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Dietary Patterns, Physical Activity, Sleep, and Risk for Dementia and Cognitive Decline

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Abstract

Purpose of Review—Diet, physical activity, and sleep are three major modifiable lifestyle factors. This selective review examines the evidence for strong and reliable associations between these three lifestyle factors and risk of dementia and cognitive decline, in an effort to assist clinicians with providing more informed answers to the common questions they face from patients.

Recent Findings—Certain aspects of nutrition can decrease risk for dementia. Physical activity has also been associated with delayed or slower age-related cognitive decline. In addition, emerging evidence links sleep dysfunction and dementia, with amyloid deposition being a possible mediator.

Summary—Data from further clinical trials are needed before more definitive conclusions can be drawn regarding the efficacy of these lifestyle interventions for lowering the risk of incident

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Chen Zhao declares that she has no conflict of interest.

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dementia and cognitive decline. Nevertheless, it is reasonable to make recommendations to our patients to adopt certain dietary changes and to engage in regular physical activity to improve cardiovascular risk factors for dementia. It is also reasonable to include questions on sleep during cognitive evaluations of the elderly, given the common co-occurrence of sleep dysfunction and cognitive impairment in the elderly population.

Keywords

Lifestyle and dementia; Diet and dementia; Nutrition and dementia; Exercise and dementia; Physical activity and dementia; Sleep and dementia; Primary prevention dementia; Prevent dementia; Lifestyle and cognition; Diet and cognition; Nutrition and cognition; Exercise and cognition; Physical activity and cognition; Sleep and cognition; Modifiable factors dementia; Risk factors dementia

Introduction

This review focuses on three major modifiable lifestyle risk factors for potential primary prevention of dementia: dietary patterns, physical activity, and sleep. Clinicians quite commonly encounter patients who ask whether changes in diet or exercise can impact their future risk of dementia. Sleep is also commonly viewed by the public as an integral component of general health and well-being; and interestingly, there is burgeoning evidence suggesting a link between sleep dysfunction and incident dementia. This selective review examines the evidence for strong and reliable associations between these three lifestyle factors and risk of dementia, with a focus on data from longitudinal studies and RCTs when possible, in an effort to assist clinicians with providing more informed answers to the common questions they face from patients.

Dietary Patterns and Dementia

Diet likely influences dementia risk via multiple mechanistic pathways. Dietary changes can potentially improve cardiovascular risk factors, counteract oxidative stress, and/or decrease inflammation. A primary prevention trial found that participants on the Mediterranean diet (MeDi) had decreased risk of cardiovascular disease events compared to participants on a low-fat control diet [1•]. One randomized clinical trial found that plasma total antioxidant capacity levels increased after a 1-year intervention of the MeDi in participants with cardiovascular risk factors [2]. The MeDi has also been associated with decreased inflammatory markers in multiple intervention trials [3–7]. A systematic review found that in general, Western-type meat-based diets have been associated with greater inflammation, while vegetable and fruit-based diets have been associated with decreased inflammation [8]. In addition, there is preliminary data suggesting an intriguing link between gut microbiome dysbiosis, neuroinflammation, and neurodegeneration [9–11]. Insofar as dietary choices can impact the composition of the gut microbiome, this may be another mechanistic pathway through which diet may impact dementia risk and is an avenue of active ongoing research.

Traditionally, studies of diet focus on either the contributions of individual nutrients or foods or the combined effects of multiple nutrients via dietary-pattern analysis. A recent review of nutrition and cognition found that evidence of an association between nutrition and cognitive outcomes appeared to be stronger for healthy dietary patterns than for individual nutrients or food groups [12•]. Dietary-pattern analysis has several advantages over the study of individual nutrients. When whole foods are distilled into one or several nutrients, benefits of multiple other nutrients, including those previously unidentified, are lost. It is also plausible that the effects of individual nutrients are either augmented or diminished by the presence of other nutrients. As a result, studies of individual nutrients might fail to account for the synergistic contribution of other nutrients [13].

