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Dietary Patterns Associated with Alzheimer's Disease and Related Chronic Disease Risk: A Review

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Dietary Patterns Associated with Alzheimer's Disease and Related Chronic Disease Risk: A Review

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Abstract

The world's population is growing older due to improved healthcare and nutrition. As a result, Alzheimer's disease (AD) prevalence is rapidly increasing. The focus of the current research climate is shifting from understanding AD pathology and diagnosis to primary prevention and intervention strategies. Diet represents one potential intervention strategy accessible to all. Accumulating evidence suggests diet plays a major role in risk and development of AD and AD-related chronic diseases of the periphery like cardiovascular disease (CVD) and diabetes. This paper reviews studies that have explored the relationship between "a priori" dietary patterns, AD and AD-related chronic disease risk. The dietary patterns we will review are the healthy eating index, healthy diet indicator, recommended food score, and the Mediterranean diet (MeDi).

Our review of the literature suggests a generally positive association between healthy diet patterns, AD and AD-related chronic disease risk; however the magnitude of the protective effect is modest in many studies. Consequently, we can only confidently conclude that the MeDi is associated with reduced AD risk, and further studies on the remaining indices need to be carried out. It is our opinion that a combination of dietary scores could predict overall dietary quality and chronic disease risk to a greater extent than one score individually.

Analysis in multi-ethnic cohorts, investigating combinations of scores must be completed before firm conclusions can be reached on the ideal combination of scores.

Obtaining further insight into the association between dietary patterns, AD and AD-related chronic disease risk may help in prioritizing public health efforts and provide a stronger basis for recommendations to improve dietary patterns.

Keywords: Dietary patterns; Alzheimer's disease; Chronic disease; Cardiovascular disease; Diabetes; Obesity; Coronary heart disease; Healthy diet indicator; Healthy eating index; Recommended food score; Mediterranean diet

Introduction

Diet plays a major role in the risk and development of neurodegenerative diseases such as Alzheimer's disease (AD [1-3]) and chronic diseases of the periphery like cardiovascular disease (CVD) and diabetes. Accumulating evidence indicates CVD and diabetes are risk factors for AD [4-11].

Individuals consume diets that contain both nutrient and non-nutrient substances rather than single foods. Consequently, misleading conclusions on the effect of consumption of a single nutrient, food or dietary component on health outcomes can be drawn. It may be more useful to examine indices of food and nutrient intake that express several related aspects of diet concurrently rather than focus on consumption of single nutrients [12].

The purpose of this review is to examine the published literature to evaluate approaches for measurements of diet quality and dietary patterns, and their association with AD and AD- related chronic disease risk. This review focuses on theoretically defined dietary patterns, created 'a priori' based on current nutrition knowledge [1]. There are other, 'a posteriori', methods to produce dietary patterns, including principle components analysis and reduced rank regression. These patterns are not discussed in this review due to their differences when compared to „a priori' methods, their exploratory nature, and their limitations [13]. Posterior methods are based on complex statistical analyses that require investigator led selection of a limited number of components to summarise the food patterns. The identified patterns also depend on the study cohort, thereby limiting comparison between studies [14].

This review aims to address the following questions; 1) Do dietary indices reflect the multidimensional nature of diet quality? 2) Are higher index scores associated with reduced Alzheimer's disease risk? 3) Is there a dietary score more predictive of Alzheimer's disease and related chronic disease risk? Obtaining insight into the association between habitual dietary patterns, AD and AD-related chronic disease risk will lead to prioritizing public health efforts and provide a stronger basis for recommendations to improve dietary patterns.

Background and Calculation of each Dietary Index

Healthy Eating Index (HEI)

The HEI is a summary measure of diet quality that was developed by Kennedy et al. [15] to incorporate nutrient needs and dietary guidelines

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for the US consumer into one measure that can be used as a basis for nutrition promotion activities by the US Department of Agriculture (USDA). It is based on a ten-component system of five food groups, four nutrients, and a measure of variety in food intake. Each component has a score from zero to ten, giving a total possible score of 100; Table 1 shows the components and scoring criteria. The number of foods used in the HEI is limited and the HEI does not provide information about specific foods [16]. Publication of an update to the dietary guidelines in 2005 necessitated the revision of the HEI, and so the HEI-2005 was formed. Changes in the HEI-2005 include: separating vegetables into two groups (total vegetables, and dark green and orange vegetables and legumes), making two groups for grains (total grains, and whole grains), removing the variety component and including consumption of oils [17]. McCullough et al. [18] altered the HEI to form the Alternate HEI (AHEI) which emphasizes: the diet content of fruit and vegetables, nuts and soy, cereal fibre, the ratio of white to red meat, and prolonged use of multivitamin supplements. In 2005, Shatenstein et al. [19] adapted the HEI to Canadian dietary guidelines. The Canadian Healthy Eating Index (CHEI) has nine components each worth ten points, except the fruit and vegetables component which is worth 20 points. Like the original HEI, the CHEI has a maximum of 100 points.

Recommended Food Score (RFS)

Kant et al. [20] developed the RFS to measure overall diet quality in the Breast Cancer Detection and Demonstration project. The RFS is based on reported consumption of foods recommended by current dietary guidelines. Due to the measurement error associated with quantity of foods reportedly consumed, they designed the RFS to be independent of reported amounts. Current dietary guidelines emphasise consumption of fruits, vegetables, whole grains, lean meats or meat alternatives, and low fat dairy, therefore all questionnaire items corresponding to these groups contributed to the score. The RFS was calculated as the sum of 23 items from food frequency questionnaires (FFQ), corresponding to dietary guidelines, subjects consumed at least once a week.

