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Dementia Risk Reduction: Why Haven't the Pharmacological Risk Reduction Trials Worked? An In-Depth Exploration of Seven Established Risk Factors

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REVIEW ARTICLE

Dementia risk reduction: why haven't the pharmacological risk reduction trials worked? An in-depth exploration of seven established risk factors

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Abstract

Identifying the leading health and lifestyle factors for the risk of incident dementia and Alzheimer's disease has yet to translate to risk reduction. To understand why, we examined the discrepancies between observational and clinical trial evidence for seven modifiable risk factors: type 2 diabetes, dyslipidemia, hypertension, estrogens, inflammation, omega-3 fatty acids, and hyperhomocysteinemia. Sample heterogeneity and paucity of intervention details (dose, timing, formulation) were common themes. Epidemiological evidence is more mature for some interventions (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) than others. Trial data are promising for anti-hypertensives and B vitamin supplementation. Taken together, these risk factors

highlight a future need for more targeted sample selection in clinical trials, a better understanding of interventions, and deeper analysis of existing data.

KEYWORDS
anti-hypertensives, anti-inflammatories, blood pressure, cholesterol, dementia, diabetes mellitus, homocysteine, hormone therapy, hypertension, inflammation, omega-3 fatty acids

1 | INTRODUCTION

The last 20 years have seen a substantial growth in research on risk factors for cognitive decline and dementia.[1,2] In 2013, this led to an international petition to the G8 Dementia Summit asking governments to promote research into modifiable risk factors and the prevention of dementia.[3] In the evidence base, multiple longitudinal cohort and medical record studies have examined dementia risk factors and have been combined into systematic reviews and meta-analyses,[1,2] and the field is now starting to see reviews of reviews.[4,5] However, recent attention has also focused on a critical examination of gaps in the current evidence base.[6] A key aspect of the latter is the contrast between the epidemiological evidence and the data from clinical trials, where interventional trial results for dementia outcomes typically fail to reflect those of observational risk factor epidemiology. Despite the consensus regarding the main risk factors for dementia, this contrast with trial results leaves the evidence in support of risk reduction still comparatively lacking, as demonstrated in evidence summaries used to inform the recent World Health Organization (WHO) dementia risk reduction guidelines.[7]

Here, we discuss and explore possible explanations for the divergence in findings between the risk factor epidemiology and the risk reduction trials. We draw on expertise from the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) Professional Interest Area (PIA) on Clinical Trials and Methodology and leading international experts to appraise and synthesize the evidence, highlight the areas of discrepancy, and propose the needed next steps. We have selected seven exemplar core risk factors associated with altered dementia risk. For each of these, a plausible mechanism exists for the association between the risk factor and cognition. Even so, trial evidence for risk reduction remains incomplete. To reduce the potential for bias in the trial evidence, the selected risk factors are those that lend themselves to blinded pharmacological intervention. These include the following risk factors for which pharmaceutical agents are already in use: type 2 diabetes and antidiabetic medications; dyslipidemias and statins; blood pressure and anti-hypertensive agents; inflammation and nonsteroidal anti-inflammatory drugs (NSAIDs); and estrogen and hormone replacement therapy (HRT). Alongside this, we also examine two nutritional risk factors and nutritional interventions: omega-3 fatty acids and their supplementation and hyperhomocysteinemia and B vitamins. The review and commentary is divided into seven separate sections, each considering one of these risk factors, with each section drafted and shaped separately by experts in the related field. Each section summarizes the rationale, the potential biological mechanisms, the epidemiological evidence for the risk factor, and the clinical trial evidence for risk reduction, and provides recommendations for future observational and clinical trial work.

2 | TYPE 2 DIABETES MELLITUS

2.1 | Diabetes and dementia: An introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disorder characterized by hyperglycemia, insulin secretion deficiency, and insulin resistance. T2DM has a global prevalence of ≈9%, and this is expected to increase with a younger age at onset, particularly in low- to middle-income countries.[8] It is associated with increased mortality and co-morbidity due to microvascular (ie, retinopathy, neuropathy, nephropathy) and macrovascular (ie, cardiovascular and cerebrovascular disease) complications.[9] The causes of T2DM are multifactorial and include a complex interplay of genetics[10] and lifestyle factors, including obesity, a sedentary lifestyle, and energy-dense but nutrient-poor diets.[11]

2.2 | Potential mechanisms

The pathophysiological mechanisms underlying the link between T2DM and dementia are unclear.[12] Some plausible mechanisms include (1) vascular pathways from co-morbidities and complications of T2DM (eg, hypertension and cerebrovascular disease[13]); (2) cerebral insulin resistance pathways contributing to neurodegeneration and disruption of cerebral proteins[12–14] (this discovery even led to suggestions that Alzheimer's disease (AD) be considered as "Type III diabetes"[14]); and (3) pathways through which hyperglycemia may accelerate amyloid plaque aggregation and tau neurofibrillary tangle formation via accelerated formation of advanced glycation end products.[15]

2.3 | Epidemiological evidence that T2DM is a risk factor for dementia

Longitudinal epidemiological studies have consistently demonstrated associations between T2DM and its associated features of hyperglycemia and insulin resistance, with risk of cognitive impairment and dementia.[16–20] For example, a meta-analysis of 28 prospective

observational studies demonstrated that, compared to those without T2DM, persons with T2DM had a 73% increase in risk of all-cause dementia, 56% increased risk of AD, and 127% increase of vascular dementia.[19] Caution must be applied, however, since the confounding that is a major challenge to inferring causality from epidemiological evidence is particularly pertinent in a complex disorder like T2DM that has many contributing factors, co-morbidities, and complications. For example, most studies investigating the link between T2DM and dementia do not adjust for common cause factors such as pre-morbid intelligence quotient (IQ), education, and socioeconomic position, which are the biggest predictors of cognitive function and impairment later in life, and strong predictors of T2DM.[21,22] Information on the mediating effects of complications and co-morbidities (eg, hypertension) are also often lacking. In addition, these studies have relied on clinical rather than neuropathological diagnoses of AD and so are limited by misclassification of the outcome.[23] When T2DM has been examined as a risk factor for Alzheimer's pathology, no association is observed; T2DM is associated with cerebrovascular pathology, however.[24,25]

A further consideration is to what extent participants in epidemiological studies may have untreated, or undiagnosed, T2DM, especially given the socially patterned and health care–dependent nature of diagnoses and treatment.

It would be useful for studies to incorporate more objective measures of the underlying T2DM disease, such as hemoglobin A1c (HbA1c) level and insulin resistance, which would help elucidate more mechanistic processes. Although epidemiological studies have attempted to link these T2DM processes with dementia and cognition outcomes,[26] we need more evidence from studies with large sample sizes assessing the association between T2DM disease processes with the whole spectrum of dementia, including the impact on cognitive function and the level and progression of neuropathology associated with dementia, prior to overt clinical expression.[27–29] This would help strengthen or weaken our evidence base for a causal association between the disease processes of T2DM and dementia.

Self-reported, or linkage with, medication records would also be beneficial, and there have been efforts to use T2DM medication data as a main exposure in epidemiological studies,[30] but these have yielded inconsistent results. Careful consideration of timings of treatment, duration of treatment, and compliance with treatment would help to elucidate some of these issues.

Mendelian randomization studies use genetic predictors of T2DM as potential causal instruments to assess causality in settings where confounders are known to be unmeasured. To date, studies have reported null associations between the genetic risk of T2DM, glucose and insulin resistance, and all-cause dementia and AD,[31–34] perhaps indicating that there is not a causal relationship between T2DM and later-life dementia per se, but implicating other pathways related to T2DM.[22,24] Other causal inference methods are increasingly becoming applicable for clinical medicine and observational studies,[35] but as of yet have not been applied to investigate the association between T2DM and dementia.

RESEARCH IN CONTEXT

1. Systematic review: The authors have reviewed and critically appraised the current evidence for pharmacological risk modification and dementia risk reduction for seven leading modifiable dementia risk factors (type 2 diabetes, dyslipidemia, hypertension, estrogens, inflammation, omega-3 fatty acids, and hyperhomocysteinemia).
2. Interpretation: Critical appraisal of the evidence base uncovered overlapping themes and knowledge gaps common to multiple risk factors. Sample heterogeneity and paucity of intervention details (dose, timing, formulation) were common.
3. Future directions: There remains a potential for dementia risk modification, particularly for anti-hypertensive use and vitamin B supplementation. Further work is needed to fully establish this: evaluating impact and reducing bias. Targeted and methodologically sophisticated investigations are now urgently needed to drive forward our understanding in this area and to inform recommended targets for concrete and effective risk reduction strategies.

Future studies should endeavor to measure confounding and mediating influences and may consider applying causal inference methods alongside more traditional methods to infer more accurate causal estimates of the impact of T2DM on cognitive impairment and dementia risk.

