td>Political activities:</td>
</tr>
<tr>
<td>Organizational activities:</td>
</tr>
<tr>
<td>Mental activities:</td>
</tr>
<tr>
<td>Socio-cultural activities:</td>
</tr>
<tr>
<td>Social activities:</td>
</tr>
<tr>
<td>Physical activities:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes:</td>
</tr>
<tr>
<td>Outcome measurement:</td>
</tr>
<tr>
<td>Time:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis strategy:</td>
</tr>
<tr>
<td>Confounders:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results, limitations, source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number:</td>
</tr>
<tr>
<td>Effect estimates:</td>
</tr>
<tr>
<td>Political</td>
</tr>
<tr>
<td>Mental</td>
</tr>
<tr>
<td>Socio-cultural</td>
</tr>
</tbody>
</table>
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

### Social 0.01 0.904
Organizational -0.03 0.628
Physical, all 0.21 0.05 0.375
Men -0.06 0.477
Women 0.14 0.055

**Significant trends:** Significant association between later cognition and earlier political, mental, and socio-cultural activities. Physical activities had a significant association with cognition only among women.

**Limitations:**

**Author:**
1. Low level for moderate drinking.
2. Absence of a baseline measure of cognition

**Reviewer:**
1. Unclear reporting of study design and process.
2. Do not report how many people developed cognitive issues

**Source of funding:** Swedish Research Council (2007-1947) obtained by Marti G. Parker and by the Zenith award from the Alzheimer’s Association (ZEN-02-3895) to Margaret Gatz

---

**Authors:** Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S; JPHC Study Group

**Year:** 2009

**Citation:** Endocrinology Journal 56(3): 459-68

**Country of study:** Japan

**Aim of study:** Assess association between psychological factors and the onset of diabetes

**Study design:** Community-based, prospective cohort study

**Quality score:** (+++, + or -): +

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**Source population**

**Number of people:** 95,373

**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 55,826

**Characteristics:** J and K cells

**Location:** Ninohe, Yokote, Saku, Chubu, and Katsushika. Mito, Nagaoka, Chuohigashi, Kamigoto, Miyako and Suita

**Recruitment strategy:** Not reported

**Length of follow-up:** 10 years

**Response rate and loss to follow-up:** 75%, 32,369 men and 39,344 women

**Eligible population:** Middle-aged Japanese adults 40-69 years

**Excluded populations:** Individuals who had; cardiovascular disease, chronic liver disease, kidney disease or any type of cancer (n=4,515), also excluded any subjects with diabetes at baseline (n=3,092). Individuals who had missing baseline data for any of the exposure parameters (n=9,256). Individuals with a body mass index of less than 14 or more than 40 (n=741).

---

**Exposures at midlife**
### Relevant exposures
- Behaviours, diet

### Time
- 1990-1993

### Measurement of exposure
- Self-administered questionnaire, food frequency questionnaire

Mental stress was assessed based on three levels of response (low, medium and high) to the question, 'How much stress do you feel in your daily life?'

Type A behavioural patterns: competitive drive, speed and impatience, aggressiveness and irritability

### Outcomes at 55 years or over

#### Outcomes
- Diagnosed diabetes

#### Outcome measurement
- 94% of the self-report cases of diagnosed diabetes were confirmed by medical records

#### Time
- 5- or 10-years after wave 1

### Analysis

#### Analysis strategy
- Logistic regression

#### Confounders
- Age, body mass index, smoking status, alcohol intake, family history of diabetes, physical activity, history of hypertension, and coffee consumption

### Results, limitations, source of funding

#### Number
- 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women

#### Effect estimates:

##### Odds ratios for the 10-year incidences of diabetes mellitus according to perceived mental stress

**Men**
- Low Perceived Mental Stress (reference)
- Medium Perceived Mental Stress 1.19 (1.01-1.40)
- High Perceived Mental Stress 1.36 (1.13-1.63)
  - p for trend 0.001

**Women**
- Low Perceived Mental Stress (reference)
- Medium Perceived Mental Stress 1.12 (0.94-1.34)
- High Perceived Mental Stress 1.22 (0.98-1.51)
  - p for trend 0.080

##### Odds ratios for the 10-year incidences of diabetes mellitus according to levels of Type A behaviour pattern index

**Men**
- 4 (reference)
- 3 1.06 (0.91-1.22)
- 2 1.00 (0.84-1.20)
- 1 1.09 (0.94-1.27)
  - P for trend 0.381

**Women**
- 4 (reference)
- 3 0.93 (0.79-1.09)
- 2 1.03 (0.85-1.26)
- 1 1.22 (1.01-1.47)
  - P for trend 0.031
### Odds ratios (95%CI) for the 10-year incidences of diabetes mellitus according to levels of constituent items of Type A behaviour pattern index

**Men**
- Low (reference)
- Impatience (reference)
- Irritability (reference)
- Aggressiveness (reference)
- Competitiveness (reference)

<table>
<thead>
<tr>
<th>Level</th>
<th>Impatience</th>
<th>Irritability</th>
<th>Aggressiveness</th>
<th>Competitiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>1.01</td>
<td>1.08</td>
<td>1.05</td>
<td>0.87</td>
</tr>
<tr>
<td>High</td>
<td>1.02</td>
<td>1.14</td>
<td>1.12</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**Women**
- Low (reference)
- Impatience (reference)
- Irritability (reference)
- Aggressiveness (reference)
- Competitiveness (reference)

<table>
<thead>
<tr>
<th>Level</th>
<th>Impatience</th>
<th>Irritability</th>
<th>Aggressiveness</th>
<th>Competitiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>1.05</td>
<td>0.99</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td>High</td>
<td>1.23</td>
<td>1.16</td>
<td>1.08</td>
<td>1.01</td>
</tr>
</tbody>
</table>

### Odds ratios (95% CI) for the 10-year incidences of diabetes mellitus according to coffee consumption

**Men**
- Almost never (reference)
- 1-2 days per week 0.93 (0.80-1.08)
- 3-4 days per week 0.84 (0.71-1.01)
- 1-2 cups/day 0.84 (0.73-0.97)
- 3-4 cups/day 0.83 (0.68-1.02)
- >5 cup/day 0.82 (0.60-1.12)

p for trend 0.006

**Women**
- Almost never (reference)
- 1-2 days per week 0.90 (0.76-1.06)
- 3-4 days per week 0.95 (0.77-1.17)
- 1-2 cups/day 0.81 (0.69-0.96)
- 3-4 cups/day 0.82 (0.45-0.84)
- >5 cup/day 0.40 (0.20-0.78)

p for trend <0.00

**Significant trends:** The risk of diabetes increased with an increasing stress level, especially among...
This association remained almost unchanged after adjustments for known risk factors of diabetes, type A and hours of sleep.

**Limitations:**
1. Assessment of diabetes mellitus was based on the results of a self-reported questionnaire.
2. Perceived mental stress was assessed based on a single simple question


**Authors:** Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Hercberg S, Galan P
**Year:** 2012
**Citation:** Journal of Nutrition 142(5): 909-15
**Country of study:** France
**Aim of study:** Evaluated association between empirically derived dietary patterns in midlife and cognitive performance
**Study design:** Randomized, double-blind, placebo-controlled, primary prevention trial
**Quality score: (+, + or -):** -

**Source population**

<table>
<thead>
<tr>
<th>Number of people</th>
<th>12,741</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Study (eligible and selected) population**

<table>
<thead>
<tr>
<th>Number of people</th>
<th>3054</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Cells J &amp; K</td>
</tr>
<tr>
<td>Location</td>
<td>France</td>
</tr>
<tr>
<td>Recruitment strategy</td>
<td>Not reported. At end of trial phase, the participants were invited for an additional 2-y follow-up for the SU.VI.MAX 2 observational study</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>13.4 ± 0.7 y</td>
</tr>
<tr>
<td>Response rate and loss to follow-up</td>
<td>Not reported</td>
</tr>
<tr>
<td>Eligible population</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Excluded populations:** Younger than 45 y at baseline (n = 1267), those with missing neuropsychological test scores (n = 1136), those with fewer than 3 dietary records during the first 2 y of follow-up (n = 1085), or those with missing data on any of the covariates (n = 308). Dietary records that reported <100 or >6000 kcal/d were excluded; men reporting <800 kcal/d and women reporting <500 kcal/d in 60% or more of their dietary records were also excluded.

**Exposures at midlife**

<table>
<thead>
<tr>
<th>Relevant exposures</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>1995–1996</td>
</tr>
<tr>
<td>Measurement of exposure</td>
<td>24-h dietary records. Food and nutrient intakes were based on the reported mean intakes across all 24-h records</td>
</tr>
</tbody>
</table>
### Outcomes at 55 years or over

**Outcomes:** Cognitive performance  
**Outcome measurement:** Neuropsychological tests  
**Time:** 2007–2009

### Analysis

**Analysis strategy:** ANCOVA  
**Confounders:** Age, gender, intervention group, education, alcohol and energy intake, number of dietary records, physical activity, BMI, tobacco use, self-reported memory troubles, diabetes, hypertension, follow-up time, history of cardiovascular disease, and depressive symptoms and, for women, menopausal status and hormone therapy use.

### Results, limitations, source of funding

**Number:** 3054  
**Effect estimates:**

#### Healthy pattern

**Global cognitive function**  
Q1 48.9 ± 0.7  
Q2 49.4 ± 0.7  
Q3 50.8 ± 0.7  
Q4 50.1 ± 0.7  
P2 0.001  

**Verbal memory**  
Q1 49.1 ± 0.7  
Q2 49.5 ± 0.7  
Q3 50.6 ± 0.7  
Q4 50.3 ± 0.7  
P2 0.01

**Executive functioning**  
Q1 49.3 ± 0.7  
Q2 49.6 ± 0.7  
Q3 50.6 ± 0.7  
Q4 49.8 ± 0.7  
P2 0.13

#### Traditional pattern

**Global cognitive function**  
Q1 50.1 ± 0.7  
Q2 49.5 ± 0.7  
Q3 49.6 ± 0.7  
Q4 49.9 ± 0.7  
P2 0.68  

**Verbal memory**  
Q1 50.2 ± 0.7  
Q2 49.8 ± 0.7  
Q3 49.6 ± 0.8  
Q4 49.7 ± 0.7  
P2 0.32  

**Executive functioning**  
Q1 49.9 ± 0.7
Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Significant trends:** A healthy and a traditional DP were identified. In the multivariate model, the healthy pattern was associated with better global cognitive function (50.1 ± 0.7 vs. 48.9 ± 0.7; P-trend = 0.001) and verbal memory (49.7 ± 0.4 vs. 48.7 ± 0.4; P-trend = 0.01).

**Limitations:**

**Author**
1. Cognitive evaluation was not available at baseline.
2. Empirically derived DP showed some limitations regarding food groupings, factor selection, and labelling.
3. Sample likely included the more compliant or health-conscious participants.
4. Residual confounding

**Reviewer**
1. Unclear reporting.
2. From intervention study but little detail of impact of intervention on groups

**Source of funding:** French National Research Agency (no. ANR-05-PNRA-010), the French Ministry of Health, Mederic, Sodexo, Ipsen, MGEN, and Pierre Fabre

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**Authors:** Khalili P, Nilsson PM, Nilsson JA, Berglund G

**Year:** 2002

**Citation:** Journal of Hypertension 20(9): 1759-64

**Country of study:** Sweden

**Aim of study:** Examine to what degree smoking habits modulate the relationship between systolic blood pressure and risk for cardiovascular morbidity and mortality

**Study design:** Population-based screening study

**Quality score:** (+++, + or -): +

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**Source population**

**Number of people:** 22,444

**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** Not reported

**Characteristics:**

Q1
n 3249
Age (years) 42.2
Smoking habits* (%) 59.0/41.0
BMI (kg/m2) 23 (2.8)

Q2
n 6846
Age (years) 42.6
Smoking habits* (%) 51.9/48.1
BMI (kg/m2) 24 (2.9)

Q3
<table>
<thead>
<tr>
<th>n</th>
<th>Age (years)</th>
<th>Smoking habits* (%)</th>
<th>BMI (kg/m²)</th>
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<tbody>
<tr>
<td>2272</td>
<td>43.0</td>
<td>50.0/50.0</td>
<td>25 (3.2)</td>
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<td>4947</td>
<td>44.0</td>
<td>45.9/54.1</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>4215</td>
<td>46.0</td>
<td>43.9/56.1</td>
<td>26 (3.6)</td>
</tr>
<tr>
<td>915</td>
<td>48.4</td>
<td>38.9/61.1</td>
<td>27 (3.9)</td>
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</tbody>
</table>

**Location:** Malmo, Sweden

**Recruitment strategy:** Not reported

**Length of follow-up:** Averaged a mean of 17 years

**Response rate and loss to follow-up:** Mean attendance rate 71%

**Eligible population:** Middle-aged men

**Excluded populations:**

### Exposures at midlife

**Relevant exposures:** Smoking

**Time:** Not reported

**Measurement of exposure:** Self-reported questionnaire

### Outcomes at 55 years or over

**Outcomes:** Cardiovascular events

**Outcome measurement:** Local and national registers. A first cardiovascular event was defined as the first recorded cardiovascular event during follow-up, including fatal and non-fatal cases of ischaemic heart disease and cerebrovascular disease

**Time:** End of 1996

### Analysis

**Analysis strategy:** Calculated using direct standardization and expressed as risk ratios with 95% confidence intervals

**Confounders:** Age, systolic blood pressure, diastolic blood pressure, body mass index, cholesterol, triglycerides, or history of diabetes

### Results, limitations, source of funding

**Number:** Not reported
**Effect estimates:**

Morbidity RR (95%CI) between smokers and non-smokers
Q1 1.9 (1.5–2.4)
Q2 2.1 (1.8–2.5)
Q3 2.3 (1.8–2.9)
Q4 1.8 (1.5–2.1)
Q5 1.7 (1.5–2.0)
tHTs 1.4 (1.1–1.8).

Mortality RR (95%CI) between smokers and non-smokers
Q1 1.8 (1.4–2.3)
Q2 2.5 (2.1–3.0)
Q3 2.7 (2.0–3.6)
Q4 2.2 (1.9–2.7)
Q5 2.5 (2.1–2.9)
tHTs 1.8 (1.3–2.5)

**Significant trends:** Increasing systolic blood pressure levels is associated with an increasing risk of future cardiovascular events and mortality, an association modified by smoking habits. Treated hypertensive patients were at increased risk in spite of antihypertensive drugs

**Limitations:**

**Author:** Unclear reporting

**Reviewer:** Not reported

**Source of funding:** Swedish Society of Medicine

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**Authors:** Kimm H, Lee PH, Shin YJ, Park KS, Jo J, Lee Y... Jee SH

**Year:** 2011

**Citation:** Archives of Gerontology and Geriatrics 52(3): e117-22

**Country of study:** Republic of Korea

**Aim of study:** Determine the effects of vascular risk factors, such as blood pressure, diabetes and smoking in the mid-life or the late-life on dementia risk

**Study design:** Prospective cohort study

**Quality score:** (+++, + or -): +

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**Source population**

**Number of people:** 1,329,525

**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 848,505

**Characteristics:**

**Men**

Number 490,445

Age at enrolment (year) 51.9 ±8.7

BMI (kg/m²) 23.3± 2.3

Alcohol drinking (g/day) 15.4 ± 32.2

Diabetes 6.8

Hypertension 42.8

Smoking status
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
### Results, limitations, source of funding

**Number:** 3252

**Effect estimates:**

HR (95% CI)

**Men**

**AD**
- Diabetes 1.6 (1.3–2.0)
- Ex-smokers 1.0 (0.8–1.2)
- Current smokers 1.1 (0.9–3.4)
- Pre-hypertension 1.1 (0.9–1.4)
- Stage 1 hypertension 1.3 (1.0–1.6)
- Stage 2 hypertension 1.4 (1.1–1.8)
- Borderline cholesterol 1.2 (1.0–1.4)
- High cholesterol 1.2 (1.0–1.5)

**VaD**
- Diabetes 2.0 (1.5–2.8)
- Ex-smokers 0.9 (0.7–1.3)
- Current smokers 1.1 (0.8–1.5)
- Pre-hypertension 1.0 (0.7–1.5)
- Stage 1 hypertension 1.7 (1.2–2.5)
- Stage 2 hypertension 2.6 (1.7–3.8)
- Borderline cholesterol 1.3 (1.0–1.6)
- High cholesterol 1.1 (0.8–1.6)

**Unspec.**
- Diabetes 1.3 (1.0–1.7)
- Ex-smokers 0.9 (0.7–1.2)
- Current smokers 1.2 (1.0–1.5)
- Pre-hypertension 1.0 (0.8–1.3)
- Stage 1 hypertension 1.2 (0.9–1.5)
- Stage 2 hypertension 1.5 (1.1–2.0)
- Borderline cholesterol 0.9 (0.7–1.0)
- High cholesterol 1.0 (0.8–1.3)

**All**
- Diabetes 1.6 (1.3–1.8)
- Ex-smokers 1.0 (0.8–1.1)
- Current smokers 1.2 (1.0–1.3)
- Pre-hypertension 1.0 (0.9–1.2)
- Stage 1 hypertension 1.3 (1.1–1.5)
- Stage 2 hypertension 1.6 (1.4–1.9)
- Borderline cholesterol 1.0 (0.9–1.2)
- High cholesterol 1.1 (0.9–1.3)

**Women**

**AD**
- Diabetes 1.4 (1.1–1.7)
- Ex-smokers 1.2 (0.9–1.5)
- Current smokers 1.3 (1.1–1.5)
- Pre-hypertension 1.1 (0.9–1.3)
- Stage 1 hypertension 1.1 (0.9–1.3)
- Stage 2 hypertension 1.2 (0.9–1.4)
- Borderline cholesterol 1.0 (0.9–1.2)
- High cholesterol 1.1 (0.9–1.3)

**VaD**
Diabetes  2.8(2.0–3.9)
Ex-smokers  0.9(0.5–1.5)
Current smokers  1.5(1.1–2.1)
Pre-hypertension  1.2(0.8–1.7)
Stage 1 hypertension  1.5(1.0–2.2)
Stage 2 hypertension  2.3(1.6–3.3)
Borderline cholesterol  1.1(0.8–1.4)
High cholesterol  0.9(0.7–1.3)

Unspec.
Diabetes  1.4(1.1–1.9)
Ex-smokers  0.9(0.7–1.2)
Current smokers  1.2(1.0–1.5)
Pre-hypertension  1.1(0.9–1.4)
Stage 1 hypertension  1.2(1.0–1.5)
Stage 2 hypertension  1.4(1.1–1.7)
Borderline cholesterol  1.0(0.8–1.2)
High cholesterol  1.1(0.9–1.4)

All
Diabetes  1.6(1.4–1.9)
Ex-smokers  1.1(0.9–1.3)
Current smokers  1.3(1.1–1.5)
Pre-hypertension  1.1(1.0–1.3)
Stage 1 hypertension  1.1(1.0–1.3)
Stage 2 hypertension  1.3(1.2–1.6)
Borderline cholesterol  1.0(0.9–1.1)
High cholesterol  1.0(0.9–1.2)

**Significant trends:** Diabetes increased the risk of either dementia in Alzheimer’s disease or vascular dementia in men and women.

**Limitations:** Accuracy of dementia data used from hospitalisation of NHIC has not been validated as for an outcome measurement.

**Source of funding:** Seoul City R&BD program [10526]

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**Authors:** King DE, Mainous AG 3rd, Geesey ME

**Year:** 2007

**Citation:** American Journal of Medicine 120(7): 598-603

**Country of study:** USA

**Aim of study:** Determine the frequency of adopting a healthy lifestyle in a middle-aged cohort, and determine the subsequent rates of cardiovascular disease and mortality among those who adopt a healthy lifestyle

**Study design:** Cohort study

**Quality score:** (++ + or -): +

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**Source population**

**Number of people:** 15,792

**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 15,708

**Characteristics:**
(n = 15,708) %

<p>| | |</p>
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<td>4.9</td>
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<tr>
<td>No</td>
<td>95.1</td>
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</table>

**Location:** Four communities across the United States  
**Recruitment strategy:** Probability sampling then selection involves sampling age-eligible persons from listings and then identifying their households  
**Length of follow-up:** 6 years  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Adults age 45-64  
**Excluded populations:** Not reported

**Exposures at midlife**

**Relevant exposures:** Diet, smoking, physical activity  
**Time:** 1987 to 1989  
**Measurement of exposure:** The ARIC dietary questionnaire consisted of items regarding the frequency of consumption of various foods over the previous year. A healthy lifestyle was characterized by having all 4 of the following lifestyle characteristics: eating at least 5 fruits and vegetables daily; exercising minimum of 2.5 hours per week; BMI maintained between 18.5 and 30 kg/m²; and not smoking  
For each physical activity the hours per week and the months per year are reported, and these values then were used to calculate the average number of hours per week spent on that activity over the course of the year
Current smokers identified by questionnaire during each visit.

### Outcomes at 55 years or over

**Outcomes:** All-cause mortality and fatal or non-fatal cardiovascular disease

**Outcome measurement:** State death certificates

Identified participants who developed fatal or non-fatal cardiovascular disease from those whose underlying cause of death was coded as cardiovascular disease, or who had an MI, a silent MI, diagnosed coronary heart disease, a coronary heart disease procedure, or a definite or probable stroke

**Time:** End of the year 1998

### Analysis

**Analysis strategy:** Multiple logistic regression

**Confounders:** Age group, gender, race, education, family income, and histories of hypertension, diabetes, elevated cholesterol, and previous coronary heart disease

### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

Switchers to Healthy Lifestyle and Persistently Healthy Compared to Persistently Unhealthy Individuals

**Cardiovascular Disease Event**

OR (95% CI)

Switched from Unhealthy to Healthy Lifestyle 0.65 (0.52-0.81)
Persistently Unhealthy (<4 Healthy Factors at Both Visits) 1.00 (reference)

**Death**

OR (95% CI)

Switched from Unhealthy to Healthy Lifestyle 0.60 (0.39-0.92)
Persistently Unhealthy (<4 Healthy Factors at Both Visits) 1.00 (reference)

**Significant trends:** Individuals who are older, female, with a college education, with family annual incomes greater than $35,000, or with no history of hypertension are more likely to have switched than others

**Limitations:**

Author: Misclassification via exaggerated exercise frequency or intake of fruits and vegetables

Reviewer: Unclear no. of deaths

**Source of funding:** Not reported

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**Authors:** Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M… Folsom AR

**Year:** 2001

**Citation:** Neurology 9;56(1): 42-8

**Country of study:** USA

**Aim of study:** To determine the influence of smoking on cognitive change

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +
**Source population**
15,792 men and women ages 45-64 years recruited from Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD in 1987-89 using probability sample
Clinical examination administered in 1987-89 with response rate of 46% in Jackson, and 65% in the other communities
13% of Forsyth County sample was black; the other sites consisted of predominantly white individuals

**Study (eligible and selected) population**
In 1990-92 (baseline for this study), 14,348 participants underwent cognitive evaluation with follow-up 6 years later, during which 10,963 respondents (76%) were re-tested

**Sociodemographics:** 8,729 white individuals and 2,234 black individuals.
6% of subjects had less than 9th grade education

**Follow-up:** 6 years follow-up since 1990-92 (baseline)

**Exclusion:** Individuals with history of stroke or TIA (n=300)

**Attrition:** Participants who dropped out or died were more impaired than those who returned for follow-up

**Exposures at midlife**
Self-reported smoking (never, former, current categories)

**Outcomes at 55 years or over**
Cognitive change: change in follow-up scores minus baseline scores for cognitive testing using:
- Delayed Word Recall (DWR) test
- Digit Symbol Subtest (DSS) of the Wechsler Adult Intelligence Scale-Revised
- First Letter Word Fluency (WF) test

**Analysis**

**Analysis strategy:** Linear regression was used to determine the influence of smoking on cognitive chang

**Confounders:** Age, gender, race-center, education level, and use of CNS medications

**Results, limitations, source of funding**
Smoking was not associated with declines on any of the cognitive tests

**Limitations:** Limited cognitive battery

**Source of funding:** None reported

**Authors:** Lahti J, Laaksonen M, Lahelma E, Rahkonen O
**Year:** 2010
**Citation:** Preventive Medicine 50(5-6): 246-50
**Country of study:** Finland
**Aim of study:** To determine the impact of physical activity on physical health functioning
**Study design:** Longitudinal
**Quality score:** (+++, + or -): +
**External validity score:** (+++, + or -):
**Source population**

Baseline questionnaire was administered to 13,346 employees ages 40, 45, 50, and 55 in Helsinki during 2000, 2001, and 2002 (response rate: 67%). At follow-up, in 2007, 7330 completed the survey (response rate: 83%).

**Study (eligible and selected) population**

Analysis restricted to 5,437 women and 1,257 men

**Sociodemographics:** Mean ages of women and men were 49 and 51, respectively

**Exclusion:** Participants with missing information (n=636)

**Attrition:** -

**Exposures at midlife**

The average weekly hours of physical activity during leisure time or community during the last 12 months were used to calculate the volume of physical activity.

Time spent in physical activity and intensity were used to create the following participant categories:
- Inactive
- Active moderate
- Active vigorous or vigorous activity only
- Very active moderate
- Very active vigorous
- Conditioning (moderate and vigorous activity or vigorous activity only)

**Outcomes at 55 years or over**

Physical health functioning was measured by the Short-Form 36 (SF-36)

High scores on the SF-36 are related to better health

The SF-36 demonstrates good construct validity, has high internal consistency and test-retest reliability.

**Analysis**

**Analysis strategy:** Sex-specific proportions were calculated to determine the percentage of participants with poor or good physical health functioning at follow-up by baseline physical activity. Means were also computed.

**Confounders:** Age, baseline physical health functioning and limiting longstanding illness, working conditions, working overtime and BMI, smoking and alcohol consumption.

**Results, limitations, source of funding**

- The more vigorous the physical activity, the greater the physical functioning mean scores appeared to be for both sexes
- Among women, the lowest percentage of poor physical health functioning at follow-up was reported for the active vigorous group (22%, [95% CI: 19%, 25%])
- Among men, the lowest percentage of poor physical health functioning was reported for the active moderate and active vigorous group (22%, [17%, 27%], and 22%, [16%, 28%], respectively)
- Among women, the highest percentage of good physical health functioning at follow-up was reported for the very active moderate group (27%, [24%, 30%]), while for men it was reported for the conditioning group (29%, [24%, 35%])

**Limitations:**

1. Limited generalizability as sample consisted predominantly of relatively healthy, middle-aged, public sector female employees
2. Reverse causality may be possible as sicker participants may be less able to engage in physical activity
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
better cognitive function) and participants were classified as demented, cognitively declined, and healthy TELE and TICS and sensitive and specific and correlate well with the MMSE

### Analysis

**Analysis strategy:** Multinomial logistic regression was used to assess the association between coffee intake and mild cognitive impairment or dementia, with twins being treated as individuals, not pairs (clustering taken into account). The association between cognitive performance and coffee intake was also assessed for discordant twin pairs

**Confounders:** Education, age at the interview, sex, BMI, binge drinking, smoking, life satisfaction, cardiovascular disease, hypercholesterolemia, hypertension, and diabetes

### Results, limitations, source of funding

- The prevalence of dementia according to the TELE and TICS was: 9.8% and 7.8% (respectively) for those ages 65-69 years; 11.9% and 7.9% for those ages 70-74 years; 19.1% and 15.6% for those ages 75-79 years; 31.7% and 25.3% for those ages 80-84 years; and 53.0% and 47.0% for those older than 84 years
- Coffee consumption was not associated with dementia or mild cognitive impairment
- The twin-pair analysis of twins discordant for coffee consumption and cognitive score showed that the correlation between cognitive function and coffee drinking was not statistically significant

**Limitations:** Unable to assess if rate of coffee consumption affects rate of cognitive decline

**Source of funding:** None reported

### Authors

Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M… Kivipelto M

**Year:** 2006

**Citation:** Dementia & Geriatric Cognitive Disorders 22(1): 99-107

**Country of study:** Finland

**Aim of study:** To determine the association between fat intake at midlife and risk of dementia and Alzheimer’s disease

**Study design:** Longitudinal

**Quality score:** (+++, + or -): ++

### Source population

Randomly selected participants from the survivors of population-based samples from North Karelia and Kuopio provinces; samples drawn from the national population register

At least 250 subjects of each sex and 10-year age group chosen

62.1% (n=900) and 37.9% (549) of participants were women and men, respectively

### Study (eligible and selected) population

A random sample of **1449** participants examined once in 1972, 1977, 1982, or 1987 were re-examined in 1998 (ages 65-79 years)

**Sociodemographics:** Mean age at midlife examination was 50.4 years and 71.3 years at follow-up

**Participation rate:** 77%-96%

**Follow-up:** Mean length of follow-up 21 years

**Exclusion:** -
### Attrition:
- 

### Exposures at midlife

**Dietary habits** assessed through self-administered questionnaire

Most questions were qualitative or frequency-based; consumption of milk, sour milk, eggs, coffee, tea, sugar in tea/coffee assessed quantitatively

Daily number of bread slices and type of spread used and amount of spread per slice (i.e. 0, 2.5, 5, 10, 15 g)

Fat intake from milk, sour milk and spreads calculated – served as indicator of total fat intake

Calculated polyunsaturated [PUFA], monounsaturated [MUFA], saturated fatty acids [SFA] derived from spreads

### Outcomes at 55 years or over

Cognitive status assessed using MMSE; if score <=24, invited to clinical phase for dementia diagnosis

### Analysis

**Analysis strategy:** Logistic regression used to assess influence of fat intake and dementia and AD development

**Confounders:** Midlife age, gender, education, follow-up time, milk fat and other subtypes of fats from spreads, midlife vascular risk factors including smoking status, systolic blood pressure, cholesterol and BMI, history of vascular disorders including MI, stroke, and diabetes; effect modification of APOE4 by fat intake assessed

### Results, limitations, source of funding

- 117 diagnosed with dementia, of which 76 had AD
- Proportion of demented persons was higher among those having used very little or no fat (from milk and spreads) compared to moderate users (31.6% [n=37] and 24.6% [n=458], respectively; p-value=0.02)
- 28.2% [n=33] and 24.8% [n=462] of demented and non-demented people consumed large amounts of fats
- Odds of developing dementia were lower for those consuming moderate amounts of polyunsaturated fats from spreads compared to those consuming low amounts [OR=0.40, 95% CI: 0.17-0.94; and 2]
- Odds of developing dementia and AD were higher for those consuming moderate amounts of saturated fats from spreads in comparison with those consuming low amounts [OR=2.45, (1.10-5.47), and OR=3.82, (1.48-9.87), respectively]
- Among APOE4 carriers, the odds of developing dementia was lower for those with moderate PUFA intake compared to those with low PUFA intake [OR=0.29, 95% CI: 0.09-0.89]; the reverse was observed for SFA

**Limitations:**

1. Limited reliability of self-reported dietary data
2. Residual confounding, i.e. intake of fat from other sources and other nutrients may influence association with dementia/AD
3. Long-term fat intake may be more likely to influence disease risk
4. Selective survival: those with high SFA intake may have died from vascular disease – may differ from survivors
5. Misclassification of dementia diagnosis by using medical records (under-diagnosis)

**Source of funding:** EVO grants from Kuopio University Hospital, Academy of Finland, Alzheimer...
Authors: Lajous M, Willett WC, Robins J, Young JG, Rimm E, Mozaffarian D, Hernán MA
Year: 2013
Citation: American Journal of Epidemiology 1;178(3): 382-91
Country of study: US
Aim of study: To determine whether changes in fish consumption in midlife affect the risk of coronary heart disease
Study design: Longitudinal
Quality score: (++, + or -): ++

Source population
51,529 US male health professionals ages 40-75 years enrolled in 1986 (Health Professionals Follow-up Study)
121,701 US female nurses ages 30-55 years enrolled in 1976 (Nurses’ Health Study)

Study (eligible and selected) population
See ‘Source population’

Follow-up:
Health Professionals Follow-up Study: 1990 until CHD diagnosis, death, censoring, or June 2008, whichever came first
Nurses’ Health Study: Time of return of 1986 participant questionnaire to CHD diagnosis, death, censoring, or December 2008, whichever came first

Exclusion: Health professionals who (male [n], female [n]):
i) Did not respond or provided insufficient information for survey (n=14,485, 55,328)
ii) Died (n=779, 92)
iii) Had MI (n=432, 6)
iv) Had CVD, diabetes, cancer (n=6,300, 9,653)
v) Had missing variable data or implausible energy intake (n=4,726, 2,850)
Attrition: -

Exposures at midlife
Fish intake and red meat intake were assessed using a semi-quantitative food frequency questionnaire that was first administered to males in 1986 and females in 1984 and 1986, and both sexes every 4 years thereafter
Validated questionnaire evaluated average consumption of specific portion sizes of food items in the past year, with response options ranging from ‘never or less than once a month’ to ‘6 or more per day’
Food item intake was summed and daily nutrient intakes were based on nutrient content of specified portion and frequency of food item intake
Total nutrient and energy intake was calculated and based on the sum of nutrient intakes from different foods
Total alcohol intake was also calculated

Outcomes at 55 years or over
Total, nonfatal, and fatal CHD were assessed
Nonfatal myocardial infarctions occurring during follow-up were identified using medical records, while deaths were identified through relatives, postal authorities, or the National Death Index (medical records, death certificates, autopsies used to identify cause of death)

### Analysis

**Hypothetical interventions:** A randomised trial of fish intake on 18-year risks of CHD outcomes in men and 22-year risks of CHD outcomes in women was emulated using observational data.

The effect of the following hypothetical ‘threshold’ interventions was assessed: intake of fish (measured in servings/week) of: 1) 0; 2) at least 1; 3) at least 2; 4) at least 3; or 4) at least 5 (servings/week)

At each 4-year interval, fish intake is increased to the threshold for those who eat fewer fish servings than the threshold (e.g., the threshold for intervention 3) is at least 2 servings/week); otherwise, it remains unchanged

‘Isocaloric’ interventions were also considered in which red meat intake was replaced by fish intake to achieve the following serving amounts: 6) at least 1 (serving/week); 7) at least 2; 8) at least 3; 9) at least 5

Increase to the threshold was not undertaken if neither fish nor red meat consumption was reported

**Analysis strategy:** The standardised risk of CHD outcomes under hypothetical interventions was assessed using the parametric g-formula. Pooled logistic and linear regression models were used to estimate probability density functions. Monte Carlo simulations were conducted

**Confounders:** Age, parental history of myocardial infarction, oral contraceptive use, body mass index, smoking, menopausal status, hormone replacement therapy, physical activity, aspirin use, vitamin E supplement use, multivitamin supplement use, high blood pressure, high cholesterol, diabetes, angina or coronary artery bypass grafting, stroke, and intakes of calories, trans-fats, alcohol, cereal fibre, red meat, and fish

### Results, limitations, source of funding

**Males**
No significant associations were reported for males

**Females:**
Meat replaced with fish: the lowest risk for *total coronary heart disease* was reported when meat was replaced with fish to attain >=3 servings/week (Risk ratio=0.81, [0.68, 0.95])

The lowest risk for *fatal coronary heart disease* was reported when: meat was replaced with fish to attain >=5 servings/week (Risk ratio=0.68, [0.37, 0.99]); and when >=5 fish servings/week were consumed (Risk ratio=0.66, [0.36, 0.98])

**Limitations:**
1. Measurement error when attempting to quantify dietary change
2. Potential residual confounding; particularly in men, as they may have been more focused on preventing CVD and making dietary changes in presence of slightly elevated BP or glucose/lipid levels

**Source of funding:** National Institutes of Health

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**Authors:** Lang IA, Guralnik JM, Melzer D  
**Year:** 2007  
**Citation:** Journal of the American Geriatric Society 55(11): 1836-41  
**Country of study:** US
**Aim of study:** To assess whether body mass index and level of physical activity are associated with impaired physical function

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

### Source population

**Health and Retirement Study (HRS):**
10,086 US participants ages 50-59 years at baseline in 1998 and still alive in 2004.
After baseline face to face interviews, phone interviews were conducted every even-numbered year.

**English Longitudinal Study of Aging (ELSA):**
19,924 English participants born on or before February 29, 1952 were identified for cross-sectional survey in 1998, 1999, 2001.
11,392 individuals recruited for ELSA study (eligible respondents 65.7%)

### Study (eligible and selected) population

**HRS:** Analysis restricted to 8,702 participants.

**Sociodemographics:** 4569 were women and 1,031 had 0-9 years of full-time education, baseline mean age of 60.2 years.

**ELSA:** Analysis restricted to 1,507 out of 3,335 respondents ages 50-69 years with baseline exposure information measured in 1998-99, who participated in second ELSA wave in 2004, and had recommended weight or above and were nondisabled at baseline.

**Sociodemographics:** 837 were women and 134 had 0-9 years of full-time education, baseline mean age of 58 years.

**Median length of follow-up:**
- **HRS:** 72 months
- **ELSA:** 73 months

### Exclusion:

**HRS:**
- *BMI <20 (353)*
- *Participants with one or more mobility problems (n=1,370)*

**ELSA:**
- *Participants who died or were ineligible for follow-up (n=2,596)*
- *BMI <20 (n=64)*
- *Participants with long-term conditions (n=1,764)*

### Attrition:

- -

### Exposures at midlife

**BMI**
In HRS, self-reported weight and height at baseline and follow-up used to calculate BMI, which was classified as: recommended weight (20-24.9), overweight (25-29.9), or obese (>=30).
In ELSA, weight and height measured by clinicians at baseline and follow-up, and same BMI categories used as for HRS.

**Physical activity**
In HRS, participants asked about participation in vigorous physical activity (e.g., sports) at least 3 times/week over last 12 months, with yes/no answer options.
In ELSA, respondents asked about the number of days/week that they undertook activities, such as housework or gardening, manual labour, participating in vigorous sports for 30 minutes or longer, and a summary measure was subsequently created. ELSA participants were also categorized into whether or not they participated in vigorous activity at least 3 days/week.

### Outcomes at 55 years or over

#### Physical function

Mobility impairment was ascertained for HRS participants through questions on difficulty with walking or climbing stairs. Measured physical performance impairment in ELSA respondents was measured by clinician using a modified version of the Short Physical Performance Battery that assessed balance, chair stands, and grip strength; a physical performance score out of 12 was allocated to each participant (with 7 or less representing impairment).

#### Analysis

**Analysis strategy:** Logistic regression was used to assess the influence of physical activity on incident impaired physical function (ELSA) and self-reported mobility impairment (HRS) by baseline BMI category.

**Confounders:** Age, sex, health behaviours, socioeconomic status, and baseline functional limitations, smoking, drinking.

#### Results, limitations, source of funding

- Participants who reported being active at least three times per week had a lower incidence of physical impairment than those with lower levels of reported physical activity for each weight category in both HRS and ELSA.

**Limitations:** Self-reported physical activity.

**Source of funding:** National Institutes of Health Award, Intramural Research Program, National Institute on Aging, NIH.


Citation: Osteoporosis International 12(9): 763-8.

Country of study: USA.

Aim of study: To determine the influence of weight loss in middle-aged and older women and risk for hip fracture.

Study design: Longitudinal.

Quality score: (+++, + or -): +

Source population:
US women surveyed on nutrition and weight history in 1971-75 (baseline).
Study restricted to 2180 out of 2410 community-dwelling white women ages 50–74 years who met inclusion criteria.

**Follow-up:** 33,174 person-years of observation during 22 years

Time from date of examination to date of hip fracture, or date of last follow-up interview, or date of death for those without a hip fracture.

**Exclusion:** Women with:

i) A history of hip fracture at baseline (n=51)

ii) Loss to follow (n=139)

iii) Missing data (n=40)

**Attrition:** 139 women lost to follow-up. At baseline, excluded women were older, less physically active, and weighed less than participants.

### Exposures at midlife

Body weight and weight history self-reported at baseline in 1971-75

Self-reported maximum lifetime weight was ascertained and the percent weight loss was calculated as:

\[ \frac{\text{maximum weight} - \text{baseline weight}}{\text{maximum weight}} \times 100 \]

Proportional weight loss categorized into: 1) <5%; 5% to <10% and >=10%; and 2) <10% and >=10%

### Outcomes at 55 years or over

Hip fractures identified through death certificates and hospital records

### Analysis

**Analysis strategy:** Cox proportional hazards regression was used to determine the influence of weight loss on hip fracture risk.

**Confounders:** Age at baseline, body mass index at maximum weight, smoking, alcohol consumption in the past year, history of chronic conditions and level of non-recreational physical activity.

**Stratification:** BMI, age

### Results, limitations, source of funding
- 171 hip fractures identified
- Mean age at hip fracture was 71.7 years for women ages 50-64 years, and 81.1 years for women ages 65-74 years
- Incidence rates of hip fracture appeared to increase with increasing age and weight loss

**Women aged 50-64 years at baseline:**
Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.54, [1.10, 5.86])

**Women aged 65-74 years at baseline:**
Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.04, [1.37, 3.04])

When <10% weight loss was used as the reference category, the relative risks changed minimally for both age groups

**Women with BMI <26.2 (kg/m²) at baseline:**
Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.37, [1.32, 4.27])

**Limitations:**
1. Cannot generalise to other age groups, races, or older men
2. Self-reported weight (potentially bias association towards the null)
3. Weight fluctuation was not taken into account

**Source of funding:** None reported

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**Authors:** Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ

**Year:** 2004

**Citation:** American Journal of Epidemiology 159(10): 959-96

**Country of study:** USA

**Aim of study:** To determine the influence of midlife dietary intake of antioxidants on risk of late-life incident dementia

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**
8,006 Japanese-American men, born between 1900-19, and residing in Oahu, Hawaii in 1965 were clinically evaluated and interviewed in 1965-68 when they were aged 45-68 years (examination 1), with follow-up examinations/interviews in 1968-70 (examination 2) and 1971-74 (examination 3)

3,734 people (80% of those eligible) ages 71-93 years participated in 1991-93 survey on neurodegenerative disease (examination 4) with 2 re-examinations for dementia after assessments in 1994-96 (examination 5) and 1997-99 (examination 6)

**Study (eligible and selected) population**
Analysis restricted to 2,459 participants free of dementia in 1991-93 and who underwent follow-up examinations until 1999

**Follow-up:** 30.2 years

**Sociodemographics:** Mean ages at examinations 1 and 4 were 51.2 and 76.3 years

Median number of years of education was 12
Exclusion: Participants with:
  i) Dementia (n=226)
  ii) Atypical diet (n=226)
  iii) Died during follow-up (n=516)
  iv) Nonresponse at examination 5 (n=307)

Attrition:
  a) Excluded individuals with atypical diet were similar to participants with respect to age, education, and BMI at exam. 1 and intake of supplemental vitamins
  b) Those who died during follow-up were, at exam. 1, older, less educated, reported lower energy intake and were less likely to use supplements
  c) Non-responders at examination 5 were older at exam. 1, had lower intakes of beta-carotene and vitamin C, and were less likely to use supplements

Exposures at midlife

24-hour dietary recall assessed through interview in 1965-68
Participants also queried on frequency of consumption of 26 food and drink items at examinations 1 and 3
Flavonoid intake was assessed through mean intake of tea assessed at examinations 1 and 3
Intakes of beta-carotene, vitamin C, vitamin E, and flavonoids were divided into quartiles; the median energy-adjusted intakes for the first, second, third, and fourth quartiles, respectively, were: 16, 71, 296, and 1,101 μg/day for beta-carotene; 23, 69, 128, and 219 mg/day for vitamin C, 3.8, 10.7, 18.0, and 29.9 mg/day for vitamin E; and 2.0, 2.9, 4.5, and 8.2 mg/day for flavonoids

Outcomes at 55 years or over

Dementia was ascertained through screening using the Cognitive Abilities Screening Instrument and evaluated through a neurologic examination, neuropsychological testing, and an informant interview
Subjects with dementia underwent blood tests and brain imaging

Analysis

Analysis strategy: Cox proportional hazards regression was used to determine influence of midlife intake of antioxidants and risk of late-life cognitive impairment

Confounders: Age, education, smoking status, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, and apolipoprotein E e4

Results, limitations, source of funding

- 235 participants developed dementia over 30.2 years of follow-up (102 Alzheimer’s disease cases, 38 cases of Alzheimer’s disease with cerebrovascular disease, 44 vascular dementia cases, 51 cases due to other causes)

Vitamin E intake:
- Compared to the first quartile of vit. E intake, the risk for dementia and Alzheimer’s disease was greater for those in the second quartile of vit. E intake (dementia RR=1.47, [1.01, 2.14] and Alzheimer’s disease RR=1.84, [1.04, 3.25], respectively)
- Compared to the first quartile of vit. E intake, the risk for Alzheimer’s disease with and without cerebrovascular disease was greater for those in the second and fourth quartiles of vit. E intake (RR=1.92, [1.16, 3.18], RR=1.78, [1.06, 2.98], respectively)
- There was a significant association between high intake of antioxidants and risk for Alzheimer’s disease with and without contributing cerebrovascular disease (RR=1.82, [1.04, 3.21])
Limitations:
1. High nonparticipation at first follow-up and death rates
2. The short 24-hour recall period of food intake may be inaccurate in determining average intake of antioxidants

Source of funding: National Institutes of Health, the National Institute on Aging, and the National Heart, Lung, and Blood Institute

Authors: Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen TP, Kauhanen J
Year: 2013
Citation: Journal of Affective Disorders 5;150(2): 682-5
Country of study: Finland
Aim of study: Examine the association between dietary zinc intake and depression
Study design: Population-based prospective study
Quality score: (+++, + or -): +

Source population
Number of people: Not reported
Demographics: Not reported

Study (eligible and selected) population
Number of people: 2682
Characteristics:
Discharge diagnosis of depressive disorder
Age (years) 54.3(48.5–54.4)
HPL depression scores 2(0–3)
Living alone, n (%) 8(13.3)
Length of education (years) 8(6–10)
Smoking (cigarette-years) 0(0–287)
Alcohol consumption (g/week) 41.1(7.6–116.1)
Energy expenditure (kcal/d) 85.8(32.1–179.6)
Regular use of vitamins and trace elements, yes (%) 7(11.7)
Body mass index (kg/m2) 26.8(25.0–28.5)
Total energy intake (kJ/d) 10,451(8708–12,780)
Zinc RDI met (≥9 mg/d), n (%) 60(100.0)
Dietary zinc (energy-adjusted)(mg) 14.4(12.7–16.4)

No depression
Age (years) 54.3(48.9–54.5)
HPL depression scores 1(0–2)
Living alone, n (%) 282(12.5)
Length of education (years) 8(6–10)
Smoking (cigarette-years) 0(0–173)
Alcohol consumption (g/week) 30.7(6.2–88.5)
Energy expenditure (kcal/d) 88.2(31.8–193.4)
Regular use of vitamins and trace elements, yes (%) 165(7.3)
Body mass index (kg/m2) 26.4(24.5–28.9)
Total energy intake (kJ/d) 9621 (8122–11,289)
Zinc RDI met (≥9 mg/d), n (%) 2129 (94.3)
Dietary zinc (energy-adjusted)(mg) 14.3 (12.9–16.0)
### Test statistics and P value
- Age: Z = -2.2 and 0.026
- HPL depression scores: Z = -2.7 and 0.006
- Living alone: χ² = 0.0 and 0.846
- Length of education: Z = 0.0 and 0.968
- Smoking: Z = -0.5 and 0.597
- Alcohol consumption: Z = -0.7 and 0.467
- Energy expenditure: Z = 0.0 and 0.993
- Regular use of vitamins and trace elements, yes: χ² = 1.60 and 0.204
- Body mass index: Z = -0.7 and 0.476
- Total energy intake: Z = -2.7 and 0.008
- Zinc RDI met: – 0.076c
- Dietary zinc: Z = -0.3 and 0.795

### Location
Kuopio region of eastern Finland

### Recruitment strategy
Not reported

### Length of follow-up
20 years

### Response rate and loss to follow-up
Not reported

### Eligible population
Finnish men

### Excluded populations
Individuals who at baseline had elevated depressive symptoms. Data were incomplete for 82 participants

### Exposures at midlife

#### Relevant exposures
- Diet, smoking, physical activity

#### Time
March 1984 and December 1989

#### Measurement of exposure
4-day food recording during baseline examination

The current number of cigarettes, cigars and pipefuls of tobacco smoked daily and the duration of regular smoking in years were recorded using a self-administered questionnaire.

Physical activity was assessed using the 12-month Physical Activity Questionnaire.

### Outcomes at 55 years or over

#### Outcomes
Depressive symptoms

#### Outcome measurement
Depression was defined as having received a hospital discharge diagnosis of unipolar depressive disorder.

#### Time
Not reported

### Analysis

#### Analysis strategy
Cox proportional hazards model

#### Confounders
Age, baseline depression severity, smoking, alcohol use, physical exercise and the use of dietary supplements

### Results, limitations, source of funding

#### Number
60 (2.7%)

#### Effect estimates
Receiving diagnosis of depression and energy-adjusted dietary zinc intake
RR 1.02, 95%CI 0.96–1.08, p = 0.595

Lowest tertile of energy-adjusted zinc intake and a diagnosis of depression.
Future hospital discharge diagnosis of depression and baseline HPL depressions core
RR 1.39, 95% CI 1.15–1.67, p=0.001

Significant trends: No association was observable between the risk of receiving a hospital discharge diagnosis of depression and the energy-adjusted dietary zinc intake as a continuous measure. No association was observed between belonging to the lowest tertile of energy-adjusted zinc intake and a future hospital discharge diagnosis of depression.

Limitations:
1. Study comprised exclusively of men.
2. The number of individuals who received a hospital discharge diagnosis of depression was fairly small.
3. May not have detected the cases with milder depression.

Source of funding: The authors conducted this study as part of their work, without external funding.

Authors: Leosdottir M, Nilsson PM, Nilsson JA, Berglund G
Year: 2007
Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(5): 701-6
Country of study: Sweden
Aim of study: To determine whether total fat intake, saturated, monounsaturated, or polyunsaturated fat intake are risk factor for cardiovascular events
Study design: Longitudinal
Quality score: (+++, + or -): ++

Source population
74,138 individuals, comprising men born between 1923-45 and women born between 1923-50 were recruited from 1991 through 1996

Study (eligible and selected) population
28,098 enrolled individuals (60.6% were women)
40% participation rate
Follow-up: Date of study entry until occurrence of cardiovascular event or end of follow in year 2002. Mean follow-up of 8.4 years
Exclusion: Individuals with history of acute coronary event or ischemic stroke (women: n=168, men: n=536)
Attrition: 100 women and 64 men lost to follow-up mainly due to out-of-country emigration.
Mortality higher in non-participants

Exposures at midlife
Dietary intake was assessed through 7-day menu diary, questionnaire assessing meal patterns, food item consumption frequencies and portion sizes, as well as interviews
Intake of fat, protein, carbohydrates, and alcohol recorded in grams/day, and relative fat intake measured as percentage of non-alcohol energy from fat
Reproducibility and validity of dietary measurement methods established
Intake divided into quartiles of total fat intake, saturated, monounsaturated, and polyunsaturated fat intake; the ratio between unsaturated and saturated fat intake was also obtained
Outcomes at 55 years or over

Fatal and nonfatal CVD event cases identified through local and national registries

Analysis

Analysis strategy: Cox proportional hazards regression used to assess influence of fat intake on risk for cardiovascular events in total, as well as risk for acute coronary events or ischemic stroke

Confounders: Age, smoking habits, alcohol consumption, socioeconomic status, marital status, physical activity, body mass index, fibre intake, and blood pressure; adjustments were also made for total fat intake for the ratio between unsaturated and saturated fats

Results, limitations, source of funding

1556 fatal and non-fatal events (908 acute coronary events and 648 ischemic strokes) occurred

Cardiovascular events:
- Compared to the first quartile of monounsaturated/sat. fat intake ratio, the risk for cardiovascular events was lower for women in the second quartile of monounsaturated/sat. fat intake ratio (HR=0.77, [0.61, 0.98]); similar findings were observed among women for polyunsaturated/sat. fat intake ratio (HR=0.77, [0.61, 0.97])
- Compared to the first quartile of polyunsaturated/sat. fat intake ratio, the risk for cardiovascular events was lower for women in the third quartile of polyunsaturated/sat. fat intake ratio (HR=0.78, [0.62, 0.99]);

Acute coronary events:
- Compared to the first quartile of monounsaturated/sat. fat intake ratio, the risk for acute coronary events was lower for women in the second quartile of monounsaturated/sat. fat intake ratio (HR=0.71, [0.51, 0.99]); similar findings were observed among women for saturated fat intake (HR=0.67, [0.45, 0.99])

Limitations:
1. Residual confounding (e.g., trans-fatty acids not measured)
2. Assessment of diet at only one point in time raises issue of reliability of dietary assessment
3. Self-reported dietary assessment may lead to underreporting of energy and fat intake
4. Low participation rate
5. Possible healthy-cohort effect

Source of funding: The Swedish Scientific Council, The Swedish Cancer Foundation, Anna Jonssons Memorial Fund, the Swedish Heart and Lung Foundation, The European Commission, and The Region of Skane, Sweden

Authors: Levitan EB, Mittleman MA, Håkansson N, Wolk A

Year: 2007

Citation: American Journal of Clinical Nutrition 85(6): 1521-6

Country of study: Sweden

Aim of study: Tested the hypothesis that men consuming diets high in glycemic index or glycemic load have a greater risk of cardiovascular disease

Study design: Prospective observational study

Quality score: (+++, + or -): +

Source population
**Number of people:** 48,850  
**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 36,246  
**Characteristics:**

#### Quartile of dietary glycemic load

**Quartile 1:** Age (y) 58.7 ± 9.1; BMI (kg/m²) 25.8 ± 3.3; Physical activity (min/d) 53.9 ± 42.7; Cigarette smoking (%) Never 31.4, Past 39.2, Current 29.4; Education (%) Less than high school 63.1, High school 16.0, University 20.9; Alcohol (g/d) 14.8 ± 13.2

**Quartile 2:** Age (y) 58.7 ± 9.3; BMI (kg/m²) 25.6 ± 3.2; Physical activity (min/d) 56.7 ± 43.2; Cigarette smoking (%) Never 37.7, Past 38.0, Current 24.4; Education (%) Less than high school 63.5, High school 16.1, University 20.5; Alcohol (g/d) 11.5 ± 9.6

**Quartile 3:** Age (y) 59.0 ± 9.5; BMI (kg/m²) 25.5 ± 3.2; Physical activity (min/d) 57.6 ± 43.2; Cigarette smoking (%) Never 40.1, Past 37.7, Current 22.2; Education (%) Less than high school 67.3, High school 15.0, University 17.7; Alcohol (g/d) 9.5 ± 8.7

**Quartile 4:** Age (y) 59.4 ± 9.7; BMI (kg/m²) 25.6 ± 3.3; Physical activity (min/d) 58.6 ± 45.3; Cigarette smoking (%) Never 40.0, Past 37.0, Current 23.1; Education (%) Less than high school 73.8, High school 12.7, University 13.5; Alcohol (g/d) 7.1 ± 7.4

**Location:** Vastmanland and Orebro Counties in central Sweden  
**Recruitment strategy:** Mailed a four-page questionnaire  
**Length of follow-up:** 6 years  
**Response rate and loss to follow-up:** 49%

**Eligible population:** All men in two Swedish counties aged 45–79 years  
**Excluded populations:** Men providing incorrect national identification numbers or who did not provide national identification numbers (n=260), who returned blank questionnaires (n=92), or who had a previous diagnosis of cancer (n=2592), history of cardiovascular disease before 1 January 1998 or a history of diabetes (n=5069) determined from record linkage and self-report, those who did not report their height and weight or who reported implausible energy intakes

### Exposures at midlife

**Relevant exposures:** Diet  
**Time:** 1997 and 1998  
**Measurement of exposure:** Food-frequency questionnaire

### Outcomes at 55 years or over

**Outcomes:** Myocardial infarction, ischemic stroke, hemorrhagic stroke, and cardiovascular mortality and all-cause mortality  
**Outcome measurement:** Inpatient, cause-of-death, and death registries  
**Time:** 01 January 1998 until 31 December 2003 for myocardial infarction, ischemic stroke, hemorrhagic stroke, and cardiovascular mortality; until 31 December 2005 for all-cause mortality.

### Analysis

**Analysis strategy:** Cox proportion hazard models  
**Confounders:** Cigarette smoking, body mass index, physical activity, demographic characteristics,
and nutritional factors

Results, limitations, source of funding

Number: Myocardial infarction (n=1324), ischemic stroke (n=692), cardiovascular mortality (n=785), or all-cause mortality (n=2959), hemorrhagic stroke (n= 165)

Effect estimates:

Relative risks (RRs) CVD and mortality by quartile of dietary GI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Quartile</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.91 (0.77, 1.07)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>0.96 (0.82, 1.13)</td>
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<td></td>
<td>Q4</td>
<td>0.99 (0.84, 1.17)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>1.21 (0.97, 1.50)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>1.12 (0.89, 1.41)</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>1.09 (0.85, 1.38)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>1.11 (0.71, 1.72)</td>
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<tr>
<td></td>
<td>Q3</td>
<td>1.04 (0.66, 1.63)</td>
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<td></td>
<td>Q4</td>
<td>1.19 (0.77, 1.83)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Q1</td>
<td>1</td>
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<tr>
<td></td>
<td>Q2</td>
<td>0.98 (0.80, 1.21)</td>
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<tr>
<td></td>
<td>Q3</td>
<td>0.93 (0.74, 1.15)</td>
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<tr>
<td></td>
<td>Q4</td>
<td>1.09 (0.88, 1.36)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>1.02 (0.92, 1.14)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>0.96 (0.86, 1.07)</td>
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<tr>
<td></td>
<td>Q4</td>
<td>1.06 (0.95, 1.19)</td>
</tr>
</tbody>
</table>

CVD and mortality by quartile of dietary GL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Quartile</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.91 (0.77, 1.08)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>1.02 (0.83, 1.25)</td>
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<tr>
<td></td>
<td>Q4</td>
<td>1.04 (0.80, 1.34)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.94 (0.74, 1.19)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>0.95 (0.72, 1.26)</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>1.05 (0.74, 1.49)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.98 (0.60, 1.59)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>1.57 (1.01, 2.44)</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>1.44 (0.91, 2.27)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.93 (0.74, 1.17)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>1.06 (0.81, 1.37)</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>1.13 (0.81, 1.56)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Q1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>0.90 (0.80, 1.00)</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>0.95 (0.83, 1.08)</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>0.94 (0.79, 1.11)</td>
</tr>
</tbody>
</table>

| Source of funding: Swedish Research Council/Longitudinal Studies. EBL was supported by a grant from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT) and a National Heart, Lung, and Blood Institute training grant (HL07374) |
Characteristics:

Fatty-fish intake

**Never** Age (years) 58.0 + 9.8; Physical activity (MET h/day) 41.9 + 5.1; Body mass index (kg/m2) 25.7 + 3.5; Cigarette smoking Current 1605 (27.6); Past 1963 (33.8); Never 2245 (38.6); Education Less than high school 4218 (72.6), High school 773 (13.3), University 822 (14.1); Alcohol (g/day) 8.7+10.8

<1 servings/week Age (years) 59.3 + 9.6; Physical activity (MET h/day) 41.9 + 5.0; Body mass index (kg/m2) 25.6 + 3.2; Cigarette smoking Current 2675 (25.0); Past 3972 (37.1); Never 4053 (37.9); Education Less than high school 7800 (72.9), High school 1406 (13.1), University 1494 (14.0); Alcohol (g/day) 9.2 + 9.6

1 serving/week Age (years) 58.9 + 9.2; Physical activity (MET h/day) 41.4 + 4.8; Body mass index (kg/m2) 25.6 + 3.2; Cigarette smoking Current 3808 (23.0), Past 6375 (38.4), Never 6405 (38.6); Education Less than high school 10 683 (64.4), High school 2622 (15.8), University 3283 (19.8); Alcohol (g/day) 11.4 + 9.9

2 servings/week Age (years) 61.0 + 9.2; Physical activity (MET h/day) 41.5 + 4.8; Body mass index (kg/m2) 25.8 + 3.3; Cigarette smoking Current 1235 (23.1), Past 2161 (40.5), Never 1944 (36.4); Education Less than high school 3427 (64.2), High school 789 (14.8), University 1124 (21.1); Alcohol (g/day) 12.6 + 11.0

Exposures at midlife

Relevant exposures: Diet

Time: 1997 and 1998

Measurement of exposure: Food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Heart failure

Outcome measurement: Inpatient, cause-of-death, and death registries

Time: 2004

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at <60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol

Results, limitations, source of funding

Number: 97 (563 hospitalisations and 34 deaths)

Effect estimates

Fatty-fish intake

**Never** 1 (reference)

<1 serving/week 0.93 (0.72 – 1.21)

1 serving/week 0.88 (0.68 – 1.13)

2 serving/week 0.99 (0.73 – 1.33)

>3 serving/week 0.97 (0.61 – 1.55)

Quintiles of marine omega-3 fatty acids

1.1 (reference)
Significant trends: Moderate intake of fatty fish and marine omega-3 fatty acids was associated with lower rates of HF, though the association for fish intake was not statistically significant.

