

# DEMENTIA PREVENTION

## CONTENTS

<b>1. Key Messages.....</b>	<b>2</b>
<b>2. Practice Points – What can I do? (Summary of best evidence September 2018).....</b>	<b>4</b>
<b>3. Literature Review .....</b>	<b>5</b>
a) Methods .....	5
b) Results .....	6
<b>4. References.....</b>	<b>26</b>

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Disclaimer: This document is a general guide, to be followed subject to the clinician's judgment and person's preference, choices and decisions in each individual case. The guideline is designed to provide information to assist decision making and is based on the best evidence available at the time of development of this publication.

# 1. Key Messages

- No disease modifying treatments are currently available for Alzheimer's Disease (AD).<sup>1</sup>
- Brain damage caused by transient ischaemic attacks (TIAs) and stroke is irreversible and increases the risk of subsequent dementia in late-life.
- Collectively modifiable risk factors account for more cases of dementia than genetic risk factors.
- Many of the risk factors for dementia are also risk factors for other diseases such as cancer, heart disease, diabetes and stroke. There is therefore an economy in approaching prevention across these multiple outcomes, particularly in the management of vascular risk factors.
- Middle-age appears to be a critical period when risk factors emerge that increase late-life risk of dementia.<sup>2</sup>
- Many risk factors for dementia are modifiable by lifestyle change, medication and avoidance of environmental hazards. Based on each person's individual risk profile mid- and later life modifications for risks include:
  - smoking cessation;
  - physical activity according to Australia's Physical Activity and Sedentary Behaviour Guidelines <sup>3</sup>;
  - healthy eating taking into account medical conditions, including 2+ fish meals per week and the Mediterranean diet;
  - reducing problem alcohol consumption;
  - increasing social participation and cognitively engaging activities;
  - optimising sleep hygiene and promoting healthy sleep patterns;
  - maintaining normal BMI;
  - reducing high total serum cholesterol in middle-aged adults;
  - for people with diabetes, maintain usual lifestyle and pharmaceutical management;
  - for patients with depression, treating according to depression guidelines;

- managing vascular risk factors (hypertension, atrial fibrillation etc.) according to guidelines;
- de-prescribing Benzodiazepines and Anticholinergics where possible; and
- not prescribing hormone replacement therapy (HRT) for cognitive symptoms.

Note: Throughout this chapter, Alzheimer's disease is abbreviated as AD and Vascular dementia, VaD.

## 2. Practice Points – What can I do? (Summary of best evidence September 2018)

Risk Factor	Present in Mid-life	Present in Late-life	Recommendation
<b>Smoking</b>	Increases risk	Increases risk	Support cessation (even in later life). Refer to programs
<b>Physical activity</b>	Reduces risk	Reduces risk	Prescribe according to <a href="#">Australia's Physical Activity and Sedentary Behaviour Guidelines</a> . <sup>3</sup>
<b>Diet</b>	Presumably reduces risk*	Reduces risk	Healthy eating taking into account medical conditions (e.g. diabetes). Recommend eating 2+ fish meals per week, support diet with nutrient pattern similar to Mediterranean diet.
<b>Alcohol</b>	Hazardous increases risk		Assess alcohol consumption, refer problem drinking for treatment. Recommend NHMRC guidelines. Methodological difficulties in assessing exposure to alcohol. No evidence to recommend consumption of alcohol.
<b>Low social engagement</b>	-	Increases risk	Advise increase in social participation.
<b>High cognitive engagement</b>	May reduce risk	Reduces risk	Advise increase in cognitively engaging activities
<b>Sleep disorders</b>	May increase risk	Increase risk	Advise on sleep hygiene, refer to sleep clinic
<b>Overweight/obesity</b>	Increases risk	No association	Advise maintaining weight in normal BMI range. Reduce overweight/obesity in middle age.
<b>High Cholesterol</b>	Increases risk	No association	Advise reduction of high total serum cholesterol in middle-aged adults
<b>Diabetes</b>	Increases risk	Increases risk	Usual lifestyle and pharmaceutical management. Include cognitive impairment as potential complication in education and assessment.
<b>Hypertension</b>	Increases risk	May increase risk	Treat according to Heart Foundation guidelines
<b>Atrial Fibrillation</b>	Increases risk	Increases risk	Treat in accordance with guidelines e.g. Heart Foundation Guidelines
<b>Stroke</b>	Increases risk	Increases risk	Manage vascular risk factors to reduce risk of future stroke
<b>Depression</b>	Increases risk	Increases risk	Treat as per guidelines e.g. RANZCP Guidelines
<b>Statins</b>	-	May Reduce risk	Usual practice. Note no RCT evidence of benefit.
<b>Anti-hypertensives</b>	May Reduce risk	May Reduce risk	Treat according to Heart Foundation guidelines
<b>Benzodiazepines</b>	-	Increases risk	De-prescribe where possible
<b>Anti-inflammatories</b>	NSAIDs may reduce risk	NSAIDs may reduce risk	No RCT evidence of benefit. Usual practice for other conditions, not indicated for cognition.
<b>HRT</b>	No association	No association	Do not prescribe for cognitive symptoms
<b>Anticholinergics</b>	-	Increases risk	De-prescribe where possible

\* Note that some for many risk factors, there is no or insufficient information available on whether they increase risk of dementia in mid-life or late-life. Inferences can be made about some (e.g. smoking, diet) based on the wider literature and their impact on heart disease or stroke. For some risk factors, RCT evidence is not consistent with cohort studies (e.g. statins)

### 3. Literature Review

Evidence for risk factors for Alzheimer's disease (AD) and dementia is largely obtained from long-term cohort studies that have examined characteristics that predict the transition from normal aging to AD or dementia. Typically, studies exclude individuals who have these conditions at baseline, and then examine baseline predictors of incident disease identified at study follow-ups. This epidemiological research is observational. Randomized controlled trials are required to establish the treatment effects for individual protective factors such as medications or lifestyle modification.

