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Bridging the Translation Gap: From Dementia Risk Assessment to Advice on Risk Reduction

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Abstract

Dementia risk reduction is a global health and fiscal priority given the current lack of effective treatments and the projected increased number of dementia cases due to population ageing. There are often gaps among academic research, clinical practice, and public policy. We present information on the evidence for dementia risk reduction and evaluate the progress required to formulate this evidence into clinical practice guidelines. This narrative review provides capsule summaries of current evidence for 25 risk and protective factors associated with AD and dementia according to domains including biomarkers, demographic, lifestyle, medical, and environment. We identify the factors for which evidence is strong and thereby especially useful for risk assessment with the goal of personalising recommendations for risk reduction. We also note gaps in knowledge, and discuss how the field may progress towards clinical practice guidelines for dementia risk reduction.

Key words: Risk factor, Alzheimer disease, cognitive decline, prevention, risk assessment.

Introduction

Until effective therapeutics for Alzheimer's disease (AD) are available, secondary prevention is an important focus for health professionals in relation to dementia. Secondary prevention encompasses risk reduction in those with multiple established risk factors for dementia, as well as interventions to slow progression of cognitive decline in adults with cognitive impairment or minor neurocognitive disorders (1). The development and integration of risk assessment and clinical risk management for AD and dementia is emerging rapidly in the research field, with the development of online risk assessment tools, education programs and lifestyle interventions (2, 3). However, for this research to have substantial public policy improvements, it must be translated, tested, and evaluated in clinical and community settings. At present, risk management, including risk reduction and protection elevation, is the only available approach with potential for a large impact on the projected rates of dementia given population aging. The emerging focus on the development and implementation of efficacious dementia risk reduction protocols is consistent with best practice as applied to other chronic conditions or diseases and it has the advantages of being relatively inexpensive and translatable.

The development of clinical practice guidelines and policies relating to dementia prevention requires a sound evidence base on risk and protective factors, as well as a framework for applying advice to relevant population-subgroups. This review provides an overview of 25 risk and protective factors for late-life AD and dementia and then describes how this knowledge may inform the development of risk assessment procedures and risk management targets in the context of clinical practice guidelines.

Multidomain assessment of risk and protective factors for AD

Many studies report research on risk and protective factors in relation to AD, while some only report results in relation to a general outcome of dementia. In this article we consult published meta-analyses and large-scale cohort studies to note which risk and protective factors have been linked to AD specifically or to AD and dementia more generally. There are fewer reports relating risk and protective factors specifically to vascular cognitive impairment because the prevalence of distinct vascular dementia (VaD) is lower than AD: hence, this review does not address that outcome. There is often both vascular and Alzheimer pathology contributing to neurocognitive disorders. Notably, a lack of precision in diagnosis is a feature of the observational research on which much of the risk and protective factors have been based.

Established risk and protective factors for AD and dementia come from several domains, exacerbating the complexity of conducting a thorough risk

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assessment. That some factors may operate interactively or synergistically increases the need for careful interpretation of risk profiles. Assessing multiple domains of risk simultaneously permits an evaluation of overall risk profile, including the development of panels of risk factors, risk factor composite scores, and interactions among two or more synergistic risk factors. Systematic review and meta-analysis of the current state of knowledge of risk factors for dementia is beyond the scope of a single article. We present a summary of the current knowledge in this area, drawing on key review articles, meta-analyses (1, 4-8) and individual papers, with more detail provided on recent findings on diet and dementia risk, which is an emerging area of interest.

Our framework for linking risk and protective factors to individual patient outcomes is depicted in Figure 1 (adapted from (9)). This figure shows the relationships between risk and protective factors for dementia, and clinical assessment goals. As depicted in the first column, there are five clusters of risk and protective factors, including biomarkers (not reviewed in this article), demographic factors, lifestyle, medical and environmental risk. The second column illustrates that these factors flow together in individual cases and likely interact (synergistically, interactively, complementary) in unique ways to lead to individualized outcomes. The third column identifies three general clusters of cognitive/clinical status outcomes, including relatively healthy brain and cognitive aging, typical non-demented cognitive trajectories, and cognitive impairment and dementia. Subsequently, the fourth column presents an associated direction of personalized consultation regarding risk-related recommendations. For healthy brain aging, advice will focus on sustained protective support and risk reduction. For typical or normative aging, advice should focus on risk reduction and increase in protective behaviors. For preclinical dementia or MCI, advice may focus on immediate risk control and perhaps reduction, especially targeting modifiable factors in the medical and lifestyle domains. Table 1 summarises the information on risk and protective factors as organized into the same demographic, lifestyle, medical and environmental domains.