Healthy Diet Indicator (HDI)

The HDI was calculated using the dietary guidelines for the prevention of chronic disease, defined by the World Health Organisation [21]. A dichotomous variable is generated for each food group or nutrient that is included in these guidelines. If a person's intake is within the recommended range this variable is coded as 1; otherwise it is coded as 0. The HDI is the sum of all these dichotomous variables (Table 2).

Mediterranean Diet (MeDi)

The MeDi is characterized by a high intake of vegetables, legumes, fruits, cereals, fish and unsaturated fatty acids (mostly in the form of olive oil), low intake of saturated fatty acids, meat and poultry, low-to-moderate intake of dairy products (mostly cheese and yoghurt), and a regular but moderate amount of alcohol (mostly wine and generally with meals). This diet includes many dietary components reported to be beneficial in reducing neuronal degenerative disease risk [22-29], and therefore has received much attention. The MeDi has been associated with lower risk for dyslipidemia [30,31], hypertension [30-33], abnormal glucose metabolism [31,32] and coronary heart disease (CHD; [27,31,34,35]). To construct the MeDi score, an individual is assigned a value of 1 for either (a) - each beneficial component

Component Number	Component	Range of Score	Criteria for Minimum Score of 0	Criteria for Maximum Score of 10
1	Grains (servings/d)	0 - 10	0	6 - 11 [ab]
2	Vegetables (servings/d)	0 - 10	0	3 - 5 [ab]
3	Fruits (servings/d)	0 - 10	0	2 - 4 [ab]
4	Milk (servings/d)	0 - 10	0	2 - 3 [ab]
5	Meat (servings/d)	0 - 10	0	2 - 3 [ab]
6	Total Fat (% of total energy)	0 - 10	≥ 45	≤ 30
7	Saturated Fat (% of total energy)	0 - 10	≥ 15	< 10
8	Cholesterol (mg/d)	0 - 10	≥ 450	< 300
9	Sodium (mg/d)	0 - 10	≥ 4800	< 2400
10	Variety (number of different food items consumed over 3 days)	0 - 10	≤ 6	16

Abbreviations: servings/d, servings per day; mg/d, milligrams per day

[a]Depends on recommended energy intake. [b]Individuals with intake between the minimum and maximum ranges were assigned scores proportionately (15).

Table 1: HEI scoring criteria.

	Dichotomous Value	
Nutrient or food group (daily intake)	**1**	**0**
Saturated fatty acids (% of total energy)	0 – 10	> 10
Polyunsaturated fatty acids (% of total energy)	3 - 7	< 3 or > 7
Protein (% of total energy)	10 - 15	< 10 or > 15
Complex carbohydrates (% of total energy)	50 - 70	< 50 or > 70
Dietary fibre (g)	27 - 40	< 27 or > 40
Fruits and vegetables (g)	> 400	< 400
Pulses, nuts, seeds (g)	> 30	< 30
Monosaccharides and disaccharides (% of total energy)	0 – 10	> 10
Cholesterol (mg)	0 – 300	> 300

Abbreviations; g, grams; mg, milligrams (73)

Table 2: Criteria used for calculating HDI.

(fruits, vegetables, legumes, cereals, and fish) if the caloric-adjusted consumption was at or above the gender-specific median or (b) - each detrimental component (meat and dairy products) where caloric-adjusted consumption was below the gender-specific median or (c) - for a ratio of monounsaturated fats to saturated fats at or above the median. Individuals are also assigned a value of 1 for mild to moderate alcohol consumption (>5 to <25 g/d for females and >10 to <50 g/d for males); scores are summed to generate the overall score. The MeDi score ranges from 0 to 9, with a higher score indicating a greater adherence to the MeDi.

Comparing MeDi scores between studies is difficult, as study specific median cut offs are commonly used. Non-Mediterranean cohorts are less likely to adhere strictly to a diet typical of Mediterranean countries, meaning subjects with high MeDi adherence may be categorized as low MeDi adherence compared with Mediterranean populations. Despite this, such studies provide support for the notion that beneficial effects of the MeDi are extended to different populations [35-37].

Cognition and Diet Indices

Cognitive decline is the progressive loss of cognitive functions, including memory, and may lead to dementia of which AD is the most common type, accounting for 60-80% of cases [38]. Cognitive decline may however lead to other types of dementia, including vascular dementia, dementia with Lewy bodies and fronto-temporal dementia. Wengreen et al. [39] analysed the dietary data of 3634 men and women from the Cache County Study on Memory and Aging; they computed a RFS (57 items, 1 point for consumption ≥ 1-3 times/month) and a non recommended food score (NRFS; calculated using the following foods consumed ≥ 3 times/week; processed meats, refined bread and grains, French fries and chips, and sweets). A higher RFS score was associated with better cognitive test scores. Those in the highest quartile of RFS scored 1.80 points higher on the baseline Modified Mini-Mental State Examination than those in the lowest quartile of RFS ($p<0.001$). The difference between the RFS quartile groups widened over 11 years of follow up; those with the highest RFS declined by 3.41 points compared with a 5.2 point decline by those with the lowest RFS. This effect more than doubled when individuals were stratified for carriage of an Apolipoprotein (APOE) ε4 allele (the most common genetic risk factor for AD). The majority (90%) of participants in this study are members of the Church of Jesus Christ of the Latter-day Saints (Mormon) religion, which discourages drinking alcohol or smoking, and low smoking and drinking rates are observed in the study participants. The low smoking rate is likely to contribute to the increased longevity and low burden of chronic disease. The RFS was associated with many diet and lifestyle factors, and thus it is not possible to determine whether the observed effects on cognition are conferred by nutrients provided by diet or from other behaviours that may be associated with diet quality and variety among the elderly.