Due to the relative advantage of dietary pattern analysis over the study of individual nutrients, this review will focus primarily on dietary patterns. There are two major approaches to dietary pattern analysis: hypothesis-driven dietary pattern analysis (which makes use of dietary quality indexes or scores) and data-driven dietary pattern analysis (which makes use of factor or cluster analysis). Hypothesis-driven dietary patterns have the advantage of indexes that are easily constructed, which allows for easy and consistent comparison across multiple studies [13]. Consistency and plausibility are essential components of Hill’s criteria [14] for determination of causality. Furthermore, the top-down a priori approach of hypothesis-driven dietary pattern analysis is easily understood and translates naturally into clinical practice recommendations. Therefore, we will focus on hypothesis-driven dietary patterns in this selective review. For a selective list of RCTs on dietary patterns, please refer to Table 1.

Mediterranean Diet

Among the dietary patterns that have been studied, the MeDi has received the most attention. The MeDi is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil in salad dressing and cooking), but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly in the form of cheese or yogurt); a low intake of meat and poultry; and a regular but moderate amount of alcohol, primarily in the form of wine and generally during meals.

Some longitudinal studies found no association between MeDi and cognitive function [15–20] or incident dementia [21], while other longitudinal studies found a protective effect of MeDi on cognitive function [22,23] or MCI/incident dementia [24–27]. A meta-analysis found that high adherence to MeDi is associated with reduced risk of both MCI and advanced cognitive impairment (AD, lower scores on cognitive testing) [28].

A RCT of MeDi on a non-Mediterranean population, the MedLey study, found no beneficial effect of MeDi on cognitive functioning, as compared to a habitual (control) diet [29]. The PREDIMED trial randomized individuals with vascular risk factors to either a MeDi diet supplemented with extra virgin olive oil (EVOO), MeDI supplemented with mixed nuts, or a control (low-fat diet) group. Among a subgroup of participants from one of the 11 recruitment centers (PREDIMED- NAVARRA) who received cognitive assessments, the MeDi diet groups performed better on cognitive tests (Clock Drawing Test, MMSE) than the control groups, after 6.5 years of the interventions. There was a low incidence of dementia (35 out of 1055 participants of PREDIMED-NAVARRA), and the study was likely underpowered to address the effect of MeDi on dementia risk [30]. Another substudy of

PREDIMED (PREDIMED-BARCELONA) showed that those randomized to the MeDi diet had cognitive improvements on the Rey Auditory Verbal Learning Test (a test of verbal learning and episodic memory) as well as the Color Trail Test (a test of attention, visuomotor speed, and cognitive flexibility), after 4 years, while those on the control diet showed cognitive decline [31]. While there were certain protocol deviations leading to inconsistent randomization of a subset of participants, a protective effect of MeDi groups on incidence of cardiovascular events was still found after correction of these deviations [1•]. It remains to be seen whether the associations between MeDi and cognitive outcomes observed in the original PREDIMED substudies will still remain after new analyses are completed which correct for protocol deviations. Overall, a systematic review of 32 studies from 25 unique cohorts (including five RCTs and 27 observational studies) found that a majority of studies found an association between MeDi and improved cognitive function, a decreased risk of cognitive impairment, or decreased risk of dementia, or AD [32].