Within the field of dementia there are still relatively few treatment trials compared with other areas of medicine. This is because of the long time-frames needed to follow individuals for dementia, and sample attrition of those who develop medical conditions and dementia. Many of the risk factors for dementia are also risk factors for other diseases such as cancer, heart disease, diabetes and stroke. There is therefore an economy of approaching prevention across these multiple outcomes, particularly in the management of vascular risk factors.

#### Why dementia risk reduction?

Most cases of dementia occur in adults aged over 80 and are of mixed aetiology. Development of a drug to modify the course of AD is not imminent. Even if such a product becomes available, it will not address vascular cognitive impairment which contributes to and compounds AD. Moreover, it is possible that cases of dementia may be prevented by reducing risk factors at the population level or delaying the onset of disease in older adults.

#### a) Methods

For this chapter, we drew on evidence reported our umbrella review of the quality and quantity of observational evidence on risk factors for dementia<sup>4</sup> as well as relevant recent publications in the field. For the published review, searches of PubMed and the Cochrane databases were conducted in September 2018, and abstracts screened by at least two researchers. Results are based on effects identified in meta-analyses of specific risk factors. The review for these guidelines was restricted to population-based studies so that case-control and randomized controlled trials were not included. Articles were screened and organized by risk

factor and dementia type. Results were collated according to findings from studies measuring exposure in mid-life, late-life or a combined age-group.

## **b) Results**

This literature review includes the results of our search and is organized into 8 Lifestyle factors, 7 Medical Factors and 6 Medicines.

### **Lifestyle factors**

#### **Smoking**

Our review identified 6 published meta-analyses on smoking as a risk factor for dementia, published between 2007 and 2015.<sup>5-10</sup> Overall the studies showed that that current smokers in mid-life have about 30% increased risk of Any dementia compared to never smokers.

As most of the studies used in the meta-analyses were cohorts that were recruited in old age, there is insufficient evidence to make statements on the risk of subtypes of dementia associated with mid-life smoking. In older adults, current smokers had an increased risk of AD (40-99%), Vascular dementia (VaD) (26-78 %) and Any dementia (16-43 %).

In general, results showed that former smokers did not have an increased risk of any type of dementia. There is also some evidence from a smoking cessation trial of older adults in Perth, Australia showing that smoking cessation in adults aged over 70 is associated with less brain atrophy than continued smoking.<sup>11</sup> This individual study needs replication but suggests that smoking cessation is beneficial for reducing the risk of dementia even in old age. Overall the evidence is consistent in showing that smoking increases risk of late-life dementia.

There are areas where we lack knowledge. For example, we do not know how smoking increases risk of early-onset dementia. There is insufficient evidence to evaluate the role of moderating variables that may increase or decrease the effect of smoking. The most obvious one is the APOE e4 allele but synergistic effects have been reported in individual studies for diabetes.<sup>12</sup>

#### **Physical activity**

We identified 8 meta-analyses that evaluated the association between physical activity and risk of late-life dementia. They included studies that had follow-ups ranging from 1 to 31 years. The results of these studies were consistent in showing

that physical activity in mid-life and late-life, reduces the risk of incident AD and Vascular Dementia (VaD). Higher levels of physical activity in middle age have been associated with reduced risk of all-cause dementia in late life of around 20-40%. Activity undertaken in old-age is associated with reduced risk by about 35-40% of incident AD and VaD in several meta-analyses. One study compared adults meeting National Guidelines to those not meeting guidelines and found a 40% reduction in risk of AD, but even studies comparing less well defined 'high' versus 'low' groups found protective effects of physical activity.<sup>13</sup>

Despite the general finding of the benefit of physical activity, more research is needed to inform prescription of physical activity to prevent dementia. For example, we do not know the maximum benefit that can be obtained or whether there is a level of physical activity at which benefits cease accruing or is even harmful. General principles can be derived from the literature but specific details for topics such as the best exercise for adults with specific chronic conditions, and the benefits of water-based versus land-based activity, require further research. Physical activity can also increase certain risks, for example, falls. In populations already at increased risk of falls, exercise prescription needs to be tailored.

### **Dietary nutrients, foods and dietary patterns**

Research into diet and risk of dementia is divided into three parts in this overview. First, we report all the meta-analyses of associations between individual nutrients and risk of AD and dementia. Second, meta-analyses of individual foods and their associated AD/Dementia risk are reviewed. Finally, we review the association between dietary patterns and risk of AD and dementia.

The dietary nutrients that have been examined in relation to AD and dementia in meta-analyses include beta carotene, vitamins B, C, D, E, folate, omega 3 fatty acids and polyunsaturated fatty acids (PUFA). Analysis of individual nutrients is made difficult by the need to adjust for other risk and protective factors and dietary components.

Individual foods for which there are meta-analyses available include tea, coffee, fruit and vegetables, and fish. The only dietary pattern examined in relation to AD and dementia risk for which there is sufficient data for a meta-analysis is the Mediterranean pattern of eating.

Almost all the available information on dietary risk and protective factors for dementia is drawn from studies including older adults or combined age-range studies. Dietary, cooking and shopping habits may change in the prodromal phase of dementia so results that depend entirely on cohorts examined in older age may reflect changes already associated with impending dementia. Dietary patterns are also determined by culture, income and household patterns and traditions.

## **Dietary nutrients**

### **Beta-carotene**

One meta-analysis of 5 combined age cohort studies evaluated the association between beta-carotene and risk of AD<sup>14</sup> and found no association. The included studies had follow-up periods of 3.9 to 30.2 years. Interpretation of these data is limited by the potential confounding by other antioxidant properties in the diet.

### **Vitamin C**

Two meta-analyses examined the association between dietary intake of Vitamin C and risk of AD. One examined late life exposure in 6 cohort studies and found a 24% reduced risk<sup>14</sup> and the other pooled 6 studies of combined exposure ages and also found a reduced risk of 26% (0.55-0.93).<sup>10</sup> One meta-analysis examined the association between Vitamin C and Any dementia, pooling 8 studies and finding an 11% risk reduction.<sup>6</sup>

### **Vitamin D**

Three meta-analyses evaluated the association between Vitamin D and risk of dementia.