A study by Huijbregts et al. [40] using the same Seven Countries Study that was used to develop the HDI, showed, in four of the five cohorts, a healthy diet is associated with a reduced prevalence of mild cognitive impairment (MCI; MCI often but not always precedes AD). However, there was a lack of variation in dietary intake, and therefore the HDI in Finland and the Netherlands only ranged from 0 - 5, and in the Italian cohorts only from 0 - 7; the strongest association between MCI and HDI being observed in the Italian cohorts. In east Finland, men with a healthier diet had lower cognitive functioning cross-sectionally; this implies somewhat counter intuitively that healthier diets are associated with impaired cognition. However CVD mortality was high in this cohort, and consequently over the past 20 years the geographical area has been subjected to a health education campaign aimed at improving dietary habits. Therefore, it is possible that the former unhealthy habits were contributing to the cognitive decline, and the present improved diet is due to the health campaign.

Corrêa Leite et al. [41] verified the result of Huijbregts et al. [40] in 1651 subjects in northern Italy. They found that higher HDI is significantly associated with better cognitive performance in the elderly. Both of these reports are limited due to the cross-sectional nature of the data. Cross-sectional studies do not differentiate between cause and effect, so there is a real possibility that cognitive impairment could influence dietary habits.

Scarmeas et al. have published several papers on MeDi and AD in an American population [23,24,26]. In these studies they have found that higher adherence to the MeDi is associated with lower risk for AD and slower cognitive decline. In 2009, they reported that higher adherence to the MeDi was associated with lower risk of developing MCI and MCI conversion to AD [25]. However, overall dietary measurement error may be increased by inaccuracies in dietary reports by subjects with cognitive problems, and differential adherence to MeDi could be an indirect index of AD severity. A cross-sectional Australian study reported that healthy controls had a higher adherence to the MeDi than MCIs and AD participants. This study included 723 healthy controls, 98 MCIs and 149 ADs from the Australian Imaging, Biomarkers and Lifestyle study of ageing. The MeDi in the healthy control group was associated with change in Mini-Mental State Examination score over an 18-month time period, suggesting that diet is not confounded by cognitive performance and giving greater confidence in cognition and MeDi study results [42]. In a French study of 1410 individuals aged 65 and over, without dementia at baseline and with a follow up assessment within five years, it was observed that each additional unit of the MeDi score was associated with fewer Mini-Mental State Examination errors at follow up [43].

By contrast, the Personality and Total Health (PATH) through life study observed that greater adherence to MeDi was not protective against cognitive decline. The apparent lack of protection could be explained by the heterogeneous nature of the study population. Furthermore, only 66 participants from the original 1528 demonstrated any cognitive decline in the four year follow up; a limitation with respect to sufficient statistical power to detect the MeDi effects. The primary outcomes of the study were MCI, a clinical dementia rating of 0.5, or any mild cognitive disorder at follow up [44].

A prospective study by Gu et al. [45] concluded that a favourable association between higher adherence to MeDi and lower risk of AD did not seem to be mediated by high sensitivity C- reactive protein (index of systemic inflammation), fasting insulin or adiponectin (indices of metabolic profile). While biomarker levels were only measured at baseline, it has been shown that circulating levels of these biomarkers are relatively stable over three years [46,47]. Other aspects of the inflammatory and metabolic pathways were not captured by the biomarkers measured by Gu et al. [45] and may however, be relevant to the observed MeDi-AD association, for example α1-antichymotrypsin and interleukin-6.

A cohort of 3790 individuals from Chicago aged 65 or over, followed for 7.6 years has shown the MeDi to be associated with slower rates of cognitive decline, but no such associations were observed for HEI scores. Cognitive testing was however, limited and comprised of four tests completed every three years [48].

The CHEI was used to assess diet quality and its association with cognitive data in the Québec Longitudinal Study on Nutrition and Successful Aging (NuAge). Cognition was assessed at four annual visits using the Modified Mini-Mental State Examination and the CHEI was calculated from a 78-item FFQ. In 1488 adults aged 67-84 years of age, females had a higher CHEI (78.7 ± 9.1 verses 75.7 ± 9.4 in males, $p<0.0001$). Total CHEI was not associated with cognition either at baseline or over the three year follow up. Poor quality of diet was associated with the less educated, smokers, those with poor social engagement, symptoms of depression, a higher waist: hip ratio and those who reported financial insecurity.