The role of biomarkers: Indicators of mechanisms

Risk and protective factors exert detectable and potentially manageable influence on the course of neurodegenerative disease through relatively diffuse or as yet undetermined biological mechanisms. In some cases, biological markers (biomarkers) can be linked to somewhat more specific biological pathways associated with cognitive impairment, AD, and dementia. It is likely that biomarkers will play an increasingly important role in risk assessment in the future (eg (10)). Given the heterogeneity of aetiologies, mechanisms and phenotypes of dementia, biomarkers and their pathways may be ultimately used in compiling risk profiles for groups or individuals. Notably, modifiable risk factors that interact with specific biomarkers offer specific opportunities for early alterations in the course of the disease. Although a review of biomarkers for AD is beyond the scope of this article, the information provided by some well-known and typically accessible biomarkers can provide crucial supplemental information for the overall dementia risk profile (11). However, it is known that at autopsy, a large minority of individuals who died without dementia have AD neuropathology (12, 13); hence, detection of disease processes does not necessarily mean that an individual will develop AD. This uncertainty does not change the need to target preventive strategies among at-risk individuals but indicates that individuals with biomarkers for AD may not necessarily express the clinical symptoms. (Autosomal mutations are an exception.) As with all diseases that have multiple risk factors, where prediction (prior to diagnosis) is never entirely accurate, and which develop after decades of gradual accumulation of pathology, a comprehensive risk appraisal is required.

Eventually, biomarkers of common pathogenic processes leading to brain ageing and concomitant Alzheimer pathology may provide a framework by which to organise risk and protective factors. For example, markers of inflammation are evident in a number of conditions that increase risk of AD including abdominal obesity, Type II diabetes and exposure to air pollution. However, most useful for present purposes would be information pertaining to genetic variants with known and elevated risk for AD. A recent large meta-analysis of genome-wide association studies in those of European ancestry found 11 new susceptibility loci for AD (14). The current state of knowledge indicates important supplemental information for constructing risk profiles could include (at least) APOE ε4 status. For this article, we turn attention to risk and protective functions from the four domains of factors that operate through indirect (and often modifiable) pathways.

The demographic domain

Demographic risk factors include both modifiable and determinable non-modifiable characteristics, and enable profiling of population sub-groups at increased risk of dementia using population-level characteristics. Risk of AD and dementia strongly increases with chronological age (15), and in most countries is higher for women than men (15, 16). Low levels of formal school education increases the risk of AD and dementia (17). At present it is unknown whether increasing levels of education later in life confers the same protection as equivalent years of education obtained earlier in life. Higher levels of education appear to be associated with high level of cognitive function into late life, but not with reduced

