Towards consensus

The role of memory services in addressing modifiable risk factors for early Alzheimer's disease and mild cognitive impairment

This information is intended for Healthcare Professionals only.

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A multidisciplinary advisory group was convened by Nutricia to develop this briefing document. The aim is to provide healthcare professionals with information and resources to advise people in the early stages of cognitive impairment (mild cognitive impairment or MCI) and early Alzheimer's disease (AD) on what they can do to help themselves to maintain a 'healthy brain', and potentially reduce their risk of developing AD, or at least delay the impact the disease is known to have on people.

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The document focuses largely on non-medical interventions that healthcare professionals can inform and guide people to undertake for themselves, with or without additional support, as appropriate. Sources of further information and support, as well as a list of references on which this document is based, are provided.

Towards consensus: The role of memory services in addressing modifiable risk factors for early Alzheimer's disease and mild cognitive impairment

While there is greater understanding of the pathophysiology of Alzheimer's disease (AD), the underlying causative factors have not yet been fully uncovered. Causation is likely to be multifactorial – age and genetics certainly are implicated. Medical conditions, such as stroke, diabetes and hypertension, may also contribute to an increased risk of developing AD.[1] More recently, increasing evidence has emerged that modifiable risk factors appear to have a significant role to play. These include nutrition,[2] physical exercise,[3] social engagement,[4] cognitive stimulation,[5] smoking[6] and alcohol consumption.[7] In line with this evidence, the Lancet Commission on Dementia urges healthcare professionals to be ambitious about prevention.[8] The Commission says that intervening to manage modifiable risk factors for dementia is advisable. It states: "We recommend active treatment of hypertension in middle aged (45–65 years) and older people (aged older than 65 years) without dementia to reduce dementia incidence. Interventions for other risk factors might have the potential to delay or prevent a third of dementia cases".[8] The NICE Guideline 'Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset' recommends promoting a healthy lifestyle to reduce the risk of, or delay the onset of, disability, dementia and frailty by helping people to:[9]

- *improve their diet*
- *be more active*
- *reduce their alcohol consumption*
- *stop smoking*
- *lose weight and maintain a healthy weight if necessary*

Background

Approximately 50 million people in the world have dementia, with nearly 10 million new cases per year.[10] In the UK, it is estimated that 850,000 people have dementia and that this will rise to over 1 million by 2025.[11] Dementia is the leading cause of mortality in England and Wales, accounting for 12.7% of all registered deaths.[12] Alzheimer's Research UK estimates that Alzheimer's disease (AD) costs the UK over £26 billion annually, this being made up of £11.6 billion in informal care, £10.3 billion in social care and £4.3 billion attributed to health care costs.[13]

Evidence for modifiable risk factors in dementia[14] supports the idea that people can take action to promote brain health and slow cognitive decline – one of the earliest symptoms of AD.[8] Evidence points to the benefit of early intervention.[15] In 2014, the World Dementia Council asked the Alzheimer's Association to evaluate and report on the state of the evidence on modifiable risk factors for cognitive decline and dementia, and a summary of this evaluation was subsequently published by Baumgart et al. in 2015, in which the authors assert that the addressing of modifiable risk factors for dementia can no longer just be a matter of academic discussion but requires action.[16] Consistent with this, the Lancet Commission on Dementia recommends that health professionals be ambitious about prevention, since estimates suggest that a delay in onset of 1 year could prevent more than 9 million cases of dementia by 2050, and a delay in onset of 5 years could halve the prevalence of dementia globally.[8]

Early Alzheimer's disease and mild cognitive impairment

People with mild cognitive impairment (MCI), and their partners and/or family, notice deterioration in one or more cognitive domains, including memory, executive function, attention, language, and visuospatial skills. The deterioration becomes evident over time, and exceeds that expected for their age and educational background.[17]

The rate of progression from MCI to dementia is 10% in clinical settings and 5% in community settings.[18] Conversely, a meta-analysis has shown that reversion rates of 23% and 10% are seen from population and clinical-based studies, respectively, implying that this is a dynamic diagnosis. Interventions to promote improved health or cognitive functioning may therefore be very useful at this relatively early stage.[19] Patients with MCI or in the early stages of AD might benefit from interventions for modifiable risk factors,[14,20–25] many of which can be undertaken themselves, once signposted, without direct medical intervention or supervision.

