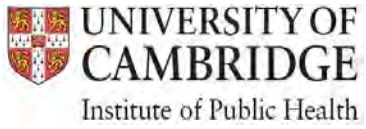



# DISABILITY, DEMENTIA AND FRAILTY IN LATER LIFE: MID-LIFE APPROACHES TO PREVENT OR DELAY THE ONSET OF THESE CONDITIONS

**REVIEW 2** - Behavioural risk factors in mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions

**REPORT (v3)**

**Produced by** Cambridge Institute of Public Health, University of Cambridge

http://www.iph.cam.ac.uk

**Review team** Louise Lafortune*
Sarah Kelly*
Steven Martin
Isla Kuhn
Olivia Remes
Andy Cowan
Carol Brayne

* First co-authorship

**Date** 3rd July 2014

**For further details please contact:**

Dr Louise Lafortune
Senior Research Associate
Institute of Public Health, Forvie Site
University of Cambridge School of Clinical Medicine
Box 113 Cambridge Biomedical Campus
Cambridge, CB2 0SR
ll394@medschl.cam.ac.uk

NICE invitation to tender reference: DDER 42013

# Table of Contents

5. DISCUSSION ..... 13
1. INTRODUCTION ..... 24
1.1 Background ..... 24
1.2 Aims of the review ..... 25
1.3 Research questions ..... 25
1.4 Operational definitions ..... 28
1.5 Equality and equity issues ..... 28
1.6 Review team ..... 29
2. METHODOLOGY ..... 29
2.1 Searches ..... 29
2.2 Population ..... 31
2.3 Behavioural risk factors – scope ..... 31
2.4 Review outcomes ..... 33
2.5. Inclusion criteria – types of studies ..... 33
2.6 Inclusion criteria – Dates of studies to be included ..... 34
2.7 Inclusion criteria – observational studies ..... 34
2.9 Identification of relevant studies ..... 35
2.10 Quality Assessment ..... 36
2.11 Description of overall Quality Ratings ..... 36
2.12 Data extraction ..... 37
2.13 Synthesis of evidence ..... 37
3. FINDINGS ..... 37
3.1 Searches ..... 37
3.2 Characteristics of included studies ..... 39
Table 9. Overview of included studies – Physical activity ..... 40
Table 10. Overview of included studies – Physical Inactivity ..... 66
Table 11. Overview of included studies – Diet and components of diet ..... 67
Table 12. Overview of included studies – Smoking ..... 103
Table 13. Overview of included studies – Smokeless tobacco (snus)* ..... 125
Table 14. Overview of included studies – Alcohol ..... 126
Table 15. Overview of included studies – Weight change/weight cycling* ..... 136
Table 16. Overview of included studies – Combined lifestyles ..... 137
Table 17. Overview of included studies – Leisure/cognitive activity/social networks ..... 139
3.2.1 Quality and applicability of studies ..... 141
3.2.2 Structure of evidence statements ..... 141

3.3 Evidence statements for PHYSICAL ACTIVITY (PA) ..... 141
3.4 Evidence statements for PHYSICAL INACTIVITY/SEDENTARY BEHAVIOUR (IN) 146
3.5 Evidence statements for DIET (DI)..... 148
3.6 Evidence statement for SMOKING (SM) ..... 163
3.7 Evidence statements for ALCOHOL (AL) ..... 170
3.8 Evidence statements for WEIGHT CHANGE, WEIGHT CYCLING (WC)..... 175
3.9 Evidence statements for LEISURE/COGNITIVE ACTIVITY/SOCIAL NETWORKS (LC) ..... 177
3.10 Evidence statements for COMBINED LIFESTYLE (CL) ..... 179
3.11 Evidence statements for SMOKELESS TOBACCO (ST)..... 181
3.12 Evidence statements for DISADVANTAGED GROUPS ..... 182
4. DISCUSSION ..... 185
5. OVERALL SUMMARY AND RECOMMENDATIONS..... 190
6. BIBLIOGRAPHY ..... 192
6.1 Bibliography cited in the report ..... 192
6.2 Bibliography of included studies ..... 193

**Abbreviations**

| | |
|---|---|
| ADL | Activities of Daily Living |
| AL | Alcohol |
| CIPH | Cambridge Institute of Public Health |
| CL | Combined Lifestyles |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPH | Centre for Public Health |
| CPHE | Centre for Public Health Excellence |
| CVD | Cardiovascular disease |
| DG | Disadvantaged Groups |
| DH | Department of Health |
| DI | Diet |
| EC | Eye Care |
| HB | Health Behaviours |
| IADL | Instrumental Activities of Daily Living |
| LC | Leisure and Cognitive activities |
| LGBT | Lesbian, gay, bisexual and transsexual |
| NCCs | Non-communicable Chronic Conditions |
| NICE | National Institute for Health and Care Excellence |
| NIHR SPHR | National Institute of Health Research School of Public Health Research |
| OECD | Organisation for Economic Co-Operation and Development |
| PA | Physical Activity |
| RCT | Randomised controlled trials |
| SES | Socioeconomic status |
| SM | Smoking |
| WC | Weight Change (weight cycling) |
| WCRF | World Cancer Research Fund |
| WHO | World Health Organisation |

**Operational definitions**

| | |
|---|---|
| Successful ageing | Successful ageing is defined as survival to an advanced age while maintaining physical and cognitive function, functional independence and a full and active life. It means that morbidity and disability are compressed into a relatively short period before death, in line with the 'compression of morbidity' theory. |
| Disability | Disability will refer to any long-term restriction on the ability to perform an activity in the manner, or within the range, considered normal. |
| Dementia | Dementia will refer to a progressive, degenerative condition caused by diseases of the brain. Whether it occurs alone, in addition to, or as a combination of, chronic conditions, it is characterised by cognitive and non-cognitive symptoms of variable frequency and severity. |
| Frailty | Frailty will refer to a syndrome characterised by age-related declines in functional reserves where a small insult (e.g. infection, loss of partner) results in a striking and disproportionate change in health state. Frail older adults experience an increased risk of adverse outcomes such as falls, fractures, comorbidity, disability, dependency, hospitalisation, need for long-term care and mortality. |
| Non-communicable chronic conditions | Non-communicable chronic conditions will include cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, obesity, visual and hearing conditions, and some cancers that may be associated with behavioural risk factors. |
| Disadvantaged populations | Disadvantaged populations will include (but are not limited to) low socioeconomic status, ethnic minority groups, lesbians, gay, bisexual and transsexual (LGBT) community groups, travellers and other groups with protected characteristics under the equality and diversity legislation. |

# EXECUTIVE SUMMARY

## 1. INTRODUCTION

### 1.1 Background

The Department of Health (DH) has asked the National Institute for Health and Care Excellence (NICE) to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model will underpin the guidance. The reviews look for evidence on a wide range of potential influences on well-being in later life (i.e. demographic, economic, geographical, physical, cultural and social factors), and at the effectiveness and cost effectiveness of available interventions to act on these factors. This second report presents the findings of the evidence review of behavioural risk factors in mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions.

### 1.2 Aims and review questions

The overarching research question for the suite of three evidence reviews is which primary prevention approaches to be adopted in mid-life are most effective and cost-effective to prevent and delay the onset of disability, dementia, frailty, and other non-communicable chronic conditions in later-life.

The specific question addressed in this review (Review 2) is:

- What behavioural risk factors in mid-life are associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions? How strong are the associations and how does this vary for different subpopulations?

The two other reviews focus on key issues for people in mid-life that prevent or limit, or which help or motivate them to take up and maintain healthy behaviours (Review 1), and the effectiveness and cost effectiveness of mid-life interventions for increasing uptake and maintenance of healthy behaviours, and the extent to which different interventions to foster healthy behaviours prevent or delay ill health in later life (Review 3).

## 2. METHODS

The review reports quantitative evidence from observational studies (longitudinal cohort studies) for behavioural risk factors in mid-life (exposure) that are associated with successful ageing, and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions (outcomes).

Exposures of interest include:

- Behavioural risk factors including less sedentary behaviour, increased physical activity, improved diet, weight loss or control, cessation or reduction of smoking, reduction or modification of alcohol consumption, to maintain sufficient levels of social activity and avoid loneliness, avoidance of excessive exposure to noise and addressing hearing and/or sight loss, or to improve/modify multiple behavioural risk factors and health behaviours in general.
- Behavioural risk factors at individual, family, community, subnational or national level.
- Behavioural risk factors in a range of settings including primary and secondary care, and workplace and community settings in the private, public, voluntary or commercial sectors.

Outcomes of interest include: dementia, disability (activities of daily living (ADL), instrumental activities of daily living (IADL), independence, mobility), frailty, healthy life span and measures healthy ageing, quality of life, participation, non-communicable chronic conditions including cardiovascular diseases and stroke, renal disease, cancer, chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis and bone health.

The population covered by the review includes adults aged 40 to 64 years for the general population, and adults aged 18-39 from disadvantaged populations, with outcomes at follow-up in people aged 55 and over. The review does not cover people with and treated for pre-existing conditions (i.e. dementia, frailty, disability, non-chronic communicable conditions) nor does it cover the treatment (i.e. drugs, dietary supplements), diagnosis and care and management of these conditions.

We conducted a thorough search of the scientific and grey literature to identify studies published in English since 2000 that reported results of multivariate analyses for these associations. A minimum follow-up of five years was required for inclusion (as follow-up of less than five years is unlikely to be sufficient for the development and measurement of dementia, disability, frailty or pre-conditions associated with behavioural risk factors). Cross-sectional and qualitative studies are excluded.

Two reviewers screened the title and abstract of identified references independently. Primary studies that met the inclusion criteria were assessed for quality using available tools from NICE (CPH methods manual).

Quantitative evidence from cohort studies is synthesised descriptively by behavioural risk, for a range of late life outcomes. Data specific to health inequalities and vulnerable communities are assessed and findings are summarised separately where sufficient data is available.

For each key issue or factor of interest an evidence statement was generated which provides an aggregated summary of all of the relevant studies. Applicability ratings (i.e. directly applicable, partially applicable or not applicable) are proposed for each evidence statement to judge how similar the population(s), setting(s), intervention(s) and outcome(s) of the included studies are to those outlined in the review question.

## 3. RESULTS

*Overall findings*

This review includes 164 observational longitudinal cohort studies that have reported on the association between the following behavioural risk factors in midlife:

- Physical activity, physical inactivity
- Diet
- Smoking and smokeless tobacco (snus/snuff)
- Alcohol
- Weight change, weight cycling
- Combinations of lifestyle behaviours (combined lifestyles)
- Leisure, cognitive activity, social networks

and the following categories of outcomes:

- Successful ageing (including quality of life, well-being)
- Dementia
- Disability & frailty
- Overall mortality
- Cardiovascular outcomes (mortality; morbidity)
- Diabetes, metabolic syndrome, insulin sensitivity
- Cancer

- Mental health
- Other non-communicable chronic diseases

Studies reporting other behavioural risk factors (including behaviours related to vision and hearing) were sought but none were found that met the inclusion criteria.

The evidence for this review is reported in 3 tiers of data:

1. Overall summary tables are presented that summarise visually the overall trend of the data – showing whether outcomes are improved, poorer or null (based on statistical significance) for each health behaviour (Tables 1 through 8 below).
2. Summary tables of included studies for each health behaviour with a summary of the characteristics and data for each study and a summary of outcomes (Tables 9 through 17). Data presented in the tables is only from multivariate models. Where the authors report findings for multiple models, the most adjusted (or most relevant) model has been used in the summary tables and the evidence statements. Where a paper reports the same outcome at different timepoints that paper has not been excluded, the data at different timepoints has been reported but it has been pointed out in the evidence statements. It only applies to a few studies.
3. Full evidence tables (Appendix A) that show the full extracted data for each included study.

Overall, the quality of studies is good (most studies were rated as high or moderate quality) and most of them are directly or partially applicable to the UK context. Studies conducted in the UK were prioritised in the synthesis of data and the evidence and applicability statements.

**EVIDENCE STATEMENTS (see page 141 onwards)**

## 4. OVERALL SUMMARY

*Supported by summary tables 1 through 8, below.*

### Physical activity (PA)

For PA and inactivity, 45 reports were included. The available data covers different levels and intensity of PA and a few studies report specific types of activity (e.g. walking, active commuting). There is consistent evidence that midlife physical activity has a beneficial effect

on later life healthy ageing, dementia, disability and other chronic disease outcomes. One study (out of 45 studies) reported a negative outcome, i.e. increased risk of bladder cancer in men participating in vigorous activity at midlife. Beneficial effects were reported for both men and women.

The promotion of physical activity in all midlife populations including men and women and different ethnic groups should be addressed by the guidance. All types of activity appear to have a positive relationship with outcomes.

**Diet (DI)**

For diet, 48 studies were included. Evidence was found covering midlife dietary patterns and consumption of dietary components, such macronutrients and for specific foods. There is some consistent evidence (but from a limited number of studies) that a healthy diet in general (studies included e.g. ADA diets) or Mediterranean diet, and fruit and vegetables have beneficial effects on late life outcomes. There is also consistent evidence (again from a limited number of studies) that higher consumption of saturated fat or processed and red meat (reported together) in midlife is associated with poorer ageing, disability, dementia, frailty outcomes and non-communicable conditions. There was some evidence (from a limited number of studies) that coffee consumption in moderation may be beneficial.

A healthy diet (standard guidelines) or Mediterranean-type diet could be recommended, also diets which minimise consumption of saturated fat, increase fruit and vegetable intake with moderate consumption of processed or red meat. Coffee consumption in moderation.

**Alcohol (AL)**

Twenty-four prospective cohort studies were included on alcohol intake. Evidence specific to midlife alcohol consumption was mixed. Some studies reported negative outcomes e.g. for dementia, mortality and cancer and some more positive outcomes e.g. for ageing and mental health. However studies found were sparsely distributed among different outcomes. Two studies reported moderate quality evidence of higher risk of dementia in non-drinkers and heavy drinkers compared to moderate drinkers, but limited evidence was available specific to midlife. There was limited evidence, from one study, that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance in later life.

It is not clear from the findings of this review whether there is a safe level of alcohol consumption, so caution should be exercised in making recommendations in that respect.

**Smoking (SM)**

The review found a wealth of evidence from longitudinal cohort studies (n=57) relating to the association between midlife smoking and late life outcomes. There is consistent evidence that midlife smoking has a detrimental effect on later life dementia, disability and other chronic disease outcomes including: healthy ageing, mobility, dementia, CVD outcomes, cancer (lung, pancreatic, colorectal, cancer mortality) and total mortality. Smoking had a detrimental effect on all populations for which studies were found, including men and women and in different ethnic groups.

**Smokeless tobacco (SNUS)**

Only one study was found which suggested that smokeless tobacco may be associated with improved diabetes related outcomes but evidence for midlife relationship with later outcomes was very limited.

**Weight change, weight cycling (WC)**

Four studies were included that reported an association between weight change patterns in midlife and later outcomes. One study reported increased risk of hip fracture in those losing greater than 10% of their body weight (as determined from maximum weight during follow up). Two studies reported null relationships with weight loss/gain or cycling, one with mortality as an outcome and one with diabetes as an outcome. One study reported increased risk of dementia with weight change in midlife (independent of the direction of weight change). There was some limited evidence that being overweight or obese appeared to be a more important factor in the association with diabetes than weight change in midlife.

**Combined healthy lifestyle programmes (CL)**

There is some consistent evidence (from 3 studies) that combinations of lifestyle behaviours (not smoking, fruit and veg intake, maintaining healthy weight, regular exercise, moderate alcohol intake) have beneficial outcomes for ageing well, disability, dementia, frailty outcomes and non-communicable conditions.

Consideration could be given to programmes which combine at least two or more aspects of healthy behaviour (from PA, healthy diet, non-smoking, alcohol in moderation, leisure activities)

**Leisure activities/social activities**

There is some evidence that those who participate in a diverse range of intellectual, passive, physical and leisure activities in midlife have better cognitive outcomes, however the number of studies specific to midlife with later life outcomes was limited and activities varied across studies. There was insufficient consistent data in midlife to determine if the relationship was causal or related to baseline cognitive ability.

Consideration could be given to improving social support and access to activities. This could be incorporated into healthy lifestyle programmes (with evaluation to build the evidence base).

**Other health-related behaviours**

Evidence was sought but not found within the inclusion criteria for other behaviours including vision and hearing related behaviours.

**Disadvantaged groups/health inequalities**

Data relating to disadvantaged groups was also limited with some sparse data on people with low SES, ethnic minority groups and gender in midlife with relevant outcomes. This data is summarised above for each health behaviour. No relevant data was found for other groups covered by the equality and diversity legislation.

## 5. DISCUSSION

This review aimed to identify if there were any specific issues or behavioural risk factors at midlife that should be considered by the PHAC team when designing the guidance. It synthesises the evidence from observational studies (longitudinal cohort studies) for the association between modifiable behavioural risk factors in midlife (age 40-65 years) and dementia, disability and frailty, and non-communicable conditions in later life (age >65 years).

Included studies reported follow up from 5 years to 36 years. Most of the data used to assess behaviour was self-reported with little objective data, although many of the smoking studies used biochemical confirmation of smoking status. In general outcome data was assessed objectively using clinical data and medical records or registers. Included studies were mainly from OECD countries and most were from Europe and the US with a fairly good representation of studies from the UK.

Limitations & gaps in evidence - Limited evidence was found specifically relating to midlife behaviours for leisure activities including cognitive activities and social networks, weight change and weight cycling, smokeless tobacco, and sight and hearing risks. While many diet-related studies were found they covered a broad range of diets and dietary components. There were some diets or dietary components for which studies specifically pertaining to midlife were not found. Data relating to disadvantaged groups was also limited. Some sparse data on people with low SES, ethnic minority groups and gender in midlife was found. No longitudinal data was found relevant to other groups covered by the equality and diversity legislation such as LGBT groups or travellers.

Limitation of the review - The remit of this review was specifically to identify midlife behavioural risk factors for dementia, disability, frailty outcomes and common NCCs in later life. Determinants of these outcomes over the whole lifecourse were not included. Also, the review only includes longitudinal observational studies, which can show an association between midlife risk factors and later life outcomes, but not causality.

Due to the wide scope of the review, the large amount of literature covering behavioural risk factors and the outcomes of interest, and the timescales for the review, the searches were focused on studies with midlife-related terms in the title, abstract or related MeSH indexing to identify those studies that specifically aimed to report on midlife exposure. The implication of this pragmatic approach is that cohort studies that have followed individuals from mid- to late life and reported associations of interest without specifying midlife terms in the title or abstract were not identified by the searches. This might explain some of the gaps in evidence and further work is ongoing (though beyond the scope of this report) to address this limitation.

Because a very large amount of data was found for a wide range of risks and outcomes, the search limitations are unlikely to have an impact on the overall findings. In fact, it appears that a lot of what we know of the associations between behavioural risk factors and late life outcomes comes from studies conducted in people in mid-life. So, where caution should be exercised is in extrapolating the mid-life associations to older age groups – the direction and magnitude of these associations vary across the life cycle. This is the focus of several work packages undertaken by NIHR SPHR Ageing Well programme, which should complement the findings of this review with regards to identifying behavioural risk factors that are amenable to change for improved health outcomes in later life.

**Table 1. Overall summary of studies of PHYSICAL ACTIVITY/INACTIVITY and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.3.1PA** | **2.3.2PA** | **2.3.3PA** | **2.3.4PA** | **2.3.5PA** | **2.3.6PA** | **2.3.7PA** | | **2.3.8PA** |
| √√√<br>[+][++][++]<br>UK,UK,US | √√√√√ 0<br>[+][+][-][+][-] [+]<br>UK,It,Ice,Fin,US, Fin | (√√)(√√)√√ 00<br>([+])([+])[+][-] [++][-]<br>UK,Swe,US,Ice, Swe, US<br>(2 light but not heavy √) | (√√)√√√<br>([+])[+][+][+]<br>UK,Fin,Den,Ger | (√√)(√√√)√√√√<br>([+])([+])[+][+][++][+]<br>UK,Fin,Swe,Ger,Gre,Den | √√ (√√√)<br>[+]([+])<br>UK,Nor | 0(√0X)0√<br>[+]([+])[+][+]<br>UK,UK,UK,Fin<br>X=increased risk of bladder cancer/vig act (OR= 2.1 (95%CI 1.1-4.0) | | √ 0<br>(5 y not 10y)<br>[+][-]<br>UK,Aust |
| **Physical inactivity** | | | | | | | | |
| | 0<br>[-]<br>Den | | 0<br>[+]<br>Fin | (X0)<br>[+]<br>Fin | | | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**Table 2. Overall summary of studies of DIET (DI) and dietary component***

| Evidence statement ref. | Diet or components of diet | Successful ageing | Disability & frailty | Dementia | Total mortality | CVD outcomes | Diabetes (MetS) | Cancer | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|---|---|
| **2.5.1DI** | Healthy dietary pattern | √√ | √ | | | | √ | 0 | | √ |
| **2.5.1DI** | Mediterranean diet | √ | | | | √√ | | | | √ |
| **2.5.1DI** | Western diet | X | | | | | | | | |
| **2.5.2DI** | Fruit and vegetables | | √<br>0 0 | √<br>0 | √√<br>0 | √<br>0 | 0 | 0 0 | √ | |
| **2.5.3DI** | Fat (saturated) | | X | X | | 0 | X | | | |
| **2.5.3DI** | Fat (polyunsaturated) | | | √ | | 0 | | | | |
| **2.5.3DI** | Fat (monounsat) | | | | | 0 | | | | |
| **2.5.3DI** | Fat (total) | | | | | 0 | | X | | |
| **2.5.4DI** | Fish | | | | X | √<br>0 | √ women<br>0 men | | √ | |
| **2.5.5DI** | Meat | | √ (>1 per 2 d) | | | √ (1-2/wk) | | | | |
| **2.5.5DI** | Red and processed meat | | | | | X | X | X X | | |
| **2.5.6DI** | Coffee | | 0 | √<br>0 | | X (heavy) | √√ | | √√ | 0 |
| **2.5.6DI** | Tea | | | | | | | | √ | 0 |
| **2.5.6DI** | Caffeine | | | | | | | | √ | 0 |
| **2.5.7DI** | Milk | | | | | | | √ | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **2.5.8DI** | Salt | | | | | | | X | | |
| **2.5.9DI** | Glycaemic index/GL | | | | | √0 | | | | |
| **2.5.10DI** | Protein | | | | | 0 | | 0 | | |
| **2.5.11DI** | Chocolate | | | | | √ (1-3 times/month only) | | | | |
| **2.5.12DI** | Fibre | | | | | | | 0 | | |
| **2.5.13DI** | Micronutrients | | | 0 | | | | √ | | 0 |
| **2.5.13DI** | Flavonoids | | | 0 | | √ | | 0 | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

**Table 3. Overall summary of studies of SMOKING (SM) and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.6.1SM** | **2.6.2SM** | **2.6.3SM** | **2.6.4SM** | **2.6.5SM** | **2.6.6SM** | **2.6.7SM** | **2.6.9SM** | **2.6.8SM** |
| XXX | XX (mobility)<br>0X0X (fract) | XXXXXX (dementia)<br>00XXX (cognition) | X(XXX)XXX<br>√√√√√√<br>(Ex-smokers) | XXXXXX0 (mortality)<br>XXXXXXXXXXX0 (CVD) | XXX0 (Dia)<br>X0 (MetS) | XXXXXX<br>(lung, pancreatic,colorectal,cancer) | X (kidney disease)<br>0 (ex smoker) | No studies |
| All [+] | [+][-] (mobility)<br>All [+] (fracture) | All [+] | All [+] | All [+] (mortality)<br>3[++] 9[+] (CVD) | All [+] | All [+] | [+] | |
| UK,Fin,US | Swe,US<br>Swe,Swe,UK,Aust | US,US,US,Kor,US,US<br>Us,Nor, UK,UK,NL | UK,3Fin,Jp,Sing, Is | US,Cz,Jp,Jp,Is,SingCh<br>UK,UK,Jp,Jp,Swe,Jp,Swe,Swe,US,US,Swe | UK,Fin,Jp,Nor | UK,UK,Jp,Jp,Jp,Sing | Jp | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**Review 4. Overall summary of studies of ALCOHOL (AL) and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events & mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.7.1AL** | **2.7.2AL** | **2.7.3AL** | **2.7.4AL** | **2.7.5AL** | **2.7.6AL** | **2.7.7AL** | **2.7.8AL** | **2.7.9AL** |
| √X | X (ADL)<br>0X (fract) | X0<br>(dementia APOE4)<br><br>0<br>(cognition)<br><br>XX<br>(Abstainers (compared to mod or infreq)<br><br>XXX<br>Heavy drinkers (APOE4 compared to non-drinkers) | X | 000<br><br>XX<br>(Heavy cf occasional)<br><br>√<br>(Reg cf occasional) | X<br>(Diabetes - mod or high)<br><br>X0√<br>(MetS) | 000X | 0 (COPD) | √ |
| [++][+] | [-]<br>[+][+] | All[+][ | [++] | [+][++][+]<br>[++][+]<br>[+] | [+]<br>[+][+][+] | [+][+][++][+] | [-] | [-] |
| US, US | US<br>Swe, UK | Fin, UK<br>FR<br>Fin,UK<br>Fin,Fr,Fin | UK | UK, Ch, NL<br>UK, Jp<br>UK | Jp<br>UK,UK,US | UK,UK,US,Jp | Europe | Aust |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**Table 5. Overall summary of studies of WEIGHT CHANGE/CYCLING (WC) and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.8.1WC** | **2.8.2WC** | **2.8.3WC** | **2.8.4WC** | **2.8.5WC** | **2.8.6WC** | **2.8.7WC** | **2.8.8WC** | **2.8.9WC** |
| | Weight loss of > 10% from max<br><br>X (hip fracture)<br><br>[+]<br><br>US | Weight variability<br><br>X<br><br>[+]<br><br>Israel | Weight cycling<br><br>0<br><br>[+]<br><br>US | | Weight cycling when OW at midlife<br><br>X<br><br>[++]<br><br>US | | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**TABLE 6. Overall summary of studies of ACTIVITIES (LC) and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.9.1LC** | **2.9.2LC** | **2.9.3LC** | **2.9.4LC** | **2.9.5LC** | **2.9.6LC** | **2.9.7LC** | **2.9.8LC** | **2.9.9LC** |
| 0<br>[+]<br>UK | 0<br>[-]<br>Swe | √ (dementia)<br>√√√ (cognition)<br>[-]<br>[++][++][++]<br>US<br>Aust, US, Swe | | | | | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**TABLE 7. Overall summary of studies of COMBINED HEALTHY LIFESTYLE (CL) and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.10.1CL** | **2.10.2CL** | **2.10.3CL** | **2.10.4CL** | **2.10.5CL** | **2.10.6CL** | **2.10.7CL** | **2.10.8CL** | **2.10.9CL** |
| | | √0 (cog)<br>[++][+]<br>US, UK | √ √<br>[++][+]<br>US, UK<br>(no of healthy behaviours) | √0<br>[++][+]<br>US, UK<br>(no of healthy behaviours) | 0<br>[+]<br>UK | 0<br>[+]<br>UK | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

**TABLE 8. Overall summary of studies of SMOKELESS TOBACCO and dementia, disability, frailty, chronic disease***

| Successful ageing | Disability and frailty | Dementia | Total mortality | CVD outcomes (events and mortality) | Diabetes (MetS) | Cancer (and cancer mortality) | Other chronic diseases | Mental health |
|---|---|---|---|---|---|---|---|---|
| **2.11ST** | | | | | **2.11.1ST** | | | |
| | | | | | √ (insulin, weight)<br><br>[+]<br><br>Swe | | | |

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

# 1. INTRODUCTION

## 1.1 Background

Non-communicable chronic conditions and disability in later life are heavily influenced by behaviours across the life course, which in turn are influenced by a variety of wider contextual social, economic, and organisational factors (Kuh 2002; Clegg 2013). Although these outcomes manifest themselves in later life, the processes leading to ill health have been shown to start in mid-life (Newman et al. 2011; Singh-Manoux et al. 2011; Wills et al. 2011). The four main behavioural risk factors[1], i.e. smoking, excessive consumption of alcohol, poor diet and low levels of physical activity, contribute to close to half of the burden of illness in developed countries (WHO 2002). And it is well known that these risks, which tend to co-occur or cluster, are unequally distributed in the population.

It is encouraging that European and UK specific epidemiology data over the last two decades show that it is possible to prevent or delay morbidity and mortality related to behavioural risk factors (Barnes and Yaffe 2011). Data also shows that people who adopt healthy behaviours are more likely to age successfully and have improved quality of life (Khaw et al. 2008; Myint et al. 2011; Sabia et al. 2012). However, finding effective ways to change people's behaviours is a challenging task without a good understanding as to why people engage in unhealthy behaviours, or do not undertake unhealthy ones.

Although many good systematic reviews have looked at the links between specific and multiple behavioural risk factors and individual chronic conditions, evidence on the association between these behaviours in *mid-life* across a range of late life outcomes and for subgroups of the population has yet to be comprehensively assessed. That is particularly true for the relationship between behavioural risk factors and frailty, where the operational definition of this complex syndrome is still controversial; and for dementia where the many unknowns about the natural history of the disease make the development of effective preventive interventions even more challenging. A good understanding of cultural, ethnic, and geographic differences in how people view and interpret health risks and health behaviours is also necessary for these interventions to work.

[1]The collective term for these risk factors is the subject of much debate, with people from different fields preferring different terminology, each having a view about what is pejorative and what is not. Phrases used range from 'unhealthy or healthy behaviours' and 'poor health behaviours', health promoting behaviours, 'lifestyle risks', behavioural risk factors. We will use the terms healthy behaviours and behavioural risk factors interchangeably in this report.

In that context, the Department of Health (DH) has asked National Institute for Health and Care Excellence (NICE) to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model underpin the guidance. The reviews looked for evidence on a wide range of potential influences on well-being in later life (i.e. demographic, economic, geographical, physical, cultural and social factors), and at the effectiveness and cost effectiveness of available interventions to act on these factors. This second report presents the findings of the evidence review of behavioural risk factors in mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions.

### 1.2 Aims of the review

This review is the second of three to be conducted to inform the guidance on which primary prevention behaviours to be adopted in mid-life are most effective and cost-effective to prevent and delay the onset of disability, dementia, frailty in later life. The full scope of the guidance is available in the final scope document (Final Scope, NICE 2013) that incorporates stakeholder comments from a 4-week public consultation (21 March to 18 April 2013).

### 1.3 Research questions

The specific question addressed in this review (Review 2) is:

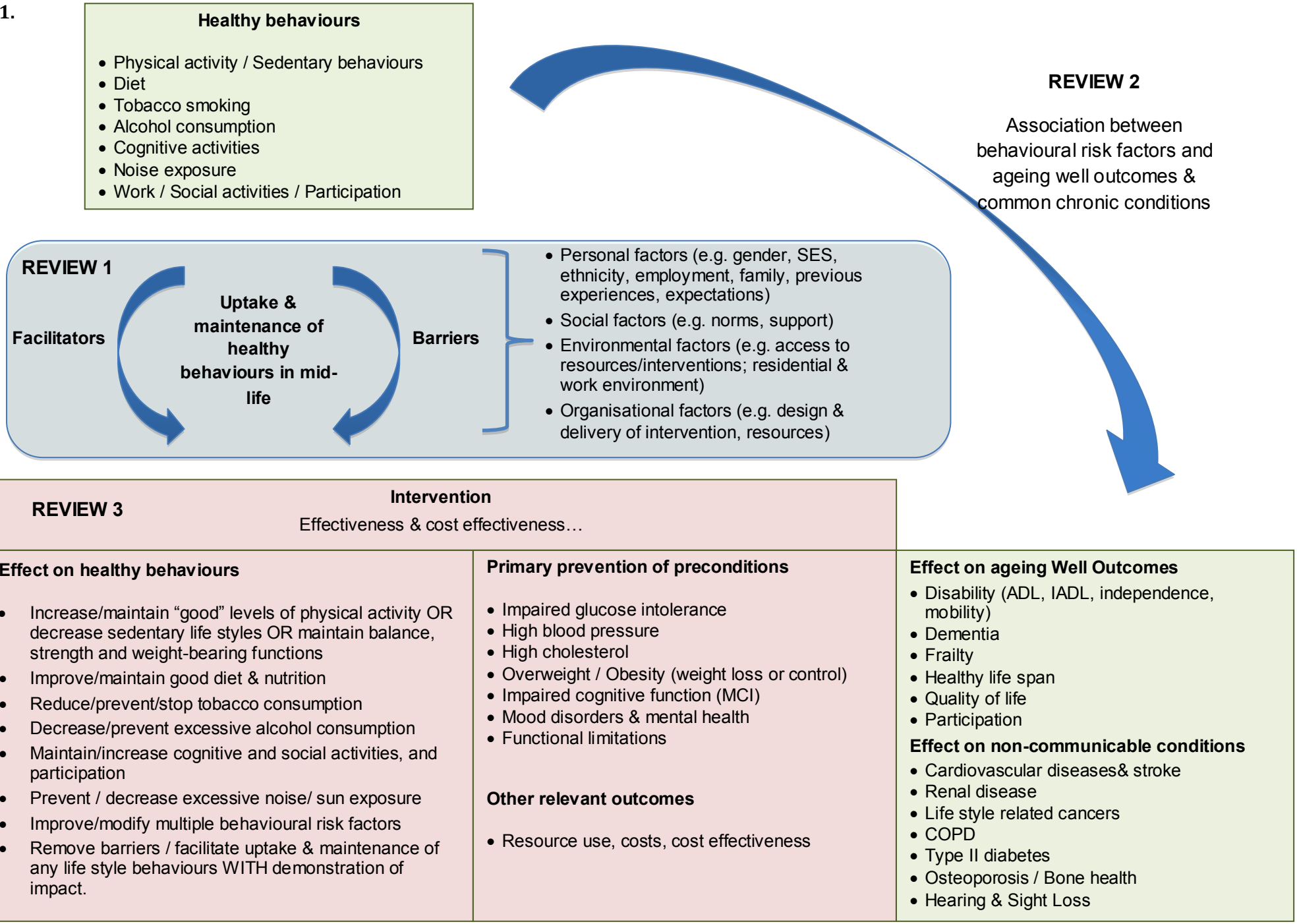
- What behavioural risk factors in mid-life are associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions? How strong are the associations and how does this vary for different subpopulations?

The two other evidence reviews (presented separately) address the following questions:

- Review 1: What are the key issues for people in mid-life that prevent or limit, or which help or motivate them to take up and maintain healthy behaviours, and to what extent do they have an effect? How does this differ for subpopulations, for example by ethnicity, socioeconomic status or gender?
- Review 3: What are the most effective and cost-effective mid-life interventions for increasing the uptake and maintenance of healthy behaviours? To what extent do the different health behaviours prevent or delay disability and frailty related to modifiable behavioural risk factors? To what extent do the different health behaviours prevent or delay dementia? To what extent do the different health behaviours prevent or delay non-communicable chronic conditions?

A conceptual overview of the three reviews and how Review 2 fits into the overall scheme is presented in Figure 1. The model details behavioural risk factors in mid-life, interventions to improve or maintain healthy behaviours, intermediate biological risk factors that can be influenced by healthy behaviours and preventable outcomes relating to dementia, disability, frailty or non-communicable chronic conditions in later life. The model was used to inform the searches and selection of studies for the review.

