| Section A: CPH to complete | |
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| **Name:** | Oliver Mytton |
| **Job title:** | Honorary Specialty Registrar |
| **Address:** | Centre for Diet and Activity Research (CEDAR),<br>MRC Epidemiology Unit<br>University of Cambridge School of Clinical Medicine |
| **Guidance title:** | Disability, dementia and frailty in later life - mid-life approaches to prevention |
| **Committee:** | PHAC D |
| **Subject of expert testimony:** | Promoting Brain Health: Delaying dementia: evidence from observational studies |
| **Evidence gaps or uncertainties:** | [Please list the research questions or evidence uncertainties that the testimony should address] |
| What is the evidence linking the behavioural risk factors of alcohol consumption, diet, physical activity and smoking with the development of dementia? | |
| What is the evidence linking related "biological" risk factors: obesity, diabetes, blood pressure and blood cholesterol? | |
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| **Section B: Expert to complete** | |
| **Summary testimony**: | [Please use the space below to summarise your testimony in 250 – 1000 words – continue over page if necessary ] |

A review of the observational evidence linking four behavioural risk factors and four medical risk factors with dementia was presented. This work was part of a broader piece of work undertaken by the UK Health Forum concerning the development of a primary prevention agenda around dementia, and integrating this with the prevention of other non-communicable diseases. For this reason the review focused on four behavioural risk factors (alcohol, diet, physical activity and smoking) and four linked medical risk factors (blood pressure, diabetes, obesity and serum cholesterol) that are linked both to dementia and many of the major non-communicable diseases. Unlike the remit of the PHAC, the UK Health Forum review was not restricted to mid-life exposures.

<u>Aetiology of dementia</u>

Before discussing the evidence from observational studies a number of observations were made about our present understanding of the aetiology of dementia. First some authors have advocated a life-course model for conceptualising dementia development. This model suggests that there may be a variety of factors that an individual may be exposed to throughout or during life, which may either protect against or increase the risk of developing dementia in later life. This model suggests that development of dementia (at least for some people) may be an inevitable consequence of becoming old, and it may be more helpful to think of delaying the onset of dementia rather than preventing dementia. Second within cardiovascular disease, it is well established that a set of behaviours (e.g. physical inactivity) contributes to the development of a set of medical or intermediate risk factors (presentation of which will be influenced by genetic factors) which lead to the development of sub-clinical disease (e.g. atherosclerosis) and subsequently symptoms and disability. A similar conception of disease aetiology may be

appropriate for dementia, and it is thought that medical risk factors can contribute to changes in the brain (e.g. loss of neurones, plaque formation and inflammation) which are thought to have a role in development of dementia. Third the review has not made a distinction between the different types of dementia (principally Alzheimer's and vascular), because it is often hard to reliably identify the two in epidemiological studies (e.g. pathology studies indicate a large degree of overlap), and even when they are separated it appears as if the relationships between risk factor and the two major types of dementia are similar. Fourth it was also noted that age-specific incidence of dementia has declined markedly in several western countries. While the reasons for the decline are not known, one favoured explanation is that the reduction in vascular risk (e.g. due to smoking cessation and medical management) that has led to a marked reduction in the incidence of stroke and heart disease, has also lead to a reduction in dementia incidence.

Review methods

A systematic review of *Pubmed* was undertaken to identify existing systematic reviews of the epidemiological evidence linking the four behavioural risk factors and four medical risk factors with dementia. Full description of the methods (and findings) is included in the UK Health Forum report. [1]

Review findings

There is some observational evidence to link the four behavioural risk factors (alcohol, diet, physical activity and smoking) and dementia. There is also observational evidence linking other vascular risk factors (diabetes, blood pressure, obesity and serum cholesterol) to dementia. Given the importance of the behavioural risk factors in the development of these vascular (or medical) risk factors, this may strengthen the evidence linking these behaviours to dementia.

The observational evidence is of variable quality (e.g. consistency of observed associations, replication in different populations, and adjustment for confounders). Nonetheless for some behaviours, noticeably physical activity and smoking, where it is consistent and appears robust to adjustment for potential confounders, it is persuasive. [2,3] It should also be noted that there are some short-term trials of physical activity in older people showing improvements in cognition.

The associations between diet and dementia have not (yet) been well explored (or at least not been reported in systematic reviews). [4,5] Despite this, because of the strong evidence linking diet to a set of medical risk factors, which in turn are linked to dementia, it seems likely that associations between diet and dementia do exist. Most authors favour a U- or J-shaped relationship between alcohol consumption and dementia. However the point at which excess consumption of alcohol increases risk of dementia has not been clearly characterised. [6]

Most of the epidemiological evidence has emerged in the last 10 years. The nature of the evidence at present largely permits us to comment on whether there is an association. Some work has looked at how the association may be modified by age or genetic factors (APOE gene), but less work has considered how the associations may vary for other sub-groups (e.g. different ethnic groups). Studies that have looked at different age-groups (typically mid-life vs late-life) tend to suggest that mid-life may be particularly important in terms of dementia risk, which might be consistent with other work suggesting that the dementia arises from long-term pathological changes in the brain. Very little work (in terms of systematic reviews) has considered how the different risk factors may interact to cause dementia.

On the basis of the observational evidence there have been several trials launched in

Europe, typically involving modifying a set of behaviours and medical risk factors, to understand the effect on cognition or dementia. [7,8]

Summary

Broadly the observational evidence supports “a vascular hypothesis” to the aetiology of some dementias (both Alzheimer’s dementia and vascular dementia). Stronger trial evidence may take many years to emerge (and indeed may not be possible given the strong medical indication for treatment of vascular risk factors in mid and late-life). If we accept that the observational evidence is likely to indicate a true causal relationships (as many researchers suggest), then it seems appropriate to align advice around the prevention of dementia with the prevention of cardiovascular disease. Other additional factors (not considered here: e.g. depression and head injuries) might also be important in the prevention of dementia.

**References (if applicable):**


1) Promoting Brain Health: Developing a prevention agenda linking dementia and other non-communicable diseases. UK Health Forum, 2014 [In Press]
2) Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr. 2008 Dec 23;8:36.
3) Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med. 2009 Jan;39(1):3-11. Epub 2008 Jun 23.
4) Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. J Nutr Health Aging. 2012 Jul;16(7):626-30.
5) Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, Llewellyn DJ. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology. 2013 Jul;24(4):479-89.
6) Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry. 2009 Jul;17(7):542-55.
7) Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Nissinen A, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimers Dement. 2013 Nov;9(6):657-65
8) In-MINDD (INnovative Midlife Intervention for Dementia Deterrence). http://www.inmindd.eu (accessed 14 November 2013).