Adverse events of medications should also be considered. A review published in 2017 showed that patients taking prescription and over-the-counter medications with significant anticholinergic burden have an increased risk of developing dementia in older age.[26]

Other risk factors for developing MCI and AD are similar to those for heart disease.[27] So the mantra "what is good for your heart is good for your brain"[15] might be a helpful way to remember preventative measures that can be taken to reduce the risk of developing dementia.

Modifiable risk factors – making a difference

As part of the Memory Services National Accreditation Programme (MSNAP), memory services are expected to:

- offer personalised healthy lifestyle advice, such as advice on healthy eating, physical activity, reducing alcohol intake and access to smoking cessation services (standard/criterion 4.2.5)[28]
- provide or signpost/refer on to services that will offer information, advice and support on dietary interventions to help the person adapt dietary intake to help achieve full nutritional requirements (standard/criterion 4.2.6)[28]
- provide information about improving general health, living positively and maximising quality of life after diagnosis, where appropriate. This could include using mental exercise, physical activity, dietary advice alongside drug therapy, maintaining activities, lifestyle management, social engagement, religious and spiritual needs (standard/criterion 3.8.7.8).[28]

Modifiable risk factors fall broadly into four areas where there is evidence to support interventions that may help delay cognitive decline or reduce the risk of developing AD (see **Table 1**).

Table 1. Key risk factors associated with developing MCI and AD

Domain	Risk factors
Medical	Hearing loss,[29–31] Diabetes,[16,32–37] Hypertension,[16,38] Obesity,[16,39] Dyslipidaemia,[16,40,41] Vascular risk,[16,35] Anticholinergic medicines[42–45]
Psychosocial	Depression, Apathy and anxiety,[16,37,46,47] Feelings of loneliness,[48,49] Lack of social interaction and isolation,[50] Lack of cognitive leisure activities[51–54]
Lifestyle	Lack of physical activity,[53–56] Smoking,[6,22,57] Alcohol[58–61]
Nutrition	Poor diet,[14,21,24,25,36,62] Lack of nutritional precursors and cofactors for phospholipid membrane formation[24,63]

1. Medical

Varying levels of evidence exist for links between a number of medical risk factors (e.g. mid-life hypertension, obesity, mid-life dyslipidaemia, diabetes, anticholinergic medicines, hearing loss) and cognitive impairment.[16,26,31–35,38,42,46,64–66]

Hearing loss

Age-related hearing loss is associated with the risk of developing dementia.[29] While the reason for this association is unclear,[8] emerging evidence from studies such as the English Longitudinal Study of Ageing (ELSA) suggests that age-related hearing loss is a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment, and dementia.[30,31,67] Additional research and randomised clinical trials are warranted to examine the effect of treatment on cognition and to explore possible causal mechanisms underlying this relationship.[31]

Mid-life hypertension

Although an association between mid-life hypertension and cognitive decline is at best inconsistent, a systematic review of meta-analyses, observational studies and randomised controlled trials found that treatments of hypertension (in particular, calcium channel blockers and angiotensin system blockers) may reduce the risk of cognitive decline and dementia.[16,38]

Hyperlipidaemia

Research into a possible association between hyperlipidaemia (elevated cholesterol and/or triglycerides) in mid- and late-life and the risk of dementia has yielded inconsistent findings, and no association between hyperlipidaemia and vascular dementia has been found.[16,40] Observational studies with patients taking statins have seemed to show a reduction in risk for dementia, although larger cohort studies have thus far failed to reproduce these findings.[16] Moreover, a Cochrane review of randomised controlled trials concluded that statins given in later life to people at risk of vascular disease do not prevent cognitive decline or dementia.[41]

Mid-life obesity

Evaluation of several meta-analyses, reviews and studies found that mid-life obesity is associated with an increased risk of dementia,[16] and there is evidence that obesity in early-to-mid adulthood may have an immediate detrimental impact on cognitive functioning.[39] This association may change with age, since being overweight in later life has been associated with reduced risk of dementia.[16]

Diabetes

In 2015, Baumgart et al. stated that evidence has shown a link between lower cognitive performance and an increase in the risk of dementia among individuals with diabetes, and that "on balance, the association between diabetes and dementia appears strong, but not conclusive".[16] Further, they cite a recent meta-analysis that demonstrated that individuals with MCI and diabetes were more likely to progress to dementia than individuals with MCI and no diabetes.[16,37] Some evidence suggests diabetes increases dementia risk not only through vascular pathways but also through the interactions of other biological mechanisms related to diabetes itself, such as insulin resistance and impaired glucose metabolism.[36]

Anticholinergic burden (ACB)