This demonstrates a relationship between diet quality and risk factors for chronic diseases associated with cognition. Cognitive decline was modest in this cohort, which could be explained by the cohort being recruited as a relatively healthy, cognitively intact group at a high functioning level, compared to cohorts used by Scarmeas et al. and Wengreen et al. which were from wider, population based samples [49]. Risk factors for AD are increasingly found to be similar to those for vascular dementia [50]. Dietary patterns and preferences for different foods are similar in patients with vascular dementia or AD. A study where two groups of patients were compared with elderly normal controls, found that AD patients had a greater preference than normal controls for sugar and sweet foods, but did not significantly differ in preference for foods high in complex carbohydrates and protein. This "craving" for sweet foods was also present in vascular dementia patients [51]. The Rotterdam study with an average follow up of six years, found that light-to-moderate alcohol consumption is associated with a reduced risk of dementia (AD, vascular and other dementia) in individuals aged 55 years or older, this effect seems to be unaffected by the source of the alcohol [52]. Due to similar risk factors, including hypertension, diabetes, atrial fibrillation and atherosclerosis, it can be hypothesized that dietary patterns which predict risk for AD should also predict risk for vascular dementia. However, to our knowledge, there have been no studies conducted examining the relationship between the MeDi and risk of vascular dementia. Table 4 (Included as supplementary data) has a summary of all studies reviewed in this section.

Cardiovascular Disease and Diet Indices

Accumulating evidence suggests that many CVD risk factors may also directly influence AD risk [53,54]. The cluster of cardiovascular risk factors known as "metabolic syndrome", i.e. abnormalities in insulin, glucose and lipoprotein metabolism, hypertension and abdominal obesity, have been long recognized to be associated with AD [55]. Mid-life obesity has been associated with future dementia [56] and temporal lobe atrophy [57] in a number of longitudinal studies. The most widely used cholesterol lowering drugs (statins) have been shown to reduce amyloid beta (Aβ) burden in animal models [58] and may reduce the risk or slow the progression of early stage AD [59-61]. Increased high density lipoprotein (HDL) levels are known to reduce CVD risk and are also inversely associated with plasma Aβ levels, indicating that HDL may be an important clearance transport protein for Aβ [62]. Apolipoprotein E (apoE) is one of several different classes of apolipoproteins which transport lipids in plasma and cerebrospinal fluid (CSF). The importance of apoE in CVD has been recognised for many years [63-66]. ApoE2 and apoE3 are preferentially located on HDL, and are known to bind and clear Aβ in vitro, whereas apoE4 is linked to enhanced amounts of diffuse Aβ42 plaques in the brain [67]. The mechanism by which apoE4 protein leads to this is poorly understood, but it seems to be associated with the steady-state levels of Aβ peptides, presumably due to its inability to clear Aβ from the brain [67]. Elevated plasma homocysteine levels have been associated with increased risk of carotid atherosclerosis and stroke [68]. Both carotid atherosclerosis and stroke have been shown to increase the risk of AD [69]. In the Nurses Health Study [70] of 67,272 females who were free of cancer, diabetes and vascular disease at baseline, participants with a higher HEI score were not at lower risk overall of major chronic disease during the 12 year follow up period. Being in the highest HEI quintile was associated with a 14% reduction in CVD risk (Relative Risk (RR): 0.86; 95% Confidence Interval (CI): 0.72 - 1.03), but there was no association with cancer risk.

The same authors also completed a study to investigate whether HEI scores predict chronic disease risk in 51,529 men [71]. They observed a weak inverse association between HEI score and risk of chronic major disease (comparing highest with lowest quintile of the HEI, RR: 0.89; 95% CI: 0.79 - 1.00; p for trend <0.001). Men in the highest HEI quintile were 28% less likely to develop CVD than those in the lowest HEI quintile. It was speculated that HEI scores can differ depending on the method of collection of dietary intake. Consequently, 127 randomly selected cohort members had two sets of weighed, seven-day food records collected six months apart, and scores between the two methods were found to not be significantly different. Another possible explanation for the modest findings is that important food components are not represented by the HEI, or that some components of the HEI are not important in relation to major chronic disease risk. Interestingly, these studies used the diagnosis of chronic disease (defined as CVD, cancer, or death, whichever came first) as the end point whereas other studies typically have used mortality as an end point. Case fatality can be influenced by early diagnosis, access to optimal medical care, and compliance to treatment, so the use of mortality as an end point is potentially confounded by behaviours that are difficult to measure or control. Therefore, studies with diagnosis of chronic disease and mortality as end points cannot be compared directly. Both cohorts were well educated, had a relatively homogenous socioeconomic status and were mostly Caucasian. The homogeneity increased the internal validation of the study by reducing confounding factors that are hard to measure. However, this homogeneity also provides little information on the ability of the HEI to predict lower chronic disease risk in other racial or educational backgrounds [70,71]. Chiuve et al. [72] used the AHEI to estimate the burden of CHD that could potentially be avoided through a healthy lifestyle, for the Health Professionals follow-up study. With the exception of multivitamin use, the AHEI components were given a score of 0-10. The seven specific components were as follows: percent energy from trans fat (≥ 4%, ≤ 0.5%), ratio of polyunsaturated: saturated fat (≤ 0.1, ≥ 1), ratio of chicken plus fish: red meat (0, ≥ 4), daily servings of fruit (0, ≥ 4), vegetables (0, ≥ 5), and grams of cereal fibre (0, ≥ 15). The eighth component, multivitamin use for ≥ 5 years, was dichotomous to avoid overweighting this component (yes=7.5, no=2.5 points). Men in the low-risk group for all five lifestyle practices (low risk lifestyle practices include: (1) absence of smoking, (2) body mass index <25 kg/m^2, (3) moderate-to-vigorous activity ≥ 30 minutes per day, (4) moderate alcohol consumption (5 to 30 g/d), and (5) the top 40% of the distribution of the AHEI) had an RR of 0.37 (95% CI: 0.26 - 0.53), compared with the remaining men in the population. This translates to a population-attributable risk of 62% (95% CI: 49%, 74%); therefore 62% of coronary events may have been avoided by adhering to the five low risk lifestyle practices. A combination of healthy lifestyle characteristics was strongly inversely associated with risk even among men taking medication for coronary risk factors (among men taking medication for hypertension or hypercholesterolemia, 57% (95% CI: 32% - 79%) of all coronary events may have been prevented with a low-