**Figure 1.**


Healthy behaviours
Physical activity / Sedentary behaviours
Diet
Tobacco smoking
Alcohol consumption
Cognitive activities
Noise exposure
Work / Social activities / Participation
REVIEW 2
Association between behavioural risk factors and ageing well outcomes & common chronic conditions
REVIEW 1
Facilitators
Uptake & maintenance of healthy behaviours in mid-life
Barriers
Personal factors (e.g. gender, SES, ethnicity, employment, family, previous experiences, expectations)
Social factors (e.g. norms, support)
Environmental factors (e.g. access to resources/interventions; residential & work environment)
Organisational factors (e.g. design & delivery of intervention, resources)
REVIEW 3
Intervention
Effectiveness & cost effectiveness…
Effect on healthy behaviours
Increase/maintain "good" levels of physical activity OR decrease sedentary life styles OR maintain balance, strength and weight-bearing functions
Improve/maintain good diet & nutrition
Reduce/prevent/stop tobacco consumption
Decrease/prevent excessive alcohol consumption
Maintain/increase cognitive and social activities, and participation
Prevent / decrease excessive noise/ sun exposure
Improve/modify multiple behavioural risk factors
Remove barriers / facilitate uptake & maintenance of any life style behaviours WITH demonstration of impact.
Primary prevention of preconditions
Impaired glucose intolerance
High blood pressure
High cholesterol
Overweight / Obesity (weight loss or control)
Impaired cognitive function (MCI)
Mood disorders & mental health
Functional limitations
Other relevant outcomes
Resource use, costs, cost effectiveness
Effect on ageing Well Outcomes
Disability (ADL, IADL, independence, mobility)
Dementia
Frailty
Healthy life span
Quality of life
Participation
Effect on non-communicable conditions
Cardiovascular diseases& stroke
Renal disease
Life style related cancers
COPD
Type II diabetes
Osteoporosis / Bone health
Hearing & Sight Loss

### 1.4 Operational definitions

- Successful ageing is defined as survival to an advanced age while maintaining physical and cognitive function, functional independence and a full and active life. It means that morbidity and disability are compressed into a relatively short period before death, in line with the 'compression of morbidity' theory (Fries 2011).
- Disability will refer to any long-term restriction on the ability to perform an activity in the manner, or within the range, considered normal.
- Dementia will refer to a progressive, degenerative condition caused by diseases of the brain. Whether it occurs alone, in addition to, or as a combination of, chronic conditions, it is characterised by cognitive and non-cognitive symptoms of variable frequency and severity.
- Frailty will refer to a syndrome characterised by age-related declines in functional reserves where a small insult (e.g. infection, loss of partner) results in a striking and disproportionate change in health state. Frail older adults experience an increased risk of adverse outcomes such as falls, fractures, comorbidity, disability, dependency, hospitalisation, need for long-term care and mortality (Clegg 2013).
- Non-communicable chronic conditions (NCCs) will include cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, obesity, visual and hearing conditions, and some cancers that may be associated with behavioural risk factors.
- Disadvantaged populations will include (but are not limited to) low socioeconomic status, ethnic minority groups, lesbians, gay, bisexual and transsexual (LGBT) community groups, travellers and other groups with protected characteristics under the equality and diversity legislation.

### 1.5 Equality and equity issues

A core aim of this programme of evidence review is to identify prevention approaches that are tailored to mid-life populations, focusing on those that have the greatest potential to maintain well-being in later life and avoid or reduce inequalities. The reviews synthese and highlight the evidence pertaining to groups or subgroups of the population that are at increased risk of ill health or less likely to benefit from preventive interventions because of biological, psychosocial factors, environmental factors – or a combination thereof (Ben-Shlomo 2003).

It is hoped that the combined outputs will summarise an evidence base that address key areas of concern for government and society – how to optimise health and well-being, and reduce inequalities in our ageing societies; how to tackle at a population level increasing

health and social care demand; and how to change policy and practice through better use of research.

### 1.6 Review team

The expertise of the review team and the role of each member in the review are presented in Appendix D.

## 2. METHODOLOGY

### 2.1 Searches

An iterative approach involving the whole team was undertaken to develop the search strategies. The key steps were:

a) Initial team discussions around research questions.
b) Initial drafting of search building at least (but not exclusively) on the final scope for this guidance, comments received from key stakeholders on the draft scope, high quality peer-review systematic reviews (when available) on same or similar topics for each key domains of the strategy, (e.g. health, preventative interventions, behaviours, etc.);
c) Testing of individual components and development of the review specific strategies in key databases;
d) Refining of specific review strategies upon discussion with information specialist;
e) Updating of search strategies based on reviewers comments;
f) Adaptation of strategies to individual databases (i.e. Mesh terms or filters in one database don't usually apply to other databases);
g) Running of search and uploading of references in individual Endnote data bases (for specified time period, i.e. since 2000);
h) Create a combined Endnote database (master file); delete duplicate and prepare for title screening;
i) Identification of potential included studies; selection of full text for further assessment; identification of included and excluded studies.

Searching was conducted in two stages: 1) searching for primary longitudinal cohort studies using an observational study search filter agreed with CPH), and 2) where there are no primary studies covering a topic or area, targeted searches were conducted for relevant systematic reviews in adults in general as appropriate, using a systematic review search filter agreed with CPH.

We searched the following electronic databases for peer-reviewed studies published since year 2000 (with host platform):

- MEDLINE (including MEDLINE – in-process) (Ovid)
- EMBASE (Ovid)
- PsycINFO (Ovid)
- CINAHL (EBSCO host)
- Health Management Information Consortium (Ovid)
- Social Science Citation Index (Web of Knowledge)

The following additional databases were searched for systematic reviews published since year 2000:

- HTA database
- The Cochrane Collaboration databases (www.thecochranelibrary.com)
    - Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness

Searches were restricted to publications in English language. The detailed search strategies used to identify primary studies and systematic reviews are presented in Appendix E.

Finally, we conducted a thorough grey literature search (simultaneously for all three reviews) to identify publications that may provide a source of relevant data. The websites searched are:

- NHS Evidence Search (www.evidence.nhs.uk)
- Open Grey (www.opengrey.eu)
- Public Health Observatories (www.apho.org.uk)
- Health Evidence Canada (www.healthevidence.org)
  Alzheimer's Society (www.alzheimers.org.uk)
- RNIB (www.fightforsight.org.uk)
- Fight for Sight (www.fightforsight.org.uk)
- Action on Hearing Loss (www.actiononhearingloss.org.uk)
- Beth Johnson Foundation (www.bjf.org.uk)
- British Library (http://www.bl.uk)
- Campbell Collaboration (http://www.campbellcollaboration.org)
- Department of Health (https://www.gov.uk/government/publications)
- E-Print Network (http://www.osti.gov/eprints/)
- Google Scholar (http://scholar.google.co.uk)
- Grey Literature Report (http://www.greylit.org)

- Lenus (http://www.lenus.ie/hse/)
- OAlster (http://www.oclc.org)
- Public Health Europe (http://ec.europa.eu/health/index_en.htm)
- RAND Health (http://www.rand.org/health.html)
- Scirus (http://www.scirus.com)
- World Health Organisation (http://www.who.int/en/)

We did not conduct additional hand searches nor did we contact authors for additional data. However, the publication list of the Behaviour and Health Research Unit at the University of Cambridge (led by Professor Theresa Marteau) was searched for relevant publications as well as the responses to the NICE call for evidence relating to this guidance conducted between 31/5/2013 and 28/6/2013.

Records retrieved from the searches are reported according to Appendix C of the CPHE methods manual in Appendix F.

### 2.2 Population

The populations covered by this review include:

- Adults aged 40-64 years, with a particular focus on people at increased risk of disability, dementia, frailty, or other non-communicable chronic conditions (NCCs) due to behavioural risk factors.
- Adults aged 39 and younger from disadvantaged populations (as they are at increased risk of ill health and more likely to develop multiple morbidities). Disadvantaged populations include (but is not limited to) low socioeconomic status; ethnic minority groups; lesbian, gay, bisexual, transsexual (LGBT) groups; travellers, and other groups with protected characteristics under the equality and diversity legislation.

This review does not cover the following populations:

- Adults with any type of dementia or pre-existing cognitive impairments in mid-life.
- Adults who are receiving treatment for a non-communicable chronic condition.
- Adults who have a disability associated with behavioural risk factors will not be included for that particular condition or disability.

### 2.3 Behavioural risk factors – scope

This review focuses on:

- Behavioural risk factors for people in mid-life (aged 40 to 64) that are associated with successful ageing or the development and progression of: disability, dementia, frailty

(including bone health) and common NCCs in older age (age 55 and over). Examples of the latter include cardiovascular diseases and stroke, type 2 diabetes, chronic obstructive pulmonary disease, renal disease, osteoporosis and bone health, visual and hearing conditions and some cancers that may be associated with lifestyle (these may be defined by the types of studies found).

- Behavioural risk factors for younger adults (aged 18 to 39) from disadvantaged populations (as defined in section 2.2) that are associated with successful ageing or the development and progression of: disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in older age (age 55 and over). As disability, frailty and common non-communicable chronic conditions may present earlier in people from disadvantaged populations, outcomes for this group would not be restricted to those in people aged 55 and over.

- Behavioural risk factors by people in mid-life (aged 40 to 64) that are associated with the development and progression of 'preconditions' for disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in later life (age 55 and over). Such preconditions include high blood pressure, impaired glucose intolerance, high cholesterol, overweight/obesity, impaired cognitive function, mood disorders, and functional limitations.

- Behavioural risk factors for younger adults (aged 18 to 39) from disadvantaged populations (as defined in section 2.2) that are associated with the development and progression of preconditions for disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in later life.

The scope of the review includes:

- Behavioural risk factors including less sedentary behaviour, increased physical activity, improved diet or components of diet (e.g. fat intake, fruit and vegetable intake), weight loss or control, cessation or reduction of smoking, reduction or modification of alcohol consumption, to maintain sufficient levels of social activity and avoid loneliness, avoidance of excessive exposure to noise and addressing hearing and/or sight loss, or to improve/modify multiple behavioural risk factors and health behaviours in general.
- Behavioural risk factors at individual, family, community, subnational or national level (these may be targeted at specific groups, particularly those who are at increased risk, or who are from disadvantaged groups, or at healthcare professionals).

- Behavioural risk factors in a range of settings including primary and secondary care, and workplace and community settings in the private, public, voluntary or commercial sectors.

Associations between health-related behaviours in mid-life and ageing well outcomes and NCCs, and between health-related behaviours and 'preconditions' such as overweight or obesity, or hypertension or raised cholesterol are covered by the scope of the review and the guidance. However, associations in people with existing dementia, disability, frailty or NCCs fall outside the scope of this review and the guidance. Associations between preconditions and dementia, disability, frailty or NCCs also fall outside the scope of this review.

Finally, the scope of the review does not cover:

a. Use of drugs to prevent or treat dementia and non-communicable chronic conditions;
b. Use of dietary supplements;
c. Diagnosis and care of disability, dementia, frailty and common non-communicable chronic conditions;
d. Management of existing disability, dementia, frailty and common non-communicable chronic conditions;
e. Recreational drug use;
f. Management of obesity, including medical and surgical interventions for obesity;
g. Organisational interventions, policies and laws.

### 2.4 Review outcomes

Evidence for behavioural risk factors in mid-life that are associated with successful ageing, and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions, namely quantitative evidence of associations.

These quantitative outcomes include the extent of the association between the type, level and amount of behavioural risk factor and ageing well or morbid outcomes including dementia, disability, frailty and NCCs.

### 2.5. Inclusion criteria – types of studies

a) The first tier of evidence for this review include primary longitudinal cohort studies that provide information on the association between behavioural risk factors at mid-life and ageing well or morbid outcomes including disability, dementia, frailty, and NCCs.

Only cohort studies that have conducted multivariate analyses are included in this review. Studies that conducted only univariate analysis are excluded.

Cross-sectional studies are excluded from the review as they would only show a cross-sectional association, and would not provide information on the impact of behavioural risk factors in later life. Any cross-sectional analyses reported in studies in addition to longitudinal analyses are excluded also.

Qualitative studies are excluded from the review, as they would not provide any quantitative evidence of an association between behavioural risk factors and ageing well or morbid outcomes in later life.

Abstracts, letters and editorials are excluded. Theses are excluded, although we sought relevant published peer-reviewed papers based on thesis data. Where found theses were included if they meet the inclusion criteria for the review.

b) The protocol stated that where no primary longitudinal cohort studies in mid-life populations are found to cover a potentially relevant topic or area of interest, systematic reviews or meta-analyses of quantitative longitudinal observational studies in adult populations in general were to be searched for and included if appropriate. We did not conduct specific searches of systematic reviews (because coverage from primary studies was deemed sufficient) but we did assess the systematic reviews identified in the primary searches and those identified through Review 1. In the end, no systematic reviews were included.

### 2.6 Inclusion criteria – Dates of studies to be included

Systematic reviews and primary studies published from year 2000 onwards.

### 2.7 Inclusion criteria – observational studies

For the purposes of this review, we included longitudinal cohort studies.

Population:

Studies in adults at mid-life (aged 40 to 64 years for the general population) with outcomes at follow-up in people aged 55 and over. A younger age cut point (i.e. 55 years as opposed to 60 or 65 years) was selected with recognition of the fact that disease processes can be accelerated in disadvantaged populations.

Studies in adults from disadvantaged populations (as defined in section 2.2) aged 18-39 with outcomes at follow-up in later life, even if not in people aged 55 and over.

Studies would not be excluded on basis of country of origin, however, where the study was conducted was considered in the applicability ratings.

Exposure:

Behavioural risk factors in the populations described above including (but not limited to) increase/maintain physical activity or decrease sedentary lifestyles; maintain balance, strength and weight-bearing functions; improve/maintain good diet (or components of diet) and nutrition; smoking cessation or reduction or prevention of smoking; decrease/moderate alcohol consumption or prevent excessive consumption; improve/modify multiple behavioural risk factors; healthy behaviours in general, increase/maintain social activity or prevent loneliness; increase or maintain/address management of sight loss or hearing loss, body weight, avoid excessive exposure to noise.

Outcomes**:** Dementia, disability (activities of daily living (ADL), instrumental activities of daily living (IADL), independence, mobility), frailty, healthy life span, quality of life, participation, NCCs including cardiovascular diseases and stroke, renal disease, cancer, chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis and bone health.

Timescale: Follow-up of 5 years or over (follow-up of less than 5 years is unlikely to be sufficient for the development and measurement of dementia, disability, frailty or pre-conditions associated with behavioural risk factors)

Language: English language studies only.

### 2.8 Inclusion criteria – systematic reviews

Population, exposure and outcomes to be included as for observational studies (section 2.7).

Systematic reviews or meta-analyses of longitudinal cohort studies in adults that have reported multivariate analyses and have follow-up of 5 years or longer were to be included if they answer the review question. None were included.

The process for using review level material is described in more detail below.

### 2.9 Identification of relevant studies

Titles and abstracts were screened independently by SK and SM using the inclusion criteria described above. Differences between reviewer's results were resolved by discussion and when necessary in consultation with a third reviewer (LL). If after discussion, there was still

doubt about a study's relevance for the review the full paper was obtained.

Full paper copies were obtained (AC, SK, LL) for studies identified by the title/abstract screening. For primary studies, decisions were made based on inclusion and exclusion criteria. Full paper screening was carried out independently by SK and SM. Any differences of opinion about inclusion/exclusion were resolved during discussion between the two reviewers or by consultation with a third reviewer (LL or NS). If after discussion, there was still doubt about a study's relevance for the review, the paper was retained and reassessed after quality assessment and data extraction.

A flow chart summarises the number of papers included and excluded at each stage of the process (Figures 2). Studies excluded at the full paper screening stage are listed in Appendix G along with the reason for exclusion.

### 2.10 Quality Assessment

Only primary studies (longitudinal cohort) are included in the review. Study design was assigned using the glossary of study designs (appendix D, CPHE methods manual) and the algorithm for classifying study designs (appendix E, CPHE methods manual).

Quality appraisal of cohort studies was done (SM, OR, SK) using the relevant quality appraisal checklist in the NICE methods manual (Appendix D; CPHE methods manual). Each full paper was assessed by one reviewer and checked for accuracy by another. A minimum of 10% of the studies was fully double assessed. Any discrepancy between reviewers was resolved by discussion.

### 2.11 Description of overall Quality Ratings

- ++ All or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter.
- + Some of the checklist criteria have been fulfilled, where they have not been fulfilled or adequately described the conclusions are unlikely to alter.
- - Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter

QA ratings included in evidence summary statements: [++]/[+]/[-]

### 2.12 Data extraction

Data was extracted (SM, OR, SK, LL) on study detail, population and setting, study design, outcomes and method of analysis, and results. To ensure accurate reporting the data extraction pro-forma was piloted against on a selection of papers. Due to the number of studies and the timeframe we had to complete the review, we did not doubly extract data for 10% of the papers as specified in the protocol; data extraction was instead verified while writing the evidence statements.

### 2.13 Synthesis of evidence

Only quantitative evidence is included in this review. Findings are narratively synthesised and presented to inform guidance. Data specific to health inequalities and vulnerable communities are assessed and findings are summarised separately where sufficient data is available.

Information about included studies is presented in both narrative and evidence table sections of the review, and in sufficient detail, to ensure clear and transparent links between recommendations and evidence (Section 5, Appendix K, CPHE methods manual).

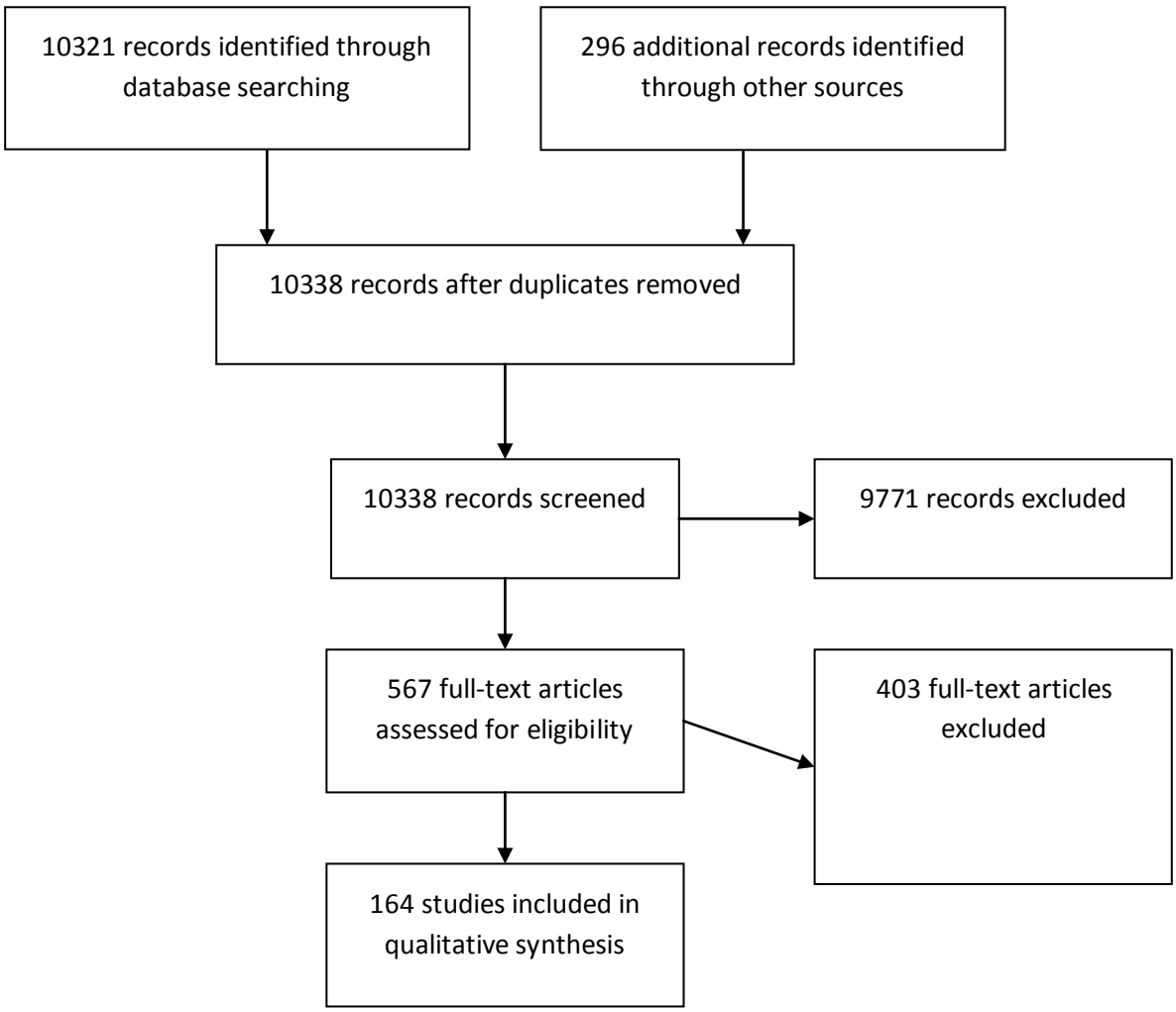
For each key question or issue an evidence statement provide an aggregated summary of all of the relevant studies (Sections 5.5.1 to 5.5.5 CPHE methods manual). Applicability ratings are used to assess each evidence statement to judge how similar the population(s), setting(s), exposure(s) and outcome(s) of the included studies are to those outlined in the review question (Section 5.6 CPHE methods manual). Each evidence statement has been rated as 'directly applicable, partially applicable or not applicable' by the reviewers.

## 3. FINDINGS

### 3.1 Searches

The searches for primary studies and the grey literature (Figure 2; Appendix F) located 10,338 articles after removing duplicates, 567 of which had relevant titles and abstracts. Of the 567 selected for full text assessment, 164 are included in the review. In light of the number of primary studies included in this review, we did not search for systematic reviews. None of the systematic reviews identified via the searches conducted for Review 1 were included. Appendix G lists the excluded studies and the reasons for exclusion. In total, 164 studies are included in the review and form the basis of the evidence statements.

**Figure 2. Search results for primary studies**



### 3.2 Characteristics of included studies

This review includes 164 longitudinal cohort studies reporting on the association between the following behavioural risk factors:

- Physical activity, physical inactivity
- Diet
- Smoking and smokeless tobacco (SNUS)
- Alcohol
- Weight change, weight cycling
- Combined lifestyles
- Leisure, cognitive activity, social networks

and the following categories of outcomes:

- Successful ageing (including quality of life, well-being)
- Dementia
- Disability & frailty
- Overall mortality
- Cardiovascular outcomes (mortality; morbidity)
- Diabetes, metabolic syndrome, insulin sensitivity
- Cancer
- Other chronic diseases
- Mental health

An overview of included studies is provided in Tables 9 to 17, with more details provided in the evidence tables (Appendix A).

**Table 9. Overview of included studies – Physical activity**

| **PHYSICAL ACTIVITY – SUCCESSFUL AGEING**<br>Note: A positive association (+) with PA is the better outcome | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Country** | **n** | **Age at baseline** | **Length of follow-up** | **Exposure measurement** | **Outcome** | **Outcome measure** | **Results association (-/+/0)** | **Quality/ Applicability** |
| Britton 2008 | UK (England) | 5823 | 35-55 | 17 years | Self-reported questionnaire<br><br>Frequency and number of hours per week. | Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome and with good physical and mental functioning. | Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals. | Successful aging<br><br>Men: +<br><br>Women: + | +/++ |
| Hamer 2013 | UK (England) | 3454 | 63.7 (SD 8.9) | 8 years | Self-reported Questionnaire<br><br>(shown to have moderate correlation with objective measure of accelerometry)<br><br>Frequency and intensity of participation in PA. | Healthy ageing defined as: (1) being free from major chronic disease; (2) having no major impairment of cognitive function; (3) having no major limitation of physical functions and (4) and having good mental health. | Disease status: self-reported physician diagnosis of major chronic diseases<br>Cognitive function: neuropsychological tests.<br>Mental health: validated depression scale | Healthy ageing<br><br>Baseline PA:<br><br>Inactive: 1<br>Moderate: +<br>Vigorous: +<br><br>Change in PA<br><br>Remained inactive: 1.00<br>Became active: +<br>Remained active: + | ++/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sun 2010 | US | 13535 | 60 (mean age) | 14 years | Self-reported<br><br>Questionnaire<br><br>Leisure PA | Successful survival - no history of 11 major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations. | Telephone Interview for Cognitive Status (TICS), which is modelled on the Mini-Mental State Examination administered by trained study nurses. | Successful survival<br>(Mean)<br>METS 0.9h/wk 1<br>3.6 0<br>7.9 +<br>16.2 +<br>37.1 + | ++/+ |

**Footnotes (applies to all tables):**

i. Data is from multivariate models.
ii. Where multiple models have been reported data from the most adjusted (or most relevant) model has been used.
iii. + = significant positive association, – = significant inverse association, 0 = no significant association

**PHYSICAL ACTIVITY – DEMENTIA OUTCOMES**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Andel 2008<br><br>(case control study) | Sweden | 264 dementia<br>2870 controls (90 twin pairs) | Mean 48.1 (SD 4.9) | 31.4 years | Self-reported<br><br>Questionnaire (4 point scale) | Dementia (and sub-analysis for Alzheimer's disease) | Screening for cognitive impairment followed by full clinical evaluation | Dementia<br>Hardly any: 1<br>Light: **–**<br>Regular: –<br>Heavy: **0**<br><br>Alz Dis<br>Hardly any: 1<br>Light: **–**<br>Regular: –<br>Heavy: **0** | +/ + |
| Carlson 2008 | US | 147 twin pairs | 45 (SD 3) | 20-40 years | Self-reported questionnaire<br><br>Frequency of participation on a scale of 1 to 5 | Dementia | Screening for cognitive impairment followed by dementia questionnaires and neurological and neuropsychological testing | Dementia<br><br>Dementia risk: **0** | ++/+ |
| Chang 2010 | Iceland | 4761 | 51 | 26 years | Interview and self-report of no. of hours per week in 3 categories | Cognitive function | Cognitive function assessed using cognitive tests | Better cognitive function<br><br>Those who were more active in mid-life had better cognitive function<br><br>None 1.00<br><br></= 5h/wk: **+**<br>>5h/wk: **+** | -/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Chang 2010 | Iceland | 4945 | 51 (SD 7) | 26 years | Interview (2 questions) and self-report of no. of hours per week in 3 categories | Dementia | DSM-IV dementia diagnosed according to 3 step protocol: MMSE or digit symbol substitution test; diagnostic cognitive test battery; neurological test and interview | Dementia<br>None: 1<br></= 5h/wk: —<br>>5h/wk: **0** | -/+ |
| Elwood 2013<br><br>(Caerphilly cohort study) | UK (Wales) | 2235 | 45-59 | 30 years | Self-reported (method?)<br><br>Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit | Cognitive impairment<br><br>Dementia | Interview, examination, primary care and hospital records. | Cog impairment: —<br><br>Dementia: — | +/++ |
| Morgan 2012<br><br>(Caerphilly cohort study) | UK (Wales) | 1005 | 45-59 | 16 years | Self-reported questionnaire data assessed:<br>*work-related physical activity<br>*leisure-time physical activity:<br>*Composite type, frequency, and duration of leisure-time physical activity score | Dementia | Cognitive function screening using CAMCOG<br>*Clinical assessment | Dementia<br><br>Leisure time PA: **0**<br><br>Occupational PA: **0** | +/++ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Sabia 2009 | England | 5123 | 44 (mean) | 17 years<br><br>(85-88 to 02-04) | Self-reported<br><br>Questionnaire | Cognitive function | Cognitive tests to measure executive function (reasoning, verbal fluency measures) | Short-term association (5y)<br>Low PA: 1<br>High PA: **+**<br><br>Long-term association (17y)<br>Low PA: 1<br>High PA: **0** | +/++ |
| Friedland 2001 (case-control study) | US | 193 cases/358 controls (for total study, not reported for 40-59 year olds) | 40-59 | >12 (not fully reported) | Self reported or surrogate reported (for cases); Questionnaire<br><br>Physical intensity: total hours/month – sports, garde-ning, walking | Alzheimer's Disease | Neuropsychological, laboratory, and neurological exams and all had x-ray computed tomography or MRI scans of the brain. | Phys intensity**:** **0** | -/+ |
| Rovio 2005 | Sweden | 2000 | 50 | 21 years | Self-reported<br><br>Questionnaire<br><br>Leisure time PA | Dementia<br><br>Alzheimer's disease | Cognitive status by MMSE was determined, and participants who scored 24 or less were referred for further neurological and cardiovascular exams. | Dementia<br><br>Sedentary: 1<br>PA at least 2/wk: **–**<br><br>Alzheimer's disease<br><br>Sedentary: 1<br>PA at least 2/wk: **–** | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Rovio 2007<br><br>(same study as Rovio 2005) | Sweden | 1449 | 50 | 21 years | Self-reported questionnaire<br><br>Occupational commuting PA | Dementia<br><br>Alzheimer's disease | Cognitive status by MMSE was determined, and participants who scored ≤24 were referred for further neurological cardiovascular exams. | Dementia<br>Sedentary 1<br>PA at least 2/wk **0**<br><br>Alzheimer's disease<br>Sedentary 1<br>PA at least 2/wk **0** | +/+ |

**PHYSICAL ACTIVITY – DISABILITY & FRAILTY**

Note: a negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Englund 2011 (case-control study) | Sweden | 81 cases/ 156 controls | 57 (SD 5) | 11 years | Self-reported questionnaire<br><br>Commuting activities, occupational physical activity, exercise, leisure time activities, walking and bicycling activities | Hip fracture | All fracture cases were identified from a prospective injury database | Walking:<br><br>Low: 1<br>Mod: —<br>High: **0**<br><br>Spare time activity:<br><br>Low: 1<br>Mod: —<br>High: — | -/+ |
| Englund 2013 (case-control study) | Sweden | 376 cases/402 controls | 54 (SD 6) | 11 years | Self-reported questionnaire<br><br>Commuting activities, occupational physical activity, exercise, leisure time activities, walking,bicycling activities. | Wrist fracture | All fracture cases were identified from a prospective injury database | Commuting activity:<br><br>Low: 1<br>Mod: 0<br>High: —<br><br>Occupational activity:<br><br>Low: 1<br>Mod: 0<br>High: 0<br><br>Training activity: 0<br><br>Cycling:<br><br>Low: 1<br>Mod: 0<br>High: 0 | -/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Lang 2007 | UK [England (ELSA study), and US] | 8702 (US)& 1507 (UK) (from 2 studies | 50-69 (mean 60.2 & 58) | 6 years | Questionnaire<br><br>(frequency and intensity) | Physical mobility | Self-reported questionnaire (US study), clinician applied Physical Performance Battery (UK study) | Incidence of impaired physical mobility<br><br>UK study (ELSA): –<br>US study: – | +/++ |
| Ostbye 2002 | US | 7845 (HRS study) 5037 | 51-61 | 5-6 yrs | Self-reported<br><br>Questionnaire<br><br>Intensity and frequency of PA | Disability (impairment that limits amount of paid work;<br>ADL in activities necessary for survival<br><br>IADL for activities necessary to manage in society)<br><br>Self- reported health<br><br>Health care use | Questions with yes/no options for disability, ADL, IADL. Health care use.<br><br>For self- reported health - categories | Disability<br>Light: –<br>Mod: –<br>Heavy: –<br><br>ADL & IADL<br>Light: –<br>Mod: –<br>Heavy: –<br><br>Stairs/Blocks<br>Light: –<br>Mod: –<br>Heavy: –<br><br>Poor health<br>Light: –<br>Mod: –<br>Heavy: –<br><br>Hospitalised<br>Light: –<br>Mod: –<br>Heavy: – | -/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Patel 2006 | Italy | 1001 | 40-60 | 7 years | Retrospective recall at age 74 of PA in mid-life (age 40-60) | Mobility | Ability to walk 400m | Unable to walk 400 meters:<br><br><u>Men</u><br>Low Reference<br>Moderate **0**<br>Vigorous **–**<br><br>p for trend p = <0.001<br><br><u>Women</u><br>Low Reference<br>Moderate **0**<br>Vigorous **0**<br><br>p for trend p = 0.620 | +/+ |
| Szoeke 2006 | US | 224 | 50 (mean) | 11 years | Self-reported Questionnaire (1 question, daily PA, no PA) | Osteoarthritis (hand and knee) | X-rays | <u>Osteoarthritis</u><br><br>PA **0** | +/+ |

**PHYSICAL ACTIVITY – DISABILITY & FRAILTY**

Note: A positive association (+) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Chang 2013<br><br>(same study as Chang 2010, different outcomes) | Iceland | 4753 | 51 (SD 7) | 25 years | Interview (2 questions) and self-report of no. of hours per week in 3 categories | Lower extremity function | Gait speed (6m walk)<br>Timed up and go test<br>Knee extension strength | <u>Better lower extremity function (LEF)</u><br><br>Those who were active in mid-life had better LEF<br><br>Inactive: 1<br>Active: **+** | -/+ |
| Lahti 2010 | Finland | 5437 women, 1257 men | 49-51 | 5-7 years | Self-reported<br><br>Questionnaire<br><br>Leisure time PA<br><br>Commuting PA: volume, intensity | Physical health function | SF-36 Physical health function questionnaire | <u>Better physical function</u><br><br>**Women:**<br><br>Inactive vs Conditioning PA: **+**<br><br>Inactive vs active mod, active vig, very active mod, very active vig PA: **0**<br><br>**Men:**<br><br>Inactive vs active mod, active vig, very active mod, very active vig, conditioning PA: **0** | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Malmberg 2006 | Finland | 1791 | 40-64 | 16 years | Self-reported<br><br>Questionnaire<br><br>Leisure time PA<br><br>(intensity, frequency, duration) | Mobility (stair climbing, difficulty in walking) | Self -reported | Difficulty walking<br><br>**Men:**<br>Fitness activity:<br>≥3 times /wk: 1<br>2 times/wk: **+**<br>Once/wk: **+**<br><once/wk: **+**<br>None : **+**<br><br>Global LTPA**:** **0**<br>LTPA energy ex **0**<br>LTPA freq – int **0**<br>Commuting **0**<br><br>**Women:**<br>Fitness activity: **0**<br>Global LTPA**:** **0**<br>LTPA energy ex **0**<br>LTPA freq – int **0**<br>Commuting **0** | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association [a,b,c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Nokes 2012 | US | 244 | 35-45 | 6 years | Accelerometer (over 7 days)<br><br>PA volume and intensity | Change in bone mineral density (BMD) | 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) | <u>Gain in bone mineral density:</u><br><br>Low PA volume: 1<br>Moderate: **+**<br>Moderate-high: **+**<br><br>PA intensity: **0** | +/+ |
| Patel 2006 | Italy | 1001 | 40-60 | 7 years | Retrospective recall at age 74 of PA in mid-life (age 40-60) | Mobility | Short Physical Performance Battery | <u>Better physical perf</u><br>Short Physical Performance Battery<br>Men b weight (SE)<br>Low 1<br>Moderate **0**<br>Vigorous **+**<br>p for trend p = 0.023<br><br>Women b weight (SE)<br>Low 1<br>Moderate **0**<br>Vigorous **+**<br>p for trend p = 0.024 | +/+ |