DASH (Dietary Approaches to Stop Hypertension) Diet

Another dietary pattern with the potential to attenuate dementia risk is the DASH (Dietary Approaches to Stop Hypertension) diet. The DASH diet consists of a combination diet high in vegetables and fruits and low in fat. In a multicenter RCT, DASH was found to decrease blood pressure significantly with an effect comparable to the effect observed in drug monotherapy trials for hypertension [33•]. Blood pressure is one potential mediator by which diet could influence dementia risk. An Agency for Healthcare Research and Quality (AHRQ) systematic review in 2017 found positive evidence from prospective cohort studies and mixed results from RCTs on the relationship between blood pressure management and dementia risk [34•]. Higher accordance to DASH has been associated with better cognitive test performance [23] as well as slower cognitive decline [35], in prospective cohort studies. A RCT randomized participants to the DASH diet alone, the DASH diet combined with a behavioral weight management program (which included exercise and caloric restriction), or a usual diet control group. Those on the DASH diet alone had improved psychomotor speed performance relative to controls, while those on the combination of DASH diet with behavioral weight management measures had improved performance on both psychomotor speed and executive function-memory-learning tests relative to controls. [36]

Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet

The MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) is a hybrid of the Mediterranean and DASH diets, which focuses on plant-based foods and limited intakes of saturated fats, similar to both the Mediterranean and DASH diets. In contrast to both, however, the MIND diet uniquely specifies consumption of green leafy vegetables and berries and does not specify high fruit consumption (3–4 servings/day in both DASH and MeDi), high dairy consumption (2+ servings/day in DASH), high potato consumption (2 servings/day in MeDi), or high fish consumption (> 6 meals/week in MeDi) [37•].

In a prospective study of 960 participants, it was recently reported that consumption of 1 serving daily of green leafy vegetables was associated with slower cognitive decline of a global cognitive score on cognitive testing over 5 years of follow-up. When individual nutrients were examined, vitamin K, lutein, nitrate, folate, kaempferol, and alpha-tocopherol were each associated with slower cognitive decline, while beta-carotene was not [38]. This is consistent with their prior findings that high vegetable intake (but not fruit intake) was associated with a slower rate of cognitive decline in the elderly. Specifically, individuals who consumed two or more vegetable servings daily were equivalent to 5 years younger age on cognitive testing. Of the different vegetable types, green leafy vegetables showed the strongest association [39].

A prospective study found that high adherence and moderate adherence to MIND were both associated with decreased risk of AD [37•]. A phase 3 RCT of the MIND diet is underway, in which non-demented, overweight participants with suboptimal diets are randomized to either the MIND diet plus mild caloric restriction or to a usual diet plus mild caloric restriction (NCT02817074).

Conclusions and Caveats of Dietary Pattern Analysis

A cohort study of 923 participants compared the effects of three distinct dietary patterns: MeDi, DASH, and MIND on risk for AD. Those with the highest tertile and second highest tertile of MIND diet score had 53 and 35% reduced risk of AD, respectively, compared to those with the lowest tertile score. For the MeDi and DASH, only those with the highest tertile adherence scores had reduced AD risk. The authors concluded from this that high adherence to all three diets may reduce AD risk, while moderate adherence to the MIND diet may be enough to decrease AD risk [37•].

There are reasons to suspect that studies about diet and dementia could incorrectly estimate in either direction the true effect of diet on risk for dementia. Most studies exploring associations between diet and risk for dementia have been conducted in elderly individuals, in whom the ability to modify the disease course with diet might be limited. Had nutritional interventions been made earlier in life, the effect of diet on cognitive decline might have been greater than has been seen in studies thus far. Observational studies of diet and cognition may be affected by residual confounders with diet being a surrogate for other unmeasured behaviors. Specifically, lifestyle behaviors may confound dietary patterns. For example, the Mediterranean lifestyle includes potentially protective factors such as having lengthy meals, sharing meals, postlunch siestas, and social support [40•]. Studies of MeDi have not typically accounted for these factors as potential confounders. Finally, although most dietary assessment tools have some validity in reflecting lifelong behaviors even when recorded in late life, they may not adequately reflect temporal variations in diet on a year to year basis, and it is unclear whether dietary intake during particular critical periods (of either normal development or disease pathogenesis) may affect dementia risk to a greater extent than during other time periods.