Table 1. Summary of findings on risk and protective factors for AD and dementia

		Period of life affected by risk factor		
Risk Factor	**Meta-analyses**	**Mid Life**	**Late Life**	**Comments**
Demographic				
Age	Yes (15, 16)	Yes	Yes	Consistent finding of increasing prevalence and incidence of AD and dementia with age.
Sex	Yes (16)	Yes	Yes	Many studies find rates higher for females at older ages. It is unclear how much this relates to greater longevity in women.
Education	Yes (17)	Yes	Yes	Reliable across multiple systematic reviews of high quality cohort studies. May moderate effects of neuropathology on cognition. RCTs not possible.
Ethnicity/race	No	Yes	Yes	Emerging evidence that AD prevalence differs with ethnicity, race and geographical location. Far more research is required to quantify these effects and identify how risk factors are moderated by ethnicity and race.
Lifestyle				
Physical activity	Yes (8)	insufficient evidence	Yes	Few studies have used adequate measures of physical activity. Studies also confounded by selection effects.
Diet	Yes (36, 41)	Yes	Yes	Evidence for protective effects of fish, and Mediterranean diet. Small number of studies. Effect of moderate alcohol may be confounded by selection factors.
Smoking	Yes (47)	Yes	Yes	Reliable across multiple cohort studies and supported by cessation interventions.
Mental activity	No	Yes	Yes	Mixed findings from cohort studies. Few high quality RCTs. Large RCT suggests short term benefits that do not impact risk over 5 years.
Social engagement	No	insufficient evidence	Yes	Difficult to control for the effect of cognitive decline on social engagement in late-life.
Medical				
Hypertension/Hypotension	Yes (61)	Yes	Yes	Mixed results from systematic reviews of AD.
Atrial Fibrillation	Yes (113)	insufficient evidence	Yes	Risk increased for all-cause dementia.
Stroke	Yes (66)	insufficient evidence	Yes	Risk increased for both AD and VaD.
Diabetes and pre-diabetes	Yes (114)	Yes	Yes	Reliable across multiple cohort studies for diabetes as a risk for VaD and AD. Emerging consistent data for pre-diabetes.
Bodyweight and adiposity	Yes (71, 115)	Yes	Yes	Both high BMI and decline in BMI in mid-life related to dementia risk. In late life >60 high BMI protective.
Cholesterol	Yes (74)	Yes	insufficient evidence	Variable measures of cholesterol across different studies.
Traumatic Brain Injury	No	Yes	insufficient evidence	Mixed findings from cohort studies. Many studies have inadequately defined AD or TBI, and used retrospective designs.
Depression	Yes (78, 116)	Yes	Yes	Late-life depression may represent a prodrome of AD.
Homocysteine	Yes (86, 117)	insufficient evidence	Yes	A causal relationship between AD and homocysteine levels is not supported. RCTs show no effect on dementia risk of reducing homocysteine through B vitamin supplements.
Medications				
Statins	Yes (118, 119)	insufficient evidence	Yes	Observational data suggest a neuroprotective effect, but RCTs have shown inconsistent effects.
Anti-hypertensives	Yes (120, 121)	insufficient evidence	Yes	Antihypertensive treatments shown to reduce the risk of all-cause dementia, vascular dementia and to benefit overall cognition, although these effects differed by drug class. Antihypertensive use did not decrease risk of AD, cognitive decline or cognitive impairment.
Anti-inflammatories	Yes (122)	insufficient evidence	insufficient evidence	Observational data suggest a protective effect especially in long-term users. A single RCT showed no significant effect on AD risk.

HRT	Yes (123)	insufficient evidence	insufficient evidence	An early meta-analysis indicated decreased risk for dementia in HRT users. The risks and benefits of HRT to women's health require further evaluation.
Anticholinergics	No	insufficient evidence	Yes	Converging evidence as reversible cause of cognitive decline in older adults.
Environment				
Pesticide	No	insufficient evidence	Yes	Consistent across small number of multiple cohort studies for increased risk of PD and AD.
Air-pollution	No	Yes	Yes	Few prospective studies with dementia as an outcome, but effects found for cognition.

rate of decline (18). In a related area, results have been inconsistent regarding bilingualism as a possible protective factor against late onset dementia. Although some evidence has suggested bilinguals have a delayed onset of dementia due to increased cognitive reserve (19) others have studied samples including monolinguals and bilinguals and found no difference in rate of cognitive decline or onset of dementia (20). A demographic characteristic that is rarely discussed in detail is race. It appears that specific racial and ethnic groups have higher rates of AD risk factors. Some groups may have a higher or lower risk in relation to specific biological risk factors such as APOE (21), with evidence the APOE ε4 allele does not influence dementia progression in sub-Saharan Africans. Among developing countries, prevalence estimates of dementia for adults aged 65 and older are higher in certain Asian and Latin American countries, but are low (1-3%) in India and sub-Saharan Africa (22). A recent study has shown that adults of Hispanic origin have earlier onset of dementia than non-Hispanics, adjusting for APOE genotype (23). However, not enough data are available to produce quantitative pooled estimates of these effects. Far more research is required to evaluate how risk profiles vary by race and ethnicity, which may potentially explain significant variation in the strength of specific genetic, medical or lifestyle factors as risk or protective in relation to AD. However, there is now sufficient evidence to incorporate age and sex into risk scores for incident dementia.

Lifestyle domain

Lifestyle-related risk factors for AD and dementia have been the focus of much recent research due to their modifiability. The prime lifestyle factors for which there is a body of evidence in relation to dementia risk include physical activity, diet, smoking, cognitive engagement and social engagement.