It is widely acknowledged that anticholinergic medications have a detrimental impact on cognitive performance and evidence has shown that exposure to strong anticholinergic drugs is associated with an increased risk of dementia.[42–45] The use of polypharmacy in elderly people is high, and many commonly prescribed drugs have anticholinergic effects, including neuropsychiatric drugs (e.g. tricyclic antidepressants, antipsychotic agents, antiepileptic drugs, antiparkinsonian medication) and a range of non-psychoactive drugs (e.g. antihistamines, antispasmodics, antiulcer agents, bronchodilators, diuretics, corticoids, cardiovascular medications).[44] Studies where anticholinergic agents were administered to young adults produced similar effects to age-related cognitive decline, affecting memory, name/face recall, psychomotor speed and verbal reasoning ability.[45] Calculating the potential anticholinergic burden in patients can be easily facilitated by using a recognised ACB Calculator.

2. Psychosocial

Depression and anxiety

The risk of dementia has been found to be increased among individuals with depression, and there appears to be a link between cognitive decline and symptoms of depression.[47] However, it is not entirely clear whether depression is a risk factor for dementia or an early indicator of changes associated with the condition.[16] In patients with MCI, depression, anxiety and apathy may be linked to a progression to dementia.[37]

A study carried out to investigate potential associations between symptoms of depression in mid-life and late-life and the risks of dementia, AD and vascular dementia found that there was an increased risk for dementia in those with mid-life and late-life depression.[46] When the incidence of AD and vascular dementia were examined separately, subjects with late-life depressive symptoms only had a two-fold increase in AD risk, whereas subjects with both mid-life and late-life symptoms had more than a three-fold increase in vascular dementia risk.[46] It was therefore concluded that depressive symptoms in mid-life or late-life are associated with an increased risk of developing dementia. Depression that begins in late-life may be part of the AD prodromal stage, while recurrent depression may be associated with increased risk of vascular dementia.[46]

Social engagement and cognitive stimulation

Public Health England reported data from 22 studies, including over 29,000 participants, which demonstrate a 46% lower risk of dementia among people with high levels of mental activity than those with low mental activity.[50] It has been suggested that being socially active can help reduce the risk of dementia by improving mood, relieving stress, reducing the risk of depression and reducing loneliness.[52] Other reviews of the evidence suggest no clear link between social engagement and the risk of dementia, mainly due to the fact that many studies included cognitive training as part of the design, so this could not be separated from social engagement for risk reduction.[16]

Data from the Health and Retirement Study, which included over 12,000 participants who were followed up for 10 years, demonstrated that loneliness was associated with a 40% increased risk of dementia, independent of social isolation.[49] These findings support those of other studies reporting that feelings of loneliness, rather than social isolation, appear to predict dementia onset.[48]

Cognitive training

The Alzheimer's Society has stated that a daily 'brain workout' (by doing puzzles, word searches or crosswords, playing cards or learning something new, such as another language) can help reduce the risk of dementia.[68] Learning to speak a second language appears to equip the brain with resources that make it more resilient to diseases such as the dementias.[68] A Cochrane review identified many randomised controlled trials of mental engagement/cognitive training interventions that have demonstrated improvements in immediate and delayed recall among those in the treatment group, compared with the control group.[52]

3. Lifestyle

Physical activity

People who undertake physical activity have been found to have a lower risk of dementia than those who do less exercise.[55] Physical activity has a range of health benefits, including contributing to a reduced risk of cardiovascular and cerebrovascular diseases, diabetes, obesity and hypertension.[55]

In a review of the evidence for the benefits of regular exercise, Ahlskog et al. concluded that "ongoing, moderate-intensity physical exercise should be considered as a prescription for lowering cognitive risks and slowing cognitive decline across the age spectrum".[53]

In 2017, a large systematic review of studies looking at the link between physical activity and dementia and its sub-types concluded that physical activity is a beneficial or an important modifiable risk factor for reducing the risk of AD, all-cause dementia and cognitive decline, but not vascular dementia.[54] Physical activity is most beneficial for AD, which accounts for about 60–70% of dementia cases. The results further reveal that moderate physical activity may be enough to reduce the risk of all-cause dementia.[54]

Smoking

Cardiovascular disease, stroke, diabetes, hypertension and hypercholesterolemia have been individually cited as modifiable risk factors for AD and vascular dementia.[22,57] Since smoking is linked to an increased risk of developing these conditions, is it prudent to consider smoking a modifiable risk factor for dementia. Consistent with this, evidence suggests that previous and active smoking is associated with a significantly increased risk for AD.[6]