There were no studies examining exposure in midlife. One review<sup>15</sup> of two cohort studies found that Vitamin D deficiency was associated with a 21% increased risk of AD. One review of 5 prospective studies found that Vitamin D deficiency was associated with a 54% increased risk of Any dementia.<sup>16</sup> Another review of 3 studies found low vitamin D was associated with a 52% increase of risk for Any dementia.<sup>6</sup>

### **Vitamin E**

Three meta-analyses examined vitamin E and risk of dementia. There was one study<sup>10</sup> examining late-life exposure and risk of AD in a pooled analysis of 6 studies that

found a 27% reduced risk of AD. A further meta-analysis looking at Any dementia found a 20% reduced risk with vitamin E intake from 10 pooled studies.<sup>6</sup>

## **Folate**

One systematic review that combined three cohort studies to examine a combined age exposure to folate and risk of AD found it protective.<sup>10</sup>

## **Fat**

Three meta-analyses have been published examining the association between dietary fat and risk of dementia.<sup>10, 17, 18</sup> The dietary fats examined include long chain omega 3 fatty acids (DHA/EPA) and polyunsaturated fatty acids (PUFA). Dietary fats are typically measured using food frequency questionnaires in cohort studies and the total PUFA estimated in grams/day. One review<sup>17</sup> pooled three studies and found that among older adults, higher intake of dietary long chain fatty acids was associated with reduced risk of AD. One review<sup>17</sup> pooled two studies and found that among older adults, higher intake of dietary long chain fatty acids was not associated with risk of Any dementia.

Two reviews pooled data on fat intake and AD in combined age samples. One reported<sup>10</sup> no association for effects pooled over 4 studies for DHA and three studies for EPA. The second review reported no association for the pooled results from 2 studies.<sup>18</sup>

## **Foods**

### **Fish**

One review of 6 studies<sup>17</sup> found that fish consumption in late life was associated with 36% reduced risk of AD. However, another review<sup>17</sup> of 5 studies found no association of fish consumption in late life and risk of Any dementia.

Two reviews of fish and AD risk including middle-aged and older adults were identified. The first included 3 cohort studies and found fish consumption was associated with reduced risk of AD of about 50%. The second<sup>18</sup> pooled results of 4 cohort studies and also found fish to be protective against AD but with a smaller effect of 5% reduction. One review of 4 studies of combined age range found that fish consumption protected against Any dementia. Another review of 3 studies found late life fish consumption was associated with a 21% risk reduction.<sup>6</sup> Most studies

found eating fish 2-3 times per week or 3+ times per week was the threshold at which protection was measured. Overall, the benefits of fish appear great for AD than Any dementia and data are lacking for VaD.

## **Coffee**

Our review identified five meta-analyses of the effect of coffee on risk of dementia, of which five related coffee risk to AD<sup>10, 19-22</sup>; and three related coffee to and combined outcome of dementia or cognitive impairment.<sup>20-22</sup> There were no meta-analysis data specifically for midlife exposure to coffee and late-life risk of VaD or Any dementia.

One study<sup>10</sup> pooled three cohort studies with follow-ups of 5 to 25 years among older adults and found coffee consumption was associated with reduced risk of AD. A second review<sup>19</sup> reported pooled analysis of 2 cohort studies of combined ages and found a protective effect for AD, however, a study that combined outcomes of dementia and cognitive decline and pooled results for 11 prospective studies did not find any benefit of coffee.<sup>21</sup>

The findings for coffee are generally consistent in showing a protective effect for AD. However, the studies contributing to the meta-analyses varied in their measure of exposure and have varied research designs. Additional, and more recent studies are needed to provide a stronger evidence base for coffee and to evaluate the association of coffee with VaD and Any dementia and whether coffee-drinking specifically in middle age has similar protective effects.

## **Tea**

One systematic review of 4 studies covering mid- and late-life with 2-6.4 years of follow-up found a 35% reduced risk of AD associated with tea consumption.<sup>23</sup>

## **Healthy dietary patterns**

Two reviews pooled from two and four studies respectively, conducted in older adults, found a protective effect of the Mediterranean dietary pattern, with an approximately 30-35% reduced risk of AD.<sup>6, 24</sup> One review pooled results from 4 cohort studies that examined healthy dietary pattern in a combined age-group and risk of AD<sup>10</sup> and found healthy diet was protective RR = 0.46 (95% CI .41, .91).

Despite the media discussion about diet and cognitive health, the evidence base is limited. Available studies suggest that a Mediterranean style diet is protective against

AD, but meta-analyses are lacking that examine exposure among middle-aged adults and for non-AD dementia.

### **Summary for dietary components and patterns**

Overall, reviews of studies of older adults or combining middle and older aged adults have found that higher intake of Vitamin C, Vitamin E, and folate, fish, tea and coffee consumption are associated with reduced risk of AD. Mediterranean diet, and healthy dietary pattern are associated with reduced risk of AD. Low vitamin D is associated with increased risk of AD and risk of Any dementia. Dietary fats (DHA/EPA) were not associated with risk of Any dementia, but fish consumption and higher intake of Vitamin B was found to be protective.

There is no review level evidence on dietary intake in middle-aged adults and risk of late-life dementia. There is no evidence on dietary intake and risk of VaD. The information on dietary patterns is limited with few dietary patterns having been thoroughly studied. Fruits and vegetables are included in the protective diets and provide the protective nutrients.

### **Alcohol**

There were four systematic reviews that included meta-analyses reporting on alcohol and risk of dementia. One reported solely on AD,<sup>10</sup> one examined Any dementia,<sup>6</sup> and the other two examined dementia of any type, AD and VaD separately.<sup>25, 26</sup> Excess alcohol may be associated with reduced brain volume<sup>27</sup> increased risk of raised blood pressure and both cardio and cerebrovascular events.<sup>28</sup> However, it has been suggested that low to moderate consumption may be associated with some level of reduced risk potentially via increased High Density Lipoprotein (HDL) cholesterol, decreased insulin resistance and a reduced inflammatory state.<sup>29</sup>

Only one of the meta-analyses reported results separately for populations consuming alcohol in midlife or late-life. One of the systematic reviews included only populations classified by Medline, Embase or PsychInfo® as aged 65 and older which resulted in the majority of constituent studies reporting on late-life populations.