Physical Activity and Dementia

Physical activity has been shown to promote neurogenesis in the dentate gyrus of the hippocampus in animal studies [41] and increase cerebral blood volume in the dentate gyrus in humans [41]. Hippocampal cortical volume has been shown to be a predictor of conversion from MCI to Alzheimer's disease [42]. Physical activity has also been shown to promote neural functional recovery after ischemic insult [43] and neuronal survival after neurotoxic injury [44] in animal studies. One potential mediator of these effects is circulating IGF-I (insulin-like growth factor), a potent neurotrophic factor, which when blocked by administration of an antibody in rodents, abrogates the protective effect of exercise on neural injury [44]. More generally speaking, cardiovascular fitness has been associated with increased cerebral blood flow [45] as well as decreased age-related cortical atrophy [46].

Physical activity is associated with reduced risk of dementia in several observational studies of non-demented individuals [47, 48] as well as individuals with MCI [49, 50], though not in all studies [51]. A systematic review and meta-analysis of 21 longitudinal cohort studies on physical activity and dementia risk found that non-demented participants with higher physical activity levels had 14% decreased risk of dementia compared to non-demented participants with lower activity levels. Furthermore, a meta-analysis of 17 longitudinal cohort studies found that higher levels of physical activity were protective against cognitive decline. It should be noted that a heterogeneous mix of studies were included in the review, with follow-up times ranging from 1 to 26 years for dementia and 1 to 21 years for cognitive decline. Sensitivity analysis limited to studies with follow up time 10 years or longer still found a smaller protective effect of physical activity on both dementia and cognitive decline [52•]. It is unclear from the existing data whether one form of physical activity is better than another (i.e., aerobic vs resistance training vs stretching/ toning activities, such as yoga or tai chi) in terms of reducing risk of dementia [34•].

Though overall, the evidence from prospective studies is suggestive, reverse causation remains a possibility. Motor changes and physical decline following dementia onset are expected sequelae of disease pathogenesis. For physical inactivity to be a potential modifiable causal factor for dementia, temporality has to be clearly established. Furthermore, there is evidence that a decline in gait speed may precede dementia onset by as much as 7 years [53]. It is possible that decreased physical activity may be part of the preclinical prodrome before a dementia diagnosis or even a MCI diagnosis is made. Additionally, the relationship between physical activity and dementia risk might be confounded by other factors, such as causal or protective genetic factors or environmental factors such as sunlight exposure/vitamin D levels. Nevertheless, accounting for some of these potential causal or protective genetic factors, a twin-study in a Finnish cohort found that vigorous physical activity was associated with reduced risk of dementia in later life [54]. Similarly, a New York study found that physical activity and MeDi were each independently associated with reduced risk of AD [47].

RCTs of physical activity interventions in cognitively intact participants have had mixed results. Lifestyle Interventions and Independence for Elders (LIFE), a randomized controlled trial (RCT) of 1635 older sedentary adults randomized to either 24-months of moderate-intensity physical activity (walking, resistance training, and flexibility exercises) or health education, found no differences between the groups in terms of cognitive outcomes [55•]. Smaller RCTs have found positive effects of aerobic exercise [56, 57] and resistance training [58] on cognition. Results are pending from the EXERT (Exercise in Adults with Mild Memory Problems) trial (NCT02814526), an ongoing trial which randomizes 300 participants with mild memory problems and functional impairment (CDR 0.5) to either a moderate-to-high intensity aerobic training program or a stretching-balance-range of motion exercise program, to assess the effects of physical activity on cognition, functional status, brain atrophy, blood flow, and CSF biomarkers of AD.

Based on an evaluation of 19 RCTs rated as having low or medium risk of bias, a recent AHRQ systematic review concluded that there is encouraging but inconclusive evidence that physical activity may delay or slow age-related cognitive decline. It also concluded that there is insufficient evidence whether increasing physical activity prevents, delays, or slows MCI or clinical Alzheimer's-type dementia, despite suggestive associations seen in observational studies. Of note, 18 of the RCTs included in the review were of short duration (lasting 1 year or less) [34•]. Further research is needed, which focuses on a cognitively intact population, includes longer follow-up, and clearly distinguishes between different forms of physical activity.