Physical activity

There is consistent evidence that physical activity is associated with reduced AD and dementia risk, with higher levels of activity associated with the lowest risk (24). The benefits of physical activity for cognitive health appear to accumulate over the life course. For example, higher fitness levels in young adulthood has been linked with better cognitive outcomes in mid-adulthood (25), and better midlife fitness has been linked to reduced risk of late-life dementia (26). However, there is also evidence that taking up physical activity in old age can still impact positively on cognitive and functional performance (27). The effect of physical activity on brain ageing and neurodegeneration is also corroborated by neuroimaging studies and intervention studies (28, 29) and intervention durations of 6 months and longer are reported as being more effective than shorter durations (30). To date, the majority of positive findings of trials are from samples of cognitively healthy older adults. A much smaller number of trials to date focused on trials with at-risk populations, especially those with subjective memory complaints or mild cognitive impairment. Some studies have reported significant benefits in the cognitive domains of attention, executive functions and memory (31, 32); however, other reports did not demonstrate such benefits (33). The inconsistency in results highlights the need for more high-quality later randomized controlled trials and a number of those are currently under way.

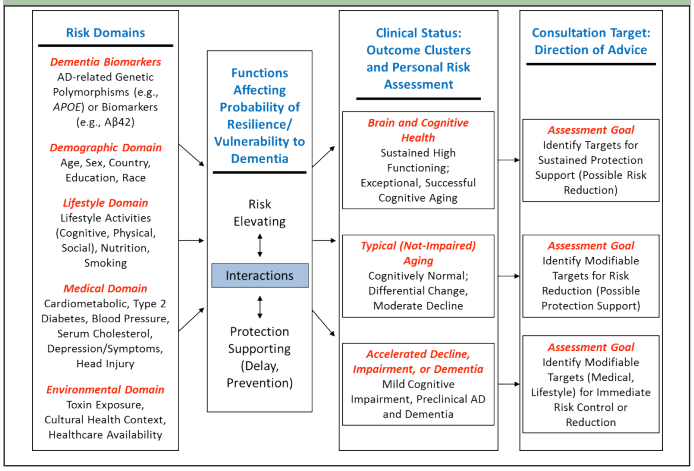
Dietary components and dietary patterns

The dietary component with the strongest link to AD and dementia risk reduction is oily fish, with three or more servings a week being associated with lower risk (34, 35). Studies have consistently shown a relationship between low levels of alcohol intake (rather than abstinence) and reduced risk of AD, dementia and cognitive decline (36, 37). However, it is possible that this association partly reflects selection bias. Specifically, abstainers may include former heavy drinkers, with resultant poor cognitive and general health, and heavy drinkers are less likely to persist in longitudinal studies (38) . There is some evidence that n-3 fatty acids (39) and Vitamin B may be beneficial for those in the early stages of decline although a recent meta-analysis of 11 trials found no cognitive benefits associated with Vitamin B supplementation (40).

The Mediterranean diet (MeDi) (Figure 2) was shown in a meta-analysis of five studies conducted with over 2-8 years follow-up to be associated with 33% reduced risk of

cognitive impairment (MCI or AD) (41) and adherence to the MeDi has also been associated with reduced cognitive decline (42, 43). The cognitive benefits of the MeDi were confirmed by a 5-year randomised controlled trial (RCT). Those who consumed a MeDi supplemented with extra-virgin olive oil or mixed nuts had higher mean Mini-Mental State Examination (MMSE) scores and Clock Drawing Test scores than those who consumed a low fat control diet (44). The DASH diet (Dietary Approaches to Stop Hypertension) (45) includes whole grains, poultry, fish, and nuts and is reduced in saturated fats, red meats, sweets, and sugar-containing beverages. The two studies that have investigated associations between DASH dietary patterns and cognitive decline both found the DASH diet to be protective against cognitive decline (43, 46).

Figure 1. Model of Multidomain influences on major cognitive phenotypes in ageing including AD and dementia. Risk assessment and consultation goals are indicated for each phenotype



Adapted from Dolcos et al (2012)