2.4 | Diabetes-related therapeutics: Dementia reduction trials

Randomized controlled trial (RCT) results to date do not suggest that anti-diabetic agents as used to treat diabetes are associated with better cognitive outcomes. [36] Efforts to summarize the effects of anti-diabetic agents on cognitive impairment include a Cochrane review of seven RCTs up to 2017[36] that found no evidence to favor T2DM treatment to prevent cognitive impairment or dementia. Indeed, there have even been indications that anti-diabetic agents seem to increase the risk of cognitive impairment, potentially via hypoglycemic episodes.[36] Although there were initial indications of a potentially beneficial effect on the incidence of dementia with pioglitazone,[37] a thiazolidinedione insulin sensitizer thought to have a role in microglia regulation, two phase III trials in patients with mild cognitive impairment (MCI) (ClinicalTrials.gov identifier: NCT01931566 and NCT02284906) were terminated early because of a lack of efficacy on primary outcomes, namely, a change in composite cognitive score over 24 months compared to placebo. Overall evidence from trials to date is deemed low quality due to the risk of bias in the studies and imprecision

of the results, for example, the lack of data on blinded assessment of outcomes, inconsistencies with the primary outcome measures, patient selection and exclusion criteria, low event rates, and wide confidence intervals.[36] Furthermore, RCTs of anti-diabetic medication as an intervention for dementia were usually in populations with MCI, mild dementia cases, [38] or those genetically at risk for dementia,[27,29,39–41] and mostly exclude participants with a diagnosis or treatment of T2DM, and in some cases, exclude based on glucose level thresholds.[42] There are very limited studies that have included at least some participants with diabetes,[43,44] which in turn enables a different research question to be addressed: whether there are beneficial effects of AD disease progression in diabetic patients with AD. In these cases, the placebo group often continues their existing treatment for T2DM, apart from the anti-diabetic agent of interest in the trial. This is a significant challenge, and more evidence is needed from larger studies enrolling patients with and without T2DM, with a comprehensive history and a range of treatments to enable subgroup analyses.

We also recommend that epidemiological and RCT studies make it clearer in their documentation whether participants with T2DM were excluded, and if so, how this is defined, given that this information is often not easily accessible.

2.5 | Methodological differences between observational studies and trials, discussion, and recommendations for future work

Epidemiological studies and RCTs have heterogeneity and methodological variations that make them difficult to compare. The two approaches often differ in diagnostic criteria and duration of T2DM; treatment, duration, and dosage of anti-diabetic agents; follow-up times; populations under investigation; and cognitive outcomes,[19] with trials having been limited in their attempts to reproduce real-life exposures and outcome effects.

Recommendations detailing the potential for alleviating such limitations in future work in T2DM and cognition include:

(i) Where randomization in trials offer gains in precision of controlled exposure and removal of confounding, RCTs do not mimic real-life exposures. For example, many studies do not consider duration of T2DM, prior management, and anti-diabetic agent(s) of choice, or consider the underlying metabolic effect of treatment, such as the level of glycemic control, hyperinsulinemia, and insulin resistance on cognitive impairment.

Our recommendation on measurement of exposure: Given the dynamic metabolic features of T2DM, complex risk factors, and the co-morbidities and complications of T2DM, future RCTs and observational studies should take a life-course phenotyping participants. This may include measurement of underlying metabolic features and co-morbidities, duration of T2DM, and medication history, which will enable suitable matching, monitoring, and the ability to better address these potential confounders and mediators in the study design.

(i) Randomization may weaken the exposure signal because however precisely isolated it is for the trial, it is likely to occur with complex co-morbidities in real life.

Our recommendation for treatment: Given that dementia results primarily from complex progressive disorders, it may be reasonable to conduct trials with drugs that have actions at multiple targets[45] and multi-modal trials for dementia.[46]

(i) Existing RCTs in this area lack reliable measures to detect clinically relevant cognitive change and have frequently been of short duration when considering the assessment of cognitive change. Most studies have used the Mini-Mental State Examination (MSE), which is not sensitive to early or subtle changes in cognition over short time periods and which may be less sensitive to vascular cognitive impairment.[47]

Our recommendation on measure of outcome: Future trials should aim to capture sufficient follow-up to measure clinically relevant change and to facilitate this using a battery of tests designed to cover a range of domains of cognitive function, capture individual-level changes in cognition,[48] and differentiate pre-morbid abilities (ie, using discrepancies between crystallized and fluid functioning, whereby the former is relatively spared in preclinical AD).[49]

(i) Epidemiological studies and clinical trials have differing drivers for sample selection and attrition.

Our recommendation for sample selection and follow-up: Future studies examining the relationship between diabetes and cognition should carefully characterize participants to include appropriate at-risk populations. Studies should also aim to build in mechanisms for longer-term outcome collection, ideally through longitudinal prospective data collection that integrates phenotyping of features of T2DM (hyperglycemia and insulin resistance) across the life course when the exposure may exert maximal influence and follow-up, even in the face of shorter-term differential attrition.

3 | CHOLESTEROL/STATINS

3.1 | Cholesterol, statins, and dementia: An introduction

Multiple epidemiological studies have shown an association between reduced dementia risk and statin use, reporting odds ratios of 0.6 to 0.9.[50–57] Experimental data using both in vitro and in vivo animal models of AD suggest pleiomorphic effects of the statins in relation to the pathogenesis of degenerative disease.[58] Such effects include direct actions on cholesterol lowering, influences on related cardiovascular

risks including T2DM and hypertension, alterations in inflammatory pathways, modulation of intracellular trafficking and neurotransmitter release, as well as indirect effects on amyloid beta (Aβ)- and tau-related alterations that are associated with neurodegeneration.[58]

3.2 | The "Statin Paradox": Introduction and mechanisms

Statins exert their primary effect by competitively inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the first and key rate-limiting enzyme of the cholesterol biosynthetic pathway.[58] Statins mimic the natural substrate molecule, HMG-CoA, and compete for binding to the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) enzyme. This leads directly to effects on overall circulating cholesterol levels. The indication for statin use includes reduction in hypercholesterolemia, which has been linked to increased risk of cardiovascular and cerebrovascular events. Such consequences can be directly responsible for the development of cognitive impairment and dementia; or, more frequently, can be associated with cerebrovascular disease that interacts additively and possibly even synergistically with other neurodegenerative pathways.[52] Much research has also suggested that genetic alterations affecting cholesterol trafficking and modulating pathways are related directly to increased risk of AD, suggesting the potential for other risk reduction pathways.[50]

3.3 | Cholesterol and statins: The epidemiological evidence

The epidemiological associations between statin use and reduced risk of dementia have been reviewed in several recent publications including an update of the Cochrane database.[50,53–57,59,60] These data clearly demonstrate an association between statin use and a lowered risk for all-cause dementia, and AD specifically, but notably they provide conflicting results for the reduction of dementia caused by cerebrovascular disease. The influence of aging adds complexity here because much work in the field is focused on the relationship of midlife rather than late-life hypercholesterolemia in modulating dementia risk.[51] Accordingly, some of the variability seen in epidemiological studies may be related to the timing and exposure characteristics for the statin therapy identified as possibly modulating risk for future decline in cognition and in the development of dementia. Yet, other work has suggested that the various statin drugs are not uniform in their effects on degenerative disease processes but instead have specific characteristics that may differ. Consequently, when statins are clustered as a uniform exposure in epidemiological association studies, such exposure may reduce the opportunity for clarity and may lead to inconsistent results.[56,61] Major factors include type of statin, dosage, length of exposure, and timing in the life-course when exposure occurred. Yet, the data are sufficiently conclusive to warrant clinical trials of statin therapy to reduce the risk and or delay the progression of cognitive decline and degenerative dementia.

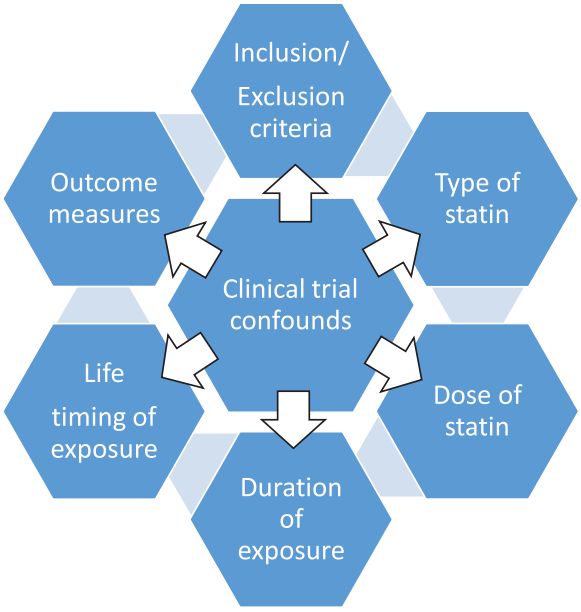

FIGURE 1 Confounds that have plagued clinical trials of statin therapy

3.4 | Cholesterol and statins: The clinical trial evidence for statins and their influence on dementia risk

Several studies have, therefore, investigated the hypothesis that statin therapy may be beneficial for the treatment of dementia. However, despite the promising epidemiological and observational data, results have been disappointing,[56,61] as the trial data appear to contradict the epidemiological data. Attempts at an explanation for this discrepancy have focused back on the multiple sources of low precision inherent in the epidemiological studies, including again the type of statin, dosage, length of exposure, and timing of exposure in the life-course[56,61] (Figure 1). In addition, many trial design considerations may explain the discrepancy. These include inclusion and exclusion criteria that restrict participants in ways that are inconsistent with observational studies, for example, different population characteristics and selection of statin, and dose, duration of exposure, and timing in the life-course, which are again discordant with observational results.[22,53,61] We consider each of these considerations in the sections to follow.