Sleep and Dementia

Over half of the elderly endorse sleep complaints most of the time, while fewer than 20% rarely or never have sleep complaints [59]. The high prevalence of sleep dysfunction and the existence of interventions to improve sleep make sleep an attractive target for attempts at risk modification for the primary prevention of dementia in the elderly. While abundant cross-sectional evidence suggest a linkage between poor sleep and poor cognition [60–64] as well as dementia [63, 65], longitudinal studies, especially those employing objective measures of sleep, are much fewer in number. In contrast to dietary patterns and physical activity, there have been no RCTs to date on sleep interventions for the primary prevention of dementia. Due to the lack of RCT evidence establishing causality, it is particularly unclear whether sleep dysfunction precedes dementia and is a potential modifiable risk factor for dementia, or whether sleep dysfunction is merely one of the sequelae of dementia.

Despite this ambiguity, multiple mechanisms have been proposed for how sleep dysfunction could mediate the development of dementia, making a causal relationship both plausible and coherent. Sleep deprivation may activate non-specific immune parameters and induce a state of low level systemic inflammation [66•], affect synaptic remodeling [67], or decrease clearance of neurotoxic metabolites [68•]. Specifically, sleep deprivation may decrease amyloid clearance [68•] or alter normal amyloid metabolism [69•]. Active immunization with AB42 in a study using the APPswe/PS16E9 murine model actually normalized both the sleep-wake cycle and diurnal fluctuation of interstitial fluid ABeta [70]. In a small study of 26 cognitively normal participants, sleep deprivation for one night counteracted the physiologic decrease in CSF AB42 in the morning, which may contribute to AB42 accumulation over time [69•]. Similarly, in participants with indwelling lumbar catheters, those deprived of sleep for 36 h had increased CSF AB38, AB40, and AB42 levels by 30%, as compared to a normal sleep control group and a sleep induced with sodium oxybate group [71•].

Emerging cross-sectional evidence also links self-reported sleep dysfunction (as measured by questionnaire) with increased amyloid burden in the brain, both on PET Amyloid imaging [72], and on CSF biomarkers for AD [73•]. Betaamyloid burden in the medial prefrontal cortex may impair non-REM slow wave activity, which could disrupt memory consolidation [74] and has been associated with lower CSF AB42 levels [75]. In contrast to these findings, another study found that decrease in REM sleep % was associated with worse performance on some cognitive tests (but not the MMSE) [62]. This study did not include amyloid imaging and it remains unclear whether impairment of particular stages of sleep increases risk of dementia.

Additionally, sleep-disordered breathing (SDB) may cause intermittent hypoxemia to the brain. A review of 16 crosssectional and two longitudinal studies found that most studies found associations between SDB and cognition. The authors postulate a microvascular model, in which chronic intermittent hypoxemia leads to a vasculopathy and subsequent cognitive decline [63]. It is also possible that apnea may affect the interaction between glymphatic flows of metabolites from ISF into CSF [76]. These prior findings are consistent with a recent cross-sectional study of 580 participants which found associations with SDB indices with cognitive impairment [60].

In light of these findings, a recent editorial in neurology suggested that evaluation of cognitive impairment in the elderly should include asking questions about SDB, and an evaluation for SDB in the elderly should include a screen for cognitive impairment [77•]. There is a lack of uniformity in the literature for how sleep dysfunction is assessed. Many studies use subjective sleep questionnaires. One large cohort study of 1041 participants found significant associations between self-reported sleep inadequacy and daytime sleepiness with dementia [78]. The concordance, however, between self-reported sleep disturbance and objective sleep measures is unclear and likely varies depending on the specific questionnaire. Nevertheless, subjective sleep dysfunction likely captures some general aspect of objective sleep dysfunction. Other studies use proxies such as wrist actigraphy for the gold standard of polysomnography, and again, may not accurately capture specific domains of sleep dysfunction.