**PHYSICAL ACTIVITY – OVERALL MORTALITY**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Hu 2005 | Finland | 47212 | 25-64 (mean age 41-46) | 17.7 years | Self-reported<br>Questionnaire<br>Occupational/<br>Leisure PA | All cause mortality | National and hospital registers | **Men**<br>Total mortality<br>Low 1.00<br>Moderate: –<br>High: –<br>P-value for trend <0.001<br>**Women**<br>Total mortality<br>Low 1.00<br>Moderate: –<br>High: –<br>P-value for trend <0.001 | +/+ |
| Holtermann 2009 | Denmark | 4952 | 40-59 | 30 years | Self-reported questionnaire<br>Occupational/<br>leisure PA | All cause mortality | Official national registers | *Among men with moderate physical work demands:*<br>All cause mortality<br>Low Leisure PA : 1<br>Mod Leisure PA: –<br>High Leisure PA : – | +/+ |
| Menotti 2006 | Italy | 1712 | 40-49 | 5 years | Self-reported questionnaire | All cause mortality | Death certificates, hospital and medical records, interviews with physicians and relatives. | All cause mortality: – | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association [a,b,c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Yu 2003<br><br>(Caerphilly cohort study) | UK (Wales) | 1975 | 45-59 | 10.5 years | Self- reported<br><br>Questionnaire (Minnesota Leisure Time Physical Activity).<br><br>Leisure-time PA<br><br>Total energy expenditure on activities<br><br>Occupational PA | **CVD**, cancer, mortality from all causes | National Health Service Central Registry | Heavy intensity activity<br><br>All-cause death: **–** | +/++ |
| Elwood 2013<br><br>(Caerphilly cohort study) | UK (Wales) | 2235 | 45-59 | 30 years | Self-reported (method?)<br><br>Regular exercise: walking ≥2 miles to work each day, cycling ≥ten miles to work each day, 'vigorous' exercise described as a regular habit | Death | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Death: – | ++/++ |

**PHYSICAL ACTIVITY – CARDIOVASCULAR OUTCOMES**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Harmsen 2006 | Sweden | 6193 | 47-55 | 28 years | Self-reported questionnaire<br><br>Leisure time PA | Stroke | Hospital records, national register | Risk of stroke:<br><br>Low leisure PA: **0** | +/+ |
| Hu 2004 | Finland | 18892 | 25-74 (mean age 42-48) | 9.8 years | Self-reported<br><br>Questionnaire<br><br>Occupational/<br><br>Leisure PA | CVD | National and hospital registers | Risk of CVD<br>**Men**<br>Physical activity<br>Low: 1.00<br>Moderate: **–**<br><br>High: **–**<br>P trend 0.007<br><br>Women<br>Physical activity<br>Low: 1.00<br>Moderate: **–**<br><br>High: **–**<br>P trend 0.02 | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Hu 2005 | Finland | 47212 | 25-64 (mean age 41-46) | 17.7 years | Self-reported<br><br>Questionnaire<br><br>Occupational/<br><br>Leisure PA | CVD | National and hospital registers | **Men**<br>Cardiovascular mortality<br>Low 1.00<br>Moderate –<br><br>High –<br>P-value for trend <0.001<br><br>**Women**<br>Cardiovascular mortality<br>Low 1.00<br>Moderate: –<br>High: –<br>P-value for trend <0.001 | +/+ |
| Hu 2007 | Finland | | 25-64 (mean age 42-49) | 18.9 years | Self-reported<br><br>Questionnaire<br><br>Occupational/<br><br>Leisure PA | CHD | National and hospital registers | CHD events<br>**Men**<br>Occupational PA<br>Low: 1<br>Moderate: –<br>High: –<br>P trend 0.007<br><br>**Women**<br>Physical activity<br>Low: 1<br>Moderate: –<br>High: –<br>P trend 0.02 | +/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Yu 2003<br><br>(Caerphilly cohort study) | UK (Wales) | 1975 | 45-59 | 10.5 years | Self- reported<br><br>Questionnaire (Minnesota Leisure Time Physical Activity Questionnaire).<br><br>Leisure-time PA<br><br>Total energy expenditure on activities<br><br>Occupational PA | CVD | National Health Service Central Registry | Total activity:<br><br>CHD death: **–**<br><br>(trend p-value=0.039)<br><br>Heavy intensity activity<br><br>CVD death: **–**<br><br>CHD death: **–** | +/++ |
| Meisinger 2007 | Germany | 3501 men, 3475 women | 45-74 | 8.6 years | Interview<br><br>(4 level graded activities: none, < 1h/wk; 1-2 h/wk, >2 h/wk) | Myocardial Infarction | In and out of hospital registries | Myocardial infarction<br><br>Men: Leisure sports<br>None: 1<br>Low **0**<br>Med: **0**<br>High: **0**<br><br>Women:<br>None: 1<br>Low **0**<br>Med: **–**<br>High: **–** | +/+ |
| Pitsavos 2004 | Greece (Corfu) | 529 | 49 ±6 | 40 years | Physical activity levels were assessed by self reports of habitual, occupational and leisure-time | Stroke mortality | Previous clinical records filled out by the study's research group, or by hospital records, or by necroscopy records, or by info from family or hospital doctors, other specialists, family or | Presence of LVH<br>PA status<br>Sedentary: 1<br>Moderate **–**<br>Hard **0**<br><br>Absence of LVH<br>PA status | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | activities | | relatives, friends and any other witnesses. | Sedentary) 1<br>Moderate **–**<br>Hard **0** | |
| Holtermann 2009 | Denmark | 4952 | 40-59 | 30 years | Self-reported questionnaire<br><br>Occupational/<br><br>leisure PA | Ischaemic heart disease | Official national registers | *Among men with moderate physical work demands:*<br><u>IHD mortality</u><br><br>Low Leisure PA: 1<br>High Leisure PA: **–** | +/+ |
| Elwood 2013<br><br>(Caerphilly cohort study) | UK (Wales) | 2235 | 45-59 | 30 years | Self-reported<br><br>(method?)<br><br>Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit | Vascular disease | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Vascular disease**: 0** | +/++ |

**PHYSICAL ACTIVITY – DIABETES / METABOLIC SYNDROME/INSULIN SENSITIVITY**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Hu 2003 | Finland | 13290 | 35-64 | 12 years | Self-reported<br>Questionnaire<br>Occupational/<br>Leisure<br>Commuting PA | Type 2 diabetes | National registers | Occupational physical activity<br>**Men 0**<br>**Women 0**<br><br>**Men and women combined**<br>Light 1.00<br>Moderate: **–**<br>Active: **–**<br><br>p value for trend 0.020<br><br>Commuting physical activity<br>Men **0**<br>Women **0**<br>Men and women combined<br>≥30 min **–**<br><br>p value for trend 0.048<br><br>Leisure-time physical activity<br>Men: **0**<br>Women: **0**<br><br>Men and women | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | combined<br>Low 1.00<br>Moderate: **0**<br>High: **0** | |
| Elwood 2013<br><br>(Caerphilly cohort study) | UK (Wales) | 2235 | 45-59 | 30 years | Self-reported<br><br>(method?)<br><br>Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit | Diabetes | Interview, examination, primary care and hospital records.. | Diabetes: — | ++/++ |
| Ekelund 2005 | UK (England) | 605 | 53 (mean) | 5.6 years | Physical activity energy expenditure measured using the flex heart rate method | Metabolic syndrome | Blood samples | <u>PA energy expenditure</u><br><br>Metabolic syndrome summary score: **–** | +/++ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Holme 2007 (Oslo study) | Norway | 6382 | 40-49 | 28 years | Self-reported physical activity at work and leisure | Metabolic syndrome<br><br>Diabetes | Metabolic syndrome presence of at least 3 out of the following 5 criteria: 1) triglycerides >=1.7 mmol/l adjusted for the last meal, 2) glucose >= 6.1 mmol/l adjusted for the last meal, 3) BMI >=30 kg/m2, 4) blood pressure >= 135/85 mmHg, and 5) HDL cholest <1.03 mmol/l<br><br>Diabetes definition included self-reported diabetes, antidiabetic medication, insulin use or non-fasting glucose >=11.1 mmol/l | Metabolic syndrome<br><br>sedentary/light PA: ref:<br>moderate: –<br>mod vig: –<br>vigorous: –<br><br>Diabetes<br>sedentary/light PA: ref:<br>moderate: –<br>mod vig: –<br>vigorous: – | +/+ |
| Riserus 2007 | Sweden | 770 | 50 | 20 yrs (70-73 to 91-95) | Self-reported Questionnaire<br><br>Leisure-time PA was assessed using a validated questionnaire with 4 activity levels: sedentary, moderate, regular, athletic. | Insulin sensitivity | Hyperinsulinemic – euglycemic clamp used to calculate glucose infusion rate | Insulin sensitivity<br><br>Leisure PA: – | +/+ |

**PHYSICAL ACTIVITY – CANCER**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (–/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Stevens 2009 | England and Scotland | 1.29 million women | 50-64 (mean 56) | 96-01 to 2005-07<br>Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for mortality | Self-reported<br><br>Questionnaire<br><br>Strenuous exercise/Any exercise | Incident and fatal pancreatic cancer | National Health Service Central Register (deaths, cancer registrations with ICD codes) | PA (times per week) and incidence/mortality):<br><1 : 1.00<br>1 **0**<br>2-3: **0**<br>>/= 4 **0** | +/++ |
| Wannamethee 2001 | UK (England) | 7630 | 40-59 | 18.8 years | Self- reported<br><br>Questionnaire<br><br>Total PA<br><br>(total physical activity score based on frequency and type (intensity) of activity. | Cancer | Death certificates, cancer registry, postal questionnaires. | Total cancer:<br><br>No PA 1.00<br>Occasional PA **–**<br>Vigorous PA **–**<br>p for trend <0.0001<br><br>Upper digestive tract cancer (oral, esophagus, stomach cancer)<br><br>No PA 1.00<br>Moderate-vigorous PA **–**<br><br>Bladder cancer<br><br>No PA 1.00<br>Vigorous PA **+**<br>*vigorous exercise was associated with a significantly *increased* risk of bladder cancer. | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Prostate cancer<br>No PA 1.00<br>Vigorous PA –<br><br>No sig association found for lung, stomach, colorectal, lymphatic/haematopoetic cancers. | |
| Hu 2005 | Finland | 47212 | 25-64 (mean age 41-46) | 17.7 years | Self-reported<br><br>Questionnaire<br><br>Occupational/<br><br>Leisure PA | CVD<br>Cancer<br>All cause mortality | National and hospital registers | **Men**<br><u>Total mortality</u><br>Low 1.00<br>Moderate: –<br><br>High: –<br><br>P-value for trend <0.001<br><u>Cardiovascular mortality</u><br>Low 1.00<br>Moderate –<br><br>High –<br>P-value for trend <0.001<br><u>Cancer mortality</u><br>Low 1.00<br>Moderate: **0**<br><br>High: –<br>P-value for trend 0.05<br><br>**Women**<br><u>Total mortality</u><br>Low 1.00 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Moderate: **–**<br><br>High: **–**<br>P-value for trend <0.001<br><u>Cardiovascular mortality</u><br>Low 1.00<br>Moderate: **–**<br><br>High: **–**<br>P-value for trend <0.001<br><u>Cancer mortality</u><br>Low 1.00<br>Moderate: **–**<br><br>High: **–**<br>P-value for trend 0.005 | |
| Elwood 2013<br><br>(Caerphilly cohort study) | UK (Wales) | 2235 | 45-59 | 30 years | Self-reported<br><br>(method?)<br><br>Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit | Cancer | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Cancer: **0** | +/++ |

**PHYSICAL ACTIVITY – MENTAL HEALTH**

Note: A negative association (-) with PA is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Wiles 2007<br><br>(Caerphilly cohort study) | UK (Wales) | 2512 | 45-59 | 10 years | Self- reported<br><br>Questionnaire (Minnesota Leisure Time Physical Activity Questionnaire).<br><br>Leisure-time PA<br><br>Total energy expenditure on activities<br><br>Occupational PA | Common mental disorders, comprising anxiety and depression | Validated psychiatric disorders screening questionnaire, report of antidepressant/ anxiolytic use. | *5-year follow-up:<br>Mental disorders<br><br>Total leisure PA<br>Low: 1<br>Med: 0<br>High: 0<br><br>% time in heavy PA<br>Low: 1<br>Med: –<br>High: –<br><br>*10-year follow-up:<br>Total leisure PA<br>Low: 1<br>Med: 0<br>High: 0<br><br>% time in heavy PA<br>Low: 1<br>Med: 0<br>High: 0 | ++/++ |
| Xu 2010 | South East Queensland, Australia | 564 | 45-60 yrs (mean 55) | 2001-06 | Self-reported Questionnaire<br>Four options including “none,” “1–2 times/week,” “3–times/week” 4 times/week,” and “5–6 times/week”<br>The intensity and | General mental well-being, and psychological symptoms | SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire | Correlations between PA and 1) anxiety, 2) depression, 3) psychological symptoms, 4) SF-36 mental health:<br><br>For 1, 2,3,4 above separately<br><br>None ref | -/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | the duration of exercise were not measured. | | | 1-2/wk 0<br>3-4/wk 0<br>5-6/wk 0 | |

## Table 10. Overview of included studies – Physical Inactivity

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Christensen 2006 | Denmark | 376 | 50, 60, 70 | 25 years | Self-reported physical inactivity in leisure time assessed in 5 categories | Disability at age 75 | Functional ability assessed by interviewer-administered Mob-T scale that measures tiredness after performing mobility activities. | Disability at age 75<br>At age 50: **0**<br><br>At age 60:<br></= 7 y school: **0**<br>> 7 y school: **0** | -/+ |
| Haapanen-Niemi 2000 | Finland | 2212 (295 PA) | 35-63 | 16 years | Leisure time physical activity (LTPA):<br>1) an index for total energy expenditure in LTPA (23 questions)<br>2) a single-item self-assessment of physical activity. | Mortality: all cause; CHD and CVD | National census data (Finland) | CVD mortality<br><br>1) LTPA index:<br>High: 1.00<br>Mod: **0**<br>Low: **0**<br><br>2) Single item LTPA<br>Vigorous: 1.00<br>None: **+**<br><br>All cause mortality<br><br>1) LTPA index:<br>High: 1.00<br>Mod: **0**<br>Low: **0**<br><br>2) Single item LTPA<br>Vigorous: 1.00<br>None: **0** | +/+ |

**Footnote:** where multiple outcomes have reported the most adjusted data in this table; sig = p</=0.05; ns = not significant (p>0.05)

## Table 11. Overview of included studies – Diet and components of diet

**DIET – SUCCESSFUL AGING**

Note: a positive association (+) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Akbaraly (2013) | UK | 8815 | 35-55 years | 18 years | Dietary patterns and adherence to the Alternative Healthy Eating Index (AHEI)<br><br>Clinical examination, self-reported questionnaire, food-frequency questionnaire | Mortality, chronic diseases, and functioning | Hospital data, register linkage, and screenings every 5 years | Ideal aging<br><br>Western-type diet (high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products)<br>Top tertile compared to the bottom tertile:<br>–<br><br>Healthy diet pattern:<br><br>Top tertile compared to the bottom tertile:<br>**0** | +/++ |
| Britton (2008) | UK | 5823 | 35-55 years (mean: 44) | 20 years | 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 | Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome) with good physical and mental functioning | Walking speed, lung function, Alice Heim 4-I cognitive test, physical component score of the 36-item Short Form General Health Survey >self-reported questionnaires, medication use, clinical examinations, | Men<br><br>Good diet vs poor diet:<br>**+** | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | or vegetables eaten less often than daily.<br><br>Self-reported questionnaires | | | | |
| Samieri (2013) | United States | 10670 | Upper 50s, lower 60s (SD: 59) | 15.2 years | Dietary patterns Self-reported FFQ<br><br>Alternative Healthy Eating Index-2010 (AHEI-2010) and Alternate Mediterranean diet scores. | "Healthy" aging was defined as survival to 70 years or older with maintenanceof 4 health domains: no major chronic diseases or major impairments in cognitive or physical function or mental health. | Questionnaire on disease incidence every 2 years. Telephone interviews for cognitive status | <u>Healthy ageing</u><br><br><u>Healthy eating index diet:</u><br>Q1 low ref 1.00<br>Q2 **0**<br>Q3 **0**<br>Q4 **+**<br>Q5 **+**<br><br>P trend<0.001<br><br><u>Med diet score</u><br><br>Q1 low ref 1.00<br>Q2 **+**<br>Q3 **+**<br>Q4 **+**<br>Q5 **+**<br>P trend =0.002 | +/+ |

**DIET – DISABILITY/FRAILTY OUTCOMES (1)**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Nakamura (2009) | Japan | 2316 | 47-60 years | 19 years | Diet<br><br>Telephone interviews. Face-to-face interviews at home. Self-administered lifestyle questionnaire | Activities of daily living (ADL) | Participants were asked about 5 basic ADL items | Impaired ADL<br><br>Meat (no. times in 2 days)<br><1/2 d ref 1.00<br>≥1/2 days —<br>(less impaired ADL)<br>Fish<br><1/day 1.00<br>≥1/day 0<br><br>Egg<br><1/day 1.00<br>≥1/day 0<br><br>Mortality<br><br>Meat, fish, egg: **0** | +/+ |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Diabetes<br>Vascular disease<br>Cancer<br>Cognitive impairment<br>Dementia<br>Death | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Cog impairment:<br>**0** | +/++ |
| Eskelinen (2008) | Finland | 1449 | SD: 50.2 | 21 years | Dietary fat intake (total, saturated, polyunsaturated, monounsaturated)<br><br>Self-reported | Cognitive impairment (MCI) | Mini Mental State Examination, immediate word recall tests, Category Fluency Test.<br>psychomotor speed with Purdue Peg Board task letter digit substitution | Cognitive impairment:<br><br>Total fat<br>Low (0-38 g/d): 1<br><br>High(>38 g/d) **+**<br><br>Sat fat | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | validated semi-quantitative food-frequency questionnaire | | test.<br>Executive function with the Stroop test . | Low (0-21.6 g/d): 1<br><br>High(>21.6 g/d) **+** | |
| Laitala (2009) | Finland | 2606 | Mean age 46-52 | 28 years | Coffee intake<br><br>Self-reported questionnaire, telephone interviews (TELE, TICS, MMSE) | Cognitive performance (MCI) | TELE screening and the Telephone Interview for Cognitive Status (TICS)<br><br>*TELE and TICS are sensitive and specific and correlate well with the MMSE | <u>MCI</u><br><br><u>Coffee (cups/d)</u><br><br>0-3 (ref) 1<br>3.5-8 **0**<br>>8 **0** | ++/+ |

**DIET – DISABILITY/FRAILTY OUTCOMES (2)**

Note: a positive association (+) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Kesse-Guyot (2012) | France | 3054 | SD: 52.1 | 13.4 years | Diet<br><br>Self-reported 24-h dietary records.<br><br>'Healthy pattern' -+ve: fruit,veg, wholegrains, fresh dairy products, vegetables,, breakfast cereal, tea, vegetables, vegetable fat, nuts, fish.<br><br>'Traditional pattern' - +ve: vegetables, vegetable fat, meat, poultry. | Cognitive performance | Clinical examination, neuropsychological evaluation<br><br>(verbal fluency, the RI-48 cued recall test, the trail-making test, and forward and backward digit span).<br><br>Three composite variables, for global cognitive function, verbal memory, and executive functioning, were reported. | <u>Better cognitive performance</u><br><br>High score 'healthy pattern' (Q4 vs Q1) **+**<br>P trend 0.001<br>(Executive fn)<br><br>High score 'traditional pattern'<br>(Q4 vs Q1)<br>P trend 0.06<br>(Global cog fn) — | -/+ |
| Nooyens (2011)<br><br>Doetinchem Cohort Study | Netherlands | 2613 | 43-70 years | 10 years | Fruit and vegetables<br><br>Self-reported FFQ. | Cognitive decline | Neuropsychological test battery | <u>Change in cognitive function</u><br><br><u>Fruit and vegetables:</u> **0**<br><br><u>Fruit:</u> **0**<br><br><u>Vegetables:</u> **0** | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Legumes: **0**<br>Juices: **0** | |
| Sabia (2009) | UK | 5123 | 35-55 years | 17 years | Fruit and veg intake<br><br>Self-reported questionnaire (1 question about frequency) | Cognitive function | Executive function was derived from 3 measures: a measure of reasoning and 2 measures of verbal fluency.<br><br>Memory was assessed by using a test of short-term verbal memory | Executive function:<br>Fruit & veg(servings/d)<br>>/= 2 vs <2: **+**<br>Memory **0** | +/+ |

**DIET – DEMENTIA OUTCOMES**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Eskelinen (2009)<br><br>CAIDE study | Finland | 1409 | SD: 50.4 | 21 years | Coffee and tea consumption<br>*coffee drinking categorized as: 0-2 cups/day (low), 3-5 cups/day (moderate), >5 cups/day (high)<br>*Tea consumption categorized as: none (0 cups/day), drinking tea (>=1 cups/day)<br><br>Self-reported validated semi-quantitative food-frequency questionnaire | Dementia | *cognitive status assessing through screening, clinical and differential diagnosis<br>*participants with score <=24 on MMSE referred for clinical examination for dementia diagnosis or not. | Dementia risk:<br><br>Coffee: – lower for those consuming moderate amounts of coffee (3-5 cups/day)<br><br>compared to low amounts (0-2 cups/day).<br><br>Tea **0** (all associations)<br><br>*for APOE4 carriers:<br><br>Coffee: – | +/+ |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Dementia | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Dementia: **0** | +/++ |
| Hughes (2010) | Sweden | 3779 (3424 non- | Mean age 48 | 30 years | Diet questionnaire – single item on 4 | Dementia | Cognitive screening by phone, full clinical evaluation using | Dementia<br><br>No/small fruit& veg | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | demented, 355 dementia cases) | | | point scale on fruit and veg intake<br><br>(“great part”, “medium part”, “small part”, or “no part”) | | standard diagnostic criteria | intake: 1.00 (ref)<br><br>Medium or great Fruit & veg intake: — | |
| Laitala (2009)<br><br>Finnish Twin cohort study | Finland | 2606 | Mean age 46-52 | 28 years | Coffee intake<br><br>Self-reported questionnaire, telephone interviews (TELE, TICS, MMSE) | Dementia | TELE screening and the Telephone Interview for Cognitive Status (TICS)<br><br>*TELE and TICS are sensitive and specific and correlate well with the MMSE | <u>Dementia</u><br><br><u>Coffee (cups/d)</u><br><br>0-3 (ref) 1.00<br>3.5-8 **0**<br>>8 **0** | ++/+ |
| Laitinen (2006) | Finland | 1449 | SD: 50.4 | 21 years | Dietary fat (Sat fat and polyunsat fat from spreads)<br><br>Self-reported questionnaire.<br><br>(Qualitative or frequency based) | Dementia | Cognitive status assessed using MMSE; if score <=24, invited to clinical phase for dementia diagnosis | <u>Dementia</u><br><br><u>Polyunsat fat (PUFA)</u><br><br>Moderate amounts PUFA vs Low amounts PUFA: —<br><br>Moderate amounts sat fat vs Low amounts sat fat: **+**<br><br><u>APOE4 carriers</u><br><br>Moderate amounts PUFA vs Low amounts PUFA: —<br><br>Moderate amounts sat fat vs Low amounts sat fat: **+** | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Laurin (2004) | US (Hawaii) | 2459 | 45-68 years (Mean: 51.2) | 30.2 years | Dietary antioxidants<br><br>24-hour dietary recall interviews, clinical examinations, self-reported FFQ questionnaire | Dementia (and subtypes) | Cognitive Abilities Screening Instrument and then evaluated through a neurologic examination, neuropsychological testing, and an informant interview | Dementia<br><br>β-carotene **0**<br><br>vitamin C **0**<br><br>flavonoids **0**<br><br>vitamin E<br><br>Q1 1.00 ref<br>Q2 **+**<br>Q3 0<br>Q4 0<br><br>Alzheimer's disease<br><br>β-carotene **0**<br><br>vitamin C **0**<br><br>flavonoids **0**<br><br>vitamin E<br><br>Q1 1.00 ref<br>Q2 **+**<br>Q3 0<br>Q4 0<br><br>Alzheimer's disease w/w'out cerebrovascular disease<br><br>β-carotene **0**<br><br>vitamin C **0** | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | flavonoids **0**<br><br>vitamin E<br><br>Q1 1.00 ref<br>Q2 **+**<br>Q3 0<br>Q4 **+**<br><br>Vascular dementia:<br>**0** | |

**DIET – TOTAL MORTALITY**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Osler (2003) | Denmark | 7540 | 30-70 years | 36 years | Fish intake<br><br>Self-reported questionnaires | Data on all-cause mortality, CHD mortality, incident CHD | National Board of Health Register of Cause of Death and the National Patient Register | All cause mortality<br><br>Men (times)<br><1/month vs once/wk: —<br><br>Men and women<br>2/month vs once/wk: —<br><br>*among males and females combined, as well s 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) | +/+ |
| Seccareccia (2003) | Italy | 1536 | 45-65 years | 30 years | Veg intake<br><br>Home visits. Interviews using a dietary history interview sheet. Self-reported 7-day food-use diaries. | Total mortality | Official death certificates, hospital physicians, interviews with relatives of the deceased and other witnesses. | Total mortality<br><br>Vegetable intake (for each increase of 20g/day): — | +/+ |
| Akbaraly (2013) | UK | 8815 | 35-55 years | 18 years | Dietary patterns and adherence to the | Total and CVD mortality | Hospital data, register linkage, and screenings every 5 years | Ideal aging | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Alternative Healthy Eating Index (AHEI)<br><br>Clinical examination, self-reported questionnaire, food-frequency questionnaire | | | Western-type diet (high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products) Top tertile compared to the bottom tertile: —<br><br>CVD and non-CVD deaths<br><br>Healthy eating<br>High adherence to the AEHI: — | |
| Strandhagen (2000) | Sweden | 792 | Age 54 | 26 years | Fruit and vegetable intake<br><br>Self-reported FFQs | Total mortality, | Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records | Total mortality<br><br>Fruit: —<br>Veg: **0** | ++/+ |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Total mortality | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Death: **0** | +/++ |

**DIET – CVD OUTCOMES**

Note: a positive association (+) with diet is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Leosdottir (2007)<br><br>Malmo Diet and Cancer Study | Sweden | 28000 | 45-70 years | 8.4 years | Dietary fat intake<br><br>Self-reported 7 day menu diary, FFQ and interviews | Cardiovascular events | Information on prevalent and incident fatal or nonfatal CVD events was gathered from local and national registries. | Cardiovascular events<br><br>Total fat:<br><br>Women: **0**<br>Men: **0**<br><br>Sat fat:<br><br>Women: **0**<br>Men: **0**<br><br>Monounsat fat:<br><br>Women: **0**<br>Men: **0**<br><br>Polyunsat fat:<br><br>Women: **0**<br>Men: **0** | +/+ |
| Beulens (2007) | Netherlands | 1417 | 49-70 | 8-12 years | Glycemic index and glycemic load in the previous year<br><br>Food frequency questionnaire (validated) | 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<br><br>*vital status information obtained from municipal administration registries; cause of death obtained from GPs | CVD risk<br><br>Glycemic load (GL)<br><br>Highest vs lowest quartile: **+**<br><br>(The higher the quartile of energy-adjusted glycemic load, the greater the risk for CVD) | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (p-value for trend: 0.033)<br><br>Glycemic index (GI)<br><br>Highest vs lowest quartile: **+**<br><br>(p-value for trend: 0.02) | |
| Levitan (2007)<br><br>Cohort of Swedish men | Sweden | 36246 | 45-79 years | 6 years | Glycaemic index (GI) and glycaemic load (GL)<br><br>Self-reported FFQ questionnaire | CVD events<br><br>CVD mortality<br><br>All cause mortality | Hospital discharge and cause of death registries | Myocardial infarction:<br><br>GI or GL **0**<br><br>Ischemic stroke:<br><br>GI or GL **0**<br><br>Hemorrhagic stroke:<br><br>GI or GL **0**<br><br>Cardiovascular mortality:<br><br>GI or GL **0**<br><br>All cause mortality:<br><br>GI or GL **0** | +/+ |
| Levitan (2009)<br><br>Cohort of Swedish men | Sweden | 39367 | 45-79 years | 7 years | Dietary fatty fish consumption, marine omega-3 fatty acids<br><br>Food frequency questionnaires | Heart failure<br><br>Hospitalisation for and death from heart failure | Swedish inpatient and cause-of-death registers | Heart failure<br><br>Fatty fish (servings):<br><br>Never 1.00<br><1/wk 0<br>1/wk 0 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | with 5 questions on fish intake | | | 2/wk 0<br>>/=3/wk 0<br><br><u>Marine omega-3 fatty acids:</u><br><br>Never 1.00<br><1/wk 0<br>1/wk —<br>2/wk 0<br>>/=3/wk 0 | |
| Levitan (2010)<br><br>Swedish mammography cohort | Sweden | 36019 | 48-83 years | 9 years | Glycaemic index (GI) and glycaemic load (GL)<br><br>Self-reported FFQ questionnaire | Heart failure<br><br>Hospitalisation for and death from heart failure | Swedish inpatient and cause-of-death registers | <u>Heart failure events:</u><br><br>GI or GL **0** | +/+ |
| Guallar-Castillon (2012) | Spain | 40757 | 29-69 | 5 years | Dietary patterns<br><br>Interviews, self-reported food diaries, questionnaire | CHD events and mortality | Hospital discharge registers<br><br>CHD events were classified on the basis of symptoms, signs, biomarkers, and electrocardiogram | <u>Definite CHD events</u><br><u>Westernized Diet Pattern</u><br>Quintile 1: 1 Ref.<br>Quintile 2: 0<br>Quintile 3: 0<br>Quintile 4: 0<br>Quintile 5: 0<br>P for trend 0.51<br><br><u>Evolved Mediterranean Pattern</u><br>Quintile 1) 1 Ref.<br>Quintile 2) —<br>Quintile 3) —<br>Quintile 4) —<br>Quintile 5) —<br>P for trend 0.0013 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Happonen (2004) | Finland | 2005 | 42-60 years | 14 years | Coffee<br><br>Interview - checked 4-d food diary<br><br>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. | CHD events and mortality | National hospital discharge registry; diagnostic information was collected from the hospitals and classified using identical diagnostic criteria | <u>CHD events or mortality</u><br><br>Coffee intake category<br>None **0**<br><br>Light **0**<br><br>Moderate 1.00 (ref)<br><br>Heavy **+** | +/+ |
| Lajous (2013) Health Professionals Follow-up Study/ Nurses Health Study | United States | 79569 (25797 men, 53772 women) | 40-75 years (men) Mean age 56.5 (SD 9.3)<br><br>30-55 (women) Mean age 52.1 (SD7.1) | 22 years | Fish consumption<br><br>Food frequency questionnaire, self-reported surveys | CHD<br><br>( total, nonfatal, and fatal CHD) | Medical records, relatives, postal authorities, or the National Death Index (medical records, death certificates, autopsies used to identify cause of death) | <u>CHD HPFU Study</u><br><br>Males: all associations: **0**<br><br>Females:<br>Meat replaced with fish:<br>*the lowest risk for *total coronary heart disease* was reported when meat was replaced with fish to attain >=3 servings/week<br>–<br><br>*the lowest risk for *fatal coronary heart* | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *disease* was reported when: meat was replaced with fish to attain >=5 servings/week: —<br><br>and when >=5 fish servings/week were consumed: — | |
| Menotti (2012) | Italy | 1139 | 45-64 years | 40 years | Mediterranean diet pattern measured by the Mediterranean Adequacy Index (MAI).<br><br>Weighed food records and dietary recall with experienced dietitians. | CHD fatal events | Hospital and medical records. Interviews with physicians and relatives of deceased | <u>CHD mortality</u><br><br>MAI(1 unit): —<br><br>*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 | -/+ |
| Mostofsky (2010)<br><br>Swedish Mammography Cohort | Sweden | 31823 | 48-83 years | 9 years | Chocolate intake<br><br>Self-reported questionnaire. FFQ. | Heart failure | Link to inpatient and cause-of-death registers | <u>Heart failure</u><br><br>Chocolate (servings):<br><br>None (ref)<br>1-3/month —<br>1-2/wk 0<br>3-6/wk 0<br>1 or >1/d 0<br><br>(p for quadratic trend = 0.0005). | ++/+ |
| Mursu (2008) | Finland | 1950 | 42-60 years | 15.2 years | Dietary flavonoid intake<br><br>Self-reported | Ischaemic stroke and CVD mortality | Regional coronary and stroke register teams collected data on strokes from hospitals | <u>Ischemic stroke</u><br><br>Total flavonoids:0<br>Flavonols: — | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | questionnaire, later checked by interviewer. | | and wards of health centres and classified the events, as explained in detail previously. Data on strokes from the beginning of 1993 were obtained from national hospital discharge and death registers. | (Highest vs lowest quintile)<br><br><u>CVD mortality</u><br><br>Total flavonoids:**0** | |
| Preis (2010) | United States | 43960 | 40-75 | 18 years | Dietary protein<br><br>Food frequency questionnaire (every 4 yrs). | Ischemic heart disease | A review of medical or hospital records. Examination of National Death Index, medical records and autopsy reports. | <u>Ischemic heart disease</u><br><br><u>Q5 vs Q1</u><br><br>Total protein: **0**<br><br>Animal protein **:0**<br><br>Veg protein: **0** | ++/+ |
| Qiu (2003) | China | 50,252 | 40+ (SD: 55.3) | 6 years | Frequency of food intake<br><br>Door to door survey about lifestyle and health conducted by trained physicians. | Cerebrovascular disease mortality | Follow-up reports completed by village physicians | <u>Cerebrovascular disease mortality</u><br><br><u>Meat (times):</u><br><br>Never/seldom: 1.00 (ref)<br><br>1/2 a month: —<br><br>>1/wk: **0** | +/+ |
| Strandhagen (2000) | Sweden | 792 | Age 54 | 26 years | Fruit and vegetable intake<br><br>Self-reported FFQs | Mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death | Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records | <u>Total mortality</u><br><br>Fruit: —<br>Veg: **0**<br><br><u>CVD mortality</u><br><br>Fruit: —<br>Veg: **0** | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD<br><br>Fruit: **0**<br>Veg: **0**<br><br>Cancer<br><br>Fruit: **0**<br>Veg: **0**<br><br>Cancer mortality<br><br>Fruit: **0**<br>Veg: **0** | |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Vascular disease | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Vascular disease: **0** | +/++ |