Alcohol

The effect of alcohol intake on the risk of dementia is less clear. Studies suggest a U-shaped relationship between regular consumption and cognitive function: frequent heavy consumption decreases cognitive performance, whereas regular light and moderate consumption may have a protective impact.[58] Chronic heavy alcohol consumption can cause thiamine deficiency and lead to Korsakoff's syndrome, characterised by symptoms including severe memory loss and amnesia.[59–61]

4. Nutrition

Diet

Emerging evidence suggests that maintaining a healthy diet can protect against cognitive decline, possibly due to associated reductions in cardiovascular risk factors.[62,69–72] For instance, it has been shown that a higher adherence to the Mediterranean Diet – broadly described as relatively low in red meat and high in whole grains, fruits and vegetables – was associated with a lower incidence of AD.[72] Similarly, greater adherence to the Dietary Approaches to Stop Hypertension (DASH) diet was associated with better average cognitive function.[69] Since diabetes, pre-diabetes and high 'normal' blood glucose levels have also been linked to neurodegenerative processes,[70] diets that limit carbohydrate intake have also been proposed as a potential preventative tool.[73]

Effective dietary interventions can have far-reaching implications for public health, especially with the growing burden of dementia in an aging population. High-quality diets, such as the Mediterranean and DASH diets, can be further modified and simplified, such as in the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet, to provide better protection against dementia.[71] The MIND diet, for instance, emphasises the dietary components and servings linked to neuroprotection and dementia prevention, but promotes lower servings than those specified for the DASH or Mediterranean diet,[71] which can potentially improve adherence.

Nutritional supplementation

There has been a growing interest in recent years in nutritional supplementation as a way to maintain a 'healthy brain' and reduce cognitive decline.[62] Previous studies have looked at a range of nutritional factors to modify clinical progression of AD. A clinical trial carried out in 2010, called VITACOG, studied the effect of high doses of folic acid, vitamin B6 and vitamin B12 on brain atrophy in patients with mild memory problems (MCI).[74] The results of this study were promising, showing that the accelerated rate of brain atrophy in elderly subjects with MCI can be slowed by treatment with homocysteine-lowering B vitamins.[74] However, the beneficial effect of B vitamin treatment on brain atrophy was observed only in subjects with high plasma ω-3 fatty acids. It also suggested that the beneficial effect of ω-3 fatty acids on brain atrophy may be confined to subjects with good B vitamin status.[75] Furthermore, the Swedish OmegAD study, involving over 200 patients, which explored the effects of dietary ω-3 fatty acid supplementation on cognitive functions in patients with mild to moderate AD, showed that the administration of ω-3 fatty acid in this patient group did not delay the rate of cognitive decline. However, positive effects were observed in a small group of patients with mild AD.[76]

Standardised extract from the leaves of the Ginkgo biloba tree (EGb761) has also been explored as a potential nutritional supplement for dementia in clinical trials.[77,78] Although this showed some promise in early studies, the evidence overall is inconsistent. A more recent systematic review and meta-analysis demonstrated no convincing evidence that Ginkgo biloba extract supplementation in late-life can prevent the development of dementia.[78]

Synaptic loss is an important feature of early AD and the formation of new synapses is dependent on key nutritional elements that are known to be deficient in people with AD, such as omega-3 fatty acids,[79] folate and vitamins B12, C and E,[80,81] as well as other important micronutrients.[82] While the correction of specific deficiencies is necessary to improve nutritional status, currently there is no generally applicable evidence to recommend the use of single-agent micronutrient supplementation at any stage of dementia, or for its prevention.[62] Conversely, there is emerging evidence that supplementation with a combination of such micronutrients may be more promising, consistent with the fact that a deficiency in any precursor has the potential to be a rate-limiting step in the Kennedy pathway (involved in neuronal membrane and synapse formation).[63] An example of such a multinutrient combination, which has been tested in the clinical trial setting, is Fortasyn Connect – a combination of docosahexaenoic acid; eicosapentaenoic acid; uridine monophosphate; choline; vitamins B12, B6, C, E, and folic acid; phospholipids; and selenium.[83] Souvenaid® is a Food for Special Medical Purposes for the dietary management of patients with early AD, which contains the nutritional combination Fortasyn Connect. Two previous randomised clinical trials in patients with mild AD dementia reported that daily intake of Fortasyn Connect for 3 or 6 months improved memory performance.[24,25] LipiDiDiet, the first randomised, controlled, double-blind study in prodromal AD, showed that Fortasyn Connect had no significant effect on the primary endpoint of cognitive performance using a neuropsychological test battery over 2 years.[21] However, it demonstrated significant benefit on secondary endpoints, including domains of cognition affected by AD and hippocampal atrophy.[21] It is anticipated that an intervention such as this would take time to have an effect and would benefit people earlier in their disease course.[84] Multinutrient supplementation during early AD, either alone or in combination with other prevention strategies, warrants further investigation.[84]