Longitudinal studies which also use objective sleep measures are limited (see Table 2 for a selective list of studies). One longitudinal study of 966 participants found no relationship between obstructive sleep apnea (OSA) on polysomnography and later-life impaired cognition [79]. Another longitudinal study of 321 participants found that decreased REM sleep % on polysomnography was associated with increased risk of dementia [80]. While there is some suggestive evidence that sleep dysfunction may lead to development of dementia, overall, there is a lack of uniformity in how the studies were conducted, making interpretation of findings challenging. Furthermore, while it is plausible that treating sleep problems may improve cognition and/or decrease dementia risk, studies testing this hypothesis are limited. One RCT found a modest improvement on some cognitive measures in mild AD patients after CPAP [81]. It remains unclear whether sleep intervention before dementia onset could attenuate future risk of developing dementia. Theoretically, chronic sleep deprivation could lower the threshold for development of AD, by being a causal partner as one component of a sufficient cause for AD, possibly through decreased clearance of beta-amyloid. Further research is needed to tease out the complex relationship between sleep and dementia.

Multimodal Interventions and Dementia

Several major RCTs have involved multimodal interventions. The Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA) randomized 3526 participants to either a nurse-led multi-domain intensive vascular care group or a usual care control group. Specifically, participants visited a nurse every 4 months for assessments of cardiovascular risk factors, including smoking habits, diet, physical activity, weight, and blood pressure. Participants were given tailored counseling regarding lifestyle depending on their results. After 6 years, no significant difference in incident dementia was found between the two groups, and the authors speculate that this may in part be due to the high standards of care provided in the usual care group [82].

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study randomized 1260 individuals in Finland aged 60–77 years with cardiovascular risk factors and cognitive abilities at the mean or slightly lower to receive either a 2-year multimodal intervention involving diet, exercise, cognitive training and vascular-risk monitoring (experimental arm), or general health advice (control arm). The dietary component emphasized consumption of fruit and vegetables, wholegrain cereal products and low-fat milk, and meat products; sucrose intake limited to 50 g/day; vegetable margarine and rapeseed oil instead of butter; and at least two portions of fish per week. Relative to the control group, the multimodal intervention resulted in improved cognitive function among these individuals at high risk for cognitive decline [83].

Another multimodal intervention studying the effect of modifiable lifestyle factors on cognitive decline was less encouraging. The Multimodal Alzheimer Preventive Trial (MAPT) included 1680 non-demented individuals who either endorsed a spontaneous memory complaint to their physician or had limitations in one ADL or slow gait speed. Participants were randomized to one of four arms of a 3-year intervention: a multidomain intervention (43 2-h sessions combining cognitive training, physical activity, and nutrition, along with three preventive sessions to reduce cardiovascular risk factors) plus omega-3 polyunsaturated fatty acids, the same multidomain intervention plus placebo, omega-3 polyunsaturated fatty acids alone, or placebo alone. The nutrition component of the multidomain intervention consisted of 15 min every 2-h session of nutritional advice based on guidelines established by the French National Nutrition and Health Programme. In contrast to FINGER, in MAPT, no significant difference in cognitive decline was identified between the placebo group and any of the intervention groups [84]. The reasons for discrepant findings in FINGER and MAPT are uncertain but could in part relate to participant selection, intervention intensity, or adherence [85].