Inclusion and exclusion criteria. One critical difference between the many null-finding statin clinical treatment trials and observational studies is that persons enrolled in clinical trials were not recruited based on dysregulated lipid status.[53,61] Indeed, some trials excluded from enrollment those participants whose lipid status revealed dysregulation.[53,61] The contrast with clinical use (and resultant observational studies) is obvious. Secondary analyses of the data from several clinical trials have implicated genetic background, especially apolipoprotein E gene (*APOE*) ε4 status as a primary modulator of statin effects that may be related to risk of cognitive decline in dementia.[50] Further trials should take such considerations into

account when designing maximally appropriate inclusion/exclusion criteria.

Selection of statin: Clinical trials of statins for cognitive outcomes have focused largely on atorvastatin and pravastatin. Although other, smaller trials included other statins, meta-analytic studies of the potential beneficial effect of statin therapy have typically considered statins as a single group. Yet, clinical experience suggests that the statins are quite diverse in their effects on high-density lipoprotein (HDL) as well as low-density lipoprotein (LDL) modulation. Common practice dictates that if a patient fails one statin, another agent should be tried. Such flexibility in selection of agents has not yet been incorporated into clinical trial methodology. Thus many who are intolerant of the assigned statin in a trial might have benefited from an alternate drug.

Statin dose: The dosage of statins in clinical trials for the prevention of cognitive decline and dementia have typically been in the mid-range based on studies of systemic cholesterol modification, without the inclusion of adaptive trial design to enable maximum dose for unique participants. This issue relates partially to the usual inclusion and exclusion criteria for such trials, which, unlike in clinical use, do not consider the type or severity of dyslipidemia when selecting a statin agent or dose.[53,61] At least with respect to dose, consideration of an adaptive design protocol might allow flexibility in optimizing dose, based on systemic pharmacodynamic profiles, for prevention of cognitive decline. To date, a central nervous system (CNS)–specific pharmacodynamic profile that might guide optimal statin dosing for dementia prevention has not been established.

Duration of exposure: The majority of clinical trials testing statin use for the prevention of dementia or cognitive decline have had relatively short durations, typically about 2 years.[53,61] By contrast, the observational data on cognitive consequences of statin use for modulation of cardiovascular risks suggests that a much longer duration of exposure may be necessary for the desired effect on cognition.[54,56] Prolonged trials of statin therapy should therefore be considered when designing new trials of statins for the prevention of cognitive deficits.

Timing of exposure across the life-course: As noted above, a critical issue with the discrepancy between observational and clinical trial data regarding the potential benefits of statin therapy in preventing cognitive decline may be the timing of exposure across the life-course. Observational studies often include exposure at any point in the life-course, especially in midlife or early old age.[54,56] By contrast, most statin trials to date have enrolled persons at older age and several with some level of existing cognitive impairment, when, arguably, a great deal of neural damage is already evident.[53,61,62] Although it would be prohibitively costly to conduct a clinical trial that tests later-life cognitive consequences of midlife exposures, there may be ways to achieve the same aims, using new technologies to detect early changes of neurocognitive disorders or ancillary cognitive studies of midlife trials and looking at the late-life conversion to dementia; such studies may ultimately provide the answers as to whether statin therapy can intervene in the development of late-life cognitive decline and dementia.

3.5 | Statins and cognition: Conclusions and recommendations for future work

Although the number of prospective, randomized, placebo-controlled clinical trials that have failed to provide evidence for the benefit of statin therapy in reducing the incidence of cognitive decline in dementia argue strongly against further investigations in this area, the data supporting the use of such therapy from observational studies is overwhelmingly supportive of further investigations.[50,51,53–61,63,64] The field is now poised to look back and reconsider essential clinical trial flaws in the design and conduct of such research in an attempt to improve on the critical confounds of inclusion and exclusion criteria for the participants, selection of statin, statin dose, duration of exposure, and timing in the life-course when the exposure should maximally exert its influence.[56,61] Understanding the discrepancies between observational and clinical trial data regarding the use of statins for the prevention of cognitive decline in dementia is critical to uncovering whether the observational data represents pure epi-phenomena that is unrelated to the underlying disease course.

Recommendations for future clinical trials of statin therapy include:

1. Selection of an appropriate population including those with cholesterol/lipid dysregulation
2. Adaptive design in the selection and dose of statin therapy
3. Enhanced duration of exposure with consideration of timing within the degenerative cascade when therapy may prove most beneficial. Creative approaches such as ancillary cognitive studies of midlife trials, looking at the late-life conversion to dementia are warranted.

4 | BLOOD PRESSURE AND ANTI-HYPERTENSIVES

4.1 | Blood pressure and anti-hypertensives: An introduction

Epidemiological evidence has consistently shown a relationship between higher blood pressure (BP) and an increased risk of developing cognitive decline and dementia.[65] Several plausible mechanisms support the potential for raised BP driving impairment in brain structure and function.[66] BP reduction is possible via several established classes of anti-hypertensive medication that are widely available and present in treatment pathways for cardiovascular risk reduction.[67] However, relatively few trials of anti-hypertensive drugs have measured cognitive outcomes or incident dementia, and those that have, have been largely inconclusive.

4.2 | Potential mechanisms linking raised blood pressure to impaired cognition

Mechanisms by which raised BP may lead to impaired cognitive function and dementia have been summarized elsewhere.[66,68] They include damage to the vascular structure (eg, increased risk of clinical and subclinical stroke, promotion of atherosclerosis, vascular remodeling and stiffening reducing effective perfusion, small vessel disease leading to white matter lesions and microvascular rarefaction leading to loss of microvessels), and to function (eg, disruption of endothelial cell function leading to impaired microvascular flow, disruption of the neurovascular coupling attenuating the ability for cerebral blood flow to respond to neural activity, impaired autoregulation, and loss of blood-brain barrier integrity).[66,68,69] There is also evidence to suggest that high BP and vascular risk may be associated with deposition of Aβ.[66,70–72]

4.3 | Epidemiology of blood pressure and cognition

Alongside the plausible mechanisms there are a large number of epidemiological studies linking raised BP to incident cognitive decline or dementia.[73,74] This is particularly the case for raised BP in midlife, implying a role for aging similar to the evidence for raised cholesterol. A 2005 review highlights 11 of 13 studies reporting a relationship between higher BP and incident cognitive decline or dementia in populations 40s to 50s and followed for ≈20 years.[65] In contrast, for populations in their 60s and 70s, although high BP remains a risk factor the evidence is more mixed. The same 2005 review found only 6 of 21 studies reporting higher pressures in later life associated with increased risk and a further 3 studies reporting a U-shaped relationship, with both low and high pressures associated with increased risk.[65] More recent work supports the need for a life-course perspective highlighting characteristics particularly relevant to BP[75,76] : for example, chronicity, the change in diastolic and systolic pressure with aging and the steeper rise and subsequent fall in pressure observed 2 to 5 years before dementia diagnosis and the potential for differential mortality in higher and lower BP populations. It is in the context of this epidemiology that we must examine evidence from the trials.

4.4 | Anti-hypertensives: Randomized controlled trials and dementia

Several randomized controlled and blinded trials of anti-hypertensives have assessed cognition or dementia outcomes. However, their results have been largely inconclusive.[77,78] In general, cognition and incident dementia have been secondary end points, or assessed in ancillary studies, in trials designed primarily to examine the cardiovascular benefits of antihypertensive use in later-life populations. This point has driven three main issues when considering evidence for the potential of anti-hypertensives to reduce the risk of cognitive decline and dementia: (1) the length of follow-up, (2) the selection of an appropriately aged population, and (3) the assessment of cognitive function and cognitive decline.

(1) The primary focus on cardiovascular outcomes has typically resulted in relatively short follow-up for cognition, and some trials have even been stopped early following observed cardiovascular benefit. The early stopping and lack of long follow-up (most are less than the recommended minimum of 5 years)[78,79] has very likely exacerbated a lack of statistical power to detect cognitive and dementia outcomes, as these develop more gradually over time. For example, mean follow-up in anti-hypertensive trials that have measured dementia (double-blind randomized phase rather than longer term open-label follow-up) ranges from 2.0 to 4.3 years.[77] (2) A common focus of anti-hypertensive trials for elderly individuals may also mean that the intervention ignores the most relevant, younger (midlife, or earlier adult life) target population for cognition and anti-hypertensive use. The trial populations have, by design, been drawn from people in early late life or older. Most of the trials recruited populations entirely from later life (≥60 years), and even the trials open to including people in their 50s arrived at mean baseline ages in the mid-60s. Trials that report on cognitive outcomes show similar issues.[78] (3) Most of the trials have also used a relatively insensitive cognitive screening instrument as the primary cognitive assessment tool. This limits their ability to detect more subtle cognitive change.[78]

Trials in this area have also been constrained by the development of the cardiovascular evidence base. That is, as the cardiovascular evidence base has grown, the drug-prescribing guidelines and thresholds for treatment have changed. Guideline changes to recommend treatment in a new population drives consequent ethical requirements to treat, thus shaping the populations that can be selected for each subsequent trial, or having limiting effects on recruitment due to accommodating aspects around prior exposures.[80] This has driven each new trial to recruit to different baseline BPs, ages, or cardiovascular risk profiles, thereby furthering the heterogeneity across the evidence base.