**DIET – METABOLIC SYNDROME**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Kato (2009) | Japan | 55826 | 40-69 | 10 years | Coffee consumption<br><br>Self-reported FFQ questionnaire | Diabetes | 94% of the self-report cases of diagnosed diabetes were confirmed by medical records | <u>Diabetes</u><br><br><u>Coffee consumption</u><br><br><u>Men</u><br>almost never 1.00 (ref)<br><br>1-2 days per week **0**<br><br>3-4 days per week **0**<br><br>1-2 cups/day —<br><br>3-4 cups/day **0**<br><br>>5 cup/day **0**<br><br>p for trend 0.006<br><br><u>Women</u><br>almost never 1.00 (ref)<br><br>1-2 days per week **0**<br><br>3-4 days per week **0**<br><br>1-2 cups/day **0**<br><br>3-4 cups/day —<br><br>>5 cup/day —<br><br>(p for trend <0.001 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Song (2004)<br><br>Nurses Health Study | United States | 37309 | 45+ years | 8.8 years | Red meat intake<br><br>FFQs. Annual self-reported questionnaire. Contact with some primary care physicians. | Diabetes | Self-reported diagnosis of diabetes followed by telephone interview. | Diabetes<br><br>Highest vs lowest quintile<br><br>Red meat: **+**<br>P trend<0.001<br><br>Processed meat: **+**<br>P trend 0.001 | +/+ |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Diabetes | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Diabetes: **0** | +/++ |
| Tuomilehto (2004) | Finland | 16670 | 35-65 years | 12 years | Self-reported questionnaire. | Diabetes | National Hospital Discharge Register and the Drug Register of the National Social Insurance Institution | Diabetes<br><br>Coffee cups/d<br><br>Women<br><br></=2: 1.00<br>3-4: **0**<br>5-6: –<br>7-9: –<br>>/=10: –<br>P trend <0.001<br><br>Men<br><br></=2: 1.00<br>3-4: **0**<br>5-6: **0**<br>7-9: **0**<br>>/=10: – | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | P trend 0.12<br><br><u>Men and women</u><br><br></=2: 1.00<br>3-4: **0**<br>5-6: —<br>7-9: —<br>>/=10: —<br>P trend <0.001 | |
| Villegas (2010) | China | 64191 | 40-70 years | 6.9 years | Dietary patterns<br><br>Dietary intake, in-person interviews. Dietary patterns were assessed using K-means cluster analysis. Cox regression model for T2D. | Diabetes | Self report of diabetes and at least one of the following criteria as recommended by American Diabetes Association: fasting glucose level 57 mmol/l on at least two separate occasions, or an oral glucose tolerance test (OGTT) with a value 511.1 mmol/l, and/or use of hypoglycaemic medication (i.e. insulin or oral hypoglycaemic drugs). | <u>Diabetes</u><br><br>Dietary pattern low in staples and highest in dairy milk: —<br><br>Dietary pattern with highest energy intake: **0**<br><br>(Reference was dietary pattern highest in staples) | ++/+ |
| Villegas (2011) | China | 116156 (51963 men, 64193 women) | 40-74 years | 12 years | Fish, shellfish, long chain n-3 fatty acids<br><br>Detailed in-person interviews. Questionnaires. | Diabetes | Biennial in person surveys via Shanghai statistic registry | <u>Diabetes</u><br><br><u>Women</u><br><br><u>Fish intake</u><br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 —<br>Q4 —<br>Q5 **0**<br>Ptrend 0.006 | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | <u>Shellfish</u><br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 –<br>Q4 –<br>Q5 –<br>Ptrend 0.003<br><br><u>Men</u><br><br><u>Shellfish</u><br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 –<br>Q4 –<br>Q5 **0**<br>Ptrend 0.003 | |
| Riserus (2007) | Sweden | 770 (plus sub-sample of 440) | 50 | 20 years | Saturated fat intake (using fatty acid composition as a biomarker of saturated fat intake (“saturated fat index”) | Insulin sensitivity | Direct assessment using euglycemic clamp. | <u>Insulin sensitivity</u><br><br><u>Saturated fat index:</u><br>–<br><br>*Increasing sat fat, lower insulin sensitivity*<br>(in all subjects and normal weight subjects only) | +/+ |

**DIET – CANCER**

Note: a positive association (+) with diet is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Wang (2009) | United States | 38408 | 45+ years | 11.5 years | Dietary flavonoids<br><br>Semi-quantitative FFQ<br>. | Cancer | Questionnaires, deaths ascertained through family member reports, postal authorities, National Death index; cancer was identified through pathology or cytology reports. | Total cancer<br><br>Total or individual flavonoids: **0**<br><br>**Other cancers:-**<br><br>breast cancer, colorectal cancer, lung cancer, endometrial cancer, ovarian cancer: **0**<br><br>stomach, pancreatic, bladder, brain, thyroid, cervical cancer, lymphoma/leukemia): **0** | +/+ |
| Tsugane (2004) | Japan | 39065 | 40-59 years | 11 years | Salt and salted food intake<br><br>Self-reported questionnaires: | Gastric cancer | Link to cancer registry | Gastric cancer<br><br>Salt intake<br>Men: **+**<br>Highest vs lowest<br>P trend<0.001<br><br>Women: **0** | +/+ |
| Masaki (2003) | Japan | 5644 | 40-69 | 10 years | Dietary patterns<br><br>Self-reported FFQ. questionnaire | Stomach cancer | Medical examinations, detailed statements of medical care (performed for insured persons) by medical care facilities. | Stomach Cancer<br><br>Vegetable and fruit pattern<br>Low 1.00<br>Middle 0<br>High 0<br>P trend 0.56 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Western breakfast<br>Low 1.00<br>Middle 0<br>High 0<br>P trend 0.20<br><br>Meat<br>Low 1.00<br>Middle 0<br>High 0<br>P trend 0.07<br><br>Rice/snacks<br>Low 1.00<br>Middle 0<br>High 0<br>P trend 0 .05<br><br>There were no clear associations between the four major dietary patterns and stomach cancer risk | |
| Ruder (2011) | United States | 292797 | 40-61 years | 10 years | FFQ questionnaire (self-reported) assessed retrospectively | Colorectal cancer | Primary diagnoses of adenocarcinoma identified through state cancer registries | Risk of colorectal cancer<br><br>Calcium: —<br>Vitamin A: — Vitamin C: —<br>Fruit: — Milk: — (lower risk of colon cancer)<br><br>Total fat: **+**<br>Red meat **+**<br>Processed meat: **+**<br><br>Rectal cancer<br>Fibre **0**<br>Milk — | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Strandhagen (2000) | Sweden | 792 | Age 54 | 26 years | Fruit and vegetable intake<br><br>Self-reported FFQs | Cancer morbidity and cancer death | Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records | <u>Cancer</u><br><br>Fruit: **0**<br>Veg: **0**<br><br><u>Cancer mortality</u><br><br>Fruit: **0**<br>Veg: **0** | ++/+ |
| Elwood (2013) | UK (Caerphilly) | 2235 | 45-59 years | 30 years | 3+ portions of fruit and veg/day<br><br>Self-report, food-frequency questionnaire, cognitive function tests | Cancer | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | <u>Cancer:</u> **0** | +/++ |

**DIET – OTHER CHRONIC DISEASES**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Walda (2002) | Finland, Italy and The Netherlands | 2917 | 50-69 years | 20 years | Antioxidant, fruit, vegetable and fish intake .<br><br>Cross-check dietary history method. FFQ. Interviews. | Chronic obstructive pulmonary disease (COPD) mortality | Access to clinical records | COPD mortality<br><br>Fruit: —<br>Vit C: **0**<br>Vit E: **0**<br>B-carotene **0**<br>Veg: **0**<br>Fish: — | +/+ |
| Hu (2007) | Finland | 29335 | 25-64 years | 18.9 years | Tea and coffee consumption<br><br>Self-reported questionnaire. | Parkinson's disease | National Social Insurance Institution's Register on special reimbursement for drug costs | Risk of Parkinson's Disease<br><br>Volume of coffee consumption (cups/d)<br>Men<br>0 1<br>1–4 **0**<br>5 or > —<br>P-trend<br>0.063<br><br>Women<br>0 1<br>1–4 **0**<br>5 or > —<br>P-trend<br>0.073<br><br>Men and Women<br>0 1<br>1–4 —<br>5 —<br>P-trend<br>0.005 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Volume of tea consumption<br>Men<br>0 1<br>1–4 **0**<br>5 **0**<br>P-trend<br>0.31<br><br>Women<br>0 1<br>1–4 **0**<br>5 –<br>P-trend<br>0.11<br><br>Men and Women<br>0 1<br>1–4 **0**<br>5 –<br>P trend<br>0.038<br><br>**Significant trends**<br>Coffee drinking is associated with a lower risk of PD. More tea drinking is associated with a lower risk of PD | |
| Ross (2000) | US Hawaii | 8004 | 45-68 years | 30 years | Coffee, dietary caffeine<br><br>24 h recall dietary intake by a dietitian | Parkinson's Disease | Hospital records, ongoing review of death certificates, cross-check of records of local neurologists with cohort | Parkinson's Disease<br><br>Coffee (drinkers vs non-drinkers): –<br><br>Caffeine: – | +/+ |

**DIET – MENTAL HEATH**

Note: a negative association (-) with diet is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Xu (2010) | Australia | 564 | 45-60 years | 5 years | Caffeine consumption<br><br>Self-report questionnaire Only 1 question on caffeine dichotomized (yes/no) | Mental health (mental wellbeing, depression, anxiety) | SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire, | <u>Anxiety</u><br><br>Caffeine drinkers vs non-caffeine: **0**<br><br><u>Depression</u><br><br>Caffeine drinkers vs non-caffeine: **0**<br><br><u>Psychological symptoms</u><br><br>Caffeine drinkers vs non-caffeine: **0**<br><br><u>SF-36 Mental Health</u><br><br>Caffeine drinkers vs non-caffeine: **–**<br><br>(lower mental health in caffeine drinkers) | -/+ |
| Hodge (2013) | Australia | 8660 | 50-69 years | 12 years | Dietary patterns [defined by factor analysis or the Mediterranean Diet Score (MDS)]<br><br>The "Australian" diet:(negative loadings for olive oil and | Psychological distress | Kessler Psychological Distress Scale (K10). | Highest vs lowest adherence to Mediterranean Diet (MDS). **–**<br><br>Highest vs lowest adherence to traditional Australian Diet: **–** | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | feta cheese, and positive loadings for breakfast cereal, wholemeal bread, cheddar cheese, vegetables<br><br>Food frequency questionnaire | | | | |
| Lehto (2013) | Finland | 2600 | 42-61 years | 20.1 years | Energy-adjusted dietary zinc intake<br><br>4-day food record | Depressive symptoms | Depression was defined as having received a hospital discharge diagnosis of unipolar depressive disorder | <u>Depression</u><br><br><u>Energy adjusted zinc intake:</u> **0** | +/+ |
| Ruusanen (2010) | Finland | 2232 | 42-60 years | 17.5 years | Coffee, tea, caffeine<br><br>4day food recording, self-reported, checked by nutritionists | Severe depression | National hospital discharge register | <u>Coffee (ml/d)</u><br>None 1<br>Light (<375): —<br>Moderate(375-813): **0**<br>Heavy: —<br><br><u>Tea (ml/d)</u><br>None 1<br>Light (<375): **0**<br><br><u>Caffeine</u><br>All categories: **0** | +/+ |

**DIET – PRECONDITIONS (FOR DEMENTIA, DISABILITY, FRAILTY)**

Note: a positive association (+) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Wang (2012) | United States | 28082 | 39+ | 12.9 years | Fruit and vegetable consumption<br><br>Semi-quantitative FFQs. | Hypertension | Incident hypertension was identified from annual follow-up questionnaires. | Fruit & veg: **0**<br><br>Fruit: **0**<br><br>Vegetables: **0** | +/+ |
| Wang (2008) | United States | 28766 | 45+ years (SD 53.8) | 10 years | Dairy products<br><br>Self-reported questionnaire | Incidence of hypertension | 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 | Low fat dairy<br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 **0**<br>Q4 **0**<br>Q5 –<br>Ptrend 0.001<br><br>High fat dairy<br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 **0**<br>Q4 **0**<br>Q5 **0**<br>Ptrend 0.17<br><br>Total dairy<br><br>Q1 ref 1.00<br>Q2 **0**<br>Q3 –<br>Q4 –<br>Q5 –<br>Ptrend 0.003 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Song (2006) | United States | 28349 | 45+ years | 9.8 years | Dietary magnesium<br><br>Self-reported<br><br>FFQ. | Hypertension | Hypertension based on self-reported BP, treatment, and/or physician diagnosis | Hypertension<br><br>Highest vs lowest quintile<br><br>Magnesium: **0** | +/+ |
| Miura (2004) | United States | 1710 | 40-55 years<br><br>(Mean 48.5) | 39 years | Fruit and vegetables<br><br>Standardised interviews and questionnaires, by two nutritionists | Systolic or diastolic blood pressure | Standard mercury sphygmomanometers | *Systolic blood pressure* (men)<br><br>Vegetables (cups/month)<br><14 ref<br>14–42 **0**<br>>42 **0**<br><br>Fruits (cups/month)<br><14 ref<br>14–42<br>>42 **0**<br>14–42 —<br>>42 **0**<br><br>Fish (120-g units/month)<br>None (ref)<br><4 **0**<br>4–8 **0**<br>>8 **0**<br><br>Beef-veal-lamb (120-g units/month)<br><br>8–20 **+**<br>>20 +<br><br>Pork (120-g units/month)<br><br>4–8 **+**<br>>8 **0** | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Poultry (120-g units/month)<br>4–8 **0**<br>>8 **0**<br><br>*Diastolic blood pressure*<br><br>Vegetables (cups/month)<br>14–42 **0**<br>>42 **0**<br><br>Fruits (cups/month)<br>14–42 **0**<br>>42 **0**<br><br>Fish (120-g units/month)<br><4 **0**<br>4–8 **0**<br>>8 **0**<br><br>Beef-veal-lamb (120-g units/month)<br>8–20 **0**<br>>20 **+**<br><br>Pork (120-g units/month)<br>4–8 **0**<br>>8 **0**<br><br>Poultry (120-g units/month)<br>4–8 +<br>>8 + | |

**DIET – PRECONDITIONS (OBESITY)**

Note: a negative association (-) with diet is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Liu (2003) | United States | 74091 | 38-63 years | 12 years | Changes in intakes of dietary fibre and grain products<br><br>Self-reported<br><br>Food frequency questionnaires. | Changes in weight and development of obesity | Self-reported height and body weight at 2-4 year intervals<br><br>(when self-reported and measured weights were compared in a sample of participants, correlation was 0.96) | <u>Obesity (BMI >/=30)</u><br><br><u>Wholegrains (change in intake)</u><br>Q1 (ref) 1.00<br>Q2 –<br>**Q3** –<br>**Q4** –<br>**Q5 (high intake)** –<br>P trend 0.0002<br><br><u>Refined grains (change in intake)</u><br>Q1 (ref) 1.00<br>Q2 **0**<br>**Q3** **0**<br>**Q4** **0**<br>**Q5 (high. intake)** **0**<br><br><u>Dietary fibre (change in intake)</u><br>Q1 (ref) 1.00<br>Q2 –<br>**Q3** –<br>**Q4** –<br>**Q5 (highest intake)** –<br>P trend <0.0001<br><br><u>Weight gain >/= 25 kg</u><br><br><u>Wholegrains (change in intake)</u><br><br>Q1 (ref) 1.00 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Q2 **0**<br>**Q3 0**<br>**Q4 0**<br>**Q5 (highest intake) 0**<br><br><u>Refined grains (change in intake)</u><br><br>Q1 (ref) 1.00<br>Q2 **0**<br>**Q3 0**<br>**Q4 0**<br>**Q5 (highest intake) 0**<br><br><u>Dietary fibre (change in intake)</u><br>Q1 (ref) 1.00<br>Q2 –<br>**Q3** –<br>**Q4** –<br>**Q5 (highest intake)** –<br>P trend <0.0001 | |
| He (2004) | United States | 74063 | 38-63 years | 12 years | Fruit and vegetables<br><br>Self-reported semi quantitative food frequency questionnaire | Obesity defined as BMI >=30 kg/m2 and major weight gain as weight gain of 25 kg or more during follow-up | Self-reported body Weight captured through questionnaire every other year; when self-reported weight was compared with measured weight, correlation was 0.96 | <u>Obesity</u><br><u>Change in fruit and veg (servings/day):</u><br><br>-2.36 1.00 (ref)<br>-0.49 –<br>+0.64 –<br>+1.83 –<br>+3.99 –<br>P trend <0.0001<br><br><u>Weight gain >/+25kg:</u><br><br><u>Change in fruit and</u> | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | veg (servings/day):<br><br>-2.36 1.00 (ref)<br>-0.49 **0**<br>+0.64 **0**<br>+1.83 –<br>+3.99 –<br>P trend 0.01<br><br>Similar trends also reported for fruits or vegetables separately | |

**Footnotes:**

I. Data is from multivariate models.
II. Where multiple models have been reported data from the most adjusted (or most relevant) model has been used.
III. + = significant positive association, – = significant inverse association, 0 = no significant association

## Table 12. Overview of included studies – Smoking

**SMOKING – SUCCESSFUL AGEING / QUALITY OF LIFE / WELL-BEING**
Note: A positive association (+) with smoking is the better outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Britton 2008 | England | 5823 (civil servant) | 35-55 | 17yrs | Self-report<br>• Never, former, current smoker | Successful aging, i.e. free from major disease and good physical & mental health | Walking speed, lung function, Alice Heim 4-I cognitive test, physical component SF36, self-report, medication use, clinical examinations, | Current smoker: 1<br>• Non-smoker: **+**<br><br>Less exposure: **+** (in men & women) | +/++ |
| Strandberg 2008 | Finland | 1658 | 40-55 | 26yrs | Self-report<br>• 5 categories from never >20) | Bodily pain, general health, Mental health/emotional wellbeing, role limitations owing to mental problems or to physical health, Social functioning, Energy vitality, Physical functioning | RAND-36/SF-36 | *All dimensions:*<br>• Never smoker: **+**<br>• Smoking: **–**<br><br>*Except Role limitations owing to physical fx:*<br>• Never smokers: **+**<br>• Smoking: **0** | +/+ |
| Wilcox 2006 | USA | 5820 Japanese American men | Mean 54yrs (45-68) | Up to 40yrs | Self-report<br>• Ever or never | Overall survival<br>• Non survivors: before age 75, 80, 85, 90<br>• Usual survivors + disabled<br>• Usual survivors: wt major chronic diseases no disability<br>• Exceptional survivors | Obituaries in local newspapers (English and Japanese) and through surveillance of hospital discharge records | Nonsurvival vs survival at 85yr<br>• Ever smoker: +<br><br>Usual survival vs Except. survival<br>• Ever smoker: + *(borderline association)* | ++/- |

**SMOKING – FRAILTY/DISABILITY (including fractures)**

Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Agahi 2013 | Sweden | 1060 | 30-50 | Up to 34yrs | Interview:<br>• None, light, heavy smoker (>10 cig/day)<br>• Current, persistent & former smoker | Mobility impairment (rate of increase / progression)<br><br>Musculoskeletal pain (rate of increased / progression)<br><br>Psychological distress | **Mobility impairment:** Index measuring ability to walk, run go up stairs (0=no problem; 3=problem all 3 domains)<br><br>**Musculoskeletal pain:** Pain index in past 12 months ranging from 0 (no pain) to 6 points (severe pain)<br><br>**Psychological distress** 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) | **Mobility impairment:**<br>Non Smoker: 1<br>• Persist heavy: +<br>• Former heavy: +<br>• Former light: +<br><br>Persist non-smoker: 1<br>• All categories: +<br><br>**Musculoskeletal pain:** 0<br><br>**Psychological distress:**<br>Persist non-smoker: 1<br>• Heavy smoker: + | -/++ |
| Ostbye 2002 | US | 7,845 | 51-61 years | HRS: 6yrs | Self-report<br>Heavy smokers (1+ pack cig./day), light (<1 pack/day), former smokers (quit < 3 years, quit 3-15 years, quit 15+ years ago), never smokers | Disability<br>• ADL<br>Impaired mobility<br>• difficulty walking<br>• climbing stairs<br>•<br>Self-reported health<br><br>Hospitalisation | Participant interviews | Never smoked = 1<br>***FOR all specific outcomes:***<br>• Heavy: +<br>• Light: +<br>• Former <3yrs: +<br>• Former 3-15yrs: +<br>• Former 15+yrs: 0 | -/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Englund 2013 | Sweden | 778 | 54±5.9 | 11.2±2.6 | Self-report<br>Never, former, current smoker | Wrist fracture | Injury-fracture database | Never smoker: 1<br>• Former: 0<br>• Current: 0 | +/++ |
| Holmberg 2006 | Sweden | 22444 (M)<br>10902(W) | Men: 27-61 yrs<br>Women: 28-58 yrs | 19yrs (M)<br>15yrs (W) | Self-report<br>• Smoke or not | Incident low-energy fractures (those resulting from falling from standing height or less)<br>• Any fracture, vertebral, forearm, hip, humerus, ankle | Data linkage with hospital medical, radiological files | Non-smoker: 1<br>(vs smoker)<br>**Women:**<br>• Vert fracture: +<br>• All other types: 0<br>**Men:**<br>• Any fract: +<br>• Forearm fract: 0<br>• Vert fracture: +<br>• Prox humerus: +<br>• Ankle: 0<br>• Hip: + | +/++ |
| Moayyeri 2009 | UK | 25,311 | W: 64.7 (8.4)<br>M: 61.9 (9.7)<br>(40-75yrs) | 11.3yrs (SD = 1.5; range 9.2–14.1) | Self-report<br>• Never; former, i.e. as much as one cig/day for more than 1 yr; current | Osteoporotic fractures | Hospital records & ICD 9-10 diagnostic codes | Never smoker: 1<br>• WomenCurrent: 0<br>• Men current: 0 | +/++ |
| Szoeke 2006 | Australia | 438 | 46-52 | 11 years | Self-report (Y/N) | Osteoarthritis | X-ray | Never smokers: 1<br>Smoking: + | +/- |

**SMOKING – DEMENTIA**
Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Sabia 2008 | England | 5388 | 35-55 | 85-88 to 97-99 | Self-report<br>• Never, long-term ex-smoker; recent ex-smoker, current<br><br>Current smoker: pack-years based on g/day with 1 cig.=1g and 1 cigar=3g | Memory, reasoning, vocabulary, semantic and phonemic fluency | Cognitive function battery of tests (e.g., 20-word free recall test, Alice Heim AH4 Group Test of General Intelligence, Mill Hill Vocabulary Test, verbal fluency tests) | **(OR of being in the lowest quintile of cognitive function)**<br>Never smoker: 1<br>*Memory*<br>• LT ex-sm.: –<br>• Recent ex.: 0<br>• Current sm.: +<br><br>*Reasoning*<br>• LT ex-sm.: 0<br>• Recent ex-sm.: 0<br>• Current sm.: 0<br><br>*Vocabulary*<br>• LT ex-sm.: –<br>• Recent ex-sm.: –<br>• Current sm.: 0<br><br>*Phonemic fluency*<br>• LT ex-sm.: –<br>• Recent ex-sm.: 0<br>• Current sm.: 0<br><br>*Semantic fluency*<br>• LT ex-sm.: –<br>• Recent ex-sm.: –<br>• Current sm.: 0 | +/++ |
| Sabia 2009 | England | 5123 | Mean 56yrs | 5yrs | Self-report current smoking | Cognitive function<br>Short-term assoc. with poor executive function & memory | Cognitive tests to measure executive function (reasoning, verbal fluency measures) | Current smoking<br><br>No: 1<br>Yes: + | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nooyens 2008 | Netherlands | 1964 | 56.0 (7.0) | 5yrs | Self-report<br>Never, former, current, recent quitter, resumed smoking | Cognitive decline | Neuropsychological test battery,15-Word Verbal Learning Test, Stroop Color–Word Test<br>Animal Naming Verbal Fluency Tes | Never Smoker: 1<br>• Mem function: +<br>• Speed of cog processing: +<br>• Cog Flexibility: +<br>Global cog Fx: 0 | +/+ |
| Alonso 2009 | USA | 11,151 | 45-64 | Up to 10yrs | Self-report<br>Never, former, current smoker | Incident dementia | Participant & proxy report; chart abstraction; 3 cognitive tests | Never smoker: 1<br>• Current: + | +/+ |
| Whitmer 2005 | USA | 8,845 | 40-44 | 27yrs<br>('64-'03) | Self-report<br>never or ever smoked | Dementia | Electronic medical records | Never smoker: 1<br>Smoking: + | +/- |
| Rusanen 2011 | USA | 21,123 | 50-60 | 17yrs | Self-report<br>Never; former; current smoker: less than 0.5 pack/day, 0.5-1 pack/day, 1-2 packs/day, 2+ packs/day | Dementia, Alzheimer's disease AD), vascular dementia (VD) | Electronic health records with ICD codes | Never smoker: 1<br>***Dementia***<br>Current-pack/d:<br>• <0.5: 0<br>• 0.5-1: +<br>• 1-2: +<br>• >=2: +<br>***AD***<br>• Former: 0<br>Current, pack/d:<br>• <0.5: 0<br>• 0.5-1: 0<br>• 1-2: 0<br>• >=2: +<br>***VD***<br>• Former: 0<br>Current, pack/d:<br>• <0.5: 0<br>• 0.5-1: 0<br>• 1-2: +<br>>=2: 0 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Kimm 2011 | Korea | 3252 | Men 51.9 ±8.7<br><br>Women 53.6 ±9.9 | 14yrs | Self-report Never, former, current smoker | Dementia<br>Alzheimer's disease AD, vascular dementia VD, unspecified | ICD-10; medical history, physical, neuro. lab and imaging evaluation | Never smoker: 1<br>**AD & VD - Men**<br>• Former: 0<br>• Current: 0<br>**AD & VD - Women**<br>• Former: 0<br>• Current: +<br>**Unspec – both sex**<br>• Former: 0<br>• Current: +<br>**All – both sex**<br>• Former: 0<br>Current: + | +/+ |
| Tyas 2003 | Hawaii | 3734 | (mid-life) | ('65–'71) and ('91–'96) | Self-report<br>Never, former, current smoker | Vascular dementia | DSM-III-R | Smoking:<br>+ | +/- |
| Debette 2011 | USA | 1352 | 61±9 | 10yrs | Self-report Smoke or not | White matter, total brain, and LV temporal horn volume<br><br>Verbal memory, visuospatial memory and exec. function | Brain MRI techniques<br><br>Validated cognitive tests | White matter vol.: 0<br>Total brain vol.: -<br>Temp. horn vol +<br>Verbal memory: 0<br>Visual memory: 0<br>Exec function: 0 | +/+ |
| Knopman 2001 | USA | 10,963 | 47-70 | 6yrs | Self-report<br>Never, former, current smoker | Cognitive change | Change in follow-up scores minus baseline scores for cognitive testing using: Delayed Word Recall test, the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised, First Letter | Never: 0<br>Former: 0<br>Current: 0 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | World Fluency test | | |
| Strand 2013 | Norway | 48,793 | 35–50 | 35yrs | Self-report | Dementia death | Death with ICD codes | Non-smokers: 0<br>Current <15: 0<br>Current 15+: 0 | ++/- |

**SMOKING – OVERALL MORTALITY**
Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Shaper 2003 | Britain | 7735 | 40–59 | 22yrs ('78-'00) | Self-report<br>8 categories; none to current | Total mortality | National Health Service register | Never smoker: 1<br>• Pipe/cigar (primary & secondary): +<br>• Former: 0<br>Current: + | ++/++ |
| Strandberg 2008 | Finland | 1658 | 40-55 | 26yrs ('74-'00) | Self-report (5 categories from never >20) | Mortality | National Population Information System of the Finnish Population Register Centre | Never smoker: -<br>Smoking: + | +/+ |
| Qiao 2000 | Finland | 1673 | Not reported | 35yrs | Self-report<br>Never, former, current smoker | Mortality (range of specific outcomes) | Death certificate | Men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers | +/+ |
| Pelkonen 2000 | Finland | 1582 | Not reported | 30yrs | Self-report<br>Never, former, current smoker<br><br>Exp: Smoking cessation | Mortality | Death certificate | Smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking | ++/+ |
| Lim 2013 | Singapore | 48,251 | 45-74 | 93-98 to 2009 | Self-reported<br>• Never,<br>• Long-term quitters (quitter at baseline and f/u interview),<br>• New quitters | Mortality: all-cause, lung cancer, other cancers, coronary heart disease, stroke, chronic obstructive | Nationwide death registry with ICD code | Current smoker: 1<br>*All-cause*<br>• New quitters: -<br>• LT quitters: -<br>• Never: -<br><br>*Other than lung* | -/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | (baseline smoking and quitter at f/u interview),<br>• Current smokers (smoking at baseline and f/u interview) | pulmonary disease | | *cancer mortality*<br>• New quitters: 0<br>• LT quitters: -<br>• Never: - | |
| Gerber 2012 | Israel | 4633 | 50.1±6.5 | Median 26yrs (quartiles 1–3: 16–35) | Self-report<br>• Never, former; current 1–10, current 11–20, current more than 20 cigarettes per day<br><br>Exposure: change in smoking intensity | All cause mortality | Mortality register | Maintained: 1<br>*All cause mortality*<br>• Increased: 0<br>• Reduced: -<br>• Quit: - | ++/+ |
| Hara 2002 | Japan | 41,484 | 40-59 | Never: 64,986 PA<br><br>Former: 42,798 PA<br><br>Current: 103,537 PA | Self-report<br>Never, former, current smoker | All cause mortality | Death certificates | Never smoked: 1<br>Former (M & F): 0<br>Current (M & F): + | +/+ |

**SMOKING – CARDIOVASCULAR MORTALITY**
Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Blanco-Cedres 2002 | USA | 8,816 | 40-59yrs | 25yrs | Self-report<br>Past/current status | CHD death, CVD death, all-cause mortality (per strata cholesterol levels) | Social Security Administration and National Death Index records | Non-smoker: 1<br>• CHD Current: +<br>• CVD Current: +<br>• All cause mort. current: +<br>*Across all choles. levels* | +/+ |
| Boudik 2006 | Prague | 926 men | Mean 46.1 (Middle aged men) | 21yrs | Self-report<br>non-smokers; <15cig/d; >=15cig/day (heavy); ex heavy smokers <1yr | Atherosclerotic CVD mortality | Outpatient departments, postal questionnaires, and registry offices | <15cig/d = 1<br>>=15cig/d: + | -/+ |
| Baba 2006 | Japan | 41,307 | 40-59yrs | 11yrs | Self-report:<br>• Never, ex, current smoker<br>• Additional categories for male 'current smokers': 1-14, 15-34, >35/day | Acute coronary events [MI, sudden cardiac death, other fatal coronary events] | MI (Monica criteria)<br>Death certificates | Never smoker: 1<br>• Current: +<br>• Past smoker: +<br>• Men: + (increase with increase # of cig/day<br>• Women: + | +/+ |
| Hara 2002 | Japan | 41,484 | 40-59 | Never: 64,986 PA<br><br>Former: 42,798 PA<br><br>Current: 103,537 PA | Self-report<br>Never, former, current smoker | Circulatory death | Death certificates | Never smoked: 1<br>• Former (M & F): 0<br>• Current (M): -<br>• Current (F): + | +/+ |
| Gerber 2012 | Israel | 4633 | 50.1±6.5 | Median 26yrs (quartiles 1–3: | Self-report<br>• Never, former; | CVD death<br>Non-CVD death | Mortality register | Maintained: 1 | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 16–35) | current 1–10, current 11–20, current more than 20 cigarettes per day | | | *CVD mortality*<br>• Increased: 0<br>• Reduced: -<br>• Quit: - | |
| Lim 2013 | Singapore | 48,251 | 45-74 | 93-98 to 2009 | Self-reported<br>• Never,<br>• Long-term quitters (quitter at baseline and f/u interview),<br>• New quitters (baseline smoking and quitter at f/u interview),<br>• Current smokers (smoking at baseline and f/u interview) | Mortality from coronary heart disease, stroke, chronic obstructive pulmonary disease | Nationwide death registry with ICD code | Current smoker: 1<br><br>*CHD mortality*<br>• New quitters: 0<br>• LT quitters: -<br>• Never: -<br><br>*Stroke mortality*<br>• New quitters: 0<br>• LT quitters: 0<br>• Never: -<br><br>*COPD mortality*<br>• New quitters: 0<br>• LT quitters: -<br>Never: - | -/+ |
| Qiu 2003 | China | 50,069 | 55.3±11.8 | 6yrs | Self-report<br>• Never, former, current smoker | CVD death | Physician report to township hospital | Non-smoker: 1<br>• Former: 0<br>• Current: 0 | +/- |
| Gerber 2012 | Israel | 4633 | 50.1±6.5 | Median 26yrs (quartiles 1–3: 16–35) | Self-report<br>• Never, former; current 1–10, current 11–20, current more than 20 cigarettes per day | CVD death<br>Non-CVD death | Mortality register | Maintained: 1<br><br>*CVD mortality*<br>• Increased: 0<br>• Reduced: -<br>• Quit: - | ++/+ |
| Lim 2013 | Singapore | 48,251 | 45-74 | 93-98 to 2009 | Self-reported<br>• Never, | Mortality from coronary heart | Nationwide death registry with ICD code | Current smoker: 1 | -/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | • Long-term quitters (quitter at baseline and f/u interview),<br>• New quitters (baseline smoking and quitter at f/u interview),<br>• Current smokers (smoking at baseline and f/u interview) | disease, stroke, chronic obstructive pulmonary disease | | *CHD mortality*<br>• New quitters: 0<br>• LT quitters: -<br>• Never: -<br><br>*Stroke mortality*<br>• New quitters: 0<br>• LT quitters: 0<br>• Never: -<br><br>*COPD mortality*<br>• New quitters: 0<br>• LT quitters: -<br>Never: - | |
| Qiu 2003 | China | 50,069 | 55.3±11.8 | 6yrs | Self-report<br>• Never, former, current smoker | CVD death | Physician report to township hospital | <u>Non-smoker:</u> 1<br>• Former: 0<br>• Current: 0 | +/- |