Conclusions

The study of lifestyle modifications on dementia risk is inherently challenging for multiple reasons. Many lifestyle factors are difficult to evaluate using the RCT, which is the gold standard for assessment of causality. Loss to follow-up is of concern and lack of long-term adherence to drastic dietary changes may be more likely than compliance with taking a PO investigational agent. RCTs of short duration may not be adept at detecting effects of long-term interventions such as physical activity on dementia risk. Moreover, some potential risk factors, particularly sleep patterns, may reflect early symptoms of dementia rather than being in a potential causal pathway, and some longitudinal cohort studies may capture sleep only in aging or among the elderly. Due to the lack of RCTs examining sleep interventions in a cognitively intact population (as compared to studies on diet and physical activity), the directionality of the association between sleep dysfunction and cognitive impairment is particularly unclear; however, emerging evidence linking short-term sleep deprivation with altered beta-amyloid metabolism is certainly intriguing and offers a plausible mechanism by which chronic sleep problems could contribute to elevated dementia risk in the long-term. Lastly, lifestyle modifiable factors are closely related to other cultural habits and social behaviors, which may act as confounders of the true relationship between the lifestyle factor itself and risk for dementia.

The AHRQ has made specific recommendations for methodological improvements for future studies on preventing cognitive decline and dementia, including [34•]: increasing participation of underrepresented populations, identifying higher risk individuals and tailoring interventions, beginning interventions at younger ages, increasing length of follow up, using consistent cognitive outcome measures across trials, integrating cognitive outcome measures into trials with other primary purposes, including biomarkers as intermediate outcomes, and conducting large-scale trials to test the effectiveness of an intervention in a community or clinical practice setting. By making these methodological improvements, we may improve internal validity, increase external validity, and overall increase our likelihood of distinguishing the true causal effects of lifestyle factors on dementia risk. In addition to improving clinical trial design, it remains worthwhile to conduct observational studies of large cohorts, for the advantages of long-term follow-up, the possibility of examining interactions between multiple lifestyle factors, and to address issues ofgeneralizability of findings via replication studies in different populations.

In summary, there is strong observational evidence and encouraging but inconclusive results from some RCTs that certain aspects of nutrition may impact risk for dementia in late life. Similarly, there is strong observational data that physical activity may impact risk for dementia; however, RCTs of physical activity as a short-term intervention have yielded mixed results. Regarding sleep, there is again strong observational data linking sleep dysfunction and dementia risk. Furthermore, emerging evidence linking sleep dysfunction with brain amyloid burden strengthens a potential causal relationship between sleep dysfunction and dementia, with amyloid acting as a potential mediator. Despite these intriguing findings, it remains unclear whether intervening in sleep dysfunction can impact long-term dementia risk.

As clinicians, it is reasonable to make recommendations to our patients to adopt certain dietary changes and to engage in regular physical activity to improve cardiovascular risk factors for dementia. Moreover, there are myriad non-neurological health benefits to such recommendations. Furthermore, given the common co-occurrence of cognitive impairment and sleep dysfunction in the elderly, cognitive evaluations in the elderly should also include questions on sleep.