### **Alcohol and risk of Any dementia**

Two meta-analyses compared drinkers to non-drinkers and risk of any type of dementia, reporting a 34%<sup>25</sup> and a 35%<sup>26</sup> decreased risk in those who consumed alcohol.

Three meta-analyses that looked at level of alcohol consumption and risk of Any dementia. One looked at light to moderate consumption compared to non-drinkers and reported a 26% reduced risk<sup>25</sup>; the other two looked at general consumption, and heavy or excessive consumption compared to non-drinkers and found no relationship with Any dementia.<sup>6, 25</sup> Further examination of the data by sex found similar results for men and women. A meta-analysis including women only and comparing light to moderate consumption to non-drinkers found a 27% reduction in Any dementia. For the corresponding men-only analysis the results showed a 45% reduction.<sup>25</sup>

### **Alcohol and risk of Alzheimer Disease**

Two meta-analyses compared drinkers to non-drinkers and risk of AD. The meta-analyses reported a 34% decreased risk in drinkers,<sup>25</sup> and a 40% decreased risk combined risk ratio.<sup>26</sup> One meta-analysis compared ever drinking to never drinkers and risk of AD and reported a 57% reduction in risk associated with consumption of alcohol.<sup>10</sup>

For light to moderate consumption compared to non-drinkers meta-analyses reported a 28% reduction in risk,<sup>25</sup> and a 39% decreased risk.<sup>10</sup> For heavy or excessive consumption compared to non-drinkers there was no relationship between alcohol consumption and risk of AD.<sup>25</sup> Similarly for high levels of consumption compared to low or no consumption (3 studies) there was no relationship with AD.<sup>10</sup>

Further examination of the data by sex found similar results for men and women. A meta-analysis including women only and comparing light to moderate consumption to non-drinkers found a 17% reduction in AD. For the men-only analysis the results showed a 42% reduction.<sup>25</sup>

### **Alcohol and risk of Vascular Dementia (VaD)**

One meta-analysis compared drinkers to non-drinkers and found no association with VaD.<sup>26</sup>

However further meta-analyses comparing light to moderate drinkers to non-drinkers for risk of VaD reported a 25% reduction in the light to moderate drinkers. There was no relationship with risk of VaD when heavy or excessive alcohol consumption was compared to non-drinkers.<sup>25</sup> The reduction in risk of VaD seen when comparing light

to moderate drinkers to non-drinkers was sustained when men and women were examined separately. For women, the reduction was 43% and for men 51%.<sup>25</sup>

In summary, despite the evidence suggesting a 20-30% decreased risk of dementia associated with low to moderate alcohol consumption caution should be applied. Although the reviews had consistent findings, there was a level of overlap in their constituent studies. There is also no clear or consistent definition of low to moderate consumption in the evidence base, and there are methodological issues with regard to the accuracy of self-reported alcohol consumption. There is the possibility that those in the non-drinking group may include previous heavy drinkers or those with ill health, thus biasing this group to be at higher risk.

### **Cognitive engagement**

There were 2 reviews of cognitive engagement and risk of dementia that included meta-analysis.<sup>10, 30</sup> Both reported results combined for mid-life and late-life exposure. One reported results for AD<sup>10</sup> one for Any dementia.<sup>30</sup> There is no standardized method of assessing cognitive activity that is used across cohort studies. Unlike the field of say depression, there are not well validated, widely used questionnaires, and this is largely due to the nature of the exposure being variable, occurring in different settings and culturally specific. Cognitive engagement has changed over recent decades with the increase in computer use and internet, making it difficult to obtain consistent measures over time and between cohorts. In cohort studies focussing on dementia outcomes, data on cognitive activity have typically been collected via self-report on cognitively engaging activities such as reading, attending museums, writing letters, playing cognitively stimulating games and using computers.

In an analysis that combined ages, and pooled 5 studies with 5 to 12 years of follow-up,<sup>10</sup> findings demonstrated that cognitive activity was associated with 47% reduced risk of AD. The result remained significant after removing one study that introduced significant heterogeneity. Another analysis<sup>30</sup> found a protective effect of cognitive engagement for risk of Any dementia. Risk reduction for Any dementia ranged from 39% in an analysis of intellectual activities in 3 cohort studies combining ages, and 42% for stimulating activities pooling 2 studies. No data were available on the association between cognitive engagement and VaD.

Reverse causality is always a potential explanation for results showing that adults with more cognitively engaged lifestyle have reduced risk of dementia. Cognitive

engagement may reduce with cognitive impairment.<sup>31</sup> The plausibility of this protective association is enhanced by neuroimaging research demonstrating neuroplasticity in adulthood, with beneficial changes occurring from cognitively demanding activities and occupations. Similarly, when exposure to cognitively stimulating activities in early and mid-life are associated with reduced risk of dementia in late-life, this to some extent mitigates the possibility of reverse causation. Overall, we conclude that a cognitively engaged lifestyle in adulthood is associated with reduced risk of late-life AD and Any dementia.

### **Social engagement**

There is no standard definition or measure of social engagement used in epidemiological studies of dementia. The types of measures used cover variables such as social network size, satisfaction with social networks, frequency of social contact, and loneliness. There was 1 review of social relationships and risk of dementia that included meta-analysis.<sup>32</sup>

One review reported results for various measures of social engagement and risk of Any Dementia in late-life. It pooled 6 studies and found that lower social participation was associated with a 41% increased risk, and that less social contact was associated with a 57% increased risk in an analysis of 8 studies, and more loneliness were associated with 58% increased risk, but low satisfaction with social network size was not associated with increased risk in 5 studies.<sup>32</sup>

Reverse causality is always a potential explanation for results showing that adults with more socially engaged lifestyle have reduced risk of dementia. Social engagement may reduce with cognitive impairment.<sup>33</sup> Overall, the current evidence suggests that higher levels of social engagement and participation in late-life are associated with reduced risk of dementia and loneliness increases risk of dementia. Satisfaction with social networks does not appear to be associated. Further, long-term studies and interventions increasing social engagement are required to fully understand the types of social engagement that are beneficial, and the quantity needed to confer protection.