**SMOKING – CARDIOVASCULAR OUTCOMES**
Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Shaper 2003 | Britain | 7735 | 40–59 | 22yrs | Self-report<br>8 categories; none to current | Cardiovascular events | Questionnaires on recall of doctor | Never smokers: 1<br>• Pipe/cigar (primary and secondary): +<br>• Former: 0<br>• Current: + | ++/+ |
| Humphries 2001 | UK | 3052 men | 55.7±3.2 | 11yrs | Self-report<br>• Never; former, i.e. as much as one cig/day for more than 1 yr; current | Coronary hearth disease (according to APOE genotype) | ECG | Never smoked: 1<br>Ex-smokers<br>• E3/E3 : 0<br>• E2+ : 0<br>• E4+ : 0<br><br>Smokers<br>• E3/E3 : 0<br>• E2+ : 0<br>• E4+ : ++ | +/+ |
| Satoh 2006 | Japan | 2,764 | 35-44 | 10yrs | Self-report | Coronary Artery Disease | Subject's clinical chart | Non-smoker: 1<br>Smokers: 0 | +/- |
| Mannami 2004 | Japan | 19,782 men and 21,500 women | 40-59 | 90-92 to 01 (total of 461,761 person-year follow-up) | Self-reported smoking (never-smokers, ex-smokers, and current smokers; current smokers: number of cigarettes 1 to 19/d, 20 to 39/d,<br>• and >= 40/d) | Total stroke,<br>Intraparenchyma hemorrhage,<br>Subarachnoid hemorrhage,<br>Ischemic stroke | Medical records, death certificates with ICD codes | Never smoked: 1<br><br>Former - Men or Women:<br>• Range of CV outcomes: 0<br><br>Current – Men:<br>• Total stroke: +<br>• Intraparenchymal haemorrhage: 0<br>• Subarachnoid haemorrhage: +<br>• Ischemic stroke + | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | • Lacunar infarct: +<br>• Large-artery occlusive infart: +<br>• Embolic infarct: 0<br><br><u>Current – Women</u>:<br>• Total stroke: +<br>• Intraparenchymal haemorrhage: 0<br>• Subarachnoid haemorrhage: na<br>• Ischemic stroke 0<br>• Lacunar infarct: +<br>• Large-artery occlu. Infart: na<br>• Embolic infarct: 0<br><br>*Details on smoking intensity available* | |
| Harmsen 2006 | Sweden | 7457 | Middle-age men | 28yrs | Self-report<br>• never smokers & former smokers coded non-smoker; current smokers | Stroke | First ever stroke from multiple sources | <u>Non-smoker</u>: 1<br>Smoking: + | +/+ |
| Nakayama 2000 | Japan | 998 | 40-64yrs | 20yrs | Not reported | Stroke | Laboratory and diagnostic imaging examined by clinicians | Smoking : +<br>PAF: 14.9 (+) | +/- |
| Janzon 2004 | Sweden | 10619 | 49 yrs (28.3-57.6) | 14.0±4.5yrs (range 0.5–21.9 years) | Self-report<br>• Never, former, low smoker <10cig/day, medium smoker>10 <20 cig/day; heavy smoker >20cig/day | Myocardial infarction (according to other risk factors) | Malmo Myocardial Infarction register and from the Swedish Myocardial Infarction register | <u>Never smoker</u><br>• Normotension 0<br>• Hypertension +<br>• Norm Chol 0<br>• High Chol: +<br>• No diabetes 0<br>• Diabetes +<br><br><u>Ex-smoker</u><br>• Normotension 0 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | • Hypertension +<br>• Norm Chol 0<br>• High chol: +<br>• No diabetes +<br>• Diabetes +<br><br><u>Current smoker</u><br>• Normotension +<br>• Hypertension +<br>• Norm Chol +<br>• High chol: +<br>• No diabetes +<br>Diabetes + | |
| Dubas 2007 | Sweden | 7388 | 47-55 | 28yrs<br>('70-'98) | Self report (5 point scale; 1 cig=1g tobacco) | All AMI | At discharge or death with ICD codes | <u>Never smoker</u>: 1<br>Former: +<br>1–14 g/day: +<br>15–24 g/day: +<br>>25 g/day: +<br><br>Smoking (1–5): + | ++/+ |
| | | | | | | Coronary bypass | At discharge or death with ICD codes | <u>Never smoker</u>: 1<br>Former: 0<br>1–14 g/day: 0<br>15–24 g/day: 0<br>>25 g/day: +<br><br>Smoking (1–5): + | |
| Halperin 2008 | USA | 13,529 | 52.4±8.9 | Med 14.5yrs<br>Max 20.5yrs | Self-report<br>• never, former, current, #cig /day | Hypertension | Self-reported BP and/or the initiation of antihypertensive | <u>Never smoker</u>: 1<br>• Past: +<br>• <20cig/day: +<br>• ≥20cig/day: -<br>• Current: + | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Räikkönen 2001 | USA | 541 | 48.0±1.5 | 9.2yrs; SD, 3.4 years | Self-report<br>• Number of cig/day | Hypertension | Use of BP medication and/or had elevated systolic BP or diastolic BP on 2 consecutive | • Smoking (no/yes) 0 | +/- |
| Khalili 2002 | Sweden | 22 444 – (not clear) | Mean 42.2 | 17yrs | Self-report | Relationship between systolic BP Cardiovascular | Registers (local & national) | Non-smoker: 1<br>• CVD Morbidity: +<br>• CVD Morbidity (in BP drugs): +<br>• Mortality: +<br>• Mortality (in BP drugs): + | +/+ |

**SMOKING - DIABETES/METABOLIC SYNDROME**

Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Wannamethe 2001 | UK | 7735 | 40-59 | 16.8 yrs | Self-report<br>8 categories; none to current | Type 2 diabetes | Self-report postal questionnaires and review of all death certificates | Never smoker: 1<br>Smoking: + | +/+ |
| Patja 2005 | Finland | 41 372 | 25–64 | Mean follow-up 21 years | Self-report<br>• Never, former, current smoker - smokers);<br><br>Current smokers: <20 vs. >20 cig. | Type 2 diabetes | Hospital discharge register, social insurance drug register | Never smoker: 1<br>**Men:**<br>• Former: 0<br>• Current <20cig/day: +<br>• Current >=20cig/day: +<br><br>**Women:**<br>• Former: 0<br>• Current <20cig/day: +<br>• Current >=20cig/day: +<br><br>**Men and women combined:**<br>• Former: 0<br>• Current <20cig/day: +<br>• Current >=20cig/day: + | -/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Sairenchi 2004 | Japan | 39,528 men and 88,613 women | 40-79 (sub group: 40-59) | 93-02 | Self report<br>• Never, former, current smoker<br>For smoker: number of cigarettes smoked per day) | Type 2 diabetes mellitus | Annual follow-up examinations with measurement of plasma glucose levels and interview on diabetes medications | Never smoker: 1<br>*Men:*<br>• Former: +<br>• Current: +<br>• < 20 cig/day: +<br>• >=20 cig/day: +<br>*Women:*<br>• Former: 0<br>• Current: +<br>• <20 cig/day: +<br>• >=20 cig/day: + | +/+ |
| Fogelholm 2000 | Finland | 1143 | 36-88 | 10 yrs ('85-'95) | Self-reported smoking (smoker vs. non-smoker)<br>• | Weight change | Self-report | Never smoker: 1<br>Smoking: + | +/+ |
| Holme 2007 | Norway | 6382(M) | 40-49 | 28yrs | Self-report<br>• Never, former, current smoker | Metabolic syndrome | 3 out of 5 clinical criteria | Never smoker: 1<br>• Current: + | +/++ |
| | | | | | | Diabetes | Clinical assessment | Never smoker: 1<br>Current: 0 | |
| Riserus 2007 | Sweden | 770 | 50 | 20 yrs (70-73 to 91-95) | Self-report<br>• Smoke vs not | Insulin sensitivity | Hyperinsulinemic – euglycemic clamp used to calculate glucose infusion rate | Never smoker: 1<br>• Smoking: 0 | +/+ |

**SMOKING – CANCERS**

Note: A positive association (+) with smoking is a **worst** outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Shaper 2003 | Britain | 7735 | 40–59 | 21.8yrs<br>(20 – 22.5) | Self-report<br>8 categories; none to current | Cancer | The cancer registry | • Never smokers: 1<br>• Pipe/cigar (primary and secondary): +<br>• Former: +<br>• Current: + | ++/++ |
| Stevens 2009 | England Scotland | 1.3 million | 50-60<br>(women) | 5-9yrs | Self-report<br>Never, former, current smoker | Pancreatic cancer | NHS central register | • Never smoker: 0<br>• Former: -<br>• Current (<15): + | ++/++ |
| Otani 2003 | Japan | 19,862 (cohort 1)<br><br>10,212 (cohort 2) | 48.9 (6.0) (cohort 1)<br><br>53.4 (8.2) (cohort 2) | 10yrs (cohort 1)<br><br>7yrs (cohort 2) | Self-report<br>• Never, former, current smoker<br><br>Smoker: Pack-years <20, 20–29, 30–39, 40+ | Colorectal cancer<br>Invasive colorectal cancer<br>Colon cancer<br>Rectal cancer | JPHC cancer registry based on site codes | Never smoker: 1<br>*Colorectal*<br>• Former: 0<br>• Current: +<br>Pack-years<br>• <20: 0<br>• 20–29: 0<br>• 30–39: +<br>• 40+: 0<br>*Invasive Colorectal*<br>• Former: +<br>• Current: +<br>Pack-years<br>• <20: 0<br>• 20–29: 0<br>• 30–39: 0<br>• 40+: +<br>*Colon / rectal*<br>• Former: 0<br>• Current: 0 | +/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Pack-years<br>• <20: 0<br>• 20–29: 0<br>• 30–39: +<br>• 40+: 0 | |
| Sobue 2002 | Japan | 91,738 | 40–69 | 9yrs | Self report<br>Never, former, current smoker | Squamous cell small cell carcinoma | Histologic examination of specimens from surgery or autopsy, biopsy or cytology | • Non-smoker: 0<br>• Former: +<br>Current: + | ++/+ |
| | | | | | | Adenocarcinoma | Histologic examination of specimens from surgery or autopsy, biopsy or cytology | • Non-smoker: 0<br>• Former: -<br>Current: + | |
| Lim 2013 | Singapore | 48,251 | 45-74 | 93-98 to 2009 | Self-reported<br>• Never,<br>• Long-term quitters (quitter at baseline and f/u interview),<br>• New quitters (baseline smoking and quitter at f/u interview),<br>• Current smokers (smoking at baseline and f/u interview) | Lung cancer, mortality from other cancers, coronary heart | Nationwide death registry with ICD code | Current smoker: 1<br>*Lung cancer*<br>• New quitters: -<br>• LT quitters: -<br>• Never: -<br>*Other than lung cancer mortality*<br>• New quitters: 0<br>• LT quitters: -<br>• Never: - | -/+ |

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association | Quality/Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Inoue 2004 | Japan | 92,792 | 40-69 (mean 53) | 10 yrs | Self report<br>Never, former, current smoker | Cancers<br>Death (due to cancer) | Active patients' notification from local major hospitals; data linkage with population-based cancer registries; death certificate | Never smoker: 1 (M & W)<br>• Former: +<br>• Current: +<br># daily cig (dose):<br>• Men: +<br>• Women: -<br>Pack/year (dose):<br>• Men: +<br>• Women: -<br>Age started smoke:<br>• Men: +<br>• Women: - | +/+ |
| | | | | | | Total cancer death | Death certificate | Never smoker: 1 (M&W)<br>• Men former: +<br>• Men Current: +<br>• Women former: -<br>• Women current: +<br># daily cig (dose): -<br>Pack/year (dose): -<br>Age started smoke:<br>• Men: +<br>• Women: - | |

| **SMOKING – OTHER OUTCOMES**<br>Note: A positive association (+) with smoking is a **worst** outcome | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Noborisaka 2013 | Japan | 6998 | Men 84.3% bt 30-59yrs<br><br>Women 86.3% bt 30-59yrs | 6 yrs | Self-report<br>• Never, former, current up to one pack/day, current smokers > one pack/day | Chronic kidney condition | Categorisation in subjects based on single measurements of proteinuria and eGFR | Non-smoker: 1<br>• Former: 0<br>• Smoking: + | +/- |

## Table 13. Overview of included studies – Smokeless tobacco (snus)*

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association (–/+/0)* | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Nafziger (2007) | Sweden | 82927 | 30-60 | 10 years | Health surveys, medical examinations | Maintaining weight | BMI | User: -<br>Non-user: + | ++/+/- |
| Östenson 2012 | Sweden | 2382 | 47.2<br>(46.9–47.4) | 10 years | Self-report<br>Never, former, current smoker **of SNUS** | Type 2 diabetes | Oral glucose tolerance test | Never use SNUS: 1<br>• Former: 0<br>• 1-5 boxes/w: 0<br>• >5 boxes/w: +<br>• Consistent smo.: 0<br>• Former : 0<br><br>Never smoker: 1<br>• 1–15 cig/day: 0<br>• >15 cig/day + | +/- |

*Note: A positive association (+) with smoking is a **worst** outcome

## Table 14. Overview of included studies – Alcohol

**ALCOHOL – DISABILTY/FRAILTY**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Ostbye 2002 | US | HRS study: 7,845 people | HRS study: ages 51-61 yrs | HRS: 92-98 | Self-reported alcohol intake and history of drinking problems | Disability, impaired mobility, self-reported health, and health care utilization | Participant interviews | **HRS study:**<br>*1) ADL dependence; 2) difficulty climbing stairs; 3) difficulty walking; 4) poor health; 5) hospitalized, respectively*<br>Up to 2 drinks/day (ref: never drinking):<br>1)- 2)- 3)- 4)- 5)-<br><br>2+ drinks/day (ref: never drink.):<br>1)0 2)0 3)0 4)- 5) 0<br><br>Past drinking problem (ref: never drink.):<br>1)+ 2)+ 3)+ 4)+ 5)+ | -/+ |
| Englund 2013 | Sweden | 778 | 49-61 | 85-08 | Self-report (coded as "teetotaller" or "alcohol user") | Wrist fracture | Prospective injury-fracture database | **Alcohol level**<br>None 1.00<br>User: 0 | +/- |
| Moayyeri 2009 | UK | 25311 | 40-75 years | 1993–1997 to 2007 | Self-report ('How many alcoholic drinks do you have each week?) | Osteoporotic fractures | Death certificates and linkage of the National Health Service number with the East Norfolk Health Authority | **Alcohol level**<br>Men<br>None 1.00<br>User: +<br><br>Women<br>None 1.00<br>User: 0 | +/+ |

**ALCOHOL – DEMENTIA**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Virta 2010 | Finland | 1,486 | Mean age in 1981: 51.7 yrs (SD: 6.1) | 1975-81 to 1999-07 (mean follow-up: 22.8 yrs.) | Self-reported total weekly (for beer, wine) or monthly (for spirits) alcohol intake:<br>*1 drink=12 g ethanol; 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)<br>*# of pass-outs<br>*binge drinking at least monthly | Cognitive function | TELE, a self-report telephone interview | Abstainer: +<br>Light drinker: 1.00<br>Moderate: 0<br>Heavy: +<br><br>Binge drinking: no: 1.00<br>Yes: +<br><br>Number of pass-outs:<br>0: 1.00<br>1: 0<br>>2: + | ++/++ |
| Elwood 2013 | Caerphilly, UK | 1,320 men | 45–59 | 1979-04 | self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include | Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia | Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological | Diabetes: 0<br>Vascular disease: 0<br>Cancer: 0<br>Any impairment: 0<br>Dementia: 0<br>Death: 0 | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | abstinence) | | examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score) | | |
| Sabia 2009 | England | 5,123 | Mean age 56 yrs | 97-99 to 02-04 | Self-reported alcohol units in last 7 days; 1unit=8 g ethanol | Cognitive function | Cognitive tests to measure executive function (reasoning, verbal fluency measures) | **Alcohol consumption (units/week):**<br>0: +<br>1-14: 1.00<br>>=15: 0 | +/++ |
| Sabia 2011 | France | 4073 men | Ages 40–50 for men and 35–50 for women | 10 yrs (1992 to 2002-04) | Self-reported units of alcoholic drinks (beer, wine, aperitif, spirits) consumed (1 unit: 10–12 g of alcohol) in a week<br>*mean alcohol consumption over 10 yrs | Cognitive performance (psychomotor speed, attention and reasoning) measured | Digit Symbol Substitution Test (DSST) | **Drinks/week by occupational position (Low/ intermediate/ high position):**<br>0 drinks/wk: 0/0/0<br>1-3 d/wk: 0/0/0<br>4-14 d/wk: 1.00<br>15-21 d/wk: 0/0/0<br>>21 d/wk: -/0/0 | +/++ |
| Anttila 2004 | Finland | 632 women and 386 men | Mean age 48.3 yrs | 1972-77 to 1998 | Self-reported frequency of alcohol intake: never drank, drank infrequently (less than once a month), drank frequently (several times a month) | Cognitive function | MMSE; DSM-IV dementia diagnosis | **Dementia:**<br>Never: 0<br>Infrequent: 1.00<br>Frequent: 0<br><br>**Mild cognitive impairment:**<br>Never: +<br>Infrequent: 1.00<br>Frequent: + | +/++ |

**ALCOHOL – CARDIOVASCULAR OUTCOMES**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Beulens 2007 | Netherlands | 1,417 | 49-70 yrs | 1993-97 to 2005 | Self-reported alcohol intake (<=10, 11-25, 26-50, >50 g/day) | cardiovascular disease (coronary heart disease, cerebrovascular accidents, cardiovascular disease) | hospital discharge diagnoses with ICD codes (CVD); municipal administration registries (vital status); GP (cause of death) | U-shaped relationship between alcohol-intake and CVD risk | ++/- |
| Wannamethee 2002 | England, Wales, and Scotland | 7157 | 40-59yrs | ('78–'80)-(2000) | Self-report (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) | Major coronary heart disease events | 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-report questionnaires | **Alcohol level**<br>non-drinkers: 1.0<br><br>occasional drinkers who took up regular drinking: +<br><br>continuing regular drinkers: +<br><br>stable occasional drinkers: 0 | +/+ |
| Emberson | England, | 7,735 | 40–59 | 1978/1980 to | Self-report (A | cardiovascular | Established "tagging" | **Alcohol level** | ++/+ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2005 | Wales, and Scotland | | years | 1998/2000 | five-point scale from zero (none) to four (heavy)) | morbidity | procedures provided by the National Health Service central register | None 1.00<br>Occasional 1.00<br>Light : -<br>Moderate *0*<br>Heavy + | |
| | | | | | | all-cause mortality | Established ‘‘tagging’’ procedures provided by the National Health Service central register | **Alcohol level**<br>None: 0<br>Occasional 1.00<br>Light: -<br>Moderate: 0<br>Heavy: + | |
| Qiu 2003 | China | 50069 | 40-80+ | 1994/1996-2000 | Self-report | CVD death | Clinical visit by practitioner to town | **Alcohol level**<br>Non-drinker 1.00<br>Ex-drinker: 0<br>Current drinker: 0 | +/ - |
| Iso 2004 | Japan | 19 544 | 40-59 | 1990-2000 | Self-report (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) | Stroke | computer tomographic scan and/or magnetic resonance images | **Alcohol level**<br>**<450g ethanol pw:** 0<br>**>450 g ethanol pw:** + | +/ - |
| Elwood 2013 | Caerphilly , UK | 1,320 men | 45–59 | 1979-04 | self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence) | Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia | Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score) | Diabetes: 0<br>Vascular disease: 0<br>Cancer: 0<br>Any impairment: 0<br>Dementia: 0<br>Death: 0 | +/++ |

**ALCOHOL – DIABETES/METABOLIC SYNDROME**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Elwood 2013 | Caerphilly, UK | 1,320 men | 45–59 | 1979-04 | Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence) | Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia | Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score) | Diabetes: 0<br>Vascular disease: 0<br>Cancer: 0<br>Any impairment: 0<br>Dementia: 0<br>Death: 0 | +/++ |
| Waki 2005 | Japan | 28,893 | 40-59 yrs | 10 yrs (baseline: 1990) | Self-reported total daily alcohol intake based on type, freq., quantity of alcohol and alc. content: e.g., 180 ml sake has 23g ethanol, 180 ml sochu has 36g ethanol | Incident type 2 diabetes | Self-report | **Alcohol intake in g/day (men/women):**<br>Non-drinkers and eth. intake on <=3 days/month:<br>1.00, 1.00<br>0 <ethanol <=4.9: 0, 0<br>4.9 < ethanol <=11.5: +, 0<br>ethanol >11.5: 0, 0 | +/+ |
| Wannamethee 2003 | England, Wales, Scotland | 7,608 men | 40-59 yrs | 1978-80 to 1983-85 | Self-reported freq., quantity and type of alcohol (1 unit UK alc.= about 10 g alcohol) *occasional drinkers (e.g. <1 unit/week); light-moderate (e.g. | BMI | Weight gain using height and weight measurements | **Baseline - f/u changes in alcohol intake (5 yrs):**<br>Stable intake:<br>None-occasional: 1.00<br>Light-moderate: 0<br>Heavy: +<br><br>Changed intake:<br>Light-moderate (*at* | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1-20 units/week), heavy (e.g. 21-42 units/week), very heavy (e.g. >42 units/week – used for 'ex-heavy'/'new heavy') | | | *baseline*) to none-occasional (*at f/u*): 0<br>None-occasional to light-moderate: 0<br>Ex-heavy: 0<br>New heavy: + | |
| Wang 2010 | US | 19,220 | 38-89 yrs | 12.9 yrs. follow-up (baseline: 1992-95) | Self-reported freq. of alcohol intake over the past year ('never' to '6+ per day')<br>*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 | Overweight or obesity | Self-reported f/u weight and baseline height used for BMI:<br>**overweight:** 25 to 30 kg/m2<br>**obese:** >=30 kg/m2 | Total alcohol intake (g/day) (association with **overweight or obese; obese)**:<br>0: 1.00, 1.00<br>>0- <5: 0, -<br>5- <15: -, -<br>15- <30: -, -<br>>= 30: -, - | +/+ |

**ALCOHOL – CANCER**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Stevens 2009 | England and Scotland | 1.29 million women | | 96-01 to 2005-07<br>Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for mortality | Self-reported alcohol intake | Incident and fatal pancreatic cancer | National Health Service Central Register (deaths, cancer registrations with ICD codes) | **Alcohol units per week and RR for incidence/mortality):**<br>None: + / +<br>1-2: 0 / 0<br>3-6: - / -<br>7-13: 0 / 0<br>14+: 0 / 0 | +/++ |
| Flood 2008 | USA | 49238 | older than 50 y | 1995–1996 to 2000 | Self-report (question not detailed) | Colorectal cancer | probabilistic linkage between cancer registry databases | **Alcohol level**<br>None 1.00<br>User: 0 | ++/ - |
| Otani 2003 | Japan | 90004 | 40–59<br>Cohort 1<br><br>40–69<br>Cohort 2 | Cohort I<br>After January 1, 1990-1999<br><br>Cohort II<br>January 1, 1993–1994-1999 | Self-report (less than 1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, and everyday) | Colorectal cancer | Cancer registry | **Alcohol level**<br>Men<br>None 1.00<br>User: +<br><br>Women<br>None 1.00<br>User: 0 | +/ - |
| Elwood 2013 | Caerphilly, UK | 1,320 men | 45–59 | 1979-04 | Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence) | Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia | Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score) | Diabetes: 0<br>Vascular disease: 0<br>Cancer: 0<br>Any impairment: 0<br>Dementia: 0<br>Death: 0 | +/++ |

**ALCOHOL – OTHER**

Note: a positive association (+) with alcohol is the worst outcome

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results association[c] (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Xu 2010 | South East Queensland, Australia | 564 | 45-60 yrs | 2001-06 | Self-reported alcohol use:<br>>never<br>>drank in past<br>>occasionally<br>>regularly | General mental well-being, and psychological symptoms | SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire | **Correlations between alcohol and 1) anxiety, 2) depression, 3) psychological symptoms, 4) SF-36 mental health:**<br>*Alcohol*<br>Never: ref<br>Past drinker:<br>1)- 2)0 3)0 4)0<br>Occasionally:<br>1)0, 2)0, 3)0, 4)0<br>Regularly:<br>1)0, 2)0, 3)0, 4)0 | -/+ |
| Sun 2011 | US | 13,894 | 70+ | 84-00 | Self-report (avg. alcohol intake in g/day over 1 year)<br>Portion size:<br>13.2 g alcohol of beer; 10.8 g of wine, 15.1 g of liquor | Successful ageing (free of major chronic diseases, no major cognitive impairment, physical impairment, or mental health limitations) | **Chronic diseases:**<br>Questionnaire, medical record review, pathology report review, telephone interview<br><br>**Cognitive function:**<br>Telephone Interview for Cognitive Status (TICS)<br><br>**Physical function and mental status**<br>Medical Outcomes Study Short-Form Health Survey (SF-36) | **Days of alcohol use/week:**<br>Nondrinker: 1.00<br>1-2: 0<br>3-4: +<br>5-7: + | ++/+ |
| Willcox 2006 | island of Oahu | 5820 | 45-68yrs | Not reported | Self-report (High alcohol intake was dichotomized as 3 or + drinks/d) | Overall survival | Survival | **Alcohol level**<br><3 1.00<br>>3 - | ++/- |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lin 2005 | Japan | 110,792 | 40 to 79 years | 1988–1990 to 1999 | Self-report (‘nondrinkers’ reported no alcohol drinking in the past; ‘never or almost never”; “exdrinkers”; “current drinkers”) | All-cause mortality | Death certificates | **Alcohol level**<br><23 g/d 0<br>>23 g/d + | ++/ - |
| Emberson 2005 | England, Wales, and Scotland | 7,735 | 40–59 years | 1978/1980 to 1998/2000 | Self-report (A five-point scale from zero (none) to four (heavy)) | cardiovascular morbidity | Established ‘‘tagging’’ procedures provided by the National Health Service central register | **Alcohol level**<br>None 1.00<br>Occasional 1.00<br>Light : -<br>Moderate 0<br>Heavy + | ++/+ |
| | | | | | | all-cause mortality | Established ‘‘tagging’’ procedures provided by the National Health Service central register | **Alcohol level**<br>None: 0<br>Occasional 1.00<br>Light: -<br>Moderate: 0<br>Heavy: + | |
| Tabak 2001 | Finland, Italy, Nether-lands | 2,953 men (Finland: 1,186 men; Italy: 1,183; Netherlands: 667) | 40-59 | 20 yrs (1965-70 to 1990) | Self-reported drinks:<br>none, <=1 per week (occasional); <=1 drink/week, >1 and <=3 drinks /day (light); >3 and <=9 /day; >9 /day | chronic obstructive pulmonary disease mortality | clinical records, from family doctors, specialists, relatives, with ICD codes | Nondrinkers: 1.00<br>Light drinkers: 0<br>Higher alcohol consumption: 0<br>e.g., >9 drinks /day: 0 | -/+ |

## Table 15. Overview of included studies – Weight change/weight cycling*

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association (-/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Field (2009) | United States | 44842 | 30-55 | 16 years | Weight cycling:<br><br>Postal questionnaire | Mortality | Next of kin, the postal service, or ascertained by the National Death Index | Mild: 0<br>Severe: 0 | +/- |
| Langlois (2001) | United States | 2180 | 50-74 | 22 years | Weight loss of >10% from max:<br><br>Self-report | Hip Fracture | Hospital records and death certificates | 50–64 years: +<br>65–74 years: + | ++/+ |
| Ravona-Springer (2013) | Israel | 10000 | 40-70 | 36 years | Weight variability (independent of direction of weight change):<br><br>Interviews, clinical assessments | Dementia | Interview and Hebrew version of the Modified Telephone Interview for Cognitive Status | Wt change I: 0<br>Wt change II: 0<br>Wt change III: +<br>Wt change IV: + | +/- |
| Waring (2010) | United States | 1577 | 40-50 | 11 years | Weight loss/gain/cycling: Interviews, clinical examinations, laboratory tests | Diabetes | Nonfasting plasma glucose level and/or reported treatment with insulin or an oral hypoglycemic agent | Weight loss: 0<br>Weight gain: 0<br>Weight cycling: 0 | ++/- |

*Note: a positive association (+) with alcohol is the worst outcome

## Table 16. Overview of included studies – Combined lifestyles

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association (–/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| King (2007) | United States | 15708 | 45-64 | 11-13 years | Interviews, questionnaire, medical examination | Cardiovascular disease | A single variable in the ARIC dataset (PRVCHD05) | Switched from Unhealthy to Healthy Lifestyle<br><br>1 healthy behaviour: 0 *(nsig)*<br>2 healthy behaviours: 0 *(nsig)*<br>3 healthy behaviours: - *(sig)*<br>4 healthy behaviours: - *(sig)* | ++/+/- |
| | | | | | | Mortality | State death certificates | Switched from Unhealthy to Healthy Lifestyle<br><br>1 healthy behaviour: 0 *(nsig)*<br>2 healthy behaviours: - *(sig)*<br>3 healthy behaviours: - *(sig)*<br>4 healthy behaviours: - *(sig)* | |
| Agrigoroaei (2011) | United States | 4995 | 33-84 | 9-10 years | Telephone interviews | Episodic memory<br><br>Executive functioning | Brief Test of Adult Cognition<br>Brief Test of Adult Cognition | behavioural protective factors + *(sig)*<br>behavioural protective factors + *(sig)* | ++/+/- |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Elwood (2013) | Caerphilly, UK | 1,320 men | 45–59 | 1979-04 | Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence) | Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia | Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score) | Diabetes: 0<br>Vascular disease: 0<br>Cancer: 0<br>Any impairment: 0<br>Dementia: 0<br>Death: 0 | +/++ |
| | | | | | Self-reported<br><br>(method?)<br><br>Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit | Diabetes<br><br>Vascular disease<br><br>Cancer<br><br>Cognitive impairment<br><br>Dementia<br><br>Death | Interview, examination, primary care and hospital records. Deaths and cancer from ONS. | Diabetes: –<br><br>Vascular disease: **0**<br><br>Cancer: **0**<br><br>Cog impairment: –<br><br>Dementia: –<br><br>Death: – | /++ |

## Table 17. Overview of included studies – Leisure/cognitive activity/social networks

| Study | Country | n | Age at baseline | Length of follow-up | Exposure measurement | Outcome | Outcome measure | Results Association (–/+/0) | Quality/ Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Bielak (2012) | Australia | 7152 | 20-24: 2404<br>40-44: 2530<br>60:64: 2551 | 7 years | Activity engagement<br><br>Self-reported survey | Perceptual speed | Symbol Digit Modalities Test | Activity Engagement<br>20: +<br>40: +<br>60: + | ++/+ |
| | | | | | | Short-term memory | California Verbal Learning Test | Activity Engagement<br>20: +<br>40: +<br>60: + | |
| | | | | | | Working memory | Wechsler Memory Scale | Activity Engagement<br>20: +<br>40: +<br>60: + | |
| | | | | | | Episodic memory | CVLT-Delayed | Activity Engagement<br>20: +<br>40: +<br>60: + | |
| | | | | | | Vocabulary | Spot-the-Word Test | Activity Engagement<br>20: +<br>40: +<br>60: + | |
| Britton (2008) | UK (England) | 5823 | 35-55 | 17 years | Social network Self-reported questionnaire<br><br>Frequency and number of hours per week. | Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome and with good physical and mental functioning. | Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals. | Successful aging<br><br>Men and women<br><br>Low: 1<br>Medium 0<br>High 0 | +/++ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Friedland (2001) | United States | 193 cases/358 controls (for total study, not reported for 40-59 year olds) | 40-59 | >12 (not fully reported) | Diversity and intensity of participation in intellectual, passive and physical activities<br><br>Self-reported or surrogate reported (for cases)<br><br>Questionnaire Physical intensity (total hours per month – sports, gardening, walking) | Alzheimer's Disease | Neuropsychological, laboratory, and neurological exams and all had x-ray computed tomography or MRI scans of the brain. | Intellectual activity: -<br>Physical activity: -<br>**Passive activity: -** | -/+ |
| Holtzman (2004) | United States | 354 | 50+ | 12.4 years | Larger social networks<br><br>Interviews | Cognition | MMSE | Risk of low MMSE score: - | ++/+ |
| Kareholt (2011) | Sweden | 1643 | 57.4 | 20+ years | Baseline leisure activity (political, mental, socio-cultural, social, physical, and organizational activities.<br><br>Interviews | Cognition | MMSE | Association of type of activity with cognition<br><br>Political: +<br>Mental: +<br>Socio-cultural: +<br>Social: 0<br>Organisational: 0<br>Physical: 0 | ++/+ |
| Raikkonen (2001) | United States | 541 | 42-50 | 9.2 years | Social support Questionnaires plus clinical examinations | Hypertension | Random-zero muddler sphygmomanometer | Women: 0 | ++/+ |

3.2.1 Quality and applicability of studies

Appendix C summarises the quality of included studies. These scores are also integrated in the summary statements and in the evidence tables. An applicability statement is provided for each evidence statement.

Overall, the evidence cited in the review is good (or very good) and the applicability directly or partially applicable.

3.2.2 Structure of evidence statements

Evidence statements are organised in the same way as the summary tables presented in the previous section: for each risk factors, the evidence is reported by individual outcome category.

To facilitate cross-reference to the PH guideline, the first digit of the evidence statements refers to the review (i.e. here always 2 for Review 2), the other digits follow the numbering system for this report (3.1, 3.2, etc.), and the letters refer to risk factors.

**3.3 Evidence statements for PHYSICAL ACTIVITY (PA)**

Summary data for PA studies is reported in Table 9.

**2.3.1PA** Healthy Ageing / Quality of Life / Well-being

**There is consistent evidence from good quality studies that PA in mid-life is related to healthy and successful ageing outcomes from studies followed up from eight to 17 years**.

Three prospective cohort studies [+][1], [++][2], [++][3] reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's disease. All three studies reported a significant positive and beneficial association between mid-life PA and healthy ageing outcomes. Healthy ageing or successful survival was defined in all three studies as having no history of major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations.

[1]Britton 2008; [2]Hamer 2013; [3]Sun 2010

- **Applicability**: Directly applicable. Two studies that reported beneficial association between PA in mid-life and healthy ageing were conducted in the UK and one in the US. One UK study and one US study were high quality and the other study conducted in the

UK was of good quality. One study reported outcomes separately for men and women and in both groups PA was related to more successful ageing.

### 2.3.2PA Disability / Frailty

**There is consistent evidence that PA in mid-life is related to more positive outcomes in terms of disability and frailty in later life from studies followed up from five to 26 years. Studies were found relating to physical mobility, physical functioning, bone health.**

*Physical mobility/functioning*

Six prospective cohort studies reported on longitudinal associations between mid-life PA and physical mobility or physical functioning, gait speed or disability [+][1], [+][2], [-][3], [+][4], [+][5], [-][6]. Five of the six studies found that mid-life PA was significantly related to better mobility and functioning outcomes in later life. One study was conducted in the UK [+][1], one in Italy [+][2] , one in Iceland [-][3], one in Finland [+][4] and one in the US[-][6]. A different study from Finland reported no significant associations [+][5].

*Fractures and bone health*

Three studies reported on the association between mid-life PA and bone fractures or bone health. One study reported less risk of hip or wrist fractures 11 years later in two papers [-][8], [-][9]. One study that used accelerometry to measure PA reported improved bone mineral density in those who took part in PA in mid-life [+][10]. One study reported no significant association between mid-life physical activity and risk of osteoarthritis [+][11].

[1]Lang 2007; [2]Patel 2006; [3]Chang 2013; [4]Malmberg 2006; [5]Lahti 2010; [6]Ostbye 2002; [7]Chang 2010; [8]Englund 2011; [9]Englund 2013; [10]Nokes 2012; [11]Szoeke 2006

- **Applicability**: Partially applicable. One study that reported beneficial associations between PA in mid-life and disability/frailty was conducted in the UK, the others were conducted in in developed European countries or the US.

### 2.3.3PA Dementia & Cognition

**There is consistent evidence that PA in mid-life is related to less risk of dementia in later life from studies followed up from 12 to 40 years.**

Six prospective studies (eight papers [++][1], [+][2], [+][3], [+][4], [+][5], [+][6], [-][7], [-][8]) reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's

disease. Four of the six studies reported a significant beneficial association between mid-life PA and dementia in later life and in two studies associations were non-significant.

One study (two papers [+][3], [+][4]) conducted in the UK found an inverse association between regular or vigorous PA and dementia over 30 years. The three other studies that found an inverse association between PA and dementia were conducted in Sweden (two papers) and Iceland. The two studies that reported no significant association were conducted in the US [++][1], [-][8].

Two Swedish studies found a significant inverse association between light or regular PA but not for heavy PA [+][2], [-][7].

*Cognitive function*

Two studies were found that examined associations between mid-life PA and later life cognitive function [-][9], [+][10]. Both studies found a positive relationship between mid-life PA and improved cognitive function in later life.

[1]Carlson 2008; [2]Andel 2008; [3]Elwood 2013; [4]Morgan 2012; [5]Rovio 2005; [6]Rovio 2007; [7]Chang 2010; [8]Friedland 2001; [9]Chang 2013; [10]Sabia 2009

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The other studies that found a similar relationship were conducted in developed European countries (Sweden and Iceland). For cognitive function, both studies were conducted in the UK.

**2.3.4PA** Overall mortality

**There is consistent evidence that PA in mid-life is related to lower mortality in later life from studies followed up from five to 30 years.**

Four prospective studies (five papers [+][1], [+][2], [+][3], [+][4], [+][5]) reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's disease. All four of the studies report lower mortality in those that participate in PA in mid-life.

One study (two papers, [+][4], [+][5]) from the UK reports all cause mortality data followed up at 10 years and 30 years. Mid-life PA was associated with lower mortality at both timepoints. The other three studies were conducted in Finland [+][1], Denmark [+][2] and Germany [+][3].

Both high and moderate levels of PA compared to low levels of PA were related to lower mortality rates in two studies [+][1], [+][2]. In one study regular or vigorous exercise was associated with lower mortality and in the other study, heavy PA intensity was related to lower overall mortality rates.