risk lifestyle). Compared with men who did not make lifestyle changes during follow-up, those who adopted ≥ 2 additional low-risk lifestyle factors had a 27% (95% CI: 7% - 43%) lower risk of CHD.

Huijbregts et al. [73] developed the HDI in 1970 using five cohorts from the Seven Countries Study. The group with the highest HDI had a 13% lower risk of death compared to the group with the lowest HDI. The HDI has an even stronger inverse association with mortality for CVD; the group with the highest HDI had an 18% lowered risk of death from CVD relative to the group with the lowest HDI. To assess whether one of the components of the HDI could be responsible for the association with mortality, Huijbregts et al. applied the same model for each of the components separately. For most of the components the association was not significant, and different components were responsible for the association in different countries; consequently the authors concluded that the dietary pattern as a whole was responsible for the observed association.

Scarmeas et al. [74] demonstrated an association between MeDi and cerebrovascular disease, specifically infarcts demonstrated by magnetic resonance imaging; subjects within the highest MeDi adherence tertile had approximately 40% reduction in the likelihood of a brain infarct (Odds Ratio (OR): 0.64; 95% CI: 0.42 - 0.97; p for trend=0.04). This cohort of 707 elderly individuals was multiethnic, including Caucasians, Hispanics, and African American participants, which increases the translational nature of these results. Hispanics adhered more, and African Americans less to the MeDi, while ethnicity was not related to infarcts. Gardener et al. [75] has shown that MeDi score is inversely associated with risk of the composite outcome of ischemic stroke, myocardial infarction, or vascular death after nine years of follow-up in American males and females, with a mean age of 69 years. Dietary intake was collected at baseline and substantive changes in diet could have preceded the pathological changes that were observed. The number of ischemic strokes and myocardial infarctions was relatively small and therefore may not have provided sufficient power to detect a significant relationship for these outcomes individually. In a secondary CVD prevention trial, Vercambre et al. [76] reported that supplements of vitamins E and C, and beta-carotene did not reduce CVD disease recurrence or influence cognitive decline. In addition in 2504 of these women, who were ≥ 65 years of age and had a follow-up of 5.4 years, adherence to the MeDi was not associated with cardiovascular profile at baseline or with mean annual rate of cognitive change. Prevention of cognitive decline may be more challenging in those with existing vascular disease or risk factors. It is important to note however, that dietary intake was only measured at baseline; this may not reflect long-term dietary patterns, which may be more etiologically relevant. The MeDi has been significantly inversely associated with both systolic and diastolic blood pressure; in a cross-sectional study from a Greek population of 20,343 men and women who had never had a diagnosis of hypertension. It was found that vegetables and fruit are the principal factors that explain the overall effect of the MeDi on blood pressure [33]. However which components of fruit and vegetables that confer benefit is unknown. A higher baseline adherence to the MeDi has been associated with lower cumulative incidence of metabolic syndrome than those with the lowest adherence (p for trend=0.003).

These findings were reported in 2,563 participants of the Seguimiento Universidad de Navarra (SUN) Spanish cohort after approximately six years of follow-up. Participants were excluded at baseline if they had a body mass index >30 kg/m^2, or reported risk factors (diabetes, hypertension, hypercholesterolemia, or hypertriglyceridemia), or met the criteria for metabolic syndrome. A limitation of this study is the amount of self-reported information, including waist circumference, blood pressure, high density lipoproteins, triglycerides, and plasma glucose. It is worthy of note more than 45% of the cohort were health professionals, and therefore this self-reported information may be subject to increased bias as a results of health knowledge [77]. In a Greek cohort, Trichopoulou et al. [27] found that a higher adherence to the MeDi was associated with a reduction in total mortality, with a two-point increment in the score corresponding to a 25% reduction. Reduction in mortality was evident with respect to deaths resulting from CHD and cancer, but was more pronounced with respect to the former. However this study has limitations as it had a short follow-up period of 44 months and dietary data was collected only at baseline.

A population of 1507 men and 832 women from two different studies in 11 European countries have shown that higher adherence to the MeDi is associated with a reduced risk for all-cause mortality (Hazard Ratio (HR): 0.77; 95% CI: 0.68-0.88), CHD (HR: 0.61; 95% CI: 0.43-0.88), CVD (HR: 0.71; 95% CI: 0.58-0.88) and cancer (HR: 0.90; 95% CI: 0.70-1.17). This study had a follow-up period of 10 years, and in this time 935 participants died (371 from CVD, 233 from cancer, 122 from CHD and 23 from other causes, and 186 had an unknown cause of death). A MeDi score of four or above was associated with a lower risk of all-cause and cause specific mortality; the strongest observation was observed for CHD [35].