### **Sleep**

We identified one meta-analysis of insomnia as a risk factor for Any dementia that pooled results from 5 studies across age-groups.<sup>34</sup> That review found insomnia to be associated with a 53% increased risk of Any Dementia. No data were available to

evaluate effects for mid-life or late-life separately, or for AD or VaD. We conclude there is limited evidence that insomnia is a risk factor for Any dementia. Two meta-analyses were identified observing other sleeping behaviours. One meta-analysis found shorter versus longer sleep duration in late-life was associated with a 42% increase risk of Any dementia.<sup>35</sup> Another meta-analysis examined the presence of sleep problems versus none, finding a 47% increased risk for AD.<sup>36</sup>

## **Medical risk factors**

There were 7 medical risk factors for dementia that are regularly encountered in primary care and for which treatments are available.

### **Body mass index**

We identified 6 meta-analyses of BMI and dementia risk.<sup>10, 37-41</sup> Overall, studies were consistent in identifying that overweight BMI in mid-life increases the risk of AD, VaD and Any dementia and this effect is stronger for obese BMI. Reviews found no association between BMI in late-life and risk of dementia. When the age-range included both middle and older adults, associations were not identified. Overall the literature strongly indicates that overweight and obese BMI in middle-aged adults puts them at long-term risk of dementia. However, in the cohorts studied, older adults with BMI above the healthy range did not have increased risk of dementia. The explanation for this is unclear. It is possible that some of the findings in late-life are due to reverse causation, because weight loss occurs in the prodrome of AD.

The findings relating to low BMI are also concerning, but inconclusive at this stage. There did seem to be an increased risk of dementia for low-BMI adults compared with normal BMI adults. This finding needs further replication and evaluation of the extent to which other comorbid conditions may explain the association, particularly where the low BMI is due to another illness.

### **Cholesterol**

Our review identified five meta-analyses of the association of serum cholesterol with risk of dementia.<sup>40, 42-44</sup> One was an update by the same authors, and results were primarily drawn from two reviews. The overall finding from the reviews was that high serum cholesterol in middle aged adults is associated with an increased risk of AD in later life. There were insufficient data to make any statement on whether the increased risk also occurs of VaD.

Overall, the literature reporting cholesterol measured in late-life found no association with risk of any type of dementia. Xu, Tan <sup>10</sup> There were some limitations with the literature. Compared with other risk factors for dementia, there is a limited amount of information published on cholesterol risk. Studies differ in how they define and categorize high cholesterol, often comparing high and low quartiles within a cohort. The studies that reported the effect for mid-life used a different cut-off than that used clinically to define high cholesterol in Australia. Those studies used >6.5 mmol/l whereas the National Heart Foundation of Australia <sup>45</sup> now states the ideal goals are only listed as LDL-C (<1.8 mmol/L) and HDL-C (>1.0 mmol/L), with no combined total cholesterol level.

## Diabetes

The quantitative analysis of the literature on diabetes as a risk factor for dementia is drawn from more reviews that include more cohort studies, than nearly any other medical risk factor for dementia.<sup>10, 40, 46-51</sup> Findings are consistent across the reviews and hence results are considered robust. All reviews found that diabetes is associated with an increased risk of dementia. In mid-life, this effect has only been examined in a review that includes AD as an outcome, and the associated risk was about 40%. <sup>40</sup>

Among older adults, diabetics have 33-57% increased risk of AD,<sup>10, 47-51</sup> 51-73% increased risk of Any dementia <sup>46, 48-50</sup> and 227 to 249% increased risk of VaD.<sup>46, 48-50</sup>

The information on diabetes as a risk factor for dementia is highly consistent in demonstrating that it at least doubles the risk of VaD and increases the risk of AD. Post-mortem studies have found that diabetics demonstrate vascular pathology at higher rates than non-diabetics, but not higher rates of AD pathology.<sup>52</sup> This is consistent with the view that diabetes causes micro- and macro- vascular changes in the brain that lead to cognitive impairment and ultimately dementia.

Most studies have focussed on Type 2 diabetes as this is more prevalent than Type 1 diabetes. Cohort studies have insufficient statistical power to examine the risk associated with type 1 diabetes. However, some evidence is available to suggest that this condition also increases risk of dementia, not least because of the longer exposure as most individuals develop type 1 diabetes in their youth, whereas in Australia rates of Type 2 diabetes increase steadily from 45 years onwards but many cases are undiagnosed.<sup>53</sup>

There is no clinical trial evidence to support the capacity for optimal management of diabetes to reduce risk of dementia. However optimal management facilitates brain health and reduces complications.<sup>54</sup>

Research into diabetic medications as neuroprotective has been inconclusive<sup>55</sup> largely due to the difficulty in controlling for confounding variables in cohort studies, as well as obtaining information on adherence.

### **Hypertension/hypotension**

We identified four meta-analyses examining the association between high blood pressure and AD<sup>10, 40, 56, 57</sup> and one examining the association with VaD.<sup>58</sup> There were no meta-analyses that looked at dementia overall, regardless of dementia type. When mid- and late-life exposure were combined, there was a significantly increased risk (59%) of VaD with high blood pressure,<sup>58</sup> but no increase in risk of AD.<sup>56, 57</sup>

For exposure in midlife, one meta-analysis including five studies in total, found a 31% increased risk of AD.<sup>40</sup> For this analysis, Meng, Yu<sup>40</sup> defined exposure to high blood pressure as having hypertension or high systolic pressure or high diastolic pressure. When each category was analysed in separate meta-analyses hypertension (two studies) and high systolic pressure (three studies) were no longer significant. High diastolic pressure (three studies) retained significance and was associated with a doubling in risk.<sup>40</sup> For exposure in late life, there was one meta-analysis<sup>57</sup> reporting no association between high blood pressure and AD.