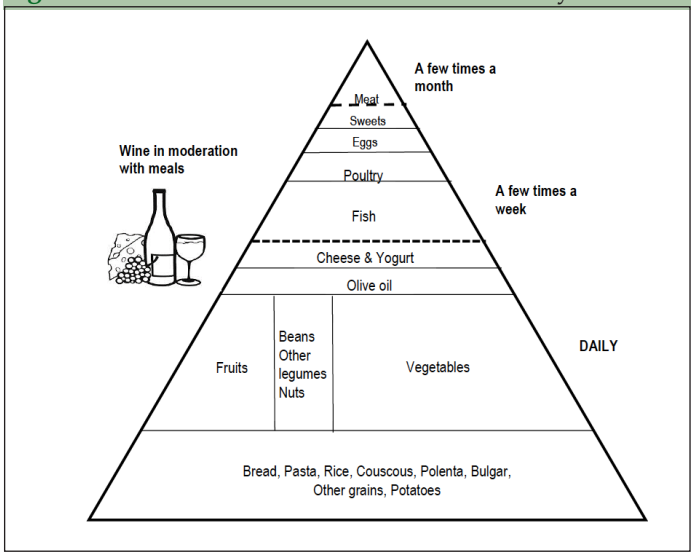
Smoking

Smoking in late-life has been shown to increase the risk of AD, VaD and dementia (47, 48) and it is inferred from this that smoking earlier in adulthood is also associated with increased risk, although specific data on this are presently lacking. Smoking cessation is associated with less late-life (over 70) cognitive decline and brain atrophy than continued smoking (49) providing strong support for advising patients to cease smoking even at older ages.

Cognitive engagement

Engaging in cognitively stimulating activities in late life (e.g., reading, playing puzzles and attending museums and concerts) is associated with a lower risk of AD and dementia (50, 51). However effective dosage and type of cognitive activity are not yet known, and to date, there is no reliable evidence for an effect of cognitive training programs on delaying dementia. Research on the benefits of cognitive engagement is often confounded, as individuals with higher initial cognitive ability also engage in more cognitively stimulating lifestyles.

Figure 2. The Traditional Mediterranean Diet Pyramid



Adapted from Willett 1995 et al. (Copyright 1994 Oldways Preservation & Exchange Trust)

Social engagement

There is consistent evidence that higher levels of social engagement are associated with reduced risk of AD and dementia (52, 53), even in adults with the APOE e4 genotype (54), and there is RCT evidence that it increases brain volume (55). Social engagement measures include different types of relationships, living arrangements, size and quantity of social networks and amount of social activities.

Medical domain

Cardiometabolic risk factors in midlife have been linked to late-life cognitive decline, AD and late-life dementia (56, 57) but late-life cardiometabolic risk factors have less clear associations with dementia. The link between abnormally high or low blood pressure in late life and dementia risk is inconsistent (58), with some evidence that low blood pressure may increase cognitive decline through reduced perfusion (59). While high blood pressure increases risk of stroke, and stroke is a strong risk factor for dementia (60), high blood pressure in late life has not been consistently linked with cognitive decline or AD. Findings relating blood pressure to risk of AD and dementia are complex, and influenced by methodological issues such as the length of follow up, whether or not treatment is evaluated, and whether trajectories are modelled that examine both increasing and decreasing hypertension at different stages of the

adult life-course (58). Support has not been found in systematic reviews for a link between hypertension and AD (61). It is possible that the inconsistency associated with blood pressure and AD is due to the measure of blood pressure used in cohort studies. Peripheral hypertension is usually measured, and yet in old age, peripheral hypertension has a low correlation with central hypertension, which is the true risk factor for cerebrovascular changes and AD (62). In general, it appears that high blood pressure in midlife may represent a risk for dementia in later life (63). If untreated, hypertension in middle age that increases into old age may increase dementia risk, although a decline in blood pressure is seen in the period prior to the development of AD.

A recent systematic review of atrial fibrillation (AF) as a risk factor for cognitive impairment (defined as MMSE<24) or any type of dementia (DSM-IV criteria) identified an increased risk associated with AF both with and without history of stroke, despite study heterogeneity (64).

Stroke has also been considered as a risk factor for AD even after controlling for the presence of other cardiometabolic risk factors such as hypertension, diabetes and heart disease (65, 66). Individuals with a history of stroke had an earlier onset as well as a higher incidence of AD relative to those without a stroke history, although the risk was highest in those with recognized vascular risk factors. It is possible that a stroke may accelerate or bring above threshold the level of neuropathology and cognitive impairment required for progression to AD in those with mild or sub-clinical pathology (65). In terms of other forms of dementia and vascular dementia in particular, a meta-analysis of 30 studies (66) reported that even after adjusting for other vascular risk factors, recurrent stroke increases the prevalence of dementia, with a rise in incidence after each additional stroke, suggesting stroke contributes significantly to the pathology leading to dementia over and above existing cardiovascular risk.