Despite these limitations, there is a growing evidence base for anti-hypertensive treatment as having a role in dementia risk reduction,[81,82] Meta-analyses, particularly those that focus on double-blind trials, generally find point estimates (odds ratio, relative risk, hazard ratio) of around 0.9 in favor of anti-hypertensive treatment reducing risk of dementia [83,84] and showing a potential for dose-response.[77,83,85] For example, trials that achieved greater than a 10 mm Hg reduction in BP between their two randomized arms had a combined 12% (95% confidence interval [CI] 22%-2%) risk reduction for incident dementia compared to a nonsignificant result (relative risk 0.98 (95% CI 0.88-1.09) in those who did not achieve this difference.[77] Questions remain as to the ideal range of BP for brain health, which may be specific to different levels of chronological, or more likely biological, age and prior BP exposure. Furthermore, recent and potentially paradoxical results from the Systolic Blood Pressure Intervention Trial (SPRINT-MIND)[85,86] have highlighted the possibility of increased cognitive risk from lowering BP too far[86] and served to once again highlight the complexities and knowledge gaps in this area.

4.5 | Blood pressure and anti-hypertensives: Summary and recommendations

In summary, although overall the direction of the epidemiology and clinical trial evidence is broadly congruent, and more congruent than some of the other risk factors, this is still insufficient to tell us whether reducing BP for dementia risk reduction is effective.

Recommendations for future work on anti-hypertensives, blood pressure, and cognition include:

1. New sophisticated analysis of the existing epidemiology and clinical trial data, for example, using causal inference methods and more appropriately taking account of competing risks alongside using more sophisticated modeling to examine the role of different achieved BP levels and attrition.
2. New data collection is needed to evaluate relevant populations. In particular we need a clear understanding of the relationship between BP and cognition over the life-course, and at ages 20, 30, or 40 years prior to dementia onset, for example, by collecting longer-term prospective or even retrospective data on both BP, cognition, and anti-hypertensives.
3. Related to point 2 above, we also need a better understanding of the role of trajectories of change in BP and any consequent change in ideal BP ranges (alongside changes in other dementia-influencing factors).
4. We need to start using sufficiently sensitive cognitive outcome measures.

5 | ESTROGEN AND HORMONE THERAPY (HT)

5.1 | Hormones and HT: Introduction and potential mechanisms

Estrogen and supplementation using oral hormone therapy (HT) have been proposed as a treatment for observed changes in memory and dementia risk in women who are experiencing menopause. There are several plausible biological mechanisms for cognitive benefits from estrogen supplementation after menopause.[87,88] Estrogen receptors are widespread in the brain and regulate synaptogenesis,[89] particularly in the hippocampus.[90] For example, rats show reduced density of dendritic spines after oophorectomy.[91] Estrogen also interacts with or modulates neurotransmitters that are important for cognition such as dopamine and serotonin.[89,92] Animal studies have also provided evidence for a "sensitive period" during which the therapeutic benefit of estrogen supplementation may occur, and suggest that estrogen-mediated cognitive benefits may be lost if treatment is commenced before, or after, a specific age.[93]

5.2 | HT and cognition: Epidemiology

Systematic reviews of the epidemiological data have consistently shown that HT is associated with reduced risk of late-life dementia.[4] Most cohort studies that report on HT in relation to dementia outcomes make comparisons between women who have "ever" used HT with those who have "never" used HRT.[94] Data are lacking on estrogen creams and the use of HT for short periods, for example, for less than 6 months.[94]

Positive early observational findings[95–97] ranged from a 39% to 50% effect size for the reduction in AD risk associated with HT use. Comparable evidence was demonstrated in one review, which showed that the strongest evidence for HT in AD risk reduction came from 2 cohort studies and 10 case-control studies, which showed a pooled 34% decrease in AD risk (95% CI 18%-47%).[89,98] An additional review found the pooled risk ratio of cohort studies using HT in AD prevention to be a 39% reduction [95% CI 24%-54%][1]. More recent observational evidence has also suggested a benefit of HT on cognition in postmenopausal women, with longer duration associated with greater benefit in the population-based Cache-County cohort study.[97,99] The 12-year follow-up of the Cache-County study found a significant "sensitive period" effect, with timing of HT commencement being significantly related to cognition (assessed using the extended mini-mental state exam, the 3MS) such that those commencing within 5 years of menopause performed better than those commencing HT 6 or more years following menopause, with greater benefit conferred to older women.[99]

Early observational data were subject to significant confounding, with depression typically not controlled, and the women who were prescribed HT being more educated, in better overall health prior to HT commencement, and leading healthier lifestyles than women not given HT.[100,101] LeBlanc et al. also note potential bias by contraindication in observational studies whereby women who already have dementia are less likely to receive HT due to issues relating to compliance and interactive effects between the HTs and existing medications.[98] Error may also be introduced in reporting, with many studies using proxy reports, which could lead to bias due to the proxy being unaware of any previous HT use. A limitation of the meta-analyses of the observational data is the lack of consistency in the information on age of exposure.[4] When measures are taken several years apart in panel surveys the exact timing of HT in relation to menopause may not be clearly specified.

5.3 | HT and cognition: Clinical trial evidence

A systematic review of the clinical trial evidence for the effect of HT on cognitive outcomes did not find benefit.[102] The Women's Health Initiative Memory Study (WHIMS), a double-blind, placebo-controlled clinical trial examining 8300 women 65 years of age or older over a 2-year period to observe the effects of HRTs and dementia progression. The trial failed to find a beneficial effect for HT in reducing dementia risk, instead finding an increase in all types of dementia.[103,104] One explanation for the discrepancy between WHIMS and early observational findings is the differences in timing of treatment onset. Whereas observational studies followed women who had commenced HT during menopause, in WHIMS, participants were randomly allocated long into the post-menopausal phase.[94] The "sensitive period hypothesis" suggests both the observational and WHIMS findings may be accurate,

with differences in effects being accounted for by the timing of treatment onset, rather than methodological concerns.[94]

When examining variation in the timing of treatment initiation, one review of RCTs found little support for the effects of HT on cognition in older women (65 years and older), although it cited potential benefits to younger women (younger than 65 years) for HT across certain cognitive domains. The author found that this was especially true for women who had symptomatic menopause and who were more recently menopausal.[105] Despite this, the author noted that although larger RCT data for older women with late-life HT exist, there is a dearth of larger RCTs that examine HT in younger women. One review of 22 double-blinded RCTs found that only 30% of women were 50 to 59 years old during baseline, the age at which women are mostly likely considered for HT to alleviate symptoms[102] and most likely relevant to the sensitive period hypothesis.

LeBlanc and colleagues[98,106] reviewed RCTs on HT and cognition and found significant heterogeneity in the cognitive tests employed across HT RCTs. Across nine RCTs, more than 40 different tests were utilized, and within the consistently used tests only 7 of 40 were used across more than one study and with varied administration. Regarding treatment, RCTs were inconsistent in the duration of administration, specific dosage, and formulation used (only two studies used the same formulation and dose).[98] The authors concluded that there is currently insufficient data regarding the attenuating effects of varied formulations and dosages on cognition. These studies also tended to be of poorer quality (only one out of 10 rated as "good"). Other authors suggest that effect sizes of RCT findings are often limited by a large age range[107] and inclusion of participants with early- and late-onset AD at baseline.[100,107] Despite the above it is also important to note that given the evidence for longer duration of HT use being associated with increased risk of cardiovascular disease, breast cancer, and stroke, HT is not currently recommended for treatment in the prevention of cognitive decline or dementia.[102,108]

5.4 | Hormones and HT: Summary and recommendations

In summary, despite the biological plausibility for estrogen being neuroprotective, and some positive findings from observational studies, the potential of HT to reduce the risk of cognitive decline and dementia is not found in RCTs to date. There are several important gaps in this literature.

Recommendations for future studies in HT and cognition include:

1. The effects of long-term HT use in perimenopausal women, and postmenopausal women ages 50 and younger on cognition should be evaluated.
2. The potential role for HT type should be considered in relation to risk of dementia with other women's health variables such as hysterectomy and oophorectomy also included for consideration.
3. Data are needed on the association between HT and Vascular Dementia (VaD) or other non-AD dementias in the observational literature.[4]
4. There is a greater need for evidence for more globally diverse data for HT in order to understand effects not only across the life-course, but across sociodemographic, racial, and cultural backgrounds.[4]

6 | INFLAMMATION AND NSAIDS

6.1 | Inflammation and NSAIDs: An introduction

In 1988, Joseph Rogers and Patrick McGeer reported the presence of Human Leukocyte Antigen – DR isotype (HLA-DR) and other T-immune cell markers around neuritic plaques in AD brains.[109,110] Sensing that such immune activity was probably contributory (not adaptive) to AD pathology, McGeer studied the relationship between rheumatoid arthritis (RA; almost always treated with anti-inflammatory drugs) and AD.[111] AD appeared to be rare in patients with RA, and vice versa. Among four explanations for this finding, McGeer considered the possibility that "AD (does) indeed develop less often in the RA population, but this is unrelated to anti-inflammatory drugs."[111] Alternatively stated, he noted the possibility of confounding by indication.