High blood pressure has been linked to AD pathology<sup>59</sup> and is an established risk factor for cerebrovascular damage, stroke and Transient Ischaemic Attack (TIA).<sup>60</sup> It may be that high blood pressure confers less risk at older ages, however, comprehensive meta-analytic data relating to dementia overall and to the different dementia types at different ages, are lacking. Furthermore, the five meta-analyses combined cohort studies with varying definitions of high blood pressure and hypertension and varying length of follow-up. Despite this, the wider health risks of high blood pressure and the benefits of treatment are well known and already comprehensively discussed by cardiovascular guidelines. At present, the best recommendation that can be made is to treat high blood pressure in accordance with guidelines.

### **Hypotension**

There was one meta-analysis relating to low diastolic blood pressure and risk of AD.<sup>10</sup> The meta-analysis included six studies and reported no relationship. There were no meta-analyses relating to low systolic pressure. There were no meta-analyses relating to dementia of any type or to VaD and none that looked at mid and late-life exposure separately. At present, the evidence related to hypotension is lacking.

In summary, there is evidence that high blood pressure is likely to increase risk of VaD and may also increase risk of AD if exposure occurs in midlife. There is no evidence that hypotension increases risk, but data is lacking. At present, the best recommendation that can be made is to treat according to the current guideline. See also section on antihypertensive use.

### **Atrial Fibrillation**

We identified three meta-analyses that examined the association between Atrial Fibrillation (AF) and risk of dementia.<sup>61-63</sup> There was one meta-analysis that reported on the association between AF and AD.<sup>10</sup> One study examined the effect of AF and VaD.<sup>61</sup> None of the meta-analyses reported results for mid and late-life.

The three analyses examining risk of Any dementia reported increased risks of 38%,<sup>61</sup> 100%<sup>62</sup>, and 42%<sup>63</sup> in those with AF. There was no evidence that presence of AF was associated with an increased risk of AD<sup>10, 61</sup>. A sensitivity and subgroup analysis of dementia subtypes from one meta-analysis<sup>61</sup> found a significant association for AF and VaD (RR 1.72; 95%CI, 1.27-2.32). Atrial fibrillation is thought to raise risk of dementia as a result of increased emboli or microemboli generated due to inefficient atrial function and causing subclinical microinfarcts or strokes.<sup>64</sup> In summary, AF is associated with an increased risk of dementia.

### **Stroke**

Stroke is an established risk factor for cognitive damage and is associated with an increased risk of dementia. Two systematic reviews and meta-analyses were identified reporting on the relationship between stroke and risk of dementia<sup>65</sup> and stroke and risk of AD.<sup>10</sup> Both combined mid- and late-life. The Pendlebury and Rothwell<sup>65</sup> review specified a focus on symptomatic stroke. They reported that in hospital-based studies, first ever or recurrent stroke is associated with a 20% increase in dementia at 3-6 months after stroke rising to ~22% at one year. For first ever stroke in population cohorts, the figure was around 6-7% at 12 months.

The Xu et al meta-analysis of 9 studies reported no relationship between stroke and AD.<sup>10</sup> There were no meta-analyses reporting on mid- and late-life separately. There were no meta-analyses reporting on VaD, however, evidence of cerebrovascular damage is a key diagnostic component of VaD meaning such an analysis would be confounded. Symptomatic stroke, both first ever and recurrent stroke, are associated with an increased risk of dementia but not of AD.

### **Renal impairment**

We identified three meta-analyses relating to renal function. One article reported on the relationship between impaired renal function and AD.<sup>10</sup> One article reported two meta-analyses, one on eGFR<60mL/min/1.72m<sup>2</sup> and one on presence of albuminuria, but combined dementia and cognitive impairment.<sup>66</sup> Neither reported results for mid- and late-life separately. There were no meta-analyses for VaD. No association was found between renal impairment and AD or between an eGFR<60 and dementia and cognitive impairment.<sup>10, 66</sup> Presence of albuminuria was associated with a 35% increased risk of dementia or cognitive decline,<sup>66</sup> but caution should be applied when interpreting this. Presence of albuminuria is not specific to renal impairment. The finding is further weakened by the combination of cognitive impairment and dementia where the cognitive impairment may represent a fluctuating state such as delirium.<sup>66</sup>

In summary, there is currently no robust meta-analytic evidence to link renal impairment to increased risk of dementia or AD. There is no evidence at all relating to VaD.

### **Homocysteine**

One meta-analysis reported on high homocysteine and risk of dementia and reported no association.<sup>67</sup> Two meta-analyses reported on high homocysteine and risk of AD.<sup>10, 68</sup> There were no meta-analyses reporting on mid- and late-life separately and none reporting on VaD.<sup>67</sup> Both meta-analyses reporting on AD found an increased risk. Xu and colleagues<sup>10</sup> combined eight studies and reported a 15% increased risk. Van Dam and Van Gool<sup>68</sup> combined three studies and reported a much larger 150% increased risk. However, caution must be applied in interpreting the two meta-analyses separately as two of the three studies in the Van Dam analysis were included in the Xu et al. meta-analysis also. Further uncertainty comes from a lack of

clarity as to the level of homocysteine classified as high in the constituent studies. The conclusion is that high homocysteine may increase risk of AD.

## Depression

There were three systematic reviews reporting seven meta-analyses relating to depression. There were two meta-analyses reporting on depression and risk of Any dementia.<sup>69, 70</sup> There were three meta-analyses examining the relationship between depression and risk of AD<sup>10, 69, 70</sup> and two meta-analyses reporting on depression and risk of VaD.<sup>69, 70</sup>

No meta-analyses were identified that examined mid-life depression and risk of dementia. Two meta-analyses reported on depression in late-life and Any dementia, both finding that depression was associated with increased risk.<sup>69, 70</sup> Diniz, Butters<sup>70</sup> (23 cohorts) found an 85% increased risk with depression and Cherbuin, Kim<sup>69</sup> reported a 98% increased risk for depression classified categorically as present or absent (11 cohorts) and a five percent increased risk (10 cohorts) per incremental increase in depression score.