There is consistent evidence that elevated blood glucose (including Type II diabetes) increases the risk for cognitive decline, AD and dementia (67), and that this risk is independent of other cardiometabolic risk factors associated with diabetes (68, 69). There is also emerging evidence that pre-diabetic and sub-clinical levels of high blood glucose also predict cognitive decline and dementia (69, 70) although there have been no meta-analyses of this association.

Obesity and being overweight during midlife has been associated with increased late-life AD and dementia risk (71) with midlife obesity conferring double the risk of late-life AD. The relationship between late-life obesity and dementia risk is unclear (71, 72) with the balance of evidence presently suggesting that it is not associated with increased risk. One study has shown that weight loss predicted AD similarly in overweight and normal weight adults, indicating that trajectory of weight loss rather than BMI was predictive of dementia in older adults (73).

High serum cholesterol during midlife is associated with elevated AD and dementia risk (74); however, this relationship is not consistently evident for high cholesterol in late life (75).

Systematic reviews have shown that clinically diagnosed depression and depressive symptoms, in both midlife and late-life, are each consistently associated with elevated risk of AD, cognitive decline and dementia (76-78). In late-life, evidence suggests that late-onset depression may also represent a prodrome of AD (79). Altogether these findings suggest that screening for depression is an essential component of risk profiling for AD.

Head injury during adulthood is associated with increased AD and dementia risk, specifically where the injuries were moderate or severe and occurred frequently (80-82). Repetitive concussion and head injuries as experienced by boxers is also associated with risk of developing a distinct neurodegenerative syndrome (83-85). Although not modifiable, information on history of head injury may contribute to an overall picture of a patient's accumulated lifetime exposure to risks for AD.

Elevated plasma homocysteine increases the risk of vascular disease and stroke (86) and has been associated, albeit inconsistently, with poorer cognitive performance and dementia risk (87). Homocysteine levels increase with age and are dependent on Vitamin B metabolism (86). A number of trials in older adults have tested whether lowering homocysteine by vitamin B supplementation slows cognitive decline (40). Those with MCI and higher initial baseline homocysteine levels demonstrated better cognitive and clinical outcomes (88) and reduced brain atrophy (89). Recent preliminary evidence also suggests that the impact of homocysteine on older-age cognition may be dependent on its interactive effects with cholesterol (90).

There is some evidence from observational studies that certain classes of drugs such as anti-hypertensives, statins (91, 92), non-steroidal anti-inflammatories (NSAIDS) (93) (but see (94)) and hormone replacement therapy (HRT) (95), are associated with reduced AD and dementia risk. However, RCTs are either lacking or, apart from some isolated findings, do not generally support dementia risk reduction through statin therapy (96) , the use of anti-hypertensives (97), or anti-inflammatories (98). A recent follow-up of RCTs indicate that HRTs have a complex pattern of risks and benefits for women's health (99) and are thus not recommended for dementia prevention. One large study showed increased risk of dementia associated with NSAIDS (94). In one review of hypertensives, a significant effect (-18% incidence) was found for diuretic or dihydropyridine calcium channel blockers as part of active treatment for hypertension, although the overall pooled effect of hypertensives was not significant (100).

Therefore, at this point in time, while medication is recommended to treat medical conditions associated with risk of AD, we lack high quality evidence of their role in prevention. On the other hand, the reduction in rates of dementia observed recently in several countries has been speculatively attributed in part to better management of cardiovascular risk factors, better health care and increased levels of education (101) .

Drugs with anticholinergic properties are used for treating common medical conditions such as asthma, urinary incontinence, seasonal allergies, insomnia, depression, and other psychiatric conditions (102, 103). Age-related decrease in cholinergic receptors and in the increase in blood-brain barrier permeability (102) increase the risk of anticholinergic medication causing cognitive impairment. The Adult Changes in Thought study found that a 10-year cumulative dose-response relationship was demonstrated between anticholinergic drug use and increased risk for all-cause dementia and AD. Associations remained robust across sub-group analyses and subclasses of anticholinergic medication use (103). These findings add weight to earlier clinical recommendations that elderly patients using anticholinergic medication should be monitored for cognitive dysfunction and if adverse effects are suspected, medications could be withdrawn (102).