Consensus recommendations on interventions that can help reduce risk of MCI and dementia

Considering the evidence base, and the lack of a strong signal for a single key factor to target for reducing cognitive decline, dementia and AD, the panel recommend a multi-domain approach for intervention.

Pragmatic interventions are illustrated below in **Box 1**: these should be considered when assessing and advising patients referred into the memory clinic setting. Information and further resources are provided in **Box 2**.

Box 1: Interventions that can help reduce risk of MCI and dementia

Medical	• Ensure blood pressure is optimal: <140/90 mmHg • Ensure body mass index is optimal: 18.5–24.9 kg/m^{2*} • Ensure cholesterol level is optimal: <5 mmol/l • Ensure no undiagnosed diabetes or if diabetic ensure control is optimal for age • Review medicines and assess for anticholinergic burden • Ensure hearing is checked
Lifestyle	• Advise and signpost smoking reduction and cessation support • Advise alcohol intake in line with current accepted unit guidelines: 14 units/week for men and women • Encourage physical activity and exercise
Psychosocial	• Adequately treat depression and anxiety • Advise on methods of cognitive training • Signpost opportunities for increasing social engagement
Nutrition	• Assess patient's general appearance • Advise on dietary principles around maintaining general health • Signpost diets with evidence of benefit, such as Mediterranean, DASH and MIND • Signpost evidence-based medical nutritional interventions

*18.5–22.9 kg/m^2 for adults from South Asia.

Box 2: Information and further resources

ACB Calculator:
www.ACBcalc.com

Age UK:
www.ageuk.org.uk/information-advice/health-wellbeing/healthy-eating/healthy-eating-guide/

Alzheimer's Society:
www.alzheimers.org.uk/info/20010/risk_factors_and_prevention/737/how_to_reduce_your_risk_of_dementia

Alzheimer's Research:
www.alzheimersresearchuk.org/about-dementia/helpful-information/reducing-the-risk/

Alzheimer Scotland:
www.alzscot.org/assets/0002/0287/Risk_Reduction_leaflet_web.pdf

BBC:
www.bbc.co.uk/sport/get-inspired/28307305

Drink aware:
www.drinkaware.co.uk

My Souvenaid:
www.mysouvenaid.co.uk

NHS website:
www.nhs.uk/oneyou/active10/home#ke2jxdbWxxHfv5OH.97

www.nhs.uk/Livewell/smoking/Pages/Gethelp.aspx

www.nhs.uk/smokefree

www.nhs.uk/Livewell/Goodfood/Pages/Healthyeating.aspx

www.nhs.uk/Livewell/alcohol/Pages/Alcoholhome.aspx

www.nhs.uk/oneyou#zUFidt65hseO5BQl.97

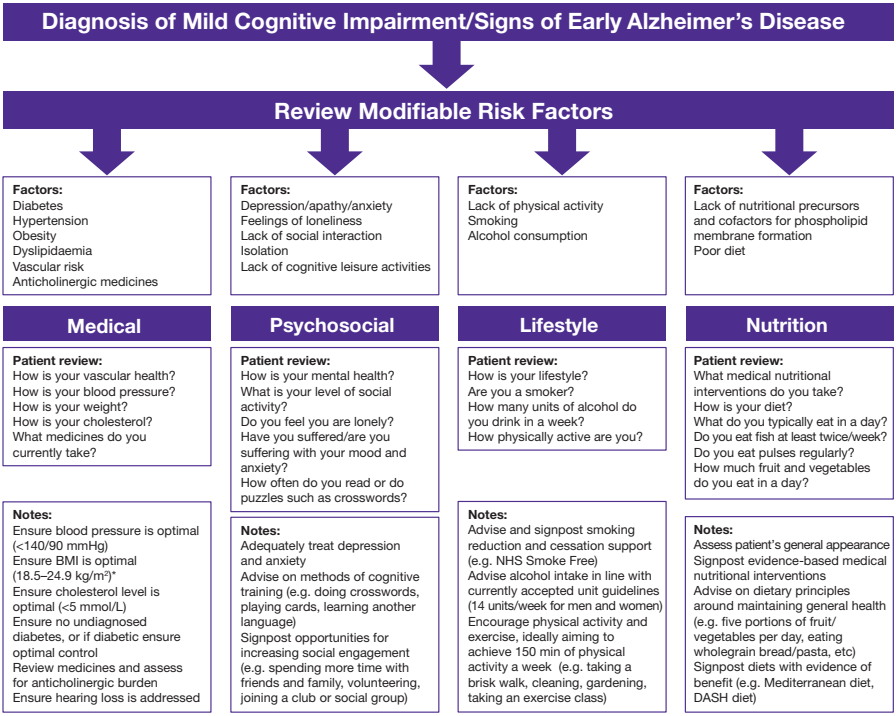
Public Health England:
https://www.gov.uk/government/publications/health-matters-midlife-approaches-to-reduce-dementia-risk/health-matters-midlife-approaches-to-reduce-dementia-risk