[1]Hu 2005; [2]Holtermann 2009; [3]Menotti 2006; [4]Yu 2003; [5]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The three other studies that found a similar relationship were conducted in developed European countries (Finland, Denmark and Germany).

**2.3.5PA** Cardiovascular (CVD) Outcomes

**There is strong evidence from six prospective studies (in nine papers, [+][1], [+][2], [+][3], [+][4], [+][5], [+][6], [+][7], [++][8], [+][9]) reported longitudinal associations between mid-life physical activity and CVD events or CVD mortality followed up between nine and 40 years.**

Six papers reported a significant beneficial association between mid-life PA and CVD risk or events in later life (stroke [+][1], CVD risk [+][2], coronary heart disease (CHD) events [+][4], myocardial infarction, ischaemic heart disease, vascular disease) and three papers reported lower CVD related mortality from stroke [++][8] , CHD [+][5] and CVD [+][3] related to PA in mid-life.

One study (two papers [+][5] ,[+][6]) that reported 10 and 30 year follow-up was conducted in the UK. One study (three papers reporting at different timepoints and for different outcomes) was conducted in Finland [+][2], [+][3], [+][4], and one in each from Sweden, Germany, Greece (Corfu) and Denmark.

[1]Harmsen 2006; [2]Hu 2006; [3]Hu 2005; [4]Hu 2007; [5]Yu 2003; [6]Elwood 2013; [7]Meisinger 2007; [8]Pitsavos 2004; [9]Holterman 2009

- **Applicability**: Directly applicable. One study that reported beneficial associations between PA in mid-life and CVD outcomes was conducted in the UK, the other five studies were conducted in in developed European countries.

**2.3.6PA** Diabetes / Metabolic Syndrome

**There is some consistent evidence that PA in mid-life is related to lower incidence of diabetes in later life from two prospective cohort studies followed up for 28 [+][4] and 30 years [+][2]. The two studies were conducted in the UK [+][2] and Norway [+][4].**

Three prospective cohort studies also reported on relationships between mid-life PA and pre-conditions for diabetes. Two reported metabolic syndrome as an outcome [+][3], [+][4] and one reported insulin sensitivity as an outcome [+][5]. All three studies reported a beneficial association between mid-life PA and the diabetes preconditions. The two studies with metabolic syndrome as an outcome were conducted in the UK [+][3] and Norway [+][4] and the study that reported insulin sensitivity was conducted in Sweden.

[1]Hu 2003; [2]Elwood 2013; [3]Ekelund 2005; [4]Holme 2007; [5]Riserus 2007

- **Applicability**: Directly applicable. Two studies that reported beneficial associations between PA in mid-life and metabolic syndrome outcomes was conducted in the UK, the other 5 study was from Norway. Two studies with metabolic syndrome as an outcome were conducted in the UK.

**2.3.7PA** Cancer

The evidence relating to the associations between PA and cancer is mixed.

Four prospective cohort studies [+][1], [+][2], [+][3], [+][4] reported longitudinal associations between mid-life physical activity and cancer or cancer mortality followed up between seven and 30 years.

One study in the UK reported no significant relationship between mid-life PA and incident and fatal pancreatic cancer [+][1], A different UK study [+][2] examined associations between total PA and a range of different cancers and found lower rates of total cancer, upper digestive tract cancers (oral, oesophagus, stomach cancer) in those who participated in moderate or vigorous PA at mid-life compared to those who did not. No significant associations were found for lung, stomach, colorectal, lymphatic/haematopoetic cancers. However, the same study [+][2] reported that vigorous exercise at mid-life was associated with a significantly *increased* risk of bladder cancer.

A third UK study found no significant relationship between mid-life PA and cancer [+][3].

Total cancer mortality was lower in those who took part in moderate or high levels of PA [+][4] in a study from Finland.

[1]Stevens 2009; [2]Wannamethee 2001; [3]Hu 2005; [4]Elwood 2013

- **Applicability**: Directly applicable. Three studies that reported beneficial associations between PA in mid-life and diabetes outcomes were conducted in the UK, the other study was from Finland. One study that reported increased risk of bladder cancer was conducted in the UK.

**2.3.8PA** Mental health

**The evidence for an association between mid-life PA and mental health is inconclusive.**

One prospective cohort study [++][1] in the UK reported less risk of anxiety and/or depression for heavy PA at five-year follow-up but not at 10 years.

One prospective cohort study [-][2] in Australia found no significant association between mental wellbeing, including anxiety and depression and mid-life PA at five years follow-up.

[1]Wiles 2007; [2]Xu 2010

- **Applicability**: Directly applicable. One study was conducted in the UK, the other study was from Australia.

### 3.4 Evidence statements for PHYSICAL INACTIVITY/SEDENTARY BEHAVIOUR (IN)

Summary of data from studies is reported in Table 10. Two studies use self-reported PA data.

**2.4.1IN** Healthy Ageing / Quality of Life / Well-being

No study found.

**2.4.2IN** Disability / Frailty

One study examined associations between mid-life inactivity disability at age 75 [-][1]. No significant association was found between inactivity in leisure time and disability at age 75.

[1]Christenson 2006

- **Applicability**: Partially applicable. The study was conducted in Denmark.

**2.4.3IN** Dementia

No study found.

**2.4.4IN** Overall mortality

One study from Finland followed up for 16 years [+][1] found no significant relationship between leisure time inactivity in mid-life and all cause mortality.

[1]Haapanen-Niemi 2000

- **Applicability**: Partially applicable. The study was conducted in Finland.

**2.4.5IN** Cardiovascular (CVD) Outcomes

One study from Finland followed up for 16 years [+][1] found a significant positive relationship between a single item measure of leisure time inactivity in mid-life and CVD mortality. However using an index measure of LTPA no significant association was found.

[1]Haapanen-Niemi 2000

- **Applicability**: Partially applicable. The study was conducted in Finland.

**2.4.6IN** Diabetes / Metabolic Syndrome

No study found.

**2.4.7IN** Cancer

No study found.

**2.4.8IN** Mental health

No study found.

### 3.5 Evidence statements for DIET (DI)

#### 2.5.1DI Overall diet / dietary patterns

Summary of data from studies is reported in Table 11. All studies reported below are observational longitudinal cohort studies that report mid-life diet or components of diet and dementia, disability, frailty outcomes in later life.

#### 2.5.1.1DI Overall diet – Healthy Ageing outcomes

*'Healthy' diet*

**There is consistent evidence from three longitudinal cohort studies [+][1], [+][2], [+][3] that a healthy diet in mid-life is related to healthy and successful ageing.** In these studies healthy ageing is defined as no major chronic diseases or major impairments in cognitive or physical function or mental health.

Two studies reported a significant positive and beneficial association between mid-life 'healthy' dietary patterns and successful ageing outcomes. In the other study, a Western dietary pattern characterised by high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products was associated with less successful ageing.

*Mediterranean diet*

There is evidence from one study that a Mediterranean type diet is associated with more successful ageing [+][3].

[1]Akbaraly 2013; [2]Britton 2008; [3]Semieri 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between healthy diet in mid-life and healthy ageing was conducted in the UK and one in the US. The UK study and US study were of moderate quality. The third study, also conducted in the UK, reporting inverse relationship with Western dietary pattern was of moderate quality also.

#### 2.5.1.2DI Overall diet – Disability / Frailty outcomes

There is some limited evidence from one study conducted in France that 'healthy' diet or dietary patterns in mid-life is related to more positive outcomes in later life, in relation to cognitive functioning. The study reported better cognitive outcomes for those consuming a 'healthy pattern' diet [-][1], characterised as consumption of fruit (fresh and dried), whole grains, fresh dairy products, vegetables, breakfast cereal, tea, vegetable fat, nuts, and fish

and negatively correlated with meat and poultry, refined grains, animal fat, and processed meat.

[1]Kesse-Guyot 2012

- **Applicability**: Partially applicable. The study that reported beneficial associations between a healthy diet or components of diet in mid-life and cognitive function was conducted in France.

**2.5.1.3DI** Overall diet – Dementia outcomes

No study found.

**2.5.1.4DI** Overall diet – Total mortality

No study found.

**2.5.1.5DI** Overall diet – Cardiovascular (CVD) Outcomes

Dietary pattern – two studies conducted in Spain and Italy reported beneficial effects of a Mediterranean diet pattern with lower risk of CHD events and mortality [+][1], [-][2].

[1]Guallar-Castillon 2012; [2]Menotti 2012

- **Applicability**: Partially applicable. Both studies were conducted in developed European (Mediterranean) countries.

**2.5.1.6DI** Overall diet – Diabetes / Metabolic Syndrome

One study conducted in China reported that a dietary pattern low in staples and high in milk was associated with less risk of diabetes [++][1].

[1]Villegas 2010

- **Applicability**: Partially applicable. The Chinese diet studies may be different from a UK diet.

**2.5.1.7DI** Overall diet – Cancer

One study conducted in Japan [+][1] found no clear associations between the four major dietary patterns studied (fruit and vegetable pattern, western breakfast, meat pattern, rice/snacks pattern) and cancer.

[1]Masaki 2003

- **Applicability**: Partially applicable. Study conducted in Japan, Japanese diet different from UK diet but a Western breakfast pattern was studied.

**2.5.1.8DI** Overall diet – Other chronic diseases

No study found.

**2.5.1.9DI Overall diet – Mental health**

*Mediterranean diet*

One study from Australia [+][1] reported less psychological distress in those with the highest compared to lowest adherence to the Mediterranean diet.

*Traditional Australian diet*

The same Australian study [+][1] also reported those with the highest compared to lowest adherence to a traditional Australian diet (positive loadings for breakfast cereal, wholemeal bread, cheddar cheese, vegetables – carrot, pumpkin, beetroot, green beans, peas, and cauliflower; some fruit, tea, margarine, pudding, cake, cream, jam, vegemite, and roast lamb), a generally healthy diet apart from some cake and puddings.

[1]Hodge 2013

- **Applicability**: Partially applicable. The study was from Australia.

**2.5.2DI – FRUIT AND VEGETABLES**

**2.5.2.1DI** Fruit and vegetables – Healthy ageing outcomes

No study found.

**2.5.2.2DI** Fruit and vegetables – Disability / Frailty outcomes

One study from the UK reported that more than two portions of fruit and vegetables a day was associated with better cognitive performance [+][1].

However, two studies reported no significant association between higher levels of fruit and vegetables and cognitive function [+][2], [+][3]. One study was conducted in the UK and one was from the Netherlands.

[1]Sabia 2009; [2]Elwood 2013; [3]Nooyens 2009

- **Applicability**: Partially applicable. Two studies were conducted in the UK, one reported a positive relationship and in one the association was not significant. The other study was conducted in the Netherlands.

**2.5.2.3DI** Fruit and vegetables – Dementia outcomes

Two studies reported relationships between fruit and vegetable intake in mid-life and dementia [+ ][1], [+][2]. One study conducted in Sweden found that medium or great amounts of fruit and vegetables compared to lower amounts were associated with less risk of dementia. One study from the UK found no significant association between three or greater portions of fruit and veg per day compared to lower intakes and dementia.

[1]Hughes 2010; [2]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK the association was not significant.

**2.5.2.4DI** Fruit and vegetables – Total mortality outcome

Three studies reported associations between fruit and/or vegetable intake and total mortality. One study from Sweden reported significantly lower risk of death in people consuming higher levels of fruit and vegetables at mid-life [+][1]. One study from Italy reported significantly lower overall mortality for each increase of 20g/day in vegetable intake [+][2]. In one UK study associations between >3 portions fruit and vegetables/day were not significant [+][3].

[1]Strandhagen 2000; [2]Seccareccia 2003; [3]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK and one from Italy the association was not significant.

**2.5.2.5DI** Fruit and vegetables – CVD outcomes

Two studies reported relationships between fruit and vegetables and CVD outcomes and/or mortality. In one study fruit and vegetable intake was associated with lower CVD mortality [+][1] and in the other study [+][2] associations between fruit and veg intake (>3/day) and CVD outcomes were not significant.

[1]Strandhagen 2000: [2]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK the association was not significant.

**2.5.2.6DI** Fruit and vegetables – Diabetes/metabolic syndrome outcomes

One study conducted in the UK reported association between fruit and vegetables and diabetes. No statistically significant association between fruit and veg intake (>3/day) and diabetes [+][1] was found.

[1]Elwood 2013

- **Applicability**: Directly applicable. The study was conducted in the UK.

**2.5.2.7DI** Fruit and vegetables – Cancer outcomes

One study from the US reported lower risk of colorectal cancer with consumption of fruit [++][1].

Two studies, from the UK and Sweden reported no significant associations between fruit and vegetables and cancer incidence or mortality [+][2], [++][3].

[1]Ruder 2011; [2]Elwood 2013; [3]Strandhagen 2000

- **Applicability**: Partially applicable. The one study that found a significant lower risk of cancer with fruit intake at mid-life was conducted in the US. The other studies were from the UK and Sweden.

**2.5.2.8DI** Fruit and vegetables – Other chronic disease outcomes

Fruit intake was significantly associated with lower risk of chronic obstructive pulmonary disease mortality in one study conducted across Finland, Italy and the Netherlands [+][1] .

[1]Walda 2002

- **Applicability**: Partially applicable. The study was conducted in developed, western European countries.

**2.5.2.9DI** Fruit and vegetables – Mental health outcomes

No study found.

**2.5.3DI – DIETARY FAT (Total, saturated, polyunsaturated (PUFA), monounsaturated (MUFA)**

**2.5.3.1DI** Fat – Healthy ageing outcomes

No study found.

**2.5.3.2DI** Fat – Disability / Frailty outcomes

One Finnish study reported that higher levels of total or saturated fat were associated with greater cognitive impairment in later life [+][1].

[1]Eskelinen 2008

- **Applicability**: Partially applicable. One study from Finland.

**2.5.3.3DI** Fat – Dementia outcomes

One study in Finland reported greater risk of dementia in those consuming moderate compared to low amounts of saturated fat but lower rates of dementia in those consuming moderate compared to low amounts of polyunsaturated fat (PUFA) [++][1].

[1]Laitinen 2006

- **Applicability**: Partially applicable. One study from Finland.

**2.5.3.4DI** Fat – Total mortality outcomes

No study found.

**2.5.3.5DI** Fat – CVD outcomes

One study from Sweden reported no significant associations between either total, saturated, monounsaturated or polyunsaturated fat and fatal or non-fatal cardiovascular events [++][1].

[1]Leosdottir

- **Applicability**: Partially applicable. One study from Sweden

**2.5.3.6DI** Fat – Diabetes/metabolic syndrome outcomes

One study conducted in Sweden reported that higher saturated fat intake at mid-life was associated with lower insulin sensitivity [+][1].

[1]Riserus 2007

- **Applicability**: Partially applicable. One study from Finland.

**2.5.3.7DI** Fat – Cancer outcomes

No study found.

**2.5.3.8DI** Fat – Other chronic disease outcomes

No study found.

**2.5.3.9DI** Fat - Mental health outcomes

No study found.

**2.5.4DI – FISH**

**2.5.4.1DI** Fish – Healthy ageing outcomes

No study found.

**2.5.4.2DI** Fish – Disability / Frailty outcomes

No study found.

**2.5.4.3DI** Fish – Dementia outcomes

No study found.

**2.5.4.4DI** Fish – Total mortality outcomes

One Danish study that measured fish intake using a self-reported food frequency questionnaire reported some limited evidence for increased mortality with greater fish consumption [+][1] in a population sample and also in those at high risk of CHD.

[1]Osler 2003

- **Applicability**: Partially applicable. One study from Denmark.

**2.5.4.5DI** Fish – CVD outcomes

One study from the US found lower risk of CHD events and mortality in women when meat was replaced with fish so that >/= 3 servings wk were consumed [++][1]. Another study from Sweden reported no significant association between fatty fish consumption and heart failure but lower risk of heart failure in those consuming marine omega 3 fatty acids once a week [+][2]. Higher intakes of marine omega 3 fatty acids were not significantly associated with heart failure.

[1]Lajous 2013; [2]Levitan 2009

- **Applicability**: Partially applicable. One study from Sweden, one from the US.

**2.5.4.6DI** Fish – Diabetes/metabolic syndrome outcomes

One study conducted in China [++][1] reported lower risk of diabetes in women eating moderate and high amounts of fish and shellfish with a significant trend with greater fish and shellfish intake. In men associations between fish intake and diabetes were not significant but lower risk of diabetes was reported for shellfish with a significant trend with greater shellfish intake.

[1]Villegas 2011

- **Applicability**: Partially applicable. One study from China.

**2.5.4.7DI** Fish – Cancer outcomes

No study found.

**2.5.4.8DI** Fish – Other chronic disease outcomes

Fish intake was associated with less risk of chronic obstructive pulmonary disease (COPD) in one study conducted across Finland, Italy and the Netherlands [+][1].

[1]Walda 2002

- **Applicability**: Partially applicable. One European study.

**2.5.4.9DI** Fish – Mental health outcomes

No study found.

**2.5.5DI – MEAT**

**2.5.5.1DI** Meat – Healthy ageing outcomes

No study found.

**2.5.5.2DI** Meat – Disability / Frailty outcomes

One prospective cohort study conducted in Japan reported on longitudinal associations between mid-life diet and activities of daily living [+ ][1]. Men who ate meat at least once every two days or more were less likely to have impairment in activities of daily living (ADL) [+ ][1] .

[1]Nakamura 2009

- **Applicability**: Partially applicable. One Japanese study.

**2.5.5.3DI** Meat – Dementia outcomes

No study found.

**2.5.5.4DI** Meat – Total mortality outcomes

No study found.

**2.5.5.5DI** Meat – CVD outcomes

One study conducted in China [+ ][1] reported lower risk of cerebrovascular disease in those consuming meat 1-2 times a month compared to those consuming no meat or those who ate meat more than once a week.

[1]Qiu 2003

- **Applicability**: Partially applicable. One study from China.

**2.5.5.6DI** Meat – Diabetes/metabolic syndrome outcomes

One study conducted in the US found increased risk of diabetes in those consuming higher versus lower levels of red and processed meat [+ ][1] with a significant trend from lower to higher intake.

[1]Song 2004

- **Applicability**: Partially applicable. One study from the US.

**2.5.5.7DI** Meat – Cancer outcomes

One study from the US [++][1] reported higher risk of colorectal cancer with consumption of red and processed meat.

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

**2.5.5.8DI** Meat – Other chronic disease outcomes

No study found.

**2.5.5.9DI** Meat – Mental health outcomes

No study found.

## 2.5.6DI – COFFEE

### 2.5.6.1 Coffee – Healthy ageing outcomes

No study found.

### 2.5.6.2DI Coffee – Disability / Frailty outcomes

One study reported no association of later life cognitive function with mid-life coffee intake [++][1].

[1]Laitala 2007

- **Applicability**: Partially applicable. One study from Finland.

### 2.5.6.3DI Coffee – Dementia outcomes

Two studies examined relationships between coffee consumption in mid-life and dementia [+][1], [++][2]. One study from Finland [+][1] reported that moderate coffee consumption (3-5 cups/day) was associated with lower risk of dementia, but not tea drinking. A different study conducted in Finland in twins found no significant association between coffee consumption and dementia [++][2].

[1]Eskelinen 2009; [2]Laitala 2007

- **Applicability**: Partially applicable. Two studies from Finland.

### 2.5.6.4DI Coffee – Total mortality outcomes

No study found.

### 2.5.6.5DI Coffee – CVD outcomes

One study from Finland reported a higher risk of CHD events and mortality with heavy coffee intake (>814 ml/d) compared to moderate coffee drinking (376-813 ml/d) [+][1]. Associations were not significant for light or no coffee drinking (0-375 ml/d) compared to moderate intake.

[1]Happonen 2004

- **Applicability:** Partially applicable. One study from Finland.

**2.5.6.6DI** Coffee – Diabetes/metabolic syndrome outcomes

Two studies reported lower risk of diabetes with coffee intake. One study from Finland reported significantly lower risk of diabetes with coffee intake in men and women [+][1]. For both men and women combined, and for women only, there was a significant trend towards lower risk for diabetes with increasing coffee consumption. In men the trend was not significant but there was a significant relationship between higher levels of coffee intake (>/= 10 cups/d) and less risk of diabetes. The other study from Japan [+][2] reported a significant inverse relationship for women consuming 3 or more cups of coffee a day with a significant trend. In men only 1-2 cups/day was significantly associated with lower risk of diabetes but there was also a significant inverse trend between coffee consumption and diabetes.

[1]Tuomilehto 2004; [2]Kato 2009

- **Applicability**: Partially applicable. One study from Finland, one from Japan.

**2.5.6.7DI** Coffee – Cancer outcomes

No study found.

**2.5.6.8DI** Coffee – Other chronic disease outcomes

Lower risk of Parkinson's disease with coffee consumption was consistently reported in two studies from Finland [+][1] and the US respectively [+][2]. In men and women combined, 1-4 cups/day or 5 cups/day compared to none were both significantly related to less risk of Parkinson's disease [+][1] .Tea drinking was also associated with less risk of Parkinson's disease at the level of 5 cups/d [+][1]. In the US study [+][2], there were lower rates of Parkinson's disease in coffee drinkers compared to non-coffee consumers. An inverse association between caffeine intake and Parkinson's disease was also reported.

[1]Hu 2007; [2]Ross 2000

- **Applicability**: Partially applicable. One study from Finland, one from US.

**2.5.6.9DI** Coffee – Mental health outcomes

One study from Australia [+][1] found no significant association between coffee drinking and anxiety, depression or psychological symptoms, but reported lower scores on the mental health scale on the SF-36 general health questionnaire.

In one study from Finland[+][2], light (<315 ml/d) or heavy (>813 ml/d) coffee consumption was associated with lower risk of severe depression. There was no association with tea or caffeine intake, although the study reported fewer tea drinkers and less tea drinking.

[1]Xu 2010; [2]Ruusanen 2010

- **Applicability**: Partially applicable. One study from Finland, one from Australia.

**There were fewer relevant studies from this point onwards, and only the outcomes and available data are reported. For all other outcomes, no studies were found.**

**2.5.7DI – MILK**

**2.5.7.1DI** Milk – Cancer outcomes

One study from the US reported lower incidence of colorectal and rectal cancer in those in the highest versus the lowest quintile of consumption of milk [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

**2.5.8DI – SALT**

**2.5.8.1DI** Salt – Cancer outcomes

One study from Japan [+][1] found a significant association between salt intake and higher risk of gastric cancer in highest versus lowest in male consumers with a significant trend with higher intake but in women the association was not significant.

[1]Tsugane 2004

- **Applicability**: Partially applicable. One study from Japan.

**2.5.9DI – GLYCAEMIC INDEX/GLYCAEMIC LOAD (GI/GL)**

**2.5.9.1DI** GI/GL – CVD outcomes

One study conducted in the Netherlands reported higher risk of CVD for those consuming diets with the highest compared to the lowest dietary glycaemic index (GI) and glycaemic load (GL) [++][1]. In another from Finland, study associations between GI/ GL and CVD events were not significant [+][2].

[1]Beulens 2007; [2]Levitan 2009

- **Applicability**: Partially applicable. One study from Finland, one from the Netherlands.

## 2.5.10DI – PROTEIN

### 2.5.10.1DI Protein – CVD outcomes

One study found no sig associations between mid-life protein intake and ischemic heart disease [++][1].

[1]Preis 2010

- **Applicability**: Partially applicable. One study from the US.

### 2.5.10.2DI Protein – Cancer outcomes

One study found no sig associations between protein and colorectal cancer [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

## 2.5.11DI – CHOCOLATE

### 2.5.11.1DI Chocolate – CVD outcomes

One study conducted in Sweden [+][1] reported lower risk of heart failure when chocolate was consumed 1-3 times month compared to no chocolate consumption. Associations at higher chocolate intakes were not significant although there was a significant trend with higher intakes of chocolate towards lower risk of heart failure [++][1].

[1]Mostofsky 2010

- **Applicability**: Partially applicable. One study from Sweden.

## 2.5.12DI – DIETARY FIBRE

### 2.5.12.1DI Fibre – Cancer outcomes

One study from the US reported no association between mid-life fibre intake and colorectal cancer [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

## 2.5.13DI – MICRONUTRIENTS / ANTIOXIDANTS / FLAVONOIDS

### 2.5.13.1DI Micronutrients – Dementia outcomes

One US study reported a non-significant relationship between mid-life dietary antioxidant intake and dementia [+][2].

### 2.5.13.2DI Micronutrients – Cancer outcomes

One study from the US [++][1] reported lower risk of colorectal cancer with consumption of dietary calcium, vitamin A and vitamin C.

### 2.5.13.3DI Micronutrients – Mental health outcomes

One study from Finland [+][3] found no association between dietary zinc intake and depression.

### 2.5.13.4DI Flavonoids – CVD outcomes

One study from Finland [+][4] found no association between total flavonoid intake and ischemic stroke but did find lower ischemic stroke risk in highest flavonol vs lowest flavonol intake.

### 2.5.13.5DI Flavonoids – Cancer outcomes

One US study found no significant relationship between flavonoids and total cancer or site-specific cancers [+][5].

### 2.5.13.6DI Flavonoids – Dementia outcomes

One US study found no significant relationship between flavonoids and dementia [+][2].

[1]Ruder 2011; [2]Laurin 2004; [3]Lehto 2013; [4]Mursu 2008; [5]Wang 2009

- **Applicability**: Partially applicable. All studies from the US or Western European countries.

**Evidence statements for diet (and components of diet) - associations between mid-life diet and PRECONDITIONS for dementia, disability, frailty**

**2.5.14DI Preconditions**

**2.5.14.1DI** Blood pressure outcomes

Two studies reported relationships between fruit and vegetable intake and blood pressure. One study conducted in the US reported less risk of hypertension with mid-life fruit intake [+][1]. In another study conducted in the US associations between fruit and vegetable intake and blood pressure were not significant [+][2].

One study from the US reported lower incidence of hypertension with increased levels of dairy intake [+][3] and another US study reported no relationship between dietary magnesium intake and hypertension [+][4].

[1]Miura 2004; [2]Wang 2012; [3]Wang 2008; [4]Song 2006

- **Applicability**: Partially applicable. All four studies from the US.

**2.5.14.2DI** Obesity outcomes

Two different papers from the same US study [+][1], [+][2] reported that increase in fruit and vegetable intake or wholegrains and dietary fibre between mid-life and later life was significantly associated with less risk of obesity or major weight gain (>/= 25kg).

[1]He 2004; [2]Liu 2003

**Applicability**: Partially applicable. Both papers were from the same US study (Nurses Health Study)

**3.6 Evidence statement for SMOKING (SM)**

Summary of data from smoking studies is reported in Table 12.

**2.6.1SM** Healthy Ageing / Quality of Life / Well-being

**There is consistent evidence from three studies demonstrating an association between smoking and healthy ageing, quality of life or well-being outcomes**. A UK study [++][1] using data from Whitehall II showed that not smoking was related to a favorable

older life (i.e. entering older age without disease and with good functioning) after adjustment for age and socioeconomic position. A study [+][2] in a socioeconomically homogeneous cohort of older Finnish men found that never-smokers lived longer than heavy smokers, and their extra years were of better quality. Health-related quality of life deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. The third study [++] looking at Japanese American men suggests that ever smoking is associated with overall survival and a borderline association with exceptional survival (i.e. free of a set of major diseases and impairments).

[1]Britton 2008 [+]; [2]Strandberg 2008 [+]; [3]Willcox 2006 [++]

- **Applicability:** Partially applicable; the UK study is highly applicable but the other two are conducted in men only, including a cohort of Japanese American.

**2.6.2SM** Disability / Frailty

**2.6.2.1SM There is consistent evidence from two studies demonstrating the dose-response relationship between smoking and impaired mobility**. A Swedish study [+][1] suggests that a history of smoking, especially heavy smoking, with or without quitting, is associated with an earlier onset, and a faster elevation, of mobility problems during the transition from middle age to old age. All smoking groups reported more pain symptoms than the non-smokers, at baseline and over time, but most of these differences did not reach statistical significance. Persistent heavy smokers reported elevated levels of psychological distress at baseline and over time. A USA study [-][2] showed a consistent adverse dose-response relationships between smoking and ill health defined in a multidimensional fashion (i.e. disability, impaired mobility, health care utilisation, self-reported health).

[1]Agahi 2013 [-]; [2]Ostbye 2002 [-]

- **Applicability:** Partially applicable; populations from Sweden and USA, but most importantly, quality of studies is [-].

**2.6.2.2SM There is inconsistent evidence from three studies demonstrating the association between smoking and low energy fractures.** A Swedish study [+][1] looking at active commuting showed no association between smoking and wrist fractures. A second Swedish [+][2] study looking at a wider range of low energy fractures showed that among women, smokers had a higher risk for vertebral fractures than non-smokers. Among men, smokers had a greater risk for low energy fractures, vertebral fractures, proximal humerus fractures, and hip fractures than non-smokers. A large UK study [+][3] showed no association between smoking and osteoporotic fractures. Although not focused on fracture, another

study [+][4], conducted in Australia, found a positive association between smoking and risk of osteoarthritis.

[1]Englund 2013; [2]Homberg 2006; [3]Moayyeri 2009; [4]Szoeke 2006

- **Applicability:** Directly applicable; but would interpret findings from UK study [+][3] with caution as osteoporotic fractures were documented using death certificates, which are not reliable as a sole source of information to document fractures (except maybe hip fractures).

**2.6.3SM** Dementia

**There is strong evidence consistent evidence demonstrating the association between smoking in mid-life and dementia or cognitive decline in later life. The association between smoking and specific types of dementia is less clear.**

Eleven cohort studies reported on the association between smoking and dementia or cognitive outcomes. In most studies, smoking was considered a cardiovascular risk factor for dementia/cognitive decline. Two UK studies [+][1,2] based on Whitehall II data showed an association between smoking and cognition. The longest follow-up (17-year) [+][1] showed that smoking in middle age is associated with memory deficit and decline in reasoning abilities; long-term ex-smokers (compared to current smokers and recent ex-smokers) are less likely to have cognitive deficits in memory, vocabulary, and verbal fluency. In a 5-year follow-up in a Dutch study [+][3], decline among smokers was greater for memory function, cognitive flexibility, and cognitive function than among never smokers. Among ever smokers, the declines in all cognitive domains were larger with increasing number of pack-years smoked.

In two USA study [+][4,5] smoking was strongly associated with subsequent risk of hospitalisation with dementia (proxy for incident dementia) in caucasians and African-Americans [+][4], and with being diagnosed with dementia in a diverse population [+][5]. In another large USA multi-ethnic cohort study with long follow-up [+][6], heavy smoking in mid-life was associated with a greater than 100% risk of dementia, AD, and VaD. A Korean study [+][7] showed an increased risk of unspecified dementia or any type of dementia in men and women who smoke compared to the never-smoker; the increased risk of Alzheimer's disease and vascular dementia was observed in women who smoke but not in men. However, a study conducted in Hawaiian men [+][8] showed an association between smoking in mid-life and a diagnostic of vascular dementia later on. In another USA study based on the Framingham offspring cohort [+][9], mid-life smoking was associated with an increased rate of progression of vascular brain injury, global and hippocampal atrophy.

Only Knopman [+][10] found that smoking at baseline was not associated with change in cognitive decline (six years follow-up). Also, a study [+][11] looking at dementia death (based on ICD codes failed to demonstrate an association with smoking.

[1]Sabia 2008; [2]Sabia 2009; [3]Nooyens 2008; [4]Alonso 2009; [5]Whitmer 2005; [6]Rusanen 2011; [7]Kimm 2011; [8]Tyas 2003; [9]Debette 2011; [10]Knopman 2001; [11] Strand 2013

- **Applicability:** Directly applicable; mostly European and US studies, good quality and mostly reliable outcome measurements.

**2.6.4SM** Overall mortality

**There is strong evidence from seven studies demonstrating a dose-response relationship between smoking in mid-life and total mortality. Compared to never smokers, smokers are at increased risk of mortality. Compared to those who maintain their smoking habit, those who reduce or quit smoking have a decreased risk of mortality.**

A UK study [+][1] showed that current smokers showed the highest RR of total mortality with a dose-response relationship with increasing number of cigarettes smoked. Compared to never smokers, primary pipe/cigar smokers showed a marginally significant increased risk of total mortality, but secondary pipe/cigar smokers showed a significantly increased risk of total mortality. Ex-cigarette smokers showed similar risk to never smokers after full adjustment.

Three related Finnish studies [+][2,3,4] and one Japanese studies [+][7] showed the corroborating results. Qiao et al. [+][3] showed that men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers. Pelkonen [+][4] concluded that smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking. Finally, Lim [+][5] showed that compared to current smokers, never smokers, long-term quitters and new quitters had a decreased risk of all-cause mortality; the same association was observed for never smokers and long-term quitters for other non-lung cancer mortality. Gerber et al (Israeal) [+][6] found that compared to those who maintained their smoking habit, individuals reduced or quit smoking had a decrease risk of all cause mortality.

[1]Shaper 2003; [2]Strandberg 2008; [3]Qiao 2000; [4]Pelkonen 2000; [5]Lim 2013; [6]Gerber 2012; [7]Hara 2002

- **Applicability:** Directly applicable; mostly European and US studies, good quality and reliable outcome measurements.

**2.6.5SM** Cardiovascular (CVD) Outcomes

**Smoking or having smoked is consistently associated with increased risk of cardiovascular mortality and cardiovascular diseases.**

**Cardiovascular Mortality –** Six studies provide evidence of a strong association between smoking and cardiovascular mortality; only one didn't. Overall, current smokers are more likely to die from cardiovascular events compared to non-smokers. Lim [+][6] showed that compared to current smokers, never smokers and long-term quitters had a decreased risk of CHD mortality and COPD mortality; the same association was observed for never smokers for stroke mortality. The relationship with former smoking status varies across studies (probably owing to great heterogeneity across studies re follow-up, outcome measurements, etc.). Only Qui [+][7], a study from China did not find an association between smoking and cardiovascular mortality.

[1]Blanco-Cedres 2002; [2]Boudik 2006; [3]Baba 2006; [4]Hara 2002; [5]Gerber 2012; [6]Lim 2013; [7]Qui 2003

- **Applicability**: Partially applicable; no studies from the UK or Europe.

**Other cardiac outcomes** – Twelve studies provide evidence of a strong association between smoking and cardiovascular events and outcomes. In a UK study [++][1], the highest risks for both CHD events and stroke were seen in heavy current smokers. Ex-cigarette smokers showed similar risk of major CHD and stroke events to never smokers. Pipe/cigar smokers (primary and secondary combined) also showed significantly higher risk compared with never smokers and non-smokers, and similar to light cigarette smokers. The other UK study [+][2] showed that smoking increases the risk of coronary heart disease in men of all *APOE* genotype genotypes but particularly in men carrying the e*4* allele. Apart from Satoh [+][3] who showed not association between smoking (vs non-smoker) and CHD, all other studies have shown an association between smoking and stroke [++][4], [+][3,5] and MI [+][6].