Limitations
1. Not able to determine HF aetiology or subtype
2. As the registers only captured cases that result in hospitalization or death results may not be generalizable to less severe HF treated on an outpatient basis
3. Misclassification of intake; estimated portion sizes
4. Residual or unmeasured confounding

Source of funding: Swedish Research Council/Committee for infrastructure; Swedish Foundation for International Cooperation in Research and Higher Education (to E.B.L.); National Heart, Lung, and Blood Institute, National Institutes of Health (F32 HL091683 to E.B.L.)
Location: Västmanland and Uppsala counties in central Sweden

Recruitment strategy: Invitation to a free-of-charge mammography examination, and a mailed questionnaire on diet

Length of follow-up: 9 years

Eligible population: Women 48-83 years old without baseline HF, diabetes, or myocardial infarction. Participants in the Swedish Mammography Cohort

Excluded populations: Participants who:
  i) Did not provide or provided incorrect national identification numbers
  ii) Reported implausible energy intakes
  iii) Had previous diagnosis of cancer or who left more than half of the food and beverage items blank
  iv) Those at baseline with a history of HF, myocardial infarction (MI), or diabetes

Exposures at midlife

Relevant exposures: Diet

Time: 1998

Measurement of exposure: Self-administered food-frequency questionnaire. Asked frequency of consumption of 96 foods and beverages over the previous year. Portion sizes for most foods were not specified.

Outcomes at 55 years or over

Outcomes: Heart failure events

Outcome measurement: Swedish inpatient and cause-of-death registers

Time: 2006

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, education, body mass index, physical activity, cigarette smoking, living alone, postmenopausal hormone use, total energy intake, alcohol intake, fiber intake, sodium intake, saturated fat, polyunsaturated fat, protein, carbohydrate, family history of MI before 60 years, self-reported history of hypertension, and self-reported history of high cholesterol.

Results, limitations, source of funding

Number: 639

Effect estimates:
Dietary glycemic index, dietary glycemic load and incidence of heart failure hospitalization or mortality

Dietary glycemic index

RR (95% CI)
1 1 (reference)
2 1.01 (0.78-1.31)
3 1.14 (0.89-1.47)
4 1.12 (0.87-1.45)
p-trend 0.31

Dietary glycemic load

RR (95% CI)
Significant trends: Dietary glycemic index did not appear to be associated with incident HF events

Limitations:
1. Only cases of HF that resulted in hospitalisation or death were recorded
2. Registers do not contain information on HF etiology or subtype
3. Assessment of medical history was based on self-report
4. Exposure misclassification; residual or unmeasured confounding

Source of funding: Swedish Research Council/Committee for Infrastructure and the Committee for Medicine, Stockholm, Sweden. Dr. Levitan was supported by a grant from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT), Stockholm, Sweden, and National Institutes of Health, Bethesda, MD, grant F32 HL091683

Authors: Lim SH, Tai BC, Yuan JM, Yu MC, Koh WP

Citation: Tobacco Control 22(4): 235-40

Country of study: Singapore

Aim of study: To assess influence of smoking (cessation) on all-cause and cause-specific mortality

Study design: Longitudinal

Quality score: (+++, + or -): -

Source population

Cohort of Hokkiens and Cantonese permanent residents or citizens of Singapore ages 45-74 years recruited between April 1993 and Dec. 1998 (baseline)
Response rate: 85%
Surviving members re-interviewed at follow-up between 1999 and 2004

Study (eligible and selected) population

63,257 people from Fujian Province and Guangdong Province interviewed at baseline, and 52,322 participants re-contacted at follow-up. Analysis restricted to 48,251 people
Follow-up: 1993-98 to 09. Date of the follow-up interview to the date of death or Dec. 31, 2009, whichever came first
Exclusion: Participants who started smoking after baseline interview (n=2564) and those whose responses were inconsistent (n=1507)
Attrition: Loss to follow-up due to death, physical disability, or participants could no longer be contacted
41 lost to follow-up due to migration or other reasons

Exposures at midlife

Self-reported smoking categorised as: current smokers (smoking at baseline and f/u interview), long-term quitters (quitter at baseline and f/u interview), new quitters (baseline smoking and quitter at f/u interview), never smokers
Outcomes at 55 years or over

Mortality: all-cause, lung cancer, other cancers, coronary heart disease, stroke, chronic obstructive pulmonary disease identified using nationwide death registry

Mortality data available through Dec. 31 2009

Analysis

Analysis strategy: Cox proportional hazards model used to assess influence of smoking (cessation) on all-cause mortality. The association between smoking and cause-specific mortality assessed using competing risks regression

Confounders: Age, year, BMI, sex, dialect, education, alcohol intake, diagnosis of physical activity, hypertension, diabetes mellitus, stroke and cardiovascular disease, and cancer

Results, limitations, source of funding

- Compared with current smokers, the risk for total mortality was lower for new quitters (HR=0.84, [0.76, 0.94]), long-term quitters (HR=0.61, [0.56, 0.67]), long-term quitters and never-smokers (HR=0.49, [0.46, 0.53])
- Compared with current smokers, the risk of lung cancer mortality was lower for new quitters (HR=0.76 [0.57, 1.00]) and long-term quitters (HR=0.44, [0.35, 0.57])
- Compared with current smokers, the risk for coronary heart disease mortality was lower for long-term quitters (HR=0.63, [0.52,0.77])

Limitations:
1. Non-differential
2. Misclassification of smoking status
3. Small sample sizes for various sub-groups
4. No validation of self-reported smoking

Source of funding: National Institutes of Health

Authors: Lin Y, Kikuchi S, Tamakoshi A, Wakai K, Kawamura T, Iso H... Ishibashi T; JACC Study Group

Year: 2005

Citation: Annals of Epidemiology 15(8): 590-7

Country of study: Japan

Aim of study: Examine the association between alcohol intake and the risk of all-cause mortality

Study design: Prospective cohort study

Quality score: (+++, + or -): ++

Source population

Number of people: 110,792
Demographics: Not reported

Study (eligible and selected) population

Number of people: 97,432
Characteristics:
Men
Nondrinkers. Age (years) 59.0±10.6; Body mass index (kg/m²) 22.5±2.9; More than high school education (%) 11.9; History of hypertension (%) 14.1; History of diabetes (%) 5.1; Current smokers (%) 49.7; Exercise > 5 hours per week (%) 5.9

Ex-drinkers. Age (years) 62.4±9.5; Body mass index (kg/m²) 22.2±3.0; More than high school education (%) 12.8; History of hypertension (%) 24.5; History of diabetes (%) 11.8; Current smokers (%) 45.8; Exercise > 5 hours per week (%) 6.7

Current drinkers (alcohol intake: g/day) 0.1–22.9. Age (years) 56.3±10.3; Body mass index (kg/m²) 22.7±2.7; More than high school education (%) 18.1; History of hypertension (%) 15.8; History of diabetes (%) 5.6; Current smokers (%) 46.9; Exercise > 5 hours per week (%) 6.2

Current drinkers (alcohol intake: g/day) 23.0–45.9. Age (years) 57.2±10.1; Body mass index (kg/m²) 22.6±2.7; More than high school education (%) 14.6; History of hypertension (%) 19.6; History of diabetes (%) 5.7; Current smokers (%) 52.6; Exercise > 5 hours per week (%) 7.4

Current drinkers (alcohol intake: g/day) 46.0–68.9. Age (years) 55.5±9.3; Body mass index (kg/m²) 22.8±2.6; More than high school education (%) 12.8; History of hypertension (%) 21.0; History of diabetes (%) 4.4; Current smokers (%) 61.7; Exercise > 5 hours per week (%) 6.4

Current drinkers (alcohol intake: g/day) > 69.0. Age (years) 53.9±9.0; Body mass index (kg/m²) 22.9±2.8; More than high school education (%) 10.6; History of hypertension (%) 19.1; History of diabetes (%) 5.2; Current smokers (%) 69.3; Exercise > 5 hours per week (%) 5.8

Women

Nondrinkers. Age (years) 57.8±10.0; Body mass index (kg/m²) 22.9±3.1; History of hypertension (%) 21.0; History of diabetes (%) 3.5; More than high school education (%) 7.6; Current smokers (%) 3.5; Exercise > 5 hours per week (%) 3.5

Ex-drinkers. Age (years) 58.2±10.2; Body mass index (kg/m²) 23.0±3.4; History of hypertension (%) 24.8; History of diabetes (%) 7.8; More than high school education (%) 7.2; Current smokers (%) 22.8; Exercise > 5 hours per week (%) 4.8

Current drinkers (alcohol intake: g/day) 0.1–22.9. Age (years) 55.0±9.6; Body mass index (kg/m²) 22.9±2.9; History of hypertension (%) 16.9; History of diabetes (%) 2.4; More than high school education (%) 10.8; Current smokers (%) 7.6; Exercise > 5 hours per week (%) 5.4

Current drinkers (alcohol intake: g/day) 23.0–45.9. Age (years) 54.9±9.9; Body mass index (kg/m²) 23.0±3.1; History of hypertension (%) 21.8; History of diabetes (%) 2.1; More than high school education (%) 7.7; Current smokers (%) 22.2; Exercise > 5 hours per week (%) 5.9

Current drinkers (alcohol intake: g/day) 46.0–68.9. Age (years) 53.0±9.3; Body mass index (kg/m²) 23.4±3.4; History of hypertension (%) 23.3; History of diabetes (%) 2.4; More than high school education (%) 7.5; Current smokers (%) 41.6; Exercise > 5 hours per week (%) 4.5

Location: 45 areas throughout Japan

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: Not reported

Eligible population: Japanese men and women aged 40 to 79 years

Excluded populations: Subjects who reported a history of cancer, stroke, or myocardial infarction

Exposures at midlife

Relevant exposures: Alcohol intake


Measurement of exposure: Self-administered questionnaire. subjects choose their drinking status from three pre-coded response categories: nondrinkers, ex-drinkers, or current drinkers
### Outcomes at 55 years or over

**Outcomes:** All-cause mortality  
**Outcome measurement:** Resident-registry data from the municipalities  
**Time:** 1999

### Analysis

**Analysis strategy:** Cox proportional-hazards models  
**Confounders:** Age, body mass index, education, history of diabetes and hypertension, cigarette smoking, and exercise

### Results, limitations, source of funding

**Number:** 9589 subjects (5902 men and 3687 women) died from all causes  
**Effect estimates:**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Nondrinkers</th>
<th>Ex-drinkers</th>
<th>Current drinkers (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all cause</td>
<td>1.00</td>
<td>1.58 (1.44–1.74)</td>
<td>0.80 (0.72–0.88)</td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>23.0–45.9</td>
<td>0.90 (0.82–0.98)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>46.0–68.9</td>
<td>0.95 (0.86–1.04)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>&gt; 69.0</td>
<td>1.32 (1.18–1.48)</td>
<td></td>
</tr>
</tbody>
</table>

**Death from cancer**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Nondrinkers</th>
<th>Ex-drinkers</th>
<th>Current drinkers (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drinkers (g/day)</td>
<td>1.50 (1.29–1.75)</td>
<td>0.82 (0.70–0.95)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>23.0–45.9</td>
<td>0.96 (0.84–1.10)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>46.0–68.9</td>
<td>1.05 (0.91–1.20)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>&gt; 69.0</td>
<td>1.31 (1.10–1.56)</td>
<td></td>
</tr>
</tbody>
</table>

**Death from cardiovascular disease**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Nondrinkers</th>
<th>Ex-drinkers</th>
<th>Current drinkers (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drinkers (g/day)</td>
<td>1.79 (1.51–2.14)</td>
<td>0.86 (0.73–1.06)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>23.0–45.9</td>
<td>0.89 (0.75–1.05)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>46.0–68.9</td>
<td>1.09 (0.92–1.30)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>&gt; 69.0</td>
<td>1.28 (1.02–1.61)</td>
<td></td>
</tr>
</tbody>
</table>

**Death from injuries and external causes**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Nondrinkers</th>
<th>Ex-drinkers</th>
<th>Current drinkers (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drinkers (g/day)</td>
<td>1.69 (0.92–3.08)</td>
<td>1.52 (0.90–2.58)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>23.0–45.9</td>
<td>1.37 (0.83–2.26)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>46.0–68.9</td>
<td>1.23 (0.71–2.13)</td>
<td></td>
</tr>
<tr>
<td>Current drinkers (g/day)</td>
<td>&gt; 69.0</td>
<td>1.99 (1.09–3.64)</td>
<td></td>
</tr>
</tbody>
</table>

**P-value**

- Death from all cause <0.001; Death from cancer <0.001; Death from cardiovascular disease 0.01; Death from injuries and external causes 0.11

**Significant trends:** Risk of all-cause mortality was lowest among current drinkers with an alcohol intake of 0.1 to 22.9 g/d. Excessive mortality associated with heavy drinking was observed for cancer, cardiovascular disease and injuries and other external causes in men, while significantly reduced mortality with light drinking was seen for cancer in men and CVD in women. For men, the benefit associated with light alcohol consumption was more apparent among nonsmokers than among smokers.

**Limitations:**

1. Self-reported alcohol consumption  
2. Low risk of total mortality among light-to-moderate drinkers may be attributable to these favorable lifestyle factors rather than to the role of alcohol consumption itself
3. We could not estimate drinking patterns such as binge drinking or drinking with meals
4. Small number of response options for frequency of drinking

**Source of funding:** Japanese Ministry of Education, Culture, Sports, Science and Technology

| Authors: | Liu S, Willett WC, Manson JE, Hu FB, Rosner B, Colditz G |
| Year: | 2003 |
| Citation: | American Journal of Clinical Nutrition 78(5): 920-7 |
| Country of study: | US |
| Aim of study: | To determine the influence of intake of whole grains on body weight and weight changes |
| Study design: | Longitudinal |
| Quality score: | (++ + or -): + |

**Source population**

121,700 US female registered nurses ages 30-55 years recruited in 1976 and followed-up every two years as part of the Nurses’ Health Study

**Study (eligible and selected) population**

74,091 women that were ages 38-63 years in 1984

**Exclusion:**

i) Participants with daily energy intakes outside the 2514 – 14665 KF range in 1980
ii) Respondents with diabetes (n=2518), cardiovascular disease (n=690), and cancer (n=4458)

**Attrition:** -

**Exposures at midlife**

Semi-quantitative food frequency questionnaire (FFQ) administered in 1984, 1986, 1990, and 1994 to measure intake of whole-grain and refined-grain foods

Participants were asked about the mean frequency of consumption of one unit of each food item of interest over the past year, with response options ranging from ‘never’ to ‘>=6 times per day’

Average grain intake in servings/day was calculated for each participant

Reproducibility and validity of FFQ has been established; when FFQ was compared to diet records, the correlation coefficients for grain products ranged from 0.71-0.77

In the analysis, grain intake was divided into quintiles; the first quintile represented the smallest change in intake

**Outcomes at 55 years or over**

Body weight, BMI, and weight changes assessed

Body weight was self-reported every two years from 1984 to 1996, height was reported in 1976

Weight change was calculated as the difference in weight or BMI between: 1) 1984 and 1986, 2) 1986 and 1990, 3) and 1990 and 1994; weight change between 1984 and 1996 was also calculated

When self-reported and measured weights were compared in a sample of participants, correlation was 0.96

**Analysis**
**Analysis strategy:** Generalised estimating equations used to determine the influence of changes in intake of whole or refined grains on weight changes

**Confounders:** Age, changes in exercise, change in smoking status, change in hormone replacement therapy status, changes in intakes of alcohol, caffeine, and total energy, changes in intakes of saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, and protein, and BMI at baseline

### Results, limitations, source of funding

- Average BMI increased over time regardless of grain intake; 6400 women became obese (BMI \( \geq 30 \)) and 657 had a major weight gain (\( \geq 25 \) kg) over 12 years

**Average changes in BMI or in weight in 2-4 years during follow-up:**

- The average change in BMI increased (meaning, greater weight gain) with increasing intake of refined-grains (linear trend test p-value <0.0001)
- The average change in BMI decreased (less weight gain) with increasing intake of dietary fiber (trend p-value: 0.0001)
- The average change in BMI appeared to decrease (less weight gain) with increasing intake of whole grains (trend test p<0.0001)
- Same results as above were reported when the average change in weight in 2-4 years was the outcome

**Average weight gain during follow-up:**

- Average weight gain became greater with increasing change in intake of refined grains (trend test p-value <0.0001), while it became lower with increasing intake of dietary fiber (trend test p-value <0.0001)

**Odds for obesity or weight gain during follow-up:**

- There appeared to be a decreasing trend in obesity (BMI \( \geq 30 \)) and major weight gain (\( \geq 25 \) kg) with larger intakes of whole grains (trend test p-values=0.0002 and 0.03, respectively); intake of refined grains appeared to be inversely related to obesity and major weight gain (trend test p-values: \(<0.0001\) and 0.04, respectively)
- There appeared to be a decreasing trend in major weight gain with larger intake of dietary fiber (trend test p-value <0.0001)
- Women with the highest increase in intake of dietary fiber had a significantly lower risk of major weight gain compared to women with the smallest change in intake of fiber \((\text{OR}=0.51, [0.39, 0.67])\)

**Limitations:**

1. Those with recent weight gain may attempt to lose weight by increasing consumption of grain products (difficult to ascertain whether increases in intake of grains prevented weight gain)
2. Participants with greater intake of whole grains and caloric restriction may be more health conscious
3. Misclassification of dietary intake may be dependent on body weight (e.g., obese people may underreport intake)
4. Residual confounding from other dietary factors

**Source of funding:** None reported

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**Authors:** Liu Y, Sobue T, Otani T, Tsugane S  
**Year:** 2004  
**Citation:** Cancer Causes Control 15(4): 349-57  
**Country of study:** Japan  
**Aim of study:** To determine the influence of fruit and vegetables on lung cancer  
**Study design:** Longitudinal  
**Quality score:** (+++, + or -): +
<table>
<thead>
<tr>
<th>Source population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two population-based cohorts of 57,591 men and 59,103 women were established through residence registries maintained by local governments and public health centres of administrative districts. Cohort I comprised inhabitants ages 40-59 years in 1990 and cohort II consisted of inhabitants ages 40-69 years in 1993. Questionnaires completed by 45,452 men (response rate: 79%) and 49,924 women (response rate: 84%) from both cohorts.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (eligible and selected) population</th>
</tr>
</thead>
<tbody>
<tr>
<td>44,774 men and 48,566 women</td>
</tr>
<tr>
<td>Follow-up: Study start date (Jan. 1, 1990 for Cohort I and Jan. 1, 1993 for Cohort II) until date of diagnosis of lung cancer, date of migration out of study area, date of death or end of follow-up Dec. 31, 1999.</td>
</tr>
<tr>
<td>Exclusion: Men (n=680) and women (n=1358) with a history of cancer.</td>
</tr>
<tr>
<td>Attrition: -</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposures at midlife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary habits were assessed in 1990 for Cohort I and 1993 for Cohort II using self-administered questionnaire. Food frequency questionnaires administered to both cohorts that assessed average consumption of food items (vegetables, fruit, fruit and vegetable juices) during past month, with the following response options '&lt;1 day/week', '1-2 days/week', '3-4 days/week', and 'almost daily' (with the additional category of 'never use' for cohort II. Participants reporting daily drinking of juice, the cups/day were further assessed. The portion size and content of food items were taken into account when calculating amount of vegetable and fruit intakes, which was subsequently divided into and analysed as tertiles ('low', 'medium', 'high'). When the questionnaire for Cohort I was compared to dietary records, correlation coefficients ranged from 0.26 to 0.52.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident cases of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, other histological types) identified through hospital records, population-based cancer registries, and death certificates.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis strategy: Cox proportional hazards model used to assess influence of dietary intake on lung cancer risk. Relative risks of Cohorts I and II were also pooled using inverse-variance weighting (cohorts combined).</td>
</tr>
<tr>
<td>Confounders: Age, gender, area, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, and pickled vegetables, smoking status, smoking duration, and number of cigarettes per day among ever smokers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results, limitations, source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>428 lung cancer cases (177 cases from Cohort I reported during 401,382 person-years of follow-up).</td>
</tr>
</tbody>
</table>
Among Cohort I participants, the risk of adenocarcinoma was greater for those in the middle consumption category of fruit intake compared to the low consumption category of fruit intake (RR=2.06, [1.20, 3.54])

Overall, there were no significant associations between vegetable and fruit consumption and incidence of lung cancer (except for the above result)

**Limitations:**
1. Residual confounding
2. Misclassification of intake of fruit and vegetables through use of a simple food frequency questionnaire

**Source of funding:** Ministry of Health and Welfare of Japan

<table>
<thead>
<tr>
<th>Authors</th>
<th>Malmberg JJ, Miilunpalo SI, Pasanen ME, Vuori IM, Oja P</th>
</tr>
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<tbody>
<tr>
<td><strong>Year:</strong></td>
<td>2006</td>
</tr>
<tr>
<td><strong>Citation:</strong></td>
<td>Journal of Aging and Physical Activity 14(2): 133-53</td>
</tr>
<tr>
<td><strong>Country of study:</strong></td>
<td>Finland</td>
</tr>
<tr>
<td><strong>Aim of study:</strong></td>
<td>Associations of the amount, frequency and intensity, and type of leisure-time physical activity with the risk of self-reported difficulty in walking and stair climbing</td>
</tr>
<tr>
<td><strong>Study design:</strong></td>
<td>Population-based cohort</td>
</tr>
<tr>
<td><strong>Quality score:</strong></td>
<td>(+, + or -): +</td>
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</table>

**Source population**

<table>
<thead>
<tr>
<th><strong>Number of people:</strong></th>
<th>6,787</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics:</strong></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Study (eligible and selected) population**

<table>
<thead>
<tr>
<th><strong>Number of people:</strong></th>
<th>1791</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics:</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Men**

- Age in 1981, years
  - 40-47 98 (234/238)
  - 48-55 92 (147/160)
  - 56-64 80 (59/74)
- Marital status
  - Married 94 (369/394)
  - Single 92 (55/60)
- Divorced, separated, or widowed 88 (14/16)
- Living community
  - Urban 95 (253/267)
  - Rural 91 (186/204)
- Education
  - Higher education 100 (21/21)
  - Secondary education 98 (119/121)
  - Vocational training 94 (176/187)
  - No education 86 (110/128)
- BMI, kg/m²
  - <25.0 93 (175/188)
  - 25.0-29.9 94 (219/233)
  - ≥30 89 (33/37)
Smoking status
Never smoked 96 (150/157)
Past smoker 91 (179/196)
Current smoker 93 (102/110)

Alcohol use, g/cby
0 88 (67/76).
0.1-12.0 95 (250/263)
>12.0 92 (122/132)

Participant in working life
Yes 95 (404/425)
No 73 (30/41)

Occupational activity
Sitting 95 (112/118)
Light or moderate movement 97 (176/182)
Heavy or very heavy movement 93 (116/125)

Did not work 68 (19/28)

Disease or symptoms
Did not prevent participation in PA 96 (335/348)
Somewhat prevented participation in PA 85 (105/124)

Women
Age in 1981, years
40-47 93 (252/270)
48-55 91 (177/194)
56-64 77(76/99)

Marital status
Married 90 (392/434)
Single 90(44/49)
Divorced, separated, or widowed 87(67/77)

Living community
Urban 90 (310/345)
Rural 90(195/217)

Education
Higher education 97 (33/34)
Secondary education 93 (124/134)
Vocational training 93 (185/198)
No education 83 (157/189)

BMI, kg/m2
<25.0 94 (244/261)
25.0-29.9 89(199/223)
>30 73 (43/59)

Smoking status
Never smoked 89 (388/434)
Past smoker 94(43/46)
Current smoker 90(71/79)

Alcohol use, g/cby
0 86 (242/282)
0.1-12.0 94 (246/262)
>12.0 100 (15/15)

Participant in working life
Yes 91 (357/391)
No 86(146/169)

Occupational activity
Sitting 91 (122/134)
Light or moderate movement 92 (267/289)
Heavy or very heavy movement 85 (44/52)

Did not work 80 (48/60)
Disease or symptoms
Did not prevent participation in PA 93 (396/428)
Somewhat prevented participation in PA 81 (109/135)

**Location:** Oja, Milunpalo, Vuori, Pasanen, Urponen. Finland

**Recruitment strategy:** Not reported

**Length of follow-up:** 16 years

**Response rate and loss to follow-up:** 77.5%

**Eligible population:** All respondents who were 40-64 years old (in 1981) and had no self-reported difficulty in walking (n=1,198) or stair climbing (n=1,000).

**Excluded populations:** Excluded all individuals who reported (in 1980) that they were substantially or totally unable to participate in physical activity because of their health status or who failed to respond to 5 or more of the 13 questions concerning physical activity

### Exposures at midlife

**Relevant exposures:** Leisure-time physical activity

**Time:** 1980-1981

**Measurement of exposure:** Three different sets of LTPA questions, two sets in 1980 and one in 1981

Used two LTPA indexes—fitness activity and commuting—to test recent evidence suggesting that energy expenditure during physical activity

The single-item self-assessment of global LTPA covered the intensity, frequency, and duration of respondents' exercise sessions as follows: .. Which of the following categories best describes your physical activity during the past 2 months?

The single-item self-assessment of global LTPA reflects the behaviour, and LTPA energy-expenditure index, the energy cost of this behaviour

### Outcomes at 55 years or over

**Outcomes:** Mobility difficulties

**Outcome measurement:** Self-reported estimate of their ability to walk 2 km and climb several flights of stairs without rest

**Time:** 1981, 1990, and 1996

### Analysis

**Analysis strategy:** Cox proportional hazards model

**Confounders:** Age, body-mass Index, disease or symptoms, and education, marital, living community, employment, occupational activity, smoking, and alcohol-consumption status

**Significant trends:**

**Men:** Rates for difficulty in walking and stair climbing were highest among the oldest; the obese; those not working; those who suffered from disease or symptoms that prevented them from participating in physical activity.

**Women:** Rates for difficulty in walking and stair climbing were highest among the oldest; the overweight or obese; those who lived in rural communities; who suffered from disease or symptoms that prevented them from participating in physical activity.

**Limitations:** Self-reported estimates

**Source of funding:** Finnish Ministry of Education, the Finnish Ministry of Social Affairs and Health, and the Yrjo Jahnsson Foundation
### Results, limitations, source of funding

**Number:** Depending upon outcome and variable:

- **Walking**
  - Men: 113-118
  - Women: 130-146

- **Stair**
  - Men: 116-127
  - Women: 176-198

**Effect estimates:**

**Relative Risks (95% CI) for Self-Reported Difficulty In Walking and Stair Climbing According to LTPA**

<table>
<thead>
<tr>
<th></th>
<th>Walking</th>
<th>Stair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Difficulty In Walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global LPTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.49 (0.77-2.88)</td>
<td>1.27 (0.77-2.09)</td>
</tr>
<tr>
<td>Low</td>
<td>1.60 (0.88-2.91)</td>
<td>0.98 (0.585-1.75)</td>
</tr>
<tr>
<td>p</td>
<td>.298</td>
<td>.531</td>
</tr>
<tr>
<td>LTPA energy expenditure index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.04 (0.66-1.66)</td>
<td>0.98 (0.585-1.75)</td>
</tr>
<tr>
<td>Low</td>
<td>1.26 (0.77-2.05)</td>
<td>1.26 (0.77-2.05)</td>
</tr>
<tr>
<td>Fitness activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3x a week</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Twice</td>
<td>2.90 (1.09-7.70)</td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>4.48 (1.70-11.79)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 per week</td>
<td>3.74 (1.47-9.54)</td>
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</tr>
<tr>
<td>No activity</td>
<td>4.15 (1.62-10.63)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>.029</td>
<td>.532</td>
</tr>
</tbody>
</table>

**Commuting**

At least once a week: 1.00

No activity: 0.86 (0.54-1.37)

p: .532

**Difficulty in Stair Climbing**

<table>
<thead>
<tr>
<th></th>
<th>Stair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Global LPTA</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.86 (0.99-3.52)</td>
</tr>
<tr>
<td>Low</td>
<td>2.30 (1.27-4.16)</td>
</tr>
<tr>
<td>p</td>
<td>.023</td>
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<tr>
<td>LTPA energy expenditure index</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.04 (0.66-1.66)</td>
</tr>
<tr>
<td>Low</td>
<td>1.26 (0.77-2.05)</td>
</tr>
<tr>
<td>LTPA frequency intensity</td>
<td>Vigorous</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.88 (0.51-0.51)</td>
</tr>
<tr>
<td>Light</td>
<td>0.98 (0.56-1.73)</td>
</tr>
<tr>
<td>No activity</td>
<td>1.42 (0.81-2.49)</td>
</tr>
<tr>
<td>P= .393</td>
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</table>

<table>
<thead>
<tr>
<th>Fitness activity</th>
<th>&gt;3x a week</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice</td>
<td>0.91 (0.46-1.82)</td>
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</tr>
<tr>
<td>Once a week</td>
<td>1.38 (0.10-2.71)</td>
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<tr>
<td>&lt;1 per week</td>
<td>1.34 (0.69-2.62)</td>
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</tr>
<tr>
<td>No activity</td>
<td>1.42 (0.81-2.49)</td>
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</tr>
<tr>
<td>P= .221</td>
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<table>
<thead>
<tr>
<th>Commuting</th>
<th>At least once a week</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>No activity</td>
<td>1.08 (0.71-1.65)</td>
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</tr>
<tr>
<td>P= .725</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Women Difficulty In Walking Global LPTA</th>
<th>High</th>
<th>1.00</th>
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</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>0.69 (0.37-1.29)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00 (0.61-1.65)</td>
<td></td>
</tr>
<tr>
<td>p = .371</td>
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</table>

<table>
<thead>
<tr>
<th>LTPA energy expenditure index</th>
<th>High</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>0.95 (0.61-1.47)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.04 (0.65-1.66)</td>
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<tr>
<td>P= .935</td>
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</table>

<table>
<thead>
<tr>
<th>LTPA frequency intensity</th>
<th>Vigorous</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>1.01 (0.61-1.66)</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>1.19 (0.73-1.94)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>1.01 (0.57-1.76)</td>
<td></td>
</tr>
<tr>
<td>P= .873</td>
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</table>

<table>
<thead>
<tr>
<th>Fitness activity</th>
<th>&gt;3x a week</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice</td>
<td>0.86 (0.49-1.52)</td>
<td></td>
</tr>
<tr>
<td>Once a week</td>
<td>0.82 (0.46-1.45)</td>
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<tr>
<td>&lt;1 per week</td>
<td>0.68 (0.38-1.21)</td>
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<tr>
<td>No activity</td>
<td>0.71 (0.41-1.25)</td>
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<tr>
<td>P= .690</td>
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<thead>
<tr>
<th>Commuting</th>
<th>At least once a week</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>No activity</td>
<td>0.79 (0.48-1.31)</td>
<td></td>
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<tr>
<td>P= .363</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Difficulty in Stair Climbing Difficulty In Walking Global LPTA</th>
<th>High</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>0.93 (0.56-1.53)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.49 (0.99-2.24)</td>
<td></td>
</tr>
<tr>
<td>p = 0.34</td>
<td></td>
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</table>
LTPA energy expenditure index
High 1.00
Moderate 0.92 (0.65-1.30)
Low 0.99 (0.64-1.51)
P=.869

LTPA frequency intensity
Vigorous 1.00
Moderate 0.95 (0.62-1.47)
Light 1.81 (1.20-2.73)
No activity 1.16 (0.73-1.85)
P=.009

Fitness activity
>3x a week 1.00
Twice 0.68 (0.42-1.12)
Once a week 0.97 (0.60-1.56)
<1 per week 0.98 (0.60-1.62)
No activity 0.78 (0.48-1.26)
P=.43

Commuting
At least once a week 1.00
No activity 0.92 (0.64-1.33)
P=.659

Authors: Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S; Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Group

Year: 2004
Citation: Stroke 35(6): 1248-53
Country of study: Japan
Aim of study: To assess the influence of smoking on fatal and nonfatal strokes
Study design: Longitudinal
Quality score: (++, + or -): +

Source population
Population-based cohort of 27,063 men and 27,435 women ages 40-59, and born between 1930 and 1949, registered in administrative districts and supervised by public health centre areas in Jan. 1, 1990
Cohort from Ninohe, Yokote, Nagano, Ishikawa

Study (eligible and selected) population
Self-administered questionnaire (capturing smoking, drinking, diet) returned by 20,665 men (76%) and 22,484 women (82%) in 1990/1992. Analysis restricted to 19,782 men and 21,500 women
Follow-up: 11 years from 1990 to 2001. Person-months calculated from date of return of the baseline questionnaire to the first end point, death, or January 1, 2002, whichever was first.
Exclusion:
 i) Individuals with stroke, myocardial infarction, angina pectoris, cancer at baseline (n=667 men and 883 women)
 ii) Those with incomplete data (n=196 men and 85 women)
 iii) Loss to follow-up (n=14 men and 14 women)
Attrition: 14 men and 14 women lost to follow-up
### Exposures at midlife

Self-reported smoking for both sexes categorised as never-smokers, ex-smokers, and current smokers; smoking habit for men categorized as: never-smoker, ex-smoker, current smoker, and number of cigarettes 1 to 19/d, 20 to 39/d, and >=40/d

### Outcomes at 55 years or over

Fatal and nonfatal strokes assessed with medical records, death certificates

### Analysis

**Analysis strategy:** The Cox proportional hazards model was used to assess the influence of smoking on fatal and nonfatal strokes

**Confounders:** Age, alcohol intake, body mass index, history of diabetes (yes), education level, sports at leisure, frequency of fruit, vegetable, and fish servings, and public health centers

### Results, limitations, source of funding

- Risks for current smokers compared with never-smokers were higher for total stroke (RR=1.27, [1.05, 1.54]), subarachnoid hemorrhage (RR=3.60, [1.62, 8.01]), ischemic stroke (1.66, [1.25, 2.20]); the respective relative risks among women were 1.98 (1.42 to 2.77), 1.53 (0.86 to 4.25), 2.70 (1.45 to 5.02), and 1.57 (0.86 to 2.87)

**Limitations:**
1. Self-reported data
2. Limited generalizability of results to women and older men

**Source of funding:** Ministry of Health, Labor, and Welfare of Japan

---

**Authors:** Masaki M, Sugimori H, Nakamura K, Tadera M

**Year:** 2003

**Citation:** Asian Pacific Journal of Cancer Prevention 4(1): 61-6

**Country of study:** Japan

**Aim of study:** Identify dietary patterns that may change stomach cancer risk

**Study design:** Cohort

**Quality score:** (+++, + or -): +

---

**Source population**

**Number of people:** 200,000

**Study (eligible and selected) population**

**Number of people:** 5,644

**Characteristics:**

**Vegetable and fruit**

- Low
- Entire cohort (%) 33.4
- Mean age (years) 50.1
- Mean BMI 23.1
Education (% university) 58.9
History of peptic ulcer (% yes) 17.9
Family history of stomach cancer (% yes) 10.3
Cigarette smoking (%)
Never 18.8
Past 21.2
Current 60.1
Alcohol drinking (%)
No 17.2
Light 32.4
Heavy 50.4

Middle
Entire cohort (%) 34.5
Mean age (years) 51.7
Mean BMI 23.2
Education (% university) 62.3
History of peptic ulcer (% yes) 20.1
Family history of stomach cancer (% yes) 8.3
Cigarette smoking (%)
Never 21.1
Past 29.3
Current 49.7
Alcohol drinking (%)
No 18.3
Light 36.3
Heavy 45.4

High
Entire cohort (%) 32.1
Mean age (years) 53.2
Mean BMI 23.2
Education (% university) 64.4
History of peptic ulcer (% yes) 22.3
Family history of stomach cancer (% yes) 10.9
Cigarette smoking (%)
Never 21.1
Past 34.3
Current 44.6
Alcohol drinking (%)
No 19.6
Light 38.3
Heavy 42.1

Western breakfast

Low
Entire cohort (%) 32.6
Mean age (years) 51.9
Mean BMI 23.4
Education (% university) 54.6
History of peptic ulcer (% yes) 20.5
Family history of stomach cancer (% yes) 10.7
Cigarette smoking (%)
Never 17.8
Past 28.6
Current 53.7
Alcohol drinking (%)
No 12.1
Light 27.9
<table>
<thead>
<tr>
<th>Level</th>
<th>Entire cohort (%)</th>
<th>Mean age (years)</th>
<th>Mean BMI</th>
<th>Education (% university)</th>
<th>History of peptic ulcer (% yes)</th>
<th>Family history of stomach cancer (% yes)</th>
<th>Cigarette smoking (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy</td>
<td>32.9</td>
<td>50.8</td>
<td>23.2</td>
<td>62.0</td>
<td>18.0</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High</td>
<td>34.5</td>
<td>52.0</td>
<td>23.0</td>
<td>68.5</td>
<td>21.6</td>
<td>10.0</td>
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</tr>
<tr>
<td>Meat</td>
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<tr>
<td>Low</td>
<td>33.7</td>
<td>53.4</td>
<td>23.2</td>
<td>63.9</td>
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<td>10.3</td>
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<tr>
<td>Low</td>
<td>35.5</td>
<td>51.1</td>
<td>23.2</td>
<td>60.0</td>
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<td>8.9</td>
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<td>Middle</td>
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</tr>
<tr>
<td>Alcohol drinking (%)</td>
<td>Never 19.2</td>
<td>Past 26.8</td>
<td>Current 54.0</td>
<td></td>
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<tr>
<td></td>
<td>No 15.9</td>
<td>Light 37.0</td>
<td>Heavy 47.1</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High</th>
<th>Entire cohort (%) 30.8</th>
<th>Mean age (years) 50.1</th>
<th>Mean BMI 23.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of peptic ulcer (% yes)</td>
<td>18.2</td>
<td>Education (% university) 61.7</td>
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<tr>
<td>Family history of stomach cancer (% yes)</td>
<td>10.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>Never 19.4</td>
<td>Past 23.6</td>
<td>Current 57.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low</th>
<th>Entire cohort (%) 33.6</th>
<th>Mean age (years) 51.4</th>
<th>Mean BMI 23.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of peptic ulcer (% yes)</td>
<td>21.4</td>
<td>Education (% university) 60.3</td>
<td></td>
</tr>
<tr>
<td>Family history of stomach cancer (% yes)</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>Never 16.0</td>
<td>Past 27.5</td>
<td>Current 56.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rice/snacks</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice/snacks</td>
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<tr>
<td>Low</td>
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<tr>
<td>Mean age (years) 51.4</td>
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<tr>
<td>Mean BMI 23.1</td>
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<tr>
<td>Education (% university) 60.3</td>
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<tr>
<td>History of peptic ulcer (% yes)</td>
<td>21.4</td>
<td></td>
<td></td>
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<tr>
<td>Family history of stomach cancer (% yes)</td>
<td>10.0</td>
<td></td>
<td></td>
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<tr>
<td>Cigarette smoking (%)</td>
<td>Never 16.0</td>
<td>Past 27.5</td>
<td>Current 56.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Middle</th>
<th>Entire cohort (%) 32.9</th>
<th>Mean age (years) 51.1</th>
<th>Mean BMI 23.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of peptic ulcer (% yes)</td>
<td>18.8</td>
<td>Education (% university) 63.0</td>
<td></td>
</tr>
<tr>
<td>Family history of stomach cancer (% yes)</td>
<td>9.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Cigarette smoking (%) | Never 18.9 | Past 27.4 | Current 53.7 |
| Alcohol drinking (%)  | No 15.8    | Light 36.5 | Heavy 47.7   |

| High                   | Entire cohort (%) 33.5 |                         |                        |

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
Mean age (years) 52.4
Mean BMI 23.2
Education (% university) 62.4
History of peptic ulcer (% yes) 20.0
Family history of stomach cancer (% yes) 10.0
Cigarette smoking (%)
Never 26.1
Past 29.6
Current 44.4
Alcohol drinking (%)
No 26.0
Light 37.4
Heavy 36.6

Exposures at midlife

Relevant exposures: Frequency of consumption of selected foods, health condition, medical history, smoking and drinking habits, exercise and leisure time, places of birth, and working situation

Time: 1988

Measurement of exposure: Self-report questionnaire

Location: Tokyo, Japan

Recruitment strategy: Not reported

Length of follow-up: 10 years of follow-up

Response rate and loss to follow-up: Subjects who had retired from their firms before the start of the study (n=8), having a past history of cancer (n=11), incomplete description of food consumption questionnaire (n=102), those identified within first year follow-up (n=71)

Eligible population: Members of the Health Insurance Society of Tokyo Stockbrokerage

Outcomes at 55 years or over

Outcomes: Stomach cancer

Outcome measurement: Detailed statements of medical care (performed for insured persons) by medical care facilities

Time: Until the dates of the events or the end of follow-up (August 31, 1998) whichever occurred first

Analysis

Analysis strategy: Cox proportional hazard regression model

Confounders: Age (10 years age groups), cigarette smoking (never, former current), alcohol drinking (no or current drinker), and history of peptic ulcer and family history of stomach cancer (yes or no).

Results, limitations, source of funding

Number: 86 incident cases of stomach cancer

Effect estimates:

Rate Ratios for Stomach Cancer According to Tertiles of Dietary Pattern

<table>
<thead>
<tr>
<th>Dietary Pattern</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle</td>
<td>1.06 (0.61-1.87)</td>
</tr>
<tr>
<td>High</td>
<td>0.78 (0.42-1.44)</td>
</tr>
</tbody>
</table>
Western breakfast
Low 1.00
Middle 0.59 (0.33-1.08)
High 0.71 (0.40-1.24)
P trend .20

Meat
Low 1.00
Middle 0.55 (0.29-1.01)
High 1.10 (0.64-1.89)
P trend .07

Rice/snacks
Low 1.00
Middle 0.52 (0.27-1.01)
High 1.19 (0.71-2.02)
P trend .05

Significant trends: There were no clear associations between the four major dietary patterns and stomach cancer risk

Limitations:
1. Relatively small size of cohort
2. Food consumption data in summer only
3. Case ascertainment only through medical records provided by various clinical sites
4. No data on histological classification of stomach cancer
5. Portion size and energy intake were not available

Source of funding: Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan: 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102

Authors: Meisinger C, Löwel H, Heier M, Kandler U, Döring A
Year: 2007
Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(6): 788-92.
Country of study: Germany
Aim of study: To examine sex-specific associations between sports activities in leisure time and incident myocardial infarction
Study design: Independent cross-sectional surveys
Quality score: (+++, + or -): +

Source population
Number of people: 7823
Demographics: Not reported

Study (eligible and selected) population
Number of people: 3501 men and 3475 women
Characteristics:
No sports activities in leisure time
Men: Age (years) 58.5 (8.0); Education ( < 12 years, %) 77.6; BMI (kg/m2) 28.1 (3.8); Regular smoking (%) 27.7; Alcohol intake 0 g/day (%) 17.7, 0.1–39.9 g/day (%) 47.0; > 40 g/day (%) 35.3;
Parental history of MI (%) 14.3

**Women:** Age (years) 58.5 (8.1); Education (< 12 years, %) 90.7; BMI (kg/m²) 28.3 (4.9); Regular smoking (%) 11.2; Alcohol intake 0 g/day (%) 52.1, 0.1–19.9 g/day (%) 33.0, > 20 g/day (%) 14.9; Parental history of MI (%) 18.4

**Low level of sports activities in leisure time**

**Men:** Age (years) 57.2 (8.0); Education (< 12 years, %) 72.1; BMI (kg/m²) 27.9 (3.3); Regular smoking (%) 24.8; Alcohol intake 0 g/day (%) 14.2, 0.1–39.9 g/day (%) 48.8, > 40 g/day (%) 37.0; Parental history of MI (%) 17.2

**Women:** Age (years) 6.1 (7.3); Education (< 12 years, %) 87.6; BMI (kg/m²) 27.7 (4.5); Regular smoking (%) 16.3; Alcohol intake 0 g/day (%) 46.0, 0.1–19.9 g/day (%) 37.3, > 20 g/day (%) 16.8; Parental history of MI (%) 20.7

**Moderate level of sports activities in leisure time**

**Men:** Age (years) 55.7 (7.6); Education (< 12 years, %) 59.8; BMI (kg/m²) 27.6 (3.3); Regular smoking (%) 21.0; Alcohol intake 0 g/day (%) 13.6, 0.1–39.9 g/day (%) 53.5, > 40 g/day (%) 32.8; Parental history of MI (%) 18.7

**Women:** Age (years) 55.8 (7.8); Education (< 12 years, %) 86.0; BMI (kg/m²) 26.6 (4.2); Regular smoking (%) 12.4; Alcohol intake 0 g/day (%) 41.5, 0.1–19.9 g/day (%) 38.5, > 20 g/day (%) 20.0; Parental history of MI (%) 23.7

**High level of sports activities in leisure time**

**Men:** Age (years) 57.2 (8.2); Education (< 12 years, %) 60.3; BMI (kg/m²) 27.3 (3.1); Regular smoking (%) 16.0; Alcohol intake 0 g/day (%) 17.7, 0.1–39.9 g/day (%) 52.5, > 40 g/day (%) 29.7; Parental history of MI (%) 19.6

**Women:** Age (years) 56.8 (7.8); Education (< 12 years, %) 81.3; BMI (kg/m²) 26.5 (4.3); Regular smoking (%) 12.4; Alcohol intake 0 g/day (%) 42.3, 0.1–19.9 g/day (%) 36.5, > 20 g/day (%) 21.2; Parental history of MI (%) 25.0

**Location:** Germany

**Recruitment strategy:** Not reported

**Length of follow-up:** Median of 8.6 years

**Response rate and loss to follow-up:** Not reported

**Eligible population:** Men and women aged 45–74 years who participated in one of the three MONICA Augsburg surveys

**Excluded populations:** 248 study participants with incomplete data on any of the included variables and 599 persons with angina pectoris or prevalent MI at baseline

**Exposures at midlife**

**Relevant exposures:** Sports activities in leisure time


**Measurement of exposure:** Standardized interview

Leisure-time physical activity was assessed by a four-level graded scale assessing leisure time activities during summer and wintertime (0, <1, 1–2 and more than 2h/week).

**Outcomes at 55 years or over**

**Outcomes:** Incidence of nonfatal MI or fatal coronary death, including sudden cardiac death

**Outcome measurement:** MONICA/KORA Augsburg coronary event registry

**Time:** 2002
### Analysis

**Analysis strategy:** Cox proportional hazard models

**Confounders:** Physical activity, age, smoking status, alcohol intake, history of diabetes, education and parental history of MI, intermediary risk factors actual hypertension, dyslipidemia, and BMI

### Results, limitations, source of funding

**Number:** 295 men and 91 women

**Effect estimates:**
- No sports activities in leisure time
  - Men 1.0
  - Women 1.0
- Low level of sports activities in leisure time
  - Men 1.01 (0.73–1.40)
  - Women 1.00 (0.56–1.78)
- Moderate level of sports activities in leisure time
  - Men 0.78 (0.56–1.10)
  - Women 0.49 (0.24–1.00)
- High level of sports activities in leisure time
  - Men 0.84 (0.59–1.18)
  - Women 0.21 (0.05–0.87)

**Significant trends:** Moderate or high levels of sports activities in leisure time are associated with a significantly reduced risk of MI in women, but not men from the general population

**Limitations:**
1. Self-reported information on physical activity
2. Focused on sports activities in leisure time only
3. Small number of cases in women of the two highest physical activity categories

**Source of funding:** GSF National Research Center for Environment and Health, Federal Ministry of Education, Science, Research and Technology (01 ER 9701/4) and the German Research Foundation (DFG) (TH 784/2-1)

### Authors

Menotti A, Lanti M, Puddu PE

**Year:** 2000

**Citation:** Italian Heart Journal 1(11): 749-57

**Country of study:** Italy

**Aim of study:** To describe the comprehensive disease burden related to cardiovascular diseases of atherosclerotic-hypertensive origin in a population sample of middle-aged men

**Study design:** Prospective cohort

**Quality score: (++, + or -):** +

### Source population

**Number of people:** Not reported

**Demographics:** Not reported
**Study (eligible and selected) population**

**Number of people:** 1712  
**Characteristics:**
- Age (years) 49.8 ± 5.1  
- Cigarettes (n/day) 8.7 ± 9.5  
- Diabetes(%) 4.8  
- Corneal arcus(%) 13.9  
- Vital capacity (dl) 45.7 ± 8.0  
- Cholesterol (mmol/l) 5.21 ± 1.06  
- Systolic blood pressure (mmHg) 143.6 ± 21.0  
**Location:** Crevalcore in Northern Italy and Montegiorgio in Central Italy  
**Recruitment strategy:** Not reported  
**Length of follow-up:** 2S-year follow-up  
**Response rate and loss to follow-up:** 98.8%  
**Eligible population:** Italian middle-aged men  
**Excluded populations:** Subjects with cardiovascular diseases at entry examination

**Exposures at midlife**

**Relevant exposures:** Smoking habits  
**Time:** 1960  
**Measurement of exposure:** Elicited from a questionnaire allowing us to estimate the daily average consumption of cigarettes (nlday)

**Outcomes at 55 years or over**

**Outcomes:** Morbidity and mortality  
**Outcome measurement:** Causes of death were allocated reviewing and combining together information from several sources such as death certificates, hospital and medical records, interviews with physicians, relatives of the deceased and any other witness of the fatal event. Morbidity data obtained via a) interim quinquennial; b) information obtained in relation to causes of death; c) periodic visits to local physicians and hospitals for identification of new cases; d) home visits to subjects suspected of having developed a new CV event; e) postal questionnaire and postal clinical records in a few cases  
**Time:** Not reported

**Analysis**

**Analysis strategy:** Log-linear model incorporating the Weibull distribution  
**Confounders:** Age, Cigarettes, diabetes, corneal arcus, vital capacity, cholesterol and systolic blood pressure

**Results, limitations, source of funding**

**Number:** 126 for CHD, 62 for stroke, 8 for PAD, 9 for other heart diseases, 24 for lung cancer, 126 for other cancer locations, 21 for chronic bronchitis, 8 for infectious diseases, 25 for violence, and 75 for all other causes  
**Effect estimates:** CHD-H
### Study Title

Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

### Table

<table>
<thead>
<tr>
<th>Condition</th>
<th>Coefficient T value</th>
<th>Age</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD-A</td>
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<tr>
<td>STR-H</td>
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<td></td>
</tr>
<tr>
<td>STR-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CVD</td>
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</tr>
</tbody>
</table>

Delta for Hazard ratio, Hazard ratio, (95% CI)

- Age (years): 5, 1.29, (1.19-1.39)
- Cigarettes (n/day): 10, 1.16 (1.08-1.24)

### Significant trends

Incidence of cardiovascular disease is higher than CHD

### Limitations

Not reported

### Source of funding

Personal grant to the senior author (AM) from the Association for Cardiac Research, Rome, Italy, and by a grant of the Martinson Clinical Foundation, Wayzata, Minnesota, USA.

---

### Authors

Menotti A, Lanti M, Maiani G, Kromhout D

### Year

2006

### Citation

Aging Clinical and Experimental Research 18(5): 394-406

### Country of study

Italy

### Aim of study

Survival and all-cause mortality in two cohorts of middle-aged men followed for 40 years

### Study design

Longitudinal

### Quality score

(++ + or -): +

---

### Source population

Number of people: Not reported

Demographics: Not reported

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### Study (eligible and selected) population

Number of people: 1712
Characteristics: Not reported
Location: Crevalcore in Northern Italy and Montegiorgio in Central Italy
Recruitment strategy: Not reported
Length of follow-up: 40 years
Response rate and loss to follow-up: 98.8%
Eligible population: Middle-aged men
Excluded populations: Not reported

Exposures at midlife
Relevant exposures: Physical activity, cigarette smoking, diet
Time: 1960
Measurement of exposure: Questionnaire

Outcomes at 55 years or over
Outcomes: Causes of death and morbidity
Outcome measurement: Death certificates, hospital and medical records, interviews with physicians and relatives of the deceased, and any other witnesses of fatal events.
Time: Not reported

Analysis
Analysis strategy: Proportional hazard model
Confounders: Age; father history, mother history, family history of cardiovascular diseases; marital status children; job related physical activity, cigarette smoking, diet of any type followed by subjects; height, weight, body mass index (BMI), trunk/height ratio, biacromial diameter, bicrystal diameter, shoulder/pelvis shape, laterality linearity index, tricipital skinfold thickness, subscapular skinfold thickness, arm circumference; systolic blood pressure. Diastolic blood pressure, mean blood pressure, heart rate: vital capacity, forced expiratory volume; serum cholesterol, urine protein, urine glucose: baldness, corneal arcus, xanthelasma; diagnoses of Cardiovascular diseases, cancer, diabetes, chronic bronchitis, history of lung tuberculosis, bronchial asthma, peptic ulcer, intestinal diseases, liver diseases, gall bladder diseases, kidney stones, other genito-urinary diseases; thyroid disease; minor ECG abnormalities at rest, exercise ECG abnormalities

Results, limitations, source of funding
Number: 1434 deaths (83.8%)
Effect estimates:
Risk factor Coefficient and (SE) Hazard ratio (95% confidence) Standardized Coefficient and (rank)
Age 0.1021 (0.0064) 1.67 (1.56-1.77) 0.5152 (1)  
Father history -0.1692 (0.0679) 1.18 (1.04-1.35) 0.0689 (10)  
Mother history 0.2166 (0.0695) 1.24 (1.08-1.42) 0.0875 (7)  
Physical activity -0.0986 (0.0446) 0.91 (0.83-0.99) -0.0636 (13)  
Cigarette smoking 0.0194 (0.0029) 1.21 (1.15-1.29) 0.1841 (3)  
Body mass index (linear) -0.1425 (0.0721) 0.57 (0.33-1.00) ---  
Body mass index (quadratic) 0.0025 (0.0013) 1.65 (0.99-2.74) ---  
Mid-arm circumference -0.0036 (0.0017) 0.91 (0.84-0.99) -0.0840(8)  
Mean blood pressure 0.0205 (0 0024) 1.36 (1.27-1.46) 0.2764 (2)  
Forced expiratory volume in 3/4 sec -0.5770 (0.1256) 0.87 (0.81-0.92) -0.1439(4)
Table 1: Significant trends in cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>1960-1965 Odds Ratio (95% CI)</th>
<th>2000-2004 Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>0.0851 (0.0271) 1.09 (1.03-1.15) 0.0908 (6)</td>
<td></td>
</tr>
<tr>
<td>Corneal arcus</td>
<td>0.1838 (0.0795) 1.20 (1.03-1.40) 0.0643 (12)</td>
<td></td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>0.550 (0.21421) 1.74 (1.14-2.65) 0.0685 (11)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of cardiovascular disease</td>
<td>0.3714 (0.1315) 1.45 (1.12-1.88) 0.0761 (9)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of cancer</td>
<td>2.1717 (0.4554) 8.77 (3.59-21 42) 0.1232(5)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of diabetes</td>
<td>0.2193 (0.1103) 1.25 (1.00-1.55) 0.0549 (14)</td>
<td></td>
</tr>
</tbody>
</table>

**Significant trends:** During a 40-year period 15 mainly cardiovascular risk factors were highly predictive of all-cause mortality and survival in middle-aged men.