Royal College of Nursing:
https://www.rcn.org.uk/clinical-topics/dementia/understanding-dementia

Walking for Health:
www.walkingforhealth.org.uk

Summary of approaches to help address modifiable risk factors for early AD and MCI

Figure adapted from: Hope K. *Br J Nurs.* 2020;29(8):460–9[85]



*18.5–22.9 kg/m² for adults from South Asia.
BMI=body mass index; DASH=Dietary Approaches to Stop Hypertension

References

1. Edwards III GA, Gamez N, Escobedo G Jr, Calderon O, Moreno-Gonzalez I. Modifiable risk factors for Alzheimer's disease. *Front Aging Neurosci*. 2019;11:146.
2. Antal M, Péter S, Eggersdorfer M. Alzheimer's Disease: an epidemiologic disaster from nutritional perspective. *J Nutrit Health Food Sci*. 2017;5(1):1-14.
3. Brini S, Sohrabi HR, Peiffer JJ, et al. Physical activity in preventing Alzheimer's disease and cognitive decline: a narrative review. *Sports Med*. 2018;48(1):29-44.
4. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. *Neurotoxicology*. 2017;61:143-87.
5. Yates LA, Ziser S, Spector A, Orrell M. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. *Int Psychogeriatr.* 2016;28(11):1791-1806.
6. Durazzo TC, Mattsson N, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. *Alzheimers Dement*. 2014;10(3 Suppl):S122-45.
7. Ballard C, Lang I. Alcohol and dementia: a complex relationship with potential for dementia prevention. *Lancet Public Health*. 2018;3(3):e103-e104.
8. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-734.
9. NICE Guideline (NG16). Dementia, disability and frailty in later life - mid-life approaches to delay or prevent onset. London: NICE, 2015. Available at: www.nice.org.uk/guidance/ng16. Accessed May 2020.
10. World Health Organization. Dementia Key Facts; 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed May 2020.
11. Alzheimer's Society. Facts for the Media; 2019. Available at: www.alzheimers.org.uk/about-us/news-and-media/facts-media. Accessed May 2020.
12. Office for National Statistics. Deaths registered in England and Wales (series DR): 2017; 2018. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredinenglandandwalesseriesdr/2017. Accessed 06 March 2020.
13. Alzheimer's Research UK. Dementia Statistics Hub. Available at: www.dementiastatistics.org/statistics/cost-by-sector-in-the-uk/. Accessed May 2020.
14. Deckers K, van Boxtel MP, Schiepers OJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015;30(3):234-46.
15. Cummings J, Scheltens P, McKeith I, et al. Effect size analyses of Souvenaid in patients with Alzheimer's disease. *J Alzheimers Dis*. 2017;55(3):1131-9.
16. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement*. 2015;11(6):718-26.
17. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-9.

18. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009 Apr;119(4):252-65.
19. Canevelli M, Grande G, Lacorte E, et al. Spontaneous reversion of mild cognitive impairment to normal cognition: a systematic review of literature and meta-analysis. *J Am Med Dir Assoc*. 2016;17(10):943-8.
20. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819-28.
21. Soininen H, Solomon A, Visser PJ, et al; LipiDiDiet clinical study group. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. *Lancet Neurol*. 2017;16(12):965-75.
22. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255-63.
23. Alzheimer's Society. *Dementia research roadmap for prevention, diagnosis, intervention and care by 2025. An opportunity to align national dementia strategies and research*. London: Alzheimer's Society, 2018.
24. Scheltens P, Kamphuis PJ, Verhey FR, et al. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. *Alzheimers Dement*. 2010;6(1):1-10.e1.
25. Scheltens P, Twisk JW, Blesa R, et al. Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. *J Alzheimers Dis*. 2012;31(1):225-36.
26. Naharci MI, Cintosun U, Ozturk A, et al. Effect of anticholinergic burden on the development of dementia in older adults with subjective cognitive decline. Psychiatry Clin Psychopharmacol 2017;27(3):263-70.
27. Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, et al. Nutrition for the ageing brain: Towards evidence for an optimal diet. *Ageing Res Rev*. 2017 May;35:222-40.
28. Copland E, Hodge S, Clary L, Cartwright V (eds). *Memory Services National Accreditation Programme (MSNAP). Standards for Memory Services*. Sixth Edition. London: Royal College of Psychiatrists' Centre for Quality Improvement, 2018. Available at: https://www.rcpsych.ac.uk/docs/default-source/improving-care/ccqi/quality-networks/memory-clinics-msnap/msnap-standards-6th-edition-2018.pdf?sfvrsn=d3a9bc94_2. Accessed May 2020.
29. Uchida Y, Sugiura S, Nishita Y, Saji N, Sone M, Ueda H. Age-related hearing loss and cognitive decline - the potential mechanisms linking the two. *Auris Nasus Larynx*. 2019;46(1):1-9.
30. Davies HR, Cadar D, Herbert A, Orrell M, Steptoe A. Hearing impairment and incident dementia: findings from the English Longitudinal Study of Ageing. *J Am Geriatr Soc*. 2017;65(9):2074-81.
31. Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2018;144(2):115-26.
32. Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med*. 2014;161(11):785-93.
33. Crane PK, Walker R, Larson EB. Glucose levels and risk of dementia. *N Engl J Med*. 2013;369(19):1863-4.

34. Kim TE, Lee DH, Kim YJ, et al. The relationship between cognitive performance and insulin resistance in non-diabetic patients with mild cognitive impairment. *Int J Geriatr Psychiatry*. 2015;30(6):551-7.
35. Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol*. 2009;66(3):324-8.
36. Mushtaq G, Khan JA, Kamal MA. Biological mechanisms linking Alzheimer's disease and type-2 diabetes mellitus. *CNS Neurol Disord Drug Targets*. 2014;13(7):1192-201.
37. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry*. 2015;172(4):323-34.
38. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs*. 2015;29(2):113-30.
39. Dye L, Boyle NB, Champ C, Lawton C. The relationship between obesity and cognitive health and decline. *Proc Nutr Soc*. 2017;76(4):443-54.
40. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. *J Alzheimers Dis*. 2017;56(1):215-28.
41. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev*. 2016;(1):CD003160.
42. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ*. 2018;361:k1315.
43. Coupland CA, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med*. 2019 Jun 24. doi: 10.1001/jamainternmed.2019.0677. [Epub ahead of print].
44. López-Álvarez J, Sevilla-Llewellyn-Jones J, Agüera-Ortiz L. Anticholinergic drugs in geriatric psychopharmacology. *Front Neurosci*. 2019;13:1309.
45. Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006;332(7539):455-9.
46. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry*. 2012;69(5):493-498.
47. Mirza SS, Wolters FJ, Swanson SA, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry*. 2016;3(7):628-35.
48. Holwerda TJ, Deeg DJ, Beekman AT, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). *J Neurol Neurosurg Psychiatry*. 2014;85(2):135-42.
49. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Loneliness and risk of dementia. *J Gerontol B Psychol Sci Soc Sci*. 2018 Oct 26. doi: 10.1093/geronb/gby112. [Epub ahead of print]
50. Public Health England. Health matters: midlife approaches to reduce dementia risk; 2016. Available at: https://www.gov.uk/government/publications/health-matters-midlife-approaches-to-reduce-dementia-risk/health-matters-midlife-approaches-to-reduce-dementia-risk. Accessed May 2020.

51. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med*. 2006;36(4):441-54.
52. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*. 2011;(1):CD006220.
53. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc*. 2011;86(9):876-84.
54. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. *Biomed Res Int*. 2017;2017:9016924.
55. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med*. 2011;269(1):107-17.
56. Cammisuli DM, Innocenti A, Franzoni F, Pruneti C. Aerobic exercise effects upon cognition in mild cognitive impairment: a systematic review of randomized controlled trials. *Arch Ital Biol*. 2017;155(1-2):54-62.
57. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol*. 2017;74(10):1246-54.
58. Gutwinski S, Schreiter S, Priller J, Henssler J, Wiers CE, Heinz A. Drink and think: impact of alcohol on cognitive functions and dementia - evidence of dose-related effects. *Pharmacopsychiatry*. 2018;51(4):136-43.
59. Arts NJ, Walvoort SJ, Kessels RP. Korsakoff's syndrome: a critical review. *Neuropsychiatr Dis Treat*. 2017;13:2875-90.
60. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. *Alzheimers Res Ther*. 2019;11(1):1.
61. Wiegmann C, Mick I, Brandl EJ, Heinz A, Gutwinski S. Alcohol and dementia – what is the link? A systematic review. *Neuropsychiatr Dis Treat*. 2020;16:87-99.
62. Vandewoude M, Barberger-Gateau P, Cederholm T, et al. Healthy brain ageing and cognition: nutritional factors. *Eur Geriatr Med*. 2016;7(1):77-85.
63. Sakamoto T, Cansev M, Wurtman RJ. Oral supplementation with docosahexaenoic acid and uridine-5'-monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res*. 2007;1182:50-9.
64. Risacher SL, McDonald BC, Tallman EF, et al; Alzheimer's disease neuroimaging initiative. association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol*. 2016;73(6):721-32.
65. Solomon A, Kåreholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology*. 2007;68(10):751-6.
66. Cournot M, Marquié JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology*. 2006;67(7):1208-14.
67. Ray J, Popli G, Fell G. Association of cognition and age-related hearing impairment in the English Longitudinal Study of Ageing. *JAMA Otolaryngol Head Neck Surg*. 2018;144(10):876-82.
68. Alzheimer's Society. How to reduce your risk of dementia; 2019. Available at: www.alzheimers.org.uk/about-dementia/risk-factors-and-prevention/how-reduce-your-risk-dementia. Accessed May 2020.

69. Berendsen AA, Kang JH, van de Rest O, Feskens EJM, de Groot LC, Grodstein F. The Dietary Approaches to Stop Hypertension diet, cognitive function, and cognitive decline in American older women. *J Am Med Dir Assoc*. 2017;18(5):427-32.
70. Cherbuin N, Walsh EI. Sugar in mind: Untangling a sweet and sour relationship beyond type 2 diabetes. *Front Neuroendocrinol*. 2019;54:100769.
71. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement*. 2015;11(9):1007-14.
72. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol*. 2006;59:912-21.
73. Włodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). *Nutrients*. 2019;11(1).
74. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*. 2010;5(9):e12244.
75. Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. *Am J Clin Nutr*. 2015;102(1):215-21.
76. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol*. 2006;63(10):1402-8.
77. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. *JAMA*. 1997;278(16):1327-32.
78. Charemboon T, Jaisin K. Ginkgo biloba for prevention of dementia: a systematic review and meta-analysis. *J Med Assoc Thai*. 2015;98(5):508-13.
79. Jicha GA, Markesbery WR. Omega-3 fatty acids: potential role in the management of early Alzheimer's disease. *Clin Interv Aging*. 2010;5:45-61.
80. Smach MA, Jacob N, Golmard JL, et al. Folate and homocysteine in the cerebrospinal fluid of patients with Alzheimer's disease or dementia: a case control study. *Eur Neurol*. 2011;65(5):270-8.
81. Glasø M, Nordbø G, Diep L, Bøhmer T. Reduced concentrations of several vitamins in normal weight patients with late-onset dementia of the Alzheimer type without vascular disease. *J Nutr Health Aging*. 2004;8(5):407-13.
82. Olde Rikkert MG, Verhey FR, Sijben JW, et al. Differences in nutritional status between very mild Alzheimer's disease patients and healthy controls. *J Alzheimers Dis*. 2014;41(1):261-71.
83. van Wijk N, Broersen LM, de Wilde MC, et al. Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination. *J Alzheimers Dis*. 2014;38(3):459-79.
84. Rasmussen J. The LipiDiDiet trial: what does it add to the current evidence for Fortasyn Connect in early Alzheimer's disease? *Clin Interv Aging*. 2019;14:1481-92.
85. Hope K. Role of nurses in addressing modifiable risk factors for early Alzheimer's disease and mild cognitive impairment. *Br J Nurs*. 2020;29(8):460-9.

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