6.2 | NSAIDS: Further observational data

Two years later, a co-twin control study investigated a broad agnostic array of antecedent exposures in 50 AD-discordant twin pairs. This search revealed only that a history of arthritic conditions or anti-inflammatory treatments was inversely associated with the occurrence of AD.[112] The study's authors then investigated NSAID use versus AD in a sample of siblings from families with a multiplex history of AD dementia,[113] finding an inverse association between a report of sustained NSAID use and the onset of AD. These analyses considered a historical report of "arthritis" (not otherwise specified), which appeared not to modify onset except in those treated with NSAIDs. In the ensuing years, numerous epidemiological studies—some including attempts to control for confounding by indication and inclusion of a control exposure (acetaminophen / paracetamol)—suggested a benefit of sustained NSAID use. This trend reached its zenith with publication in the *New England Journal of Medicine* of findings from the Rotterdam Study.[114] The Rotterdam cohort was relatively youthful for an investigation of dementia (median age at entry of mid- to late-60s). Relying on a prescription registry, it suggested a time-dependent inverse association between AD and NSAIDs, culminating in an 80% reduction in incidence for persons with ≥5 years of continuous NSAID use.

6.3 | Contrast with randomized controlled trials of NSAIDS

The following years witnessed a series of carefully conducted RCTs that failed to affirm the observational findings. The Alzheimer's Disease Cooperative Study (ADCS) reported clinical trials of

prednisone (a powerful immunosuppressant), and, a few years later, two NSAIDs (naproxen and rofecoxib). Both failed to show benefit in AD patients.[115,116] A trial of the anti-malarial drug hydroxychloroquine (which also has substantial immunosuppressant activity) showed no benefit.[117] An RCT of rofecoxib (a selective cyclo-oxygenase 2 [COX-2] inhibiting NSAIDs) failed to suggest that drug's ability to postpone "conversion" of MCI to AD dementia.[118] Here, the hazard ratio (HR) for conversion to AD with assignment to rofecoxib was a worrisome 1.46 (95% CI 1.09-1.94). Shortly thereafter, the ADAPT research group reported similarly adverse findings in 25 incident cases, relating the risk of incident AD dementia to the treatment of asymptomatic elderly (age ≥70 years) with the COX-2 inhibitor celecoxib (HR 4.11, 95% CI 1.30-13.0) or naproxen sodium (HR 3.57, 95% CI 1.09-11.7) versus placebo.[119] Because ADAPT was stopped early, its incident AD cases became evident after no more than 3 years of treatment, suggesting that these persons had advanced pre-symptomatic disease when treatments were initiated. The latter conjecture was supported to some degree in the 3-year ADAPT Follow-up Study, which showed dissipation of the adverse associations, [120] and by a detailed analysis of the original ADAPT data suggesting that naproxen treatment accelerated cognitive decline among the one-third of participants showing the greatest rate of decline.[121]

These findings seemed to suggest that the ideal population for NSAID treatment would be at-risk "young-elderly" persons without inflammatory disease. Participants should then be further removed from their possible age at onset of AD dementia. But the difficulty for such trials lay in measurement of the progression of pre-symptomatic AD. Only with such measurement could one expect to see that NSAID treatments would retard this progression. Attempting to address this problem, Canadian investigators assembled a younger (median age 63 years) asymptomatic cohort for PResymptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD cohort).[122] Their risk of AD was likely increased by a requirement that each had a parental or multiple-sibling history of AD dementia. They were evaluated annually using the 45-minute Repeatable Battery for Assessment of Neuropsychological Status, [123] and a broad array of other evaluative procedures, as detailed in reference[122] and a companion paper that describes the development of a composite indicator of pre-symptomatic AD progression, the "Alzheimer Progression Score" (APS).[121]

Some 200 members of the PREVENT-AD cohort were enrolled in INTREPAD, a 2-year placebo-controlled RCT of naproxen sodium 220 mg, b.i.d.[124] The INTREPAD primary outcome was the APS—after validation efforts in the remaining ≈175 PREVENT-AD participants had shown its excellent longitudinal stability and portability to the trial sample. Slightly more than half of INTREPAD participants also donated annual cerebrospinal fluid (CSF) samples for immune marker studies.[125] The trial results indicated (1) a significant increase in participants' APS over the 2-year trial interval, but (2) no suggestion of any mitigation in this change among naproxen-assigned individuals. No single component of the APS showed any suggestion of benefit from naproxen.

6.4 | Later observational studies affirm the trial results and suggest adverse consequences of NSAID use among very elderly persons

Perhaps resolving the discord between trial and observational study results, more recent observational data appear mostly to side with the available trial results. Since 2000, numerous investigations have shown null or worse association between NSAID exposure and AD incidence. A consistent feature of these later studies was their reliance on populations considerably older than the Rotterdam cohort. Thus the elderly (age at entry 65-106 years) population-based MoViES cohort study found no association of NSAID use with occurrence of AD (data described in[126]). Similar results were observed in the Religious Orders Study – Memory and Aging Project (mean age at entry = 75 years with mean follow-up of 12 years).[127] Perhaps most surprising, results from the population-based Adult Changes in Thought observational study suggested a strong apparent *increase* in AD incidence among "heavy" users of NSAIDs (data from computerized prescription registry; hazard ratio 1.66 with 95% CI 1.24-2.24).[128] These persons had consumed ≥500 defined daily doses of NSAIDs over two or more years but were again quite elderly, with a median age at entry of 75 years and follow-up typically of a decade or more. Given the well-known epidemiologic relation of age to AD incidence (eg, >20% cumulative incidence by age 80), and recent awareness that AD pathological changes begin a decade or more prior to symptoms, cohorts in their late 70s and beyond would likely include >30% of participants with demonstrable evidence of (pre-symptomatic) AD pathology.[129,130] In sum, the single most consistent finding of the observational data on NSAIDs appears to be a lack of benefit (and even a potential for harm) when persons in later old age are exposed to NSAIDs.

6.5 | Should we attempt further RCTs for AD prevention using NSAIDs? Summary and recommendations

The disappointing results from INTREPAD suggest that participants in any new trial should be even younger, probably younger than 60 years of age, and perhaps without prominent AD risk factors. The size and duration required for such a trial would likely render it prohibitively costly and difficult to execute. If this sort of trial were, nonetheless, contemplated, its sponsors should probably consider several other experimental findings:

- Should the trial choose a different NSAID intervention? Only a select group of NSAIDs have a capacity to inhibit gamma secretase activity, which is an important step in the cleavage of the amyloid precursor protein to Aβ fragments, ostensibly essential (if perhaps not causal) for early AD pathogenesis.[131] Some authors have, therefore, lamented the fact that none of the completed NSAID RCTs tested ibuprofen or other "gamma secretase-modulating" (GSM) agents. But observational data, at least, suggest that GSM activity may

not be important. A meta-analysis of six key cohort studies whose 17,000 participants had contributed 77,000 person-years of observation showed the familiar result of reduced dementia incidence among chronic NSAID users.[126] But the data failed to show any difference in apparent "protection" offered by GSM NSAIDs compared with others, or in the apparent effects of their most common exemplars ibuprofen and naproxen.

- Will the chosen intervention cross the blood-brain barrier in sufficient concentration to modify the brain "inflammatory" (innate immune) changes that accompany AD pathogenesis? Findings among INTREPAD participants showed that treatment with low-dose naproxen (the conventional NSAID most commonly used in AD trials) produces appreciable levels in the CSF.[125] These levels represent only about 1% of concentrations found in the plasma of treated subjects, but this result is not necessarily surprising given that about 99% of naproxen in plasma appears to be protein-bound (and therefore of doubtful effect).
- Will the chosen agent have appreciable effects on important immune and inflammatory markers in CSF (therefore, probably in brain)? Another finding from the study of INTREPAD CSF was that assignment to naproxen resulted in little or no consistent change in levels of important immune markers indicating "inflammatory" brain changes. Accordingly, there may be significant concern that none of the NSAID treatment or prevention trials used "anti-inflammatory" agents that would be likely to affect the changes described by Rogers, McGeer, et al.[109,110]

6.6 | Concluding thoughts on the disparity between the NSAID trial and observational results

The earliest published work on this topic considered the possibility of confounding by indication. None of the described observational studies was able in multivariate analyses to exclude the possibility that an apparent benefit with NSAIDs was attributable to confounding by an inflammatory diathesis. In particular, the above-cited meta-analysis of six cohorts[126] considered the possible influence of an "arthritis" (mostly osteoarthritis) variable. As in several other studies, this variable appeared to strengthen the inverse NSAID–AD association (arthritis sufferers are probably obligatory NSAID users). Notably, however, the "arthritis" variable itself was associated with diminished AD incidence, even after "adjusting" for reported NSAID use. If reproducible, this finding suggests little reason to expect trial results to affirm a benefit of NSAIDs in persons without evidence of inflammatory disease (an exclusion criterion in all the cited trials). We have therefore come to have strong doubts about the possible benefit of NSAIDs for AD prevention. Instead, we recently conjectured (as first discussed in McGeer's pioneering work) the aforementioned "… results may suggest re-consideration of … a pro-inflammatory diathesis (itself) as a possible explanation for the reduced AD incidence among (relatively young) NSAID users in observational studies," [124] that is, confounding by indication.

Recommendations:

1. Future work on pharmaceutical interventions for dementia risk reduction must remain vigilant to potential sources of bias, not the least those of reverse causality and confounding by indication.
2. Any contemplated new trial of anti-inflammatory interventions for AD prevention should avoid enrolling very old participants or others with evidence of advancing pre-symptomatic AD pathology.