A large study in the United States of America (USA) has found that MeDi adherence is significantly associated with reduced all-cause, CVD and cancer mortality. During 10 years of follow-up, 27,799 deaths were recorded, from an initial cohort of 380,296 men and women. In men, the multivariate hazard ratios of mortality from all-cause, cancer, and CVD for the highest verses the lowest level of adherence was 0.77 (95% CI: 0.74 – 0.80), 0.79 (95% CI: 0.73 – 0.87) and 0.76 (95% CI: 0.68 – 0.88) respectively. In women, higher adherence was associated with a 22%, 14% and 21% decreased risk of all-cause (p for trend=0.001), cancer (p for trend=0.01) and CVD (p for trend=0.01) mortality respectively. The beneficial effect was more pronounced among smokers with high adherence to the MeDi [78].

Furthermore, Benetou et al. [79] reported a two-point increase in MeDi score was associated with a 12% reduction in cancer incidence (HR: 0.88; 95% CI: 0.80 – 0.95). This was in a Greek cohort of 10,582 men and 15,041 women, of which 421 men and 430 women reported incident cancer cases over a median follow-up of 7.9 years. McCullough et al. [18] used a longer FFQ to investigate diet quality and major chronic disease risk in 38,615 men and 67,271 women. They calculated an RFS (highest score 56) and an AHEI score (ranging from 2.5 (worst) to 87.5 (best)). Men and women scoring highest on the AHEI had a 39% (RR: 0.61; 95% CI: 0.49 - 0.75) and 28% (RR: 0.93; 95% CI: 0.60 - 0.86) lower risk of CVD compared to those with the lowest scores respectively. The association of the RFS with all outcomes was weaker. The AHEI was nearly twice as predictive of overall chronic disease risk than the HEI in the same cohort [70,71] suggesting that capturing dietary choices (e.g. white verses red meat), fat quality and other behaviours (e.g. multivitamin use) predicted improved health outcome. Table 5 (Included as supplementary data) has a summary of all studies reviewed in this section.

Diabetes, Obesity and Diet Indices

Obesity is an important risk factor for CVD, type 2 diabetes, dyslipidemia, hypertension and many other chronic diseases [80,81]. Obesity results in insulin resistance [82], which has a significant impact on modulation of synaptic plasticity, learning and memory processes

that are impaired in AD [83]. Insulin receptors and insulin-sensitive glucose transporters are densely expressed in the medial temporal region of the brain that supports memory formation, indicating that insulin may have a role in maintaining normal cognitive function [84].

Guo et al. [85] found the mean HEI score to be significantly lower among obese subjects compared to normal weight subjects. The number of obese individuals was generally higher among individuals classified as having a poor diet or a diet that needed improvement (HEI score of less than 50 and 80, respectively) compared to those with a good diet (HEI score of 81 or higher), but these differences were not statistically significant [86].

The French Supplementation en Vitamins et Mineraux Antioxidants study by Drewnowski et al. [16] observed that higher HEI scores were associated with lower fat consumption, higher carbohydrate consumption, greater dietary variety, and higher fruit and vegetable consumption. Based on the HEI, 8% of this group had "poor diets" (total HEI scores<51), 89% had diets in need of "improvement" (scores 51 - 81), and only 3% had "good diets". The data showed a weak relationship with lower body mass index (BMI) values in men, and the scores appeared unrelated to plasma lipid profiles.

It has been shown in a population from the USA that with every 10-unit increase in the HEI, the odds of abdominal obesity decreased by 8.3% for women and 14.5% for men. Therefore, dietary consumption which follows the HEI is associated with a lower risk for abdominal obesity. This study used a large cohort of 15,658 men and women; however no longitudinal data were reported [87].

The combination of food groups and nutrients found in the HEI is in line with the theoretical concept that an instrument for measuring overall diet quality should combine nutrient recommendations with dietary guidelines. The HEI also offers a greater variety of statistical analyses due to the score being continuous between 0 and 100.

Data from the Third National Health and Nutrition Examination Survey indicated that HEI scores are related to abdominal adiposity

Dietary index	Strengths	Weaknesses
HEI	Based on dietary guidelines[a]. Energy intakes based on sex and age taken into account. Has a dietary variety component. Updated in 2000 and 2005. Score ranges from 0 to 100, which is beneficial for statistical analysis. Ten components. Components are food and nutrients. Has been used to make alternate scores (AHEI and CHEI). Component scores range from 0 to 10 depending on extent to which they meet guidelines (other indices are just given a score of 0 or 1 for each component).	Same weighting for each component – all components do not have the same health impact[b]. Meat is scored positively[c]. Score changes depending on items in the FFQ used[d]. Uses servings per day in calculation of the score. Size of servings is not defined, and using grams per day is preferred.
RFS	Based on dietary guidelines[a]. Only food items, therefore easy to communicate to the public. Has a corresponding NRFS. Has been used to make alternate scores (RFBS).	Same weighting for each component – all components do not have the same health impact[b]. Score changes depending on items in the FFQ used[d]. Energy intake not taken into account. No dietary variety component. Only food items included. No quantities or serving sizes used, only number of foods deemed to be beneficial which are consumed over a certain period. No specific period over which foods eaten are counted, changes for each study.
HDI	Based on dietary guidelines[a]. Energy intake taken into account. Nine components. Components are food and nutrients. Ranges used for intakes instead of single cut off values.	Same weighting for each component – all components do not have the same health impact[b]. Score changes depending on items in the FFQ used[d]. No dietary variety component.
MeDi	Energy intake taken into account. Nine components. Combination of food groups and fat intake. Mostly food based, easy to communicate to the public. Can use study medians or specific designated medians as cut offs[e]. Both non-consumers and excessive consumers of alcohol have a low score[c]. Has been used to make alternate scores (aMED). Score is not based on dietary guidelines, but on a traditional diet[f].	Same weighting for each component – all components do not have the same health impact[b]. Meat and dairy are scored negatively[c]. Score changes depending on items in the FFQ used[d]. No dietary variety component. A range rather than a simple cut off is more beneficial to give extent to which dietary guideline is met.