**Limitations:** Not reported

**Source of funding:** The company Medrisk of Roma, Italy, contributed financially to this analysis.

---

**Authors:** Menotti A, Alberti-Fidanza A, Fidanza F

**Year:** 2012

**Citation:** Nutrition, Metabolism and Cardiovascular Diseases 22(4): 369-75

**Country of study:** Italy

**Aim of study:** To test the adequacy of the Mediterranean Adequacy Index (MAI) as a predictor of CHD mortality

**Study design:** Longitudinal

**Quality score:** (+, + or -): -

---

**Source population**
Men ages 40-59 years of two rural cohorts living in Crevalcore and Montegiorgio, Italy

**Study (eligible and selected) population**
1712 men (98% of the roster) were examined in 1960; of these, 1286 men were re-examined in 1965. Study restricted to 1139 men free from CHD at study entry and with complete data

**Sociodemographics:** Mean age of 34.5 years at baseline

**Exclusion:**
- Men who died between 1960 and 1965 (n=90)
- Men with missing data (n=278)
- Men with CHD

**Attrition:** -

---

**Exposures at midlife**
The adequacy of the Mediterranean Adequacy Index (MAI), which captures the healthiness of a diet, was tested as a predictor of CHD mortality

**Mediterranean Adequacy Index (MAI):**
- In 1960, participant diet was captured through weighted-record method for 1 week during 3 seasons from a subsample of 28 men from Crevalcore and 34 from Montegiorgio
- In 1965, food intake of all participants was assessed through dietary-history method
- Dietary intake data was used to create the MAI:
  - The MAI measures the similarity of various diets to the Reference Mediterranean Dietary Pattern, and an MAI score ranging from 0 to 100 is obtained by dividing the sum of percentages of dietary energy of healthy Mediterranean diet food groups (e.g., cereals, legumes, vegetables) by the sum of the percentages of dietary energy of other food groups not characteristic of a Mediterranean diet (e.g., milk, cheese, meat, animal fats, cakes, pies, sugar)
**Outcomes at 55 years or over**

CHD deaths occurring during 40 years after 1965 examination ascertained through death certificates, medical records, physical interviews, interviews with relatives or other witnesses of fatal events

### Analysis

**Analysis strategy:** Reduced rank regression was used to derive dietary patterns with C-reactive protein, IL-6 and IL-18 as responses; partial least squares and principal components regression was also used

**Confounders:** Age, survey, BMI, place of residence (urban/rural), actual hypertension (yes/no), education level (low/ high), self-reported diagnosis of diabetes, physical activity (active/not active), energy intake (kcal/day), ratio of total cholesterol and HDL cholesterol, smoking status

### Results, limitations, source of funding

- 79 CHD fatal events in 20 years, and 162 in 40 years
- The coefficient of lnMAI was negative, and thus, had a protective effect against CHD mortality at 20 and 40 years (hazard ratios for 1 unit of lnMAI: HR=0.74, [0.55, 0.99], and HR=0.79, [0.64, 0.97] for each follow-up time period, respectively)
- Hazard ratio of 1 unit of lnMAI (2.7 units of MAI) was associated with a CHD mortality reduction of 26% and 21% at 20 and 40 years of follow-up, respectively

**Limitations:** Small sample size

**Source of funding:** None reported

### Authors

Meyer J, Döring A, Herder C, Roden M, Koenig W, Thorand B

### Year

2011

### Citation


### Country of study

Germany

### Aim of study

To determine the association between dietary patterns, subclinical inflammation, incident coronary heart disease and mortality

### Study design

Longitudinal

### Quality score

(+++ + or -): +

### Source population

Three cross-sectional surveys were conducted during 1984-1995 in Southern Germany

### Study (eligible and selected) population

981 males ages 45-64 years with complete data for survey 1 (n=594/899) and survey 3 (n=387/430) conducted in 1984-85 and 1994-95, respectively

Participants were on average 54.9 years at time of exposure assessment

### Follow-up

1984-1995 to 2002 for CHD case development or 2007 for CHD mortality

Median follow-up time until occurrence of acute coronary event was 16.7 and 7.9 years for CHD survey 1 and survey 3, respectively

Median follow-up time until death was 22.8 and 12.9 years for survey 1 and survey 3, respectively

**Exclusion:** -
**Exposures at midlife**

7-day dietary record completed by participants through surveys  
Food consumed assessed through weighing techniques and household measures

**Outcomes at 55 years or over**

Incidence of fatal or non-fatal myocardial infarction and all-cause mortality were study end points  
Deaths were identified through population registries and the underlying cause of death ascertained through death certificates, while myocardial infarctions occurring before 75 years were identified through population-based coronary event registry and questionnaire  
Self-reported non-fatal incident myocardial infarction cases were validated using hospital records/physicians  
Pro-inflammatory markers CRP, IL-6 and IL-18 measured through blood samples at the time the surveys were administered

**Analysis**

**Analysis strategy:** Reduced rank regression was used to derive dietary patterns with C-reactive protein, IL-6 and IL-18 as responses; partial least squares and principal components regression was also used  
**Confounders:** Age, survey, BMI, place of residence (urban/rural), actual hypertension (yes/no), education level (low/ high), self-reported diagnosis of diabetes, physical activity (active/not active), energy intake (kcal/day), ratio of total cholesterol and HDL cholesterol, smoking status

**Results, limitations, source of funding**

- 101 participants had an acute coronary event, and 292 died (88 died from CHD) during follow-up  
- High intakes of meat, soft drinks and beer and low intakes of vegetables, fresh fruit, chocolates, cake, pastries, wholemeal bread, cereals, muesli, curd, condensed milk, cream, butter, nuts, sweet bread spread and tea was associated with a high score of the RRR-derived pattern  
- A high score was associated with a high risk for all-cause mortality (HR=1.16, [1.00, 1.33], respectively)

**Limitations:**

1. Cannot generalise to women  
2. Limited study power  
3. Participants may have changed dietary behaviour over time, which may attenuate association between dietary behaviour at baseline and end points

**Source of funding:** Helmholtz Zentrum Munchen, the Federal Ministry of Education and Research, Berlin, German Research Foundation, Bonn, University of Ulm, the German Diabetes Center, Dusseldorf, the Federal Ministry of Health, the Ministry of Innovation, Science, Research and Technology of the state North Rhine Westphalia

**Authors:** Miura K, Greenland P, Stamler J, Liu K, Daviglus ML, Nakagawa H  
**Year:** 2004  
**Citation:** American Journal of Epidemiology 15;159(6): 572-80  
**Country of study:** USA  
**Aim of study:** Associations between food group intake and subsequent blood pressure change  
**Study design:** Prospective population study
<table>
<thead>
<tr>
<th>Quality score: (++, + or -): +</th>
</tr>
</thead>
</table>

**Source population**

**Number of people:** 5,397  
**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 2,080  
**Characteristics:**

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Age (years)</th>
<th>48.5 (4.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Height (cm)</td>
<td>174.6 (6.4)</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>78.1 (11.0)</td>
</tr>
<tr>
<td>Body mass index (weight (kg)/height (m)^2)</td>
<td>25.6 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Obesity (body mass index ≥30) (%)</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>53.0</td>
<td></td>
</tr>
</tbody>
</table>

No. of cigarettes per day: all 10.2 (11.0)  
No. of cigarettes per day: smokers 17.8 (8.8)  
Current drinker (%) 85.8  
Current alcohol consumption: all (ml/day) 16.2 (20.3)  
Current alcohol consumption: drinkers (ml/day) 118.8 (20.7)  
Education (no. of years) 11.2 (2.5)  
Total energy (kcal) 3,124 (777)  
Total fat (% of kcal) 42.8 (4.2)  

**Location:** Chicago, Illinois  
**Recruitment strategy:** Random selection  
**Length of follow-up:** 7 year  
**Response rate and loss to follow-up:** 67.1%  
**Eligible population:** Men aged 40–55 years. Employed at the Hawthorne Works of the Western Electric Company in Chicago  
**Excluded populations:** Missing baseline dietary assessments (n = 191); blood pressure (n = 72); educational attainment (n = 223); previously diagnosed diabetes mellitus (n = 31); prior myocardial infarction (n = 44), and/or fewer than three follow-up examinations between 1960 and 1966 (n = 184).

**Exposures at midlife**

**Relevant exposures:** Nutrient intake  
**Time:** 1958-1959  
**Measurement of exposure:** Two nutritionists using standardised interviews and questionnaires based on Burke’s comprehensive dietary history method

**Outcomes at 55 years or over**

**Outcomes:** Systolic blood pressure or diastolic blood pressure  
**Outcome measurement:** Standard mercury sphygmomanometers  
**Time:** 1966

**Analysis**
**Analysis strategy:** Generalised estimating equation models

**Confounders:** Baseline age, weight at each year, height, education, smoking, alcohol consumption, daily intake of 12 nutrients

### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

**Relation between baseline food intake and adjusted average annual change in men's systolic blood pressure**

<table>
<thead>
<tr>
<th>Vegetables (cups/month)</th>
<th>14–42</th>
<th>0.29</th>
<th>0.096</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;42</td>
<td>0.08</td>
<td>0.801</td>
</tr>
<tr>
<td>Fruits (cups/month)</td>
<td>14–42</td>
<td>0.29</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>&gt;42</td>
<td>0.22</td>
<td>0.307</td>
</tr>
<tr>
<td>Fish (120-g units/month)</td>
<td>&lt;4</td>
<td>0.34</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>4–8</td>
<td>0.22</td>
<td>0.286</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>0.41</td>
<td>0.085</td>
</tr>
<tr>
<td>Beef-veal-lamb (120-g units/month)</td>
<td>8–20</td>
<td>0.76</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>0.80</td>
<td>0.022</td>
</tr>
<tr>
<td>Pork (120-g units/month)</td>
<td>4–8</td>
<td>0.55</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>0.33</td>
<td>0.060</td>
</tr>
<tr>
<td>Poultry (120-g units/month)</td>
<td>4–8</td>
<td>0.21</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>0.49</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Relation between baseline food intake and adjusted average annual change in men's diastolic blood pressure**

<table>
<thead>
<tr>
<th>Vegetables (cups/month)</th>
<th>14–42</th>
<th>0.11</th>
<th>0.269</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;42</td>
<td>0.06</td>
<td>0.713</td>
</tr>
<tr>
<td>Fruits (cups/month)</td>
<td>14–42</td>
<td>0.13</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td>&gt;42</td>
<td>0.19</td>
<td>0.119</td>
</tr>
<tr>
<td>Fish (120-g units/month)</td>
<td>&lt;4</td>
<td>0.11</td>
<td>0.282</td>
</tr>
<tr>
<td></td>
<td>4–8</td>
<td>0.03</td>
<td>0.811</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>0.17</td>
<td>0.190</td>
</tr>
<tr>
<td>Beef-veal-lamb (120-g units/month)</td>
<td>8–20</td>
<td>0.29</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>0.41</td>
<td>0.022</td>
</tr>
<tr>
<td>Pork (120-g units/month)</td>
<td>4–8</td>
<td>0.06</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>0.04</td>
<td>0.735</td>
</tr>
<tr>
<td>Poultry (120-g units/month)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4–8 0.18 0.006
>8 0.25 0.031

**Significant trends:** Higher intakes of vegetables and of fruits were related to less of an increase in SBP and DBP over time. Men with a higher intake of red meat had a significantly greater increase in blood pressure. Men with a higher poultry intake had a significantly greater annual increase in blood pressure. Men with a higher fish intake tended to have less of an increase in blood pressure.

**Limitations:**

**Author**
1. Data collection for this study took place over 40 years ago
2. No information on dietary sodium chloride, potassium, magnesium, or fibre intakes
3. Misclassification of intake for each food.
5. Findings may (or may not) be generalisable beyond middle-aged, non-Hispanic White males.

**Reviewer:** No control for medication use

**Source of funding:** American Heart Association and its Chicago and Illinois affiliates; the National Heart, Lung, and Blood Institute (HL 15174, HL 21010, and HL 03387); the Chicago Health Research Foundation; the Otho S. Sprague Foundation; the Research and Education Committee of the Presbyterian-St. Luke’s Hospital; the Illinois Foundation; and private donors

**Authors:** Moayyeri A, Kaptoge S, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT

**Year:** 2009

**Citation:** European Journal of Epidemiology 24(5): 259-66

**Country of study:** UK

**Aim of study:** Estimates of fracture risk

**Study design:** Population-based cohort study

**Quality score:** (+++, + or -): +

**Source population**

**Number of people:** 25,639

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 25,311

**Characteristics:**

**Women**

Fracture
n = 649
Age (years) 64.7 (8.4)
History of fracture 117 (11.1%)
Height (cm) 160.2 (6.3)
Weight (kg) 67.4 (12.4)
Body mass index (kg/m2) 26.2 (4.5)
Current smoking 64 (9.9%)
Alcohol intake (units/week) 1.5 (0.5–4.5)

No fracture
n = 13,186
Age (years) 58.1 (9.2)
History of fracture 936 (7.1%)
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>161.0 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.0 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.508 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (units/week)</td>
<td>2.5 (0.5–6.5)</td>
<td></td>
</tr>
</tbody>
</table>

**P value**
- Age (years): 0.001
- History of fracture: 0.001
- Height (cm): 0.002
- Weight (kg): 0.2
- Body mass index (kg/m²): 0.9
- Current smoking: 0.2
- Alcohol intake (units/week): 0.001

**Men**

**Fracture**
- n = 276
- Age (years): 61.9 (9.7)
- History of fracture: 25 (9.1%)
- Height (cm): 174.4 (6.4)
- Weight (kg): 80.7 (11.9)
- Body mass index (kg/m²): 26.5 (3.4)
- Current smoking: 38 (13.8%)
- Alcohol intake (units/week): 7 (2–16.5)

**No fracture**
- n = 11,200
- Age (years): 59.0 (9.3)
- History of fracture: 654 (5.8%)
- Height (cm): 174.0 (6.6)
- Weight (kg): 80.4 (11.5)
- Body mass index (kg/m²): 26.5 (3.3)
- Current smoking: 1,362 (12.2%)
- Alcohol intake (units/week): 6 (2–14)

**P value**
- Age (years): 0.001
- History of fracture: 0.02
- Height (cm): 0.3
- Weight (kg): 0.6
- Body mass index (kg/m²): 0.9
- Current smoking: 0.4
- Alcohol intake (units/week): 0.2

**Location**: Norfolk, East Anglia

**Recruitment strategy**: Age and sex registers of general practices

**Length of follow-up**: 11.3 years (SD = 1.5; range 9.2–14.1)

**Response rate and loss to follow-up**: Not reported

**Eligible population**: Not reported

**Excluded populations**: Not reported

**Exposures at midlife**

**Relevant exposures**: Smoking and alcohol

**Time**: 1993–1997

**Measurement of exposure**: Smoking status was derived from responses to the questions “Have you...”
ever smoked as much as one cigarette a day for as long as a year?” and “Do you smoke cigarettes now?”

Alcohol consumption derived from a question “How many alcoholic drinks do you have each week?” with four separate categories of drinks.

Total alcohol consumption was estimated as the total units of drinks consumed in a week.

Outcomes at 55 years or over

Outcomes: Osteoporotic fractures

Outcome measurement: Death certificates

Time: March 2007

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, sex, history of fractures, body mass index, smoking, and alcohol intake

Results, limitations, source of funding

Number: 925 incident fractures; 334 (36%) hip fractures; 154 (17%) clinical spinal fractures; 219 (24%) wrist fractures

Effect estimates:

Any incident fracture

HR (95% CI)

Women (649 cases)

Age (years) 1.08 (1.07–1.09)

History of fracture 1.92 (1.57–2.36)

Body mass index (kg/m²) 0.99 (0.97–1.01)

Smoking status (current) 1.10 (0.85–1.43)

Alcohol intake (units/week) 0.98 (0.97–1.00)

C-index (95% CI)

Derivation dataset 0.70 (0.67–0.72)

Validation dataset 0.72 (0.67–0.76)

Men (276 cases)

Age (years) 1.04 (1.02–1.05)

History of fracture 1.53 (1.01–2.31)

Body mass index (kg/m²) 0.99 (0.96–1.03)

Smoking status (current) 1.19 (0.84–1.68)

Alcohol intake (units/week) 1.01 (1.01–1.02)

C-index (95% CI)

Derivation dataset 0.60 (0.55–0.64)

Validation dataset 0.63 (0.56–0.70)

Incident hip fracture

HR (95% CI)

Women (245 cases)

Age (years) 1.14 (1.12–1.16)

History of fracture 1.59 (1.14–2.20)

Body mass index (kg/m²) 0.96 (0.93–0.99)

Smoking status (current) 1.19 (0.77–1.83)

Alcohol intake (units/week) 0.99 (0.97–1.02)

C-index (95% CI)

Derivation dataset 0.78 (0.75–0.81)
Validation dataset 0.82 (0.78–0.87)

Men (89 cases)
Age (years) 1.15 (1.11–1.18)
History of fracture 1.73 (0.87–3.45)
Body mass index (kg/m2) 0.95 (0.89–1.01)
Smoking status (current) 1.38 (0.74–2.56)
Alcohol intake (units/week) 1.01 (0.99–1.03)
C-index (95% CI)
Derivation dataset 0.79 (0.74–0.85)
Validation dataset 0.79 (0.72–0.86)

Significant trends: Statistically significant differences between men and women. The 10-year probability of fracture was approximately 1% in both men and women aged 40–45 years rising to about 17% for women and 5% for men aged 75 years with a previous history of fracture.

Limitations:
1. Lack of BMD assessment at the beginning of follow-up.
2. Potential for under-registration of fracture outcomes in the cohort population.
3. Participants are likely to be healthier and have lower fracture rates

Source of funding: EPIC-Norfolk is supported by program grants from the Medical Research Council and Cancer Research UK with additional support from the Stroke Association, Research into Ageing, the Academy of Medical Sciences, British Heart Foundation, Department of Health, and the Wellcome Trust
sitting, walking, lifting, and the total number of hours spent at work

Leisure-time physical activity: total duration and frequency of participation in over thirty different leisure-time activities assessed over the past year, with each activity allocated an intensity score; finally, type, frequency, and duration of leisure-time physical activity were combined into a composite score for each participant

**Outcomes at 55 years or over**

Cognitive function screening using CAMCOG

Clinical assessment for case ascertainment included use of death certificates, community mental health team for older people used for those institutionalized (those clinically assessed underwent further tests and clinical exams)

Outcome categories:
1. Cognitive impairment not dementia (CIND) [further broken down into vascular vs. non-vascular CIND]
2. Dementia [vascular dementia vs. non-vascular dementia]

**Analysis**

**Analysis strategy:** Logistic regression used to assess whether work-related and leisure-related physical activity in mid-life are related to dementia or cognitive impairment

**Confounders:** Age, social class, National Adult Reading Test score, smoking status, marital status, self-reported history of vascular disease, alcohol consumption, body mass index, common mental disorder, anxiety

**Results, limitations, source of funding**

- No association between leisure-time activity and vascular or non-vascular subtypes
- No association between work-related or leisure-related activity with dementia risk

**Limitations:**
1. Residual confounding, such as social networking and engagement
2. Self-report can lead to non-differential misclassification and underestimation of true associations
3. Possible that study was underpowered
4. Associations may reflect healthy survivor effect

**Source of funding:** Medical Research Council, Alzheimer’s Society

**Authors:** Mursu J, Voutilainen S, Nurmi T, Tuomainen TP, Kurl S, Salonen JT

**Year:** 2008

**Citation:** British Journal of Nutrition 100(4): 890-5

**Country of study:** Finland

**Aim of study:** Investigate risk factors for CVD, atherosclerosis and related outcomes in middle-aged men from eastern Finland

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**

**Number of people:** 2682

**Demographics:** Not reported
**Study (eligible and selected) population**

**Number of people:** 1950

**Characteristics:**

<table>
<thead>
<tr>
<th>Quartiles of flavonoid intake (mg/d)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (lowest)</td>
<td>1950</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.9</td>
<td>5.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Leisure-time physical activity (kJ/d)</td>
<td>482.8</td>
<td>636.8</td>
</tr>
<tr>
<td>Leisure-time physical activity (kcal/d)</td>
<td>115.4</td>
<td>152.2</td>
</tr>
<tr>
<td>Smokers (%)</td>
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<tr>
<td>Alcohol intake (g/week)</td>
<td>87.1</td>
<td>136.1</td>
</tr>
<tr>
<td>Total fat intake (% of total energy)</td>
<td>40.2</td>
<td>6.4</td>
</tr>
<tr>
<td>2</td>
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<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.2</td>
<td>5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>3.5</td>
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<tr>
<td>Leisure-time physical activity (kJ/d)</td>
<td>558.6</td>
<td>638.9</td>
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<td>Leisure-time physical activity (kcal/d)</td>
<td>133.5</td>
<td>152.7</td>
</tr>
<tr>
<td>Smokers (%)</td>
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</tr>
<tr>
<td>Alcohol intake (g/week)</td>
<td>72.3</td>
<td>106.0</td>
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<td>Total fat intake (% of total energy)</td>
<td>38.6</td>
<td>6.4</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.4</td>
<td>5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>3.5</td>
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<tr>
<td>Leisure-time physical activity (kJ/d)</td>
<td>670.7</td>
<td>825.5</td>
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<tr>
<td>Leisure-time physical activity (kcal/d)</td>
<td>1603</td>
<td>197.3</td>
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<tr>
<td>Smokers (%)</td>
<td>28.9</td>
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<tr>
<td>Alcohol intake (g/week)</td>
<td>69.7</td>
<td>115.7</td>
</tr>
<tr>
<td>Total fat intake (% of total energy)</td>
<td>37.5</td>
<td>6.1</td>
</tr>
<tr>
<td>4 (highest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.2</td>
<td>5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Leisure-time physical activity (kJ/d)</td>
<td>605.4</td>
<td>677.4</td>
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<tr>
<td>Leisure-time physical activity (kcal/d)</td>
<td>144.7</td>
<td>161.9</td>
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<tr>
<td>Smokers (%)</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (g/week)</td>
<td>60.5</td>
<td>95.2</td>
</tr>
<tr>
<td>Total fat intake (% of total energy)</td>
<td>38.1</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**P values**

- Age (years): 0.001
- BMI (kg/m²): 0.506
- Leisure-time physical activity (kJ/d): 0.001
- Leisure-time physical activity (kcal/d): 0.001
- Smokers (%): 0.001
- Alcohol intake (g/week): 0.003
- Total fat intake (% of total energy): 0.001

**Location:** Finland

**Recruitment strategy:** Not reported

**Length of follow-up:** Average follow-up time of 15.2 years

**Response rate and loss to follow-up:** 82.9% of those eligible. There were no losses to follow-up

**Eligible population:** Not reported
Excluded populations: Men who had history of CHD or stroke were excluded from the study

Exposures at midlife

Relevant exposures: Smoking and alcohol
Time: March 1984-December 1989
Measurement of exposure: The number of cigarettes, cigars and pipefuls of tobacco currently smoked daily, duration of regular smoking in years, alcohol consumption, recorded with a self-administered questionnaire
Consumption of foods was assessed with an instructed 4 day food recording by household measures

Outcomes at 55 years or over

Outcomes: Ischaemic strokes and CVD deaths, atherosclerosis and related outcomes
Outcome measurement: 1984 and 1992 information of strokes were collected prospectively
1993 post obtained by computer linkage to the national hospital discharge and death registers
CVD deaths were ascertained by computer linkage to the national death registry using the Finnish social security number
Time: 1984 - 1992 and 1993. CVD deaths from study entry to 31 December 2004

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age and examination years, BMI, systolic blood pressure, hypertension medication, serum HDL- and LDL-cholesterol, serum TAG, maximal oxygen uptake, smoking, family history of CVD, diabetes, alcohol intake, energy-adjusted intake of folate, vitamin E, total fat and saturated fat intake (percentage of energy)

Results, limitations, source of funding

Number: 102 ischaemic strokes and 153 CVD deaths

Effect estimates:
Quartiles of flavonoid intake (mg/d)
1 Ischaemic stroke
Flavonols 1
Flavones 1
Flavanones 1
Flavan-3-ols 1
Anthocyanidins 1
Total sum of flavonoids 1
CVD mortality
Flavonols 1
Flavones 1
Flavanones 1
Flavan-3-ols 1
Anthocyanidins 1
Total sum of flavonoids 1
2 RR 95 % CI
<table>
<thead>
<tr>
<th>Ischaemic stroke</th>
<th>Flavonols 0.68 0.40, 1.14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flavones 1.12 0.60, 2.11</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.83 0.47, 1.47</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 1.24 0.73, 2.10</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 0.89 0.48, 1.63</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 1.65 0.98, 2.79</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>Flavonols 1.22 0.77, 1.94</td>
</tr>
<tr>
<td></td>
<td>Flavones 0.64 0.40, 1.05</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.60 0.37, 0.98</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 1.29 0.82, 2.04</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 0.51 0.30, 0.87</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 1.85 1.18, 2.90</td>
</tr>
<tr>
<td>3</td>
<td>RR 95 % CI</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>Flavonols 0.54 0.30, 0.95</td>
</tr>
<tr>
<td></td>
<td>Flavones 2.05 1.15, 3.65</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.97 0.56, 1.71</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 1.02 0.58, 1.80</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 1.58 0.91, 2.71</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 1.60 0.55, 1.81</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>Flavonols 1.42 0.88, 2.28</td>
</tr>
<tr>
<td></td>
<td>Flavones 0.64 0.40, 1.02</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.97 0.62, 1.50</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 1.03 0.64, 1.65</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 1.17 0.74, 1.86</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 1.05 0.63, 1.74</td>
</tr>
<tr>
<td>4 (highest)</td>
<td>RR 95 % CI</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>Flavonols 0.55 0.31, 0.99</td>
</tr>
<tr>
<td></td>
<td>Flavones 1.30 0.69, 2.47</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.89 0.49, 1.63</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 0.59 0.30, 1.14</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 0.88 0.47, 1.62</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 0.71 0.37, 1.37</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>Flavonols 1.26 0.75, 2.14</td>
</tr>
<tr>
<td></td>
<td>Flavones 0.65 0.40, 1.05</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.54 0.32, 0.92</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 1.06 0.64, 1.65</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 0.99 0.62, 1.85</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 1.25 0.74, 2.11</td>
</tr>
<tr>
<td>P trend</td>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td></td>
<td>Flavonols 0.027</td>
</tr>
<tr>
<td></td>
<td>Flavones 0.181</td>
</tr>
<tr>
<td></td>
<td>Flavanones 0.870</td>
</tr>
<tr>
<td></td>
<td>Flavan-3-ols 0.102</td>
</tr>
<tr>
<td></td>
<td>Anthocyanidins 0.813</td>
</tr>
<tr>
<td></td>
<td>Total sum of flavonoids 0.137</td>
</tr>
</tbody>
</table>
CVD mortality
Flavonols 0.622
Flavones 0.333
Flavanones 0.266
Flavan-3-ols 0.694
Anthocyanidins 0.193
Total sum of flavonoids 0.730

**Significant trends:** A high intake of flavonoids decreases the risk of ischaemic stroke and possibly CVD mortality

**Limitations:**
1. Could not study the main sources of flavonoids.
2. Seasonal variation in the 4d food recording

**Source of funding:** Juho Vainio Foundation and Finnish Cultural Foundation, North-Savo Foundation

---

**Authors:** Nafziger AN, Lindvall K, Norberg M, Stenlund H, Wall S, Jenkins PL… Weinehall L

**Year:** 2007

**Citation:** BMC Public Health 12;7:108

**Country of study:** Sweden

**Aim of study:** Characterise who is not gaining weight during a 10 year period in Sweden

**Study design:** Longitudinal survey

**Quality score:** (+, + or -): -

---

**Source population**

**Number of people:** 23,863

**Demographics:**
Non-participants (%)
Age (years)
30 29.9%
40 39.3%
50 30.8%
Sex
Male 50.4%
Female 49.6%
Education
Low 21.8%
Medium 52.6%
High 25.6%
Smoker 30.4%
Snuff use 28.7%
Physically inactive 42.9%

---

**Study (eligible and selected) population**

**Number of people:** 14,867

**Characteristics:**
Age (years)
3023.4%
40 39.7%
50 36.9%
Sex
Male 46.6%
Female 53.4%

Education
Low 22.8%
Medium 53.9%
High 23.4%
Smoker 24.8%
Snuff use 25.6%
Physically inactive 41.5%

Location: Västerbotten, Sweden

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: The overall follow-up rate was 68.1%; the response rate among the eligible was 74%

Eligible population: Men and women aged 30, 40 or 50 years at baseline

Excluded populations: Participants who lacked a BMI were excluded. Participants with an initial BMI <18.5 or ≥30 kg/m² were excluded. 1062 participants who moved out of the county, 503 individuals who died, and 7 who could not be located because of assignment of an anonymous civil number

Exposures at midlife

Relevant exposures: Physical activity, smoking and snuff use

Time: 1990-1994

Measurement of exposure: Participants completed a questionnaire that included questions use of tobacco products, physical activity. Participants were classified as smokers (yes/no) and snuff users (Swedish moist snuff (snus); yes/no)

Outcomes at 55 years or over

Outcomes: Weight gain

Outcome measurement: BMI

Time: 2000-2004

Analysis

Analysis strategy: Multivariate logistic regression model

Confounders: Not reported

Results, limitations, source of funding

Number: 9625 categorised as gainers

Effect estimates:
Odds Ratio (95% CI)

Men
30 yr 1.00
40 yr 1.13 (0.99, 1.30)
50 yr 2.24 (1.96, 2.56)

Women
30 yr 1.14 (0.98, 1.32)
40 yr 1.17 (1.03, 1.35)
50 yr 1.50 (1.16, 1.34)

**Body mass index (kg/m2)**
18.5–24.9 1.00
25–29.9 1.25 (1.16, 1.34)

**Year of initial survey**
1990 1.00
1991 1.19 (1.04, 1.36)
1992 1.38 (1.21, 1.56)
1993 1.43 (1.26, 1.62)
1994 1.74 (1.53, 1.98)

**Glucose metabolism**
Normal 1.00
Glucose intolerance 1.15 (0.94, 1.40)
Type 2 diabetes 1.47 (1.08, 1.99)

**Snuff use**
No 1.00
Yes 0.83 (0.74, 0.92)

**Significant trends**: Older age, being female, classified as overweight by baseline BMI, later survey year and baseline diagnosis of diabetes increased the chances of not gaining weight. Those who did not use snuff also were more likely to be non-gainers.

**Limitations**

**Author:**
1. Participation rates were not optimal.
2. Participants in this study were more likely to be of older age, women, lower education, lower baseline BMI and less likely to have cardiovascular risk factors - differences between participants and non-participants should have resulted in more conservative odds ratios

**Reviewer**: Fail to report confounders in analysis

**Source of funding**: AFA-Insurance Sweden
Men

Meat
<1/2 days
Number 375
Age, years 53.2±3.6
BMI 22.4±2.9
Smoking, % 69.9
Daily drinking, % 49.1
Professional work, % 33.7
Urban residence, % 25.3
≥1/2 days
Number 667
Age, years 52.9±3.5
BMI 22.7±2.7
Smoking, % 65.4
Daily drinking, % 52.5
Professional work, % 40.7
Urban residence, % 31.0

Fish
<1/day
Number 555
Age, years 52.9±3.5
BMI 22.5±2.9
Smoking, % 68.5
Daily drinking, % 47.9
Professional work, % 41.1
Urban residence, % 31.2
≥1/day
Number 487
Age, years 53.1±3.5
BMI 22.7±2.7
Smoking, % 65.3
Daily drinking, % 55.0
Professional work, % 34.9
Urban residence, % 26.5

Egg
<1/day
Number 599
Age, years 53.1±3.5
BMI 22.7±2.8
Smoking, % 66.9
Daily drinking, % 51.6
Professional work, % 38.7
Urban residence, % 30.4
≥1/day
Number 443
Age, years 52.9±3.5
BMI 22.4±2.9
Smoking, % 67.0
Daily drinking, % 50.8
Professional work, % 37.5
Urban residence, % 27.1

P
Meat
Age, years 0.27  
BMI 0.15  
Smoking, 0.13  
Daily drinking, 0.29  
Professional work, 0.03  
Urban residence, 0.0

Fish
Age, years 0.52  
BMI 0.14  
Smoking, 0.28  
Daily drinking, 0.02  
Professional work, 0.04  
Urban residence, 0.10

Egg
Age, years 0.51  
BMI 0.048  
Smoking, 0.97  
Daily drinking, 0.80  
Professional work, 0.69  
Urban residence, 0.25

Women
Meat
<1/2 days
Number 573  
Age, years 53.6±3.8  
BMI 23.3±3.6  
Smoking, % 9.8  
Daily drinking, % 1.8  
Professional work, % 15.4  
Urban residence, % 28.5

≥1/2 days
Number 701  
Age, years 53.1±3.8  
BMI 23.3±3.2  
Smoking, % 6.0  
Daily drinking, % 2.0  
Professional work, % 22.0  
Urban residence, % 32.0

Fish
<1/day
Number 750  
Age, years 53.1±3.7  
BMI 23.4±3.4  
Smoking, % 8.8  
Daily drinking, % 2.3  
Professional work, % 17.6  
Urban residence, % 32.0

≥1/day
Number 524  
Age, years 53.5±3.9  
BMI 23.2±3.4  
Smoking, % 6.1  
Daily drinking, % 1.3  
Professional work, % 21.0
### Urban residence, % 28.1

<table>
<thead>
<tr>
<th>Egg</th>
<th>Number 877</th>
<th>Age, years 53.3±3.8</th>
<th>BMI 23.4±3.4</th>
<th>Smoking, % 7.8</th>
<th>Daily drinking, % 1.6</th>
<th>Professional work, % 18.5</th>
<th>Urban residence, % 29.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1/day</td>
<td>Number 397</td>
<td>Age, years 53.3±3.7</td>
<td>BMI 23.2±3.3</td>
<td>Smoking, % 7.6</td>
<td>Daily drinking, % 2.5</td>
<td>Professional work, % 20.2</td>
<td>Urban residence, % 31.7</td>
</tr>
</tbody>
</table>

### P

<table>
<thead>
<tr>
<th>Meat</th>
<th>Age, years 0.02</th>
<th>BMI 0.98</th>
<th>Smoking, % 0.01</th>
<th>Daily drinking, % 0.74</th>
<th>Professional work, % 0.003</th>
<th>Urban residence, % 0.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>Age, years 0.10</td>
<td>BMI 0.39</td>
<td>Smoking, % 0.08</td>
<td>Daily drinking, % 0.23</td>
<td>Professional work, % 0.13</td>
<td>Urban residence, % 0.13</td>
</tr>
</tbody>
</table>

| Egg | Age, years 0.997 | BMI 0.39 | Smoking, % 0.90 | Daily drinking, % 0.26 | Professional work, % 0.47 | Urban residence, % 0.48 |

### Exposures at midlife

#### Relevant exposures: Diet

#### Time: 1980

**Measurement of exposure:** A lifestyle survey was also carried out using a self-administered questionnaire which included the daily consumption of meat, eggs and fish.

#### Location: 300 districts

**Recruitment strategy:** Participants from 300 randomly selected districts in 1980

#### Length of follow-up: 19 years

**Response rate and loss to follow-up:** 75%

**Eligible population:** Aged 47–59 years
Excluded populations: 286 participants who had a history of coronary heart disease (CHD) or stroke (n = 39), had missing information in the baseline survey (n = 54) or were lost to follow-up (n = 193), 427 died

Outcomes at 55 years or over

Outcomes: Activities of daily living
Outcome measurement: Participants were asked about 5 basic ADL items (modified from Katz et al.)
Time: 1999

Analysis

Analysis strategy: Multiple adjusted logistic regression model
Confounders: Age, BMI and cigarette smoking, alcohol drinking, hypertension and diabetes, serum albumin and total cholesterol concentrations, job type and urban residence

Results, limitations, source of funding

Number: 75 participants became dependent due to impaired ADL

Effect estimates:

Associations of impaired ADL or death and food intake in the meat, fish and egg intake groups

<table>
<thead>
<tr>
<th>Food</th>
<th>&lt;1/2 days</th>
<th>≥1/2 days</th>
<th>Odds ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>1</td>
<td>0.91 (0.73–1.12)</td>
<td>0.36</td>
</tr>
<tr>
<td>Fish</td>
<td>1</td>
<td>1.08 (0.87–1.33)</td>
<td>0.50</td>
</tr>
<tr>
<td>Egg</td>
<td>1</td>
<td>1.09 (0.88–1.35)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Associations of death and food intake in the meat, fish and egg intake groups

<table>
<thead>
<tr>
<th>Food</th>
<th>&lt;1/2 days</th>
<th>≥1/2 days</th>
<th>Odds ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>1</td>
<td>1.00 (0.80–1.25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Fish</td>
<td>1</td>
<td>1.06 (0.84–1.32)</td>
<td>0.65</td>
</tr>
<tr>
<td>Egg</td>
<td>1</td>
<td>1.13 (0.90–1.42)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Associations of impaired ADL and food intake in the meat, fish and egg intake groups

<table>
<thead>
<tr>
<th>Food</th>
<th>&lt;1/2 days</th>
<th>≥1/2 days</th>
<th>Odds ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>1</td>
<td>1.00 (0.80–1.25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Fish</td>
<td>1</td>
<td>1.06 (0.84–1.32)</td>
<td>0.65</td>
</tr>
<tr>
<td>Egg</td>
<td>1</td>
<td>1.13 (0.90–1.42)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
### Significant trends

Higher intake of meat was associated with a statistically significant decrease in impaired ADL occurrence. Fish and egg intake were not associated with any difference in impaired ADL occurrence. None of the 3 foods were associated with any changes in mortality.

### Limitations

1. Did not assess the baseline ADL condition.
2. No information on SES other than professional work and urban residence.
3. Diet may have changed during 19 years.

### Source of funding

Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, H17-chouju-012 and H19-chouju-014).

### Authors

Nakayama T, Yokoyama T, Yoshiike N, Zaman MM, Date C, Tanaka H, Detels R

Year: 2000

Citation: Neuroepidemiology 19(4): 217-26

Country of study: Japan

Aim of study: Determined the population attributable fraction of stroke due to hypertension, atrial fibrillation and smoking - to quantify the proportion of stroke that might be prevented

Study design:

Quality score: (++, + or -): +

Source population

Number of people: 2,302

Demographics: Not reported

Study (eligible and selected) population

Number of people: 998

Characteristics: Not reported

Location: Shibata, Japan

Recruitment strategy: Not reported

Length of follow-up: 20 years

Response rate and loss to follow-up: Response rate 69%

Eligible population: All residents aged 40 years and over
**Excluded populations:** Those with a previous history of stroke. Non-respondents in the initial survey included 184 men and 109 women, of whom 28 men and 29 women were hospitalized or were treated at clinics and 14 men and 14 women were being cared for at home.

**Exposures at midlife**

**Relevant exposures:** Smoking

**Time:** 1977

**Measurement of exposure:** Not reported

**Outcomes at 55 years or over**

**Outcomes:** Stroke

**Outcome measurement:** Laboratory and diagnostic imaging examined by clinicians

**Time:** Follow-up examination conducted annually

**Analysis**

**Analysis strategy:** Cox regression model. PAF was calculated by $pd \times ((RR - 1)/RR)$ where $pd = \text{proportion of cases exposed to the risk factor}$.

**Confounders:** BP status, Af smoking and physical activity, diabetes mellitus, obesity, drinking and age at baseline

**Results, limitations, source of funding**

**Effect estimates:**

**Adjusted RRs and PAFs of stroke incidence due to hypertension, smoking and atrial fibrillation**

<table>
<thead>
<tr>
<th></th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>hypertension controlled</td>
<td>0.96 (0.40–2.29)</td>
</tr>
<tr>
<td>hypertension untreated</td>
<td>3.94 (1.79–8.68)</td>
</tr>
<tr>
<td>hypertension uncontrolled</td>
<td>4.92 (2.19–11.05)</td>
</tr>
<tr>
<td>smoking 1.77</td>
<td>(0.96–3.27)</td>
</tr>
<tr>
<td>Af 1.94</td>
<td>(0.24–15.90)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>hypertension controlled</td>
<td>1.35 (0.60–3.04)</td>
</tr>
<tr>
<td>hypertension untreated</td>
<td>3.31 (1.24–8.83)</td>
</tr>
<tr>
<td>hypertension uncontrolled</td>
<td>3.39 (0.99–11.64)</td>
</tr>
<tr>
<td>smoking 0.00</td>
<td>(0.00–0.00)</td>
</tr>
<tr>
<td>Af 92.23</td>
<td>(25.34–335.62)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
</tr>
<tr>
<td>hypertension controlled</td>
<td>1.07 (0.59–1.92)</td>
</tr>
<tr>
<td>hypertension untreated</td>
<td>3.61 (2.01–6.50)</td>
</tr>
<tr>
<td>hypertension uncontrolled</td>
<td>3.69 (1.89–7.19)</td>
</tr>
<tr>
<td>smoking 1.84</td>
<td>(1.00–3.40)</td>
</tr>
<tr>
<td>Af 11.24</td>
<td>(3.72–33.97)</td>
</tr>
<tr>
<td>PAF, %</td>
<td>(90% CI)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
</tbody>
</table>

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions. 200
<table>
<thead>
<tr>
<th></th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Smoking</th>
<th>Af</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (All)</td>
<td>0.9 (6.5–7.8)</td>
<td>13.5 (6.3–20.1)</td>
<td>8.6 (2.9–13.9)</td>
<td>3.6 (0.3–6.7)</td>
</tr>
<tr>
<td>Hypertension (Men)</td>
<td>4.3 (–6.9–14.4)</td>
<td>10.2 (0.6–18.8)</td>
<td>4.4 (–1.7–10.1)</td>
<td>6.2 (0.2–11.8)</td>
</tr>
<tr>
<td>Hypertension (Women)</td>
<td>4.3 (–6.9–14.4)</td>
<td>10.2 (0.6–18.8)</td>
<td>4.4 (–1.7–10.1)</td>
<td>6.2 (0.2–11.8)</td>
</tr>
</tbody>
</table>

**Significant trends:** Control of smoking in Japan is the most substantial single factor for reducing the incidence of stroke in middle-aged men. Lack of treatment and control of hypertension is responsible for approximately one third of strokes in the middle-aged population of Shibata.

### Limitations:

1. Misclassification and change of exposure.
2. Smoking was self-reported.
3. Limited sample size

### Source of funding:

Ministry of Health and Welfare, Japan: Nervous and Mental Disorders (grant 3A-3) from the National Center of Neurology and Psychiatry; Cardiovascular Diseases (grant 3C-2) from the National Cardiovascular Center, and a grant from the Japan Foundation for Aging and Health
### Men (n = 4,121)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;29</td>
<td>587 (14.2)</td>
</tr>
<tr>
<td>30–59</td>
<td>3,473 (84.3)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>61 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m2)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.4</td>
<td>161 (3.9)</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>2,920 (70.9)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>928 (22.5)</td>
</tr>
<tr>
<td>&gt;30.0</td>
<td>112 (2.7)</td>
</tr>
</tbody>
</table>

**Cigarettes**

- Never smoked: 1,028 (24.9)
- Ex-smoker: 904 (21.9)
- Smoke up to >1 pack/day: 1,540 (37.4)
- Smoke >1 pack/day: 649 (15.7)

**Alcohol**

- Usually not drinking: 1,246 (30.2)
- Up to 69 mL/week of ethanol: 1,474 (35.8)
- 70–209 mL/week: 1,256 (30.5)
- >70–209 mL/week: 145 (3.5)

**Occupation**

- Clerks: 1,000 (24.3%)
- Managers/professionals: 1,144 (27.8%)
- Operators/drivers: 1,223 (29.7%)
- Service/sales: 636 (15.4%)
- Others: 118 (2.9%)

### Women (n = 2,877)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;29</td>
<td>344 (12.0)</td>
</tr>
<tr>
<td>30–59</td>
<td>2,484 (86.3)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>49 (1.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m2)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.4</td>
<td>356 (12.4)</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>2,122 (73.8)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>348 (12.1)</td>
</tr>
<tr>
<td>&gt;30.0</td>
<td>51 (1.8)</td>
</tr>
</tbody>
</table>

**Cigarettes**

- Never smoked: 2,539 (88.3)
- Ex-smoker: 57 (2.0)
- Smoke up to >1 pack/day: 273 (9.5)
- Smoke >1 pack/day: 8 (0.3)

**Alcohol**

- Usually not drinking: 2,088 (72.6)
- Up to 69 mL/week of ethanol: 673 (23.4)
- 70–209 mL/week: 108 (3.8)
- >70–209 mL/week: 8 (0.3)

**Occupation**

- Clerks: 1,129 (39.2%)
- Managers/professionals: 600 (20.9%)
- Operators/drivers: 342 (11.9%)
- Service/sales: 656 (22.8%)
- Others: 150 (5.2%)
Location: Ishikawa, Japan
Recruitment strategy: Recruited from workplaces
Length of follow-up: 6-years

Exposures at midlife

Relevant exposures: Cigarette and alcohol consumption
Time: Either 2009 or 2003
Measurement of exposure: Data on cigarette and alcohol consumption were obtained by interview
Smoking habits were classified into four categories, namely, lifelong non-smokers, ex-smokers, current smokers consuming up to one pack per day, and smokers consuming more than one pack per day.
Alcohol consumption was categorized into four levels, “non-drinkers”, “mild drinkers”, “moderate drinkers” and “heavy drinkers”
Response rate and loss to follow-up: 87.9%
Eligible population: People working in 447 various kinds of workplaces
Excluded populations: Those whose data for body weight (37 men, 50 women), urinalysis (2 men, 114 women), or PG (7 men) were not available were excluded; 13 men and five women who declared a past history of primary kidney disease; 252 men and 50 women with high PG consistent DM; 28 men and 12 women who showed severe hypertension in 2003; 4,298 men and 3,096 women showing CKD signs in 2003; five men and 88 women who did not undergo urinalysis in 2009

Outcomes at 55 years or over

Outcomes: Chronic kidney disease
Outcome measurement: Categorisation in subjects based on single measurements of proteinuria and eGFR
Time: 2009

Analysis

Analysis strategy: Multiple logistic regression
Confounders: Sex, age, BMI, BP levels, alcohol consumption, the presence of IGR and dyslipidemia, and occupation

Results, limitations, source of funding

Number: 60 men (1.5 %) and 21 women (0.7 %) developed proteinuria
Effect estimates:
Proteinuria
Odds ratio (95 % CI) p
Sex (women/men) 1.06 (0.57–1.98) 0.859
Age (year) 1.02 (0.99–1.05) 0.134
BMI levels (1–4) 1.82 (1.27–2.59) 0.001
Blood pressure levels (1–5) 1.33 (1.10–1.62) 0.004
IGR 2.35 (1.19–4.65) 0.014
hChol 1.46 (0.90–2.36) 0.130
hHDLc 1.33 (0.64–2.79) 0.449
hTG 1.20 (0.68–2.13) 0.533
hGFR 1.35 (0.52–3.45) 0.538
<table>
<thead>
<tr>
<th>Smoking status (vs. non-smokers)</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smokers 1.29 (0.48–3.42)</td>
<td>0.614</td>
</tr>
<tr>
<td>Continuous smokers 2.52 (1.50–4.25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol consumption levels (1–4)</td>
<td>0.87 (0.66–1.16)</td>
</tr>
<tr>
<td>Occupations (1–5) 1.01 (0.84–1.21)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

**Low eGFR**

<table>
<thead>
<tr>
<th>Odds ratio (95 % CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women/men)</td>
<td>1.02  (0.84–1.24)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.08  (1.07–1.09)</td>
</tr>
<tr>
<td>BMI levels (1–4)</td>
<td>1.37  (1.19–1.57)</td>
</tr>
<tr>
<td>Blood pressure levels (1–5)</td>
<td>0.97 (0.90–1.04)</td>
</tr>
<tr>
<td>lGR 0.84 (0.59–1.18)</td>
<td>0.312</td>
</tr>
<tr>
<td>hChol 1.06 (0.90–1.27)</td>
<td>0.480</td>
</tr>
<tr>
<td>hHDLc 0.92 (0.65–1.29)</td>
<td>0.625</td>
</tr>
<tr>
<td>hTG 1.44 (1.14–1.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>hGFR 0.05 (0.01–0.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Smoking status (vs. non-smokers) 0.006**

<table>
<thead>
<tr>
<th>Odds ratio (95 % CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smokers 1.05 (0.78–1.41)</td>
<td>0.735</td>
</tr>
<tr>
<td>Continuous smokers 0.74 (0.60–0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>Alcohol consumption levels (1–4)</td>
<td>0.87 (0.78–0.97)</td>
</tr>
<tr>
<td>Occupations (1–5) 0.98 (0.92–1.04)</td>
<td>0.433</td>
</tr>
</tbody>
</table>

**Significant trends**: Continuing smokers showed a twofold or more higher risk of developing proteinuria. Discontinuation of smoking substantially reduced the risk.

**Limitations**: The clinical definition of CKD requires CKD signs to be detectable for >3 months.

**Source of funding**: KAKENHI, a Grant-in-Aid for Scientific Research (C), 2010, from the Japan Society for the Promotion of Science.
Women who did not present to follow-up assessment were not significantly different from those who completed baseline and follow-up exams in terms of age, baseline hip BMD, baseline weight or objectively measured PA.

**Exposures at midlife**

Physical activity (PA) volume (sum of all activity counts or total volume of movement) and physical activity intensity (variations of activity within a specified time period) measured over 7 days after baseline assessment using valid and reliable accelerometers.

PA volume divided into ‘low’, ‘moderate’, and ‘high’

Accelerometer activity counts within a specific time period (of 10 min.) reflected physical activity intensity.

As per the 2007 American Heart Association and American College of Sports medicine guidelines, participants were required to participate in physical activity, and were categorized into the following PA intensity ranges: 1) ‘vigorous’: for those with at least 50,000 PA counts during at least 15 bouts (150 min.); 2) ‘moderate’: at least 30,000 counts during a minimum of 15 bouts; 3) ‘low’: at least 30,000 counts in fewer than 15 bouts.

**Outcomes at 55 years or over**

At baseline and at 6 year follow-up, participants had their hip scanned on the valid and reliable bone densitometer to determine bone mineral density (BMD) (predicts risk of hip fracture).

BMD change was calculated by subtracting follow-up BMD score from baseline score or value of the total hip with scores divided into quartiles and participants categorized into the following groups: ‘BMD loss’ (<25th percentile); ‘minimal BMD change’ (25-75th percentile); ‘BMD gain’ (>75th percentile).

**Analysis**

**Analysis strategy:** Power analysis determined that 155 participants needed for effect size of 0.25 with power of 0.80. Poisson regression was used to determine influence of PA on BMD.

**Confounders:** Age, baseline hip BMD, baseline body weight, weight change, time in study, menopause status, maternal history of osteoporosis, calcium intake, vitamin D intake.

**Results, limitations, source of funding**

- 59% of participants lost BMD at the hip during follow-up.
- Over 6 years, women with moderate to high PA volume levels were more likely to have hip BMD gains compared to women in the low PA volume group (RR=2.01, [1.05, 3.81]).
- Over 6 years, women with moderate PA volume levels were more likely to gain BMD at the hip than women with low PA volume (RR=1.97, [1.02, 3.79]).
- Physical activity intensity was not significant in predicting changes in BMD.

**Limitations:**

1. Limited generalizability due to homogeneous sample.
2. Not known whether PA status may have changed during follow-up and if this may have influenced outcome.

**Source of funding:** None reported.

**Authors:** Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP, van Gelder BM, Verhagen H, Verschuren WM

**Year:** 2011
**Citation:** British Journal of Nutrition 106(5): 752-61

**Country of study:** Netherlands

**Aim of study:** Habitual fruit and vegetable intake was studied in association with cognitive function and cognitive decline

**Study design:** Cohort

**Quality score:** (+++, + or -): +

### Source population

**Number of people:** 7769

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 2613

**Characteristics:**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mean SD</th>
<th>N 522</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range of total fruit and vegetable intake (g)</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>54.3 6.6</td>
</tr>
<tr>
<td></td>
<td>Sex (% women)</td>
<td>31.2</td>
</tr>
<tr>
<td></td>
<td>Highly educated† (%)</td>
<td>48.3</td>
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<tr>
<td></td>
<td>Cigarette smoker at baseline (%)</td>
<td>35.3</td>
</tr>
<tr>
<td></td>
<td>Number of pack years smoked in life</td>
<td>22.8 15.8</td>
</tr>
<tr>
<td></td>
<td>Excessive consumption of alcohol (%)</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>Inactive (%)</td>
<td>32.8</td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>67 17</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
<td>77 16</td>
</tr>
<tr>
<td>1</td>
<td>Mean SD</td>
<td>N 523</td>
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<tr>
<td></td>
<td>Range of total fruit and vegetable intake (g)</td>
<td>199 – 265</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>54.7 6.7</td>
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<tr>
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<td>Sex (% women)</td>
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<tr>
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<td>Number of pack years smoked in life</td>
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<td>Excessive consumption of alcohol (%)</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>Inactive (%)</td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>67 17</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
<td>77 16</td>
</tr>
<tr>
<td>2</td>
<td>Mean SD</td>
<td>N 523</td>
</tr>
<tr>
<td></td>
<td>Range of total fruit and vegetable intake (g)</td>
<td>265 – 334</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>55.4 7.0</td>
</tr>
<tr>
<td></td>
<td>Sex (% women)</td>
<td>54.1</td>
</tr>
<tr>
<td></td>
<td>Highly educated† (%)</td>
<td>49.1</td>
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<td></td>
<td>Cigarette smoker at baseline (%)</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td>Number of pack years smoked in life</td>
<td>16.7 16.0</td>
</tr>
<tr>
<td></td>
<td>Excessive consumption of alcohol (%)</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>Inactive (%)22.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>68 18</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
<td>77 14</td>
</tr>
<tr>
<td>Quartile 4</td>
<td></td>
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</tr>
<tr>
<td>-----------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>N</td>
<td>523</td>
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</tr>
<tr>
<td>Range of total fruit and vegetable intake (g)</td>
<td>334 – 415</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.8 7.3</td>
<td></td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>Highly educated† (%)</td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoker at baseline (%)</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Number of pack years smoked in life</td>
<td>15.8 13.8</td>
<td></td>
</tr>
<tr>
<td>Excessive consumption of alcohol (%)</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Inactive (%)</td>
<td>23.7</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>68 17</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>77 14</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quartile 5</th>
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</tr>
</thead>
<tbody>
<tr>
<td>N</td>
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<td></td>
</tr>
<tr>
<td>Range of total fruit and vegetable intake (g)</td>
<td>415 – 1131</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.0 6.8</td>
<td></td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>64.4</td>
<td></td>
</tr>
<tr>
<td>Highly educated† (%)</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoker at baseline (%)</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>Number of pack years smoked in life</td>
<td>14.5 13.3</td>
<td></td>
</tr>
<tr>
<td>Excessive consumption of alcohol (%)</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Inactive (%)</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>68 16</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>77 14</td>
<td></td>
</tr>
</tbody>
</table>

**P trends (P<0.05)**

- Age
- Sex
- Highly educated
- Cigarette smoker at baseline
- Number of pack years smoked in life
- Excessive consumption of alcohol
- Inactive

### Exposures at midlife

**Relevant exposures:** Diet, smoking and physical activity

**Time:** 1995-2002

**Measurement of exposure:** Self-administered semi-quantitative FFQ was used to assess the habitual consumption of 178 food items during the previous year. Averaged reported intakes at baseline and follow-up

Smoking and physical activity recorded in self-report questionnaire. Smoking status defined as ‘non-smoker’ or ‘current smoker’

Physical activity level was assessed by the EPIC questionnaire on physical activity

**Location:** Doetinchem

**Recruitment strategy:** From Doetinchem Cohort Study

**Length of follow-up:** 5-year

**Response rate and loss to follow-up:** 80%

**Eligible population:** 1995–7, a random sample of one-third of participants aged 45 years and older was enrolled in the study on cognitive functioning

**Excluded populations:** Participants who reported having experienced a stroke (n 77)
<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes:</strong> Cognitive decline</td>
</tr>
<tr>
<td><strong>Outcome measurement:</strong> Neuropsychological test battery</td>
</tr>
<tr>
<td><strong>Time:</strong> 2003–7</td>
</tr>
</tbody>
</table>

**Analysis**

**Analysis strategy:** Multivariate linear regression analyses

**Confounders:** Age, sex, level of education, total energy intake, intake of other fruits, vegetables, legumes and juices, and the baseline level of cognitive function, physical activity, smoking, systolic blood pressure, use of blood pressure-lowering medication, serum HDL-cholesterol, waist circumference, coffee consumption, vitality and mental health

**Results, limitations, source of funding**

**Number:** Not reported

**Effect estimates:**

Average change in cognitive function domains:

-0.14 (SD 0.77) for memory
-0.13 (SD 0.45) for information processing speed
-0.08 (SD 0.66) for cognitive flexibility
-0.10 (SD 0.42) for global cognitive function

Baseline

\[ \beta \text{ P-trend } * P < 0.05, ** P < 0.01. \]

Fruits and vegetables

- Memory 0.03
- Speed - 0.01
- Flexibility - 0.01
- Global 0.03

Fruits

- Memory 0.01
- Speed 0.01
- Flexibility 0.02
- Global 0.03

Vegetables

- Memory 0.03
- Speed - 0.04 *
- Flexibility - 0.04 *
- Global 0.00

Legumes

- Memory - 0.02
- Speed 0.00
- Flexibility 0.00
- Global 0.00

Juices

- Memory 0.00
- Speed - 0.01
- Flexibility - 0.02
- Global - 0.02

Change

Fruits and vegetables

- Memory 0.00
- Speed 0.03
Flexibility 0.00
Global 0.02
Fruits
Memory 0.00
Speed 0.01
Flexibility - 0.01
Global 0.01
Vegetables
Memory 0.03
Speed 0.07 **
Flexibility 0.03
Global 0.05 **
Legumes
Memory 0.03
Speed - 0.02
Flexibility 0.01
Global 0.03
Juices
Memory 0.01
Speed - 0.03
Flexibility - 0.01
Global 0.00

Significant trends: Total intake of fruits and vegetables was not or inconsistently associated with cognitive function and cognitive decline. Nuts had statistically significant association between fruit consumption and cognitive decline.