7 | OMEGA-3 FATTY ACIDS AND SUPPLEMENTATION

7.1 | Omega-3 and supplementation: An introduction

Mediterranean,[132] Mediterranean-Intervention for Neurodegenerative Delay (MIND),[133,134] and prudent [135,136] dietary patterns have been associated with slower cognitive decline and lower risk for developing AD. These associations may be attributable to the higher intake of plant-based foods and seafood dense in unsaturated fatty acids, vitamins and minerals, and flavonoids and polyphenolic compounds, and there is some evidence associating increased seafood consumption, omega-3 intake, or omega-3 blood levels, with a lower risk of dementia, or of cognitive decline.[137] Isolated components from these diets, including the omega-3 polyunsaturated fatty acids (n-3 PUFAs)[138,139] and the homocysteine-lowering B vitamins[140–142] (Section 8 in subsequent text) have been formally tested in slowing cognitive decline or AD progression, but the results of randomized clinical trials have been inconsistent. This section and the following Section 8 provide updates and insights into n-3 PUFAs and B vitamins, respectively, in the pursuit of developing more effective nutritional-based interventions for prevention of age-related cognitive impairment and dementia.

n-3 PUFAs have a variety of bioactive properties that regulate physiological functions and there are various potential mechanisms for the role of n-3 PUFAs in cognition. The two major n-3 PUFAs are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA is quantitatively the most abundant n-3 PUFA in human brains, whereas EPA is present in very limited amounts.[143] The small concentration of EPA in the brain does not necessarily translate into a weak biological activity. Given that EPA and DHA can inter-convert in vivo,[144] it is possible that both or either fatty acid may have similar neuroprotective effects. Although EPA is reported to have greater anti-inflammatory effects[145] and has been associated with greater white matter integrity,[146] because the majority of preclinical studies to guide pharmacokinetics (PK) and pharmacodynamics (PD) were conducted using DHA,[147] we focus on DHA in this review. It is important to note that neither EPA nor DHA can be synthesized *de novo* but can be obtained from diet/supplementation.

In contrast to the pre-clinical studies in AD mouse models that bring some support for a role for long-term and high-dose omega-3 fatty acid intake in improving measures of cognition, clinical trials testing the effect of omega-3 supplementation on cognition have largely been disappointing. We examine the pharmacological properties of omega-3s in the brain in relation to study designs to understand this discrepancy.

TABLE 1 Existing DHA formulations

DHA Ester	Formulation	Properties
Triacylglycerol ester	DHA esterified to triacylglycerol backbone	Most abundant natural form of DHA
Ethyl esters	DHA esterified to ethanol	Synthetic form that converts into TG or PL DHA after absorption
Phospholipid esters	DHA esterified to phosphatidyl choline or phosphatidyl serine	Demonstrates greater brain uptake compared with the other forms

7.2 | Omega-3 and cognition: Epidemiology

A possible role for n-3 PUFA consumption was also shown in a meta-analysis of 21 longitudinal studies (181,580 participants) with 4438 dementia cases reporting that a one-serving per week increment of dietary fish was associated with lower risks of dementia (RR 0.95, 95% CI 0.90-0.99; $P = 0.042$, I(2) = 63.4%) and AD (RR 0.93, 95% CI 0.90-0.95; $P = .003$, I(2) = 74.8%). More specifically, the increment of dietary DHA intake was associated with lower risks of dementia (RR 0.86, 95% CI 0.76-0.96; $P < .001$, I(2) = 92.7%) and AD (RR 0.63 95% CI: 0.51, 0.76; $P < .001$, I(2) = 94.5%).[137] The KORA (KOoperativen Gesundheitsforschung in der Region Augsburg)-Age study has also reported a cross-sectional association between low omega-3 index (<5.7%) and cognitive impairment in an elderly population of 720 participants with cognitive status ranging from cognitively normal to suspected dementia.[148]

7.3 | Omega-3 and cognition: clinical trials

Overall, the effects of omega-3 supplementation on cognition have been disappointing in several randomized clinical trials.[149] One possible explanation is the confounding effect observed in observational studies, where lower omega-3 levels could represent biomarkers of poor dietary networks[150] that affect several factors (other nutrient levels, lifestyles, or risk factors) and therefore intake or levels of omega-3 per se may not be causally related to dementia. However, there is good biological evidence that omega-3 intake has neuroprotective effects in AD animal models.[151] It is plausible that omega-3 supplementation started after the onset of significant neurodegeneration is too late, where the disease process may not be reversed by omega-3 supplements. There are many challenges for conducting prevention trials including identifying an omega-3 dose that gets to the brain, the population that may benefit from supplementation, the duration of supplementation, and sensitive cognitive outcomes.

7.3.1 | Omega-3 fatty acids: Dose and delivery

Animal studies provide useful information on DHA brain pharmacodynamics with AD biomarkers as readouts (amyloid, tau, synaptic functions, and makers of neurodegeneration). In a systematic review, Hooijmans et al. [151] reported cognitive and AD biomarker benefit using doses of DHA supplementation (0.6-0.24 g/kg/day). Accounting for different body surface areas of mice and adult men with a correction factor of 0.08,[152] the equivalent human DHA doses to replicate these preclinical studies would range from 0.048 to 0.19 g/kg of DHA per day. This would be equivalent to providing 3.36 to 13.3 g of DHA per day for a 70 kg individual (Table 2). These large doses of triglyceride-DHA formulas are unrealistic for human consumption and implicate the need to develop alternative DHA formulations that can escape catabolism. The effects of DHA supplementation on behavioral and biochemical measures were demonstrated in rodent models carrying amyloid mutations[153–155] or *APOE* ε4 allele knock-in models[156,157] using higher doses and long-term DHA supplementation to diet.

In humans, DHA is consumed primarily from oily fish, whereas other sources include liver and eggs. DHA supplements are commonly provided in the form of an algal-derived triacylglycerol (TG) form or in pure DHA ethyl esters (Table 1). From a pharmacological perspective, absorption of DHA is similar between TG and ethyl esters of DHA formulations.[158] Although DHA supplements penetrate into the brain, there are very few DHA dosing studies guiding the information on DHA penetration to the brain. In the omegaAD trial, 1720 mg of DHA (in ethyl esters) per day over 6 months was associated with only an 11% increase in CSF DHA levels, as opposed to a two-fold (200%) increase in plasma DHA levels.[159] In the ADCS-sponsored DHA trial, 2 g of DHA daily (Algal TG derived), a 38% increase in CSF DHA levels was observed as opposed to a 207% increase in plasma DHA levels.[160] In the DHA Brain Delivery Pilot trial that recruited cognitively normal older adults, 2 g DHA daily (Algal TG derived), led to a 28% increase in CSF DHA levels.[161] Therefore, DHA doses of less than 2 g per day may lead to relatively small [<20%] increases in CSF or brain DHA levels. This may provide an explanation whereby clinical trials using 1 g or lower doses of omega-3 were negative for cognitive outcomes.[162]

Furthermore, because the majority of ingested DHA is transported esterified to lipids, the half-life of DHA depends on the turnover of its carrier molecule. the half-life of DHA is ≈3 weeks in plasma phospholipids and 4 months in red blood cell membranes.[163] In contrast, the half-life of DHA in tissue compartments is much slower. In the brain, Umhau et al. demonstrated using ^{11}C DHA positron emission tomography (PET) scans that DHA half-life is ≈2.5 years.[164] Even within the brain, different compartments may have different DHA turnover rates, with synaptic DHA turnover occurring at faster rate[165,166] than other brain tissues. Similar to the brain, the half-life of polyunsaturated fatty acids in adipose tissues is around 3 years.[167] The slower turnover of DHA in the brain implies that a modest reduction in DHA intake or increase in DHA consumption may take several years to remodel brain DHA within neuronal membranes. Unless there is severe DHA

TABLE 2 Comparison of omega-3 study designs between human and animal trials

	Human trials using omega-3 supplementation	Animal studies using a DHA dietary intervention
Dose	0.003-0.03 g/kg/day	0.6-0.24 g/kg/day
Age at the onset of intervention	>65 years	3-4 months
Duration of intervention	4 weeks to 5 years	12 weeks to 8 months
Effects on Cognition	Null	Enhanced cognitive functions
Effects on Aβ/Tau	No change in CSF Aβ/tau[160]	Decrease tau and Aβ
Effects on synaptic functions	Not directly studied	Enhanced expression of synaptic proteins

Abbreviation: Aβ, amyloid beta.

depletion or deficiency secondary to strict dietary restriction or a metabolic defect, short-term DHA supplementation will less likely affect brain DHA levels.

Delivery of DHA to the brain may be enhanced using phospholipid DHA esters instead of TG DHA esters. Phospholipid DHA formulations have a longer plasma half-life,[168] and associate with HDL metabolism. In addition, the incorporation of DHA into the sn-1 position of dietary phospholipids can enhance its brain bioavailability[169] by limiting a phospholipase A_2–mediated loss of DHA during its peripheral circulation. Another strategy to enhance brain DHA delivery focuses on enhancing brain apoE lipidation. *APOE* lipidation is dependent on ABCA-1 activity.[170] DHA when added to the medium of glial cells in culture is incorporated into membrane phospholipids, and then secreted as the fatty acid moiety of phospholipids mostly to APOE-containing lipoproteins.[171] APOE-containing DHA exhibits a strong effect on neurite outgrowth of hippocampal neurons by increasing the number of branches.[171] Therefore, enhancing brain APOE lipidation represents a mechanism to mobilize DHA from glial stores into APOE lipoproteins and, therefore, facilitate its brain transport in tissues with greater APOE receptor expression such as the hippocampus.