[1]Shaper 2003; [2]Humphries 2001; [3]Satoh 2006; [4]Mannami 2004; [5]Harmsen 2006; [6]Nakayama 2000; [7]Janzon 2004; [8]Dubas 2007; [9]Halperin 2008; [10]Raikkonen 2001; [11]Khalili 2002

**2.6.6SM** Diabetes / Metabolic Syndrome

**Cigarette smoking is an independent and modifiable risk factor for type II diabetes; the evidence for insulin sensitivity and metabolic syndrome is not sufficient to conclude.**

Three studies, one conducted in the UK men [+][1], one in Finland [+][2] and one in Japan [+][3], demonstrated cigarette smoking is an independent and modifiable risk factor for type 2 diabetes; and one conducted in Norway didn't. The UK study [+][1] examined the effects of cigarette smoking, giving up smoking, and primary or secondary pipe or cigar smoking on the risk of type 2 diabetes. The benefit of giving up smoking was only apparent after 5 years of smoking cessation, and risk reverted to that of never-smokers only after 20 years. The risk of diabetes in those who switched from smoking cigarettes to pipe or cigars remained equal to the risk in continuing cigarette smokers. Smoking cessation is associated with weight gain and a subsequent increase in risk of diabetes, but in the long term, the benefits of giving up smoking outweigh the adverse effects of early weight gain. The Finish study [+][2] also showed that smoking of a risk factor for type 2 diabetes independently of BMI and physical activity. And another study [+][4] demonstrated that being a smoker was associated with weight loss. The longest follow-up was in a Norwegian study [+][5], which found that smoking was associated with the metabolic syndrome but not diabetes – (potential confounding and methodological may explain the later findings).

Finally, a Swedish study [+][6] looking at long-term predictors of insulin sensitivity in men found no significant association with smoking.

[1]Wannamethee 2001; [2]Patja 2005; [3]Sairenchi 2004; [4]Fogelholm 2000; [5]Holme 2007; [6]Riserus 2007.

- **Applicability**: Directly applicable. Mostly UK, European studies with long-term follow-up and good quality.

**2.6.7SM** Cancer

**Evidence from six studies showed a consistent association between smoking and cancer with a dose-response effect. The dose-response and exposure association seems to depend on the type of cancer considered**.

In a UK study [+][1] current cigarette smokers showed the highest risk of total cancer with a strong dose-response effect. Ex-cigarette smokers showed a significant increase in smoking-related cancers, particularly affecting 'other' smoking-related cancers rather than lung cancer. Compared with never smokers, pipe/cigar smokers (primary and secondary

combined) also showed a significantly higher incidence of smoking-related cancers largely due to lung cancer. Overall, the effects in pipe/cigar smokers were intermediate between never-smokers and light cigarette smokers, although risks for lung cancer were similar to light cigarette smokers. In a second UK study [+][2] looking specifically at pancreatic cancer in women, pancreatic cancer incidence was greater in current than never smokers, the risk increasing with the number of cigarettes smoked. Current smokers were at two-fold or higher risk than never smokers across all categories of height, BMI, alcohol and physical activity.

Three Japanese studies also demonstrated significant associations [+][3], [+][4]. One [+][3] showed that smoking was significantly associated with colorectal cancer in men and not significantly in women. Furthermore, long-term smoking significantly elevated the risk compared with never-smoking but a non-significant linear trend was obtained according to smoking intensity except for rectal cancer. The relative risk in smokers who also drink was also increased compared to non-drinkers – non-smokers men. Looking at lung cancer by histological types, Sobue et al [+][4] findings indicated that current cigarette smoking is associated with an elevated lung cancer risk approximately 10- to 20-fold higher for squamous cell and small cell carcinoma and 2- to 3-fold higher for adenocarcinoma in both men and women. When all histologic types were combined, the relative risk was approximately 4 in both men and women. They also showed that the lung cancer risk in men rose with increasing cigarette smoking, especially the duration of smoking among current smokers and decreased after the cessation of smoking among former smokers. Using the same cohort, another study [+][5] confirmed the strong association between smoking and cancer, and cancer related mortality in the Japanese population.

Lim [+][6] showed that compared to current smokers, never smokers, long-term quitters and new quitters had a decreased risk of lung cancer, mortality; the same association was observed for never smokers and long-term quitters for other non-lung cancer mortality.

[1]Shaper 2003; [2]Steven 2009; [3]Otani 2003; [4]Sobue 2002; [5]Inoue 2004; [6]Lim 2013

- **Applicability**: Directly applicable, two studies conducted in the UK; overall good quality studies. Note that although Japanese studies are relevant effect sizes would differ in UK population.

**2.6.8SM** Mental health

No study found.

**2.6.9SM** Others

One Japanese study [+][1] found that smoking increases the risk of chronic kidney condition.

[1]Noborisaka 2013 [+]

- **Applicability**: Limited; Japanese study and outcome measurement not optimal.

### 3.7 Evidence statements for ALCOHOL (AL)

Summary of data from Alcohol studies is presented in Table 14. We included 24 prospective cohort studies on alcohol intake between 40 and 64 years of age (midlife). These were conducted in the UK (n=7); USA (n=5); Sweden (n=1); Finland (n=2); France (n=1); the Netherlands (n=1); China (n=1); Japan (n=4); and Australia (n=1). A multi-site study (n=1) was conducted in Italy, Finland, and the Netherlands. Follow-up ranged from 4 years (Qiu 2003, Flood 2008) to 26 years (Virta 2010). There was heterogeneity in the categorisation of self-reported alcohol intake levels. Five articles (n=5) assessed the number of drinks consumed per week, one (n=1) differentiated teetotallers from alcohol users, five (n=5) documented the number of drinks per day, one (n=1) assessed the number of drinks per month, while the rest of the studies (n=12) used a combination of measurements examining alcohol intake over various time spans.

**2.7.1AL** Healthy Ageing / Quality of Life / Well-being

No study found.

**2.7.2AL** Disability / Frailty

**Two studies reported higher odds for ill health and osteoporotic fractures among alcohol drinkers compared to non-drinkers, while one study found no link between ethanol use and wrist fractures.**

A Swedish study [+][1] did not find a statistically significant association between alcohol intake and wrist fractures. Conversely, the risk for any incident osteoporotic fracture over 11 years was reported to be higher among male alcohol users compared to male teetotalers in Norfolk, UK [+][2]. A large study [-][3] of middle-aged American males and females followed from 1992 to 1998 showed that, compared to those who never drink, respondents with a past drinking problem had the highest odds for ill health in terms of ADL dependence, difficulty

climbing stairs, difficulty walking, poor health, and hospitalization (results were statistically significant).

[1]Englund 2013; [2]Moayyeri 2009; [3]Ostbye 2002

- **Applicability**: The studies are applicable, particularly the UK and Swedish studies. Generalizability may be limited as alcohol intake was measured using different categories across studies.

**2.7.3AL** Dementia

**There is consistent evidence from four studies demonstrating an association between alcohol abstinence and/or heavy drinking and cognitive impairment. One study reported no association with impairment or dementia.**

Five European longitudinal studies analysed the influence of mid-life alcohol intake and cognitive function in old age. One Finnish study [++][1] with a mean follow-up of 23 years showed an increased risk of cognitive impairment for both abstainers and heavy drinkers in comparison with light drinkers. Binge drinking and pass-outs were positively associated with cognitive impairment, as was abstaining from drinking among those without the apolipoprotein e4 allele. Similarly, alcohol abstinence among middle-aged participants in the Whitehall II study [+][2] had a higher risk of poor executive function and poor memory in comparison with those consuming moderate amounts (1-14 units/week). Conversely, a study [+][3] on men living in Caerphilly, UK did not find an association between alcohol intake and impairment or dementia. Among French people with a low occupational position, an inverse relationship was found between high alcohol intake (>21 drinks/week) and cognitive performance [+][4]. In a population-based sample [+][5] of Finnish participants, the risk for mild cognitive impairment was higher among those reporting abstinence or frequent alcohol consumption compared to people reporting infrequent drinking. Among carriers of the APOE4 allele, the risk of dementia was greater for frequent drinkers compared to non-drinkers.

[1]Virta 2010; [2]Sabia 2009; [3]Elwood 2013; [4]Sabia 2011; [5]Anttila 2004

- **Applicability:** Directly applicable. Generalizability may be limited as alcohol intake was measured using different categories across studies.

**2.7.4AL** Overall mortality

See below.

**2.7.5AL** Cardiovascular outcomes

**The evidence regarding alcohol use and cardiovascular outcomes is inconsistent.**

Three studies conducted in England, Wales, Scotland [+][1], [++][2] and Japan [+][3] showed a significant association between alcohol intake and cardiovascular outcomes. Among middle-aged men recruited from British general practices [+][1], regular drinkers had a significantly lower risk of major coronary heart disease events, coronary heart disease deaths, and cardiovascular disease deaths in comparison with occasional drinkers after full adjustment for lifestyle characteristics and pre-existing disease. In contrast, heavy drinkers (>6 drinks/day) had a higher risk of both major coronary heart disease and stroke compared to occasional drinkers (one-two times/month or on special occasions) in a cohort of middle-aged British men followed for 20 years [++][2]. The previous two studies were part of the British Regional Heart Study. A large population-based sample of Japanese men [+][3] showed a significantly higher risk for stroke (total stroke, hemorrhagic, and intraparenchymal hemorrhage) among those consuming over 450g ethanol per week compared to those drinking occasionally, one-three days per month. No significant associations were observed between alcohol intake and cardiovascular outcomes (e.g., disease development, death) in three studies conducted in Caerphilly [+][4], China [+][5], and the Netherlands [++][6]. Nevertheless, there appeared to be a U-shaped relationship between alcohol intake and cardiovascular disease risk in the latter study [++][6].

[1]Wannamethee 2002; [2]Emberson 2005; [3]Iso 2004; [4]Elwood 2013; [5]Qiu 2003; [6]Beulens 2007

- **Applicability:** The UK and Dutch studies are directly applicable; however, the inconsistency in alcohol intake measurements limits the generalizability of findings

**2.7.6AL** Diabetes/Metabolic syndrome

**Findings were inconsistent with respect to the influence of alcohol intake on diabetes/metabolic syndrome. One study did not find a link with vascular disease, another found higher odds for type 2 diabetes, while two studies reported conflicting results with respect to weight change.**

Three studies [+][1], [+][2], [+][3] found significant associations between alcohol intake levels and diabetes/metabolic syndrome, while one study[4] on men living in Caerphilly, UK did not find

an association (with vascular disease). Sex-stratified results of a Japanese study with a 10-year follow-up period [+][1] revealed significantly higher odds of type 2 diabetes mellitus among males consuming moderate or high amounts (over 4.9 g/day) of ethanol compared to male non-drinkers and infrequent occasional drinkers who consumed ethanol on three or fewer days per month. BMI-stratified findings further showed that underweight (BMI <=22kg/m$^2$) males who consumed over 23 g/day of ethanol also had a significantly higher risk for type 2 diabetes compared to those who consumed less than this amount.

A large UK study [+][2] of men selected from the registers of general practices showed that heavy drinkers had a significantly higher risk of weight gain over five years compared to non-drinkers or occasional drinkers. Also, the proportion of men with high BMI increased significantly with higher levels of alcohol intake at baseline. In contrast, a study [+][3] of predominantly white US female health professionals followed for an average of 13 years showed that increasing levels of self-reported alcohol intake were associated with decreasing incidence of overweight or obesity.

[1]Waki 2005; [2]Wannamethee 2003; [3]Wang 2010; [4]Elwood 2013

- **Applicability:** Partially applicable (particularly the UK and US studies). One UK study cannot be generalised to women. Another US study also had limited generalizability as the sample consisted predominantly of white US female health professionals. Studies also used different categories for alcohol intake, rendering the comparison of findings between studies difficult.

**2.7.7AL** Cancer

**There is consistent evidence from three studies demonstrating the absence of an association between alcohol intake and cancer, while a fourth study reported a higher risk for colorectal cancer among alcohol drinkers.**

Three studies conducted in England/Scotland [+][1], the Caerphilly region in the UK [+][2], and the US [++][3] did not find significant associations between alcohol intake and incident and fatal pancreatic cancer; cancer in general; and colorectal cancer, respectively. In contrast, sex-stratified results of a Japanese study [+][4] showed a significantly higher risk for colorectal cancer among men who drink alcohol compared to non-drinkers.

[1]Stevens 2009; [2]Elwood 2013; [3]Flood 2008; [4]Otani 2003

- **Applicability:** Directly applicable; however, self-reported alcohol consumption was derived and categorized differently across studies making comparison of findings difficult.

**2.7.8AL** Others (Mental health, survival, mortality, chronic obstructive pulmonary disease mortality)

**Two studies showed the health benefits of alcohol consumption with respect to anxiety and survival; two studies revealed the link between intake and (all-cause) mortality; while a fifth study reported no association between ethanol consumption and chronic obstructive pulmonary disease mortality.**

A study [-][1] of women from rural and urban areas of South East Queensland, Australia indicated that past alcohol drinkers had lower anxiety than non-drinkers. In a sample of Japanese-American men living in Hawaii [++][2], excessive alcohol consumption was associated with overall and exceptional survival at age 85 years (exception survival was defined as men without major chronic disease and without cognitive or physical impairment). A large Japanese prospective cohort study [++][3] showed that, compared to non-drinkers, the risk of all-cause mortality was lowest among males consuming 0.1-22.9 g/day of alcohol during 1990-99; excessive mortality was significantly associated with heavy drinking (more than 69 g/day) among men diagnosed with cancer and cardiovascular disease in this time period. A UK study [++][4] showed that alcohol intake was associated with a higher risk for all-cause mortality among middle-aged British men, while no association with alcohol was reported in relation to chronic obstructive pulmonary disease mortality among a European cohort of Finnish, Italian, and Dutch men [-][5] followed for 20 years. Finally, a large US study showed that higher levels of alcohol intake were associated with a greater likelihood of successful aging [++][6].

[1]Xu 2010; [2]Willcox 2006; [3]Lin 2005; [4]Emberson 2005; [5]Tabak 2001; [6]Sun 2011

- Applicability: Partially applicable – the UK study is directly applicable. Alcohol measurement may be imprecise.

### 3.8 Evidence statements for WEIGHT CHANGE, WEIGHT CYCLING (WC)

Summary of data from smoking studies is reported in Table 15.

#### **2.8.1WC** Healthy Ageing / Quality of Life / Well-being

No study found.

#### **2.8.2WC** Disability / Frailty

There is weak and limited evidence from one study from the US that weight loss of more than 10% of max body weight in mid-life is related to hip fracture in a study lasting 22 years.

One study ([++][1]) reported longitudinal associations between weight change and hip fracture. The impact was statistically significant for those in both age groups (50-64 and 65-74 years) who were weight-cycling in mid-life.

[1]Langlois 2001

- **Applicability**: Partially applicable. One study that reported an association between weight change/weight cycling and hip fracture was conducted in US.

#### **2.8.3WC** Dementia

There is weak and limited evidence from one study in Israel to suggest that weight change in mid-life is related to dementia in a study lasting 36 years.

One study [+][1] reported longitudinal associations between weight change and dementia. Those in the highest two quartiles of weight change had a significantly higher risk of dementia, independent of the direction of weight change.

[1]Ravona-Springer 2013

- **Applicability**: Partially applicable. One study reported an association between weight change/weight cycling and dementia was conducted in Israel.

#### **2.8.4WC** Overall mortality

There is weak and limited evidence from one study in the US that there is no association between weight cycling in mid-life and mortality in a study lasting 16 years.

One study [+][1] reported longitudinal relationships between weight change/weight cycling in midlife and death and reported no association.

[1]Field 2009

- **Applicability**: Partially applicable.The one study that reported an association between weight change/weight cycling and mortality was conducted in US.

**2.8.5WC** Cardiovascular (CVD) Outcomes

No study found.

**2.8.6WC** Diabetes / Metabolic Syndrome

There is weak and limited evidence from one study that weight change/weight cycling in mid-life is not related to type 2 diabetes in a study lasting 11 years.

One study [++][1] reported longitudinal associations between weight change/weight cycling and diabetes. The impact was not significant for weight change or weight cycling but but overall weight status was more important with those who were overweight or obese at increased risk of diabetes. In fully adjusted models, adjusted for BMI there was no effect of weight change.

[1]Waring 2010

- **Applicability**: Partially applicable. One study that reported an association between weight change/weight cycling and diabetes was conducted in US.

**2.8.7WC** Cancer

No study found.

**2.8.8WC** Mental health

No study found.

### 3.9 Evidence statements for LEISURE/COGNITIVE ACTIVITY/SOCIAL NETWORKS (LC)

Summary of data from smoking studies is reported in Table 17.

**2.9.1LC** Healthy Ageing / Quality of Life / Well-being

There is little available evidence to determine if leisure and cognitive activities, and an individual's social network in mid-life is related to successful aging in a study lasting 17 years.

One UK study [+][1] reported longitudinal associations between leisure, cognitive activities, social network and successful aging in both men and women. While there was a beneficial association these were non-significant.

[1]Britton 2008

- **Applicability**: Directly applicable. The study was conducted in the UK.

**2.9.2LC** Disability / Frailty

No study found.

**2.9.3LC** Dementia

There is some consistent evidence from three high quality studies that leisure and cognitive activities, and an individual's social network in mid-life is related to less risk of cognitive decline in later life from studies followed up seven to >12 years.

One study from the US [-][1] reported an association between diversity and intensity of participation in intellectual, physical and passive activities and lower risk of Alzheimer's disease. Three studies ([++][2], [++][3], [++][4]) reported longitudinal associations between leisure, cognitive activities, social network and dementia or cognitive impairment. All studies reported a beneficial association between mid-life factors and dementia or cognitive decline in later life however in one study the associations were non-significant for some activities including social, organisational and physical activities[4].

[1]Friedland 2001; [2]Bielak 2012; [3]Holtzman 2004; [4]Kareholt 2011

- **Applicability**: Partially applicable. No UK studies, but studies finding associations were conducted in developed non-European countries (US and Australia).

**2.9.4LC** Overall mortality

No study found.

**2.9.5LC** Cardiovascular (CVD) Outcomes

There is no evidence from any study that leisure, cognitive activity or social networks in mid-life is related to reduced hypertension. One study [++][1] was conducted and this found no correlation.

[1] Raikkonen 2001

- **Applicability**: Partially applicable. The one study reporting no association between activities in mid-life and hypertension was conducted in the US and was rated as high quality.

**2.9.6LC** Diabetes / Metabolic Syndrome

No study found.

**2.9.7LC** Cancer

No study found.

**2.9.8LC** Other chronic diseases

No study found.

**2.9.9LC** Mental health

No study found.

### 3.10 Evidence statements for COMBINED LIFESTYLE (CL)

Summary data for combined lifestyle studies is presented in Table 16.

#### **2.10.1CL** Healthy Ageing / Quality of Life / Well-being

No study found.

#### **2.10.2CL** Disability / Frailty

No study found.

#### **2.10.3CL** Dementia

There is consistent evidence that combined lifestyle in mid-life is related to less risk of dementia in later life from studies followed up 10 to 25 years.

Two studies [++][1], [+][2] reported longitudinal associations between lifestyle and dementia or cognitive impairment. Both studies reported a beneficial association between mid-life protective behaviours and dementia or cognitive decline in later life however in one study the associations were non-significant[2].

One study was conducted in the US and found a significant association between combined lifestyle and other episodic memory and executive functioning. The UK-based study found a non-significant association with dementia.

[1]Agrigoroaei 2011; [2]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The 3 other studies that found a similar relationship were conducted in developed European countries (Sweden and Iceland).

#### **2.10.4CL** Overall mortality

There is consistent evidence from high and good quality studies that reducing unhealthy behaviours or adopting a healthier lifestyle in mid-life is related to reduced death.

Two cohort studies [++][1], [ +][2] reported longitudinal associations between combined lifestyle behaviours and mortality. Two high or good quality studies reported a significant negative association between number of unhealthy behaviours and mortality.

[1]King 2007; [2]Elwood 2013

- **Applicability**: Directly applicable. Two cohort studies report a beneficial association between combined lifestyle in mid-life and mortality. One study was conducted in the UK and the other USA. Both studies were rated as good or high quality.

**2.10.5CL** Cardiovascular (CVD) Outcomes

There is inconsistent evidence from high and good quality studies that reducing unhealthy behaviours or adopting a healthier lifestyle in mid-life is related to reduced CVD from studies followed up 13 to 25 years.

Two cohort studies [++][1], [ +][2] reported longitudinal associations between combined lifestyle behaviours and Cardiovascular disease. One study reported a significant negative association between number of unhealthy behaviours and CVD[1] while the other[2] reported no association. Importantly the combined behaviours in these two studies vary.

[1] King 2007; [2] Elwood 2013

- **Applicability**: Partially applicable. The one study reporting a beneficial association between combined lifestyle in mid-life and CVD was conducted in the USA. The study reporting no association was conducted in the UK. Both studies were rated as good or high quality.

**2.10.6CL** Diabetes / Metabolic Syndrome

There is evidence that association exists between reducing unhealthy combined lifestyle behaviours in mid-life is related to diabetes from studies followed up 25 years.

One study [+][1] examined the impact of combined lifestyle on diabetes; while there was a negative correlation this was non-significant.

[1]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between changing combined lifestyle and diabetes in mid-life was conducted in the UK.

**2.10.7CL** Cancer

There is no evidence that association exists between reducing unhealthy combined lifestyle behaviours in mid-life is related to cancer from studies followed up 25 years.

One study [+][1] examined the impact of combined lifestyle on cancer; there was no correlation.

[1]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between changing combined lifestyle and cancer in mid-life was conducted in the UK.

**2.10.8CL** Other chronic diseases

No study found.

**2.10.9CL** Mental health

No study found.

### 3.11 Evidence statements for SMOKELESS TOBACCO (ST)

**2.11.1ST** Diabetes

There is some evidence to suggest that the use of smokeless tobacco (snuff/snus) in mid-life is related to successful type two diabetes in a study lasting 10 years.

One study [+][1] reported longitudinal associations between smokeless tobacco use and diabetes. The use of smokeless tobacco was associated with low insulin response but not low insulin sensitivity.

[1]Ostenson 2012

- **Applicability**: Partially applicable. One study reported an association between smokeless tobacco and was conducted in Sweden.

**2.11.2ST** Weight

There is some evidence to suggest that smokeless tobacco use in mid-life is related to weight and weight maintenance later life from studies followed up 10 years.

One study [++][1] reported that those who did not use snuff were more likely to be those who did not gain weight; the lack of snuff use increased the chances of not gaining weight.

[1] Nafziger 2007

- **Applicability**: Partially applicable. One study reported an association between smokeless tobacco and was conducted in Sweden.

### 3.12 Evidence statements for DISADVANTAGED GROUPS

The definition used for this review is that 'disadvantaged populations' includes (but is not limited to) low socioeconomic status; ethnic minority groups; lesbian, gay, bisexual and transsexual (LGBT) community groups; travellers; and other groups with protected characteristics under the equality and diversity legislation.

Studies included in this evidence statement are those that examined differential risk factors (in midlife) within the same cohort for disadvantaged groups.

**12.1 DG** Dementia

*Smoking - Ethnic minority groups*

There is weak and limited evidence from one moderate quality study conducted in the US [+][1] that in midlife smokers there is no difference in risk of developing dementia by ethnicity.

The study [+][1] examined associations between midlife smoking and incidence of dementia over twelve years in Caucasian and African American groups and found no differences in development of dementia by ethnicity.

- **Applicability**: Partially applicable. The study was conducted in the US. The study was limited to comparison of African American and Caucasian groups. There may be cultural and ethnic differences between US ethnic groups and the UK and the results may not be relevant to other ethnic groups.

*Smoking – Gender*

There is weak and limited evidence from one moderate quality study conducted in the US [+][1] that in midlife smokers there is no difference in risk of developing dementia by gender.

One study conducted in the US [+][1] that examined associations between midlife smoking and incidence of dementia over twelve years in Caucasian and African American groups found no differences in development of dementia by gender.

- **Applicability**: Partially applicable. The study was conducted in the US. The study was limited to comparison of African American and Caucasian groups. There may be cultural and ethnic differences between US ethnic groups and the UK.

*Alcohol - Low socioeconomic status (SES)*

There is weak and limited evidence from one moderate quality study conducted in France [+][2] that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance at follow up.

One study conducted in France [+][2], found that for people with a lower SES based on occupational position, those with high alcohol intake (>21 drinks/week) had poorer cognitive performance than those consuming 4 -14 drinks per week over ten years follow up. Results were based on a test measuring psychomotor speed, attention and reasoning. The DSST test (digital symbol substitution test) score difference was - 2.1 points (95% CI -3.9, -0.3). No association between alcohol consumption and cognitive performance was found in those in intermediate or high socioeconomic groups.

- **Applicability**: Partially applicable. The study was conducted in France.

**12.2 DG** Cardiovascular (CVD) Outcomes

*Smoking – Gender*

There is weak and limited evidence from one moderate quality study conducted in Japan [+][3] of little difference between midlife male or female smokers in risk of cardiovascular disease.

One study conducted in Japan [+][3] found little difference in risk of total CHD or myocardial infarction (MI) between male and female smokers. For both men and women, current smoking was positively associated with the age-adjusted risk of total CHD or MI. The multivariate relative risk for current smokers versus never smokers in men was 2.85 (95%CI 1.98, 4.12) for total CHD and 3.64 (95%CI 2.27, 5.83) for MI. For women the results were 3.07 (95%CI 1.48, 6.40) for total CHD and 2.90 (95%CI 1.18, 7.18) for MI.

- **Applicability**: Partially applicable. The study was conducted in Japan.

*Physical* activity *– Gender*

There is very weak and limited evidence from one moderate quality study conducted in Germany [+][4] of less risk of myocardial infarction (MI) in women participating in moderate or high levels of leisure time sports at midlife.

The study [+][4] reported that moderate or high levels of sports in leisure time were associated with significantly reduced risk of MI in women but not men in most fully adjusted models (adjusted for other major coronary heart disease risk factors). However this result was based on only a small number of women who participated in moderate or high levels of PA.

- **Applicability**: Partially applicable. The study was conducted in Germany.

[1] Alonso 2009; [2] Sabia 2011; [3] Baba 2006; [4] Meisinger 2007

## 4. DISCUSSION

### Findings into context & implications of findings

The DH has asked NICE to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model underpin the guidance. The reviews looked for evidence on a wide range of potential influences on well-being in later life and at the effectiveness and cost effectiveness of available interventions to act on these factors. This review (Review 2) aimed to identify if there were any specific issues or behavioural risk factors at midlife that should be considered by the PHAC team when designing the guidance. The specific objective was to synthesise the evidence for the association between modifiable behavioural risk factors in midlife (age 40-65 years) and dementia, disability and frailty in later life (DDF) (age >65 years).

A comprehensive search of the literature was conducted using a wide range of search terms to identify the range of likely behavioural risk factors (such as physical activity, diet, smoking, alcohol, overweight, social exposure and integration, and hearing and vision-related behaviours) and the broad range of potential outcomes (relating to successful or healthy ageing, quality of life or wellbeing, dementia, disability, frailty including chronic conditions such as cardiovascular outcomes, cancer, diabetes, mood disorders and mortality).

After a rigorous selection process, 164 observational longitudinal cohort studies that have measured behavioural risk factors in midlife and followed up outcomes for the same participants in later life were included in the review. The behavioural risk factors for which we found published data in midlife with relevant outcomes in later life were: physical activity and inactivity; diet and components of diet; smoking and smokeless tobacco (snuff/snus); alcohol; weight change or weight cycling; combinations of lifestyle components e.g. physical activity, diet and smoking; and leisure, cognitive activity or social networks. Studies of behaviour related to hearing or vision were sought but none were found that met the inclusion criteria for this review.

<u>Physical activity and inactivity</u>

Forty-five papers were found relating to PA, of which two specifically aimed to look at inactivity. Some studies reported multiple associations and different exposures relating to PA (an example would be a positive beneficial association with improved DDF outcomes for vigorous PA and null association for light activity) so where there are different associations

these have been reported in the tables. The available data covers different levels and intensity of PA and a few report specific types of activity (e.g. walking, active commuting).

Twelve of the PA papers were conducted in the UK. Some of these were different publications from the same study e.g. Caerphilly cohort study, but which reported different behavioural risk factors or outcomes. Other included studies were mainly from OECD countries and most were from Europe and the US.

Diet

For diet, 48 studies were included. Some studies reported more than one relevant outcome or different types of exposure (e.g. fruit or vegetables) or amounts of exposure (e.g. low, moderate or heavy coffee consumption). Three studies reported outcomes relevant to successful ageing, seven reported disability and frailty outcomes, six dementia or cognitive outcomes, five on total mortality, fifteen on CVD outcomes, seven on diabetes outcomes, six on cancer outcomes, three on mental health, and three on other communicable diseases. Six studies reported on the relationships between diet or components of diet and preconditions (as specified in Figure 1) for DDF or NCC.

Evidence was found covering midlife dietary patterns and consumption of dietary components, such as macronutrients and for specific foods. Included studies cover dietary patterns, fat (total, saturated, poly- and mono-unsaturated), protein, fibre, fruit and vegetables, fish, meat, red and processed meat, milk, salt, glycaemic index or glycaemic load, micronutrients, coffee, tea and caffeine.

There is some consistent evidence (but from a limited number of studies) that a healthy diet in general (studies included e.g. ADA diets) or Mediterranean diet, and fruit and vegetables has beneficial effects on DDF and NCC outcomes. There is also some consistent evidence (again from a limited number of studies) that higher consumption of saturated fat or processed and red meat (reported together) in midlife is associated with poorer ageing, DDF and NCC outcomes. There was some consistent evidence (from a limited number of studies) that coffee consumption in moderation may be beneficial. However, one study reported increased risk of coronary events with very heavy coffee consumption

Smoking

The review found a wealth of evidence from longitudinal cohort studies relating to the association between midlife smoking and dementia, disability, frailty outcomes (DDF). Fifty seven studies were included. Some studies reported more than one relevant outcome or different levels of exposure (e.g. heavy or light smoking and populations (e.g. current, former

and never smokers). Three studies reported healthy ageing outcomes, six with disability and/or frailty outcomes, seven reported total mortality, nineteen reported CVD outcomes, four on diabetes related outcomes, six with cancer outcomes, one on other chronic diseases (kidney disease).

There was a very consistent association across studies between midlife smoking and poorer DDF and NCC outcomes. All included studies either reported poorer outcomes for those who smoked at midlife or a very small number of studies reported a null association. No studies reported beneficial outcomes in later life for midlife smokers. The majority of studies were rated as moderate quality with a few studies of high or low quality. Studies were conducted in men and women. Only a few studies examined differential risk factors for dementia between men and women and across different ethnic groups. The limited available evidence suggests similar risks of smoking on later health outcomes by gender or ethnicity.

Smokeless tobacco

One study reported longitudinal associations between smokeless tobacco (snuff/snus) and improved diabetes related outcomes. The use of smokeless tobacco was associated with lower insulin response.

Alcohol

Twenty four prospective cohort studies were included on alcohol intake between 40 and 64 years of age (midlife), in relation to disability, dementia, cardiovascular outcomes, diabetes and metabolic syndrome, cancer and other outcomes assessed after 55 years of age (late-life). Seven studies were conducted in the UK and the rest were mainly conducted in developed OECD countries,

There was heterogeneity in the categorisation of self-reported alcohol intake levels. Five articles (n=5) assessed the number of drinks consumed per week, one (n=1) differentiated teetotallers from alcohol users, five (n=5) documented the number of drinks per day, one (n=1) assessed the number of drinks per month, while the rest of the studies (n=12) used a combination of measurements examining alcohol intake over various time spans.

Evidence specific to midlife alcohol consumption was mixed and inconsistent with smaller effect sizes than for smoking and physical activity. Some studies reported negative outcomes e.g. for dementia, mortality and cancer and some more positive outcomes e.g. for ageing and mental health. However studies found were sparsely distributed among different outcomes. Two studies reported moderate quality evidence of higher risk of dementia in non-drinkers

and heavy drinkers compared to moderate drinkers, but limited evidence was available specific to midlife.

There was limited evidence, from one study, that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance in later life.

Weight change, weight cycling

Four studies were included that reported an association between weight change patterns in midlife and later outcomes. One study reported increased risk of hip fracture in those losing greater than 10% of their body weight (as determined from maximum weight during follow up). Two studies reported null relationships with weight loss/gain or cycling, one with mortality as an outcome and one with diabetes as an outcome. One study reported increased risk of dementia with weight change in midlife (independent of the direction of weight change). However the study that reported diabetes as an outcome also examined overall weight status, being overweight or obese appeared to be a more important factor in the association with diabetes than weight change.

Combined lifestyles

Three studies reported data for combinations of lifestyle programmes. One reported relationship between uptake of number of healthy behaviours with CVD and mortality. One reported the relationship of a combination of behavioural protective factors with cognitive function and one combinations of healthy behaviours (not smoking, BMI, fruit and veg intake, regular exercise, moderate alcohol intake). In those practising at least four behaviours there was a significantly lower risk of diabetes, vascular disease, cancer, dementia and cognitive impairment and mortality.

Leisure, cognitive activity, social networks

Four studies were found that examined the relationship between midlife activities and DDF outcomes. One study reported a beneficial effect of diversity and intensity of intellectual, passive and physical activities on later risk of Alzheimer's disease. Three studies reported relationships with cognitive function, all found a beneficial association. The activities ranged from engagement with number of activities, social network size and political, mental or socio-cultural activities.

However one study examined both activity participation in relation to cognitive ability over time but also in relation to the baseline cognitive activity and the results suggested that while activity participation is related to cognitive ability across adulthood it may be intrinsically related to the baseline cognitive function (Bielak 2012).

Other health-related behaviours

Evidence was sought but not found within the inclusion criteria for other behaviours including vision and hearing related behaviours.

Disadvantaged groups/health inequalities

Data relating to disadvantaged groups was also limited with some sparse data on people with low SES, ethnic minority groups and gender in midlife with relevant outcomes. This data is summarised for each health behaviour. No relevant data was found for other groups covered by the equality and diversity legislation.

Limitations of the evidence, gaps

Most of the evidence found comes from Europe or the US or other developed OECD countries. There is a fairly good representation of studies from the UK.

Limited evidence was found specifically relating to midlife behaviours for leisure activities including cognitive activities and social networks, weight change and weight cycling and smokeless tobacco. While many diet-related studies were found they covered a broad range of diets and dietary components. There were some diets or dietary components for which studies specifically pertaining to midlife were not found. Data relating to disadvantaged groups was also limited. Some sparse data on people with low SES, ethnic minority groups and gender in midlife was found. No longitudinal data was found relevant to other groups covered by the equality and diversity legislation such as LGBT groups or travellers.

Much of the data used to assess behaviour was self-reported. For physical activity all studies used self-reports of activity except one which used accelerometry. For smoking many studies used self-reports with biochemical confirmation of smoking status. Most diet and alcohol behaviour was self-reported. However, in general outcome data was assessed objectively using clinical data and medical records or registers.

The review only includes longitudinal observational studies, which can show an association between midlife risk factors and later life outcomes. However associations from this type of study are not necessarily causal.

Limitations of the review

The remit of this review was specifically to identify midlife behavioural risk factors for DDF outcomes and common NCCs in later life. Determinants of dementia, disability, frailty over the whole lifecourse were not included. Pragmatically, due to the wide scope of the review,

the large amount of literature covering behavioural risk factors and the outcomes of interest, and the timescales for the review, the searches were focused on studies with midlife-related terms in the title, abstract or related MeSH indexing to identify those studies that specifically aimed to report on midlife exposure. The implication is that cohort studies that have followed individuals from mid- to late life and reported associations of interest without specifying midlife terms in the title or abstract were not identified by the searches. This might explain some of the gaps in evidence and further work is ongoing (though beyond the scope of this report) to address this limitation.