Limitations:
Author:
1. Baseline characteristics were different
2. Unfavourable effect of allium is not explained

Reviewer: Crude measure of habitual intake

Source of funding: Ministry of Public Health, Welfare and Sport of The Netherlands and the National Institute for Public Health and the Environment. The data up to and including 1997, including the dietary assessment method, were additionally financially supported by the Europe against Cancer programme of the European Commission

Authors: Nooyens AC, van Gelder BM, Verschuren WM
Year: 2008
Citation: American Journal of Public Health 98(12):2244-50
Country of study: Netherlands
Aim of study: Studied the effect of smoking on cognitive decline
Study design: Cohort Study
Quality score: (+++, + or -): +

Source population
Number of people: 2434
Demographics: Not reported

Study (eligible and selected) population
Number of people: 1964
### Characteristics:

- **Age, y, mean (SD)**: 56.0 (7.0)
- **Men, %**: 48.5
- **Married, %**: 
- **Lifelong cigarette smoking, pack-years, %**: 85.1
  - 0 36.4
  - 0–20 38.9
  - > 20 24.8
- **Level of education, %**:
  - Primary school: 7.6
  - Lower vocational: 26.4
  - Intermediate secondary: 17.5
  - Intermediate vocational/higher secondary: 24.3
  - Higher vocational/university: 24.2
- **Cardiovascular risk factors**:
  - **Total cholesterol, mmol/L, mean (SD)**: 5.9 (1.0)
  - **Elevated serum cholesterol level, %**: 30.0
  - **HDL cholesterol, mmol/L, mean (SD)**: 1.38 (0.39)
  - **Systolic blood pressure, mm Hg, mean (SD)**: 131.1 (17.8)
  - **Hypertension, %**: 35.6
  - **Body mass index, kg/m2, mean (SD)**: 26.3 (3.8)
  - **Self-reported diabetes or cardiovascular disease, %**: 4.1
  - **Physically active, %**: 56.2
  - **Alcohol consumption, %**:
    - No alcohol use: 30.7
    - 0–1 glass/day: 27.9
    - 1–2 glasses/day: 20.0
    - 2–4 glasses/day: 16.4
    - > 4 glasses/day: 5.0
  - **Total energy intake, MJ/day**: 8.9 (2.3)

### Location:

- **Doetinchem**

### Recruitment strategy:

- From Doetinchem Cohort Study

### Length of follow-up:

- 5 years

### Response rate and loss to follow-up:

- 71% of the eligible population took part in the cognitive testing at baseline

### Eligible population:

- All participants of the Doetinchem Cohort Study aged 45 years and older

### Excluded populations:

- Participants who reported a cerebrovascular accident (n=60)

### Exposures at midlife

- **Relevant exposures**: Smoking, diet, alcohol consumption, and physical activity
- **Measurement of exposure**: Smoking status categorised as persistent non-smoker; ex-smoker; persistent smoker, or recent quitter, resume smoking
  - Alcohol consumption classified: (1) no alcohol use, (2) 0 to 1 glass per day, (3) 1 to 2 glasses per day, (4) 2 to 4 glasses per day, and (5) more than 4 glasses per day
  - Physical activity was dichotomised as less versus more than half an hour per day of at least moderate-intensity physical activities
  - Food-frequency questionnaire was used to assess the habitual consumption of 178 food items during the previous year
### Outcomes at 55 years or over

**Outcomes:** Cognitive decline

**Outcome measurement:**

1. Neuropsychological test battery
2. 15-Word Verbal Learning Test
3. Stroop Color–Word Test
4. Animal Naming Verbal Fluency Test

**Time:** 1995-January 2000

### Analysis

**Analysis strategy:** Multivariate linear regression analyses

**Confounders:** Age, gender, level of education, alcohol consumption, hypertension, serum total and high-density lipoprotein cholesterol, body mass index, diabetes or cardiovascular disease, and physical activity, energy intake, total fat intake, coffee consumption, fish consumption, antioxidant intake, estrogen use, and marital status

### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

**Effect of the Number of Cigarettes Smoked on Change in Cognitive Functions**

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Effect (B)</th>
<th>SE (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory function (n = 1162)</td>
<td>−0.04 .03</td>
<td></td>
</tr>
<tr>
<td>Speed of cognitive processes (n = 1161)</td>
<td>−0.02 .03</td>
<td></td>
</tr>
<tr>
<td>Cognitive flexibility (n = 1165)</td>
<td>−0.03 .04</td>
<td></td>
</tr>
<tr>
<td>Global cognitive function (n = 1146)</td>
<td>−0.02 .06</td>
<td></td>
</tr>
</tbody>
</table>

**Significant trends:** No difference between smokers and never smokers in rates of decline in the speed of cognitive processes during follow-up. Decline among smokers was 1.9 times greater for memory function, 2.4 times greater for cognitive flexibility, and 1.7 times greater for global cognitive function than among never smokers

**Limitations:** No figure given for numbers of participants with cognitive decline

**Source of funding:** Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment.

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**Authors:** Osler M, Andreasen AH, Hoidrup S

**Year:** 2003

**Citation:** Journal of Clinical Epidemiology 56(3): 274-9

**Country of study:** Denmark

**Aim of study:** To determine the association between fish consumption and risk of all-cause mortality, and fatal and nonfatal coronary heart disease

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population:**

5 population studies conducted at Copenhagen County Centre for Preventive Medicine

Birth cohorts of Western suburbs of Copenhagen followed since 1964
411 men and 391 women born in 1914 were examined in 1984; 436 men born in 1936 were examined in 1987; 1955 men and 1873 women sampled from 4 birth cohorts (1922, 1932, 1942, 1952) were examined in 1982; 731 men and 739 women (born 1927, 1937, 1947, and 1957) were examined in 1987; and 980 men and 981 women (born in 1922, 1932, 1942, 1952, and 1962) were examined in 1992.

<table>
<thead>
<tr>
<th>Study (eligible and selected) population</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,007 out of 4,513 men and 3,533 out of 3,984 women.</td>
</tr>
<tr>
<td>Baseline response rate was 78%</td>
</tr>
<tr>
<td>Follow-up: from baseline until Sept. 27, 2000 for death from all causes or until Dec. 31, 1997 for fatal and nonfatal incident CHD</td>
</tr>
<tr>
<td>Exclusion:</td>
</tr>
<tr>
<td>i) Participants with CHD diagnosed during the 5 years prior to enrolment (n=109)</td>
</tr>
<tr>
<td>ii) Participants with incomplete data</td>
</tr>
<tr>
<td>Attrition: -</td>
</tr>
</tbody>
</table>

Exposures at midlife
Cardiovascular risk factors assessed through clinical examinations and questionnaires (5 surveys)
Dietary variables assessed through questionnaire, whereby participants were asked about frequency of consumption of fish food items, with response options ranging from ‘never’, ‘once a month or less’, ‘twice a month’, ‘once a week’, ‘two to three times a week’, ‘once a day’, ‘two to three times a day’, and ‘four times or more daily’
Questionnaire previously compared with dietary history – adequate in identifying levels of fish intake

Outcomes at 55 years or over
Data on all-cause mortality, CHD mortality, incident CHD obtained from National Board of Healths Register of Cause of Death and the National Patient Register

Analysis
Analysis strategy: Cox proportional hazards regression used to assess the influence of cardiovascular risk factors on fatal and nonfatal CHD outcome, or all-cause mortality. Analysis was repeated on a high-risk subgroup of 981 men 50+ years and 622 women 60+ years who were current smokers or current non-smokers, with serum cholesterol over 6-7 mmol/L
Confounders: Familial predisposition, smoking status, physical activity, alcohol, educational status, healthy diet score, total cholesterol, BMI

Results, limitations, source of funding
- At end of follow-up, death occurred in 826 men and 503 women
- Among men, the risk of all-cause mortality was lower for those consuming fish one time a month or less compared to those consuming fish once a week (HR=0.80, [0.65, 0.90])
- Among males and females combined, the risk of all-cause mortality was lower for those consuming fish two times a month compared to those consuming it once a week (HR=0.84, [0.73, 0.96])
- Among males and females combined, as well as the subgroup of high-risk participants, there was a significant linear trend of increasing risk in all-cause mortality with greater intake of fish (trend test p-values=0.02 and 0.03, respectively)
- Among males and females combined with serum cholesterol less than 5 mmol/L, CHD risk was
lowest for those consuming fish once per week; men with cholesterol levels over 7mmol/L, the
lowest CHD risk was identified for those consuming fish once per week

- Among women with lower educational levels, frequent fish intake was associated with lower risk
  for CHD

Limitations:
1. Low statistical power
2. Measurement bias due to self-reported dietary intake
3. Residual confounding

Source of funding: Danish Medical Research Council

Authors: Østbye T, Taylor DH, Jung SH
Year: 2002
Citation: Preventive Medicine 34(3): 334-45.

Country of study:
Aim of study: To determine the impact of smoking and other modifiable risk factors on ill health in
middle-aged and older people
Study design: Longitudinal
Quality score: (+++, + or -): -

Source population
At least 12,600 people born in 1931-41 were recruited for Health and Retirement Study (HRS) and
interviewed along with their spouses as part of baseline survey in 1992 (wave 1), with follow-up
surveys in 1994 (wave 2), 1996 (wave 3), and 1998 (wave 4)
Respondents ages 70 and older and their spouses comprised the baseline sample (wave 1, 1993)
were recruited for Asset and Health Dynamics Among the Oldest Old (AHEAD), with follow-up
telephone interviews conducted in 1995 (wave 2) and 1998 (wave 3)

Study (eligible and selected) population
HRS: 7,845 people ages 51-61 years
AHEAD: 5,037 people age 70+ at baseline
Exclusion: HRS participants who:
i) Were outside the age range (n=2,357)
ii) Died (n=796)
iii) Were lost to follow-up (n=1,958)
AHEAD participants who:
i) Were outside the age range (n=725)
ii) Died (n=1,853)
iii) Were lost to follow-up (n=607)
Attrition: -

Exposures at midlife
Smoking, exercise, and alcohol consumption measured at baseline for HRS and AHEAD
HRS smokers categorized as heavy (at least a pack of cigarettes/day) or light (less than one
pack/day), with former smokers categorized as quit < 3 years prior to baseline, quit 3-15 years ago, or
more than 15 years ago; AHEAD smokers categorized as current, former, and never smokers
HRS physical activity assessed through questions on 1. participation in light physical activity (3+
times/week, 1-2 times/week, 1-3 times/months, less than once a month, never); and 2. Participation in vigorous physical activity (same categories as for light activity)

>Based on these questions, participants were classified into ‘sedentary’ (no exercise), ‘heavy exercise’ (heavy physical activity 3+ times/week), ‘moderate exercise’ (heavy physical activity 1-2 times/week or light physical activity 3+ times/week), ‘light exercise’ (other) groups

Alcohol consumption divided into light to moderate drinking (up to 2 drinks/day), heavy drinking (2+ drinks/day), none; self-reported history of drinking problems ascertained

### Outcomes at 55 years or over

Ill health outcomes: disability, impaired mobility, self-reported health, and health care utilisation, were measured at waves 2-4 for HRS and 2-3 for AHEAD

**Disability**
Disability was defined as having an impairment that limits the amount of paid work that can be accomplished; ADL or impairment in activities necessary for survival (with yes/no answer options for activities assessed), and IADL or impairment in activities necessary to manage in today’s society (with yes/no answer options for activities assessed), were identified

**Impaired mobility**
Ability to walk or climb stairs (with yes/no answer options)

**Self-reported health:**
Self-perception of health status measured with answer options of excellent, very good, good, fair or poor

**Health care use:**
Proxy for ill health
Hospitalisation in the past year or admission to nursing home with yes/no options

### Analysis

**Analysis strategy**: Data for respondents who completed all waves for each study were entered into multivariate logistic regression models; each ‘ill health’ outcome (e.g. disability, impaired mobility, etc.) was assessed separately. Models with no impairment at baseline were also built

**Confounders:** Gender, race, marital status, age, education

### Results, limitations, source of funding

**AHEAD (70+ years)**
- Compared to those who never smoked, current smokers had the highest odds for ill health in terms of IADL dependence (OR=1.46, [1.21, 1.77]), difficulty climbing stairs (OR=1.67, [1.37, 2.03]), difficulty walking (OR=2.06, [1.69, 2.49]), poor health (OR=1.55, [1.29, 1.87]), hospitalization (OR=1.28, [1.08, 1.52]), nursing home placement (OR=1.68, [1.08, 2.63]); further, the odds for ill health were greater for current smokers compared to former smokers
- Compared to those with BMI 18.5-30, those with BMI 30 or greater had the highest odd for ill health in terms of ADL dependence (OR=1.76, [1.51, 2.06]), IADL dependence (OR=1.23, [1.06, 1.43]), difficulty climbing stairs (OR=2.08, [1.77, 2.46]), difficulty walking (OR=2.27, [1.94, 2.65]), poor health (OR=1.43, [1.24, 1.65]), hospitalization (OR=1.27, [1.12, 1.46]); further, the odds for ill health were generally greater for people with BMI 30 or greater compared to those with BMI less than 18.5
- Compared to those who never drink, those with a past drinking problem had the highest odds for ill health in terms of difficulty climbing stairs (OR=1.37, [1.07, 1.75]), hospitalization (OR=1.38, [1.13, 1.68])

**HRS (51-64 at baseline)**
- Compared to those who never smoked, heavy smokers (one pack or more) and former smokers

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
(quit less than 3 years), had the highest odds for ill health in terms of ADL dependence (OR=1.52, [1.27, 1.82]; OR=1.71, [1.29, 2.26], respectively), disability (OR=2.23, [1.84, 2.71]; OR=2.45, [1.81, 3.33], respectively), difficulty climbing stairs (OR=2.10, [1.86, 2.37]; OR=1.72, [1.41, 2.10], respectively), difficulty walking (OR=2.37, [2.05, 2.74]; OR=2.08, [1.65, 2.62], respectively), poor health (OR=2.06, [1.80, 2.36]; OR=1.99, [1.60, 2.48], respectively), hospitalization (OR=1.41, [1.24, 1.59]; OR=1.46, [1.20, 1.78], respectively); further, the odds for ill health were greater for light smokers (less than one pack), former smokers (quit 3-15 years), former smokers (quite more than 15 years) compared to non-smokers

Exercise had a beneficial effect on the odds of ill health
- Compared to those with BMI 18.5-30, those with BMI 30 or greater generally had the highest odds for ill health in terms of ADL dependence (OR=1.66, [1.45, 1.89]), disability (OR=1.48, [1.28, 1.72]), difficulty climbing stairs (OR=2.37, [2.16, 2.60]), difficulty walking (OR=2.10, [1.89, 2.34]), poor health (OR=1.70, [1.53, 1.88]), hospitalization (OR=1.38, [1.26, 1.51]); further, the odds for ill health were generally greater for people with BMI less than 18.5
- Compared to those who never drink, those with a past drinking problem had the highest odds for ill health in terms of ADL (OR=1.49, [1.20, 1.84]), disability OR=1.43, [1.15, 1.79], difficulty climbing stairs (OR=1.33, [1.13, 1.57]), difficulty walking (OR=1.32, [1.10, 1.60]), poor health (OR=1.29, [1.08, 1.53]), and hospitalization (OR=1.20, [1.02, 1.41])

Limitations:
1. Residual confounding (e.g., detailed data on nutritional and occupational information)
2. Construct overlap – for example, exercise may not be completely distinct from dependent ill health outcomes, such as those reflecting physical function (in AHEAD, there was some difficulty in identifying adequate controls when measuring exercise levels)

Source of funding: none reported

Authors: Östenson CG, Hilding A, Grill V, Efendic S
Year: 2012
Citation: Scandinavian Journal of Public Health 40(8): 730-7
Country of study: Sweden
Aim of study: Snus use predicts the risk of Type 2 diabetes incidence
Study design: Prospective population-based study
Quality score: (+++, + or -): +

Source population
Number of people: 12,952
Demographics: Not reported

Study (eligible and selected) population
Number of people: 2,383
Characteristics:
Consistent never snus use
N 1,431
Age: mean (95% CI) 47.2 (46.9-47.4)
BMI: mean (95% CI) 25.7 (25.5-25.8)
Physical activity during leisure time:
% sedentary (95% CI) 10.6 (9.1-12.3)
Alcohol consumption:
% highest tertile (95% CI) 28.1 (25.7-30.5)
Socioeconomic position:
% low (95% CI) 27.0 (24.7–29.4)
Current smokers among snus users/current snus users among smokers: n (%) 246 (17.2)

Consistent snus use
N 301
Age: mean (95% CI) 44.8 (44.2–45.3)
Bmi: mean (95% CI) 26.4 (26.0–26.8)
Physical activity during leisure time:
% sedentary (95% CI) 9.3 (6.5–13.1)
Alcohol consumption:
% highest tertile (95% CI) 47.5 (41.9–53.2)
Socioeconomic position:
% low (95% CI) 41.3 (35.8–46.9)
Current smokers among snus users/current snus users among smokers: n (%) 36 (12.0)

Former snus use
n 213
Age: mean (95% CI) 45.8 (45.2–46.4)
Bmi: mean (95% CI) 25.8 (25.4–26.2)
Physical activity during leisure time:
% sedentary (95% CI) 8.0 (5.0–12.4)
Alcohol consumption:
% highest tertile (95% CI) 39.2 (32.9–46.0)
Socioeconomic position:
% low (95% CI) 41.8 (35.3–48.6)
Current smokers among snus users/current snus users among smokers: n (%) 16 (7.6)

Consistent never-smoking
N 835
Age: mean (95% CI) 46.2 (45.9–46.6)
Bmi: mean (95% CI) 25.6 (25.4–25.8)
Physical activity during leisure time:
% sedentary (95% CI) 9.1 (7.3–11.2)
Alcohol consumption:
% highest tertile (95% CI) 21.7 (19.0–24.7)
Socioeconomic position:
% low (95% CI) 22.7 (20.0–25.7)
Current smokers among snus users/current snus users among smokers: n (%) 74 (8.9)

Consistent smoking
N 287
Age: mean (95% CI) 46.7 (46.1–47.3)
Bmi: mean (95% CI) 25.2 (24.8–25.6)
Physical activity during leisure time:
% sedentary (95% CI) 18.5 (14.5–23.4)
Alcohol consumption:
% highest tertile (95% CI) 42.0 (36.3–47.9)
Socioeconomic position:
% low (95% CI) 41.3 (35.8–47.2)
Current smokers among snus users/current snus users among smokers: n (%) 48 (16.8)

Former smoking
n 740
Age: mean (95% CI) 46.8 (46.4–47.1)
Bmi: mean (95% CI) 26.1 (25.8–26.3)
Physical activity during leisure time:
% sedentary (95% CI) 8.1 (6.4–10.3)
Alcohol consumption:
% highest tertile (95% CI) 40.9 (37.3–44.5)
Socioeconomic position:  
% low (95% CI) 36.5 (33.1–40.1)  
Current smokers among snus users/current snus users among smokers: n (%) 232 (31.4)

**Exposures at midlife**

**Relevant exposures:** Snus use  
**Time:** 1992–94  
**Measurement of exposure:** Subjects asked if they had ever been daily users of snus, and if so, if they were current daily users  
Subjects asked about daily cigarette smoking and categorised into never, former or current smokers  
**Location:** Four municipalities within Stockholm County  
**Recruitment strategy:** Not reported  
**Length of follow-up:** 10 years  
**Response rate and loss to follow-up:** 87% were reinvestigated with anthropometric measurements  
**Excluded population:** Middle-aged Swedish men  
**Excluded populations:** 246 control subjects and nine subjects with newly diagnosed T2D

**Outcomes at 55 years or over**

**Outcomes:** Type 2 diabetes  
**Outcome measurement:** Oral glucose tolerance test, homeostasis model assessment  
**Time:** 2002-2004

**Analysis**

**Analysis strategy:** Multiple regression analysis  
**Confounders:** Age, BMI, glucose tolerance at baseline, physical activity, alcohol consumption, socioeconomic position, family history of diabetes and smoking

**Results, limitations, source of funding**

**Number:** 99  
**Effect estimates:**  
Cases: type 2 diabetes; newly diagnosed  
OR 95% CI  
Consistent never snus use 1.0  
Consistent snus use 1.1 0.6–2.0  
Former snus use 0.5 0.2–1.2  
Consistent never snus use 1.0  
1-5 boxes/week 0.6 0.2–1.4  
>5 boxes/week 3.3 1.4–8.1  
Consistent never smoking 1.0  
Consistent smoking 1.5 0.8–3.0  
Former smoking 0.9 0.5–1.7  
Consistent never smoking 1.0  
1–15 cigarettes/day 0.8 0.3–2.1  
>15 cigarettes/day 2.4 1.0–5.8  
**Significant trends:** Men smoking at baseline and still smoking at follow-up had an increased risk of diabetes compared with never smokers
**Limitations:** Small number of cases developing diabetes

**Source of funding:** Stockholm County Council, the Swedish Research Council, the Swedish Council for Working Life and Social Research, and Novo Nordisk Scandinavia.

**Authors:** Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group

**Year:** 2003

**Citation:** Cancer, Epidemiology, Biomarkers & Prevention 12(12): 1492-500

**Country of study:** Japan

**Aim of study:** Examine the association of alcohol consumption and cigarette smoking with colorectal cancer

**Study design:** Prospective cohort

**Quality score:** (+++, + or -): +

### Source population

**Number of people:** 90,004

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** Not reported

**Characteristics:** J-M cells

**Location:**
- Cohort I: Iwate, Akita, Nagano, Okinawa, and Tokyo
- Cohort II: Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka

**Recruitment strategy:** Not reported

**Length of follow-up:** 10-year (cohort I); 7-year (cohort II)

**Response rate and loss to follow-up:** Loss to follow-up 0.04%

**Eligible population:** Middle-aged and elderly Japanese men and women

**Excluded populations:** Non-Japanese (29 men and 20 women), those who had already moved away at baseline (94 men and 57 women), and those outside of the 40–59 age parameters in cohort I (2 women). Self-reported medical history of cancer and with a diagnosis of colorectal cancer before the survey began (687 men and 1,363 women); incomplete alcohol and/or smoking items (2,225 men and 1,097 women)

### Exposures at midlife

**Relevant exposures:** Smoking, alcohol consumption, dietary habits, and other lifestyle factors

**Time:** Cohort I – after January 1, 1990

**Measurement of exposure:**
- Cohort I: Average frequency of alcohol consumption reported by: “less than 1 day/month,” “1–3 days/month,” “1–2 days/week,” “3–4 days/week,” “5–6 days/week,” and “everyday.” Subjects consuming alcoholic beverages at least once a week were also asked about types of drinks and average consumption.
- Cohort II: Asked about drinking status, i.e., never-, ex-, or current drinkers. Ex- and current drinkers
provided information on average frequency, types of drinks, and average consumption per day
Smoking habits included current and former smoking status, age at initiation of smoking, and average number of cigarettes smoked per day

Outcomes at 55 years or over

Outcomes: Colorectal Cancer
Outcome measurement: Cases of colorectal cancer were extracted from the JPHC cancer registry based on site codes. Mortality data from the Ministry of Health, Labor, and Welfare
Time: Until the date of diagnosis of colorectal cancer, the date of a subject’s death, the date of moving from a PHC area, or December 31, 1999

Analysis

Analysis strategy: Cox proportional hazards model
Confounders: Age, family history of colorectal cancer, body mass index, physical exercise, smoking status, alcohol consumption, and PHC area

Results, limitations, source of funding

Number: 716
Effect estimates: N-Q cells
Significant trends: Alcohol consumption and smoking were associated with colorectal cancer in men. Regular ethanol consumption was not associated with colorectal cancer in women
Limitations: None reported

Authors: Patel KV, Coppin AK, Manini TM, Lauretani F, Bandinelli S, Ferrucci L, Guralnik JM
Year: 2006
Citation: American Journal of Preventive Medicine 31(3): 217-24
Country of study: Italy
Aim of study: Test associations of past physical activity levels in midlife with objective measures of mobility in old age
Study design: Cohort
Quality score: (+++, + or -): +

Source population

Number of people: 1155
Demographics: Not reported

Study (eligible and selected) population

Number of people: 1001
Characteristics:
Age, M (SD) 74.8 (7.3)
Education, M (SD) 5.4 (3.3)
Cigarette smoking
Ever (vs never), % 40.2
Total pack-years among smokers, M (SD) 29.9 (22.0)
Body mass index (kg/m2), M (SD) 27.5 (4.1)

Physical Activity

20–40 years of age, %
Sedentary/minimal 0.7
Light 13.7
Moderate 55.6
Moderate/intense 16.2
Intense/strenuous 13.8
M (SD) 3.3 (0.9)

40–60 years of age, %
Sedentary/minimal 1.5
Light 22.9
Moderate 50.7
Moderate/intense 15.0
Intense/strenuous 10.0
M (SD) 3.1 (0.9)

In the past year, %
Sedentary/minimal 20.9
Light 42.5
Moderate 32.3
Moderate/intense 3.8
Intense/strenuous 0.6
M (SD) 2.2 (0.9)

Lifetime index to age 60, %
Level I 23.6
Level II 51.1
Level III 25.4

Functional outcomes
Short Physical Performance Battery, M (SD) 9.7 (3.3)
Unable to walk 400 meters, % 15.0

Location: Greve in Chianti and Bagno a Ripoli, Italy

Recruitment strategy: Probability sample

Length of follow-up: 5-8 years
Response rate and loss to follow-up: 91.6%

Eligible population: Not reported
Excluded populations: -

Exposures at midlife

Relevant exposures: Physical activity and smoking

Time: September 1998 and March 2000

Measurement of exposure: Interviewer administered questionnaire; participants asked to indicate their average level of physical activity during three age periods in life: 20 to 40 years, 40 to 60 years, and the past year

Mini-Mental State Examination was used to measure cognitive impairment

Outcomes at 55 years or over

Outcomes: Mobility
**Outcome measurement**: Short Physical Performance Battery

Subjects asked to walk a distance of four meters at their usual pace. The quickest time out of two trials was analysed.

Subjects were asked to rise from a chair and return to the seated position five times as quickly as possible while keeping their arms folded over their chest.

Subjects were asked to walk a standard 400-meter course.

**Time**: 2005 and 2006

**Analysis**

**Analysis strategy**: Linear and logistic regression models

**Confounders**: Age, education, smoking behaviour, BMI, total number of medical conditions, Mini-Mental State Examination, nerve conduction velocity, leg muscle power, range of motion of hip and ankle, ankle-brachial index, and serum haemoglobin

**Results, limitations, source of funding**

**Number**: Not reported

**Effect estimates**:

**Lifetime physical activity to age 60**

Short Physical Performance Battery

- **Men**
  - b weight (SE)
  - Level I Reference
  - Level II 0.03 (0.24)
  - Level III 0.40 (0.26)
  - p for trend p = 0.042

- **Women**
  - b weight (SE)
  - Level I Reference
  - Level II 0.27 (0.19)
  - Level III 0.90 (0.27)
  - p for trend p = 0.002

- **Unable to walk 400 meters**
  - **Men**
    - Odds ratio (95% CI)
    - Level I Reference
    - Level II 0.76 (0.18–3.29)
    - Level III 0.22 (0.04–1.19)
    - p for trend p = 0.047

  - **Women**
    - Odds ratio (95% CI)
    - Level I Reference
    - Level II 1.16 (0.40–3.30)
    - Level III 0.52 (0.13–2.08)
    - p for trend p = 0.434

**Significant trends**: Older adults who in higher levels of physical activity in midlife were significantly more likely to perform better than individuals who were less physically active.

**Limitations**:

- **Author**: Misclassification of previous physical activity
- **Reviewer**: Participants retrospectively recalled their physical activity levels in midlife
- **Source of funding**: Intramural Research Program of the National Institutes of Health, National Institute on Aging
Authors: Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J
Year: 2005
Citation: Journal of Internal Medicine 258(4): 356-62.
Country of study: Finland
Aim of study: Examine effects of smoking, obesity and physical activity on the risk of type 2 diabetes
Study design: Prospective study
Quality score: (++, + or -): +

### Source population

<table>
<thead>
<tr>
<th>Number of people: Not reported</th>
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<tbody>
<tr>
<td>Demographics: Not reported</td>
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</table>

### Study (eligible and selected) population

<table>
<thead>
<tr>
<th>Number of people: 41,372</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics:</td>
</tr>
<tr>
<td>Smoking status (men)</td>
</tr>
<tr>
<td>Never</td>
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<tr>
<td>Age (years) 41.7 (10.6); Body mass index 25.9 (3.3); Diastolic blood pressure (mmHg) 88 (12); Systolic blood pressure (mmHg) 142 (18); Education (years) 9.3 (3.9); Coffee consumption (cups) 4.6 (2.9); Alcohol drinker (%) 54.5; Low occupational physical activity (%) 30.0; Low leisure time physical activity (%) 25.8</td>
</tr>
<tr>
<td>Former</td>
</tr>
<tr>
<td>Age (years) 46.7 (10.3); Body mass index 26.9 (3.6); Diastolic blood pressure (mmHg) 89 (12); Systolic blood pressure (mmHg) 144 (19); Education (years) 9.0 (3.7); Coffee consumption (cups) 5.1 (2.9); Alcohol drinker (%) 63.8; Low occupational physical activity (%) 31.2; Low leisure time physical activity (%) 24.7</td>
</tr>
<tr>
<td>&lt;20 cigarettes day</td>
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<tr>
<td>Age (years) 42.5 (11.0); Body mass index 25.6 (3.6); Diastolic blood pressure (mmHg) 87 (12); Systolic blood pressure (mmHg) 143 (19); Education (years) 8.8 (3.8); Coffee consumption (cups) 5.6 (3.0); Alcohol drinker (%) 71.3; Low occupational physical activity (%) 33.7; Low leisure time physical activity (%) 31.3</td>
</tr>
<tr>
<td>&gt;20 cigarettes day</td>
</tr>
<tr>
<td>Age (years) 41.5 (10.0); Body mass index 25.9 (3.7); Diastolic blood pressure (mmHg) 88 (12); Systolic blood pressure (mmHg) 144 (18); Education (years) 8.3 (3.1); Coffee consumption (cups) 6.8 (3.5); Alcohol drinker (%) 77.6; Low occupational physical activity (%) 30.1; Low leisure time physical activity (%) 40.5</td>
</tr>
<tr>
<td>Smoking status (women)</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Age (years) 45.3 (10.8); Body mass index 26.0 (4.7); Diastolic blood pressure (mmHg) 85 (12); Systolic blood pressure (mmHg) 141 (23); Education (years) 9.2 (3.8); Coffee consumption (cups) 4.6 (2.3); Alcohol drinker (%) 25.9; Low occupational physical activity (%) 37.0; Low leisure time physical activity (%) 39.5</td>
</tr>
<tr>
<td>Former</td>
</tr>
</tbody>
</table>
| Age (years) 39.9 (10.5); Body mass index 26.1 (4.4); Diastolic blood pressure (mmHg) 84 (12); Systolic blood pressure (mmHg) 138 (19); Education (years) 9.5 (3.6); Coffee consumption (cups)
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

4.8 (2.5); Alcohol drinker (%) 45.3; Low occupational physical activity (%) 41.0; Low leisure time physical activity (%) 35.4

<20 cigarettes day
Age (years) 39.0 (10.5); Body mass index 25.5 (4.2); Diastolic blood pressure (mmHg) 83 (12); Systolic blood pressure (mmHg) 138 (20); Education (years) 9.0 (3.4); Coffee consumption (cups) 5.4 (2.6); Alcohol drinker (%) 55.8; Low occupational physical activity (%) 41.2; Low leisure time physical activity (%) 44.0

>20 cigarettes day
Age (years) 39.7 (9.7); Body mass index 25.9 (4.7); Diastolic blood pressure (mmHg) 84 (13); Systolic blood pressure (mmHg) 139 (21); Education (years) 8.6 (3.2); Coffee consumption (cups) 6.9 (3.3); Alcohol drinker (%) 65.2; Low occupational physical activity (%) 43.5; Low leisure time physical activity (%) 57.7

Location: Karelia, Kuopio, Turku-Loimaa and the Helsinki, Finland

Recruitment strategy: Randomly selected sample

Length of follow-up: Mean 21 years

Response rate and loss to follow-up: Random sample of 6.6%. Participation rate varied from 74% to 88%.

Eligible population: Middle-aged Finnish men and women aged 25–64 years born between 1913 and 1947

Excluded populations: Diagnosed with coronary heart disease or stroke (n =1444), diabetes (n = 804), subjects who had type 1 diabetes (n = 64) at baseline or during follow-up, and subjects with incomplete data on smoking or any other required factors (n=1222)

Exposures at midlife

Relevant exposures: Smoking, obesity and physical activity


Measurement of exposure: Self-reported questionnaire

Classified into three smoking categories: current smokers, ex-smokers and lifelong non-smokers

Occupational and leisure time physical activity were grouped into three categories in some analyses: (i) low (ii) moderate (iii) high

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Drug Register and the Hospital Discharge Register

Time: End of December 2002 or until death

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, study year, education, body mass index, systolic blood pressure, physical activity and coffee and alcohol drinking

Results, limitations, source of funding

Number: 2770

Effect estimates:
Hazard ratios for the incidence of type 2 diabetes according to smoking habits

Never smoking 1.00
Ex-smoking 1.09 (0.96–1.24)
Current smoker <20 cigarettes day 1.30 (1.15–1.47)
Current smoker >20 cigarettes day 1.65 (1.45–1.89)

Hazard ratios for the incidence of type 2 diabetes according to smoking habits and body mass index

Never-smoking
Body mass index <25 1.00
Body mass index 25–29.9 2.92 (2.48–3.45)
Body mass index >30 8.25 (6.98–9.74)

Ex-smoking
Body mass index <25 1.00 (0.70–1.42)
Body mass index 25–29.9 3.04 (2.46–3.77)
Body mass index >30 8.86 (7.15–10.9)

Current smoking
Body mass index <25 1.43 (1.15–1.78)
Body mass index 25–29.9 4.19 (3.48–5.05)
Body mass index >30 11.5 (9.46–13.9)

Hazard ratios for the incidence of type 2 diabetes according to smoking habits and physical activity

Never-smoking
High 1.00
Moderate 1.03 (0.92–1.16)
Low 1.26 (1.09–1.46)

Ex-smoking
High 1.11 (0.93–1.33)
Moderate 0.99 (0.82–1.19)
Low 1.71 (1.31–2.21)

Current smoking
High 1.32 (1.13–1.54)
Moderate 1.58 (1.37–1.82)
Low 1.72 (1.42–2.10)

Significant trends: Smoking is a risk factor for type 2 diabetes independently of BMI and physical activity

Limitations:
1. Biological markers of smoking were not measured at baseline; glucose
2. Tolerance tests were not performed during the follow-up; misclassification of exposure and outcome; did not have nutritional data; data on alcohol drinking were fairly crude

Source of funding: Finnish Academy (grants 46558, 53585, 204274, 205657)

Authors: Pelkonen M, Tukiainen H, Tervahauta M, Notkola IL, Kivelä SL, Salorinne Y, Nissinen A
Year: 2000
| **Citation:** Thorax 55(9): 746-50 |
| **Country of study:** Finland |
| **Aim of study:** Study the impact of smoking cessation on mortality over range of baseline pulmonary function |
| **Study design:** Cohort |
| **Quality score:** (+++, + or -): ++ |

**Source population**

| **Number of people:** | Not reported |
| **Demographics:** | Not reported |

**Study (eligible and selected) population**

| **Number of people:** | 1582 |
| **Characteristics:** | Not reported |
| **Location:** | Ilomantsi, Pöytyä and Mellilä in Finland |
| **Recruitment strategy:** | Not reported |
| **Length of follow-up:** | 30 year |
| **Response rate and loss to follow-up:** | (97.5% in 1959) and in subsequent re-examinations (90–97.7%) |
| **Eligible population:** | Finnish participants in the Seven Countries Study |
| **Excluded populations:** | Not reported |

**Exposures at midlife**

| **Relevant exposures:** | Smoking |
| **Time:** | Re-examinations were performed in 1964, 1969, 1974, 1984, and 1989. |
| **Measurement of exposure:** | Smoking habits were recorded at the baseline and in subsequent re-examinations by a trained nurse according to a standard questionnaire developed for the Seven Countries Study |

**Outcomes at 55 years or over**

| **Outcomes:** | Mortality |
| **Outcome measurement:** | Death certificates were collected and causes of death coded |
| **Time:** | 1959 and 1989 |

**Analysis**

| **Analysis strategy:** | Cox’s proportional hazards regression model |
| **Confounders:** | Age, BMI, diastolic blood pressure, total cholesterol and smoking |

**Results, limitations, source of funding**

| **Number:** | 1086 |
| **Effect estimates:** | All-cause mortality during 1959-89 by tertile of FEV0.75 at baseline |
Hazard ratio (95% CI) p value
Tertile of FEV0.75
Low 1.56 (1.35 to 1.81) <0.001
Middle 1.08 (0.93 to 1.26) 0.295
High 1

All cause and cause specific mortality during 1964–89 among those who quit between 1959–84 compared with continuous smokers
Hazard ratio (95% CI) p value
All cause 0.71 (0.50 to 1.00) 0.049
Cardiovascular disease 0.60 (0.37 to 0.98) 0.043
Cancer 0.58 (0.30 to 1.12) 0.105
Lung cancer 0.50 (0.14 to 1.77) 0.281
Other cancer 0.62 (0.28 to 1.33) 0.220
Respiratory diseases† 2.51 (0.65 to 9.70) 0.181
Other causes 0.91 (0.38 to 2.18) 0.833

Significant trends: Smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking

Reported limitations:
1. **Author:** Data set was too small for confident results on mortality from causes other than cardiovascular disease
2. **Reviewer:** Does not describe sample

Source of funding: Finnish Academy, the Finnish Lung Health Association, the Finnish Anti-Tuberculosis Association Foundation, and the National Institute on Aging, USA (grant EDC-1 1 RO1 AGO8762-01A1)

Authors: Pitsavos C, Panagiotakos DB, Chrysohoou C, Kokkinos P, Menotti A, Singh S, Dontas A; Seven Countries Study (the Corfu Cohort).

Year: 2004

Citation: Journal of Human Hypertension 18(7): 495-501

Country of study: Greece

Aim of study: Investigate the interaction between physical activity and left ventricular hypertrophy on stroke mortality

Study design: Cohort

Quality score: (+++, + or -): ++

Source population

Number of people: 12,763

Demographics: Not reported

Study (eligible and selected) population

Number of people: 529

Characteristics:

Presence of LVH
Age at baseline (years) 49 ±6
Current smoking (total) 30 (76%)
<10 cigarettes/day 14 (36%)
10–20 cigarettes/day 8 (20%)
>20 cigarettes/day 8 (20%)
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>Physical activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary life</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Moderate physical activity</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Hard physical activity</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23 ±4</td>
</tr>
</tbody>
</table>

Absence of LVH

<table>
<thead>
<tr>
<th>Current smoking (total)</th>
<th>308 (63%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 cigarettes/day</td>
<td>62 (13%)</td>
</tr>
<tr>
<td>10–20 cigarettes/day</td>
<td>104 (21%)</td>
</tr>
<tr>
<td>&gt;20 cigarettes/day</td>
<td>62 (13%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23 ±4</td>
</tr>
</tbody>
</table>

Location: Corfu, Greece

Recruitment strategy: Not reported

Length of follow-up: 40-year

Response rate and loss to follow-up: 95.3%

Exposures at midlife

Relevant exposures: Physical activity and smoking

Time: Since 1961 periodic visits every five years

Measurement of exposure: Physical activity levels were assessed by self-reports of habitual, occupational and leisure-time activities

Daily cigarette smoking identified by a positive response on a standardised questionnaire

Eligible population: Corfu cohort from the Seven Countries Study

Excluded populations: -

Outcomes at 55 years or over

Outcomes: Stroke mortality

Outcome measurement: Causes of death were obtained from: previous clinical records filled out by the study’s research group, or by hospital records, or by necroscopy records, or by information from family or hospital doctors, other specialists, family or relatives, friends and any other witnesses, or from the police, in case of violent causes or death occurred suddenly in public places or un-witnessed

Time: 2001

Analysis

Analysis strategy: Cox proportional hazard model

Confounders: Age, body mass index, total cholesterol, glucose, smoking and blood pressure levels
## Results, limitations, source of funding

### Number: 74 deaths

### Effect estimates:

Estimates from a backward stepwise Cox model predicting 40-year stroke mortality as a function of baseline risk factors, by LVH level

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of LVH</td>
</tr>
<tr>
<td>Physical activity status</td>
</tr>
<tr>
<td>Sedentary (reference group) 1.00 —</td>
</tr>
<tr>
<td>Moderate 0.70 (0.50–0.97)</td>
</tr>
<tr>
<td>Hard 0.75 (0.52–1.09)</td>
</tr>
<tr>
<td>Age (per 1 year) 1.12 (0.94–1.33)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg) 1.01 (0.73–1.62)</td>
</tr>
<tr>
<td>Total serum cholesterol (per 1 mmol/l) 0.86 (0.69–1.07)</td>
</tr>
<tr>
<td>Absence of LVH</td>
</tr>
<tr>
<td>Physical activity status</td>
</tr>
<tr>
<td>Sedentary (reference group) 1.00 —</td>
</tr>
<tr>
<td>Moderate 0.64 (0.45–0.91)</td>
</tr>
<tr>
<td>Hard 0.72 (0.51–1.02)</td>
</tr>
<tr>
<td>Age (per 1 year) 1.12 (1.07–1.18)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg) 1.21 (1.10–1.480)</td>
</tr>
<tr>
<td>Total serum cholesterol (per 1 mmol/l) 0.80 (0.47–1.22)</td>
</tr>
</tbody>
</table>

### Significant trends:

Physical activity was associated with a lower risk of stroke. LVH had 5.8-fold the risk of stroke among sedentary and 4.5-fold the risk among physically active men. Moderate physical activity decreased the risk of stroke by 49% in men with LVH as compared to sedentary without LVH. Hard exercise did not confer any significant reduction in stroke risk.

### Limitations:

1. Mortality data were available from this specific cohort - could not provide predictors for stroke incidence.
2. The imbalance of the sample sizes between men with and without LVH.
3. Inability to segregate thrombotic from haemorrhagic strokes.
4. Physical activity level of the active group at baseline is likely to decline with advancing age. The physically inactive group at baseline could either stay physically inactive or increase their physical activity level.

### Source of funding:

National Heart, Lung and Blood Institute Grants HE 04697, HE 6090 and HE00278

---

### Authors:

Preis SR, Stampfer MJ, Spiegelman D, Willett WC, Rimm EB

### Year:

2010

### Citation:

American Journal of Clinical Nutrition 92(5): 1265-72

### Country of study:

USA

### Aim of study:

Examine the association between dietary protein and risk of ischemic heart disease

### Study design:

Prospective study

### Quality score: (+++, + or -):

++

### Source population

Number of people: 51,529

Demographics: Not reported
### Study (eligible and selected) population

**Number of people:** 43,960

**Characteristics:**

<table>
<thead>
<tr>
<th>Q1</th>
<th>Age (y) 53 ± 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Never 3993 (45.2)</td>
<td></td>
</tr>
<tr>
<td>Past 3405 (38.6)</td>
<td></td>
</tr>
<tr>
<td>1–14 cigarettes/d 262 (3.0)</td>
<td></td>
</tr>
<tr>
<td>15–24 cigarettes/d 334 (3.8)</td>
<td></td>
</tr>
<tr>
<td>2:25 cigarettes/d 390 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown no. of cigarettes/d 105 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Missing 337 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Exercise (METs) 20.9 ± 30.1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) 25.1 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Calories (kcal/d) 2137 ± 664</td>
<td></td>
</tr>
<tr>
<td>Alcohol (% of energy) 5.9 ± 7.4</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/d) 17.5 ± 22.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3</th>
<th>Age (y) 53 ±6 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Never 4007 (47.5)</td>
<td></td>
</tr>
<tr>
<td>Past 3336 (39.5)</td>
<td></td>
</tr>
<tr>
<td>1–14 cigarettes/d 216 (2.6)</td>
<td></td>
</tr>
<tr>
<td>15–24 cigarettes/d 294 (3.5)</td>
<td></td>
</tr>
<tr>
<td>2:25 cigarettes/d 214 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown no. of cigarettes/d 72 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Missing 301 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Exercise (METs) 20.8 ± 27.4</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) 25.5 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Calories (kcal/d) 2024 ± 597</td>
<td></td>
</tr>
<tr>
<td>Alcohol (% of energy) 3.9 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/d) 10.9 ± 13.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q5</th>
<th>Age (y) 55 ± 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Never 4409 (44.9)</td>
<td></td>
</tr>
<tr>
<td>Past 4126 (42.1)</td>
<td></td>
</tr>
<tr>
<td>1–14 cigarettes/d 251 (2.6)</td>
<td></td>
</tr>
<tr>
<td>15–24 cigarettes/d 276 (2.8)</td>
<td></td>
</tr>
<tr>
<td>2:25 cigarettes/d 209 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown no. of cigarettes/d 96 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Missing 446 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Exercise (METs) 21.1 ± 29.1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) 25.9 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Calories (kcal/d) 1780 ± 574</td>
<td></td>
</tr>
<tr>
<td>Alcohol (% of energy) 2.7 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/d) 6.8 ± 9.1</td>
<td></td>
</tr>
</tbody>
</table>

**P for linear trend**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Never Referent</td>
<td></td>
</tr>
<tr>
<td>Past 0.009</td>
<td></td>
</tr>
</tbody>
</table>
1–14 cigarettes/d 0.07
15–24 cigarettes/d <0.0001
2.25 cigarettes/d <0.0001
Unknown no. of cigarettes/d 0.14
Missing 0.03
Exercise (METs) 0.89
BMI (kg/m2) <0.0001
Calories (kcal/d) <0.0001
Alcohol (% of energy) <0.0001
Alcohol (g/d) <0.0001

**Location:** Not reported

**Length of follow-up:** 18 years

**Response rate and loss to follow-up:** Not reported

**Eligible population:** Men aged 40–75 y at baseline in 1986

**Excluded populations:** Those who reported a history of myocardial infarction, angina, coronary artery bypass graft, other heart conditions, stroke, pulmonary embolism, or cancer on the baseline questionnaire. those who had an implausible caloric intake derived from the baseline or had >70 missing responses to food items

### Exposures at midlife

**Relevant exposures:** Smoking status, diet and physical activity


**Measurement of exposure:** Every four years, participants are sent a food-frequency questionnaire to assess their diet composition

### Outcomes at 55 years or over

**Outcomes:** Nonfatal myocardial infarction and fatal ischemic heart disease

**Outcome measurement:** Nonfatal MI was assessed biennially with a mailed questionnaire

Deaths ascertained by contact with family members or through the National Death Index. Fatal IHD was confirmed from the medical records or autopsy reports or if IHD was listed as the cause of death on the death certificate and there was evidence of previous IHD in the records

**Time:** 1986 and 31 January 2004

### Analysis

**Analysis strategy:** Cox proportional hazards regression model

**Confounders:** Age and quintiles of percentage of energy from saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, and calories, fibre, folate, vitamin C, magnesium, total omega-3 fatty acids, glycemic index, physical activity, family history of myocardial infarction, BMI, cigarette smoking, alcohol use, and multivitamin use, status of hypertension, hypercholesterolemia and diabetes

### Results, limitations, source of funding

**Number:** 2959

**Effect estimates:** Relative risks (RRs) and 95% CIs for total ischemic heart disease according to quintile of percentage of energy from protein
<table>
<thead>
<tr>
<th>Q1</th>
<th>Total protein 1.00 (referent)</th>
<th>Animal protein 1.00 (referent)</th>
<th>Vegetable protein 1.00 (referent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2</td>
<td>Total protein 1.03 (0.91, 1.16)</td>
<td>Animal protein 1.05 (0.93, 1.16)</td>
<td>Vegetable protein 0.96 (0.85, 1.08)</td>
</tr>
<tr>
<td>Q3</td>
<td>Total protein 1.07 (0.94, 1.21)</td>
<td>Animal protein 1.02 (0.90, 1.16)</td>
<td>Vegetable protein 0.94 (0.82, 1.08)</td>
</tr>
<tr>
<td>Q4</td>
<td>Total protein 1.03 (0.90, 1.16)</td>
<td>Animal protein 1.03 (0.90, 1.17)</td>
<td>Vegetable protein 0.94 (0.80, 1.09)</td>
</tr>
<tr>
<td>Q5</td>
<td>Total protein 1.08 (0.95, 1.23)</td>
<td>Animal protein 1.11 (0.97, 1.28)</td>
<td>Vegetable protein 0.93 (0.78, 1.12)</td>
</tr>
</tbody>
</table>

**P for trend**

|       | Total protein 0.30 | Animal protein 0.18 | Vegetable protein 0.49 |

**Relative risks (RRs) and 95% CIs for nonfatal myocardial infarction and fatal ischemic heart disease according to quintile**

<table>
<thead>
<tr>
<th>Q1</th>
<th>Total protein:</th>
<th>Non-fatal MI 1.00 (referent)</th>
<th>Fatal IHD 1.00 (referent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal protein:</td>
<td>Nonfatal MI 1.00 (referent)</td>
<td>Fatal IHD 1.00 (referent)</td>
<td></td>
</tr>
<tr>
<td>Vegetable protein:</td>
<td>Non-fatal MI 1.00 (referent)</td>
<td>Fatal IHD 1.00 (referent)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2</th>
<th>Total protein:</th>
<th>Non-fatal MI 1.01 (0.86, 1.18)</th>
<th>Fatal IHD 1.05 (0.86, 1.28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal protein:</td>
<td>Nonfatal MI 1.01 (0.86, 1.18)</td>
<td>Fatal IHD 1.12 (0.91, 1.37)</td>
<td></td>
</tr>
<tr>
<td>Vegetable protein:</td>
<td>Non-fatal MI 1.07 (0.91, 1.25)</td>
<td>Fatal IHD 0.84 (0.69, 1.02)</td>
<td></td>
</tr>
</tbody>
</table>

| Q3     | Total protein: | Non-fatal MI 1.05 (0.90, 1.23) | Fatal IHD 1.08 (0.88, 1.33) |
### Animal protein:
- Nonfatal MI: 0.99 (0.84, 1.16)
- Fatal IHD: 1.08 (0.87, 1.33)

### Vegetable protein:
- Non-fatal MI: 1.03 (0.86, 1.24)
- Fatal IHD: 0.84 (0.68, 1.05)

#### Q4

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Nonfatal MI</th>
<th>Fatal IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>1.02 (0.87, 1.20)</td>
<td>1.02 (0.83, 1.25)</td>
</tr>
</tbody>
</table>

#### Q5

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Nonfatal MI</th>
<th>Fatal IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>1.10 (0.92, 1.30)</td>
<td>1.05 (0.85, 1.30)</td>
</tr>
</tbody>
</table>

### P for trend

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Nonfatal MI</th>
<th>Fatal IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>0.30</td>
<td>0.79</td>
</tr>
</tbody>
</table>

### Significant trends
No association between dietary protein and risk of total IHD in this group of men.

### Limitations:
1. Self-administered questionnaires.
2. Study population consisted of white male health professionals.

### Source of funding
- National Institutes of Health (HL35464 and CA55075) and by the Kirschstein-NRSA Aging Training Grant (AG000158)

---

**Authors:** Qiao Q, Tervahauta M, Nissinen A, Tuomilehto J

**Year:** 2000

**Citation:** European Heart Journal 21(19):1621-6

**Country of study:** Finland

**Aim of study:** Risk of early and late death in relation to smoking and ex-smoking
**Study design:** Cohort  
**Quality score:** (++, + or -): +  

**Source population**  
**Number of people:** 1711  
**Demographics:** Not reported  

**Study (eligible and selected) population**  
**Number of people:** 1673  
**Characteristics:** Not reported  
**Location:** Finland  
**Recruitment strategy:** Not reported  
**Length of follow-up:** 35-year  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Men born between 1900 and 1919  
**Excluded populations:** Subjects known to have coronary heart disease at baseline  

**Exposures at midlife**  
**Relevant exposures:** Smoking  
**Time:** 1959 to 1989  
**Measurement of exposure:** Smoking habits was collected using a standardised questionnaire developed for the Seven Countries Study  

**Outcomes at 55 years or over**  
**Outcomes:** Mortality  
**Outcome measurement:** Review of death certificates, collection of medical information and clinical records from hospitals, and interviews with physicians and relatives of the deceased or any other witnesses of fatal events. After the 15th year of follow-up, only the reviewing and coding of official death certificates was performed.  
**Time:** End of 1994  

**Analysis**  
**Analysis strategy:** Cox proportional hazards model  
**Confounders:** Age, area of residence, body mass index, systolic blood pressure, serum cholesterol at baseline  

**Results, limitations, source of funding**  
**Number:**  
- CHD mortality ($n = 1463$)  
- Total mortality ($n = 1673$)  
**Effect estimates:**  
- Smoking status at baseline  
- Total mortality
10-year mortality
Non-smoker 1
Ex-smoker 1.74 (1.07–2.83)
Current smoker 2.16 (1.44–3.25)

35-year mortality
Non-smoker 1
Ex-smoker 1.13 (0.93–1.36)
Current smoker 1.62 (1.40–1.88)

CHD mortality
10-year mortality
Non-smoker 1
Ex-smoker 7.37 (1.66–32.70)
Current smoker 6.80 (1.64–28.22)

35-year mortality
Non-smoker 1
Ex-smoker 1.39 (1.00–1.94)
Current smoker 1.63 (1.24–2.13)

Baseline cigarettes consumption (number per day)

Total mortality
10-year mortality
Non-smoker 1
Ex-smoker
1–9 1.94 (1.01–3.74)
10–19 2.05 (1.10–3.80)
>20 1.45 (0.77–2.74)

Current smoker
1–9 1.74 (1.02–2.98)
10–19 2.26 (1.45–3.52)
>20 2.56 (1.62–4.06)

35-year mortality
Non-smoker 1
Ex-smoker
1–9 0.98 (0.72–1.33)
10–19 1.09 (0.82–1.44)
>20 1.29 (1.01–1.65)

Current smoker
1–9 1.15 (0.93–1.42)
10–19 1.76 (1.48–2.09)
>20 1.98 (1.65–2.37)

CHD mortality
10-year mortality
Non-smoker 1
Ex-smoker
1–9 8.18 (1.48–45.09)
10–19 7.32 (1.34–40.08)
>20 7.91 (1.59–39.41)

Current smoker
1–9 7.13 (1.51–33.69)
10–19 8.28 (1.92–35.76)
>20 7.16 (1.60–31.95)

35-year mortality
Non-smoker 1
Ex-smoker
1–9 1.21 (0.73–2.03)
10–19 1.47 (0.93–2.32)
>20 1.60 (1.06–2.41)
Current smoker
1–9 1.13 (0.77–1.66)
10–19 1.82 (1.33–2.48)
>20 1.96 (1.42–2.72)

Hazard ratios (95% CI) of deaths from all-cause and coronary heart disease in relation to the changes in smoking status between 1959 and 1969

**Total mortality**
Non-smoker 1
Persistent former smoker 0.97 (0.76–1.22)
Smoked in one of three examinations 1.13 (0.87–1.47)
Smoked in two of three examinations 1.18 (0.93–1.51)
Persistent current smoker 1.84 (1.54–2.19)

**CHD mortality**
Non-smoker 1
Persistent former smoker 1.12 (0.77–1.65)
Smoked in one of three examinations 1.07 (0.67–1.70)
Smoked in two of three examinations 1.08 (0.71–1.65)
Persistent current smoker 1.84 (1.36–2.48)

**Significant trends:** Men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers

**Limitations**
1. **Author:** None reported
2. **Reviewer:** Not reporting demographic characteristics of participants

**Source of funding:** Yrjo Jahnsson’s Foundation, Academy of Finland, the Sandoz Foundation for Gerontological Research and the National Institute of Health (AG-08762)

**Authors:** Qiu D, Mei J, Tanihata T, Kawaminami K, Minowa M

**Year:** 2003

**Citation:** Journal of Epidemiology 13(3): 149-56

**Country of study:** China

**Aim of study:** Clarify the risk factors of CVD deaths in rural areas

**Study design:** Cohort study

**Quality score:** (+++, + or -): +

**Source population**

**Number of people:** 50,252

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 50,069

**Characteristics:**
No. of subjects 50252
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>Age group(%)</th>
<th>40-49 years 41.1</th>
<th>50-59 23.0</th>
<th>60-69 20.8</th>
<th>70-79 12.3</th>
<th>80+ 2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) ± SD</td>
<td>55.3 ±11.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking status(%)</td>
<td>Non-smoker 57.1</td>
<td>Ex-smoker 3.0</td>
<td>Current smoker 39.9</td>
<td>Non-drinker 57.2</td>
<td>Ex-drinker 2.0</td>
</tr>
</tbody>
</table>

**Location:** Sixi, Lixi, Luoping, Putian, Luxi, Shinao, Meizhuang, and Ertang Townships in Shanggao, Wuning, Jinxian, and Gaoan Counties in Jiangxi Province, China.

**Area (%):**
- Wuning 39.7
- Shanggao 19.7
- Gaoan 19.6
- Jinxian 21.0

**Recruitment strategy:** Door-to-door

**Length of follow-up:** Six years

**Response rate and loss to follow-up:** 99.6%

**Eligible population:** Door-to-door

**Excluded populations:** 183 cases with a previous history of CVD, 632 CVD deaths. Inpatients were excluded from the study.

**Exposures at midlife**

**Relevant exposures:** Frequency of food intake, liking for fatty foods and salty foods, cigarette smoking, alcohol drinking

**Time:** September 01, 1994 and June 30, 1996

**Measurement of exposure:** Door-to-door survey

**Outcomes at 55 years or over**

**Outcomes:** CVD death

**Outcome measurement:** Village physicians who lived in the same village as cohort subjects filled out follow-up reports and submitted them to the township hospitals every 10 days

**Time:** Death from causes other than CVD, or December 31, 2000, whichever came first

**Analysis**

**Analysis strategy:** Cox proportional hazard model

**Confounders:** Sex, age group, area, cigarette smoking status, alcohol drinking status, blood pressure, BMI, marital status, fatty foods, salty foods, frequency of Chinese pickles intake, frequency of meat intake, sleeping hours per day
## Results, limitations, source of funding

**Number:** 671

**Effect estimates:**

Hazard ratios of cerebrovascular disease mortality

HR (95% CI)

<table>
<thead>
<tr>
<th>Age group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>1.00</td>
</tr>
<tr>
<td>50-59</td>
<td>2.14 (1.52-3.01)</td>
</tr>
<tr>
<td>60-69</td>
<td>5.13 (3.79-6.94)</td>
</tr>
<tr>
<td>70-79</td>
<td>11.38 (8.34-15.54)</td>
</tr>
<tr>
<td>80+</td>
<td>19.85 (13.65-28.87)</td>
</tr>
</tbody>
</table>

p for trend <0.01

(Cigarette smoking status)

Non-smoker 1.00
Ex-smoker 1.40 (0.98-2.00)
Current smoker 1.08 (0.87-1.34)

p for trend 0.59

(Alcohol drinking status)

Non-drinker 1.00
Ex-drinker 1.55 (1.04-2.31)
Current drinker 1.12 (0.93-1.34)

p for trend 0.23

(Blood pressure)

Normal 1.00
High-normal 1.38 (1.09-1.74)
Hypertension 2.06 (1.72-2.47)

p for trend <0.01

(Body mass index)

<18.5 1.00
18.5-23.9 1.12 (0.94-1.33)
>24.0 1.03 (0.68-1.58)

p for trend 0.33

(Marital status)

Married 1.00
Never married 1.25 (0.59-2.65)
Divorced 0.95 (0.42-2.13)
Widowed 1.16 (0.96-1.41)

p for trend –

(Fatty foods)

Dislike 1.00
Normal 1.24 (0.72-2.15)
Like 1.33 (0.78-2.29)

p for trend 0.23

(Salty foods)

Dislike 1.00
Normal 1.40 (1.13-1.73)
Like 1.46 (1.10-1.95)

p for trend <0.01

(Frequency of Chinese pickles intake)

Never or seldom 1.00
Once or twice per month 0.91 (0.74-1.13)
More than once per week 0.79 (0.63-0.98)
**Significant trends:** CVD mortality significantly increased in parallel with age, blood pressure and salty foods.