Environmental domain

There is evidence for increased risk of dementia (Parkinson's Disease with Dementia, and Alzheimer's Disease and other dementias) in individuals exposed to very high levels of pesticides (104, 105). While there is insufficient data to date on the link between air pollution and dementia risk, there is some evidence high levels of air pollution is associated with greater cognitive impairment in older adults (106-108) and air pollution has been associated with AD neuropathology (108).

Conclusion: From risk assessment to risk reduction

This review has evaluated evidence pertaining to 25 factors that have been associated in epidemiological literature with increased risk of AD and dementia in some studies. Some of these factors are now considered uncontroversial risk or protective factors for AD (109) despite the lack of RCT evidence. The way in which knowledge about risk factors for AD and dementia is obtained does not map well onto the hierarchical model of the widely used GRADE system for ranking the quality of evidence. This is because most of the information on dementia risk is epidemiological and not experimental. However, clinical practice guidelines typically use systems such as GRADE in their development using consensus among experts. We argue that in the field of dementia prevention, it will be necessary to carefully consider the optimal methods of grading evidence so that routinely prioritising RCTs may not be the best approach. It is more appropriate that bodies of evidence are considered holistically or integratively (animal models, short-term RCTs, long term epidemiological studies, neuropathological evidence) in relation to putative risk factors and their mechanisms. Adopting rigorous yet realistic criteria is likely to be the most pragmatic approach to developing guidelines while evidence is still being collated and evaluated in this field.

Our review demonstrates that the multiple domains of risk and protection are populated by a variety of specific factors that independently or interactively may contribute to incident dementia in older adults. The body of evidence continues to grow and understanding of risk factors is becoming increasingly nuanced with (a) synergistic and modifier effects being increasingly addressed in observational research and (b) more specific (rather than global) questions being addressed in clinical trials. Broader questions that can now start to be addressed include consideration of the requirements to develop specific clinical practice guidelines for dementia prevention, and methods for evaluating risk assessment for AD and dementia.

To move this field towards evidence-based clinical practice guidelines, research needs to provide more specific information on the quantity or dose of factors that are required for protection. For example, specific prescriptions of physical activity, or specific dietary advice, should be further evaluated in trials. Recent findings from multidomain trials will be able to guide research and personal advice (110, 111). In some cases the qualitative types or range of activities that are protective is not known. For example, the value of brain training compared with a lifestyle of active reading has never been evaluated, and water-based physical activity has rarely been evaluated in relation to level and trajectory of cognitive function in aging. This lack of specific information reduces the clarity with which practical advice may be developed and distributed to individuals.

For risk factors such as blood glucose, more specific guidelines on levels of risk are required, as recent research shows that even within the normal range, variation in blood glucose is associated with future risk of dementia (70). Clinical practice guidelines also need to take account of the patient's age and life course, considering the cumulative or synergistic effects of risk factors on other risk factors and outcomes that may ultimately increase late-life dementia risk or protection. For example, obesity in young adulthood may increase the risk of Type II Diabetes in mid-adulthood which in turn increases the risk of dementia in late adulthood.

Risk assessment for AD is now possible using well researched questionnaires, medical tests, checklists and online tools. There are now tools available to address risk in a range of ages and circumstances, from the population

level in middle age, through to risk among older adults with brain atrophy and impaired IADLs. Risk assessment tools provide clinicians with validated means of assessing risk or identifying areas where protection may be increased, when they are administered to the appropriate group.

There is not yet a standard practice in this field but the evidence is now strong enough to support personalized recommendations for risk reduction by increasing levels of education in young adulthood, increasing physical, cognitive and social activity throughout adulthood, reducing cardiovascular risk factors including diabetes in middle-age, through lifestyle and medication, treating depression, adopting a healthy diet and physical activity, avoiding pesticides and heavy air pollution and teaching avoidance of all potential dangers to brain health while enhancing potential protective factors.

Now that risk assessment for dementia is possible, researchers and policy makers can also start to identify markers of success in dementia prevention interventions. We have previously argued that risk reduction, as opposed to dementia prevention, is a more realistic and useful immediate goal when focussing on the majority of the population who are middle-aged and have no cognitive symptoms (112). At the individual level, risk reduction is the most meaningful outcome, as the time frames for dementia prevention are so long and it is not possible to estimate the true contribution of genetic risk factors at the individual level. At the population level, estimates of incidence and prevalence over decades remain the most objective measures of disease burden; however, there are other factors that may indicate success in prevention strategies. These include delaying the age of onset of dementia, slowing the progression of disease and reducing the overall health burden associated with dementia.

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