7.3.2 | Omega-3 fatty acid intake and the response to supplementation

An association has been shown between serum DHA and brain amyloid accumulation in persons at risk of dementia.[149] However, this association was driven largely by persons at the lowest quartile of serum DHA levels, that is, those who do not consume much seafood. The Multidomain Alzheimer Preventive Trial (MAPT) was designed to assess the effects of DHA (800 mg) and EPA (to a maximum of 225 mg), multidomain intervention in cognitive function in frail subjects with memory complaints older than 70 years of age. In the main analysis of MAPT, no significant effects of the interventions were found on cognition after adjustment for multiple testing. Exploratory sub-group analysis showed that participants on n-3 PUFA supplementation with a low omega-3 index (DHA + EPA ≤4.83%, representing the lowest quartile of omega-3 index distribution) at baseline showed a trend toward less cognitive decline over 36 months in comparison to subjects on placebo with low baseline omega-3 index.[172] PREVENTE4 (NCT03613844) is testing whether high dose (2 g/day) algal-derived DHA supplementation over 2 years would benefit non-demented older individuals with low baseline omega-3 intake and who are at increased risk of dementia based on *APOE* genotype and cardiovascular risk factors.

7.4 | Omega-3 fatty acids: Summary and recommendations

In summary, epidemiology studies might support a protective effect of increasing PUFA consumption when supplementation starts early and lasts for a considerable amount of time to allow n-3 to remodel within brain cells. Moreover, high dose and long-term DHA supplementation ameliorates AD pathology in rodent models. Short-term and low-dose omega-3 supplements are unlikely to produce meaningful effects sizes on cognitive outcomes with ongoing clinical trials, as these often include individuals with already-sufficient omega-3 blood levels or significant evidence of neurodegeneration, in which case reversing the pathology may not be possible. Furthermore, there are the complexities and confounding associated with dietary patterns and change in dietary patterns overtime in different populations.

1. Recommendations: Omega-3 clinical trials should begin with a focus on appropriate exposure level and sample selection, with clinical outcomes associated with lower PUFA intake and levels and responsive to supplementation and careful measure of confounding. Selection of participants at increased risk of dementia, for example, cognitively normal *APOE ε* carriers, may increase the likelihood of success.
2. Either greater doses of current TG-DHA formulations or better brain-penetrant formulations may need to be tested over longer time frames and in those without significant evidence of neurodegeneration.

8 | HOMOCYSTEINE AND B VITAMINS

Epidemiological studies have established that raised plasma total homocysteine (tHcy)—a marker of B vitamin status—and low-normal blood levels of the B vitamins folate, B6, and B12 are risk factors for

dementia, including AD.[173–177] Plausible mechanisms for this association have been described[174,175,178,179]; these include mediation by damage to the cerebral vasculature and the formation of phosphorylated tau, leading to brain atrophy.

Several meta-analyses have estimated the population attributable risk (PAR) of dementia for raised tHcy. On the assumption that raised tHcy has a prevalence of some 30% in the elderly population, estimates of PAR range from 12% to 31% in four of the meta-analyses, with a fifth estimating that the PAR is 4.3%.[176] Thus a substantial proportion of dementia may be caused by elevated tHcy.

In view of the high PAR, it is important that raised tHcy can readily be lowered by the oral administration of three B vitamins (folate, B6, and B12). The doses of these vitamins that are required to lower tHcy are considerably larger than can readily be obtained from the diet. A limited number of trials have been carried out with these high doses in people with dementia, MCI, or normal elderly but with conflicting results. Some of the reasons for these conflicting results have been discussed. [174–176]

Here, we make recommendations specifying the conditions that should be fulfilled in any trial of homocysteine-lowering B vitamins in relation to cognition, based upon Table 2 in[176]

Appropriate sample selection is needed:

1. Elevated tHcy or suboptimal B vitamin status should be present in the participants so that benefit can occur. No benefit could be expected if the participants already have an adequate B vitamin status. Hence, it is crucial to measure tHcy or B vitamins at baseline. It is noteworthy that some trials have not done this (eg, Ref 180, 181).
2. Study participants in the trial should be at risk of cognitive decline or already showing decline, but should not have a diagnosis of dementia. In patients with dementia it is likely, as is applicable for most interventions, that the degenerative process has proceeded too far for any clinically meaningful modification of the disease process to be possible. It was found, for example, in the ADCS trial[141] that patients with moderately severe dementia did not benefit from homocysteine-lowering treatment but those with mild dementia did show some benefit.

Appropriate outcomes must be measured:

1. The outcome measured must be sufficiently sensitive to change over the duration of the trial. Screening tests like MMSE have often been used in trials but these are rarely sufficiently sensitive to detect a meaningful change over a short time. More specific cognitive tests should be used and in addition, or alternatively, sensitive objective and physical measurements such as the rate of brain atrophy determined by magnetic resonance imaging (MRI)[182] can be used.
2. The duration of the trial should be long enough to measure clinically relevant change, such as cognitive decline, in the placebo group. This period should be at least 12 months and preferably 2 years, in particular if conversion to dementia is being assessed. It is noteworthy that many trials do not fulfill the criterion of cognitive decline in the placebo group: for example, in a New Zealand trial, the placebo group had an MMSE score of 29.17 ± 0.16 at baseline and 29.32 ± 1.10 after 2 years; there was no effect of B vitamin treatment.[183] In the meta-analysis by Clarke,[184] 76% of 20,431 participants in the trials did not have baseline measures of cognition, and so it was not possible to determine cognitive decline in the placebo group; this fact must cast doubt on the validity of the authors' conclusions.

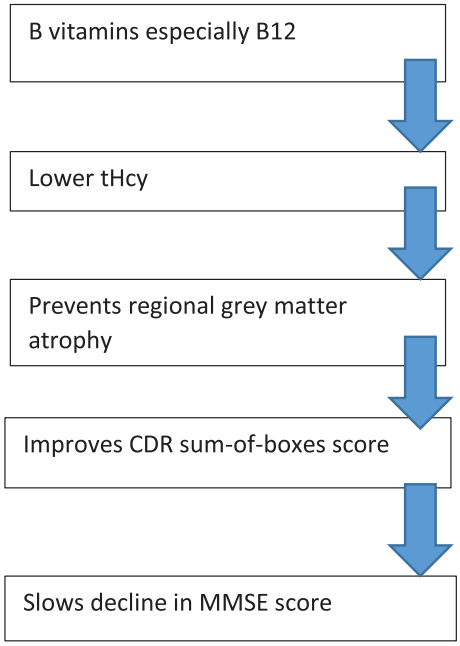

FIGURE 2 Directed acyclic graph analysis of B vitamin treatment and consequential changes in brain structure and function in mild cognitive impairment (MCI). The mediating pathway shows the optimal Bayesian network that explains the findings from the VITACOG trial
Abbreviations: CDR, Clinical Dementia Rating scale; MMSE, Mini-mental state examination; tHcy, total homocysteine.

The dose should be adequate:

1. The doses of the vitamins should be sufficient to lower tHcy in the majority of the participants, which means that food-based vitamins will not be adequate. Doses needed are typically: folate 0.4 to 0.8 mg, B6 10 to 20 mg, and B12 0.5 mg, and these can be taken orally.

Analyses should take appropriate account of subgroups, confounding, and interaction:

1. It is crucial that the analyses pre-specified in the trial protocol include subgroup analysis in relation to baseline levels of tHcy and/or of the B vitamins. It may be that the beneficial effect will be the greater, the higher the baseline tHcy.
2. The protocol should specify analyses adjusted, or stratified, according to other factors known to influence cognitive decline, such as

Key:
Areas where discrepancies have been identified between the observational and clinical trial evidence base X
No discrepancy identified or no evidence available ☐

	High blood pressure and anti-hypertensives	High cholesterol and statins	Diabetes and treatment of diabetes	Hormone regulation and hormone therapy	Omega 3 fatty acid and supplementation	Homocysteine and Vitamin B	Inflammation and NSAIDs
Target population (age). The epidemiological evidence is generally most robust for risk factor exposure at a particular time in the life-course, e.g., midlife. However, most clinical trials have taken place in populations at different ages, e.g., late-life.	X	X		X			X
Population subgroups to consider. Different subgroups may respond differently to risk reduction (e.g., there may be differences between those with and without a genetic risk profile). These may need to be selected for in trial populations.	X	X	X	X	X	X	X
Level of baseline risk factor /level of severity. Risk factor levels may differ in clinical trial and epidemiological samples. E.g., population samples will likely include people with a greater range of severity than a selective clinical trial population.	X	X	X	X	X	X	
Dementia type, balance of pathology/severity. Population samples are likely to show a range of dementia severity and pathology whereas interventions may need to be targeted to a specific at risk group.	X	X		X	X		X
Type of treatment/drug class/specific drug. Some drugs may have direct effects on cognition and therefore be more effective than others. Trials are usually selective in their choice of treatment whereas observational studies will have a range of treatment types.	X	X	X	X	X		X
Combined treatments. Combined treatments changing multiple risk factors may be required to achieve benefit. Trials are likely to have focused on individual treatments.					X	X	
Dose of intervention. Trials usually select a restricted range of doses which may miss the therapeutic level needed for cognition. Epidemiological studies are more likely to have a range of doses but often do not report details of doses.	X	X	X		X	X	
Expected goal level/size of the change in risk factor required. To select an at risk population and test the efficacy of risk reduction in a trial population we need more evidence to understand the risk factor levels that are associated with the best cognitive outcomes.	X	X	X		X		
Duration of intervention /length of clinical trials. Treatment is usually required long-term, whereas trials run for a few years at most.	X	X	X	X	X	X	X

FIGURE 3 Common areas of discrepancy identified by expert review for each of the seven risk factors

age and *APOE* genotype, and to factors like omega-3 fatty acids and antiplatelet drugs that appear to interact specifically with B vitamins (see subsequent text).