**Limitations:**

Author: None reported

Reviewer:

1. Misclassification and change of exposure.
2. Behaviours are self-reported

**Source of funding:** Not reported

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**Authors:** Räikkönen K, Matthews KA, Kuller LH

**Year:** 2001

**Citation:** Hypertension 38(4): 798-802.

**Country of study:** USA

**Aim of study:** Test the hypotheses that the trajectory of psychological risk increases the risk for the development of hypertension and that blood pressure levels fluctuate with psychological changes.

**Study design:** Began as a prospective study

**Quality score:** (+, + or -): +

---

**Source population**

**Number of people:** Not reported

**Demographics:** Not reported

---

**Study (eligible and selected) population**

**Number of people:** 541

**Characteristics:**

**Hypertensives**

Mean±SD (coefficient of variation)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensives</th>
<th>Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, y</td>
<td>48.0±1.5</td>
<td>47.6±1.6</td>
</tr>
<tr>
<td>Age at the time of menopause, y</td>
<td>52.6±3.1</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8±5.2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Physical activity, kJ/wk</td>
<td>4847±5010</td>
<td>26.8±5.2 (5.6)</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>9.0±12.6 (88.1)</td>
<td></td>
</tr>
<tr>
<td>Current smoking (yes), n (%)</td>
<td>24 (32)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes among smokers, n/d</td>
<td>20.5±11.6 (77.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Normotensives**

Age at baseline, y 47.6±1.6
Age at the time of menopause, y 52.6±2.6
BMI, kg/m2 24.4±4.3 (5.2)
Physical activity, kJ/wk 6217±7276 (229)
Alcohol consumption, g/d 8.4±10.0 (92.2)
Current smoking (yes), n (%) 123 (28.5)
Cigarettes among smokers, n/d 19.3±12.0 (74.9)

Location: USA
Recruitment strategy: Driver’s license list
Length of follow-up: 9.2 years; SD, 3.4 years; range, 1 to 14 years
Response rate and loss to follow-up: -
Eligible population: Middle-aged women
Excluded populations: -

Exposures at midlife
Relevant exposures: Physical activity, alcohol use, and cigarette smoking
Time: 1983-1984
Measurement of exposure: Cigarette smoking defined as the number of cigarettes smoked per day
Alcohol intake defined as the amount of current alcohol intake per day converted into grams of absolute alcohol

Outcomes at 55 years or over
Outcomes: Hypertensive
Outcome measurement: Use of antihypertensive medication and/or had elevated systolic BP or diastolic BP on two consecutive exams
Time: Not reported

Analysis
Analysis strategy: Cox proportional hazards
Confounders: Age, race, years of education, parental history of hypertension, baseline blood pressure, body mass index, physical activity, alcohol use, and cigarette smoking

Results, limitations, source of funding
Number: 75
Effect estimates:
Biological and Health Behaviour Predictors of Hypertension Incidence
Predictor, b, P, Hazards Ratio (95% CI)
Race (white/African American) 0.16, 0.67, 1.18 (0.57–2.44)
Parental history (no/yes) 0.76, 0.005, 2.15 (1.26–3.66)
Age at baseline (y) 0.12, 0.14, 1.12 (0.96–1.31)
Education (y) -0.04, 0.13, 0.96 (0.78–1.19)
BMI (kg/m2) 0.05, 0.04, 1.05 (1.01–1.10)
Physical activity (kJ/wk) -0.45, 0.12, 0.64 (0.36–1.13)
Alcohol consumption (g/d) 0.84, 0.17, 2.31 (0.71–7.54)
Smoking status (no/yes) 0.40, 0.19, 1.50 (0.83–2.72)

Significant trends: Increasing levels of anger, decreasing levels of social support, and high anxiety increase the likelihood of women's development of hypertension in midlife
Limitations:
1. Bias due to unavailability of follow-up
2. Missing data for BP or for prescription of antihypertensive medication, and psychological changes occurring between the available data points.
3. Participants had a different number of evaluations (range, 2 to 8 visits) across the follow-up

Source of funding: National Institutes of Health grant HL-28266, the Pittsburgh Mind-Body Center (HL-65111 and HL-65112), and the John D. and Catherine T. MacArthur Foundation Research Network on Socioeconomic Status and Health

Authors: Rantakömi SH, Laukkanen JA, Sivenius J, Kauhanen J, Kurl S
Year: 2013
Citation: Acta Neurologic Scandinavica 127(3): 186-91
Country of study: Finland
Aim of study: Examine the association between hangover and the risk of stroke
Study design: Longitudinal population-based study
Quality score: (+++, + or -): +

Source population
Number of people: 2682
Demographics: Not reported

Study (eligible and selected) population
Number of people: 2466
Characteristics:
Age, years 52.9 (5.3); BMI, kg/m2 26.8 (3.6); Current smokers, % 31.4; Current smoking, pack-years 8.2 (16.1); Alcohol consumption, g/week 74.3 (126.4); Systolic blood pressure, mmHg 133.9 (16.9); Diastolic blood pressure, mmHg 86.6 (10.4); Serum HDL-cholesterol, mM 1.3 (0.3); Serum LDL-cholesterol, mM 4.0 (1.0); Symptomatic CHD or CHD history, % 76.0; CHD in family, % 48.6; C-reactive protein, mg/l 2.4 (4.1); Diabetes, % 5.2; Atrial fibrillation, % 1.3; Cardiac failure, % 6.9
Location: Kuopio, Finland
Recruitment strategy: Participants of the Kuopio Ischemic Heart Disease Risk Factor Study
Length of follow-up: 15.7 years
Response rate and loss to follow-up: Not reported
Eligible population: Men aged 42, 48, 54, 60 years at baseline and living in the town of Kuopio and surrounding rural communities
Excluded populations: Individuals with strokes prior to the baseline investigation were excluded

Exposures at midlife
Relevant exposures: Alcohol consumption
Time: March 1984 and December 1989
Measurement of exposure: Nordic alcohol consumption inventory

Outcomes at 55 years or over
Outcomes: Stroke
**Outcome measurement:** 1984 and 1992 ascertained through the Finnish part of the WHO MONICA stroke register. Incidence between 1993 and 2004 obtained by computerised linkage to the Finnish national hospital discharge registry and death certificate registers

**Time:** March 1998 and February 2001

### Analysis

**Analysis strategy:** Cox proportional hazards regression model

**Confounders:** Age, current smoking, serum high density lipoprotein cholesterol, serum low density lipoprotein cholesterol, BMI, SBP, myocardial ischemia during exercise, symptomatic CHD and CHD in family, CRP, diabetes, and total alcohol consumption, atrial fibrillation and cardiac failure

### Results, limitations, source of funding

**Number:** 206 (167 ischemic strokes)

**Effect estimates:**

<table>
<thead>
<tr>
<th>Risk of any stroke according to Hangover</th>
<th>Hangover &lt;1</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of ischemic stroke according to Hangover</td>
<td>Hangover &lt;1</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Hangover &gt;1</td>
<td>2.45 (1.18–5.12)</td>
</tr>
</tbody>
</table>

**Significant trends:** At least one hangover a year is related to an increased risk of ischemic stroke in men

**Limitations:**
1. Absence of women and elderly from the cohort
2. Misclassification of exposure

**Source of funding:** Juho Vainio Foundation and Yrjo Jahnsson Foundation, Helsinki; Finland

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**Authors:** Ravona-Springer R, Schnaider-Beeri M, Goldbourt U

**Year:** 2013

**Citation:** Neurology 30;80(18): 1677-83

**Country of study:** Israel

**Aim of study:** Analyse the relationship between body weight variability and dementia

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

---

**Source population**

**Number of people:** 11,876

**Demographics:** Not reported

---

**Study (eligible and selected) population**
<table>
<thead>
<tr>
<th>Characteristics:</th>
<th>BMI category, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I:</strong> Age, 47.9; BMI in 1963 18.8; Ever smoked, % 82; Diabetic, % 2.0; SES rank (mean 0–4) 2.07</td>
<td></td>
</tr>
<tr>
<td><strong>Group II:</strong> Age, 49.0; BMI in 1963 23.1; Ever smoked, % 70; Diabetic, % 4.1; SES rank (mean 0–4) 2.57</td>
<td></td>
</tr>
<tr>
<td><strong>Group III:</strong> Age, 49.3; BMI in 1963 27.1; Ever smoked, % 66; Diabetic, % 4.3; SES rank (mean 0–4) 2.68</td>
<td></td>
</tr>
<tr>
<td><strong>Group IV:</strong> Age, 49.6; BMI in 1963 31.5; Ever smoked, % 68; Diabetic, % 8.2; SES rank (mean 0–4) 2.36</td>
<td></td>
</tr>
<tr>
<td><strong>Location:</strong> Israel</td>
<td></td>
</tr>
<tr>
<td>Recruitment strategy: <strong>Stratified sampling</strong></td>
<td></td>
</tr>
<tr>
<td>Length of follow-up: 34-35 years</td>
<td></td>
</tr>
<tr>
<td>Response rate and loss to follow-up: 86.2%</td>
<td></td>
</tr>
<tr>
<td>Eligible population: Civil servants and municipal employees aged 40 years and above</td>
<td></td>
</tr>
<tr>
<td>Excluded populations: 173 men born outside six predefined geographical areas</td>
<td></td>
</tr>
</tbody>
</table>

### Relevant exposures at midlife

**Leisure time physical activity**

**Time:** 1965

**Measurement of exposure:** Subjects asked: "What degree of leisure time physical activity do you practice?": 1) almost no physical activity 2) inconsistent physical activity, 3) daily physical activity, 4) daily effortful physical activity

### Outcomes at 55 years or over

**Outcomes:** Dementia

**Outcome measurement:** Hebrew version of the Modified Telephone Interview for Cognitive Status. Clinical assessment included the Dementia Questionnaire, Mini-Mental State Examination, Global Deterioration Scale, and Hachinski Ischemic Scale. Dementia was diagnosed using DSM-IV criteria.

**Time:** 1999/2000

### Analysis

**Analysis strategy:** Logistic regression

**Confounders:** Age, diabetes mellitus, body height, and SES

### Results, limitations, source of funding

**Number:** 307 had dementia, 175 had CIND

**Effect estimates:**

- Group of baseline BMI
  - OR (95%CI) p
  - I 1.43 (0.75–2.71) NS
  - III 1.05 (0.79–1.40) NS
### IV 1.25 (0.73–2.14) NS

**Significant trends:** Midlife variations in weight may antecede late-life dementia

**Limitations:**
1. Lack of information on the incidence of dementia in subjects from original study reported dead before follow-up
2. Brain imaging not performed in dementia assessment

**Source of funding:** NIA R01 AG034087 and the Graubard 431 Fund (M.S.-B.), the American Federation for Aging Research (AFAR), Young Investigator Award 2011, and NIRG-11-205083 Alzheimer’s Association, 2012 (R.R.-S.).

| Authors | Risérus U, Arnlöv J, Berglund L |
| Year | 2007 |
| **Citation:** | Diabetes Care 30(11): 2928-33 |
| **Country of study:** | Sweden |
| **Aim of study:** | To identify predictors of insulin sensitivity |
| **Study design:** | Longitudinal |
| **Quality score:** (+, + or -): + |

**Source population**
2,322 men age 50 years from Uppsala, Sweden were invited and participated in baseline investigation in 1970-73
1,221 out of 2,322 men (73% of survivors) participated at re-examination in 1991-95

**Study (eligible and selected) population**
Analysis restricted to 770 men with complete data

**Follow-up:** 20 yrs (1970-73 to 1991-95)

**Exclusion:**
1. 124 subjects taking glucose-lowering medication or who had diabetes
2. Subjects treated with drugs for cardiovascular disease (n=251)
3. Non-participants (n=460)
4. Subjects with incomplete data (n=76)

**Attrition:** 422 men died and 219 moved

**Exposures at midlife**
Self-reported smoking and physical activity
Smoking categorised as smoking versus non-smoking
Physical activity assessed using validated questionnaire and participants categorized into ‘sedentary’, ‘moderate’, ‘regular’, and ‘athletic’ groups

**Outcomes at 55 years or over**
Insulin sensitivity of men at age 70 was calculated as glucose infusion rate using hyperinsulinemic – euglycemic clamp

**Analysis**
**Analysis strategy:** Multivariate regression was used to identify independent predictors of insulin sensitivity

**Confounders:** BMI, triglycerides, HDL cholesterol, glucose, blood pressure, physical activity, saturated fat biomarkers, and socioeconomic status, baseline fasting insulin

**Results, limitations, source of funding**

- Smoking did not significantly predict insulin sensitivity
- Physical activity significantly predicted insulin sensitivity ($\beta=0.25, [0.08, 0.42]$)

**Limitations:**
1. Lack of clamp measurements at baseline
2. Survival bias with unhealthy men (high insulin resistance) more likely to die follow-up
3. Residual confounding (e.g. abdominal obesity)
4. Cannot generalise to younger age groups, women, ethnicities other than Caucasians

**Source of funding:** The Swedish Society for Medical Research

**Authors:** Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH... White LR

**Year:** 2000

**Citation:** Journal of the American Medical Association 283(20): 2674-2679

**Country of study:** USA

**Aim of study:** To explore the association of coffee and dietary caffeine intake with risk of Parkinson Disease

**Study design:** Prospective cohort

**Quality score:** (++, + or -): +

**Source population**

- **Number of people:** 8006
- **Demographics:** Not reported

**Study (eligible and selected) population**

- **Number of people:** 8004
- **Characteristics:** Not reported
- **Location:** Oahu, Hawaii
- **Recruitment strategy:** Not reported
- **Length of follow-up:** 30 years
- **Response rate and loss to follow-up:** Not reported
- **Eligible population:** Enrolled in the Honolulu Heart Program
- **Excluded populations:** Two prevalent cases of PD

**Exposures at midlife**

- **Relevant exposures:** Diet
- **Measurement of exposure:** Interviews, 24-hour dietary recall and physical evaluation
Outcomes at 55 years or over

Outcomes: Parkinson Disease

Outcome measurement: Pre-91 review of all cohort members’ hospitalisation records; death certificates; medical records

After 1991, the diagnosis of PD was based on complete re-examinations of the entire cohort


Analysis

Analysis strategy: Cox proportional hazards regression model

Confounders: Age and pack-years of cigarette smoking

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Nondrinker 5.1 (1.8-14.4)
4 to 8 2.7 (1.0-7.8)
12 to 16 2.5 (0.9-7.3)
20 to 24 2.0 (0.6-6.4)
>28 Reference

Test for trend P<.001

Nondrinkers vs drinkers 2.2 (1.4-3.3)

Significant trends: Higher coffee and caffeine intake is associated with a significantly lower incidence of Parkinson Disease

Limitations:

Author:
1. Population is Japanese-American men with older age at diagnosis
2. Generalisations to younger-onset cases, women, and other ethnic groups cannot be made with certainty

Reviewer: No characteristics provided

Source of funding: United States Department of the Army grant DAMD17-98-1-8621; National Institutes of Health, National Institute on Aging contract N01-AG-4-2149; National Heart, Lung, and Blood Institute contract N01-HC-05102; and VA Medical Research funds

Authors: Rovio S, Kåreholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H… Kivipelto M

Year: 2005

Citation: Lancet Neurology 4(11): 705-711

Country of study: Finland

Aim of study: Investigate the association between leisure-time physical activity at midlife and the subsequent development of dementia and Alzheimer’s disease

Study design: Population-based cohort

Quality score: (+++, + or -): +
<table>
<thead>
<tr>
<th><strong>Source population</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people:</strong> 2000</td>
</tr>
<tr>
<td><strong>Demographics:</strong> Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Study (eligible and selected) population</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people:</strong> 1449</td>
</tr>
<tr>
<td><strong>Characteristics:</strong></td>
</tr>
<tr>
<td><strong>Active:</strong> Age at midlife (years) 50.8 (6.1); Men: women 228 (44.3%): 287 (55.7%); Re-examination measurements Alzheimer’s disease 10/510 (2.0%); History of stroke 32 (6.2%); Smokers 234 (45.4%); Alcohol drinkers 380 (73.8%); Dementia 15 (2.9%); Education (years) 8.7 (3.6); Age at re-examination (years) 71.5 (4.0)</td>
</tr>
<tr>
<td><strong>Sedentary:</strong> Age at midlife (years) 49.5 (5.8); Men: women 265 (36.0%): 471 (64.0%); Re-examination measurements (late-life); Alzheimer’s disease 31/729 (4.3%); History of stroke 61 (8.3%); Smokers 325 (44.2%); Alcohol drinkers 532 (72.3%); Dementia 38 (5.2%); Education (years) 8.7 (3.4); Age at re-examination (years) 70.9 (3.9)</td>
</tr>
<tr>
<td><strong>Location:</strong> North Karelia and Kuopio, Finland</td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong> Randomly selected from the survivors of a population-based cohort</td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong> Follow-up time (years):</td>
</tr>
<tr>
<td><strong>Active</strong> 20.7 (5.0)</td>
</tr>
<tr>
<td><strong>Sedentary</strong> 21.3 (4.7)</td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong> 72.5%</td>
</tr>
<tr>
<td><strong>Eligible population:</strong> Individuals aged 65–79 years by the end of 1997. Participants of the Cardiovascular risk factors, Aging and Incidence of Dementia study.</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong> Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Exposures at midlife</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relevant exposures:</strong> Leisure-time physical activity</td>
</tr>
<tr>
<td><strong>Time:</strong> 1972, 1977, 1982, or 1987</td>
</tr>
<tr>
<td><strong>Measurement of exposure:</strong> Self-administered questionnaire</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Outcomes at 55 years or over</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Outcomes:</strong> Dementia and AD</td>
</tr>
<tr>
<td><strong>Outcome measurement:</strong> APOE genotypes by use of PCR and Hhal Digestion. Diagnostic and Statistical Manual of Mental Disorders. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria</td>
</tr>
<tr>
<td><strong>Time:</strong> 1998</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Analysis</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Analysis strategy:</strong> Multiple logistic regression</td>
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<tr>
<td><strong>Confounders:</strong> Age at re-examination, sex, education, follow-up time, and locomotor disorders, APOE e4 genotype, midlife body-mass index, systolic blood pressure, cholesterol, and history of myocardial infarction, stroke, and diabetes mellitus, smoking status and alcohol drinking</td>
</tr>
</tbody>
</table>

| **Results, limitations, source of funding** |
**Number:** 117 persons had dementia and 76 had AD

**Effect estimates:**
- **Odds ratio (95% CI) for active vs sedentary group**
  - Dementia: 0.47 (0.25–0.90)
  - Alzheimer’s disease: 0.35 (0.16–0.80)

**Significant trends:** Leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in life

**Limitations:**
1. Survival bias
2. Dementia cases may have been lost because of cut-off
3. Reliability of physical activity data

**Source of funding:** EVO 5772720 from Kuopio University Hospital, grant IIRG-04–1345 from Alzheimer Association, Academy of Finland grants 103334 and 206951, the Gamla Tjänarinnor Foundation, and the SADF

**Authors:** Rovio S, Kareholt I

**Year:** 2007

**Citation:** Journal of Geriatric Psychiatry 22: 874–882.

**Country of study:** Finland

**Aim of study:** Clarify the association between work-related physical activity and dementia/AD

**Study design:** Prospective cohort study

**Quality score:** (+++, + or -): +

**Source population**

**Number of people:** 2000

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 1449

**Characteristics:**
- **Active:** Age at midlife (years) 48.6 (47.9–49.4); Age at re-examination (years) 70.4 (70.0–70.8); Education (years) 8.7 (3.4); Men 272 (37.6); Women 452 (62.4); Body mass index (kg/m2) 26.2 (3.5); Physically active during leisure- time 267 (36.9); Persons employed in manual work 233 (32.2); Persons having low income 309 (42.7); Commuting physical activity: Sedentary 482 (66.6), Moderately active 184 (25.4), Active 58 (8.0); Smokers 303 (41.9)
- **Sedentary:** Age at midlife (years) 51.2 (50.2–52.1); Age at re-examination (years) 70.6 (70.0–71.0); Education (years) 9.1 (3.7); Men 180 (41.5); Women 254 (58.5); Body mass index (kg/m2) 26.7 (3.8); Physically active during leisure- time 207 (47.7); Persons employed in manual work 81 (18.7); Persons having low income 179 (41.2); Commuting physical activity: Sedentary 202 (46.5), Moderately active 218 (50.2), Active 14 (3.2); Smokers 208 (47.9)

**Location:** Kuopio or Joensuu, Sweden

**Recruitment strategy:** Random recruitment

**Length of follow-up:**
- Active 22.1 (4.2)
- Sedentary 19.6 (5.3)
**Response rate and loss to follow-up:** 73%

**Eligible population:** Participants of the Cardiovascular risk factors, Aging and Dementia Study. Aged 65–79 years by the end of the year 1997

**Excluded populations:** 22 persons (one with AD) with missing data about occupational physical activity

---

### Exposures at midlife

**Relevant exposures:** Occupational and commuting physical activity

**Time:** 1972, 1977, 1982, or 1987

**Measurement of exposure:** Self-report questionnaire.

- ‘How physically heavy is your work?’
- ‘How many minutes do you walk, bicycle or have some other physical activity when you are going to and from work?’

---

### Outcomes at 55 years or over

**Outcomes:** Dementia and Alzheimer’s dementia

**Outcome measurement:** Cognitive status was screened with the Mini-Mental State Examination. Participants scored <24 referred for further neurological, cardiovascular and neuropsychological examinations.

Diagnosed demented according to the DSM-IV or NINCDS-ADRDA

**Time:** 1998

---

### Analysis

**Analysis strategy:** Multiple logistic regression model

**Confounders:** Age, sex, education, follow-up time, locomotor symptoms, main occupation during life, income at midlife, leisure-time physical activity, socio-economic status, other subtype of work-related physical activity, BMI, total serum cholesterol, SBP, the ApoE e4 genotype and vascular disorders

---

### Results, limitations, source of funding

**Number:**

61 DSM-IV

48 NINCDS-ADRDA

**Effect estimates:**

**Association between occupational physical activity and the risk of dementia and Alzheimer’s disease**

- **Sedentary**
  - Dementia 1
  - Alzheimer’s 1

- **Active**
  - Dementia 1.45 (0.66–3.17)
  - Alzheimer’s 1.90 (0.73–4.95)

**Association between commuting physical activity and the risk of dementia and Alzheimer’s disease**

---
**Sedentary**
Dementia 0.58 (0.26–1.28)
AD 0.36 (0.13–0.96)

**Moderately active**
Dementia 1
AD 1

**Active**
Dementia 0.46 (0.10–2.17)
AD 0.48 (0.09–2.58)

**Significant trends:** Neither occupational nor commuting physical activity were sufficient to protect against dementia and AD later in life

**Limitations**

**Author:**
1. Survival bias
2. Residual confounding

**Reviewer:** Self-reported physical activity

**Source of funding:** EVO 5772720 from Kuopio University Hospital, grant IIRG-04-1345 from Alzheimer Association, Academy of Finland grants 103334 and 206951, the Gamla Tjanarinnor Foundation, the SADF, Juho Vainio Foundation and Finnish Cultural Foundation

---

**Authors:** Ruder EH, Thiébaut AC, Thompson FE, Potischman N, Subar AF, Park Y… Cross AJ

**Year:** 2011

**Citation:** American Journal of Clinical Nutrition 94(6): 1607-1619

**Country of study:** USA

**Aim of study:** To assess the influence of midlife (and adolescent) diet on colorectal cancer risk

**Study design:** Longitudinal

**Quality score:** (+++, + or -): ++

---

**Source population**
Prospective cohort study of men and women ages 50-71 years living in California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Texas, Arizona, Atlanta (GA), Detroit (MI)
Baseline questionnaire completed in 1995-1996 by 617,119 people

**Study (eligible and selected) population**
Cohort for this study included 292,797 participants (171,171 men and 121,626 women)
92.8% and 58.5% of participants were white and male
Mean age of 62.8 years at administration of risk factor questionnaire

**Follow-up:** Follow-up from receipt of risk factor questionnaire (1995-1996) until censoring at the end of 2006 or when the participant moved out of the cancer registry areas, had a cancer diagnosis, or died, whichever came first. 5% lost to follow-up as a result of moving out of 10 states

**Exclusion:** Excluded people for whom either the baseline [n=6959] or the risk factor questionnaire [n=3424] was completed by proxy respondents, those with prevalent cancer at the administration of the baseline [14,565] or risk factor [n=4297] questionnaires, those who had a death only report for any cancer [n=983], those with 0 PY of follow-up [n=19], and those in the extremes of energy intake for...
diet in the previous 12 months [n=2334]

Attrition: -

Exposures at midlife

Baseline questionnaire completed in 1995-1996

6 months later, risk factor questionnaire assessing dietary intake 10 years previously (when participants were around 40-61 years) was administered - comprised 37-item food-frequency questionnaire (FFQ)

Databases used to capture information on energy, carbohydrate, protein, calcium
9 categories of frequency of consumption ranging from ‘never’ to ‘2 or more times per day’

Diet 10 years before baseline: portion size estimated using the median sex-specific portion size from NHANES III; energy and nutrient intakes (carbohydrate, total fat protein, calcium, vitamins A and C) based on NHANES III

Exposures assessed: carbohydrate, total fat, protein, fibre, calcium, vitamin A, vitamin C, grains, vegetables, fruit, milk, red meat, processed meat, solid fat, sweet baked goods

Outcomes at 55 years or over

Colorectal cancer (primary diagnoses of adenocarcinoma identified through state cancer registries)

Analysis

Analysis strategy: Cox proportional hazards regression used to estimate the influence of midlife diet on colorectal cancer risk

Confounders for assessment of intake of energy and nutrients: Energy at ages 12-13 years, energy in recent adulthood, nutrient of interest in recent adulthood, age at completion of risk-factor questionnaire, sex, BMI, race, education, physical activity, alcohol consumption, smoking, use of nonsteroidal anti-inflammatory drugs, use of HRT, self-report of a first-degree relative with a history of colon cancer

Confounders for assessment of food group intake: Same as above with the addition of use of aspirin and ibuprofen

Results, limitations, source of funding

- 3773/292,797 people had colorectal cancer
- Those in the highest intake category 10 y previously for calcium (HR: 0.83; 95% CI: 0.73, 0.94), vitamin A (HR: 0.81; 95% CI: 0.71, 0.92), vitamin C (HR: 0.83; 95% CI: 0.72, 0.95), fruit (HR: 0.84; 95% CI: 0.73, 0.97), and milk (HR: 0.78; 95% CI: 0.67, 0.90) had a lower risk of colon cancer, but a higher risk of colon cancer was observed for total fat (HR: 1.15; 95% CI: 1.01, 1.30), red meat (HR: 1.31; 95% CI: 1.12, 1.53), and processed meat (HR: 1.24; 95% CI: 1.06, 1.45). For rectal cancer, milk was inversely associated (HR: 0.75; 95% CI: 0.58, 0.96) with risk

Limitations:
1. Self-reported data leading to possible misclassification
2. Fibre values from NHANES 1999-2000 possible source of error

Source of funding: None reported

Authors: Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA
Year: 2011
Citation: Archives of Internal Medicine 28;171(4): 333-9
Country of study: USA

Aim of study: To assess influence of midlife smoking on dementia, AD, and VaD

Study design: Longitudinal

Quality score: (+++, + or -): +

Source population

33,108 members ages 50-60 years of Kaiser Permanente Medical Care Program of Northern California participated in health examination in 1978-85

Study (eligible and selected) population

Analysis restricted to 21,123 surviving participants who were members of health plan in 1994

Mean age in 1994 (at onset of outcome follow-up) of participants was 71.6 years

Follow-up: For cases, person-years calculated since Jan 01, 1994. Censoring at dementia diagnosis, date of death, date of end of Kaiser membership, or end of follow-up in July 31, 2008

Exclusion:

i) People with missing data (n=1045)

ii) Individuals with dementia diagnosis other than outcomes assessed

Attrition: -

Exposures at midlife

Self-reported smoking assessed using interview

Participants categorised as never smokers; former smokers; current smokers, which were further categorized into: less than 0.5 packs/day, 0.5-1 pack/day, 1-2 packs/day, 2+ packs/day

Outcomes at 55 years or over

Dementia, Alzheimer's disease (AD), vascular dementia (VaD) assessed using electronic health records from Jan. 1, 1994 to July 31, 2008

Analysis

Analysis strategy: Cox proportional hazards model used to assess influence of midlife smoking on dementia, AD, and VaD

Confounders: Age, sex, education, race, marital status, midlife BMI, hyperlipidemia, diabetes, hypertension, heart disease, and stroke during the follow-up, alcohol intake

Results, limitations, source of funding

- Compared to non-smokers, the risk of dementia was higher among those smoking: more than 2 packs per day (HR=2.14, [1.65, 2.78]), 1-2 packs per day (HR=1.44, [1.26, 1.64]), and 0.5-1 packs per day (HR=1.37, [1.23, 1.52])
- There was no association between smoking and AD risk
- Those smoking more than 2 packs per day in midlife were almost 3 times (HR=2.72, [1.20, 6.18]) more likely to develop VaD later in life than the non-smoking individuals

Limitations:

1. Possible outcome misclassification (e.g. of dementia diagnosis)
2. AD or VaD cases may have been missed in those who died prior to 1994 resulting in selective survival effect
### Influence of smoking cessation on dementia risk was not assessed

**Source of funding:** The National Graduate School of Clinical Investigation, EVO grants from Kuopio University Hospital, and grants from the Juho Vainio Foundation and Maire Taponen Foundation; Kaiser Permanente Community Benefits Grant and National Institute of Health and Academy of Finland

| Authors | Ruusunen A, Virtanen JK, Lehto SM, Tolmunen T, Kauhanen J, Voutilainen S |
| Year | 2011 |
| Citation | European Journal of Nutrition 50(2): 89-96 |
| Country of study | Finland |
| Aim of study | Investigate whether serum n - 3 polyunsaturated fatty acids or n – 6 to n - 3 ratio is associated with risk of severe depression |
| Study design | Prospective follow-up |
| Quality score: (++, + or -): | + |

**Source population**

| Number of people | 2682 |
| Demographics | Not reported |

**Study (eligible and selected) population**

| Number of people | 2077 |
| Characteristics: | |
| Age (years) | 52.9 (5.2); Marital status: living alone (%) 11.8; Socio-economic status (points) 9.1 (4.6); Smoking (%) 31; Body mass index (kg/m2) 26.9 (3.4); HPL depression score 1.3 (1.3); Alcohol consumption (grams/week) 71 (126) |
| Location | Kuopio, Finland |
| Recruitment strategy | Not reported |
| Length of follow-up | 18 years |
| Response rate and loss to follow-up | Cohort II 85.6% |
| Eligible population | Men aged 42–60 years at baseline |
| Excluded populations | Men without information on serum fatty acids (n = 155), men with missing dietary data (n = 41), those with significant depressive symptoms at baseline (n = 321) and a history of mental illness (n = 88) |

**Exposures at midlife**

| Relevant exposures | Diet |
| Time: | |
| Cohort I: | 1984 and 1986 |
| Cohort II: | 1986 and 1989 |
| Measurement of exposure | Dietary intake of foods, beverages and nutrients was quantitatively assessed by a 4-day food recording. Fatty acids from one gas chromatographic run without pre-separation |

**Outcomes at 55 years or over**
Outcomes: Depression

**Outcome measurement:** Diagnosed by a physician. Computer linkage to the national hospital discharge register, which covers every hospitalisation in Finland

**Time:** End of 2007

### Analysis

**Analysis strategy:** Cox proportional hazards model

**Confounders:** Age, examination year, baseline socioeconomic status, alcohol consumption, smoking, maximal oxygen uptake and body mass index

### Results, limitations, source of funding

**Number:** 46

**Effect estimates:**

Relative risk and (95% CI) of severe depression according to tertiles of serum fatty acids

\[ n - 3 (EPA + DHA + DPA) \]

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<tr>
<td>2</td>
<td>0.41 (0.19; 0.91)</td>
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<td>0.55 (0.26; 1.12)</td>
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<td>0.71 (0.38; 1.43)</td>
<td>1.25 (0.59; 2.65)</td>
<td>0.62 (0.31; 1.25)</td>
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\[ n - 6 \]

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<td>0.96 (0.45; 2.04)</td>
<td>0.96 (0.47; 1.96)</td>
<td>0.99 (0.48; 2.04)</td>
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<td>1.25 (0.59; 2.65)</td>
<td>1.25 (0.59; 2.65)</td>
<td>1.43 (0.70; 2.91)</td>
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**EPA**

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<td>0.62 (0.31; 1.25)</td>
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<td>0.62 (0.31; 1.25)</td>
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**DHA**

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<td>0.96 (0.47; 1.96)</td>
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<td>1.25 (0.59; 2.65)</td>
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**Linoleic acid**

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<td>3</td>
<td>1.43 (0.70; 2.91)</td>
<td>1.43 (0.70; 2.91)</td>
<td>1.43 (0.70; 2.91)</td>
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**Alpha-linolenic acid**

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<td>1.60 (0.75; 3.43)</td>
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**Arachidonic acid**

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<td>3</td>
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<td>0.62 (0.30; 1.29)</td>
<td>0.62 (0.30; 1.29)</td>
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\[ n - 6/n - 3 ratio \]

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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions. 253
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

---

### Significant trends

Neither serum n–3 PUFA concentration nor n-6/n-3 ratio was associated with risk of severe depression.

### Limitations

1. Number of depressed subjects was relatively small
2. Study was limited to subjects with severe depression requiring hospitalisation
3. Lack of power
4. Use of a single measurement of these fatty acids may underestimate the association

### Source of funding

Finnish Graduate School of Psychiatry, Juho Vainio Foundation and Yrjo Jahnsson Foundation

---

### Authors

Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S

### Year

2010

### Citation

Public Health Nutrition 13(8): 1215-20

### Country of study

Finland

### Aim of study

Assess the association between coffee, tea and caffeine and the risk of depression

### Study design

Population-based cohort study

### Quality score

(+++, + or -): +

---

### Source population

**Number of people:** 2682

**Demographics:** Not reported

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### Study (eligible and selected) population

**Number of people:** 2232

**Characteristics:**

<table>
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<th>Mean or % (SD)</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Marital status: living alone (%)</td>
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<tr>
<td>Smoking (%)</td>
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<tr>
<td>BMI (kg/m2)</td>
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<tr>
<td>Socio-economic status (points)</td>
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<tr>
<td>HPL depression score (points)</td>
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<tr>
<td>Coffee consumption (ml/d)</td>
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<tr>
<td>Tea consumption (ml/d)</td>
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<tr>
<td>Alcohol intake (g/week)</td>
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**Location:** Kuopio, Finland

**Recruitment strategy:** Not reported

**Length of follow-up:** 11 years
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<tr>
<th><strong>Response rate and loss to follow-up:</strong></th>
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<tr>
<td><strong>Eligible population:</strong></td>
<td>Men not found to be depressive at the baseline examinations and had no previously diagnosed psychiatric disorder</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong></td>
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<table>
<thead>
<tr>
<th><strong>Exposures at midlife</strong></th>
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<tbody>
<tr>
<td><strong>Relevant exposures:</strong></td>
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<tr>
<td><strong>Time:</strong></td>
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<td><strong>Measurement of exposure:</strong></td>
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<tr>
<td><strong>Analysis strategy:</strong></td>
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<tr>
<td><strong>Confounders:</strong></td>
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<table>
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<tr>
<th><strong>Results, limitations, source of funding</strong></th>
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<tbody>
<tr>
<td><strong>Number:</strong></td>
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<tr>
<td><strong>Effect estimates:</strong></td>
</tr>
<tr>
<td>Coffee intake</td>
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<td>None 1 (ref)</td>
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<tr>
<td>Light 0.29 (0.08, 0.98)</td>
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<tr>
<td>Moderate 0.48 (0.17, 1.36)</td>
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<tr>
<td>Heavy 0.25 (0.07, 0.91)</td>
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<td>P value 0.035</td>
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<td>Tea drinker 1.40 (0.78, 2.51)</td>
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<td>P value 0.252</td>
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<td><strong>Significant trends:</strong></td>
</tr>
<tr>
<td><strong>Limitations:</strong></td>
</tr>
<tr>
<td>Author</td>
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<tr>
<td>1. The number of cases was relatively low</td>
</tr>
<tr>
<td>2. Limited to participants with severe depression requiring hospitalisation</td>
</tr>
<tr>
<td>3. Measuring changes in coffee drinking habits</td>
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**Reviewer**
1. Survival bias
2. Residual confounding
3. Self-reported physical activity

**Source of funding:** Finnish Graduate School of Psychiatry, the Juho Vainio Foundation and the Yrjo Jahnsson Foundation

| **Authors:** Sabia S, Guéguen A, Berr C, Berkman L, Ankri J, Goldberg M, Zins M, Singh-Manoux A |
| **Year:** 2011 |
| **Citation:** Addiction 106(1): 93-101 |
| **Country of study:** France |
| **Aim of study:** To assess association between alcohol intake and cognitive function by occupational position |
| **Study design:** Longitudinal |
| **Quality score:** (+++, + or -): + |

**Source population**
Cohort of 20,625 employees ages 40-50 years for men and 35-50 years for women of France’s national electricity and gas company established in 1989
In 2002-04, 10,537 participants (9,399 men) over the age of 55 years were invited and were eligible for cognitive testing

**Study (eligible and selected) population**
Analysis restricted to 4,073 out of 4,525 men (denominator represents 48.2% of target population) who underwent cognitive testing and had complete data
**Follow-up:** Approximately 10 years
**Exclusion:** Participants with incomplete data (n=452)
**Attrition:** -

**Exposures at midlife**
Self-reported alcohol intake assessed annually using validated questionnaire
Frequency and daily consumption of alcoholic beverages in the week preceding questionnaire administration were used to calculate units of alcoholic drinks consumed in a week (with 1 unit=10-12 g alcohol)
Mean alcohol consumption and change in alcohol intake over 10 years prior to cognitive testing assessed
Participants were classified into the following drinking categories: no alcohol consumption, 1–3 drinks/week (occasional drinkers), 4–14 drinks/week (light drinkers), 15–21 drinks/week (moderate drinkers), and more than 21 drinks/week (heavy drinkers)

**Outcomes at 55 years or over**
Cognitive performance assessed in 2002-04 using Digit Symbol Substitution Test (DSST), which measures psychomotor speed, sustained attention and logical reasoning
Analysis

**Analysis strategy:** ANCOVA used to assess association between alcohol intake and cognitive performance by occupational position

**Confounders:** Age, screening centre, marital status, and smoking history

Results, limitations, source of funding

- Among those with low occupational position, participants consuming more than 21 drinks/week had a mean score on the DSST that was 2.1 points lower (95% CI: −3.9, −0.3) than those consuming 4–14 drinks/week
- Associations between DSST and alcohol consumption were observed only in the lower educational group
- Compared to stable alcohol consumption, great increase and decrease in alcohol consumption were both associated with lower DSST score only in the low occupational group (−3.9 points (95% CI: −6.1, −1.7) and −3.5 points (95% CI: −6.2, −0.7) respectively for high increase and decrease compared to stable alcohol consumption); p for interaction=0.003

**Limitations:**
1. Unable to distinguish regular alcohol intake from binge drinking
2. Possible bias due to missing data
3. Cannot generalise to women and unemployed people

**Source of funding:** European Science Foundation, National Institute on Aging

Authors: Sabia S, Nabi H, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A

Year: 2009

Citation: American Journal of Epidemiology 15;170(4): 428-37

Country of study: England

Aim of study: To assess the influence of unhealthy or high risk behaviours on poor executive function and memory

Study design: Longitudinal

Quality score: (+++, + or -): +

Source population

10,308 London-based office staff, ages 35-55 years initially examined in 1985-88

Study (eligible and selected) population

Analysis restricted to 5,123 participants
Mean age at baseline in 1997-99 was 56 years
Follow-up: 1997-99 to 02-04
Exclusion: -
Attrition: During the 17-year follow-up, 50% of original cohort lost to follow-up

Exposures at midlife

Self-reported health behaviours at baseline (alcohol, smoking, physical activity, diet):
Self-reported alcohol units in last 7 days, with 1 unit = 8 g ethanol; intake categorized as no alcohol, 1–14 units, and
15 or more units of alcohol per week ('high risk' behaviour defined as abstinence from alcohol)
Self-reported smoking ('high risk' behaviour defined as current smoker)
Self-reported frequency and duration of physical activity used to compute hours per week of activity intensity level ('low risk' behaviour defined as more than 2.5 hours per week of moderate physical activity or more than 1 hour per week of vigorous physical activity)
Self-reported dietary behaviour including frequency of fruit and vegetable intake ('low risk' behaviour defined as eating fruits and vegetables 2 or more times per day)

Outcomes at 55 years or over
Cognitive function tests used to measure executive function (reasoning, verbal fluency measures) during clinical examination in 2002-04

Analysis
Analysis strategy: Logistic regression to assess the influence of unhealthy or high risk behaviours on poor executive function and memory
Confounders: Age, sex, socio-economic status

Results, limitations, source of funding
- The odds for poor executive function were higher among current smokers compared to non-smokers (OR = 1.30, [1.01, 1.67]), non-drinkers compared to those who consumed 1-14 units/week (OR = 1.71, [1.39, 2.10]), those with high levels of physical activity compared to low levels (OR = 1.19, [1.01, 1.39]), those who consumed fruits and vegetables >= 2 times per day compared to those who consumed less than this amount (OR = 1.60, [1.36, 1.89])
- The odds for poor memory were higher among non-drinkers compared to those who consumed 1-14 units/week (OR = 1.34, [1.08, 1.66]), those who consumed fruits and vegetables >= 2 times per day compared to those who consumed less than this amount (OR = 1.35, [1.14, 1.59])
- The odds of poor executive function were higher among those with all four unhealthy behaviours (in terms of diet, physical activity, alcohol, smoking) compared to those with no unhealthy behaviours (OR = 5.12, [2.46, 10.70])

Limitations:
1. Limited generalizability
2. High loss to follow-up
3. Frequency, and not amount, of fruit and vegetable intake assessed

Source of funding: British Medical Research Council; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the Agency for Health Care Policy and Research; and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

Authors: Sabia S, Marmot M, Dufouil C, Singh-Manoux A
Year: 2008
Citation: Archives of Internal Medicine 168(11): 1165–1173
Country of study: England
Aim of study: Used to assess the association between smoking status and cognitive function
Study design: Longitudinal
<table>
<thead>
<tr>
<th>Quality score: (++, + or -): +</th>
</tr>
</thead>
</table>

**Source population**

10,308 London-based civil servants (6895 men and 3413 women) ages 35-55 years recruited in 1985
73% response rate
Baseline examination undertaken in 1985-88 (phase 1); subsequent phases of data collection undertaken (e.g., phase 5 in 1997-99; phase 7 in 2002-04)

**Study (eligible and selected) population**

Analysis restricted to 5,388 participants ages 35-55 years
Follow-up: 1985-88 to 97-99. Mean of 17.1 years of follow-up
Exclusion: Non-responders (n=2204)
Attrition: Individuals who had died (n=274)

**Exposures at midlife**

Self-reported smoking status, age at smoking initiation or stopping if ex-smoker, and mean number of cigarettes/cigars, ounces of tobacco smoked per week assessed using questionnaire
Smoking categories created: never smoker (those who never smoked), current smoker at phase 5, long-term ex-smoker (those who stopped before phase 1), and recent ex-smoker (stopped smoking between phase 1 and phase 5)
Grams of tobacco smoked per day (1 cigarette=1g and 1 cigar=3g) used to calculate smoking pack-years

**Outcomes at 55 years or over**

Cognitive function at phase 7 assessed (memory, reasoning, vocabulary, semantic and phonemic fluency) using battery of tests: 20-word free recall test, Alice Heim AH4 Group Test of General Intelligence, Mill Hill Vocabulary Test, verbal fluency tests

**Analysis**

Analysis strategy: Cox proportional hazards regression models used to assess the association between smoking status at phase 1 and cognitive function at phases 5 and 7
Confounders: Age, sex, marital status, education, socioeconomic position, alcohol use, frequency of fruit and vegetable intake, physical activity

**Results, limitations, source of funding**

Odds ratio of being in the lowest quintile of change in cognitive function between phase 5 (1997-99) and phase 7 (2002-04):
Compared to never smokers, current smokers (OR=1.40, [1.11, 1.75]) and recent ex-smokers (OR=1.38, [1.07, 1.77]) were more likely to show a decline in reasoning

Odds ratio of being in the lowest Quintile of Cognitive Function at phase 5 as a function of smoking status (1997-1999):
Compared to never smokers, current smokers were more likely to show a decline in memory (OR=1.37, [1.10, 1.73])
Compared to never smokers, recent ex-smokers were less likely to show a decline in vocabulary, phonemic fluency, and semantic fluency (OR=0.73, [0.60, 0.87]; OR=0.73, [0.61, 0.87]; and OR=0.75,
[0.63, 0.89], respectively); similar findings were reported for recent ex-smokers

**Limitations:**
1. Self-reported smoking habits (social desirability)
2. Limited generalizability due to homogeneity of cohort
3. Useful to include additional study phases to better study intra-individual change

**Source of funding:** British Medical Research Council; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the Agency for Health Care Policy and Research; and by the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

**Authors:** Sairenchi T, Iso H, Nishimura A, Hosoda T, Irie F, Saito Y, Murakami A, Fukutomi H

**Year:** 2004

**Citation:** American Journal of Epidemiology 15;160(2): 158-62

**Country of study:** Japan

**Aim of study:** To assess influence of smoking on the development of type 2 diabetes mellitus

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**
192,125 Japanese individuals (63,379 men and 128,746 women) ages 40-79 years underwent health check-ups in 1993

**Study (eligible and selected) population**
Analysis restricted to 39,528 men and 88,613 women

**Follow-up:** 1994 to 2002. Annual follow-up examinations until diagnosis of diabetes mellitus or end of 2002

**Exclusion:**
1. 3,614 men and 3,645 women with fasting plasma glucose greater than 7 mmol/L or a non-fasting plasma glucose level greater than 11.1 mmol/L
2. 1,333 men and 1,646 women with history of diabetes mellitus at baseline
3. Non-participants of 1994 survey (18,904 men and 34,842 women)

**Attrition:** 28% of participants lost to follow-up

**Exposures at midlife**
Self-reported never smokers, ex-smokers, current smokers of <20 cigarettes/day, or current smokers of ≥20 cigarettes/day

**Outcomes at 55 years or over**
Incident type 2 diabetes diagnosed when fasting plasma glucose level was greater than 7 mmol/L or a non-fasting plasma glucose level of greater than 11.1 mmol/L and/or person had begun to receive diabetes treatment

**Analysis**

**Analysis strategy:** Cox proportional hazards regression was used to assess influence of smoking on
the development of type 2 diabetes mellitus

**Confounders:** Age, alcohol intake, body mass index, systolic blood pressure, antihypertensive medication use, fasting status, plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level

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**Results, limitations, source of funding**

3,704 incident cases of type 2 diabetes mellitus among men and 4,286 cases among women

**Men:**
- Among those 40-59 years of age, current smokers had greater risk of type 2 diabetes compared to never smokers (RR=1.37, [1.18, 1.60])
- Among those 60-79 years, current smokers had higher risk for type 2 diabetes compared to never smokers (RR=1.20, [1.08, 1.34])

**Women:**
- Among those 40-59 years of age, current smokers had greater risk of type 2 diabetes compared to never smokers (RR=1.45, [1.18, 1.79])
- Among those 60-79 years, current smokers had higher risk for type 2 diabetes compared to never smokers (RR=1.34, [1.09, 1.66])

**Limitations:**
1. Incomplete follow-up
2. Residual confounding by physical activity and dietary habits

**Source of funding:** None reported
### Exposures at midlife

#### Relevant exposures: Diet

#### Time: 1984 and 1986

**Measurement of exposure:** Averaged information from the 1984 and 1986 FFQs. Food intake converted into nutrient intake by multiplying the consumption of each food by its nutrient content, using the U.S. Department of Agriculture database

### Outcomes at 55 years or over

#### Outcomes: “Healthy” and “usual” aging

#### Outcome measurement: Biennial questionnaires

Considered persons free of 11 chronic diseases, with no impairment in cognition, no physical disabilities, and intact mental health as healthy agers

Remaining classified as usual agers

#### Time: 2000

### Analysis

**Analysis strategy:** Logistic regression models

**Confounders:** Age; education; husband’s education; marital status; parents’ occupations when the nurse was aged 16 years; family history of diabetes, cancer, and myocardial infarction; physical activity; smoking; multivitamin and aspirin use; body mass index; history of high blood pressure; and hypercholesterolemia

### Results, limitations, source of funding

**Number:** Healthy Agers (n=1171); Usual Agers (n=9499)

**Effect estimates:**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>AHEI-2010 score</th>
<th>A-MeDi score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>0.78 (0.69–1.01)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>1.40 (1.29–1.52)</td>
<td>1.11 (1.02–1.21)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>1.37 (1.10–1.67)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>1.46 (1.28–1.67)</td>
<td>1.17 (1.07–1.28)</td>
</tr>
</tbody>
</table>

**P Value for Trend**
Significant trends: Better diet quality at midlife seems to be strongly linked to greater health and wellbeing in persons surviving to older ages

Limitations:
1. Could not exclude participants with impaired cognition, mental health, and physical function in midlife
2. Followed participants until age 70 years rather than through death or onset of a condition that would classify them as no longer healthy
3. Measurement error in the assessment of dietary patterns
4. Residual confounding
5. Included female, mostly white health care professionals

Source of funding: National Cancer Institute, National Institutes of Health

**Authors:** Satoh H, Nishino T, Tomita K, Saijo Y, Kishi R, Tsutsui H  
**Year:** 2006  
**Citation:** Internal Medicine 45(5): 235-9  
**Country of study:** Japan  
**Aim of study:** Elucidate the relationship between risk factors and the coronary artery disease  
**Study design:** Follow-up study  
**Quality score: (++, + or -): +**

**Source population**
- **Number of people:** 2,867  
- **Demographics:** Not reported

**Study (eligible and selected) population**
- **Number of people:** 2,764  
- **Characteristics:**  
  - **CAD:** Age 41.2 ± 2.7; Smokers (%) 89.7; BMI 25.6 ± 3.2  
  - **No-CAD:** Age 42.6 ± 2.8; Smokers (%) 66.8; BMI 23.5 ±2.8  
- **Location:** Hokkaido, Japan  
- **Recruitment strategy:** Not reported  
- **Length of follow-up:** 10 years  
- **Response rate and loss to follow-up:** Not reported  
- **Eligible population:** Men working in a company in Hokkaido, Japan  
- **Excluded populations:** Not reported

**Exposures at midlife**
- **Relevant exposures:** Diet  
- **Time:** 1995  
- **Measurement of exposure:** Blood samples

**Outcomes at 55 years or over**
### Outcomes
Coronary artery disease

### Outcome measurement
Examination of each subject’s clinical chart

### Time
2005

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### Analysis

**Analysis strategy:** Cox Proportional hazard model

**Confounders:** Age, body mass index, smoking habit, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, and triglyceride

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### Results, limitations, source of funding

**Number:** 35 cases of CAD during the follow up; 25 myocardial infarctions and 10 angina pectoris

**Effect estimates:**

#### Hazard Ratios for Coronary Artery Disease with Confidence Intervals for Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.92 (0.82-1.03)</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.47 (0.86-7.10)</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI</td>
<td>1.10 (0.98-1.23)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.10 (0.91-1.35)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.24 (1.12-1.36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.42 (0.28-0.63)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>1.14 (1.05-1.24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglyceride (Log)</td>
<td>0.98 (0.37-1.94)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**Significant trends:** Total cholesterol, high-density lipoprotein cholesterol and fasting plasma glucose were found to be important risk factors for CAD, and the combination of these risk factors was associated with CAD

**Limitations:**
1. Could not determine the occurrence of CAD events in 78 subjects
2. Only male workers in a single company; power might not be adequate

**Source of funding:** Not reported

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### Authors
Seccareccia F, Alberti-Fidanza A, Fidanza F, Farchi G, Freeman KM, Mariotti S, Menotti A

### Year
2003

### Citation
Annals of Epidemiology 13(6): 424-30

### Country of study
Italy

### Aim of study
Examine prospectively the relationship between vegetable consumption and long-term survival

### Study design
Observational study

### Quality score
(++, + or -): +

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### Source population
Number of people: 1,712
**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 1536  
**Characteristics:**  
- **Age (years):** 54.7  
- **Smokers/Non-smokers (ratio):** 1.36  
- **No. cigarettes/day (all subjects):** 8.7  
- **Physical activity:** Light (%) 14.1, Moderate (%) 25.3, Heavy (%) 60.7  
- **Location:** Crevalcore and Montegiorgio, Italy  
**Recruitment strategy:** Not reported  
**Length of follow-up:** 30 years  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Italian males of the Seven Countries Study, aged 45–65 years  
**Excluded populations:** 28 subjects due to missing data

### Exposures at midlife

**Relevant exposures:** Diet  
**Time:** 1960  
**Measurement of exposure:** Staff visited participants' homes to observe eating habits and interview subjects using a dietary history interview sheet. Also included 7-day food-use diary

### Outcomes at 55 years or over

**Outcomes:** Total and cause-specific mortality  
**Outcome measurement:** Official death certificates, hospital physicians, relatives of the deceased and other witnesses  
**Time:** 1965–1995

### Analysis

**Analysis strategy:** Cox proportional hazards model  
**Confounders:** Age, daily energy intake, smoking, physical activity, systolic blood pressure, total cholesterol, body mass index and fruit consumption

### Results, limitations, source of funding

**Number:** 1096 deaths (308 coronary heart disease, 325 from cancer, 158 from cerebrovascular disease and 305 from all other causes  
**Effect estimates:**  
- Vegetables (g/day) (HR for every additional 20 g/day) 0.97 (0.94–0.99)  
**Significant trends:** There is a positive association between vegetable intake and life expectancy  
**Limitations:**  
- **Author:** None reported  
- **Reviewer:**
1. Survival bias  
2. Residual confounding  
3. Some observational data but largely self-reported diet

**Source of funding:** Study was carried out within the Italian section of the FINE (Finland, Italy, the Netherlands Elderly) Study, partly supported by “Il Progetto CUORE—Epidemiology and Prevention of Ischaemic Heart Disease” of the Italian Ministry of Health

<table>
<thead>
<tr>
<th>Authors: Shaper AG, Wannamethee SG, Walker M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2003</td>
</tr>
<tr>
<td>Citation: Journal of Epidemiology 32(5): 802-8</td>
</tr>
<tr>
<td>Country of study: UK</td>
</tr>
<tr>
<td>Aim of study: Quantify the effects of primary and secondary pipe and cigar smoking on major cardiovascular events, cancer incidence, and all-cause mortality</td>
</tr>
<tr>
<td>Study design: Prospective study</td>
</tr>
<tr>
<td>Quality score: (++, + or -): ++</td>
</tr>
</tbody>
</table>

**Source population**

<table>
<thead>
<tr>
<th>Number of people: 7735</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics: Not reported</td>
</tr>
</tbody>
</table>

**Study (eligible and selected) population**

<table>
<thead>
<tr>
<th>Number of people: 7121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics:</td>
</tr>
<tr>
<td><strong>Never</strong></td>
</tr>
<tr>
<td>Mean age (years) 48.6; Smoking (years) 0; Tobacco usage (g/day) 0; % Manual 45.3; % ‘Active’ 48.0; % Heavy drinkers 5.3; % Obese 8.8; BMI (kg/m2) 25.65</td>
</tr>
<tr>
<td><strong>Ex-cigarette smoker</strong></td>
</tr>
<tr>
<td>Mean age (years) 50.7; Smoking (years) 19.3; Tobacco usage (g/day) 0; % Manual 54.8; % ‘Active’ 40.0; % Heavy drinkers 9.4; % Obese 9.8; BMI (kg/m2) 26.06</td>
</tr>
<tr>
<td><strong>Primary pipe/cigar</strong></td>
</tr>
<tr>
<td>Mean age (years) 49.9; Smoking (years) 26.7; Tobacco usage (g/day) 11.5; % Manual 34.2; % ‘Active’ 44.7; % Heavy drinkers 6.0; % Obese 6.0; BMI (kg/m2) 25.27</td>
</tr>
<tr>
<td><strong>Secondary pipe/cigar</strong></td>
</tr>
<tr>
<td>Mean age (years) 50.4 Smoking (years) 31.7; Tobacco usage (g/day) 14.7; % Manual 50.9; % ‘Active’ 41.8; % Heavy drinkers 11.0; % Obese 7.5; BMI (kg/m2) 25.49</td>
</tr>
<tr>
<td><strong>Cigarettes 1–19/day</strong></td>
</tr>
<tr>
<td>Mean age (years) 50.5; Smoking (years) 32.5; Tobacco usage (g/day) 10.4; % Manual 67.0; % ‘Active’ 38.1; % Heavy drinkers 10.7; % Obese 5.8; BMI (kg/m2) 25.00</td>
</tr>
<tr>
<td><strong>Cigarettes 20/day</strong></td>
</tr>
<tr>
<td>Mean age (years) 50.4; Smoking (years) 33.0; Tobacco usage (g/day) 20.0; % Manual 66.8; % ‘Active’ 30.0; % Heavy drinkers 13.0; % Obese 5.6; BMI (kg/m2) 24.92</td>
</tr>
<tr>
<td><strong>Cigarettes 21+/day</strong></td>
</tr>
<tr>
<td>Mean age (years) 49.7; Smoking (years) 33.2; Tobacco usage (g/day) 30.9; % Manual 66.9; % ‘Active’ 25.4; % Heavy drinkers 21.0; % Obese 7.5; BMI (kg/m2) 24.93</td>
</tr>
<tr>
<td>Location: 24 British towns</td>
</tr>
<tr>
<td>Recruitment strategy: Age-sex registers of one general practice in each town</td>
</tr>
<tr>
<td>Length of follow-up: Mean 21.8 years</td>
</tr>
<tr>
<td>Response rate and loss to follow-up: 78%</td>
</tr>
<tr>
<td>Eligible population: Men aged 40–59 years</td>
</tr>
<tr>
<td>Excluded populations: Men with missing data on smoking</td>
</tr>
</tbody>
</table>
### Exposures at midlife

**Relevant exposures:** Pipe and cigar smoking  
**Time:** 1978-1989  
**Measurement of exposure:** Self-report questionnaire

### Outcomes at 55 years or over

**Outcomes:** Major coronary heart disease and stroke events, cancer incidence, and deaths from all causes  
**Outcome measurement:** Men were asked whether a doctor had ever told them that they had CHD, stroke, diabetes, and a number of other disorders. Information on death was collected through the established ‘tagging’ procedures provided by the National Health Service registers  
Cancer morbidity is based on follow-up until December 1997. Cancer cases were ascertained by death certificates, the cancer registry, and by questionnaires on recall of doctor diagnoses sent to survivors in 1992, 1996, and in 1998.  
**Time:** December 2000

### Analysis

**Analysis strategy:** Cox proportional hazards model  
**Confounders:** Age, social class, body mass index, physical activity, systolic blood pressure, serum total cholesterol, alcohol intake, and anti-hypertensive treatment

### Results, limitations, source of funding

**Number:** 1133 major CHD events and 440 stroke events, 919 new cancers and 1994 deaths  
**Effect estimates:**

#### Major CHD events

<table>
<thead>
<tr>
<th>Type</th>
<th>Effect Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ex-cigarette smoker</td>
<td>1.10 (0.91, 1.36)</td>
<td></td>
</tr>
<tr>
<td>Primary pipe/cigar</td>
<td>1.59 (1.05, 2.39)</td>
<td></td>
</tr>
<tr>
<td>Secondary pipe/cigar</td>
<td>1.72 (1.32, 2.22)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 1–19/day</td>
<td>1.85 (1.49, 2.30)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 20/day</td>
<td>2.12 (1.69, 2.67)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 21+/day</td>
<td>2.30 (1.86, 2.84)</td>
<td></td>
</tr>
</tbody>
</table>

#### Major stroke events

<table>
<thead>
<tr>
<th>Type</th>
<th>Effect Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ex-cigarette smoker</td>
<td>1.13 (0.82, 1.56)</td>
<td></td>
</tr>
<tr>
<td>Primary pipe/cigar</td>
<td>1.83 (0.98, 3.42)</td>
<td></td>
</tr>
<tr>
<td>Secondary pipe/cigar</td>
<td>1.55 (1.02, 2.37)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 1–19/day</td>
<td>1.91 (1.35, 2.68)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 20/day</td>
<td>1.78 (1.22, 2.61)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 21+/day</td>
<td>2.12 (1.50, 2.99)</td>
<td></td>
</tr>
</tbody>
</table>

**Significant trends:** Pipe and cigar smoking, whether primary or secondary, carries significant risk of smoking-related ill health
Limitations:
1. Number of primary pipe/cigar smokers is relatively small
2. Residual confounding

Source of funding: Department of Health (England)

Authors: Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S; JPHC Study Group
Year: 2002
Citation: International Journal of Cancer 10;99(2): 245-51
Country of study: Japan
Aim of study: Update the findings of relative risk associated with cigarette smoking for lung cancer by histologic type
Study design: Population-based cohort study
Quality score: (+++, ++ or -): ++

Source population
Number of people: 91,738
Demographics: Not reported

Study (eligible and selected) population
Number of people: 57,591 men (26,998 in Cohort I and 30,593 in Cohort II) and 59,103 women (27,397 in Cohort I and 31,706 in Cohort II)
Characteristics: Not reported
Location:
Cohort I: Ninohe in Iwate Prefecture, Yokote in Akita Prefecture, Saku in Nagano Prefecture, Ishikawa in Okinawa Prefecture and Katsushika in the Tokyo Metropolitan area
Cohort II: Mito in Ibaraki Prefecture, Kashiwazaki in Niigata Prefecture, Chuohigashi in Kochi Prefecture, Kamigoto in Nagasaki Prefecture, Miyako in Okinawa Prefecture and Suita in Osaka Prefecture
Recruitment strategy: Population registries maintained by the local city, town or village office
Length of follow-up: Various
Response rate and loss to follow-up: 34 persons were lost to follow-up within the study period
Eligible population: Inhabitants in the study areas, aged 40–59 years old in Cohort I and 40–69 years in Cohort II at the beginning of the each study
Excluded populations: 123 men and 79 women were found to be ineligible for the study cohort (no Japanese nationality 49, late reports of out-migration before the start of the follow-up 151 and wrong birthday 2). 4,656 persons moved out of the study area

Exposures at midlife
Relevant exposures: Smoking
Time:
1990 for Cohort I
1993 for Cohort II
Measurement of exposure: Self-report questionnaire
## Outcomes at 55 years or over

### Outcomes: Lung cancer

**Outcome measurement:** Local major hospitals and the from population-based registries  
**Time:** Up to December 31, 1999

### Analysis

**Analysis strategy:** Cox proportional hazards model  
**Confounders:** Age and area

### Results, limitations, source of funding

**Number:** 422  
**Effect estimates:**

#### All incident cases

**Men**  
Non-smoker 1.0  
Former smoker 2.2 (1.4–3.4)  
Current smoker 4.5 (3.0–6.8)  

**Women**  
Non-smoker 1.0  
Former smoker 3.7 (1.4–10.2)  
Current smoker 4.2 (2.4–7.2)  

#### Squamous cell + small cell carcinoma

**Men**  
Non-smoker 1.0  
Former smoker 5.1 (1.8–14.6)  
Current smoker 12.7 (4.7–34.7)  

**Women**  
Non-smoker 1.0  
Former smoker 10.8 (1.2–94.4)  
Current smoker 17.5 (4.9–62.1)  

#### Adenocarcinoma

**Men**  
Non-smoker 1.0  
Former smoker 1.3 (0.7–2.5)  
Current smoker 2.8 (1.6–4.9)  

**Women**  
Non-smoker 1.0  
Former smoker 4.3 (1.3–13.8)  
Current smoker 2.0 (0.8–5.0)  

**Significant trends:** Lung cancer risk in men rose with increasing cigarette smoking, especially the
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Authors:** Song Y, Manson JE, Buring JE, Liu S  
**Year:** 2004  
**Citation:** Diabetes Care 27(9): 2108-15  
**Country of study:** USA  
**Aim of study:** Prospectively assess the relation between red meat intake and incidence of type 2 diabetes  
**Study design:** Randomised, double-blind, placebo-controlled trial  
**Quality score:** (+++, + or -): ++

**Source population**

**Number of people:** 39,876  
**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 37,309  
**Characteristics:**

**Total meat**

**Quintile 1**
- Median intake (servings/day): 0.63
- Age (years): 54.6±7.5
- Smoking (%): Current 11.4; Never 51.3, Past 37.4
- Exercise (%): Rarely/never 17.2; 1–3/week 32.2; >4/week 14.2
- Alcohol consumption (%): Rarely never 49.2; 1–3 drinks/month 12.8; 1–6 drinks/week 28.7; >1 drink/day 9.29
- Postmenopausal hormone use (%): Never 46.0; Past 10.7; current 43.4; Mean BMI (kg/m²): 24.8±4.3

**Quintile 5**
- Median intake (servings/day): 2.27
- Age (years): 53.5±6.7
- Smoking (%): Current 15.3, Never 51.5, Past 33.2
- Exercise (%): Rarely/never 22.5; 1–3/week 29.2; >4/week 7.65
- Alcohol consumption (%): Rarely never 45.9; 1–3 drinks/month 12.4; 1–6 drinks/week 31.3; >1 drink/day 10.4
- Postmenopausal hormone use (%): Never 49.3; Past 10.8; Current 440.0; Mean BMI (kg/m²): 227.1±5.5

**Location:** USA  
**Recruitment strategy:** Not reported  
**Response rate and loss to follow-up:** Not reported  
**Length of follow-up:** 8.8 years  
**Eligible population:** Participants in the Women's Health Study aged >45 years who were free of cardiovascular disease, cancer, and type 2 diabetes  
**Excluded populations:** Individuals with >70 items left blank in their SFFQ and with energy intake outside the range of 2,514 kJ (600 kcal) and 14,665 kJ (3,500 kcal), with reported diabetes at baseline, and with completed data on meat consumption

**Limitations:**

1. Limited number of small cell carcinomas  
2. Baseline data may not represent the lifelong patterns

**Reviewer:** Misclassified exposure

**Source of funding:** Ministry of Health, Labour and Welfare of Japan.

**Duration of smoking among current smokers and decreased after the cessation of smoking among former smokers**

**Limitations:**

1. Limited number of small cell carcinomas  
2. Baseline data may not represent the lifelong patterns
Exposures at midlife

Relevant exposures: Diet

Time: 1993

Measurement of exposure: 131-item semi-quantitative food frequency questionnaire. Four categories for red meat and total processed meat (1/week, 1/week, 2-4/week and 5/week)

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Contacted 473 women with self-reported diabetes who provided a blood sample.