Similarly, two meta-analyses reported on depression in late-life and AD and found depression to be associated with increased risk.<sup>69, 70</sup> Diniz, Butters<sup>70</sup> found an 65% increased risk with depression (17 cohorts) and Cherbuin, Kim<sup>69</sup> reported a doubling in risk of AD with depression classified as present or absent (10 cohorts) and a six percent increased risk (10 cohorts) per incremental increase in depression score.

For VaD, Diniz, Butters<sup>70</sup> reported that presence of depression more than doubled risk of VaD (5 cohorts). Whereas Cherbuin, Kim<sup>69</sup> reported no relationship for presence of depression (3 cohorts) or per incremental increase in depression score (2 cohorts). One meta-analysis reported on depression and AD in combined mid- and late-life populations<sup>10</sup> reporting an 8% increased risk. Additional adjustment for publication bias did not meaningfully alter the result.

Potential sources of bias include the classification and diagnosis of depression. Although the Cherbuin, Kim<sup>69</sup> review in particular sought to reduce bias in this area, there is the possibility that the constituent studies were not all representative of the populations they were drawn from, and the study follow-up varied from 2.5-30 years. We conclude that depression in late-life is associated with an approximate doubling

in risk of Any dementia, AD, and VaD. Depression in mixed mid and late-life populations is associated with an 8% increased risk of AD.

## Medicines

We review 7 medicines that have been evaluated for their potential risk or protective association with AD and dementia.

### Statins

There were 5 reviews of statins and risk of dementia that included meta-analysis.<sup>10, 71-73</sup> Of these, 4 reported results for AD,<sup>10, 73, 74</sup> none reported findings on VaD and 4 reported reviews of Any dementia risk including meta-analysis.<sup>71-74</sup> There was no review data on whether statin use is associated with risk of VaD.

Some reviews compiled results according to whether participants took lipophilic with non-lipophilic statins<sup>71</sup> and others used a general classification of any statin use versus no statin use.<sup>10, 73, 74</sup>

**Late-life exposure and AD:** Three reviews report pooled estimates for statins taken in late-life and risk of AD and two showed a protective effect. One review pooled 13 studies and found 30% risk reduction.<sup>72</sup> The second pooled 2 studies and found longer statin use was protective compared with shorter use.<sup>10</sup> The latter study also pooled 7 studies to compare current use with never using statins and found current users had a 41% reduced risk of AD.<sup>10</sup> One review found no significant increase in risk of AD and no difference in cognitive impairment (10 studies).<sup>74</sup>

**Late-life exposure and Any dementia:** Four reviews evaluated the risk of Any dementia associated with use of statins.<sup>71, 72</sup> Two reviews found protective effects. The first took into account duration of use. That review reported 29% risk reduction for statin use. Five studies with 6.2 years of follow up provided data to estimate a 2% risk reduction with 50 cases needed to be treated to prevent one case of dementia.<sup>71</sup> The second meta-analysis of 12 studies reported a pooled 18% risk reduction for participants using statins for 6 months or more compared with non-users<sup>72</sup> in random effects analysis.

Observational studies of older adults show that statin use is associated with reduced risk of AD and Any dementia. Note that observational studies are subject to bias and this finding of a protective effect of statins has not been established in randomized controlled trials; therefore, it has been argued that methodological factors explain the

discrepancy.<sup>75</sup> Statin users may differ from non-statin users on other measures that are linked to risk of dementia. For example, they may have better self-care and compliance with chronic disease management, have higher incomes and be more educated. Despite high cholesterol being associated cardiovascular disease, there are no reviews providing information on whether statins affect the risk of VaD and it is unclear whether other factors such as hypertension, physical activity or BMI moderate the impact of statin use on risk of dementia. Considering the lack of RCT data in support of a protective role of statins, it appears that results from observational studies may be overly optimistic about their potential benefits. However, definitive studies have yet to be conducted.

### **Antihypertensives**

There were six systematic reviews that included meta-analyses on antihypertensive use and risk of dementia.<sup>10, 56, 76-79</sup> One review focused solely on diuretics,<sup>79</sup> the others categorized antihypertensive use as present or absent. When mid- and late-life were combined, antihypertensive use was associated with a ~16% reduced risk of dementia (any type), evidence from two meta-analyses,<sup>78, 79</sup> a 33% reduced risk of VaD, one meta-analysis<sup>78</sup> and a reduced risk of AD, two meta-analyses; one reporting an 18% reduced risk with use of diuretics<sup>79</sup> and one a 27% reduced risk.<sup>10</sup> However, two meta-analyses (which included the same constituent studies) also reported no relationship between antihypertensive use and AD.<sup>56, 78</sup>

In late-life, one meta-analysis reported a 16% reduced risk of Any dementia.<sup>76</sup> There were no meta-analyses for late-life and dementia type and none for mid-life. There was no evidence in favour of any one class of antihypertensive above and beyond the others. The evidence on antihypertensive use most often comes from cohort studies and clinical trials combined. One article ran meta-analyses separating out the clinical trial and cohort constituents and reported no relationship for clinical trials, a 16% reduced risk for cohort studies and a 14% reduced risk of Any dementia when trials and cohort studies were combined.<sup>78</sup>

There are several placebo-controlled clinical trials of antihypertensives where data has been collected on incident dementia and where comparisons of treated versus untreated (placebo) groups are available. The trials tend to be of relatively short duration and include predominantly older adults. Although the trials tend to suggest the possibility of a positive association between antihypertensive treatment and

lower risk of dementia, in fact all but two report no statistically significant results.<sup>80</sup> Of the two that reported a protective effect, one accrued a very low number of dementia cases,<sup>81</sup> and the other found the protective effect only in those with recurrent stroke in a post-stroke, post-transient-ischaemic attack population who were not required to have hypertension.<sup>82</sup>

The difference in clinical trial and cohort results may be due to the relatively larger number of cohort studies, or the longer follow up of cohort studies. The higher grade of evidence obtained from clinical trials may indicate that the impact of antihypertensives is not significant for dementia outcomes. Despite this, the wider health risks of high blood pressure, and the benefits of treatment are well known and already comprehensively discussed by cardiovascular guidelines. At present, the best recommendation that can be made is to treat high blood pressure in accordance with guidelines.