[a]Also a negative point as it reflects nutritional knowledge and guidelines at the time and requires updating regularly as nutritional knowledge and guidelines are updated.

[b]Components that affect health to a greater extent should have a greater weight in the score, weighing is based on current dietary knowledge so requires regular updating and there may controversy between researchers on suitable weighing for each component.

[c]Moderate amounts of meat consumption is beneficial. Excessive and no consumption is unfavourable. Therefore a single cut off cannot be used to categorize consumption of meat. The HEI rewards all levels of consumption, and the MeDi rewards no and low consumption only. Both excessive and non-consumers should have a low score and only moderate consumption a high score. This is the same for alcohol and dairy.

[d]There is choice in which items from the FFQ should be included in each of the component scores; these 'choices' will cause differences in the scores, making it harder to compare results between studies, as researchers reach different conclusions about which items are included.

[e]Study specific medians have disadvantages, for example, the median might not reflect a healthy intake level and will differ between populations and studies, but it does mean that half the cohort will have a positive score and half negative. Specific designated medians have a disadvantage in that intake of a particular component may be below the cut off level for almost all subjects, causing the component be omitted from the score as it will not add value.

[f]Could also be argued as a negative point.

Abbreviations: MeDi, Mediterranean diet; aMED, alternate Mediterranean diet; HEI, healthy eating index; AHEI, alternate healthy eating index; CHEI, Canadian healthy eating index; HDI, healthy diet indicator; RFS, recommended food score; NRFS, non recommended food score; RFBS, recommended food and behaviour score; FFQ, food frequency questionnaire;

Table 3: Strengths and weaknesses of dietary indices.

[85]. The same cohort was also used to assess the HEI as a measure of dietary status through its correlation with nutritional biomarkers. HEI scores were correlated with serum and red blood cell folate, vitamins C and E and carotenoids (α-carotene, β-carotene, β-cryptoxanthin and lutein-zeaxanthin). The mean concentration of these nutrients increased with increasing HEI score. These biomarkers are limited in scope; most represent nutrients found in fruit and vegetables, rather than those found in meat, milk or grain products. HEI scores were not associated with serum ferritin, serum selenium, serum calcium, and vitamins A and D. HEI scores were considerably higher among vitamin and mineral supplement users. However, when the analysis was rerun without these supplement users, the results were similar; although it is possible that residual confounding by supplement use accounts for some of the associations reported [88].

Haveman-Nies et al. [89] presented results from the Survey in Europe on Nutrition and the Elderly: a Concerted Action (SENECA) study (n=1282) and the Framington Heart Study (n=828). Dietary intake varied widely across the European and American research centres. In general, the Southern European centres and Framington had higher mean HDI, indicating higher dietary quality when compared to the northern European centres. The researchers also found that, in general, two healthy lifestyle factors, non-smoking and physical activity, were associated with higher dietary quality. Furthermore, subjects with a low quality diet were more overweight in comparison to subjects with a high quality diet.

Mendez et al. [90] have investigated MeDi and obesity. In people already overweight when the study started, 7.9% of women and 6.9% of men became obese over the mean 3.3 year follow-up, and a high MeDi was associated with significantly lower likelihood of becoming obese (Women; OR: 0.69; 95% CI: 0.54-0.89. Men; OR: 0.68; 95% CI: 0.53-0.89).

However in normal weight individuals who became overweight, MeDi was not associated with a lower risk for this progression. Although weight was measured at baseline by study co-ordinators, it was self-reported at follow-up; measurement error may have attenuated the results. Mendez et al. used an extensive computerized diet-history instrument with over 600 items to capture intake over the previous year. The number of items included is greatly increased compared to other studies [48,74,77,78,91], and participant fatigue when completing a questionnaire of this length may have impaired response accuracy.

In a cohort of 13,380 Spanish graduates, who were followed for approximately four years, participants that adhered closely to the MeDi had a lower risk of diabetes. A two-point increase in the MeDi score was associated with a 35% relative reduction in the risk of diabetes (incidence rate ratio 0.65; 95% CI: 0.44-0.95). A limitation of this study however, is the number of cases of diabetes identified at follow-up; 33 from an initial cohort of 13,380, which compromises statistical power. Among participants with the highest MeDi adherence, there was a high prevalence of risk factors for diabetes, including older age, higher BMI, family history of diabetes, personal history of hypertension, and a high proportion of ex- smokers. One would therefore have predicted a higher incidence of diabetes amongst this group; the reduced risk of diabetes suggests high MeDi adherence offers substantial potential for diabetes prevention. As reported earlier in this review, the MeDi has a role in CVD prevention, and given that there are many common risk factors for CVD and diabetes, it is expected that the MeDi is also protective against diabetes [91]. Table 6 (Included as supplementary data) has a summary of all studies reviewed in this section.