The American Diabetes Association diagnostic criteria confirmed self-reported diagnosis of diabetes in 406 (91%) of 446 women who responded via telephone interview.

A random sample of 147 women with self-reported diabetes was mailed a supplemental diabetes questionnaire, also using the ADA criteria to parallel the telephone interview.

124 women were classified as having type 2 diabetes by the supplemental questionnaire. 113 of the 124 women gave permission to contact their primary care physician.

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, BMI, total energy intake, exercise, alcohol intake, cigarette smoking, and family history of diabetes, intakes of dietary fibre, magnesium, glycemic load, and total fat

Results, limitations, source of funding

Number: 1558

Effect estimates:

Red meat

<1 time/week 1.00
1 time/week 1.16 (0.85–1.58)
2–4 times/week 1.09 (0.83–1.43)
>5 times/week 1.25 (0.94–1.67)
P for trend 0.07

Total processed meat

<1 time/week 1.00
1 time/week 1.03 (0.91–1.18)
2–4 times/week 1.17 (1.01–1.36)
>5 times/week 1.38 (1.11–1.71)
P for trend 0.003

Significant trends: Higher consumption of total red meat, especially various processed meats, may increase risk of developing type 2 diabetes in women

Limitations:
1. Residual confounding
2. Participants might change their diets after developing some diseases
3. High degree of statistical collinearity
4. Limited variation of intakes could lead to insufficient statistical power
5. Unable to assess levels of specific chemicals added or produced in different food preparation methods

Source of funding: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-02767

Authors: Song Y, Sesso HD, Manson JE, Cook NR, Buring JE, Liu S
Year: 2006
Citation: American Journal of Cardiology 15;98(12): 1616-21
Country of study: USA
Aim of study: Assess the hypothesis that magnesium intake is beneficial in the primary prevention of hypertension
Study design: Randomised, double-blind, placebo-controlled trial
Quality score: (+++, + or -): ++

Source population
Number of people: 39,876
Demographics: Not reported

Study (eligible and selected) population
Number of people: 28,349
Characteristics:
Q1 Median intake (mg/d) 253; Mean age (yrs) 53; Mean body mass index (kg/m2) 26; Alcohol consumption (g/d) 4.8; Current smoker 18%; Vigorous exercise (>4 times/wk) 6.3%
Q3 Median intake (mg/d) 320; Mean age (yrs) 54; Mean body mass index (kg/m2) 25; Alcohol consumption (g/d) 5.0; Current smoker 14%; Vigorous exercise (>4 times/wk) 11%
Q5 Median intake (mg/d) 400; Mean age (yrs) 55; Mean body mass index (kg/m2) 25; Alcohol consumption (g/d) 4.2; Current smoker 10%; Vigorous exercise (>4 times/wk) 19%
Location: USA
Recruitment strategy: Not reported
Length of follow-up: Median follow-up of 9.8 years (mean 8.0)
Response rate and loss to follow-up: Not reported
Eligible population: Female United States health professionals aged >45 years with complete data on magnesium intake and other major lifestyle variables and without hypertension at baseline
Excluded populations: Those with previous myocardial infarction, stroke, transient ischemic attack, or cancer

Exposures at midlife
Relevant exposures: Diet
Time: 1992
Measurement of exposure: 131-item semi-quantitative food frequency questionnaire.

Outcomes at 55 years or over
**Outcomes:** Hypertension  
**Outcome measurement:** Self-reported BP, treatment, and/or physician diagnosis  
**Time:** Not reported

**Analysis**

**Analysis strategy:** Cox proportional-hazards models  
**Confounders:** Age, randomized treatment, family history of MI before 60 years of age, exercise, alcohol use, postmenopausal hormone use, multivitamin use, smoking, total energy intake, body mass index, history of diabetes mellitus, high cholesterol, dietary intakes of saturated fat and cholesterol, glycemic load, and sodium intake

**Results, limitations, source of funding**

**Number:** 8,544  
**Effect estimates:**

**Quintile of Magnesium Intake**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Total magnesium intake</th>
<th>Dietary magnesium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.02 (0.95–1.10)</td>
<td>1.00 (0.93–1.07)</td>
</tr>
<tr>
<td>3</td>
<td>1.02 (0.95–1.10)</td>
<td>1.02 (0.95–1.10)</td>
</tr>
<tr>
<td>4</td>
<td>0.96 (0.89–1.03)</td>
<td>0.89 (0.83–0.97)</td>
</tr>
<tr>
<td>5</td>
<td>0.93 (0.86–1.02)</td>
<td>0.91 (0.83–0.99)</td>
</tr>
</tbody>
</table>

**P trend:** 0.03  
**P trend:** 0.002

** Significant trends:** Higher intake of dietary magnesium may have a modest effect on the development of hypertension in women

**Limitations:**

1. Measurement errors of dietary intakes  
2. Diet was assessed once  
3. Magnesium coexisted with many nutrients in the diet  
4. Residual confounding  
5. Included only female health professionals who were predominantly white

**Source of funding:** Grants DK66401, DK62290, CA-47988, HL-43851, and HL-65727 from the National Institutes of Health, Bethesda, Maryland

**Authors:** Stevens RJ, Roddam AW, Spencer EA, Pirie KL, Reeves GK, Green J, Beral V; Million Women Study Collaborators

**Year:** 2009

**Citation:** International Journal of Cancer 15;124(10): 2400-5

**Country of study:** England and Scotland

**Aim of study:** To assess influence of risk factors on incident or fatal pancreatic cancer

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

**Source population**

13 million middle-aged women invited for breast cancer screening in England and Scotland were recruited for study in 1996-01

**Study (eligible and selected) population**
1.29 million women

**Follow-up:** 96-01 to 2005-07.
Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for cancer mortality

Incidence of pancreatic cancer: participants followed from date of recruitment to date of pancreatic cancer diagnosis, date of death, or last date of follow-up, whichever came first

Pancreatic cancer mortality: follow-up from recruitment until death from pancreatic cancer, death from other cause, or study end

Date of follow-up for cancer incidence was Dec. 31 2002- Dec. 31 2006, and for mortality Dec. 31, 2007

**Exclusion:** Women with cancer other than non-melanoma skin cancer before recruitment

**Attrition:** -

### Exposures at midlife

Self-reported smoking (never, former, current categories), alcohol consumption in units/week, strenuous exercise (enough to cause sweating/rapid heartbeat), any exercise

### Outcomes at 55 years or over

Incident and fatal pancreatic cancer identified through National Health Service Central Register (deaths and cancer registrations)

### Analysis

**Analysis strategy:** Cox proportional hazards model used to assess influence of risk factors on incident or fatal pancreatic cancer

**Confounders:** Age, region, socioeconomic status, smoking, body mass index and height

### Results, limitations, source of funding

- Current smokers had a high risk of incident pancreatic cancer compared to never smokers (RR 2.39, 95% CI 2.10–2.73)
- The incidence of pancreatic cancer increased with increasing BMI; the risk of incidence among obese women (BMI≥ 30.0 kg/m²) was higher compared to women with BMI 22.5–25.0 kg/m² (RR=1.34, [CI 1.13–1.57])

**Limitations:** Self-reported exposure measurements

**Source of funding:** None reported

**Authors:** Strand BH, Langballe EM, Hjellvik V, Handal M, Næss O, Knudsen GP>… Bjertness E; GENIDEM-Group

**Year:** 2013

**Citation:** Journal of Neurological Sciences 15;324(1-2): 124-30.

**Country of study:** Norway

**Aim of study:** Investigate the association of midlife vascular disease risk factors with dementia death

**Study design:** Cohort study

**Quality score:** (+++, + or -): ++

**Source population**
**Number of people**: Not reported  
**Demographics**: Not reported

### Study (eligible and selected) population

**Number of people**: 48,793  
**Characteristics**:  
Mean age (sd) and High edu.  
Oppland 42.7 (4.4) 50%  
Sogn og Fjordane 42.5 (4.2) 57%  
Finnmark 42.4 (4.3) 42%  
**Location**: Finnmark, Sogn og Fjordane, and Oppland, Norway  
**Recruitment strategy**: Not reported  
**Length of follow-up**:  
Person-yrs  
Oppland 765,891  
Sogn og Fjordane 416,700  
Finnmark 322,008  
**Response rate and loss to follow-up**: 88%  
**Eligible population**: Participated in the baseline NCS screening in 1974–78 and age 35–50 years at the time of screening  
**Excluded populations**: Not reported

### Exposures at midlife

**Relevant exposures**: Physical activity and smoking habits  
**Time**: 1974-78  
**Measurement of exposure**: Physical examination and a questionnaire with self-reported questions

### Outcomes at 55 years or over

**Outcomes**: Dementia death  
**Outcome measurement**: Cause of Death Registry  
**Time**: 2009

### Analysis

**Analysis strategy**: Cox proportional-hazards models  
**Confounders**: Age at screening, county, education, history of CVD, history of diabetes, physical inactive, smoking, BMI and cholesterol

### Results, limitations, source of funding

**Number**: 486 dementia deaths (187 Alzheimer's; 299 non-Alzheimer's dementia)  
**Effect estimates**:  
**History of CVD** 0.98 (0.68, 1.43), Overall p-value 0.925  
**History of diabetes** 2.38 (1.30, 4.34), Overall p-value 0.005  
**Physical inactive** 1.14 (0.92, 1.43), Overall p-value 0.238  
**Smoking** Non-
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Significant trends:** People suffering from high cholesterol levels, diabetes or underweight in midlife are at increased risk of dying from or with dementia later in life

**Limitations**
1. Misclassify the cause of death and self-reported exposures
2. Measurement errors in exposures
3. Changes during follow-up

**Source of funding:** Not reported
Alcohol consumption, median (interquartile range), g/wk 210 (98-308)

**Location:** Finland

**Recruitment strategy:** Not reported

**Length of follow-up:** 26 years

**Response rate and loss to follow-up:** 87.9%

**Eligible population:** White men born 1919-1934 of similar socioeconomic status who were participating in the Helsinki Businessmen Study. All participants were white businessmen or executives with similar socioeconomic and job status.

**Excluded populations:** 581 men with any chronic disease or who were taking regular prescription medication and 160 men who reported smoking cigars or pipes

### Exposures at midlife

**Relevant exposures:** Smoking

**Time:** 1974

**Measurement of exposure:** Mailed questionnaires

### Outcomes at 55 years or over

**Outcomes:** Health-related quality of life and mortality

**Outcome measurement:** Mailed questionnaires and the Finnish national registers

**Time:** 2000

### Analysis

**Analysis strategy:** Spearman rank coefficients

**Confounders:** Age and subjective health in 1974, body mass index, one-hour–postload glucose level, and alcohol consumption

### Results, limitations, source of funding

**Number:** 372 died

**Effect estimates:**

Amount of daily cigarettes predicted mortality in a graded manner (P<.001).

Large differences were seen for the scales of physical functioning and role limitations owing to physical health; never-smokers gained 13.7 and 11.7 higher points, denoting a difference of 17% and 16%, respectively, compared with those smoking >20 cigarettes a day

The physical component summary score showed a graded deterioration of HRQoL with an increasing number of cigarettes smoked daily (global P=.01)

**Significant trends:** HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never-smokers lived longer than heavy smokers, and their extra years were of better quality

**Limitations:**

1. High cessation rate
2. Did not update of the changes in participants’ smoking habits between 1974 and 2000
3. Could not measure the baseline HRQoL with RAND-36/SF-36 in 1974

**Source of funding:** The Academy of Finland, the Sohlberg Foundation, the Ida Montin Foundation, Helsinki University Central Hospital, and the Finnish Foundation for Cardiovascular Research.
**Authors:** Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H  
**Year:** 2000  
**Citation:** European Journal of Clinical Nutrition 54(4): 337-41  
**Country of study:** Sweden  
**Aim of study:** Investigate the long-term effect of fruit and vegetable consumption on mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death among middle-aged and elderly men  
**Study design:** Prospective cohort study  
**Quality score:** (++ , + or -): ++

### Source population

**Number of people:** 792  
**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 730  
**Characteristics:**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pieces of fruit (Means)</th>
<th>Body weight (kg)</th>
<th>Body mass index</th>
<th>Smoking (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>76.3; Body mass index 25.0; Smoking (%) 64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>75.7; Body mass index 24.6; Smoking (%) 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>76.7; Body mass index 25.1; Smoking (%) 51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-7</td>
<td>77.5; Body mass index 25.2; Smoking (%) 46</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Location:** Goteborg, Sweden  
**Recruitment strategy:** Sample was drawn from the population register consisting of all men born in 1913 on a day divisible by three (i.e. the third, sixth, ninth day of each month) and living in the city of Goteborg  
**Length of follow-up:** 26±5 years  
**Response rate and loss to follow-up:** 92%  
**Eligible population:** Included in The Study of Men Born in 1913  
**Excluded populations:** Not reported

### Exposures at midlife

**Relevant exposures:** Diet and smoking  
**Time:** 1967  
**Measurement of exposure:** Self-report food frequency questionnaire

### Outcomes at 55 years or over

**Outcomes:** Mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death  
**Outcome measurement:** Death certificates, autopsy reports and medical records were studied for those who died. Information on cancer incidence was obtained from the official Swedish Cancer register
Analysis

**Analysis strategy:** Stepwise Cox's proportional hazard model

**Confounders:** Smoking, hypertension and S-cholesterol

Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit</td>
<td>0.92 (0.84 - 1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.30 (1.21 - 1.41)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.48 (1.23 – 1.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>S-cholesterol</td>
<td>1.13 (1.04 - 1.22)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Significant trends:** Daily fruit consumption seems to have positive effect on long-term survival independently of other traditional cardiovascular risk factors like smoking, hypertension and cholesterol

**Limitations:**

**Author:** None reported

**Reviewer:**

1. Misclassify the cause of death and self-reported exposures
2. Measurement errors in exposures
3. Changes during follow-up

**Source of funding:** Swedish Medical Research Council (K98-274-06276-17) King Gustav V and Queen Victoria's Foundation, and the Goteborg University

Authors: Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F

Year: 2010

Citation: Archives of Internal Medicine 25;170(2): 194-201.

Country of study: USA

Aim of study: Explore the relation between mid-life physical activity, including walking, and successful aging

Study design: Prospective cohort study

Quality score: (+++ or -): ++

Source population

**Number of people:** 121,700

Demographics: Not reported

Study (eligible and selected) population

**Number of people:** 13,535

Characteristics:

**Successful survivor** Age at baseline (year) 60.1±2.5; Age at cognitive function assessment (year)
Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Usual survivors** Age at baseline (year) 60.6±2.5; Age at cognitive function assessment (year) 74.2±2.3; Physical activity (METs, hr/wk) 14.1±19.7; Walking activity (METs, hr/wk) 7.2±9.7; BMI (kg/m2) 25.5±4.4; Alcohol intake (g/d) 6.7±9.9; Red meat (serving/d) 1.1±0.5, Fruits and vegetables (serving/d) 5.2±2.0; Smoking status (%) Never smoked 46.4, Past smoker 36.2, Current smoke 1–14 cigarettes/d 6.3, Current smoke 15–24 cigarettes/d 6.9, Current smoke ≥25 cigarettes/d 4.2; Education (%) Registered nurse 79.0, Bachelor 14.9, Master 5.8, Doctorate 0.4

**Location:** USA

**Recruitment strategy:** Not reported

**Length of follow-up:** 14 years

**Response rate and loss to follow-up:** Not reported

**Eligible population:** Nurses’ Health Study participants who were free of major chronic diseases at baseline in 1986 and had survived to age 70 years or older as of 1995–2001

**Excluded populations:** History of any of the 11 (cancer, diabetes, myocardial infarction, coronary artery bypass graft surgery, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson’s disease, multiple sclerosis, and amyotrophic lateral sclerosis) chronic diseases at baseline (n=2,361); who had missing physical activity data at baseline (n=2,724); those who skipped more than 2 items on the mental health scale at age 70 years or older, or more than 5 items on the physical function scale in the SF-36 (n=795)

**Exposures at midlife**

**Relevant exposures:** Physical activity

**Time:** 1986

**Measurement of exposure:** Self-report questionnaire. Asked average time per week in the past year spent on leisure-time physical activities.

Medical Outcomes SF-36 Health Status Survey

**Outcomes at 55 years or over**

**Outcomes:** Successful aging

**Outcome measurement:** No history of 11 major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations

**Time:** 2000

**Analysis**

**Analysis strategy:** Multivariate logistic regression

**Confounders:** Age at baseline, education, husband’s education, marital status, postmenopausal hormone use, smoking status, family history of heart disease/diabetes/cancer, polyunsaturated to saturated fat ratio, intakes of trans fat, alcohol, and cereal fiber, and intakes of fruits and vegetables and red meat

**Results, limitations, source of funding**

**Number:** 1,456 successful agers

**Effect estimates:**
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>METs, hr/wk</th>
<th>Total Physical Activity, Quintiles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Lowest)</strong></td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.96 (0.78, 1.18)</td>
</tr>
<tr>
<td>3</td>
<td>1.30 (1.08, 1.57)</td>
</tr>
<tr>
<td>4</td>
<td>1.25 (1.03, 1.51)</td>
</tr>
<tr>
<td>5</td>
<td>1.76 (1.47, 2.12)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Walking, Quintiles**

| **1 (Lowest)** | 1.0 |
| 2 | 0.99 (0.80, 1.22) |
| 3 | 1.15 (0.94, 1.40) |
| 4 | 1.42 (1.17, 1.72) |
| 5 | 1.37 (1.10, 1.67) |
| **P for trend** | 0.0003 |

**Significant trends:** Higher levels of physical activity associated with better health status. Physical activity improves overall health

**Limitations:**

1. Limited to women
2. Successful survival as of age 70 years
3. Self-reported physical activity levels
4. Residual confounding
5. Did not assess physical and mental health status at baseline

**Source of funding:** AG13482, AG15424, and CA40356 from the National Institutes of Health and the Pilot and Feasibility program sponsored by the Boston Obesity Nutrition Research Center (DK46200)

**Authors:** Sun Q, Townsend MK, Okereke OI, Rimm EB, Hu FB, Stampfer MJ, Grodstein F

**Year:** 2011

**Citation:** PLoS Medicine 8(9): e1001090

**Country of study:** USA

**Aim of study:** To assess the influence of alcohol intake on the odds of successful aging

**Study design:** Longitudinal

**Quality score:** (+++, + or -): ++

**Source population**

121,700 female registered nurses recruited in 1976 for Nurses' Health Study and followed every two years thereafter

**Study (eligible and selected) population**

Analysis restricted to 13,894 participants who survived to 70+ years of age through to year 2000

**Sociodemographics:** Median age of 58 years at midlife for participants

**Follow-up:** 1980-84 through to 2000. Biennial follow-up rate ranged from 99.2% in 1986 to 94.6% in 2000
Exclusion:

i) Heavy drinkers (>45g/day) at midlife (n=268)
ii) Those diagnosed with chronic conditions included in the successful aging definition prior to baseline in 1984 (n=2,196)
iii) Those with insufficient/missing data (n=2253)
iv) Individuals reporting previous diagnosis of alcohol dependence or chronic liver disease (n=130) or with past alcohol problems (n=674)

Attrition:

Exposures at midlife

Midlife alcohol use was identified using averaged reports from the 1980 and 1984 validated food frequency questionnaires (FFQ)

Self-reported average total alcohol intake in grams per day over a year was assessed with response options ranging from 'almost never' to '6+ servings per day'

Alcohol consumption based on frequency of alcohol intake and alcohol content in beverages (e.g., 13.2 g alcohol for 1 bottle of beer, 10.8 g for 1 glass of wine, 15.1 g for 1 drink of liquor)

High level of reproducibility and validity of alcohol measurement on the FFQ

Correlation coefficient between FFQ and diet records ranged from 0.84-0.90

To assess drinking patterns of alcohol, 1986 FFQ was used in determining the number of drinking days/week

Outcomes at 55 years or over

Successful aging defined as being free of 11 major chronic diseases and having no major cognitive impairment, physical impairment, or mental health limitations, and survival until at least age 70 years

Outcomes assessed using medical record review, pathology report review, telephone interview, questionnaires

Telephone Interview for Cognitive Status (TICS) used to assess cognitive function (1995-2001); TICS has high reliability (r=0.97) and validity

SF-36 used to assess physical function and mental health

Analysis

Analysis strategy: Logistic regression used to assess the influence of alcohol intake on the odds of successful aging

Confounders: Age at baseline; body mass index; physical activity; smoking status; education; husband’s education; marital status; postmenopausal hormone use; family history of heart disease; family history of diabetes; family history of cancer; history of hypertension; history of high cholesterol; use of aspirin; and intakes of fruits and vegetables, whole grains, fish, and red meat

Results, limitations, source of funding

• 1,491 participants aged successfully
• The odds of successful aging to age 70+ were higher among those consuming 5.1-15.0 g/day and 15.1-30.0 g/day alcohol compared to nondrinkers (OR=1.19, [1.01, 1.40], and OR=1.28, [1.03, 1.58], respectively)
• Similar findings were observed when drinking pattern at midlife in 1986 was assessed in relation to odds of successful aging (e.g., higher odds of successful aging with greater alcohol use)

Limitations:

1. Cannot generalise to other ethnic groups (sample consisted predominantly of participants of...
<table>
<thead>
<tr>
<th>Source of funding: None reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Szoeke CE, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L</td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
</tr>
<tr>
<td><strong>Citation:</strong> Bone 39(5): 1149-1155</td>
</tr>
<tr>
<td><strong>Country of study:</strong> Australia</td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To determine the factors associated with the development of radiological osteoarthritis</td>
</tr>
<tr>
<td><strong>Study design:</strong> Population-based prospective study</td>
</tr>
<tr>
<td><strong>Quality score:</strong> (+++, + or -): +</td>
</tr>
<tr>
<td><strong>Source population</strong></td>
</tr>
<tr>
<td><strong>Number of people:</strong> 438</td>
</tr>
<tr>
<td><strong>Demographics:</strong> Not reported</td>
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<tr>
<td><strong>Study (eligible and selected) population</strong></td>
</tr>
<tr>
<td><strong>Number of people:</strong> 224</td>
</tr>
<tr>
<td><strong>Characteristics:</strong></td>
</tr>
<tr>
<td>Age (years) 49.66 (2.47)</td>
</tr>
<tr>
<td>Weight (kilograms) 68.62 (13.59)</td>
</tr>
<tr>
<td>BMI (kg/m2) 25.92 (4.84)</td>
</tr>
<tr>
<td>Current smoker 33 (15.7%)</td>
</tr>
<tr>
<td>Daily physical activity 56 (24.90%)</td>
</tr>
<tr>
<td>Weekly physical activity 94 (41.80%)</td>
</tr>
<tr>
<td>Infrequent physical 27 (12.00%)</td>
</tr>
<tr>
<td>No physical activity 46 (20.40%)</td>
</tr>
<tr>
<td><strong>Location:</strong> Melbourne, Australia</td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong> 11 years</td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Eligible population:</strong> Participants in the Melbourne Women’s Midlife Health Project</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Exposures at midlife</strong></td>
</tr>
<tr>
<td><strong>Relevant exposures:</strong> Physical activity and smoking</td>
</tr>
<tr>
<td><strong>Time:</strong> 1991</td>
</tr>
<tr>
<td><strong>Measurement of exposure:</strong> Self-administered and face-to-face questionnaires</td>
</tr>
<tr>
<td><strong>Outcomes at 55 years or over</strong></td>
</tr>
<tr>
<td><strong>Outcomes:</strong> Osteoarthritis</td>
</tr>
</tbody>
</table>
### Analysis

**Analysis strategy:** Multiple logistical regression

**Confounders:** Age, BMI and physical activity, smoking and hormone use

### Results, limitations, source of funding

**Number:** 28 women (56%) radiological OA. 49 (21.6%) knee osteoarthritis. 101 (44.5%) hand osteoarthritis

**Effect estimates:**

**Hand OA**

RR (95.0% CI)

- Age (years) 1.01 (0.9–1.2); Mean BMI (kg/m²) over 11 years 1.02 (0.9–1.1); Never used hormone therapy 2.33 (1.0–1.1); Physical activity at 20–29 Trend; Smoking ever 1.01 (1.0–5.7)

**Knee OA**

RR (95.0% CI)

- Age (years) 1.4 (1.1–1.8); Mean BMI (kg/m²) over 11 years 1.2 (1.1–1.3); Never used hormone therapy 2.9 (0.8–11.6); Physical activity at 20–29 Trend; Smoking ever 0.9 (0.8–1.0)

**Significant trends:** Increasing age, BMI and history of more frequent physical activity in younger years were risk factors for radiological knee OA. Never having used hormone therapy was a risk factor for radiological hand and knee OA

**Limitations:**

1. Only 57% of the initial participants had complete data
2. Did not have the power to detect very weak risk factors for OA
3. Self-reported exposures
4. No data on incident osteoarthritis

**Source of funding:** Shepherd Foundation

---

**Authors:** Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A, Nissinen A… Kromhout D

**Year:** 2001

**Citation:** Epidemiology 12(2): 239-45

**Country of study:** Finland, Italy, Netherlands

**Aim of study:** Used to assess association between alcohol consumption and 20-year COPD mortality

**Study design:** Longitudinal

**Quality score:** (+++, + or -): -

**Source population**

Samples of men ages 40-59 years recruited in 1960 from seven countries and with vital status information during 30 years of follow-up
### Study (eligible and selected) population
Analysis restricted to Finnish, Italian, Dutch cohorts comprising **2,953 men**

**Follow-up:** Approximately 20 years from 1965-70 to 1990

**Attrition:** 1,729 men died over 20 years of follow-up

### Exposures at midlife
Alcohol consumption in 1965-1970 estimated using cross-check dietary history method
Participants categorised into: none, <=1 drink per week (occasional), >1 per week and <=3 per day (light), >3 and <=9 per day, and >9 per day (with 1 drink = 10 grams alcohol)

### Outcomes at 55 years or over
Chronic obstructive pulmonary disease (COPD) mortality assessed between 1970 and 1990 using clinical records, family doctors, specialists, relatives, other sources

### Analysis
**Analysis strategy:** Cox proportional hazards model used to assess association between baseline alcohol consumption and 20-year COPD mortality

**Confounders:** Age, BMI, energy intake, cigarette smoking, and country

### Results, limitations, source of funding
- 73 men died from COPD during follow-up
- U-shaped relation between alcohol use and COPD mortality

**Limitations:** None reported

**Source of funding:** None reported

### Authors
Tsugane S, Sasazuki S, Kobayashi M, Sasaki S

### Year
2004

### Citation

### Country of study
Japan

### Aim of study
To examine if salt-preserved foods and salt increase the risk of stomach cancer

### Study design
Prospective study

### Quality score
(++, + or -): +

### Source population
**Number of people:** 54,498

### Demographics
Not reported

### Study (eligible and selected) population
**Number of people:** 18,684 men, 20,381 women

### Characteristics
Men

1 (low) Age (years) 48.7; Current smokers (%) 49; Daily alcohol drinkers (%) 25; Fruit and vegetables Fruit 2.3, Green vegetables 3.2, Yellow vegetables 2.4, Other vegetables 3

2 Age (years) 49; Current smokers (%) 51; Daily alcohol drinkers (%) 34; Fruit and vegetables Fruit 2.9, Green vegetables 3.4, Yellow vegetables 2.6, Other vegetables 3.5

3 Age (years) 49.4; Current smokers (%) 54; Daily alcohol drinkers (%) 42; Fruit and vegetables Fruit 3.1, Green vegetables 3.6, Yellow vegetables 2.7, Other vegetables 3.9

4 Age (years) 49.9; Current smokers (%) 56; Daily alcohol drinkers (%) 46; Fruit and vegetables Fruit 3.4, Green vegetables 3.6, Yellow vegetables 2.8, Other vegetables 4.1

5 Age (years) 50.1; Current smokers (%) 56; Daily alcohol drinkers (%) 47; Fruit and vegetables Fruit 3.5, Green vegetables 4, Yellow vegetables 2.9, Other vegetables 4.4

Women

1 (low) Age (years) 48.9; Current smokers (%) 8.2; Daily alcohol drinkers (%) 2.1; Fruit and vegetables Fruit 3.2, Green vegetables 3.6, Yellow vegetables 3.1, Other vegetables 3.5

2 Age (years) 49.3; Current smokers (%) 6.5; Daily alcohol drinkers (%) 2.7; Fruit and vegetables Fruit 4, Green vegetables 3.9, Yellow vegetables 3.3, Other vegetables 4.1

3 Age (years) 49.7; Current smokers (%) 4.7; Daily alcohol drinkers (%) 1.8; Fruit and vegetables Fruit 4.3, Green vegetables 4, Yellow vegetables 3.4, Other vegetables 4.4

4 Age (years) 50; Current smokers (%) 3.6; Daily alcohol drinkers (%) 2; Fruit and vegetables Fruit 4.5, Green vegetables 4.1, Yellow vegetables 3.5, Other vegetables 4.6

5 Age (years) 50; Current smokers (%) 4.2; Daily alcohol drinkers (%) 2.2; Fruit and vegetables Fruit 4.5, Green vegetables 4.2, Yellow vegetables 3.5, Other vegetables 4.7

Location:

Cohort I: Ninohe in Iwate Prefecture, Yokote in Akita Prefecture, Saku in Nagano Prefecture, Ishikawa in Okinawa Prefecture and Katsushika in the Tokyo Metropolitan area

Cohort II: Mito in Ibaraki Prefecture, Kashiwazaki in Niigata Prefecture, Chuohigashi in Kochi Prefecture, Kamigoto in Nagasaki Prefecture, Miyako in Okinawa Prefecture and Suita in Osaka Prefecture

Recruitment strategy: Population registries maintained by the local city, town or village office

Length of follow-up: Various

Response rate and loss to follow-up: 34 persons were lost to follow-up within the study period

Eligible population: Inhabitants in the study areas, aged 40–59 years old in Cohort I and 40–69 years in Cohort II at the beginning of the each study

Excluded populations: Self-reported serious illness at baseline as well as non-Japanese subjects; subjects who had already moved away at the baseline and subjects who reported extreme total energy intake

Exposures at midlife

Relevant exposures: Diet

Time: 1990

Measurement of exposure: Self-report questionnaire

Outcomes at 55 years or over

Outcomes: Gastric cancer

Outcome measurement: Death certificates, diagnosed cases of cancer were reported by hospitals, cases of gastric cancer were extracted from the cancer registry
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Time:** 2001

### Analysis

**Analysis strategy:** Cox proportional-hazards model

**Confounders:** Age in 1990, cigarette smoking, and fruit and vegetable intake and PHC area.

### Results, limitations, source of funding

**Number:** 486

**Effect estimates:**

**Relative risks (RR) of incident gastric cancer by quintiles of salt intake at baseline**

**Men**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Effect Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Reference</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.89 – 2.09</td>
</tr>
<tr>
<td>3</td>
<td>0.88 – 2.07</td>
</tr>
<tr>
<td>4</td>
<td>1.01 – 2.34</td>
</tr>
<tr>
<td>5</td>
<td>0.98 – 2.29</td>
</tr>
</tbody>
</table>

**P for trend 0.08**

**Women**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Effect Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Reference</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.41 – 1.37</td>
</tr>
<tr>
<td>3</td>
<td>0.45 – 1.48</td>
</tr>
<tr>
<td>4</td>
<td>0.25 – 0.95</td>
</tr>
<tr>
<td>5</td>
<td>0.61 – 1.94</td>
</tr>
</tbody>
</table>

**P for trend 0.85**

**Significant trends:** Restriction of salt and salted food intake is a practical strategy to prevent gastric cancer in areas with high risk.

**Limitations:**

1. Limited food items on scale
2. Precise estimation of salt intake may be implausible

**Source of funding:** Grants-in-aid for cancer research and for the second term comprehensive 10-year strategy for cancer control from the Ministry of Health, Labor and Welfare of Japan.

### Authors:


### Year:

2004

### Citation:

JAMA 291(10): 1213-1219

### Country of study:

Finland

### Aim of study:

Determine the relationship between coffee consumption and the incidence of type 2 DM

### Study design:

Prospective study

### Quality score:

(++, + or -): ++
Number of people: 16,670
Demographics: Not reported

Study (eligible and selected) population
Number of people: 7,655
Characteristics:
Daily Coffee Consumption
Men
2 Age, mean (SD), y 49.1 (8.4); Body mass index, mean (SD) 26.6 (3.7); Education, mean (SD), y 9.9 (4.2); Physical activity, No. (%) Light occupational 573 (46); Low leisure time 342 (27); Tea 847 (68); Alcohol 757 (61); Current smoker, No. (%) 211 (17); Obesity, No. (%) 214 (17)
>10 Age, mean (SD), y 46.3 (7.9); Body mass index, mean (SD) 27.3 (4.1); Education, mean (SD), y 8.4 (3.3); Physical activity, No. (%) Light occupational 279 (32); Low leisure time 311 (36); Tea 91 (11); Alcohol 482 (56); Current smoker, No. (%) 481 (56); Obesity, No. (%) 189 (22)

Women
2 Age, mean (SD), y 49.3 (8.8); Body mass index, mean (SD) 26.4 (4.9); Education, mean (SD), y 10.0 (4.0); Physical activity, No. (%) Light occupational 726 (52); Low leisure time 466 (34); Tea 920 (66); Alcohol 572 (41); Current smoker, No. (%) 93 (7); Obesity, No. (%) 278 (20)
>10 Age, mean (SD), y 45.6 (7.6); Body mass index, mean (SD) 27.5 (5.0); Education, mean (SD), y 8.6 (3.5); Physical activity, No. (%) Light occupational 128 (34); Low leisure time 164 (43); Tea 48 (13); Alcohol 145 (38); Current smoker, No. (%) 147 (39); obesity, No. (%) 82 (22)

Location: North Karelia, Kuopio, and Turku-Loimaa, Finland
Recruitment strategy: Random sample was stratified by sex and 4 equally large 10-year age groups
Length of follow-up: Mean 12 years
Response rate and loss to follow-up: 74% to 88%
Eligible population: Finnish men and women
Excluded populations: Participants diagnosed with coronary heart disease or stroke (n=590), participants with known DM at baseline (n=435), and participants with incomplete data on any variables required for this analysis (n=1016).

Exposures at midlife
Relevant exposures: Diet
Measurement of exposure: Self-administered questionnaire

Outcomes at 55 years or over
Outcomes: Type 2 diabetes
Outcome measurement: National Hospital Discharge Register and the Drug Register of the National Social Insurance Institution
Time: December 31 1998, or until death

Analysis
Analysis strategy: Cox proportional hazards regression model
Confounders: Age, study year, body mass index, systolic blood pressure, education, occupational
Results, limitations, source of funding

<table>
<thead>
<tr>
<th>Number: 381</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect estimates:</td>
</tr>
</tbody>
</table>

**Men**

<table>
<thead>
<tr>
<th>&lt;2</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>0.73 (0.47-1.13)</td>
</tr>
<tr>
<td>5-6</td>
<td>0.70 (0.45-1.05)</td>
</tr>
<tr>
<td>7-9</td>
<td>0.67 (0.40-1.12)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.45 (0.25-0.81)</td>
</tr>
</tbody>
</table>

**P for Trend** .12

**Women**

<table>
<thead>
<tr>
<th>&lt;2</th>
<th>1.00</th>
</tr>
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<tbody>
<tr>
<td>3-4</td>
<td>0.71 (0.48-1.05)</td>
</tr>
<tr>
<td>5-6</td>
<td>0.39 (0.25-0.60)</td>
</tr>
<tr>
<td>7-9</td>
<td>0.39 (0.20-0.74)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.21 (0.06-0.69)</td>
</tr>
</tbody>
</table>

**P for Trend** <.001

**Combined**

<table>
<thead>
<tr>
<th>&lt;2</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>5-6</td>
<td>0.54 (0.40-0.73)</td>
</tr>
<tr>
<td>7-9</td>
<td>0.55 (0.37-0.81)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.39 (0.24-0.64)</td>
</tr>
</tbody>
</table>

**P for Trend** <.001

**Significant trends:** Coffee drinking has a graded inverse association with the risk of type 2 DM

**Limitations:**

1. Glucose tolerance test was not performed in the baseline and follow up surveys
2. Self-report for data on coffee intake
3. Residual confounding due to measurement error

**Source of funding:** 46885, 53585, 204274, and 205657 from the Academy of Finland and the National Public Health Institute, Helsinki, Finland.

---

**Authors:** Tyas SL, White LR, Petrovitch H, Webster Ross G, Foley DJ, Heimovitz HK, Launer LJ

**Year:** 2003

**Citation:** Neurobiology of Aging 24(4): 589-96

**Country of study:** USA, Hawaii

**Aim of study:** Study the association between mid-life smoking and late-life dementia

**Study design:** Follow-up study

**Quality score:** (+++, + or -): +
### Source population

**Number of people:** 8006  
**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:** 3,734  
**Characteristics:**

**Mid-life smoking status (mean (S.E.))**
- **Never** Age (years) 78.3 (0.13); Education (years) 10.9 (0.09); Apolipoprotein (%) 17.9; Alcohol intake (oz. per month) 7.0 (0.43)
- **Former** Age (years) 77.7 (0.15); Education (years) 10.3 (0.10); Apolipoprotein (%) 19.5; Alcohol intake (oz. per month) 13.7 (0.68)
- **Current** Age (years) 76.8 (0.14); Education (years) 10.2 (0.10); Apolipoprotein (%) 18.4; Alcohol intake (oz. per month) 18.0 (0.89)

**Location:** Honolulu, USA, Hawaii  
**Recruitment strategy:** Not reported  
**Length of follow-up:** 25-31 years  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Participants in the Honolulu Heart Program  
**Excluded populations:** Fifty-six of men who were known to be smokers but could not be classified as current or former smokers

### Exposures at midlife

**Relevant exposures:** Smoking  
**Time:** 1965–1971  
**Measurement of exposure:** Self-report questionnaires, asked if smoked (never/former/current)

### Outcomes at 55 years or over

**Outcomes:** Alzheimer disease  
**Outcome measurement:** 100-point Cognitive Abilities Screening Instrument and the IQCODE. Dementia was diagnosed according to DSM-III-R criteria; probable and possible AD according to the NINCDS-ADRDA.  
**Time:** 1991–1996

### Analysis

**Analysis strategy:** Multiple logistic regression model  
**Confounders:** Age, education, presence of an apolipoprotein E-E4 allele, alcohol intake, systolic blood pressure categories, diastolic blood pressure categories, use of antihypertensive medication, ankle-brachial index, history of cerebrovascular accident and forced expiratory volume in 1s adjusted for height

### Results, limitations, source of funding
Number: AD (n = 3050) AD ± CVD (n = 3102) VaD (n = 3024)

Effect estimates:
AD Never 1.0; Former 0.93 (0.58–1.50); Current 1.17 (0.69–1.98)
AD ± CVD Never 1.0; Former 0.88 (0.58–1.33); Current 1.31 (0.85–2.01)
VaD Never 1.0; Former 0.82 (0.43–1.52); Current 1.14 (0.60–2.13)
All dementia Never 1.0; Former 0.80 (0.58–1.10); Current 1.11 (0.79–1.55)

Significant trends: Amount smoking is associated with an increasing risk of AD and Alzheimer-type neuropathology. Very heavy smoking was not associated with AD

Limitations:
Author: Restriction to Japanese-American men
Reviewer:
1. Self-report exposures;  
2. Residual confounding  
3. Survival bias

Source of funding: National Institutes of Health through National Institute on Aging contract no. N01-AG-4-2149; National Heart, Lung, and Blood Institute contract no. N01-HC-O5102; and NIH grants 1-PO1-AGO5119 and 5-P50-AGO5144

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
**Authors:** Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Rauramaa R, Viinamäki H… Kauhanen J

**Year:** 2010

**Citation:** European Journal of Cardiovascular Prevention and Rehabilitation 17(5): 524-9

**Country of study:** Finland

**Aim of study:** Investigated the association of leisure-time physical activity with the development of hopelessness during the follow-up

**Study design:** Population-based cohort study

**Quality score:** (+, + or -): +

**Source population**

**Number of people:** 2682

**Demographics:** Not reported

**Study (eligible and selected) population**

**Number of people:** 509

**Characteristics:**

- **According to hopelessness**
  - < 4 points: Age (years) 50.3 (6.6); Body mass index (kg/m2) 26.5 (3.2); Waist girth (cm) 89.0 (9.1); Alcohol consumption (g/week) 66 (8, 89); Smoker (%) 25.7; Adult socioeconomic status 7.0 (4.3)
  - > 4 points: Age (years) 51.7 (7.1); Body mass index (kg/m2) 26.4 (3.2); Waist girth (cm) 90.0 (9.2); Alcohol consumption (g/week) 68 (5, 104); Smoker (%) 38.2; Adult socioeconomic status 8.5 (4.1)

**Location:** Kuopio, Finland

**Recruitment strategy:** Not reported

**Exposures at midlife**

- **Relevant exposures:** Leisure-time physical activity

- **Time:** 1984 and 1989

- **Measurement of exposure:** Kuopio Ischemic Heart Disease Risk Factor Study 12-month LTPA Questionnaire

**Outcomes at 55 years or over**

- **Outcomes:** Hopelessness

- **Outcome measurement:** Psychological questionnaire

- **Time:** 1995-2000

**Analysis**

- **Analysis strategy:** Logistic regression analysis

- **Confounders:** Age category, smoking, alcohol consumption, cardiovascular disease and adulthood socioeconomic status, body mass index, elevated depressive symptoms, leisure-time physical activity; metabolic equivalent; maximal oxygen uptake
### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates**

<table>
<thead>
<tr>
<th>Total LTPA (min/week)</th>
<th>Effect estimates</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 270 min/week 1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>270–486 min/week</td>
<td>0.90 (0.47–1.73)</td>
<td></td>
</tr>
<tr>
<td>&gt; 486 min/week</td>
<td>0.89 (0.47–1.68)</td>
<td></td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.126</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-intensity LTPA (&lt; 4.5 METs, min/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 111 min/week 1</td>
</tr>
<tr>
<td>111–270 min/week 0.90 (0.44–1.84)</td>
</tr>
<tr>
<td>&gt; 271 min/week 1.65 (0.85–3.19)</td>
</tr>
<tr>
<td>P for linear trend 0.108</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate-to-vigorous LTPA (≥ 4.5 METs, min/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 min/week 1</td>
</tr>
<tr>
<td>61–150 min/week 0.80 (0.40–1.60)</td>
</tr>
<tr>
<td>&gt; 150 min/week 0.60 (0.32–1.13)</td>
</tr>
<tr>
<td>P for linear trend 0.112</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vigorous LTPA (≥ 7.5 METs, min/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 min/week 1</td>
</tr>
<tr>
<td>10–59 min/week 0.83 (0.44–1.56)</td>
</tr>
<tr>
<td>&gt; 60 min/week 0.57 (0.28–1.14)</td>
</tr>
<tr>
<td>P for linear trend 0.126</td>
</tr>
</tbody>
</table>

**Significant trends:** Moderate-to-vigorous physical activity seems to prevent development of hopelessness in middle-aged men.

**Limitations:**

**Author:**
1. Hopelessness scale not been compared with other hopelessness scales;
2. Includes only middle-aged white men

**Reviewer:**
1. Self-report for data on PA
2. Residual confounding due to measurement error

**Source of funding:** Academy of Finland (grants 118551, 41471, 1041086 and 2041022), the Ministry of Finland (grants 167/722/96, 157/722/97, 156/722/98), and the National Heart, Lung and Blood Institute of the USA (grant HL44199).

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**Authors:** Villegas R, Yang G, Gao YT, Cai H, Li H, Zheng W, Shu XO

**Year:** 2010

**Citation:** International Journal of Epidemiology 39(3): 889-99

**Country of study:** China

**Aim of study:** To examine how dietary patterns are associated with type 2 diabetes in middle-aged women

**Study design:** Population-based prospective study
| Quality score: (++, + or -): ++ |

<table>
<thead>
<tr>
<th>Source population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people:</strong> 81,170</td>
</tr>
<tr>
<td><strong>Demographics:</strong> Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (eligible and selected) population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people:</strong> 64,191</td>
</tr>
<tr>
<td><strong>Characteristics:</strong></td>
</tr>
<tr>
<td><strong>Cluster 1</strong> Age (years, mean ± SE) 52.5 ± 0.05; Education (%) None 13.6, Elementary school 12.8, Up to high school 63.6, College 9.9; Income level (%) &lt;10 000 18.5, 10 000–19 999 40.9, 20 000–29 999 26.4, &gt;30 000 14.2; Occupation (%) Professional 15.0, Clerical 11.8, Manual 21.9, Housewife/retired 51.2; Smoking (%) 2.7; Alcohol consumption (%) 2.1; Exercise participation (%) 32.9</td>
</tr>
<tr>
<td><strong>Cluster 2</strong> Age (years, mean ± SE) 49.1 ± 0.05; Education (%) None 2.9, Elementary school 5.2, Up to high school 73.1, College 18.8; Income level (%) &lt;10 000 11.0, 10 000–19 999 34.4, 20 000–29 999 31.7, &gt;30 000 22.9; Occupation (%) Professional 26.4, Clerical 14.5, Manual 24.1, Housewife/retired 35.0; Smoking (%) 1.5; Alcohol consumption (%) 2.3; Exercise participation (%) 33.0</td>
</tr>
<tr>
<td><strong>Cluster 3</strong> Age (years, mean ± SE) 48.1 ± 0.17; Education (%) None 2.1, Elementary school 4.1, Up to high school 76.5, College 17.4; Income level (%) &lt;10 000 13.9, 10 000–19 999 33.2, 20 000–29 999 31.4, &gt;30 000 21.4; Occupation (%) Professional 23.6, Clerical 15.1, Manual 26.8, Housewife/retired 35.0; Smoking (%) 2.2; Alcohol consumption (%) 4.6; Exercise participation (%) 32.4</td>
</tr>
<tr>
<td><strong>Location:</strong> Shanghai, China</td>
</tr>
<tr>
<td><strong>Recruitment strategy:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Length of follow-up:</strong> 6.9 years</td>
</tr>
<tr>
<td><strong>Response rate and loss to follow-up:</strong></td>
</tr>
<tr>
<td>Between 2000 and 2002 99.8%</td>
</tr>
<tr>
<td>Between 2002 and 2004 98.7%</td>
</tr>
<tr>
<td>Between 2004 and 2006 94.9%</td>
</tr>
<tr>
<td><strong>Eligible population:</strong> Middle-aged women</td>
</tr>
<tr>
<td><strong>Excluded populations:</strong> &lt;40 years or 470 years at the time of interview, participants that had extreme values for total energy intake</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposures at midlife</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relevant exposures:</strong> Diet</td>
</tr>
<tr>
<td><strong>Time:</strong> 1996 to 2000</td>
</tr>
<tr>
<td><strong>Measurement of exposure:</strong> In-person interview using a food-frequency questionnaire</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes:</strong> Type 2 diabetes</td>
</tr>
<tr>
<td><strong>Outcome measurement:</strong> Follow-up survey</td>
</tr>
<tr>
<td>Reported diagnosis of T2D and met at least one of the criteria as recommended by the American Diabetes Association</td>
</tr>
<tr>
<td><strong>Time:</strong> 1996 to 2000</td>
</tr>
</tbody>
</table>
### Analysis

**Analysis strategy:** Cox regression model

**Confounders:** Age, kcal/day, physical activity, alcohol consumption, smoking, education level, income level, occupation and hypertension, waist-to-hip ratio and BMI.

### Results, limitations, source of funding

**Number:** Not reported

**Effect estimates:**

**Associations between dietary clusters and the incidence of T2D stratified by age group**

<table>
<thead>
<tr>
<th>RR 95% CI</th>
<th>All</th>
<th>Age &lt; 50 years</th>
<th>Age &gt; 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>1.00</td>
<td>Cluster 2 0.78 (0.71–0.8); Cluster 3 1.05 (0.81–1.3)</td>
<td>Cluster 2 0.77 (0.66–0.9); Cluster 3 0.98 (0.66–1.4)</td>
</tr>
<tr>
<td>Cluster 1</td>
<td>1.00</td>
<td>Cluster 2 0.83 (0.73–0.9); Cluster 3 1.19 (0.86–1.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Significant trends:** A dietary pattern low in staple foods and high in dairy milk, which was associated with lower risk of T2D

**Limitations:**

1. Self-reports of T2D
2. Residual confounding

**Source of funding:** R01 CA070867 from the National Cancer Institute and R01 HL079123 from the National Heart, Lung and Blood Institute

### Authors

Villegas R, Xiang YB, Elasy T, Li HL, Yang G, Cai H… Shu XO

### Year

2011

### Citation

American Journal of Clinical Nutrition 94(2): 543-51

### Country of study

China

### Aim of study

Examine associations between fish, shellfish, and long-chain n-3 fatty acids and the risk of T2D

### Study design

Prospective population-based cohort study

### Quality score

(++, + or -): ++

### Source population

**Number of people:** Not reported

**Demographics:** Not reported

### Study (eligible and selected) population

**Number of people:**

- SWHS 74,942 women
- SMHS 61,500 men

**Characteristics:**
Shanghai Women’s Health Study

Q1 Age (y) 54 (46, 64); Energy intake (kcal/d) 1483.6 ± 323.4; BMI (kg/m2) 24.3 ± 3.6; Smoking (%) 4.1; Alcohol (%) 2.2; Exercise (%) 33.8; Education (%) None 22.3, Elementary 16.5, High school 53.4, College 7.8; Income level (%) I 24.0, II 41.5, III 23.0, IV 11.5; Occupation (%) Professional 11.2, Clerical 9.8, Manual labour 18.9, Housewife/retired 60.1

Q5 Age (y) 54 (46, 64); Energy intake (kcal/d) 1483.6 ± 323.4; BMI (kg/m2) 24.3 ± 3.6; Smoking (%) 4.1; Alcohol (%) 2.2; Exercise (%) 33.8; Education (%) None 22.3, Elementary 16.5, High school 53.4, College 7.8; Income level (%) I 24.0, II 41.5, III 23.0, IV 11.5; Occupation (%) Professional 11.2, Clerical 9.8, Manual labour 18.9, Housewife/retired 60.1

Shanghai Men’s Health Study

Q1 Age (y) 54 (48, 65); Energy intake (kcal/d) 1777 ± 394.7; BMI (kg/m2) 23.4 ± 3.1; Smoking (%) 60.2; Alcohol (%) 25.0; Exercise (%) 32.6; Education (%) None 11.3, Elementary 38.1, High school 32.3, College 18.2; Income level (%) I 16.4, II 46.9, III 30.2, IV 6.3; Occupation (%) Professional 20.5, Clerical 20.5, Manual labour 56.9, Housewife/retired N/A

Q5 Age (y) 49 (45, 56); Energy intake (kcal/d) 2121 ± 453.6; BMI (kg/m2) 23.7 ± 2.9; Smoking (%) 64.9; Alcohol (%) 37.4; Exercise (%) 32.8; Education (%) None 2.5, Elementary 28.9, High school 41.4, College 27.2; Income level (%) I 12.2, II 36.5, III 37.3, IV 13.6; Occupation (%) Professional 27.3, Clerical 23.8, Manual labour 48.9, Housewife/retired N/A

Location: Shanghai, China

Recruitment strategy: Two samples; the Shanghai Women’s Health Study and the Shanghai Men’s Health Study

Length of follow-up:
8.9 y for the SWHS
4.1 y for the SMHS

Response rate and loss to follow-up:
92% for women
75% for men

Eligible population:
SWHS women aged 40–70y
SMHS men aged 40–74y

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Diet

Time:
SWHS 1996 to 2000
SMHS 2002 to 2006

Measurement of exposure: In-person interview using a food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Follow-up survey.