Because a very large amount of data was found for a wide range of risks and outcomes, the search limitations are unlikely to have an impact on the overall findings. In fact, it appears that a lot of what we know of the associations between behavioural risk factors and late life outcomes comes from studies conducted in people in mid-life. So, where caution should be exercised is in extrapolating the mid-life associations to older age groups – the direction and magnitude of these associations vary across the life cycle. This is the focus of several work packages undertaken by NIHR SPHR Ageing Well programme, which should complement the findings of this review with regards to identifying behavioural risk factors that are amenable to change for improved health outcomes in later life.

## 5. OVERALL SUMMARY AND RECOMMENDATIONS

### Physical activity

There is consistent evidence that midlife physical activity has a beneficial effect on later life DDF and NCC outcomes. However, one report (from 45) reported increased risk of bladder cancer in men participating in vigorous activity at midlife.

- The promotion of physical activity in all midlife populations including men and women and different ethnic groups should be addressed by the guidance. All types of activity appear to have a positive relationship with outcomes.

### Diet

- A healthy diet (standard guidelines) or Mediterranean-type diet could be recommended, also diets which minimise consumption of saturated fat, increase fruit and vegetable intake with moderate consumption of processed or red meat. Coffee consumption in moderation.

**Smoking**

There is consistent evidence that prevention, reduction and cessation of smoking behaviour in all midlife populations including men and women and different ethnic groups could lead to improved outcomes.

- Smoking prevention, reduction and cessation in midlife should be addressed by the guidance.

**Alcohol**

- Evidence specific to midlife alcohol consumption was mixed (across studies and across outcomes). It is not clear from the findings of this review whether there is a safe level of alcohol consumption, so caution should be exercised in making recommendations in that respect.

**Combined healthy lifestyle programmes**

- Consideration could be given to programmes which combine at least two or more aspects of healthy behaviour (from PA, healthy diet, non-smoking, alcohol in moderation, leisure activities)

**Leisure activities/social activities**

There is some evidence that those who participate in a diverse range of intellectual, passive, physical and leisure activities have better cognitive outcomes.

- Consideration could be given to improving social support and access to activities. This could be incorporated into healthy lifestyle programmes (with evaluation to build the evidence base).

# 6. BIBLIOGRAPHY

## 6.1 Bibliography cited in the report

CPHE methods manual. Link: http://publications.nice.org.uk/methods-for-the-development-of-nice-public-health-guidance-third-edition-pmg4

Ben-Shlomo Y, Kuh D. (2002) A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology 31(2): 285-293.

Clegg A, Young J, Iliffe S et al. (2013) Frailty in elderly people. The Lancet 381(9868): 752-762.

Fries J, Bruce B, Chakravarty E. (2011) Compression of morbidity 1980-2011: a focused review of paradigms and progress. Journal of Aging Research 2011.

Khaw K-T, Wareham N, Bingham S et al. (2008) Combined impact of health behaviours and mortality in men and women: The EPIC-Norfolk prospective population study. PLoS Medicine 5(1): e12.

Kuh D. (2007) A life course approach to healthy aging, frailty, and capability. Journal of Gerontology. Series A: Biological Sciences and Medical Sciences 62(7): 717-721.

Liberati A, Altman DG, Tetzlaff J et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology 62: e1-e34.

Myint PK, Smith RD, Luben RN et al. (2011) Lifestyle behaviours and quality-adjusted life years in middle and older age. Age & Ageing 40(5): 589-595.

Newman AB, Glynn NW, Taylor CA et al. (2011) Health and function of participants in the Long Life Family Study: a comparison with other cohorts. Aging 3(1): 63-76.

Sabia S, Singh-Manoux A, Hagger-Johnson G et al. (2012) Influence of individual and combined healthy behaviours on successful aging. Canadian Medical Association Journal 184(18): 1985-1992.

Shea B, Hamel C, Wells G et al. (2009) AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of Clinical Epidemiology 62: 1013-1020.

Singh-Manoux A, Marmot MG, Glymour M et al. (2011) Does cognitive reserve shape cognitive decline? Annals of Neurology 70(2): 296-304.

Wills AK, Lawlor DA, Matthews FE et al. (2011) Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. PLoS Medicine 8(6): e1000440.

World Health Organization. (2002) The World Health Report 2002: Reducing risks, promoting healthy life. Geneva: World Health Organization. Available at: www.who.int/whr/2002/en/ (accessed on 27 June 2012).

## 6.2 Bibliography of included studies

Agahi N, Shaw BA. (2013) Smoking trajectories from mid-life to old age and the development of non-life-threatening health problems: a 34-year prospective cohort study. Preventive Medicine 57(2): 107-112.

Agrigoroaei S, Lachman ME. (2011) Cognitive functioning in mid-life and old age: combined effects of psychosocial and behavioral factors. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 66 Suppl 1: i130-140.

Akbaraly T, Sabia S, Hagger-Johnson G et al. (2013) Does overall diet in mid-life predict future aging phenotypes? A cohort study. American Journal of Medicine 126(5): 411-419.

Alonso A, Mosley TH, Jr., Gottesman RF et al. (2009) Risk of dementia hospitalisation associated with cardiovascular risk factors in mid-life and older age: the Atherosclerosis Risk in Communities (ARIC) study. Journal of Neurology, Neurosurgery & Psychiatry 80(11): 1194-1201.

Andel R, Crowe M, Pedersen NL et al. (2008) Physical exercise at mid-life and risk of dementia three decades later: a population-based study of Swedish twins. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 63(1): 62-66.

Anttila T, Helkala EL, Viitanen M et al. (2004) Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. BMJ 329(7465): 539.

Ascherio A, Zhang SM, Hernán MA et al. (2001) Prospective study of caffeine consumption and risk of Parkinson's Disease in men and women. Annals of Neurology 50: 56-63.

Baba S, Iso H, Mannami T et al. (2006) Cigarette smoking and risk of coronary heart disease incidence among middle-aged Japanese men and women: the JPHC Study Cohort I. European Journal of Cardiovascular Prevention & Rehabilitation 13(2): 207-213.

Beulens JW, Rimm EB, Hu FB et al. (2008) Alcohol consumption, mediating biomarkers, and risk of type 2 diabetes among middle-aged women. Diabetes Care 31(10): 2050-2055.

Beulens JW, de Bruijne LM, Stolk RP et al. (2007) High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. Journal of the American College of Cardiology 50(1): 14-21.

Bielak AA, Anstey KJ, Christensen H et al. (2012) Activity engagement is related to level but not change in cognitive ability across adulthood. Psychology and Aging 27(1):219-28.

Blanco-Cedres L, Daviglus ML, Garside DB et al. (2002) Relation of cigarette smoking to 25-year mortality in middle-aged men with low baseline serum cholesterol: the Chicago Heart Association Detection Project in Industry. American Journal of Epidemiology 155(4): 354-360.

Boudik F, Reissigova J, Hrach K et al. (2006) Primary prevention of coronary artery disease among middle aged men in Prague: twenty-year follow-up results. Atherosclerosis 184(1): 86-93.

Britton A, Shipley M, Singh-Manoux A et al. (2008) Successful aging: the contribution of early-life and mid-life risk factors. Journal of the American Geriatrics Society 56(6): 1098-1105.

Carlson M, Helms MJ, Steffens DC et al. (2008) Mid-life activity predicts risk of dementia in older male twin pairs. Alzheimer's & Dementia 4: 324–331.

Chang M, Saczynski JS, Snaedal J et al. (2013) Mid-life physical activity preserves lower extremity function in older adults: age gene/environment susceptibility-Reykjavik study. Journal of the American Geriatrics Society 61(2): 237-242.

Chang M, Jonsson PV, Snaedal J et al. (2010) The effect of mid-life physical activity on cognitive function among older adults: AGES--Reykjavik Study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 65(12): 1369-1374.

Christensen U, Stovring N, Schultz-Larsen K et al. (2006) Functional ability at age 75: is there an impact of physical inactivity from middle age to early old age? Scandinavian Journal of Medicine & Science in Sports 16(4): 245-251.

Debette S, Seshadri S, Beiser A et al. (2011) Mid-life vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 77(5): 461-468.

Dudas KA, Wilhelmsen L, Rosengren A. (2007) Predictors of coronary bypass grafting in a population of middle-aged men. European Journal of Cardiovascular Prevention & Rehabilitation 14(1): 122-127.

Ekelund U, Brage S, Franks PW et al. (2005) Physical activity energy expenditure predicts progression toward the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the Medical Research Council Ely Study. Diabetes Care 28(5): 1195-1200.

Elwood P, Galante J, Pickering J et al. (2013) Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly Cohort Study. PLoS One 8(12): e81877.

Emberson JR, Shaper AG, Wannamethee SG et al. (2005) Alcohol intake in middle age and risk of cardiovascular disease and mortality: accounting for intake variation over time. American Journal of Epidemiology 161(9): 856-863.

Englund U, Nordstrom P, Nilsson J et al. (2011) Physical activity in middle-aged women and hip fracture risk: the UFO study. Osteoporosis International 22(2): 499-505.

Englund U, Nordstrom P, Nilsson J et al. (2013) Active commuting reduces the risk of wrist fractures in middle-aged women-the UFO study. Osteoporosis International 24(2): 533-540.

Eskelinen MH, Ngandu T, Tuomilehto J et al. (2009) Mid-life coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE dtudy. Journal of Alzheimer's Disease 16(1): 85–91.

Eskelinen MH, Ngandu T, Helkala EL et al. (2008) Fat intake at mid-life and cognitive impairment later in life: a population-based CAIDE study. International Journal of Geriatric Psychiatry 23(7): 741-747.

Field AE, Malspeis S, Willett WC. (2009) Weight cycling and mortality among middle-aged or older women. Archives of Internal Medicine 169(9): 881-886.

Fogelholm M, Kujala U, Kaprio J et al. (2000) Predictors of weight change in middle-aged and old men. Obesity Research 8(5): 367-373.

Friedland RP, Fritsch T, Smyth KA et al. (2001) Patients with Alzheimer's disease have reduced activities in mid-life compared with healthy control-group members. Proceedings of the National Academy of Sciences of the United States of America 98(6): 3440-3445.
Gerber Y, Myers V, Goldbourt U. (2012) Smoking reduction at mid-life and lifetime mortality risk in men: a prospective cohort study. American Journal of Epidemiology 175(10): 1006-1012.

Guallar-Castillon P, Rodriguez-Artalejo F, Tormo MJ et al. (2012) Major dietary patterns and risk of coronary heart disease in middle-aged persons from a Mediterranean country: the EPIC-Spain cohort study. Nutrition Metabolism & Cardiovascular Diseases 22(3): 192-199.

Haapanen-Niemi N, Miilunpalo S, Pasanen M et al. (2000). Body mass index, physical inactivity and low level of physical fitness as determinants of all-cause and cardiovascular disease mortality--16 y follow-up of middle-aged and elderly men and women. International Journal of Obesity Related Metabolic Disorders 24(11): 1465-74.

Halperin RO, Gaziano JM, Sesso HD. (2008) Smoking and the risk of incident hypertension in middle-aged older men. American Journal of Hypertension 21(2): 148-52.

Hamer M, Lavoie KL, Bacon SL. (2013) Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. British Journal of Sports Medicine 48(3): 239-43.

Happonen P, Voutilainen S, Salonen JT. (2004) Coffee drinking is dose-dependently related to the risk of acute coronary events in middle-aged men. Journal of Nutrition 134(9): 2381-6.

Hara M, Sobue T, Sasaki S et al. (2002) Smoking and risk of premature death among middle aged Japanese: ten-year follow-up of the Japan Public Health Centre based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort I. Japanese Journal of Cancer Research 93(1): 6-14.

Harmsen P, Lappas G, Rosengren A et al. (2006) Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Göteborg, Sweden. Stroke 37(7): 1663-7.

He K, Hu FB, Colditz GA et al. (2004) Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. International Journal of Obesity and Related Metabolic Disorders 28(12): 1569-74.

Hodge A, Almeida OP, English DR et al. (2013) Patterns of dietary intake and psychological distress in older Australians: benefits not just from a Mediterranean diet. International Psychogeriatrics 25(3): 456-466.

Holmberg AH, Johnell O, Nilsson PM et al. (2006) Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women. Osteoporos International 17(7): 1065-77.

Holme I, Tonstad S, Sogaard AJ et al. (2007) Leisure time physical activity in middle age predicts the metabolic syndrome in old age: results of a 28-year follow-up of men in the Oslo study. BMC Public Health 12(7): 154.

Holtermann A, Mortensen OS, Burr H et al. (2009) The interplay between physical activity at work and during leisure time-risk of ischemic heart disease and all-cause mortality in middle-aged Caucasian men. Scandinavian Journal of Work, Environment and Health 35(6): 466-74.

Holtzman RE, Rebok GW, Saczynski JS et al. (2004) Social network characteristics and cognition in middle aged and older adults. The Journals of Gerontology Series B Psychological Sciences and Social Sciences 59(6): 278-84.

Hu G, Jousilahti P, Borodulin K, Barengo NC et al. (2007) Occupational, commuting and leisure-time physical activity in relation to coronary heart disease among middle-aged Finnish men and women. Atherosclerosis 194(2): 490-497.

Hu G, Tuomilehto J, Silventoinen K et al. (2005) The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47,212 middle-aged Finnish men and women. International Journal of Obesity 29(8): 894-902.

Hu G, Tuomilehto J, Silventoinen K et al. (2004) Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. European Heart Journal 25(24): 2212-9.

Hu G, Qiao Q, Silventoinen K et al. (2003) Occupational, commuting, and leisure time physical activity in relation to risk for Type 2 diabetes in middle-aged Finnish men and women. Diabetologia 46(3): 322-9.

Hughes TF, Andel R, Small BJ et al. (2010) Mid-life fruit and vegetable consumption and risk of dementia in later life in Swedish twins. American Journal of Geriatric Psychiatry 18(5): 413-20.

Humphries SE, Talmud PJ, Hawe E et al. (2001) Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospective study. Lancet 14;358(9276): 115-9.

Inoue M, Hanaoka T, Sasazuki S et al. (2004) Impact of tobacco smoking on subsequent cancer risk among middle-aged Japanese men and women: data from a large-scale population-based cohort study in Japan--the JPHC study. Preventive Medicine 38(5): 516-22.

Iso H, Baba S, Mannami T et al. (2004) Alcohol consumption and risk of stroke among middle-aged men: the JPHC Cohort I. Stroke 35(5): 1124-9.

Jakobsen MU, O'Reilly EJ, Heitmann BL et al. (2009) Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. American Journal of Clinical Nutrition 89: 1425-32.

Janzon E, Hedblad B, Berglund G. (2004) Tobacco and myocardial infarction in middle-aged women: a study of factors modifying the risk. Journal of Internal Medicine 256(2): 111-8.

Johnsen NF, Christensen J, Thomsen BL et al. (2006) Physical activity and risk of colon can cancer in a cohort of Danish middle-aged men and women. European Journal of Epidemiology 21(12):877-84. Epub 2006 Dec 8.

Kareholt I, Lennartsson C, Gatz M et al. (2011) Baseline leisure time activity and cognition more than two decades later. International Journal of Geriatric Psychiatry 26: 65–74.

Kato M, Noda M, Inoue M et al. (2013) Psychological factors, coffee and risk of diabetes mellitus among middle-aged Japanese: a population-based prospective study in the JPHC study cohort. Endocrinology Journal 56(3): 459-68.

Kesse-Guyot E, Andreeva VA, Jeandel C et al. (2012) A healthy dietary pattern at mid-life is associated with subsequent cognitive performance. Journal of Nutrition 142(5): 909-15.

Khalili P, Nilsson PM, Nilsson JA et al. (2002) Smoking as a modifier of the systolic blood pressure-induced risk of cardiovascular events and mortality: a population based prospective study of middle-aged men. Journal of Hypertension 20(9): 1759-64.

Kimm H, Lee PH, Shin YJ et al. (2011) Mid-life and late-life vascular risk factors and dementia in Korean men and women. Archives of Gerontology and Geriatrics 52(3): e117-22.

King DE, Mainous AG 3rd, Geesey ME. (2007) Turning back the clock: adopting a healthy lifestyle in middle age. American Journal of Medicine 120(7): 598-603.

Knopman D, Boland LL, Mosley T et al. (2001) Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 56(1): 42-8.

Kristenson H, Osterling A, Nilsson JA et al. (2002). Prevention of alcohol-related deaths in middle-aged heavy drinkers. Alcoholism: Clinical and Experimental Research 26(4): 478-84.

Lahti J, Laaksonen M, Lahelma E et al. (2010) The impact of physical activity on physical health functioning – A prospective study among middle-aged employees. Preventive Medicine 50(5-6): 246-50.

Laitala VS, Kaprio J, Koskenvuo M et al. (2009) Coffee drinking in middle age is not associated with cognitive performance in old age. American Journal of Clinical Nutrition 90(3) 640-6.

Laitinen MH, Ngandu T, Rovio S et al. (2006) Fat intake at mid-life and risk of dementia and Alzheimer's disease: a population-based study. Dementia & Geriatric Cognitive Disorders 22(1): 99-107.

Lajous M, Willett WC, Robins J et al. (2013) Changes in fish consumption in mid-life and the risk of coronary heart disease in men and women. American Journal of Epidemiology 1;178(3): 382-91.

Lang IA, Guralnik JM, Melzer D. (2007) Physical activity in middle-aged adults reduces risks of functional impairment independent of its effect on weight. Journal of the American Geriatric Society 55(11):1836-41.

Langlois JA, Mussolino ME, Visser M et al. (2001) Weight loss from maximum body weight among middle-aged and older white women and the risk of hip fracture: the NHANES I epidemiologic follow-up study. Osteoporosis International 12(9): 763-8.

Laurin D, Masaki KH, Foley DJ et al. (2004) Mid-life dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. American Journal of Epidemiology 159(10): 959-967.

Lehto SM, Ruusunen A, Tolmunen T et al. (2013) Dietary zinc intake and the risk of depression in middle-aged men: A 20-year prospective follow-up study. Journal of Affective Disorders 150(2): 682-5.

Leosdottir M, Nilsson PM, Nilsson JA et al. (2007) Cardiovascular event risk in relation to dietary fat intake in middle-aged individuals: data from The Malmo Diet and Cancer Study. European Journal of Cardiovascular Prevention & Rehabilitation 14(5): 701-6.

Levitan EB, Mittleman MA, Wolk A. (2010) Dietary glycemic index, dietary glycemic load, and incidence of heart failure events: a prospective study of middle-aged and elderly women. Journal of the American College of Nutrition 29(1): 65-71.

Levitan EB, Wolk A, Mittleman MA. (2009) Fish consumption, marine omega-3 fatty acids, and incidence of heart failure a population-based prospective study of middle-aged and elderly men. European Heart Journal 30(12): 1495-500.

Levitan EB, Mittleman MA, Håkansson N et al. (2007) Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. American Journal of Clinical Nutrition 85(6): 1521-6.

Lim SH, Tai BC, Yuan JM et al. (2013) Smoking cessation and mortality among middle-aged and elderly Chinese in Singapore: the Singapore Chinese Health Study. Tobacco Control 22(4): 235-40.

Lin Y, Kikuchi S, Tamakoshi A et al. (2005) Alcohol consumption and mortality among middle-aged and elderly Japanese men and women. Annals of Epidemiology 15(8): 590-7.

Liu S, Willett WC, Manson JE, Hu FB et al. (2003) Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. American Journal of Clinical Nutrition 78(5): 920-7.

Liu Y, Sobue T, Otani T, Tsugane S. (2004) Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. Cancer Causes Control 15(4): 349-57.

Malmberg JJ, Miilunpalo SI, Pasanen ME et al. (2006) Associations of leisure-time physical activity with mobility difficulties among middle-aged and older adults. Journal of Aging and Physical Activity 14(2): 133-53.

Mannami T, Iso H, Baba S et al. (2004) Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women The JPHC Study Cohort I. Stroke. 35(6):1248-53.

Masaki M, Sugimori H, Nakamura K et al. (2003) Dietary Patterns and Stomach Cancer among Middle-aged Male Workers in Tokyo. Asian Pacific Journal of Cancer Prevention 4(1): 61-6.

Meisinger C, Löwel H, Heier M et al. (2007) Association of sports activities in leisure time and incident myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. European Journal of Cardiovascular Prevention & Rehabilitation 14(6): 788-92.

Menotti A, Alberti-Fidanza A, Fidanza F. (2012) The association of the Mediterranean Adequacy Index with fatal coronary events in an Italian middle-aged male population followed for 40 years. Nutrition, Metabolism and Cardiovascular Diseases 22(4): 369-75.

Menotti A, Lanti M, Maiani G et al. (2006) Determinants of longevity and all-cause mortality among middle-aged men. Role of 48 personal characteristics in a 40-year follow-up of Italian rural areas in the Seven Countries Study. Aging Clinical and Experimental Research 18(5): 394-406.

Menotti A, Lanti M, Puddu PE. (2000) Twenty-five-year cardiovascular disease among middle-aged men. Disease burden, time shape, predictors, risk probabilities. Italian Heart Journal 1(11): 749-57.

Meyer J, Döring A, Herder C et al. (2011) Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality in middle-aged men from the MONICA/KORA Augsburg cohort study. European Journal of Clinical Nutrition 65(7): 800-7.

Miura K, Greenland P, Stamler J et al. (2004) Relation of vegetable, fruit, and meat intake to 7-year blood pressure change in middle-aged men: The Chicago Western Electric Study. American Journal of Epidemiology 159(6): 572-80.

Moayyeri A, Kaptoge S, Luben RN et al. (2009) Estimation of absolute fracture risk among middle-aged and older men and women: the EPIC-Norfolk population cohort study. European Journal of Epidemiology 24(5): 259-66.

Morgan GS, Gallacher J, Bayer A et al. (2012) Physical activity in middle-age and dementia in later life: findings from a prospective cohort of men in Caerphilly, South Wales and a meta-analysis. Journal of Alzheimer's Disease 31(3): 569-580.

Mursu J, Voutilainen S, Nurmi T et al. (2008) Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. British Journal of Nutrition 100(4):890-5.

Nafziger AN, Lindvall K, Norberg M et al. (2007) Who is maintaining weight in a middle-aged population in Sweden? A longitudinal analysis over 10 years. BMC Public Health 12;7: 108.

Nakamura Y, Hozawa A, Turin TC et al. (2009) Dietary Habits in Middle Age and Future Changes in Activities of Daily Living – NIPPON DATA80. Gerontology 55(6): 707-13.

Nakayama T, Yokoyama T, Yoshiike N et al. (2000) Population attributable fraction of stroke incidence in middle-aged and elderly people: Contributions of hypertension, smoking and atrial fibrillation. Neuroepidemiology 19(4): 217-26.

Noborisaka Y, Ishizaki M, Yamada Y et al. (2013) The effects of continuing and discontinuing smoking on the development of chronic kidney disease (CKD) in the healthy middle-aged working population in Japan. Environmental Health and Preventive Medicine 18(1): 24-32.

Nokes NR, Tucker LA. (2012) Changes in hip bone mineral density and objectively measured physical activity in middle-aged women: a 6-year prospective study. American Journal of Health Promotion (2): 121-9.

Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP et al. (2011) Fruit and vegetable intake and cognitive decline in middle-aged men and women: the Doetinchem Cohort Study. British Journal of Nutrition 106(5): 752-61.

Nooyens AC, van Gelder BM, Verschuren WM. (2008) Smoking and cognitive decline among middle-aged men and women: The Doetinchem Cohort Study. American Journal of Public Health 98(12): 2244-50.

Osler M, Andreasen AH, Hoidrup S. (2003) No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. Journal of Clinical Epidemiology 56(3): 274-9.

Østbye T, Taylor DH, Jung SH. (2002) A longitudinal study of the effects of tobacco smoking and other modifiable risk factors on ill health in middle-aged and old Americans: Results from the health and retirement study and asset and health dynamics among the oldest old survey. Preventive Medicine 34(3):3 34-45.

Östenson CG, Hilding A, Grill V et al. (2012) High consumption of smokeless tobacco (“snus”) predicts increased risk of type 2 diabetes in a 10-year prospective study of middle-aged Swedish men. Scandinavian Journal of Public Health 40(8): 730-7.

Otani T, Iwasaki M, Yamamoto S et al. (2003) Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women. Cancer, Epidemiology, Biomarkers & Prevention 12(12): 1492-500.

Patel KV, Coppin AK, Manini TM et al. (2006) Mid-life physical activity and mobility in older age: the InCHIANTI study. American Journal of Preventive Medicine 31(3): 217-24.

Patja K, Jousilahti P, Hu G et al. (2005) Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. Journal of Internal Medicine 258(4): 356-62.

Pelkonen M, Tukiainen H, Tervahauta M et al. (2000) Pulmonary function, smoking cessation and 30 year mortality in middle aged Finnish men. Thorax 55(9): 746-50.

Pitsavos C, Panagiotakos DB, Chrysohoou C et al. (2004) Physical activity decreases the risk of stroke in middle-age men with left ventricular hypertrophy: 40-year follow-up (1961–2001) of the Seven Countries Study (the Corfu cohort). Journal of Human Hypertension 18(7): 495-501.

Preis SR, Stampfer MJ, Spiegelman D et al. (2010) Dietary protein and risk of ischemic heart disease in middle-aged men. American Journal of Clinical Nutrition 92(5): 1265-72.

Qiao Q, Tervahauta M, Nissinen A et al. (2000) Mortality from all causes and from coronary heart disease related to smoking and changes in smoking during a 35-year follow-up of middle-aged Finnish men. European Heart Journal 21(19): 1621-6.

Qiu D, Mei J, Tanihata T et al. (2003) A cohort study on cerebrovascular disease in middle-aged and elderly population in rural areas in Jiangxi Province, China. Journal of Epidemiology 13(3): 149-56.

Räikkönen K, Matthews KA, Kuller LH. (2001) Trajectory of psychological risk and incident hypertension in middle-aged women. Hypertension 38(4): 798-802.

Rantakömi SH, Laukkanen JA, Sivenius J et al. (2013) Hangover and the risk of stroke in middle-aged men. Acta Neurologic Scandinavica 127(3): 186-91.

Ravona-Springer R, Schnaider-Beeri M, Goldbourt U. (2013) Body weight variability in mid-life and risk for dementia in old age. Neurology 80(18): 1677-83.

Risérus U, Arnlöv J, Berglund L. (2007) Long-term predictors of insulin resistance. Role of lifestyle and metabolic factors in middle-aged men. Diabetes Care 30(11):2928-33.

Ross GW, Abbott RD, Petrovitch H et al. (2000) Association of coffee and caffeine intake with the risk of Parkinson Disease. Journal of the American Medical Association 283(20): 2674-2679.

Rovio S, Kareholt I. (2007) Work-related physical activity and the risk of dementia and Alzheimer's disease. International Journal of Geriatric Psychiatry 22: 874–882.

Rovio S, Kareholt I, Helkala EL et al. (2005) Leisure-time physical activity at mid-life and the risk of dementia and Alzheimer's disease. Lancet Neurology 4(11): 705-711.

Ruder EH, Thiebaut AC, Thompson FE et al. (2011) Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study. American Journal of Clinical Nutrition 94(6): 1607-1619.

Rusanen M, Kivipelto M, Quesenberry CP Jr et al. (2011) Heavy smoking in mid-life and long-term risk of Alzheimer disease and vascular dementia. Archives of Internal Medicine 171(4): 333-9.

Ruusunen A, Virtanen JK, Lehto SM et al. (2011) Serum polyunsaturated fatty acids are not associated with the risk of severe depression in middle-aged Finnish men: Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. European Journal of Nutrition 50(2): 89-96.

Ruusunen A, Lehto SM, Tolmunen T et al. (2010) Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Public Health Nutrition 13(8): 1215-20.

Sabia S, Guéguen A, Berr C et al. (2011) High alcohol consumption in middle- aged adults is associated with poorer cognitive performance only in the low socio- economic group. Results from the GAZEL cohort study. Addiction 106(1): 93-101.

Sabia S, Nabi H, Kivimaki M et al. (2009) Health behaviors from early to late mid-life as predictors of cognitive function: The Whitehall II study. American Journal of Epidemiology 170(4): 428-37.

Sabia S, Marmot M, Dufouil C et al. (2008) Smoking history and cognitive function in middle age from the Whitehall II study. Archives of Internal Medicine 168(11): 1165.
Sairenchi T, Iso H, Nishimura A et al. (2004) Cigarette smoking and risk of type 2 diabetes mellitus among middle-aged and elderly Japanese men and women. American Journal of Epidemiology 160(2): 158-62.

Samieri C, Sun Q, Townsend MK et al. (2013) The association between dietary patterns at mid-life and health in aging: an observational study. Annals of Internal Medicine 159(9): 584-91.

Satoh H, Nishino T, Tomita K et al. (2006) Risk Factors and the incidence of coronary artery disease in young middle-aged Japanese men: Results from a 10-year cohort study. Intern Medicine 45(5): 235-9.

Seccareccia F, Alberti-Fidanza A, Fidanza F et al. (2003) Vegetable intake and long-term survival among middle-aged men in Italy. Annals of Epidemiology 13(6): 424-30.

Shaper AG, Wannamethee SG, Walker M. (2003) Pipe and cigar smoking and major cardiovascular events, cancer incidence and all-cause mortality in middle-aged British men. International Journal of Epidemiology 32(5): 802-8.

Sobue T, Yamamoto S, Hara M et al. (2002) Cigarette smoking and subsequent risk of lung cancer by histologic type in middle- aged Japanese men and women: The JPHC study. International Journal of Cancer 99(2): 245-51.

Song Y, Manson JE, Buring JE et al. (2004) A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women. Diabetes Care 27(9): 2108-15.

Song Y, Sesso HD, Manson JE et al. (2006) Dietary magnesium intake and risk of incident hypertension among middle-aged and older US women in a 10-year follow-up study. American Journal of Cardiology 98(12): 1616-21.

Stevens RJ, Roddam AW, Spencer EA et al. (2009) Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. International Journal of Cancer 124(10): 2400-5.

Strand BH, Langballe EM, Hjellvik V et al. (2013) Mid-life vascular risk factors and their association with dementia deaths: Results from a Norwegian prospective study followed up for 35 years. Journal of Neurological Sciences 324(1-2): 124-30.

Strandberg AY, Strandberg TE, Pitkälä K et al. (2008) The effect of smoking in mid-life on health-related quality of life in old age. Archives of Intern Medicine 168(18): 1968-74.

Strandhagen E, Hansson PO, Bosaeus I et al. (2000) High fruit intake may reduce mortality among middle-aged and elderly men. The study of men born in 1913. (2000). European Journal of Clinical Nutrition 54(4): 337-41.

Sun Q, Townsend MK, Okereke OI et al. (2011) Alcohol consumption at mid-life and successful ageing in women: a prospective cohort analysis in the Nurses' Health Study. PLoS Medicine 8(9): e1001090.

Sun Q, Townsend MK, Okereke OI et al. (2010) Physical activity at mid-life in relation to successful survival in women at age 70 years and older. Archives of Internal Medicine 170(2): 194-201.

Szoeke CE, Cicuttini FM, Guthrie JR et al. (2006) Factors affecting the prevalence of osteoarthritis in healthy middle-aged women: data from the longitudinal Melbourne Women's Mid-life Health Project. Bone 39(5): 1149-1155.

Tabak C, Smit HA, Räsänen L et al. (2001) Alcohol consumption in relation to 20-Year COPD mortality and pulmonary function in middle-aged men from three European countries. Epidemiology 12(2): 239-45.

Tsugane S, Sasazuki S, Kobayashi M et al. (2004) Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. British Journal of Cancer 90(1): 128-34.

Tuomilehto J, Hu G, Bidel S et al. (2004) Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA 291(10): 1213-1219.

Tyas SL, White LR, Petrovitch H et al. (2003) Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. Neurobiology of Aging 24(4): 589-96.

Valtonen M, Laaksonen DE, Laukkanen J et al. (2010) Sedentary lifestyle and emergence of hopelessness in middle-aged men. European Journal of Cardiovascular Prevention and Rehabilitation 17(5): 524-9.

Villegas R, Yang G, Gao YT, Cai H et al. (2010) Dietary patterns are associated with lower incidence of type 2 diabetes in middle-aged women: the Shanghai Women's Health Study. International Journal of Epidemiology 39(3): 889-99.

Villegas R, Xiang YB, Elasy T et al. (2011) Fish, shellfish, and long-chain n23 fatty acid consumption and risk of incident type 2 diabetes in middle-aged Chinese men and women. American Journal of Clinical Nutrition 94(2): 543-51.

Virta JJ, Heikkilä K, Perola M et al. (2010) Mid-life cardiovascular risk factors and late cognitive impairment. European Journal of Epidemiology 28(5): 405-16.

Virta JJ, Järvenpää T, Heikkilä K et al. (2010) Midlife alcohol consumption and later risk of cognitive impairment: a twin follow-up study. Journal of Alzheimer's Disease 22(3): 939-948.

Waki K, Noda M, Sasaki S et al. (2005) Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabetic Medicine 22(3): 323-331.

Walda IC, Tabak C, Smit HA et al. (2002) Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. European Journal of Clinical Nutrition 56(7): 638-643.

Wang L, Manson JE, Gaziano JM et al. (2012) Fruit and vegetable intake and the risk of hypertension in middle-aged and older women. American Journal of Hypertension 25(2): 180-189.

Wang L, Lee IM, Manson JE et al. (2010) Alcohol consumption, weight gain, and risk of becoming overweight in middle-aged and older women. Archives of Internal Medicine 170(5): 453-461.

Wang L, Lee IM, Zhang SM et al. (2009) Dietary intake of selected flavonols, flavones, and flavonoid-rich foods and risk of cancer in middle-aged and older women. American Journal of Clinical Nutrition 89(3): 905-12.

Wang L, Manson JE, Buring JE et al. (2008) Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. Hypertension 51(4): 1073-1079.

Wannamethee SG, Shaper AG. (2003) Alcohol, body weight, and weight gain in middle-aged men. American Journal of Clinical Nutrition 77(5): 1312-1317.

Wannamethee SG, Shaper AG. (2002) Taking up regular drinking in middle age: effect on major coronary heart disease events and mortality. Heart 87(1): 32-36.

Wannamethee SG, Shaper AG, Walker M. (2001) Physical activity and risk of cancer in middle-aged men. British Journal of Cancer 85(9): 1311-1316.

Wannamethee S. G., Shaper AG, Perry IJ. (2001) Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 24(9): 1590-1595.

Waring ME, Eaton CB, Lasater TM et al. (2010) Incident diabetes in relation to weight patterns during middle age. American Journal of Epidemiology 171(5): 550-556

Whitmer RA, Sidney S, Selby J et al. (2005) Mid-life cardiovascular risk factors and risk of dementia in late life. Neurology 64(2): 277-281.

Wiles NJ, Haase AM, Gallacher J et al. (2007) Physical activity and common mental disorder: results from the Caerphilly Study. American Journal of Epidemiology 165(8): 946-54.

Willcox BJ, He Q, Chen R et al. (2006) Midlife risk factors and healthy survival in men. JAMA 296(19): 2343-2350.

Xu Q, Anderson D, Courtney M. (2010)c A longitudinal study of the relationship between lifestyle and mental health among mid-life and older women in Australia: findings from the Healthy Aging of Women Study. Health Care for Women International 31(12): 1082-1096.

Yaffe K, Barnes D, Nevitt M et al. (2001) A prospective study of physical activity and cognitive decline in elderly women: women who walk. Archives of Internal Medicine 161(14): 1703-1708.

Yu S, Huang YC. (2003) Knowledge of, attitudes toward, and activity to prevent osteoporosis among middle-aged and elderly women. Journal of Nursing Research 11(1): 65-72.