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Table 1

Selected RCTs of dietary/multimodal interventions and cognition/dementia risk

Study	Participants	Dietary intervention	Outcome	Results
Andrieu 2017 MAPT (NCT00672685)	1680 non-demented participants aged 70+ who are cognitively at risk	Multidomain intervention (cognitive training, physical activity, nutrition counseling) + omega-3 vs multidomain intervention + placebo vs omega-3 vs placebo alone	Cognitive test composite score	No significant differences in 3-year cognitive decline were found between those receiving the interventions (multidomain, omega 3) and those receiving placebo.
Appel 1997 DASH (NCT00000544)	459 participants ages 22+ with SBP <160 and DBP 80 to 95, who are not on anti-hypertensive medications	High fruit and vegetable diet vs combination diet (high fruit and vegetable + low fat dairy + reduced fat) vs control diet (typical of average US diet: low fruits, vegetables, dairy, higher fat)	Blood pressure	Combination diet reduced SBP by 5.5 points, DBP by 3.0 points, more than control diet. High fruit and vegetable diet reduced SBP by 2.8 points, DBP by 1.1 points, more than control diet. Significantly, these reductions occurred after 2 weeks of dietary intervention, and were maintained over the next 6 weeks.
Knight 2016 MEDLEY (ACTRN12613000602729)	137 participants from a non-Mediterranean population	MeDi vs habitual control diet	Neuropsychological test battery	MeDi group did not perform significantly better than the group on habitual diets for executive functioning, speed of processing, memory, visuospatial ability, and overall age-related cognitive performance.
Martinez-Lapiscina 2013 PREDIMED-NAVARRA* (ISRCTN35739639)	522 participants with high vascular risk	MeDi + EVOO or mixed nuts vs low-fat control diet	MMSE clock drawing test	MeDi intervention (supplemented with either EVOO or nuts) resulted in higher MMSE scores and CDT scores, compared to a low-fat control diet. * Recently retracted and republished in the NEJM with new analyses, which showed similar though weaker results and similar
Moll van Charante 2016 PREDIVA (ISRCTN29711771)	3526 participants recruited from general practices	Nurse-led multidomain cardiovascular intervention Vs Usual care	Dementia disability score	No difference in incident dementia or disability was observed between groups, after 6 years of intervention.
Morris 2017 MIND (NCT02817074)	600 participants without cognitive impairment, who are overweight and have suboptimal diets.	MIND diet + mild caloric restriction vs usual diet + mild caloric restriction	Global cognitive score (based on 12 cognitive tests) MRI brain volume measures (total, hippocampal)	Pending
Ngandu 2015 FINGER (NCTO1041989)	1260 participants recruited from national surveys, with cardiovascular and dementia risk factors	Multidomain intervention (nutritional advice, exercise, cognitive training, vascular risk factor monitoring) vs general health advice	Neuropsychological test battery	Multidomain intervention had a significant effect on cognitive test performance, compared to the control group.

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Table 2

Selected studies of sleep and cognition/dementia risk

Study	Participants	Sleep measure	Outcome	Results
Cohen-Zion 2001 Longitudinal	46 community dwellers	In-home modified respitrace system pulse oximetry Self-report EDS (excessive daytime sleepiness), snoring	MMSE	Increased daytime sleepiness is associated with worse MMSE, over a 3 year follow-up Hypoxemia, snoring, are not associated with changes in MMSE
Lim, AS 2013 Longitudinal	698 non-demented adults	Actigraphy	Cognitive testing (global cognitive composite measure)	More sleep consolidation (less interruption of sleep by awakenings) attenuates effect of APOE-E4 allele on dementia risk
Lutsey 2016 Longitudinal	966 participants in the ARIC study	Polysomnography in-home	Cognitive testing	No association between severity of OSA, degree of nocturnal hypoxemia, sleep fragmentation, habituation duration, and cognitive decline No association between OSA severity and cognition
Ooms, S 2014 RCT	26 cognitively normal middle-aged men with normal sleep I: Total sleep deprivation ×24 h(n = 13) P: Unrestricted sleep (n = 13)	Polysomnography Sleep questionnaire (PSQI)	CSF biomarkers for AD (AB42, AB40, p-Tau, t-Tau, total protein)	Unrestricted sleep leads to a morning 6% physiologic decrease in CSF AB42, while sleep deprivation counteracted this decrease
Pase, M 2017 Longitudinal	321 participants from a subset of offspring of participants from the Framingham Heart Study	Polysomnography in-home	Dementia MMSE Cognitive testing	Higher REM sleep % is associated with decreased risk of incident dementia NREM sleep is not associated with dementia risk
Tsapanou, A 2015 Longitudinal	1041 non-demented participants from WHICAP	MOS-SS	Dementia	Sleep inadequacy is associated with increased risk of dementia in unadjusted and adjusted models. Daytime sleepiness is associated with increased risk of dementia in the adjusted model
Yaffe, K2011 Longitudinal	298 non-demented women in the community	Polysomnography in-home	Dementia MMSE Cognitive testing	Women with SDB had increased odds of developing MCI/dementia over 5 years of follow-up Sleep fragmentation, sleep duration, are not associated with MCI/ dementia