Reported diagnosis of T2D and met at least one of the criteria as recommended by the American Diabetes Association

Time:
### SWHS 1996 to 2000
### SMHS 2002 to 2006

#### Analysis

**Analysis strategy:** Cox regression model

**Confounders:** Age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, hypertension, and dietary pattern

#### Results, limitations, source of funding

**Number:**
- SWHS 3037 of whom 3034 had valid dietary data
- SMHS 903, valid dietary data available for 900

**Effect estimates:**
- RR (95% CI)

**Shanghai Women’s Health Study**

**Combined fish and shellfish**
- Q1 1.00; Q2 0.93 (0.83, 1.03); Q3 0.80 (0.71, 0.89); Q4 0.83 (0.74, 0.94); Q5 0.86 (0.76, 0.98)

**Fish**
- Q1 1.00; Q2 0.96 (0.86, 1.06); Q3 0.84 (0.75, 0.94); Q4 0.80 (0.71, 0.90); Q5 0.89 (0.78, 1.01)

**Saltwater fish**
- Q1 1.00; Q2 1.00 (0.90, 1.12); Q3 0.89 (0.79, 1.00); Q4 0.95 (0.85, 1.06); Q5 0.84 (0.74, 0.95)

**Freshwater fish**
- Q1 1.00; Q2 0.96 (0.86, 1.07); Q3 0.82 (0.73, 0.92); Q4 0.89 (0.80, 1.00); Q5 0.87 (0.77, 0.98)

**Shellfish**
- Q1 1.00; Q2 0.91 (0.82, 1.01); Q3 0.79 (0.71, 0.89); Q4 0.80 (0.71, 0.91); Q5 0.86 (0.76, 0.99)

**Long-chain n-3 fatty acids**
- Q1 1.00; Q2 0.90 (0.80, 1.00); Q3 0.84 (0.75, 0.94); Q4 0.87 (0.77, 0.98); Q5 0.84 (0.74, 0.95)

**P for trend**
- Combined fish and shellfish 0.004
- Fish 0.003
- Saltwater fish 0.01
- Freshwater fish 0.01
- Shellfish 0.006
- Long-chain n-3 fatty acids 0.005

**Shanghai Men’s Health Study**

**Combined fish and shellfish**
- Q1 1.00; Q2 0.93 (0.76, 1.14); Q3 0.80 (0.64, 0.99); Q4 0.88 (0.70, 1.09); Q5 0.92 (0.73, 1.16)

**Fish**
- Q1 1.00; Q2 0.92 (0.75, 1.13); Q3 0.80 (0.65, 1.00); Q4 0.89 (0.72, 1.11); Q5 0.94 (0.74, 1.17)

**Saltwater fish**
- Q1 1.00; Q2 0.72 (0.58, 0.91); Q3 1.13 (0.92, 1.37); Q4 0.87 (0.71, 1.07); Q5 0.87 (0.69, 1.09)

**Freshwater fish**
- Q1 1.00; Q2 0.86 (0.70, 1.07); Q3 0.81 (0.65, 1.00); Q4 0.95 (0.77, 1.17); Q5 0.88 (0.70, 1.09)

**Shellfish**
- Q1 1.00; Q2 0.93 (0.76, 1.12); Q3 0.70 (0.56, 0.86); Q4 0.66 (0.53, 0.82); Q5 0.82 (0.65, 1.02)
Long-chain n-3 fatty acids Q1 1.00; Q2 0.95 (0.77, 1.17); Q3 0.86 (0.69, 1.07); Q4 0.96 (0.77, 1.19); Q5 0.89 (0.70, 1.12)

**P for trend**
- Combined fish and shellfish 0.36
- Fish 0.50
- Saltwater fish 0.56
- Freshwater fish 0.49
- Shellfish 0.003
- Long-chain n-3 fatty acids 0.40

**Significant trends:** An inverse association between fish and shellfish intake and T2D in women was found

**Reported limitations:**
- **Author:** Self-reports of T2D
- **Reviewer:**
  1. Self-report for data on diet
  2. Residual confounding due to measurement error

**Source of funding:** US Public Health Service grants from the National Cancer Institute (R01 CA070867 and R01 CA082729)
1975 was 89%
1981 was 84%

**Eligible population:** Same-sexed twin pairs born in Finland before 1937 with both co-twins alive in 1967

**Excluded populations:** No baseline questionnaire data for 384 subjects; 543 subjects who had not filled the questionnaires adequately regarding alcohol consumption; 375 were not interviewed at all or not fully; three subjects had missing education information; one interviewed subject had answered all questions regarding alcohol consumption in 1981 but not in 1975; one outlier reported a daily alcohol intake of 219 grams; subjects with mild impairment in cognitive function

**Exposures at midlife**

**Relevant exposures:** Alcohol consumption and smoking
**Time:** 1975
**Measurement of exposure:** Self-report

**Outcomes at 55 years or over**

**Outcomes:** Cognitive impairment risks
**Outcome measurement:** The TELE. A self-report telephone interview
**Time:** 1981

**Analysis**

**Analysis strategy:** Logistic regression analysis
**Confounders:** Age, gender, and education

**Results, limitations, source of funding**

**Number:** Not reported
**Effect estimates:**

Alcohol consumption in 1981
OR (95% CI)
Abstainer 1.51 (1.04–2.18)
Light drinker 1.00
Moderate drinker 0.87 (0.58–1.32)
Heavy drinker 2.03 (1.17–3.54)
**Binge drinking in 1976 and 1981**
Neither 1976 nor 1981 1.00
Only 1976 or 1981 1.87 (1.04–3.38)
Both 1976 and 1981 1.98 (1.05–3.72)
Number of pass-outs in 1981
0 1.00
1–2 0.94 (0.50–1.78)
> 2 4.10 (1.54–10.94)

**Significant trends:** Both abstainers and heavy drinkers were found to have an increased risk of cognitive impairment in comparison to light drinkers. Light to moderate alcohol use is associated with
a lower risk of cognitive impairment

Limitations:
Author: None reported
Reviewer:
1. Self-report for data on exposures
2. Residual confounding due to measurement error

Source of funding: Academy of Finland (project #205954), the Sigrid Juselius Foundation and Clinical grants of Turku University Hospital

| Authors: Virtaa JJ, Järvenpää T, Heikkilä K, Perola M, Koskenvuo M, Räihä ... Kaprio J |
| Year: 2010 |
| Citation: Journal of Alzheimers Disease 22(3): 939-48 |
| Country of study: Finland |
| Aim of study: To assess the influence of alcohol intake on cognitive impairment |
| Study design: Longitudinal |
| Quality score: (+++, + or -): ++ |

Source population
3,310 individuals (same-sexed twin pairs) born in Finland before 1937 with both co-twins alive in 1967 contacted
Baseline questionnaires administered in 1975 and 1981 (response rates: 89% and 84%, resp.)

Study (eligible and selected) population
Analysis restricted to 1,486 Finnish participants comprised of same-sexed monozygotic or dizygotic twins
Mean age in 1981: 51.7 years
Follow-up: 1975-81 to 1999-07 (mean follow-up: 22.8 years)
Exclusion:
1. Lack of data (n=534)
2. Those who died (n=21)
3. Participants with incomplete interview data or missing information (n=378)
4. Insufficient data captured at both interviews (n=1)
5. Daily alcohol intake outlier (n=1)
6. Those with mild cognitive impairment at baseline
Attrition: Inadequate self-reported alcohol data mostly for women with lower levels of education

Exposures at midlife
Self-reported total weekly (for beer, wine) or monthly (for spirits) alcohol intake
1 drink=12 g ethanol
Participants categorized as abstainers, light drinkers (alcohol intake > 0 and <=3 drinks /week), moderate drinkers (> 3 and <= 7 drinks for women, > 3 and <= 14 drinks /week for men), and heavy drinkers (> 7 drinks for women, > 14 for men)
Number of pass-outs and at least monthly binge drinking assessed at baseline (1975-81)
### Outcomes at 55 years or over

Cognitive function assessed using TELE, a self-report telephone interview
Monozygotic and dizygotic twins ages 65 years and older interviewed in 1999-01 and 2003-07

### Analysis

**Analysis strategy:** Logistic regression used to assess the influence of alcohol intake on cognitive impairment

**Confounders:** Gender, age, educational level

### Results, limitations, source of funding

- The odds for cognitive impairment were higher among abstainers and heavy drinkers compared to light drinkers (OR=1.51, [1.04, 2.18]; and 2.03, [1.17, 3.54], respectively)
- The odds for cognitive impairment were higher among binge drinkers compared to non-binge drinkers (odds ratios ranged from OR=1.87, [1.04, 3.38] to OR=1.98, [1.05, 3.72])
- The odds for cognitive impairment were higher among those who passed out more than 2 times due to excess drinking compared to those who did not report pass-outs (OR=4.10, [1.54, 10.94])
- Among APOE 4 carriers: abstainers and heavy drinkers had higher odds for cognitive impairment compared to light drinkers (OR=1.96, [1.12, 3.41], OR=4.08, [1.85, 9.00], respectively)

**Limitations:**
1. Social desirability bias associated with self-reported alcohol intake
2. Telephone interview to assess cognitive function is less specific and sensitive than clinical evaluation

**Source of funding:** The Academy of Finland, the Sigrid Juselius Foundation and Clinical grants of Turku University Hospital (EVO)

### Authors

Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A… Tsugane S; JPHC Study Group

### Year

2005

### Citation

Diabetic Medicine 22(3): 323-331

### Country of study

Japan

### Aim of study

To assess the influence of alcohol consumption and other risk factors on self-reported diabetes among middle-aged Japanese people

### Study design

Longitudinal

### Quality score

(+++, + or -): +

### Source population

Japanese residents of 14 administrative districts supervised by 4 public health centres
43,149 residents ages 40-59 years living in Ninohe, Karumai, Yokote, Omonogawa, Minami-Saku County, Gushikawa, Onna completed the baseline questionnaire in 1990 (response rates: 76% for men and 82% for women)
32,126 participants completed 5- and 10-year follow-up questionnaires

### Study (eligible and selected) population

Analysis restricted to 28,893 eligible participants with complete data and who responded to the baseline, 5- and 10-year follow-up questionnaires (response rates: 70.4% for men and 78.2% for
Follow-up: 10 years

Exclusion: Participants with the following characteristics at baseline:
1. Diabetes (n=1120)
2. Cardiovascular disease (n=470)
3. Chronic liver disease (n=311)
4. Kidney disease (n=546)
5. Cancer (n=689)
6. Missing exposure data (n=298)

Attrition: No significant differences in terms of BMI and lifestyle characteristics between those who responded to both follow-up questionnaires and those who did not

Exposures at midlife

Smoking habits, alcohol intake, and physical activity assessed through self-administered questionnaires

Smoking
Smokers classified as ‘never smoked’, ‘former smokers’, ‘current smokers’
‘current smokers’ further sub-divided into: smoked 1-19 or >=20 cigarettes/day

Alcohol use
Alcohol intake measured using data on type, frequency per week, and daily quantity consumed
Total daily alcohol intake was calculated, using the alcohol content of the following beverages in calculations: 23g ethanol per 180ml of sake, 36g ethanol per 180 ml of sochu or awamori, 10g ethanol per 30ml of whisky/brandy, 6g ethanol per 60ml of wine, 23g ethanol per 633ml of beer
Participants classified as ‘non-drinkers and infrequent occasional drinkers’ (consuming alcohol on 3 or fewer days per month) or ‘drinkers’ who were further subdivided by tertiles of daily ethanol consumption

Questionnaire measured alcohol use with high degree of validity

Physical activity
Physical activity assessed through questions on leisure time sports activities
If respondents participated in sports at least once a week, they were categorized as ‘active’; otherwise, they were considered ‘inactive’

Outcomes at 55 years or over

Men who reported diagnosis of incident type 2 diabetes at 5- and/or 10-year follow-up questionnaires
To determine the validity of self-reported diabetes diagnoses:
>a sample of medical records was reviewed, and diabetes diagnosis confirmed for 82%-94% of participants
>results from blood samples of volunteering participants were compared to self-reported diabetes diagnoses; sensitivity and specificity of study questionnaire for diabetic hyperglycemia were 46% and 98%, respectively

Analysis

Analysis strategy: Multiple logistic regression used to assess contributions of smoking, alcohol use, and physical activity on type 2 diabetes incidence over 10-year follow-up period

Confounders: Age, BMI (also assessed as effect modifier), family history of diabetes, hypertension

Effect modification: Sex, BMI
### Results, limitations, source of funding

703 and 480 incident cases of diabetes among men and women, respectively, during 10-year follow-up period

#### Men
- The odds of developing diabetes over 10 years were higher among those smoking >=20 cigarettes/day and past smokers compared to never-smokers (OR=1.37, [1.11, 1.69]; OR=1.35, [1.08, 1.69], respectively)
- The odds of developing diabetes were higher among men drinking between 23-46g ethanol/day than 'non-drinkers and infrequent occasional drinkers' (OR=1.26, [1.02-1.56])

#### Women
- The odds of developing diabetes over 10 years were higher among those smoking >=20 cigarettes/day and past smokers compared to never-smokers (OR=2.94, [1.57, 5.50]; OR=2.77, [1.67, 4.61], respectively)

#### Stratification by BMI among males:
- Compared to ‘non-drinkers and infrequent occasional male drinkers’, the odds of developing diabetes over 10 years were higher among males consuming 23-46g/day and over 46g/day of ethanol (OR=1.91, [1.05, 3.46]; OR=2.89, [1.63, 5.11], respectively)

#### Limitations:
1. Self-reported information leading to possible under-estimation of OR
2. Possible follow-up bias between diabetic and non-diabetic categories (e.g. excess mortality among diabetic patients affecting response rate)

#### Source of funding: Grant-in-aid for Cancer Research and for the Second Term Comprehensive Ten-Year Strategy for Cancer Control, and Health Sciences Research grants

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**Authors:** Walda IC, Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A… Kromhout D  
**Year:** 2002  
**Citation:** European Journal of Clinical Nutrition 56(7): 638-643.  
**Country of study:** Finland, Italy and The Netherlands  
**Aim of study:** To investigate the relation of baseline antioxidant, fruit, vegetable and fish intake with chronic obstructive pulmonary disease mortality  
**Study design:** Prospective study  
**Quality score: (+++, + or -): +**

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**Source population**

**Number of people:** 2953  
**Demographics:** Not reported

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**Study (eligible and selected) population**

**Number of people:** 2917  
**Characteristics:**  
**Finland** Age in y (mean (s.d.) 59.1 (5.5), BMI in kg=m2 (mean (s.d.) 24.7 (3.8), Cigarette smoking Pack years (mean (s.d.) 21.2 (17.2), Current smoker (%) 50.4, Former smoker (%) 29.7, Never smoker (%) 19.8
### Italy

Age in y (mean (s.d.) 59.3 (4.9); BMI in kg/m² (mean (s.d.) 26.0 (3.9); Cigarette smoking Pack years (mean (s.d.) 13.7 (13.9), Current smoker (%) 50.8, Former smoker (%) 19.5, Never smoker (%) 29.7

### The Netherlands

Age in y (mean (s.d.) 59.6 (5.4); BMI in kg/m² (mean (s.d.) 25.1 (2.7); Cigarette smoking Pack years (mean (s.d.) 20.2 (15.2), Current smoker (%) 52.0, Former smoker (%) 40.3, Never smoker (%) 7.7

### Location:
Ilomantsi, Poytya and Mellila, Finland. Crevalcore and Montegiorgio, Italy. Zutphen, The Netherlands.

### Recruitment strategy:
Not reported

### Length of follow-up:
20 years

### Response rate and loss to follow-up:
Not reported

### Eligible population:
Men aged 50-69 y at baseline

### Excluded populations:
Not reported

### Exposures at midlife

#### Relevant exposures:
Diet

#### Time:
1958 to 1965

#### Measurement of exposure:
Dietary survey

### Outcomes at 55 years or over

#### Outcomes:
Chronic obstructive pulmonary disease mortality

#### Outcome measurement:
Clinical records, from family doctors, specialists and relatives and from other useful sources collected by local investigators

#### Time:
1978-1985

### Analysis

#### Analysis strategy:
Cox Proportional Hazards Model

#### Confounders:
Country, age and smoking, BMI, energy intake, alcohol consumption

### Results, limitations, source of funding

#### Number:
73

#### Effect estimates:
- Fruit intake (per 100 g) 0.86 (0.69 – 1.07)
- Vitamin E intake (per 5 mg), 0.93 (0.65 – 1.33)

#### Significant trends:
A protective effect of fruit and possibly vitamin E intake against COPD

#### Limitations:

1. Confidence intervals were wide
2. Validity and reproducibility of diet
3. Misclassification of intake
4. Data on food consumption from 1970

#### Reviewer:

1. Self-report for data on exposures
2. Residual confounding due to measurement error
**Source of funding:** Not reported

| **Authors:** | Wang L, Manson JE, Buring JE, Lee IM, Sesso HD |
| **Year:** | 2008 |
| **Citation:** | Hypertension 51(4): 1073-9 |
| **Country of study:** | US |
| **Aim of study:** | To determine the association between dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women |
| **Study design:** | Longitudinal |
| **Quality score:** | (+, + or -): + |

**Source population**

39,876 US female health professionals ages 45 years and older and free of cardiovascular disease and cancer (except non-melanoma skin cancer) were randomized into the Women's Health Study in 1992-95 (baseline)

39,310 completed semi-quantitative food frequency questionnaire (SFFQ)

**Study (eligible and selected) population**

28,886 women
Mean age of 53.8 years

**Follow-up:** 10 years

**Exclusion:** Women with:
1. Insufficient completion of the SFFQ
2. Implausible total energy intake
3. Missing data on exposure
4. Pre-randomization cardiovascular disease or cancer
5. Baseline hypertension

**Censoring:** Women who developed cardiovascular disease over study period censored on date of cardiovascular disease diagnosis

**Attrition:** -

**Exposures at midlife**

Annual follow-up SFFQ used to assess portion size of each food item that participants consumed over the previous year with responses ranging from 'never or less than once per month' to '6+ per day'

Average daily intake calculated based on intake frequency and portion size of item

Total dairy product intake summed dairy items (e.g., low-fat dairy items include skim or low-fat milk, sherbet, yogurt, and cottage/ricotta cheese, high-fat dairy items include whole milk, cream, sour cream, ice cream, cream cheese, and other cheese)

Nutrient intake was calculated based on intake frequency of item as well as the nutrient content of the specified portion size

Pearson correlation coefficients between SFFQ responses and dietary records ranged from 0.25-0.79

**Outcomes at 55 years or over**

Self-reported incident hypertension defined as meeting one of the following: new physician diagnosis
of BP; newly-initiated BP treatment; self-reported systolic BP >=140 mmHg; self-reported diastolic BP >=90 mmHg
Time of event was also captured
High validity of self-reported BP

Analysis

**Analysis strategy:** Cox regression model used to estimate the hazard ratio (presented as the relative risk of developing incident hypertension across quintiles of dairy intake

**Confounders:** Age, race, total energy intake, randomised treatment, smoking, alcohol use, exercise, postmenopausal, multivitamin use, BMI, history of diabetes and hypercholesterolemia, intake of fruit and vegetable, whole grain, red meat.

When dietary calcium and vitamin D were assessed: same confounders were included in the adjusted model as above, with the exception of: intake of fruit and vegetable, whole grain, red meat; also, additional confounders included in adjusted model were dietary sodium, fibre, saturated fats, and cholesterol

Results, limitations, source of funding

- 8,710 cases of incident hypertension identified during 10 years of follow-up
- The risk of hypertension was smaller across increasing quintiles of low-fat dairy products and total dairy products (trend test p-values: 0.001 and 0.0003)
- Trend test p-value was significant (p=0.002) for risk of hypertension across quintiles of intake of skim milk, although no clear direction of trend was evident (same observation applies to hypertension risk and quintiles of intake of dietary vitamin D, trend test p-value=0.02)
- Risk for hypertension appears to decrease with increasing intake of dietary calcium (p<0.0001)

Limitations:
1. Exposure was measured at a single point in time (subject to random error leading to underestimation of true association)
2. Self-reported outcome data
3. Residual confounding
4. Limited generalizability as cohort comprises predominantly white health professional women

**Source of funding:** National Institutes of Health, Bethesda, Md.

Authors: Wang L, Lee IM, Zhang SM, Blumberg JB, Buring JE, Sesso HD
Year: 2009
Citation: American Journal of Clinical Nutrition 89(3): 905-12
Country of study: USA
Aim of study: To assess the association between baseline flavonoid intake and the risk of total and site-specific cancers
Study design: Longitudinal
Quality score: (+++, + or -): +

Source population

39,876 female health professionals free of cardiovascular disease and cancer (except non-melanoma skin cancer) were assigned into the Women’s Health Study, a randomized double-blind, placebo-controlled trial
39,876 women completed a validated semi-quantitative food-frequency questionnaire (SFFQ), which has been shown to have reasonable validity and reproducibility
Study (eligible and selected) population

38,408 women

Sociodemographics: Predominantly white female health professionals

Follow-up: Person-years of observation were calculated from time of randomization to cancer diagnosis, death, last day of follow-up, or 16 March 2007, whichever came first

Average of 11.5 years of follow-up

Exclusion:

i) Insufficient completion of SFFQ (n=21)
ii) Women with implausible daily energy intake [n=829]
iii) Women with cardiovascular disease or cancer diagnosed before randomization but reported after randomization [n=59]

Attrition: -

Exposures at midlife

At baseline, participants were asked how often they had consumed specified unit of each food item listed in questionnaire, with responses ranging from ‘never or less than once per month’ to ‘6+ per day’

Average daily intake of each food item was calculated by multiplying intake frequency by portion size of items

Nutrient intake was calculated by multiplying unit intake frequency by nutrient content of portion size

Total flavonoids were analysed and these included 3 flavonols (quercetin, kaempferol, myricetin) and 2 flavones (apigenin and luteolin); major sources of flavonoids analysed included apples, broccoli, onions, tofu, and tea

Outcomes at 55 years or over

Confirmed cancer cases, except non-melanoma skin cancer

Every six months and then annually thereafter, data on newly-diagnosed cancer was collected through questionnaires

Deaths ascertained through family member reports, postal authorities, National Death index; cancer was identified through pathology or cytology reports, or rarely, through clinical and radiologic or laboratory marker evidence

Analysis

Analysis strategy: Cox regression was used to assess the association between 1) intake of total and individual flavonoids, or the 2) intake of flavonoid-rich foods and incidence of total invasive cancer as well as site-specific cancers

Confounders: Age, race, total energy intake, randomized treatment assignment, BMI, smoking, alcohol use, physical activity, postmenopausal status, hormone replacement therapy use, multivitamin use, family history of cancer in a parent or sibling, and intake of fruit and vegetables, fibre, folate, and saturated fat

Results, limitations, source of funding

- 3234 cancer cases identified during average of 11.5 years of follow-up
- Incidence of total invasive cancer did not differ significantly across quintiles of total and individual quantified flavonoid intakes
Lack of an association between total quantified flavonoid intake and incidence of common site-specific cancers (e.g. breast cancer, colorectal cancer, lung cancer, endometrial cancer, ovarian cancer); tests for linear trends in incidence of site-specific cancers across quintiles for each individual flavonoid were also non-significant

No association between total and individual flavonoid intake and rare site-specific cancers (e.g. stomach, pancreatic, bladder, brain, thyroid, cervical cancer, lymphoma/leukemia)

Similar lack of an association between intake of flavonoid-rich foods and total cancer, as well as site-specific common and rare cancers

Limitations:
1. Possible incomplete assessment of flavonoid intake due to missing information on certain flavonoid-containing food items
2. Quantities of flavonoids in food may differ by species variety, growth condition, maturation, preparation, and food-processing methods; therefore, these factors can contribute to random errors in intake assessment and bias results towards null
3. Random error of self-report (cumulative intake and dietary changes during follow-up not captured – can lead to underestimation of associations)
4. Lack of associations with cancer may have been due to small number of cases
5. Associations with cancer may have been present for different flavonoid intake amounts

Source of funding: None reported

Authors: Wang L, Lee IM, Manson JE, Buring JE, Sesso HD
Year: 2010
Citation: Archives of Internal Medicine 8;170(5): 453-61
Country of study: USA
Aim of study: To assess the association between alcohol consumption and risk of becoming overweight or obese in middle-aged and older women
Study design: Longitudinal
Quality score: (+++, + or -): +

Source population
39,876 US female health professionals ages 38-89 years and free of cardiovascular disease and cancer (except non-melanoma skin cancer) were randomised into the Women’s Health Study in 1992-95 (baseline)

Study (eligible and selected) population
Of 19,563 women with a baseline BMI of 18.5-25 kg/m2, analysis was restricted to 19,220 women meeting inclusion criteria

Sociodemographics: Predominantly white female health professionals
Follow-up: Average 12.9 years of follow-up
Exclusion: Women with:
i) Missing data on baseline exposure [n=5]
ii) No updated outcome information during study period [n=128]
iii) Baseline diabetes [n=194]
iv) Pre-randomization cardiovascular disease or cancer [n=17]

Attrition: -

Exposures at midlife
Self-reported alcohol intake assessed using baseline, validated, semiquantitative food frequency questionnaire (SFFQ) that measured frequency of alcohol consumption over the past year with responses ranging from ‘never or less than once per month’ to ‘6+ per day’

Alcohol intake also took alcohol content of beverages into account, assuming ethanol of 13.2g for 360 ml beer, 10.8 g for 12. ml red or white wine, and 15.1 g for 45 ml liquor

Total alcohol intake categorized as: 0, >0 - <5, 5 - <15, 15 - <30, >= 30g/day

Correlation coefficient comparing self-reported alcohol intake in questionnaire with diet records ranged from 0.81-0.90

SFFQ has demonstrated reasonable validity and reproducibility

Outcomes at 55 years or over

Incident cases of overweight or obesity assessed at 2-, 3-, 5-, 6-, and 9-year follow-up questionnaires for 19,220 women (16,322 of these women continued to have their weight updated at 11-, 12-, and 13-year follow-up time points)

BMI was calculated using self-reported weight at follow-up and height at baseline, and categorized as: normal (18.5 to <25 kg/m2); overweight (25 to 30 kg/m2); obese (>=30 kg/m2)

Cases of ‘overweight or obesity’ comprised women with a normal BMI at baseline and a BMI >=25 kg/m2 at follow-up

Cases of ‘obesity’ comprised women with a normal BMI at baseline and a BMI>=30 kg/m2 at follow-up

Time of event and censoring

For cases, time of event was estimated from last-reported normal BMI to first reported BMI >=25 kg/m2

For non-cases, time of censoring was the latest date of reported normal BMI

Women who developed diabetes during study period censored on date of diabetes diagnosis

High correlation between self-reported weight and clinic-measured weight (r=0.97)

Analysis

Analysis strategy: Cox regression model used to estimate the hazard ratio (presented as the relative risk of becoming a) overweight or obese and b) obese across categories of total alcohol intake

Confounders: Race, baseline BMI, randomised treatment (vitamin E, aspirin, B-carotene, placebo), total non-alcohol energy intake, physical activity, smoking, post-menopausal status, post-menopausal hormone use, multivitamin use, history of hypercholesterolemia, hypertension, intake of fruit and vegetables, whole grains, refined grains, red meats and poultry, low-fat dairy products, high-fat dairy products, energy-adjusted total fat, carbohydrates, fibre

Results, limitations, source of funding

- Of 19,220 women with normal baseline BMI, 7,942 (41.3%) become ‘overweight or obese’ over 12.9 years of follow-up, and 732 (3.8%) became obese during this time
- Increasing levels of alcohol consumed contributed to decreasing incidence of overweight or obesity (BMI >=25); this trend was observed for ‘all alcohol’, beer, red wine, white wine (trend test p-values: <0.0001, 0.04, < 0.0001, and <0.0001, respectively)
- For example, the risk of overweight or obesity was smallest among those consuming 15-<30 g/day of ‘total alcohol’ compared to non-drinkers (RR=0.70, [0.62, 0.79])
- Increasing levels of alcohol consumed contributed to decreasing incidence of obesity (BMI >=30); this trend was observed for ‘all alcohol’, beer, red wine, white wine, liquor (trend test p-values: <0.0001, 0.02, 0.004, 0.0003, 0.005)
- For example, the risk of obesity was smallest among those consuming >=30 g/day of ‘total alcohol’ compared to non-drinkers (RR=0.29, [0.15, 0.54])
• Similar inverse association between total alcohol intake and risk of becoming overweight or obese was observed for women in different age strata (<50, 50-<60, >=60), smoking strata, physical activity groups, and baseline BMI groups

Limitations:
1. Self-reported weight resulting in non-differential misclassification
2. Social desirability bias with respect to alcohol intake (under-report), and lack of information on change in alcohol drinking patterns over time
3. Residual confounding
4. Limited generalizability as participants were predominantly white female health professionals

Source of funding: National Institutes of Health, Bethesda, MD

Authors: Wang L, Manson JE, Gaziano JM, Buring JE, Sesso HD
Year: 2012
Citation: American Journal of Hypertension 25(2): 180-189
Country of study: USA

Aim of study: To determine the association between intake of total, subgroup, and individual items of fruits and vegetables and the risk of hypertension

Study design: Longitudinal
Quality score: (+++, + or -): +

Source population
39,876 US female health professionals ages 39-89 years, and free from cardiovascular disease and cancer (except non-melanoma skin cancer) were included in the Women's Health Study, a randomized, double-blind, placebo-controlled trial, with follow-up questionnaires every 6 months for the first year and annually thereafter

Study (eligible and selected) population
Analysis restricted to 28,082 out of 39,310 women who completed semi-quantitative food frequency questionnaire (FFQ)

Sociodemographics: Predominantly white female health professionals

Follow-up: Average follow-up of 12.9 years. Follow-up from randomization at baseline to the date of incident hypertension (outcome), the last day in the study, or Feb. 2007, whichever came first

Exclusion: Women with:
• Hypertension (systolic BP>=140 mmHg or diastolic BP >=90 mmHg or history of anti-hypertensive treatment) at baseline (n=10,751)
• (Self-reported) implausible total daily energy intake [n=829]
• Pre-randomization cardiovascular disease or cancer [n=41]
• Missing FFQ items [n=21]
• Incomplete outcome information [n=109]

Censoring: Women who developed cardiovascular disease over study period and whose treatment may influence BP

Attrition: -

Exposures at midlife
Self-reported fruit and vegetable consumption was assessed using validated FFQ that included 28 vegetable items and 16 fruit items
Participants were asked how often they had consumed a unit of each food item over the past year with responses ranging from ‘never or less than once per month’ to ‘6+ times per day’

Average daily intake of individual fruit and vegetable items was summed to create measures of a) total fruit, b) total vegetable, and c) total fruit and vegetable intake

Vegetables were also categorized into: green leafy vegetables; cruciferous vegetables; and dark and yellow vegetable

Pearson correlation coefficients comparing FFQ responses with dietary records ranged from 0.50-0.84

<table>
<thead>
<tr>
<th>Outcomes at 55 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported incident hypertension defined as meeting one of the following: physician diagnosis of BP; newly-initiated BP treatment; self-reported systolic BP &gt;=140 mmHg; self-reported diastolic BP &gt;=90 mmHg</td>
</tr>
<tr>
<td>Time of event was self-reported (correlation coefficient comparing self-reported with measured BP among health professionals: 0.60-0.72)</td>
</tr>
<tr>
<td>High validity of self-reported BP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis strategy: Cox models were used to assess influence of hypertension across levels of fruit and vegetable intake. Stratification by age, BMI, smoking status, baseline systolic/diastolic BP</td>
</tr>
<tr>
<td>Confounders: Age, race, total energy intake, randomised treatment (vitamin E, aspirin, B-carotene, placebo), smoking, alcohol use, exercise, postmenopausal status, postmenopausal hormone use, multivitamin supplement use, history of diabetes or hypercholesterolemia, intake of whole grains, red meats, low-fat dairy product, and nuts; if fruit intake was assessed, model was also adjusted for vegetable intake, and vice versa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results, limitations, source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• During 12.9 years of follow-up, 13,633 women developed incident hypertension</td>
</tr>
<tr>
<td>• There was a significant inverse association between baseline intake of apples, oranges, and raisins, and incidence of hypertension (trend test p-values: 0.03, 0.01, 0.0004);</td>
</tr>
<tr>
<td>• Women consuming 1 serving/week and 2-4 servings/week of strawberries had a slight increased risk for hypertension compared to women never or rarely consuming strawberries (trend test p-value: 0.04)</td>
</tr>
<tr>
<td>• Compared to women in the lowest category of intake (&lt;0.2 servings/day) of dark-yellow vegetables, the risk of hypertension was lowest among women in the fourth (0.6-&lt;1.0 servings/day) and highest (&gt;=1.0 servings/day) categories of intake (HR=0.93, [0.87, 0.99]; HR=0.88, [0.82, 0.95], respectively)</td>
</tr>
<tr>
<td>• Trend tests between intake of cruciferous vegetables, dark-yellow vegetables, legumes, onions, and incident hypertension were significant (p&lt;0.05); however, no clear direction was evident for the trend</td>
</tr>
<tr>
<td>• The risk of hypertension was lower among women consuming 0.6-&lt;1.0 servings/day and &gt;=1.0 servings/day of dark-yellow vegetables compared to women in the lowest intake category of &lt;0.2 servings/day (HR=0.93, [0.87, 0.99]; HR=0.88, [0.82, 0.95], respectively)</td>
</tr>
<tr>
<td>Stratification by BP: There was a significant interaction of baseline BP with fruit intake:</td>
</tr>
<tr>
<td>• &gt;Among women with baseline systolic/diastolic BP &lt;120/80 mmHg, the risk of hypertension decreased with increasing total fruit intake (trend test p-value=0.003); no trend observed for BP &gt;=120/80 mmHg</td>
</tr>
</tbody>
</table>

| Limitations: |
| 1. Fruit and vegetable intake measured at one point in time (baseline), thus introducing possible measurement error and non-differential misclassification |
2. Self-reported outcome data again leading to misclassification
3. Residual confounding by unmeasured or imprecisely measured hypertension risk factors
4. Limited study generalizability due to homogeneity of cohort in terms of race, education, and SES

**Source of funding:** National Institutes of Health, Bethesda, MD, along with an investigator-initiated grant from the California Strawberry Commission, Watsonville, CA

| Authors: Wannamethee SG, Shaper AG, Walker M |
| **Year:** 2001 |
| **Citation:** British Journal of Cancer 85(9): 1311-1316 |
| **Country of study:** England |
| **Aim of study:** To assess physical activity and risk of cancer in middle-aged men |
| **Study design:** Longitudinal |
| **Quality score:** (+++, + or -): + |

**Source population**
Prospective study of 7735 men ages 40-59 years selected from registers of general practices in 24 towns in England, Wales and Scotland; initially examined in 1978-80

**Study (eligible and selected) population**
7630 men with available data

**Follow-up:** Follow-up of 18.8 years achieved for 99% of cohort

**Exclusion:** Excluded men who were diagnosed with cancer prior to or in the same year as screening [n=42]

**Attrition:** -

**Exposures at midlife**
Physical activity assessment: regular walking or cycling (weekday journeys including travel to and from work), recreational activity (gardening, pleasure walking, do-it-yourself jobs) and sporting (running, golf, swimming, tennis, sailing, digging)

Total physical activity score calculated for each participant based on frequency and type (intensity) of activity
>categories used: inactive and occasional; light; moderate; moderately vigorous; vigorous

**Outcomes at 55 years or over**

**Analysis**
**Analysis strategy:** Cox proportional hazards model used to assess effects of physical activity on risk of cancer

**Confounders:** Age, BMI, alcohol consumption, smoking, social class

**Results, limitations, source of funding**
- 969 cases out of 7588 men
- Men who engaged in vigorous physical activity had a significantly reduced risk of total cancers compared to those who did not or engaged in occasional activity (RR=0.65, [0.44, 0.88])
- The greater the physical activity level, the lower the risk for total cancers (sig. trend, p<0.0001)
- Moderate-vigorous exercise was associated with a significantly reduced risk of combined upper digestive tract cancer (oral, esophagus, stomach cancer) (OR=0.37 [0.16, 0.86])
- Vigorous exercise was associated with a significantly increased risk of bladder cancer [OR=2.06, (1.08, 3.95)]

Limitations: Residual confounding, i.e. diet

Source of funding: Department of Health, University College Medical School, London

| Authors: Wannamethee SG, Shaper AG |
| Year: 2002 |
| Citation: Heart 87(1): 32-36 |
| Country of study: UK |
| Aim of study: Examine effects of taking up regular drinking by middle aged non-drinkers and occasional drinkers on major coronary heart disease events and total mortality |
| Study design: Prospective cohort study |
| Quality score: (++, + or -): + |

Source population

Number of people: 7,735 men
Demographics: Not reported

Study (eligible and selected) population

Number of people: 7,157 men
Characteristics:

**TT (292).** Mean age (years) 51.1: Never smoked 43.2: Current smoker (Q5) 28.1: Active (Q1) 38.3

**Ex (299).** Mean age (years) 51.2: Never smoked 16.1: Current smoker (Q5) 40.8: Active (Q1) 29.6

**Stable occ (1150).** Mean age (years) 49.7: Never smoked 30.9: Current smoker (Q5) 29.9: Active (Q1) 41.3

**New occ (782).** Mean age (years) 50.1: Never smoked 25.1: Current smoker (Q5) 33.7: Active (Q1) 38.0

**New reg (305).** Mean age (years) 49.4: Never smoked 24.5: Current smoker (Q5) 30.1: Active (Q1) 44.0

**Reg (3675).** Mean age (years) 49.6: Never smoked 22.8: Current smoker (Q5) 32.6: Active (Q1) 41.3

Location: England, Wales, and Scotland

Recruitment strategy: Men aged 40–59 years selected from the age–sex registers of general practices in each of 24 towns in England, Wales, and Scotland

Length of follow-up: 16.8 years (CI) 15.5 to 18.0 years

Response rate and loss to follow-up: 78% and 99%

Eligible population: Men in Britain

Excluded populations: Women

Exposures at midlife

Relevant exposures: Smoking, drinking, physical activity
**Time:** 1978–1980

**Measurement of exposure:** Never smoked, ex-smokers at both Q1 and Q5, ex-smokers at Q5 only, and two groups of current cigarette smokers at Q5 (1–19 and > 20/day).

A physical activity score was derived on the basis of frequency and type of activity: inactive, occasional, light, moderate, moderately vigorous, and vigorous.

Eight drinking categories: non-drinkers; occasional drinkers: < 2 units a month; light drinkers: weekend, three to six drinks a day; weekdays, one to two drinks a day; 1–15 units/week; moderate drinkers: weekend, more than six drinks a day; weekdays, three to six drinks a day; 15–42 units/week; heavy drinkers: more than six drinks a day; > 42 units/week.

In men without diagnosed coronary heart disease alcohol categories were classified into six groups: Teetotallers; Ex-drinkers; stable occasional; new occasional; new regular drinker and Stable regular drinkers.

**Outcomes at 55 years or over**

**Outcomes:** Risk of mortality and major coronary heart disease events

**Outcome measurement:** All deaths and all major coronary heart disease events occurring in the period were recorded.

A major coronary heart disease event includes non-fatal myocardial infarction, fatal myocardial infarction, and sudden cardiac death classified as caused by coronary heart disease.

Information on non-fatal myocardial infarction was obtained from reports provided by general practitioners, supplemented by regular two yearly reviews of the general practice records and by self-reported questionnaires.

**Time:** Up to December 2000

**Analysis**

**Analysis strategy:** Cox proportional hazards model. Adjustments for risk factors were based on risk factors measured at Q1 and Q5. In the adjustment, age and body mass index were fitted as continuous variables, and physical activity (six levels), smoking (five levels), social class (seven levels), employment status (yes/no), self-rated health and recall of stroke (yes/no), and diabetes (yes/no) were fitted as categorical variables.

**Confounders:** Relative risk adjusted for age, social class, smoking, BMI, physical activity, employment status, pre-existing stroke, diabetes, regular drug treatment, and self-assessed health status. Adjustment for physical activity is based on physical activity data at screening.

**Results, limitations, source of funding**

**Number:** 654 men

**Effect estimates:**

Diagnosed coronary heart disease by alcohol group

<table>
<thead>
<tr>
<th>TT (43) 95% CI</th>
<th>CHD mortality</th>
<th>CVD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate/1000 p-y</td>
<td>34.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Adjusted RR</td>
<td>1.71 (0.92 to 3.15)</td>
<td>1.62 (0.93 to 2.82)</td>
</tr>
<tr>
<td>Category</td>
<td>Cases</td>
<td>Rate/1000 p-y</td>
</tr>
<tr>
<td>----------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Total mortality</td>
<td>28</td>
<td>56.0</td>
</tr>
<tr>
<td>Ex (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD mortality</td>
<td>22</td>
<td>37.1</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>26</td>
<td>43.8</td>
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<tr>
<td>Total mortality</td>
<td>39</td>
<td>65.7</td>
</tr>
<tr>
<td>Stable occ (112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD mortality</td>
<td>31</td>
<td>22.8</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>38</td>
<td>27.9</td>
</tr>
<tr>
<td>Total mortality</td>
<td>57</td>
<td>41.9</td>
</tr>
<tr>
<td>New occ (87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD mortality</td>
<td>27</td>
<td>26.0</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>33</td>
<td>31.8</td>
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<tr>
<td>Total mortality</td>
<td>46</td>
<td>44.3</td>
</tr>
<tr>
<td>New reg (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD mortality</td>
<td>12</td>
<td>29.6</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>16</td>
<td>39.4</td>
</tr>
</tbody>
</table>
### Total mortality
- **Cases:** 23
- **Rate/1000 p-y:** 56.7
- **Adjusted RR:** 1.23 (0.75 to 2.04)

### CHD mortality
- **Cases:** 106
- **Rate/1000 p-y:** 28.3
- **Adjusted RR 95% CI:** 1.33 (0.88 to 2.00)

### CVD mortality
- **Cases:** 129
- **Rate/1000 p-y:** 34.4
- **Adjusted RR:** 1.33 (0.92 to 1.93)

### Total mortality
- **Cases:** 182
- **Rate/1000 p-y:** 48.6
- **Adjusted RR:** 1.25 (0.92 to 1.69)

**Significant trends:** Among men with a diagnosis of CHD the teetotallers and ex-drinkers had an increased adjusted risk of mortality from CHD and CVD compared with stable occasional drinkers. New regular drinkers showed no benefit for CHD mortality, and some increase (non-significant) in CVD and total mortality was observed compared with stable occasional drinkers.

**Limitations:** No limitations reported by the author.

**Source of funding:** Not reported.

#### Authors:
Wannamethee SG, Shaper AG

#### Year:
2003

#### Citation:
American Journal of Clinical Nutrition 77(5): 1312-1317

#### Country of study:
UK

#### Aim of study:
To assess the influence of alcohol consumption patterns on body weight and weight gain.

#### Study design:
Longitudinal

#### Quality score: (+++, + or -):
+

#### Source population
7,735 men ages 40-59 years selected from registers of general practices of 24 towns in England, Wales and Scotland were examined from Jan. 1978 to July 1980 as part of the British Regional Heart Study.

Response rate: 78%

At baseline, questionnaires were administered to participants, physical measurements were made and blood samples drawn.

7,275 of the surviving participants completed a postal questionnaire in 1983-85 to assess changes in health behaviours and other risk factors.

#### Study (eligible and selected) population
7,608 men

**Follow-up:** 5 years

**Exclusion:** Men with diagnosed diabetes at baseline (n=118)
### Attrition:

- **Exposures at midlife**

  **Baseline**
  Frequency, quantity and type of alcohol measured at baseline and after 5 years, with the following categories used to classify participants: non-drinkers; occasional drinkers (<1 unit/week); light-moderate (1-20 units/week), including weekend drinkers of 1-2 or 3-6 units/day and daily drinkers of 1-2 units/day; heavy (21-42 units/week), including weekend drinkers of >6 units/day and daily drinkers of 3-6 units/day; very heavy (>42 units/week), comprising daily drinkers of >6 units/day.
  
  1 unit of alcohol is approx. 10 g alcohol.
  
  Exposure was validated using biochemical and hematologic measurements.

  **After 5 years**
  Participants were asked about past and current drinking habits, and same drinking categories used as those at baseline.
  
  Men classified into stable or changed groups on the basis of intake reported at baseline and after 5 years:
  
  - **Stable groups:** Stable non-occasional (non-drinkers or occasional drinkers at baseline who remained non-drinkers or occasional drinkers after 5 years); stable light-moderate (light-moderate drinkers at both waves); stable heavy (heavy or very heavy drinkers at both waves).
  
  - **Changed groups:** Light-moderate to none-occasional (light-moderate drinkers at baseline who reported being non-drinkers or occasional drinkers after 5 years); none-occasional to light-moderate (non-drinkers or occasional drinkers at baseline who reported light-moderate drinking after 5 years); ex-heavy (heavy or very heavy drinkers at baseline who reported being non-drinkers, occasional drinkers, or light-moderate drinkers at after 5 years); new heavy (none-occasional and light-moderate drinkers at baseline who reported heavy or very heavy drinking after 5 years).

### Outcomes at 55 years or over

BMI was measured at baseline and 5 years later using height and weight measurements (kg/m²).

- High BMI: >=28 or upper quintile of BMI distribution of men at baseline.

Percentage change in body weight since baseline screening calculated:

- Weight loss was defined as a loss of >=4% of body weight, weight gain as a gain of >=4 % of body weight, while stable weight was weight gained or lost that was <4% of body weight.

  The following weight change categories were used: weight loss; stable (weight); gain of 4-10%; gain of >10% of body weight.

### Analysis

- **Analysis strategy:** Logistic regression was used to assess the influence of alcohol consumption patterns on body weight and weight gain.

- **Confounders:** Age, social class, physical activity, cigarette smoking, initial BMI.

### Results, limitations, source of funding

- The proportion of men with high BMI increased significantly with higher levels of alcohol intake at baseline.
  - At baseline: stable heavy and ex-heavy drinkers had the highest proportion of men with BMI>=28 (20.8% and 23.5%, respectively).
  - 5 years after baseline: stable (continuing) heavy drinkers and new heavy drinkers had the highest...
proportion of men with BMI >=28 (25.7% and 27.2%, respectively)

- The odds of weight gain >=4% over 5 years were greater for stable heavy drinkers compared to stable none-occasional drinkers (OR=1.29 [1.10, 1.51])
- The odds of weight gain >=4% over 5 years were greater for new heavy drinkers compared to the stable none-occasional group (OR=1.45, [1.09, 1.92])

**Stratification by smoking:**

- Among non-smokers, the odds of weight gain >=4% were greater for stable heavy drinkers compared to stable none-occasional drinkers (OR=1.75, [1.19, 2.56])
- Among non-smokers, the odds of weight gain >=4% were greater for ex-heavy drinkers compared to stable none-occasional drinkers (OR=1.55, [1.07, 2.25])

**Limitations:** Findings cannot be generalised to women

**Source of funding:** None reported

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**Authors:** Waring ME, Eaton CB, Lasater TM, Lapane KL

**Year:** 2010

**Citation:** American Journal of Epidemiology 171(5): 550-556

**Country of study:** USA

**Aim of study:** Incident diabetes in relation to weight patterns during middle age

**Study design:** Longitudinal

**Quality score:** (+++, + or -): +

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**Source population**

5,209 men and women ages 28-62 years, living in Framingham, Massachusetts, and without clinically apparent cardiovascular disease were enrolled in Framingham Heart Study in 1948-52

Biennial study visits involved an interview, a clinical examination, and laboratory tests

---

**Study (eligible and selected) population**

1,476 participants

**Follow-up:** From age 50 years to the first examination with diagnosis of incident diabetes or the last examination attended

**Exclusion:**

Of 5,079 who provided informed consent, the following were excluded:

i) Enrolled in the FHS cohort after 40 years of age [n=3,071]
ii) Did not attend FHS examinations after age 50 [n=218]
iii) Those missing BMI measurements at several study waves [n=213]

Of 1,577 study participants, individuals excluded were those:

i) Who were consistently underweight [n=20]
ii) With diabetes before 50 years [n=23]
iii) With missing data on covariates [n=58]

**Attrition:** -

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**Exposures at midlife**

Weight patterns during middle age (40-50 years) were assessed using principal component analysis

BMI from age 40 to 50 years was calculated and guided by standard BMI cut-offs (BMI<25, BMI 25-29.9, BMI>=30), participants were categorized as being normal weight, overweight, or obese
Weight change was also measured and categorized as: weight loss, stable weight, and weight gain. Weight cycling was also assessed.

### Outcomes at 55 years or over

Type 2 diabetes was ascertained through assessment of non-fasting plasma glucose level and/or reported treatment with insulin or medication for diabetes.

### Analysis

**Analysis strategy:** Cox proportional hazards regression was used to analyse the influence of weight patterns on incident diabetes.

**Confounders:** Gender, education, family history of diabetes, weight status at age 25 years, physical activity, smoking, alcohol use, hormone use, weight change, weight cycling.

### Results, limitations, source of funding

- 217 cases of type 2 diabetes diagnosed over 35,359 person-years of follow-up
- Diagnosis made at median age of 67.8 years
- Adults who were overweight during middle age had 2.9 times the rate of diabetes incidence (HR=2.9, [2.0, 4.1]) as those who were normal weight during middle age
- Adults who were obese had 7.7 times the rate of diabetes (HR=7.7, [4.9, 12.1]) as those who were normal weight

**Limitations:**
1. Fasting glucose measurements not available; study definition of diabetes may have been less sensitive than American Diabetes Association criteria
2. Potential misclassification of diabetes diagnosis date (unlikely to explain results)
3. Residual confounding due to measurement error and unmeasured variables (potential misclassification of smoking, alcohol, and hormone use at time of diagnosis; recall bias in recalled weight; information lacking on current or previous pregnancies/history of gestational diabetes)
4. Biannual measurements limited ability to detect changes occurring more frequently than every two years

**Source of funding:** None reported

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**Authors:** Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K

**Year:** 2005

**Citation:** Neurology 64(2): 277-281

**Country of study:** USA

**Aim of study:** Evaluate if midlife cardiovascular risk factors are associated with risk of late-life dementia

**Study design:** Retrospective cohort study

**Quality score:** (+++, + or -): +

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**Source population**

**Number of people:** 11,368

**Demographics:** Not reported

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**Study (eligible and selected) population**
### Number of people: 8,845

**Characteristics:**

**Diagnosis of dementia**

**No** Age at MHC exam, y 41.97 (1.42); Age in 1994, y 68.37 (2.64); Age at end of follow-up, y 76.59 (3.34); Female 4,341 (53.4); Male 3,783 (46.6); Race White 5,952 (73.6), Black 1,285 (15.9), Asian 511 (6.3), Other 360 (4.4); Education Grade school 1,093 (13.5), High school 2,766 (34.1), Trade school 529 (6.5), College 3,606 (44.4), Unknown 130 (1.6); Marital status Married 6,646 (81.8), Never married 412 (5.1), Divorced/widowed/separated 754 (9.3), Unknown 312 (3.8)

**Yes** Age at MHC exam, y 42.25 (1.39); Age in 1994, y 69.32 (2.43); Age at end of follow-up, y 74.86 (3.41); Female 410 (56.9), Male 311 (43.1); Race White 499 (69.2), Black 165 (22.9), Asian 31 (4.3), Other 26 (3.6); Education Grade school 132 (18.3), High school 240 (33.3), Trade school 45 (6.2), College 291 (40.4), Unknown 13 (1.8); Marital status Married 543 (75.3), Never married 35 (4.9), Divorced/widowed/separated 95 (13.2), Unknown 48 (6.7)

**Location:** San Francisco, Oakland, USA

**Recruitment strategy:** Members of the Kaiser Permanente Medical Care Program

**Length of follow-up:** 30 years

**Response rate and loss to follow-up:** Not reported

**Eligible population:** Participants ages 40 to 44 who were still members of the health plan in 1994

**Excluded populations:** Nine participants with missing data for sex were excluded, 1,700 with missing smoking information were excluded, and 814 with missing cholesterol information were excluded

### Exposures at midlife

**Relevant exposures:** Diet and smoking

**Time:** 1964 to 1973

**Measurement of exposure:** Interview

### Outcomes at 55 years or over

**Outcomes:** Dementia

**Outcome measurement:** Medical records

**Time:** January 1994 to April 2003

### Analysis

**Analysis strategy:** Cox proportional hazards model

**Confounders:** Age at mid-life exam, age at start of case ascertainment, race, education, and sex

### Results, limitations, source of funding

**Number:** 721

**Effect estimates:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.24 (1.04–1.48)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.46 (1.19–1.79)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>1.42 (1.22–1.66)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.26 (1.08–1.47)</td>
</tr>
</tbody>
</table>
Cardiovascular composite score
1 1.27 (1.02–1.58)
2 1.69 (1.34–2.12)
3 2.31 (1.71–3.11)
4 2.37 (1.10–5.10)

**Significant trends:** Presence of multiple cardiovascular risk factors at midlife substantially increases risk of late-life dementia in a dose dependent manner

**Limitations:**

**Author:**
1. Did not have the ability to determine subtypes of dementia
2. Self-report of physician diagnoses, medication use, and smoking

**Reviewer:**
1. Self-report for data on exposures
2. Residual confounding due to measurement error

**Source of funding:** The National Institutes of Health (1K12AR47659)
Phase II (baseline) leisure-time physical activity assessed using Minnesota Leisure Time Physical Activity questionnaire measuring type, frequency, and duration of activities in the last 12 months
> Total energy expenditure on activities calculated and divided into low, medium, and high categories; percentage of heavy-intensity physical activity divided into none, low, and high
Physical activity at current work or in last job held assessed using self-administered questionnaire (modified from the Health Insurance Plan questionnaire) focusing on time spent walking, sitting, and lifting/carrying, with scores ranging from 1 (least active) to 4 (most active)

Outcomes at 55 years or over
Common mental disorders, comprising anxiety and depression, measured at phases II and IV using validated psychiatric disorders screening questionnaire. Incident cases based on either:
- a) Meeting predefined cut-off score on screening questionnaire and report of antidepressant use in phase II or IV
- b) Report of antidepressant/anxiolytic use in phase II or IV

Analysis

Analysis strategy: Logistic regression used to assess association between leisure-time or occupational physical activity and common mental disorder during phases II-III and phases II-IV, separately

Confounders for 5-year follow-up analysis (phase II-III): Age, social class, marital status, employment status, smoking habits, alcohol consumption, social support, BMI, phase II common mental disorders score, phase II HDL cholesterol level, change in triglyceride level between phase II and phase III, phase II job demand variables

Confounders for 10-year follow-up analysis (phase II-IV): Age, social class, marital status, employment status, smoking habits, alcohol consumption, social support, BMI, phase II common mental disorder score, phase II HDL cholesterol level, change in triglyceride level between phase II and phase IV, and phase II job demand variables

Results, limitations, source of funding

5-year follow-up:
- The odds of a common mental disorder at phase III were lower among those with low and high percentage of leisure time spent in heavy-intensity activity at phase II (OR=0.61, [0.40, 0.93], and OR=0.54, [0.35, 0.83], respectively)

10-year follow-up:
- The odds of a common mental disorder at phase IV were higher among those with increasing job class activity at phase II (significant results ranging from OR=1.85, [1.06, 3.23] to OR=2.41, [1.48, 3.92])

Limitations:
1. Possible exposure and outcome (non-differential) misclassification. E.g. measuring physical activity at one point in time may cause misclassification; also, measuring disease at 2 time points may have missed relapsing cases that occurred between these two time point
2. Residual confounding: should have included other measures of SES status, e.g. housing tenure
3. Participants who were physically active in their leisure time may lead healthier lifestyles (thus; other unmeasured variables may account for observed association)
4. Cannot generalize results to women

Source of funding: Medical Research Council (MRC)

Authors: Willcox BJ, He Q, Chen R, Yano K, Masaki KH, Grove JS… Curb JD
# Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

**Year:** 2006  
**Citation:** JAMA 296(19): 2343-2350  
**Country of study:** USA  
**Aim of study:** To test whether midlife biological, lifestyle, and sociodemographic risk factors are associated with overall survival and exceptional survival  
**Study design:** Prospective cohort study  
**Quality score:** (+++, + or -): ++

## Source population

**Number of people:** 8,006  
**Demographics:** Japanese American middle-aged men (mean age, 54 [range, 45-68] years)

## Study (eligible and selected) population

**Number of people:** 5,820  
**Characteristics:**

**Exceptional.** Age at baseline, y 55.5 (5.2): Height, cm 163.2 (5.4): Weight, kg 61.8 (7.8): BMI in youth 21.8 (1.9): Ever smoker, No. (%) 364 (56.4): Smoking, pack-years 14.0 (19.6): High alcohol consumption (3 drinks/d), No. (%) 42 (6.8): 76: Alcohol consumption, oz/mo 10.3 (16.3): Physical activity index 32.8 (4.3)

**Usual, Diseased.** Age at baseline, y 55.0 (5.6): Height, cm 162.9 (5.6): Weight, kg 63.1 (8.0): BMI in youth 22.0 (2.0): Ever smoker, No. (%) 469 (62.4): Smoking, pack-years 18.8 (22.4): High alcohol consumption (3 drinks/d), No. (%) 76 (10.3): Alcohol consumption, oz/mo 12.0 (20.9): Physical activity index 32.6 (4.1)

**Usual, Disabled:** Age at baseline, y 51.7 (3.4): Height, cm 162.6 (5.6): Weight, kg 63.3 (8.8): BMI in youth 22.1 (2.1): Ever smoker, No. (%) 663 (62.8): Smoking, pack-years 19.4 (22.0): High alcohol consumption (3 drinks/d), No. (%) 123 (11.4): Alcohol consumption, oz/mo 12.6 (24.8): Physical activity index 33.4 (4.8)

**Nonsurvival:** Age at baseline, y 54.1 (5.5): Height, cm 163.0 (5.7): Weight, kg 63.3 (9.8): BMI in youth 22.3 (2.3): Ever smoker, No. (%) 2561 (76.1): Smoking, pack-years 28.1 (25.5): High alcohol consumption (3 drinks/d), No. (%) 592 (17.6): Alcohol consumption, oz/mo 16.7 (26.9): Physical activity index 32.9 (4.5)

**Location:** Island of Oahu  
**Recruitment strategy:** Not reported  
**Length of follow-up:** Up to 40 years (1965-2005)  
**Response rate and loss to follow-up:** Not reported  
**Eligible population:** Island inhabitants  
**Excluded populations:** Not reported

## Exposures at midlife

**Relevant exposures:** Smoking status, alcohol consumption, and physical activity  
**Time:** Not reported  
**Measurement of exposure:** High alcohol intake was dichotomized as 3 or more drinks/d (based on an increased risk of mortality in the HHP/HAAS cohort) or less than 3 drinks/d. Smoking was dichotomized as ever or never.
Outcomes at 55 years or over

Outcomes: Overall survival and exceptional survival

Outcome measurement: 1 of 4 phenotypes:

a) Non-survivors — men who died before a specified age (75, 80, 85, or 90 years)
b) So-called “usual survivors but disabled”—men who survived until the specified age but with physical or cognitive disability and with or without a major chronic disease;
c) Usual survivors with major chronic diseases but no disability
d) Exceptional survivors

Time: Not reported

Analysis

Analysis strategy: Continuous variables were dichotomized as high or low based on conventional cut-off points or median values. Odds ratios for mortality vs survival (for each specified age) and, among survivors, for having at least 1 morbid condition vs being free of these conditions were estimated using logistic regression models. Backward stepwise logistic regression was used to select a subset of variables in the final model (including variables significant at the .10 level).