Discussion

This article reviews the current evidence of 'a priori' defined dietary patterns and their association with AD, and AD-related chronic disease risk. Table 3 summarises the strengths and weaknesses of the dietary indices discussed in this review. The studies we have reviewed on MeDi, HDI and RFS suggest that higher index scores are associated with reduced AD risk. However, for all indices except the MeDi, we could find very limited numbers of published results on the association between index scores and AD risk or cognitive decline. For this reason, we can only confidently conclude that the MeDi is associated with a reduced AD risk, and further studies on the remaining indices need to be carried out. The two studies on the HEI and CHEI found no association with rates of cognitive decline; further analysis in different populations may confirm these results.

Evidence regarding the association of AD-related chronic disease risk (including CVD, diabetes and obesity) in relation to healthy dietary patterns from diet indices is more consistently positive; however the magnitude of the protective effect is modest in many studies. It is our opinion that a combination of dietary scores could predict overall dietary quality and chronic disease risk to a greater extent than one score individually. Analysis in multi-ethnic cohorts, investigating combinations of scores must be completed before firm conclusions can be reached on the ideal combination of scores.

Overall indices reviewed here are useful for assessing overall diet quality. The dietary indices that have nutrient and food components may better reflect the multidimensional nature of diet quality compared to the RFS for example, which includes only food items. However, the RFS has been shown to correlate with urinary potassium levels, a measure of diet quality and vegetable intake in particular. Nutritional biomarkers are considered to be a more objective measure of dietary intake and ideally dietary patterns will be used in association with biomarker outcome measures [92].

There is increasing evidence that components in the foods we consume interact with each other to impart disease protection and a higher level of health; this is food synergy [93,94]. The evidence for health benefit appears stronger when foods are inserted into synergistic dietary patterns rather than considered as individual foods or food constituents [95]. A priori patterns have advantages and disadvantages over other methods of dietary pattern analysis. They are relatively easy to compute and reflect the adherence to specific dietary patterns or guidelines. However, a priori patterns are constructed using dietary guidelines, and can therefore only be as good as these underlying guidelines. Availability of dietary guidelines is required to define dietary indices, and generally the guidelines are not disease specific, hence adherence may reduce the risk of some diseases but not others. Dietary indices need to be updated as and when dietary recommendations for the population being analysed are modified, a process therefore of continual revision. Most of the dietary indices were designed to estimate adherence to a specific diet and did not account for additional dietary constituents. Subjective choices are sometimes necessary when computing the scores, for example deciding which foods belong in which food group in the MeDi, which means the resulting score is influenced by the investigator. An association between a dietary pattern and a disease however, does not allow mechanistic insights into disease causation [14].

There is increasing evidence that the nutritional value of food is influenced in part by the structure of a persons gut microbial community, and that food determines the microbiota and the "gut microbiome" (its

vast collection of microbial genes; [96]). Developments are required for more rigorously defining the nutritional value of foods we consume and our nutritional status; for this we need to know more about our microbial differences and theirorigins, including how our lifestyles influence the assembly of gut microbial communities [97]. An example of the importance of the gut microbiome is reflected in the accumulating evidence suggesting that the normal gut microbiome contributes to the development of obesity [98-100].

There is no standard method for collecting dietary data; methods include FFQs (with different items specified, some with pictures to estimate portion size, either self-administered or interviewer administered), weighed dietary records and 24 h dietary recall. FFQ's have traditionally been used to construct dietary patterns but are subject to faulty recall of dietary intake (leading to misclassification), whereas weighed dietary records rely on a person's ability and willingness to weigh and record current diet, rather than depending on memory. All three methods do not however account for variability in nutrient absorption [101]. FFQs in theory represent intake over an extended period, which is of interest for investigating risk for chronic disease (although some record the preceding six months, others the preceding year). The majority of the scores need to be altered slightly depending on the dietary intake method used. There are also no set confounders to control for during data analyses, and those chosen can increase or decrease the association seen and make comparisons between studies difficult.

Dietary patterns are likely to vary according to sex, socioeconomic status, ethnic group and culture. It is therefore necessary to replicate the results in diverse populations. The increasing ethnically diverse nature of many populations complicates the assessment and analysis of representative dietary intake data for several reasons. First, population based studies measuring habitual dietary intake have often excluded migrants because, alongside communication issues, most research tools that are currently available have been developed for the host population and are not necessarily valid and critically assessed for their suitability in migrant groups. Second, accuracy of dietary intake data is limited, due to lack of food composition data on ethnic foods consumed by migrants. Ethnic-specific tools to measure the habitual dietary intake of individuals from predominant migrant groups are currently not available; this is a pre-requisite for the assessment of dietary patterns and for making a valid link with risk factors for chronic diseases [102]. Diet indices have not been tested extensively for their ability to predict risk of AD and AD- related chronic diseases. The number of studies on diet quality indices, plasma biomarkers, and selected lifestyle factors is still fairly limited, and there is a need for more studies to confirm associations with AD and related disease risk.

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