Relatively few published trials of B vitamins in relation to cognition have satisfied all the above criteria. These include the FACIT trial of folic acid over 3 years[140]; the VITACOG trial of folic acid, B6, and B12 in MCI over 2 years, reviewed in Smith[175]; and two trials in MCI from China on folic acid for 2 years[185] and on folic acid and B12 for 6 months.[186] All of these trials reported a beneficial effect of the B vitamin treatment on cognitive or clinical function. Many trials that were deficient in one or more of the above criteria have been reported as negative, but in fact such conclusions cannot be drawn.

The VITACOG trial not only assessed cognitive and clinical measures but also measured total and regional brain atrophy. In the intention-to-treat analysis, the B vitamin treatment in 180 participants who had volunteered for MRI scans slowed whole brain atrophy by 30% overall, but in participants with tHcy in the top quartile (>13 μmol/L) the B vitamin treatment slowed brain atrophy by 53%.[182] The slowing of brain atrophy by B vitamin treatment was not influenced by the *APOE* ε4 allele status. Regional brain atrophy, in particular in the medial temporal lobe, was markedly slowed, by almost 90%.[187]

Subsequent analysis showed that the beneficial effects of the B vitamins were restricted to participants who had a good omega-3 fatty acid status as well as elevated tHcy.[188,189] Confirmation of this interaction has come from a trial showing that a combination of folic acid and DHA treatment was more effective in improving cognition in patients with MCI than either nutrient alone.[190] A theoretical basis for this interaction between two classes of nutrients has been proposed.[175,191,192] Evidence that this interaction operates in the opposite direction as well, that is, good B vitamin status (low tHcy) facilitates the cognitive improvement after administering omega-3 fatty acids, has been provided.[193]

The VITACOG trial has drawn attention to several factors that can influence the response to treatment with B vitamins, such as the baseline level of tHcy, the possible influence of omega-3 fatty acids, and the use of aspirin by participants. For aspirin, it was found that those participants who regularly took aspirin, but not those taking other NSAIDS, showed no slowing of brain atrophy after B vitamin treatment.[182] Similarly, aspirin use appeared to interfere with the beneficial cognitive effects of B vitamins in MCI (T. Kwok et al., unpublished data). These factors, and possibly the use of other drugs such as lipid-lowering

TABLE 3 The mismatch between the epidemiological and clinical trial evidence: Challenges and opportunities

	Challenges	Opportunities
Target population in terms of age The epidemiological evidence is generally strongest for risk factor exposure in midlife; however, the majority of the clinical trials have taken place in later-life populations with a short duration of follow-up.	Unrealistic to develop clinical trials that modify risk and protective factors during mid-life and examine its effects on late-life dementia. Therefore, the trial efficacy is often examined under a hypothesis (or assumption) that given the treatment/intervention could be provided at later age, it would still show efficacy.	Important to examine differential efficacy levels across different age groups to develop sensitive outcome measures for the reliable detection of changes. Additional opportunities could include more sophisticated use of epidemiological data to understand risk factor variation and interactions over time/life-course, causal analyses of observational data,[196] or the selection of future clinical trial participants with fully characterized past histories.
Target population in terms of characteristics of the participants There is a lack of data on the potential for different levels of benefit in different sub-groups, eg, risk factor level/severity or co-occurrence, a genetic risk or variations in the balance of different contributory dementia pathologies.	The more subgroups we include, the smaller sample size for each subgroup, thereby lowing the statistical power Harmonized diagnosis of dementia sub-types are often lacking in epidemiological studies. Risk factor levels/severity and clustering may differ in clinical trial participants and epidemiological cohorts.	Careful selection of trial populations Additional epidemiological work (new studies or further precise reporting from existing data) may be required to understand the risk factor/outcome relationship across cohorts with different risk scores, chronic conditions, lifestyle factors, and baseline disease severity and pathologies.
Target intervention Type and dose of intervention drug or combination of drugs	We have not yet identified the levels of each risk factor that are associated with the best outcomes for cognition nor whether this differs by prior exposure.	Additional epidemiological work to identify potential targets for change (goals/biomarker change, etc.) supplemented by a greater understanding of the physiological processes and their potential inter-connectivity alongside trials looking at different goals or treatment targets.

drugs, should always be taken into account when trials of B vitamins are designed.

It has been concluded that the VITACOG trial has already fulfilled the criteria for disease modification in MCI,[194] with the causal pathway shown in Figure 2. Trials of a combination of B vitamins and omega-3 fatty acids are now needed in people who have elevated tHcy, to see if this simple and safe treatment can slow, or prevent, the conversion from MCI to dementia.

9 | DISCUSSION

Although dementia risk reduction has never been more important, the evidence so far, at least for the risk factors we examined, is not yet sufficient to drive clear guidelines, although some pointers have been identified. In particular, there are common areas of discrepancy between the observational and clinical trial evidence across the seven risk factors.

Experts in the relevant field appraised each of the seven risk factors independently, and yet when we pool all of these appraisals we find a series of commonalities. These are shown in Figure 3 and can be summarized as those affecting population selection (age, subgroups, key characteristics, dementia type/pathology), those relating to the risk factor (level of baseline severity, relative importance of change in risk factor level), and those relevant to treatment (drug type/class, dosage, duration of treatment, need for combination treatment).

9.1 | Limitations

We have chosen seven established risk factors that are all modifiable with pharmacological intervention, although we acknowledge that risk factor interaction or clustering is possible and single interventions are not necessarily reflective of real life. There are also risk factors where pharmacological intervention is not possible and/or where blinded clinical trials are not feasible, and they too are likely to face some of the issues we have identified; examples might include air pollution, alcohol, or social engagement. Related to this is the potential for commonalities among the mechanistic pathways. For example, a potential role for vascular and inflammatory etiologies is evident, with vascular pathways most strongly but not exclusively linked to diabetes,[13] cholesterol,[52] BP,[66,68,69] and homocysteine,[174,175,178,179] and inflammatory pathways to estrogen[195] and omega-3 fatty acids,[145] although this may not be the whole story with hyperglycemia[15] and BP[66,70–72] hypothesized to increase amyloid deposition and genetic alterations in cholesterol trafficking directly related to risk of AD.[50] Furthermore the work on NSAIDs reminds us to be "vigilant to potential sources of bias, not least those of reverse causality and confounding by indication." Further limitations come from the inherent differences between observational studies and clinical trials, where the former is able to accrue long follow-up but unlikely to modify the risk factor exposure or treatment. The latter by design has an intervention and is likely to be shorter. Finally, to take the first steps in moving the field forward, we have chosen to focus on the similarities between the different risk factor and

treatment pairs rather than the differences. However, these are also a potential source of insight. For example, age at exposure seems more pertinent to some risk factors than others. Although a full evaluation of the differences is beyond the scope of this article, we recommend that they too are explored with a view toward informing the next generation of research on dementia risk reduction.

Our use of expert appraisal could be considered as both a limitation and a strength. We did not seek to carry out a systematic review, as there are multiple systematic reviews already published for each of these seven risk factors. Instead, we have brought together expert perspectives in a consensus and critical commentary of the current evidence. In turn this has highlighted the different directions that the epidemiology and clinical trial evidence has taken across the different risk factors; for example, the availability of epidemiological evidence for some risk factors is heavily based around the risk factor exposure and outcome (eg, BP), whereas for others, the evidence is greater for the association between the treatment and the outcome (eg, HT). Altogether, this underscores the importance of a critical lens when interpreting the existing evidence and a need for a more in-depth understanding going forward.

Overall, we synthesize the challenges and opportunities (Table 3) faced across the risk factors, and we argue that the design of new observational studies and, in particular, new clinical trials, should be both informed by the issues we raise and supported by careful analyses and understanding of the existing data eg, using techniques such as causal inference).[196]

We argue that to gain a greater understanding of the remaining areas of uncertainty and the issues associated with these is a requirement. Before planning future trials and when building a robust justification for future trials, both targeted and methodologically sophisticated investigations are needed. Such evaluations might include re-examining past trials and observational data alongside a pragmatic approach, remaining alert to the possibility that interventions may not modify the risk of dementia. In this context, overall, for NSAIDs the dementia risk reduction story seems close to complete. The current clinical trial evidence arguably holds the most promise for anti-hypertensive use and supplementation by B vitamins, but even for these and other interventions, more work is needed to fully evaluate impact and reduce bias, not the least in greater understanding of the appropriate trial populations and interventions.

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