In summary, antihypertensive use may reduce risk of dementia, AD and VaD. Given the cardiovascular benefits of treating high blood pressure the best recommendation that can be made is to treat high blood pressure in accordance with guidelines.

### **Insulin sensitisers**

One review was identified that assessed effects of insulin sensitisers on AD and Any dementia.<sup>83</sup> Comparing insulin sensitiser use with none revealed a 22% reduction in risk of Any dementia. No significant results were found for AD, and no review was identified relating to VaD.

### **Benzodiazepines**

Two meta-analyses of benzodiazepine use were identified. One combined five studies and reported a 50% increase in risk of dementia with exposure to benzodiazepines in late life.<sup>84</sup> The results were similar when meta-analyses were run comparing ever versus never use, recent use compared to never use and past use compared to never use.<sup>84</sup> Another review pooled 3 studies and found a 47% increase in AD risk comparing benzodiazepine use versus none.<sup>85</sup> There were no meta-analyses relating to mid-life and none relating to AD or VaD. There is evidence that benzodiazepine use in late-life increases risk of dementia.

### **Anti-inflammatories**

There were 4 reviews of anti-inflammatories and risk of AD that included meta-analysis<sup>10, 86-88</sup> but no reviews examining whether anti-inflammatories were

associated with risk of VaD or Any dementia. Actual medications examined in reviews included aspirin, non-steroidal anti-inflammatories (NSAIDs), and corticosteroids. There were no data available on association between anti-inflammatories and risk of VaD or Any dementia.

One review found no association when comparing participants taking any anti-inflammatory with participants taking none in a pooled analysis of 6 cohorts.<sup>86</sup> A second analysis of 3 cohorts taking NSAIDs for 2 or more years reported a 58% reduced risk, and a third review of 9 cohort studies<sup>10</sup> reported a 33% reduced risk associated with any NSAIDs. One review<sup>86</sup> found no association of aspirin and risk of AD in a pooled analysis of 5 cohorts, but a second review<sup>88</sup> reported a 26% reduced risk of AD associated with taking aspirin in an analysis of 8 studies. One review<sup>88</sup> of 8 studies compared non-aspirin NSAIDs users with non-users, and found a 26% reduced risk of AD associated with NSAIDs. One review<sup>88</sup> that pooled 2 case control with 1 cohort studies, found no association with corticosteroids and AD (RR, 0.62; 95%CI, 0.26–1.46).

Therefore, meta-analysis of cohort data currently suggests that non-aspirin NSAIDs protect against AD. This has not been established in randomized controlled trials and there is not specific data on the impact of length of exposure. Data are lacking with respect to competing risk of other disease or side effects from taking NSAIDs. Currently evidence is inconclusive with respect to whether aspirin or corticosteroids are associated with risk of AD.

### **Hormone replacement therapy (HRT)**

There were 3 meta-analyses of the association between HRT and risk of AD and dementia. One review published in 2001 of only 2 studies,<sup>89</sup> one published in 2014 included 8 studies,<sup>90</sup> and another published in 2015 including 4 studies.<sup>10</sup> Most cohort studies that report on HRT in relation to dementia outcomes make comparisons between women who have ‘ever’ used HRT with those who have ‘never’ used HRT.<sup>90</sup> Oestrogen creams are not included and use for less than 6 months is not included as ‘use’ in many studies.<sup>90</sup>

No data were available to examine the impact of specific exposure during the menopausal transition or in mid-life. One meta-analysis on HRT and risk of AD combined age groups and found no association with AD.<sup>90</sup> Another found approximately 40% reduction in AD risk for oestrogen, suggesting a protective role of

exogenous hormones in AD prevention.<sup>10</sup> No data were available on the association between HRT and VaD or Any dementia.

At the current time, the evidence does not support HRT in the role of preventing AD or dementia. A recent case-control study of the Finnish drug register found a 9-17% increased risk of AD associated with HRT<sup>91</sup> and the Women's Health Initiative Memory Study (WHIMS) clinical trial found HRT increased risk of dementia when used in women aged 65 and above.<sup>92</sup> However, there are many difficulties in evaluating this association due to limitations in the quality of the available evidence and the complexity of this area.

There are many limitations with the evidence base. Reviews have not examined type of HRT and risk of dementia, but rather use of 'any' HRT. Data on duration of exposure and age of exposure are reported in some studies but as yet there are insufficient data on these variables to generate any pooled estimates of their effects. Variables such as hysterectomy and oophorectomy, and other gynaecological disease leading to HRT use are rarely considered.

### **Antacids**

Antacids include high levels of aluminium and have been investigated for their potential to increase risk of AD. We identified 1 review of antacids and risk of AD that included meta-analysis<sup>93</sup> that combined age of exposure and pooled findings from 2 studies. That study found no association of antacid consumption and risk of AD (RR=0.83(95% CI: 0.39, 1.78)). There were no data from mid-life or late-life specifically. There were no data relating antacids to risk of VaD or Any dementia.

### **General Summary and conclusion**

Our evidence review summarizes data available from meta-analyses of risk factors for AD and dementia as of September, 2018. Overall, the evidence shows there is large scope for intervention to reduce risk in the primary care setting. In addition to the usual risk factors for chronic disease such as diet and physical activity, and medical treatment of cardiovascular risk factors, some less common strategies are indicated for potential dementia prevention. These include increasing social and cognitive engagement by participation in lifestyle activities, treating depression and addressing insomnia. While some medications were associated with reduced risk of dementia in cohort studies (statins, anti-inflammatories), we currently lack RCT evidence to support prescribing these medications specifically to reduce risk of

dementia. For these medications, patients can be assured that they will not increase risk, but not that a protective effect has been established.

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