Confounders: Age-Adjusted

Results, limitations, source of funding

Number: 5,820

Effect estimates:

Age-Adjusted ORs of Selected Risk Factors for Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85

<table>
<thead>
<tr>
<th>Nonsurvival vs Survival</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever smoker</td>
<td>2.05 (1.83-2.29)</td>
<td>.001</td>
</tr>
<tr>
<td>High alcohol consumption (3 drinks/d)</td>
<td>1.97 (1.68-2.31)</td>
<td>.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual Survival vs Exceptional Survival</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever smoker</td>
<td>1.27 (1.06-1.53)</td>
<td>.01</td>
</tr>
<tr>
<td>High alcohol consumption (3 drinks/d)</td>
<td>1.84 (1.29-2.62)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Stepwise Logistic Regression Model of Risk of Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85 Years

<table>
<thead>
<tr>
<th>Nonsurvival† vs Survival</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>1.94 (1.72-2.18)</td>
<td>.001</td>
</tr>
<tr>
<td>High alcohol consumption (3 drinks/d)</td>
<td>1.58 (1.34-1.88)</td>
<td>.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual Survival‡ vs Exceptional Survival§</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>1.23 (1.01-1.50)</td>
<td>.04</td>
</tr>
<tr>
<td>High alcohol consumption (3 drinks/d)</td>
<td>1.84 (1.29-2.62)</td>
<td>.001</td>
</tr>
</tbody>
</table>
### Significant trends:

Never smoking is associated with overall survival but has only a borderline association with exceptional survival.

### Limitations:

1. Study population consists of ethnic Japanese men which limits generalizability (applicability to women)
2. Cohort effects
3. Excluded men with chronic diseases at baseline

### Source of funding:

This study was supported by contract N01-HC-05102 from the National Heart, Lung, and Blood Institute, contract N01-AG-4-2149 and grants 5 U01 AG019349-05, R01 AG027060-01 (Hawaii Lifespan Study), and K08 AG22788-02 from the National Institute on Aging, and grant 2004-0463 from the Hawaii Community Foundation.

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### Authors:

Xu Q, Anderson D, Courtney M

### Year:

2010

### Citation:

Health Care for Women International 31(12): 1082-1096

### Country of study:

Australia

### Aim of study:

To determine the influence of lifestyle factors on mental outcomes

### Study design:

Longitudinal

### Quality score:

(++, + or -): -

### Source population

10,923 women from South East Queensland, Australia recruited from rural and urban areas

### Study (eligible and selected) population

886/1,500 women ages 45-60 years were recruited and participated in 2001 survey and of these participants, 564 agreed to participate again in 2006.

Analysis restricted to 564 women.

2006 response rate: 37.6%

### Follow-up:

Non-response for 2006 survey due to:

1. Migration out of study area [n=2]
2. Death [n=3]
3. Non-participation [n=28]
4. Address change [n=104]
5. Loss to follow-up [n=13]
6. Other reasons for non-response [n=172]

### Sociodemographics:

Mean age of women was 55 years.

78.1% (n=438) of women were married or in relationships; 83.1% (n=466) were born in Australia; 28.4% (n=159) were college-educated; 40.8% (n=219) did not have paid employment; 41.8% (n=236) had family annual income less <= $40,000

### Exclusion:


Women lost to follow-up were slightly younger than those who remained (54.36 vs. 54.95 years, p=0.003)
### Exposures at midlife

Physical activity measure assessed frequency of participation in exercise each week using the following response options:
- None
- 1-2 times/week
- 3-4 times/week
- 5-6 times/week

Alcohol use was measured using the following options:
- Never
- Drank in past
- Occasionally
- Regularly

Smoking status was categorised as:
- Never smoker
- Past smoker
- Current smoker

Caffeine consumption was dichotomized (yes/no)

### Outcomes at 55 years or over

General mental well-being, and psychological symptoms including depression and anxiety were measured using SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire, respectively

Test-retest reliability of the GCS is 0.87

### Analysis

**Analysis strategy:** Logistic regression was used to determine the influence of lifestyle factors on mental outcomes

**Confounders:** BMI, sociodemographics, menopausal status, mental health status in 2001

### Results, limitations, source of funding

- Women who exercise 5-6 times per week scored 1 point lower on the anxiety scale (p=0.013), 1 point lower on the depression scale (p=0.001), 2 points lower on the psychological scale (p=0.002), and 9 points higher on the mental well-being scale (p=0.001) compared to women who did not exercise
- Women who smoked had a 6.725 point lower score in mental well-being than non-smokers (p=0.006)
- Women who consumed caffeinated drinks regularly had a lower mental well-being by 5 points compared to those who did not drink caffeinated beverages
- Past alcohol drinkers reported lower anxiety scores compared to non-drinkers (p=0.040)

**Limitations:**
1. Physical activity measurement did not include intensity and duration
2. Alcohol measurement may be imprecise; potentially useful to assess volume of alcohol consumption

**Source of funding:** None reported

**Authors:** Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K
### Year: 2001

**Citation:** Archives of Internal Medicine 161(14): 1703-8

**Country of study:** USA

**Aim of study:** To determine whether physical activity is associated with the risk of developing cognitive decline

**Study design:** Longitudinal

**Quality score:** (++, + or -): +

### Source population

9,704 predominantly white community-dwelling women 65 years of older recruited from Baltimore, Minneapolis, the Monongahela Valley near Pittsburgh, and Portland in the United States and examined in 1986-88 (baseline)

Participants examined at baseline visit also underwent biennial clinic visits and completed annual questionnaires

### Study (eligible and selected) population

Analysis restricted to **5,925** participants with cognitive test measurements at baseline and follow-up 6 and 8 years later

**Follow-up:** Mean of 7.5 years of follow-up

**Sociodemographics:** The mean age of women across quartiles of expended energy was 70.2-71.7 years, and the mean number of years of education across energy quartiles were 12.3-13.4 years

**Exclusion:**

i) Black women

ii) Women unable to walk without assistance or who had bilateral hip replacements

iii) Women with baseline cognitive impairment [n=950], with missing baseline cognitive scores [n=53] with baseline physical limitations [n=939], with missing information on physical limitations [n=10], and women who did not complete the baseline physical activity assessments [n=51]

iv) Women who died [n=596], were unavailable for follow-up [n=238], did not have follow-up cognitive measurements [n=942]

**Attrition:** Women without cognitive follow-up measurements had lower baseline scores on cognitive testing and were less physically active compared to participants (p<0.001)

### Exposures at midlife

Self-reported baseline physical activity was assessed using:

a) Interview questions on walking and stair climbing, and

b) A reliable scale measuring the frequency and duration of participation per week during the past year in 33 different physical activities (used to calculate kilocalories expended per week)

### Outcomes at 55 years or over

Cognitive assessment using MMSE performed at baseline, and follow-up 6 and 8 years later

### Analysis

**Analysis strategy:** logistic regression was used to assess the influence of physical activity (blocks walked per week or total kilocalories expended per week) on cognitive function in all women, as well as in sub-groups of women ages <=70 or >70 years; women with educational level <12 or >=12 years; and among those with or without of co-morbidities
Confounders: Baseline age, educational level, health status, functional limitation, depression score, stroke, diabetes, hypertension, myocardial infarction, smoking, oestrogen use

Results, limitations, source of funding

- 1178 (20%) participants developed cognitive decline over 7.5 years of follow-up
- Analysis of blocks walked per week (n=5,921):
  > the odds of cognitive decline were lowest among the two highest physical activity quartiles compared to the lowest activity quartile (OR=0.63 [0.52, 0.77]; OR=0.66 [0.54, 0.82])
- Analysis of total kilocalories expended per week (n=5,925):
  > the odds of cognitive decline were lowest among the two highest physical activity quartiles compared to the lowest activity quartile (OR=0.78 [0.64, 0.96]; OR=0.74 [0.60, 0.90])
- The odds of cognitive decline were low among those in the highest physical activity quartile regardless of age, comorbidities, education, (same findings observed when physical activity was assessed as blocks walked per week or kilocalories expended per week)

Limitations:
1. Self-reported data (recall bias)
2. Clinical assessment for dementia not performed, therefore cannot determine cause of cognitive decline
3. Sample was not racially diverse

Source of funding: Public Health Service, Bethesda, Md.

Authors: Yu S, Yarnell JW, Sweetnam PM, Murray L; Caerphilly study
Year: 2003
Citation: Heart 89(5): 502-6
Country of study: Wales
Aim of study: To assess the influence of leisure or job physical activity on all-cause, CHD, or CVD mortality
Study design: Longitudinal
Quality score: (+++, + or -): +

Source population
2,512 men ages 45-59 years were recruited in 1979-1983 from Caerphilly and its surrounding villages

Study (eligible and selected) population
Analysis restricted to 1975 men, including those re-examined in 1984-88 and men who had moved into the study area
Follow-up: Mean follow-up of 10.5 years
Follow-up from date of examination in 1984-88 to date of death or Sept. 25, 1997
Exclusion:
1. Men with symptomatic evidence of CHD, history of myocardial infarction, grade 1 or grade 2 angina, probable ischemia [n=393]
2. Men who died within two years of study inception [n=30]
3. Deaths from congenital anomalies or injury and poisoning were censored for analyses of all-cause mortality (n=7)
4. Men with missing data on variables related to the job physical activity questionnaire (n=23)
Attrition: -
### Exposures at midlife

**Physical activity was assessed using self-administered questionnaires:**

**Leisure physical activity**

Validated baseline Minnesota Leisure Time Physical Activity questionnaire administered in 1984-1988 to assess type and duration of leisure activities during the previous 12 months and to estimate energy expenditure (expressed as an activity index [AI] in kcal/day)

>4 AI scores characterized each person, one for each class of intensity activity and their sum total AI

**Job physical activity**

Job physical activity questionnaire (slightly modified Health Insurance Plan questionnaire) used to assess physical activity at work, or at last job with categories ranging from low to high occupational physical activity

### Outcomes at 55 years or over

Mortality from all causes, CVD, and cancer were ascertained using the National Health Service Central Registry

### Analysis

**Analysis strategy:** Cox proportional hazards regression was used to assess the influence of leisure or job physical activity on all-cause, CHD, or CVD mortality

**Confounders (for analysis of total activity during leisure):** Age, diastolic blood pressure, BMI, smoking status, social class (manual), family history of CHD among first degree relatives before age 55, history of diabetes mellitus in the past 5 years, job physical activity class

**Confounders (for analysis of heavy intensity activity during leisure):** Confounders listed above, combined light and moderate intensity activity

### Results, limitations, source of funding

252 total deaths over 10 years, with 111 deaths being caused by CVD, 82 by CHD, and 98 by cancer

**Analysis of total activity during leisure:**

- The greater the kcal/day consumed through total activity during leisure, the smaller the risk of CHD death (trend p-value=0.039)
- People expending 395.5-2747.2 kcal/day had a lower risk of CHD death than those expending 0.0-161.6 kcal/day (HR=0.55, [0.31, 0.98])

**Analysis of heavy intensity activity during leisure:**

- The greater the energy expenditure of heavy intensity activity during leisure at baseline, the smaller the risk of all-cause death, CVD death, and CHD death during follow-up (trend p-values: 0.006, 0.001, and 0.009, respectively)
- People expending 23.9-2142.9 kcal/day had a lower risk of all-cause death, CVD death, and CHD death than those expending 0.0-0.6 kcal/day (HR=0.61, [0.43, 0.86]; HR=0.38, [0.21, 0.67]; HR=0.36, [0.18, 0.73], respectively)

**Limitations:**

1. Lack of information on changes of physical activity over time can cause misclassification
2. Men with low levels of leisure-time physical activity at baseline may have already been sick; thus, the illness may have been the cause rather than the result of lack of physical activity
3. Self-reported data resulting in potential misclassification

**Source of funding:** British Heart Foundation and the Medical Research Council
APPENDIX C – Quality summary of cohort studies

Key to headings – Section 1: Population; 1.1 source population; 1.2 eligible population; 1.3 selected participants or areas. Section 2: Methods of Selection; 2.1 comparison group; explanatory variables; 2.3 contamination; 2.4 confounding factors; 2.5 setting applicability to the UK. Section 3: Outcomes; 3.1 reliable outcome measures; 3.2 outcome measurement; 3.3 important outcomes assessed; 3.4 follow-up time in exposure; NA: not applicable; NR: not reported.

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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions. 330
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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions. 331
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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
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Key to headings – Section 3.5 follow-up time meaningful; 4: Analyses; 4.1 powered to; 4.2 multiple explanatory variables; 4.3 analytical methods; 4.4 precision. Section 5: summary; 5.1 internally validity; 5.2 externally validity. NA: not applicable; NR: not reported.

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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions. 340
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APPENDIX D – Review Team

D.1 Expertise

Professor Carol Brayne – Professor Carol Brayne is Professor of Public Health Medicine in Department of Public Health and Primary Care in the University of Cambridge, Director of the Cambridge Institute of Public Health, and Lead of the Old Age theme in CLAHRC CP and the NIHR School of Public Health Research (SPHR) Ageing Well Programme. Professor Brayne is a medically qualified epidemiologist and public health academic. Since the mid-1980s her main research area has been longitudinal studies of older people following changes over time in cognition, dementia natural history and associated features with a public health perspective. She is lead principal investigator in the group of MRC Cognitive function and Ageing Study (CFAS), which has informed and will continue to inform national policy and scientific understanding of dementia in whole populations. Her group’s relevant achievements include the definitive systematic reviews of: the diagnosis of mild cognitive impairment; the effect of stroke on incident dementia; and the effect of statins on the prevention of vascular dementia. Ongoing work includes Alzheimer’s Society-funded systematic reviews of early non-pharmacological intervention for dementia and population screening for dementia; NIHR Cochrane programme of reviews of diagnostic test accuracy for dementia, and work on diabetes and dementia with the Alzheimer’s Society Vascular Dementia Systematic Review group.

Dr Louise Lafortune – Dr Lafortune is a Senior Research Associate for the Public Health and the Dementia, Frailty and End of Life theme in CLAHRC East of England, and the scientific coordinator of the NIHR SPHR Ageing Well Programme, which aims are to strengthen the evidence base for cost-effective and equitable public health interventions for older populations. Louise is specialised in Public Health and Ageing, and has nine years of industry experience in clinical trial, health economics and outcomes research. She has been involved in several projects aimed at improving care for frail older people (e.g. helped developed the joint strategic needs assessment (JSNA) for older people; support the ongoing development of integrated care for older people). In particular, she leads a programme of systematic reviews on population screening for dementia; co-lead the NIHR Cochrane programme of diagnostic test accuracy reviews for dementia; a review of systematic reviews looking at non-pharmacological interventions for behavioural problems, and a wide scope review of the literature looking at outcomes and quality of non-pharmacological interventions in early dementia. Her research interests encompass the development, evaluation and implementation of interventions and service delivery models aimed at improving care for older people.

1 CLAHRC CP: Collaboratives for Leadership in Applied Health Research and Care for Cambridgeshire and Peterborough.
individuals with complex health and social care needs, namely frail older people. Concerned with the practical application of research findings for patient benefits, her responsibilities include knowledge synthesis, public health analysis and evaluation of changes in services configuration and delivery resulting from the use of research.

Dr Sarah Kelly – Dr Kelly is an experienced systematic reviewer. Sarah was lead reviewer on a systematic review for the World Health Organisation Nutrition Guideline development group on the evidence for a relationship between sugar consumption and dental caries that was used to develop World Health Organisation (WHO) guideline recommendations. Dr Kelly was project coordinator and information specialist for a systematic review of the diet, nutrition and physical activity determinants of obesity for the World Cancer Research Fund (WCRF) that contributed to the major WCRF publication ‘Diet, Nutrition and Physical Activity determinants of Cancer (2007)’. She is lead reviewer on two Cochrane systematic reviews relating to nutrition and coronary heart disease and has contributed to a number of other Cochrane reviews about childhood obesity. She was also a reviewer on 2 systematic reviews on tracking of lifestyle behaviours from childhood to adulthood. Sarah has recently completed working on the Dementia Priority Setting Partnership with the James Lind Alliance and the Alzheimer’s Society. The project aimed to identify research priorities for dementia from a stakeholder survey including healthcare professionals, patients, carers, relatives of people with dementia that involved data management, formatting and checking of research questions against the existing evidence base for dementia and development of an evidence based research framework for dementia. Sarah has extensive experience in designing and drafting protocols, database searching and systematic search strategies, study selection and data-extraction, quality assessment, analyses and drafting of reviews.

Steven Martin – Mr Martin is an experienced Research Associate at the Cambridge Institute of Public Health (CIPH). During his time at the CIPH Steven has contributed to a number of research programmes around dementia and old age. In particular he has worked as the main systematic reviewer on a wide scoping systematic review looking at non-pharmacological interventions in early dementia and a qualitative review looking at attitudes and preferences with regards to screening for dementia. He is experienced at writing search strategies, undertaking data extraction, quality assessment and synthesis of qualitative, quantitative and mixed-methods research. Steven’s interests include the design, interpretation and synthesis of epidemiological evidence, with a particular focus on methodology and translational research aimed at improving health outcomes for vulnerable communities in society.
Olivia Remes – Ms Remes is a PhD student at the University of Cambridge, co directed by Professor Brayne and Dr Louise Lafortune. Olivia has a strong background in epidemiology and her PhD project focuses on the epidemiology of anxiety in the older population and the impact of this mental health condition of patterns of service utilisation.

Isla Kuhn – Ms Khun is Reader Services Librarian at the University of Cambridge Clinical School supporting the review team. Isla is an experienced librarian and has work with the team on all their evidence synthesis projects across a range of topics, specially ageing well and dementia.

Dr Nadja Smailagic – Dr Smailagic is a full time systematic reviewer on a NIHR funded Cochrane Collaboration programme of fifteen diagnostic test accuracy reviews for dementia. Nadja has extensive experience in designing and drafting protocols, study selection and data-extraction, quality assessment, analyses and drafting of reviews. Nadja is a GP with a background in mental health. In her previous role, she was responsible for developing the research agenda for a Mental Health Services for Older People (MHSOP) at the Nottinghamshire Healthcare NHS Trust. That involved negotiation with the Clinical Effectiveness and Clinical Governance for MHSOP, which led to the development of the ‘MHSOP Evidence into Practice Group’. Nadja also co-lead the Dementia ‘Managed Innovation Network’.

D.2 Role in the review process

<table>
<thead>
<tr>
<th>Core Staff</th>
<th>Roles &amp; responsibilities</th>
</tr>
</thead>
</table>
| Principal investigators  
- Louise Lafortune (LL)  
- Carol Brayne (CB) |  
- Scientific & clinical oversight of the project  
- Approval of reports before sending to NICE |
| Scientific coordinator / project management  
Louise Lafortune (LL) |  
- Direct contact for NICE  
- Project management  
- Technical support for development of protocols, searches, quality assessment tools, data extraction forms  
- No involvement in actual selection of studies, quality assessment and analysis  
- Support in drafting of report, final editing and approval  
- Main presenter at PHAC meetings (supported by SK) |
| First Systematic Reviewer  
- Sarah Kelly (SK) |  
- Drafting of protocols, search strategies, running searches (with support from Clinical School librarian), scanning titles, selecting full text, quality assessment, analysis and writing of draft reports |
<table>
<thead>
<tr>
<th>Role and Support</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Systematic Reviewer</td>
<td>Support LL with presentation at PHAC</td>
</tr>
<tr>
<td>Steven Martin (SM)</td>
<td>Support first reviewer with listed tasks</td>
</tr>
<tr>
<td>Forth Systematic Reviewer</td>
<td>Support first reviewer with listed task (namely for Alcohol papers)</td>
</tr>
<tr>
<td>Ms Olivia Remes</td>
<td></td>
</tr>
<tr>
<td>Admin/Technical Support</td>
<td>Ordering, printing, scanning, listing, sorting articles; preparing reference lists &amp; bibliographies (using word, excel and Endnote mainly)</td>
</tr>
<tr>
<td>Andy Cowan (AC)</td>
<td>Keeping all project files in order (according to structure agreed with NICE &amp; official processes etc.)</td>
</tr>
<tr>
<td></td>
<td>Chasing authors for information</td>
</tr>
<tr>
<td></td>
<td>Helping with formatting reports, tables, presentations, etc. (according to NICE manuals)</td>
</tr>
<tr>
<td>Extended team</td>
<td></td>
</tr>
<tr>
<td>Nadja Smailagic</td>
<td>Third reviewer (where/when necessary as arbitrator will resolve disagreements) (e.g. inclusion of studies, quality assessment, analysis)</td>
</tr>
<tr>
<td></td>
<td>Technical support (e.g. on quality assessment, data extraction, analysis)</td>
</tr>
</tbody>
</table>

### D.3 Conflicts of interest

Dr Louise Lafortune, who co-led the project with Professor Brayne, is a topic expert on the new PHAC in relation to the topic of Disability, Dementia and Frailty. The potential conflict of interest (Col) is with drafting of new recommendations based on evidence that originates from the reviews her team has produced. She has no conflict regarding evidence from other sources, nor in commenting / advising on recommendations based on evidence from any source once they have been drafted. This potential Col was handled as follows:

- For meetings - and parts of meetings - where we consider evidence that has not come from her team, she worked as a full PHAC member.
- In meetings (or the parts of meetings) where evidence reviews from her team are presented and discussed, she stepped back from the PHAC role and become a presenter / advisor to the committee. She discussed her team’s reviews and advise the committee on how to interpret / use the evidence they contain, however she did not then take an active part in drafting new recommendations based on those reviews.

The other members of the team have no conflict of interest to declare.
E.1 Sample search strategy used to identify primary studies

Sample search: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® <1946 to Present>

Note: Searches terms were modified when searching other databases.

1  ((dement* or alzheimer* or disability* or disabled or diabet* or angina or stroke or copd or frail* or bronchiti* or melanoma* or carcinoma* or cancer* or neoplasm* or tumor* or blind* or deaf* or glaucoma*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*)).ti,ab. (276946)

2  (lewy* adj2 bod* adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*)).ti,ab. (67)

3  (((coronary* or vascular* or cardiac or cardiovasc* or cardio vasc* or cerebrovasc* or heart*1 or myocardia*) adj3 (bypass* or graft* or disease* or event* or infarct* or re?vascular* or isch?emi* or peripheral* or complication* or disorder*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*))).ti,ab. (29741)

4  (((glucose adj3 (intoleran* or toleran*)) or (insulin adj3 resistan*)) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*))).ti,ab. (2630)

5  (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*)).ti,ab. (1247)

6  (((visual adj3 impair*) or (vision* adj3 disorder*) or (macular adj3 degenerat*)) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*))).ti,ab. (436)

7  (hear* adj3 (impair* or difficult* or hard* or disorder*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*))).ti,ab. (368)

8  (((cognition disorder* or cognitive impair*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or impede* or delay* or constrain*))).ti,ab. (950)

9  exp Dementia/pc (4213)

10  exp Wheelchairs/ (3567)

11  exp Cardiovascular Diseases/pc (156094)

12  exp Cardiovascular Deconditioning/ (244)

13  exp Cerebrovascular Disorders/pc (21793)

14  exp Diabetes Mellitus/pc (20043)

15  exp Pulmonary Disease, Chronic Obstructive/pc (596)
16 exp Lung Diseases. Obstructive/pc (6349)
17 exp Frail Elderly/ (6818)
18 Melanoma/pc (1547)
19 exp Blindness/pc (1957)
20 exp Vision Disorders/pc (3318)
21 exp Deaf-Blind Disorders/pc (3)
22 exp Hearing Disorders/pc (3446)
23 exp Glaucoma/pc (887)
24 exp Lung Neoplasms/pc (4337)
25 exp Skin Neoplasms/pc (4524)
26 exp Colorectal Neoplasms/pc (9228)
27 exp Colonic Neoplasms/pc (3678)
28 exp Intestinal Neoplasms/pc (9545)
29 exp Rectal Neoplasms/pc (754)
30 exp Stomach Neoplasms/pc (1463)
31 exp Mouth Neoplasms/pc (1249)
32 exp macular degeneration/pc (783)
33 exp cognition disorders/pc (2314)
34 ((ageing or aging) adj3 (well or success* or positive* or active* or healthy or unhealthy or unsuccess*)).ti,ab. (6519)
35 (compress* adj3 morbid*).ti,ab. (181)
36 or/1-35 (503786)
37 exp *Middle Aged/ (847)
38 (middle adj age*).ti. (9779)
39 (baby adj2 boomer*).ti. (221)
40 (midlife or "mid life" or "midlives" or "mid lives").ti. (1675)
41 or/37-40 (12244)
42 Epidemiologic studies/ (6282)
43 exp case control studies/ (668222)
44 exp cohort studies/ (1374003)
Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
(myocardial* adj3 (infarct* or re?vascular* or isch?emi*)).ti,ab. (174190)
(vascular* adj3 (peripheral* or disease* or complication*)).ti,ab. (56118)
(angina* or stroke*).ti,ab. (196749)
(heart* adj3 (disease* or attack* or bypass*)).ti,ab. (138679)
diabet*.ti,ab. (421288)
((glucose adj3 (intoleran* or toleran*)) or (insulin adj3 resistan*)).ti,ab. (83550)
copd.ti,ab. (27312)
(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab. (61501)
(chronic* adj3 bronchiti*).ti,ab. (10432)
frail*.ti,ab. (9086)
(lung adj3 (cancer* or neoplasm* or tumo?r*)).ti,ab. (116128)
melanoma*.ti,ab. (82712)
((bowel* or colorectal* or rect* or intestin* or colon*) adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (124255)
(stomach* adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (11225)
((oral* or mouth*) adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (14878)
(blind* or (visual* adj3 impari*) or (vision* adj3 disorder*)).ti,ab. (220907)
(deaf* or (hear* adj3 (impair* or difficult* or hard* or disorder*))).ti,ab. (45625)
glaucoma*.ti,ab. (43418)
((ageing or aging) adj3 (well or success* or positive* or active* or healthy or unhealthy or unsuccess*))_.ti,ab. (6519)
maculopath*.ti,ab. (3012)
((macul or retina* or choroid*) adj3 degener*).ti,ab. (7847)
(macula* adj2 lutea).ti,ab. (112)
(skin* adj3 (cancer or neoplasm* or tumo?r*)).ti,ab. (22468)
(cogniti* adj3 (disorder* or degenerat*)).ti,ab. (5517)
((limit* or difficult*) adj3 (mobil* or walk* or ambulat*)).ti,ab. (5193)
osteoporo*.ti,ab. (52576)
osteopenia*.ti,ab. (7137)

Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
(bone* adj3 (dens* or loss* or mass* or age* or defect* or mineral* or disease* or health*)).ti,ab. (104300)

ur?emi*.ti,ab. (25975)

((kidney* or renal*) adj3 (transplant* or graft* or fail* or disease*)).ti,ab. (212407)

(hemodialysis or haemodialysis or dialysis or pre-dialysis or predialysis).ti,ab. (118000)

(CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).ti,ab. (35716)

(obes* adj2 diabet*).ti,ab. (15199)

(mody or niddm).ti,ab. (7673)

(diabet* and (non insulin* depend$ or noninsulin* depend* or noninsulindepend* or non insulindepend*)).ti,ab. (11972)

((typ* 2 or typ* II) adj diabet*).ti,ab. (79809)

((ketoresist* or keto* resist* or nonketo* or non keto*) adj diabet*).ti,ab. (263)

((adult* or matur* or late or slow or stabl*) adj diabet*).ti,ab. (1313)

(((plurimetabolic* or metabolic) adj syndrom*).ti,ab. (29347)

(insulin* defic* adj relativ*).ti,ab. (7)

hyperglyc?em*.ti,ab. (41987)

(compress* adj3 morbid*).ti,ab. (181)

exp dementia/ (122570)

exp Disabled Persons/ (46518)

exp Wheelchairs/ (3567)

exp Cardiovascular Deconditioning/ or exp Cardiovascular diseases/ (1885236)

exp Cerebrovascular Disorders/ (277649)

exp Diabetes Mellitus/ (320101)

exp Pulmonary Disease, Chronic Obstructive/ (24783)

exp Lung Diseases, Obstructive/ (167822)

exp Frail Elderly/ (6818)

exp Lung Neoplasms/ (179429)

exp Skin Neoplasms/ (97248)

exp melanoma/ (75062)
exp intestinal neoplasms/ or exp colorectal neoplasms/ or exp colonic neoplasms/ or exp rectal neoplasms/ (173781)
exp Stomach Neoplasms/ (74319)
exp Mouth Neoplasms/ (55023)
exp Blindness/ (20465)
exp Vision Disorders/ (58963)
exp Deaf-Blind Disorders/pc or exp hearing disorders/ or exp hearing impaired persons/ (70943)
exp glaucoma/ (42761)
exp macular degeneration/ (17379)
exp retinal degeneration/ (31530)
exp retinal neovascularization/ (2366)
exp choroidal neovascularization/ (4692)
exp macula lutea/ (10257)
exp cognition disorders/ (64141)
exp mobility limitation/ (2363)
exp "bone and bones"/ (484556)
exp bone density/ (41566)
exp osteoporosis/ (45428)
exp bone diseases, metabolic/ (63376)
exp uremia/ (22454)
exp renal insufficiency/ (124924)
exp kidney failure, chronic/ (78957)
exp renal dialysis/ (92574)
exp renal dialysis/ or exp dialysis/ (115058)
exp Diabetes mellitus, non insulin dependent/ (87707)
exp Insulin resistance/ (56125)
exp hyperglycemia/ (26892)
exp Diabetes Mellitus/ (320101)
or/66-155 (4784767)
exp jogging/ (702)
exp bicycling/ (7943)
exp swimming/ (19044)
exp dancing/ (1856)
exp gardening/ (475)
exp fitness centers/ (339)
exp sedentary lifestyle/ (2625)
(health* adj3 (behavior* or behaviour*)).ti,ab. (29899)
((ageing or aging) adj3 (well or success* or positive* or active* or healthy)).ti,ab. (6481)
(food* adj3 choice*).ti,ab. (3151)
dieting.ti,ab. (2965)
(diet* adj3 (health* or balance* or fat* or salt* or sugar* or mediterranean or choice* or improv* or unhealthy or nutritious)).ti,ab. (60083)
((fruit* or vegetable* or salt* or fat* or sugar*) adj3 (intake* or consum* or eat* or ate)).ti,ab. (33245)
(undernutrition or undernourish* or under-nutrition* or under-nourish*).ti,ab. (7463)
(multimicronutrient* or multi-micronutrient* or micronutrient* or micro-nutrient* or multinutrient* or multi-nutrient*).ti,ab. (8883)
("five a day" or "5 a day").ti,ab. (179)
("health check" or "check-up").ti,ab. (5509)
"health mot".ti,ab. (285)
((eye or eyesight or sight* or vision* or visual* or hearing) adj3 (test* or check* or screen*)).ti,ab. (20270)
(smok* or tobacco or cigar* or nicotine).ti,ab. (252522)
(((Alcohol* or Drunk* or Drink*) and (consum* or misuse or abus* or intoxicat* or harmful or excess* or binge or hazardous or heavy or temperan* or abstinen*)).ti,ab. (100162)
temperan*.ti,ab. (237)
teetotal*.ti,ab. (257)
(loneli* or lonely).ti,ab. (3656)
(socialis* or socializ*).ti,ab. (9480)
(social* adj3 (isolat* or network* or contact* or alien*)).ti,ab. (17204)
(sedentary or exercis* or sport*).ti,ab. (251538)
"physical condition".ti,ab. (4515)
(balance* and (exercise* or retrain* or re-train* or reeducat* or re-educat*)).ti,ab. (6739)
inactiv*.ti,ab. (252817)
(walk* or run* or jog* or swim* or danc* or garden* or cycl* or bicycl* or bike* or recreation*).ti,ab. (1102662)
("resistance trainiing" or "aquacatic exercis*" or "wellness centre*" or "wellness center*").ti,ab. (154)
("weight gain*" or "weight los*" or "overweight" or "over weight").ti,ab. (130192)
(obesity and "related behavio*").ti,ab. (510)
(overeat* or "over eat*").ti,ab. (1973)
(waist adj3 (circumference* or measur*)).ti,ab. (16292)
((bmi or "body mass index") adj3 (gain* or loss* or lose* or lost or change*)).ti,ab. (4960)
(weight adj2 (cycling or reduc* or los* or maint* or decreas* or increas* or watch* or control*)).ti,ab. (106278)
"weight change".ti,ab. (7524)
((behavio?r or lifestyle or "life style") adj3 (change* or changing or modification or modify or modifying or therapy or therapies or program* or intervention* or counsel*)).ti,ab. (47776)
((physical* or keep* or cardio* or aerobic or fitness) adj3 (fit* or activit* or train*)).ti,ab. (115603)
### APPENDIX F – Search results

#### Table F1. Databases searches – Primary studies

<table>
<thead>
<tr>
<th>Database name</th>
<th>Search date</th>
<th># records retrieved</th>
<th>After de duplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE/in-process MEDLINE</td>
<td>12.12.13</td>
<td>1398</td>
<td>1182</td>
</tr>
<tr>
<td>EMBASE</td>
<td>12.12.13</td>
<td>1154</td>
<td>1091</td>
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<td>PsychINFO</td>
<td>12.12.13</td>
<td>3906</td>
<td>3906</td>
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<tr>
<td>CINAHL</td>
<td>12.12.13</td>
<td>423</td>
<td>423</td>
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<tr>
<td>Web of knowledge</td>
<td>12.12.13</td>
<td>3440</td>
<td>3440</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>10321</strong></td>
<td><strong>10042</strong></td>
</tr>
</tbody>
</table>

#### Table F2. Websites searched

<table>
<thead>
<tr>
<th>Database name</th>
<th>Search date</th>
<th># records retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS Evidence Search</td>
<td>26-27.11.13</td>
<td>151</td>
</tr>
<tr>
<td>Public Health Observatories</td>
<td>27.11.13</td>
<td>12</td>
</tr>
<tr>
<td>Health Evidence Canada</td>
<td>27.11.13</td>
<td>39</td>
</tr>
<tr>
<td>Beth Johnson Foundation</td>
<td>27.11.13</td>
<td>14</td>
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<tr>
<td>British Library</td>
<td>27.11.13</td>
<td>60</td>
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<tr>
<td>Department of Health</td>
<td>27.11.13</td>
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<td>E-Print Network</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>296</strong></td>
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</table>
## APPENDIX G – Excluded studies and reason for exclusion

### G.1 Primary studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albanese E, Hardy R, Wills A et al. (2012) No association between gain in body mass index across the life course and midlife cognitive function and cognitive reserve--the 1946 British Birth Cohort study. Alzheimer's &amp; Dementia 8(6): 470-482.</td>
<td>Obesity is exposure, outcome cog fn at age 53 (&lt;55y)</td>
</tr>
<tr>
<td>Alfred T, Ben-Shlomo Y, Cooper R et al. (2013) Genetic variants influencing biomarkers of nutrition are not associated with cognitive capability in middle-aged and older adults. Journal of Nutrition 143(5): 606-612.</td>
<td>Exposure not HB</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>Anonymous</td>
<td>2013</td>
</tr>
<tr>
<td>Ansari RM</td>
<td>2009</td>
</tr>
<tr>
<td>Anstey KJ, Cherbuin N, Budge M et al.</td>
<td>2011</td>
</tr>
<tr>
<td>Arnlov J, Ingelsson E, Sundstrom J et al.</td>
<td>2010</td>
</tr>
<tr>
<td>Arnlov J, Sundstrom J, Ingelsson E et al.</td>
<td>2011</td>
</tr>
<tr>
<td>Asia Pacific Cohort Studies Collaboration</td>
<td>2003</td>
</tr>
<tr>
<td>Baker DW, Sudano JJ, Albert JM et al.</td>
<td>2001</td>
</tr>
<tr>
<td>Barengo NC, Hu G, Lakka TA et al.</td>
<td>2004</td>
</tr>
<tr>
<td>Barnes DE, Yaffe K, Byers AL et al.</td>
<td>2012</td>
</tr>
<tr>
<td>Baron-Epel O, Azizi E</td>
<td>2003</td>
</tr>
</tbody>
</table>

Exposure is dementia in late life, outcome is mortality


X-sect


Exposure is waist circumference (same paper)


Exposure is waist circumference


X-sect


Not midlife - young adults


Exposure is obesity, outcome diabetes


Sleep duration and problems as exposure


Not HB


Exposure not HB


Not diagnosed health outcomes (diet quality)


SR of definitions of healthy ageing
<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>middle-aged men.</td>
<td></td>
</tr>
<tr>
<td>measures of cognition in middle-age adults.</td>
<td></td>
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<tr>
<td>health problems among middle-aged adults.</td>
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<tr>
<td>myocardial infarction in young and middle-aged women.</td>
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<tr>
<td>cardiovascular risk factors in a cohort of middle-aged Chilean</td>
<td></td>
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<tr>
<td>myocardial infarction in young and middle-aged women.</td>
<td></td>
</tr>
<tr>
<td>balance for studies in middle-aged and older adults.</td>
<td></td>
</tr>
<tr>
<td>health in middle age.</td>
<td></td>
</tr>
<tr>
<td>community-based study of middle-aged and older men and women in</td>
<td></td>
</tr>
<tr>
<td>Midlife outcomes</td>
<td></td>
</tr>
<tr>
<td>disability, dementia and frailty in later life - mid-life approaches</td>
<td></td>
</tr>
</tbody>
</table>

Statin therapy, drugs


Binge drinking and psychiatric disorders 3 yr follow up


X-sect


Relation between BMI and cognition


Exposure is depression


Midlife use of Japanese but could have been learnt in childhood, not a midlife behaviour


X-sectional


Weight at midlife, 2 year follow up


Exposure is WC/TG


Exposure is OW, not health behaviour


Exposure is BMI
<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai Q, Borenstein AR Wu Y et al. (2006)</td>
<td>Fruit and vegetable juices and Alzheimer’s Disease: The Kame Project. The American Journal of Medicine 119(9): 751-759.</td>
<td>&gt;65y at baseline</td>
</tr>
<tr>
<td>Deary IJ, Allerhand M, Der G. (2009)</td>
<td>Smarter in middle age, faster in old age: a cross-lagged panel analysis of reaction time and cognitive ability over 13 years in the West of Scotland Twenty-07 Study. Psychology &amp; Aging 24(1): 40-47.</td>
<td>Exposure is processing speed</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>den Ouden ME, Schuurmans MJ, Brand JS et al. (2013)</td>
<td>Physical functioning is related to both an impaired physical ability and ADL disability: a ten year follow-up study in middle-aged and older persons. Maturitas 74(1): 89-94.</td>
<td>2013</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td>Exposure/Outcome</td>
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<td>Findings</td>
<td></td>
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<tr>
<td>Gray L, Lee IM, Sesso HD et al. (2011)</td>
<td>Links between blood pressure and later CVD, mortality - pre-conditions</td>
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<tr>
<td>Guan JW, Huang CH, Li YH et al. (2011)</td>
<td>Exposure is hypertension</td>
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<tr>
<td>Guo X, Pantoni L, Simoni M et al. (2006)</td>
<td>Exposure is respiratory function, age 70-92 at baseline.</td>
<td></td>
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<tr>
<td>Gureje O, Ogunniyi A, Kola L et al. (2011)</td>
<td>Age &gt;65 at baseline</td>
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<tr>
<td>Gustafsson PE, Janlert U, Theorell T et al. (2012)</td>
<td>Exposure is peer problems in adolescence (16y). Outcome is metabolic syndrome in midlife.</td>
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<tr>
<td>Hall MH, Muldoon MF, Jennings JR et al. (2008)</td>
<td>X-sect</td>
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<td>Ham E, Choi H, Seo JT et al. (2009)</td>
<td>X-sect</td>
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<tr>
<td>Hamer M, Chida Y. (2009)</td>
<td>Exposure is fitness, 3 yr follow-up</td>
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<td>Summary</td>
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<tr>
<td>Hart CL, Hole DJ, Lawlor DA et al. (2007) How many cases of Type 2 diabetes mellitus are due to being overweight in middle age? Evidence from the Midspan prospective cohort studies using mention of diabetes mellitus on hospital discharge or death records. Diabetic Medicine 24(1):73-80.</td>
<td>Exposure is BMI</td>
<td></td>
</tr>
<tr>
<td>Henriksson KM, Lindblad U, Agren B et al. (2001) Associations between body height, body composition and cholesterol levels in middle-aged men. The coronary risk factor study in southern Sweden (CRISS). European Journal of Epidemiology 17: 521-526.</td>
<td>Baseline ages 37,40,43, follow up 6 years but only to 49 years mas (&lt;55 y)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
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<td>Study Details</td>
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<tr>
<td>Holtermann A, Mortensen OS, Burr H et al. (2010)</td>
<td>Long work hours and physical fitness: 30-year risk of ischaemic heart disease and all-cause mortality among middle-aged Caucasian men. Heart 96(20):1638-44.</td>
<td>Exposure is long work hours/fitness</td>
</tr>
<tr>
<td>Reference</td>
<td>Summary</td>
<td></td>
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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Johansson L, Guo X, Hällström T et al. (2013) Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer’s disease: a 38 year longitudinal population study. BMJ Open 3(9): e003142.</td>
<td>Exposure is psychosocial stressors</td>
<td></td>
</tr>
<tr>
<td>Citation</td>
<td>Section</td>
<td></td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Jovanovic GK, Zezelj SP, Malatestinić Đ et al. (2010)</td>
<td>X-sect</td>
<td></td>
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<tr>
<td>Diet quality of middle age and older women from Primorsko-Goranska County evaluated by healthy eating index and association with body mass index. Collegium Antropologicum 34 Suppl 2: 155-160.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaffashian S, Dugravot A, Brunner EJ et al. (2013)</td>
<td>Exposure is stroke risk - includes smoking but cannot be separated from other stroke risk factors</td>
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<tr>
<td>Kalmijn S, van Boxtel MP, Verschuren MW et al. (2002)</td>
<td>Outcomes are midlife</td>
<td></td>
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<tr>
<td>Kamijo T, Murakami M. (2009)</td>
<td>Intervention study review 3?</td>
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<tr>
<td>Karp A, Andel R, Parker MG et al. (2009)</td>
<td>Exposure is mentally stimulating work</td>
<td></td>
</tr>
<tr>
<td>Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. American Journal of Geriatric Psychiatry 17(3): 227-36.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karp A, Kåreholt I, Qiu C et al. (2004)</td>
<td>Exposure is level of education/SES</td>
<td></td>
</tr>
<tr>
<td>Karp A, Paillard-Borg S, Wang HX et al. (2006)</td>
<td>Exposure is in over 75 years age</td>
<td></td>
</tr>
<tr>
<td>Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. Dementia and Geriatric Cognitive Disorders 21(2): 65-73.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karpansalo M, Manninen P, Lakka TA et al. (2002)</td>
<td>Outcome is early retirement</td>
<td></td>
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<tr>
<td>Karvonen-Gutierrez CA, Ylitalo KR. (2013)</td>
<td>X-sect</td>
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<tr>
<td>Kim J, Chu SK, Kim K et al. (2011)</td>
<td>X-sect</td>
<td></td>
</tr>
<tr>
<td>Alcohol use behaviors and risk of metabolic syndrome in South Korean middle-aged men. BMC Public Health 22;11:489.</td>
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</tr>
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</table>
**Guidance title:** Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.

<table>
<thead>
<tr>
<th>Reference</th>
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<tbody>
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<td>Reference</td>
<td>Title</td>
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<td>-----------</td>
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<tr>
<td>Lewis TT, Everson-Rose SA, Karavolos K et al. (2009)</td>
<td>Hostility is associated with visceral, but not subcutaneous, fat in middle-aged African-American and white women. Psychosomatic Medicine 71(7): 733-40.</td>
</tr>
<tr>
<td>Li Y, Yatsuya H, Iso H, Tamakoshi K et al. (2010)</td>
<td>Incidence of metabolic syndrome according to combinations of lifestyle factors among middle-aged Japanese male workers. Preventive Medicine 51(2): 118-22.</td>
</tr>
<tr>
<td>Reference</td>
<td>Details</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Lindström I, Pallasaho P, Luukkonen R et al. (2011) Reduced work ability in middle-aged men with asthma from youth- a 20-year follow-up. Respiratory Medicine 105(6): 950-5.</td>
<td>Exposure is childhood asthma</td>
</tr>
<tr>
<td>Reference</td>
<td>Note</td>
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<tr>
<td>--------------------------------------------------------------------------</td>
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</table>

SR includes a number of studies in middle-aged people - check cited references


Prevalence study of functional limitation at midlife


Age 46-47 at baseline, followed for 5 years, so outcomes at age <55 years.


Mean age 44-47 at baseline, 1 year follow up, intentional weight reduction


Age 45-47 at baseline, 7 years of FU so outcomes at age <55 years


Mean age 47-48 at baseline, range 35-59, 7 yr FU. Outcomes at age <55 years. Have excluded other papers from this cohort as outcomes <55 y. This one is borderline but just under age 55 yr cut off.


Age 46-47 at baseline, followed for 7 years, so outcomes at age <55 years.


Age 42-45 at baseline, 9 years of FU so outcomes <55 years.


Outcome is aortic stiffness


Comparison of smoking cessation between young and midlife smokers
<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Reference</td>
<td>Exposure</td>
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Guidance title: Disability, dementia and frailty in later life - mid-life approaches to prevent or delay the onset of these conditions.
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<tr>
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<td>Exposure descriptors</td>
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<tr>
<td>Savva GM, Blossom CMS. (2010) Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 41:e41-e46.</td>
<td>Exposure is stroke risk - includes smoking but cannot be separated from other stroke risk factors</td>
</tr>
<tr>
<td>Reference</td>
<td>Summary</td>
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<td>Reference</td>
<td>Summary</td>
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<tr>
<td>Strandberg TE, Saijonmaa O, Tilvis RS et al. (2011)</td>
<td>Association of telomere length in older men with mortality and midlife body mass index and smoking. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 66(7): 815-20. Outcome is telomere length, not directly DDF outcomes</td>
</tr>
<tr>
<td>Takwoingi Y, Hopewell S, Tovey D et al. (2013)</td>
<td>A multicomponent decision tool for prioritising the updating of systematic reviews. BMJ 347: f7191. Not relevant topic</td>
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<tr>
<td>Reference</td>
<td>Title</td>
</tr>
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<td>-----------</td>
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<tr>
<td>Tunstall-Pedoe H. (2013)</td>
<td>The decline in coronary heart disease; did it fall or was it pushed? BMJ 344: d7809.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Description</td>
</tr>
<tr>
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</table>

Exposure is dietary methionine

Neural network modelling

Outcome is white matter lesions but not specific health conditions. Exposures are BP, TC, BMI, ApoE.

Social support is one exposure - relevant?, Mean age 45 (range 42-52), 5y follow-up so outcomes at <55y

No behaviour


The exposure we are interested in is diet and the outcome is hypertension/blood pressure (as a precondition for dementia, disability and frailty). Baseline measurements were taken at 1987-89 and follow-up at 1990-92 (Exam 2), 1993-95 (Exam 3) and 1996-98 (Exam 4). From the tables (3 and 4) the data seems to be reported for 1987-1998. So the outcome hypertension data was taken from exam 4 (1996-98). So between baseline measurements and Exam 4 there is about 9 years of follow-up. However, between exam 3 and exam 4 there is only 3 years of follow-up and it is not clear from the data reported how much of the analysis was based on 9 year follow-up and how much on 3 year follow up data.
<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>WHO Ageing Website (accessed 26.11.13)</td>
<td>Information sheet only, not primary study</td>
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<tr>
<td>Wilson D, Peters R, Ritchie K et al. (2011)</td>
<td>Latest advances on interventions that may prevent, delay or ameliorate dementia. Therapeutic Advances in Chronic Disease 2(3) 161-173.</td>
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<td>Reference</td>
<td>Note</td>
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<tr>
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<tr>
<td>Wright JL, Sherriff JL, Dhaliwal SS et al. (2011) Tailored, iterative,</td>
<td>Tailored, printed dietary feedback is as effective as group education</td>
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<tr>
<td>printed dietary feedback is as effective as group education in improving</td>
<td>in improving dietary behaviours: results from a randomised control trial</td>
</tr>
<tr>
<td>dietary behaviours: results from a randomised control trial in middle-aged</td>
<td>in middle-aged adults with cardiovascular risk factors. International</td>
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<tr>
<td>Behavioral Nutrition &amp; Physical Activity 8: 43.</td>
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<tr>
<td>Xu WL, Atti AR, Gatz M et al. (2011) Midlife overweight and obesity</td>
<td>Exposure is OW/Obesity</td>
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<tr>
<td>increase late-life dementia risk: a population-based twin study.</td>
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<td>Neurology 76(18): 1568-1574.</td>
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<td>Yaffe K, Barnes D, Nevitt M et al. (2001) A prospective study of</td>
<td>Exclude &gt;65 at baseline</td>
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<td>physical activity and cognitive decline in elderly women.</td>
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<tr>
<td>Archives of Internal Medicine 161(14): 1703-1708.</td>
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<td>Yagci N, Cavlak U, Aslan UB et al. (2007) Relationship between balance</td>
<td>Balance not behaviour</td>
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<td>performance and musculoskeletal pain in lower body comparison healthy</td>
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<td>middle aged and older adults.</td>
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<td>Archives of Gerontology &amp; Geriatrics 45(1): 109-119.</td>
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<tr>
<td>Yamada M, Kasagi F, Sasaki H et al. (2003) Association between dementia</td>
<td>Mean age &lt;40 y</td>
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<td>and midlife risk factors: the Radiation Effects Research Foundation</td>
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<td>Adult Health Study. Journal of the American Geriatrics Society 51(3):</td>
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<td>410-414.</td>
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<td>Yan LL, Daviglus ML, Liu K et al. (2006) Midlife body mass index and</td>
<td>Cannot separate health behaviour data from other risk factors</td>
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<td>Yang G, Shu XO, Gao YT et al. (2007) Impacts of weight change on</td>
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<td>prehypertension in middle-aged and elderly women. International Journal</td>
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<td>of Obesity 31(12): 1818-1825.</td>
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<td>contraceptive use, and the risk of ischemic and hemorrhagic stroke in a</td>
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<tr>
<td>Yarnell JW, Patterson CC, Thomas HF et al. (2000) Comparison of weight</td>
<td>Smoking - BMI relationship but smoking appears to be assessed at age 18</td>
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<td>in middle age, weight at 18 years, and weight change between, in</td>
<td>so not midlife.</td>
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<td>predicting subsequent 14 year mortality and coronary events: Caerphilly</td>
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<td>Prospective Study. Journal of Epidemiology &amp; Community Health 54(5):</td>
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<td>344-348.</td>
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<td>Ye X, Gao X, Scott T et al. (2011) Habitual sugar intake and cognitive</td>
<td>X-sect analysis</td>
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<td>function among middle-aged and older Puerto Ricans without diabetes.</td>
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<td>British Journal of Nutrition 106(9): 1423-1432.</td>
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<td>with intraocular pressure in middle-aged and older Japanese residents.</td>
<td>so not midlife specifically</td>
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<td>fibrillation among middle-aged and elderly Chinese. International Journal</td>
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APPENDIX H – Methodology checklists

H.1 Quality assessment for quantitative studies (cohort)

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<tr>
<th>Study identification: Include full citation details</th>
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<td>Study design:</td>
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<tr>
<td>• Refer to the glossary of study designs (appendix D) and the algorithm for classifying experimental and observational study designs (appendix E) to best describe the paper’s underpinning study design</td>
</tr>
<tr>
<td>Guidance topic:</td>
</tr>
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<td>Assessed by:</td>
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</table>

### Section 1: Population

1.1 Is the source population or source area well described?

- Was the country (e.g. developed or non-developed, type of health care system), setting (primary schools, community centres etc), location (urban, rural), population demographics etc adequately described?

- ++
- +
- −
- NR
- NA

**Comments:**

1.2 Is the eligible population or area representative of the source population or area?

- Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)?
- Was the eligible population representative of the source? Were important groups underrepresented?

- ++
- +
- −
- NR
- NA

**Comments:**

1.3 Do the selected participants or areas represent the eligible population or area?

- Was the method of selection of participants from the eligible population well described?
- What % of selected individuals or clusters agreed to participate? Were there any sources of bias?
- Were the inclusion or exclusion criteria explicit and appropriate?

- ++
- +
- −
- NR
- NA

**Comments:**
<table>
<thead>
<tr>
<th>Section 2: Method of selection of exposure (or comparison) group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Selection of exposure (and comparison) group. How was selection bias minimised?</td>
</tr>
<tr>
<td>- How was selection bias minimised?</td>
</tr>
<tr>
<td>2.2 Was the selection of explanatory variables based on a sound theoretical basis?</td>
</tr>
<tr>
<td>- How sound was the theoretical basis for selecting the explanatory variables?</td>
</tr>
<tr>
<td>2.3 Was the contamination acceptably low?</td>
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<tr>
<td>- Did any in the comparison group receive the exposure?</td>
</tr>
<tr>
<td>- If so, was it sufficient to cause important bias?</td>
</tr>
<tr>
<td>2.4 How well were likely confounding factors identified and controlled?</td>
</tr>
<tr>
<td>- Were there likely to be other confounding factors not considered or appropriately adjusted for?</td>
</tr>
<tr>
<td>- Was this sufficient to cause important bias?</td>
</tr>
<tr>
<td>2.5 Is the setting applicable to the UK?</td>
</tr>
<tr>
<td>- Did the setting differ significantly from the UK?</td>
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</table>
### Section 3: Outcomes

<table>
<thead>
<tr>
<th>3.1 Were the outcome measures and procedures reliable?</th>
<th>++ + − NR NA</th>
<th>Comments:</th>
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<tbody>
<tr>
<td>Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking −)?</td>
<td>++ + − NR NA</td>
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<tr>
<td>How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)?</td>
<td>++ + − NR NA</td>
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<tr>
<td>Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)?</td>
<td>++ + − NR NA</td>
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<table>
<thead>
<tr>
<th>3.2 Were the outcome measurements complete?</th>
<th>++ + − NR NA</th>
<th>Comments:</th>
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</thead>
<tbody>
<tr>
<td>Were all or most of the study participants who met the defined study outcome definitions likely to have been identified?</td>
<td>++ + − NR NA</td>
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<table>
<thead>
<tr>
<th>3.3 Were all the important outcomes assessed?</th>
<th>++ + − NR NA</th>
<th>Comments:</th>
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</thead>
<tbody>
<tr>
<td>Were all the important benefits and harms assessed?</td>
<td>++ + − NR NA</td>
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<tr>
<td>Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?</td>
<td>++ + − NR NA</td>
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</table>

<table>
<thead>
<tr>
<th>3.4 Was there a similar follow-up time in exposure and comparison groups?</th>
<th>++ + − NR NA</th>
<th>Comments:</th>
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<tbody>
<tr>
<td>If groups are followed for different lengths of time, then more events are likely to occur in the group followed-up for longer distorting the comparison.</td>
<td>++ + − NR NA</td>
<td></td>
</tr>
<tr>
<td>Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).</td>
<td>++ + − NR NA</td>
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</table>

<table>
<thead>
<tr>
<th>3.5 Was follow-up time meaningful?</th>
<th>++ + −</th>
<th>Comments:</th>
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</thead>
<tbody>
<tr>
<td>Was follow-up long enough to assess long-term benefits and harms?</td>
<td>++ + −</td>
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</tr>
<tr>
<td>Was it too long, e.g. participants lost to follow-up?</td>
<td>++ + −</td>
<td></td>
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</tbody>
</table>
### Section 4: Analyses

<table>
<thead>
<tr>
<th>4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?</th>
<th>++</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A power of 0.8 (i.e. it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?</td>
<td>−</td>
<td>NR</td>
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</table>

<table>
<thead>
<tr>
<th>4.2 Were multiple explanatory variables considered in the analyses?</th>
<th>++</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Were there sufficient explanatory variables considered in the analysis?</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.3 Were the analytical methods appropriate?</th>
<th>++</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Were important differences in follow-up time and likely confounders adjusted for?</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.6 Was the precision of association given or calculable? Is association meaningful?</th>
<th>++</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Were confidence intervals or p values for effect estimates given or possible to calculate?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• Were CIs wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?</td>
<td>−</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Section 5: Summary

<table>
<thead>
<tr>
<th>5.1 Are the study results internally valid (i.e. unbiased)?</th>
<th>++</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• How well did the study minimise sources of bias</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>(i.e. adjusting for potential confounders)?</td>
<td>-</td>
<td></td>
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<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Were there significant flaws in the study design?</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.2 Are the findings generalisable to the source population (i.e. externally valid)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there sufficient details given about the study to determine if the findings are generalisable to the source population?</td>
</tr>
<tr>
<td>Consider: participants, interventions and comparisons, outcomes, resource and policy implications.</td>
</tr>
</tbody>
</table>

| ++ | Comments: |
| + |  |
| - |  |