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Dietary Patterns in Alzheimer's Disease and Cognitive Aging

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Abstract

Much of the attention on diet and Alzheimer's disease (AD) or cognition among the elderly has focused on the role of single nutrients or foods, while available information on dietary pattern (DP) analysis, which better reflects the complexity of the diet, is sparse. In this review, we describe different patterning approaches and present studies performed to date that have assessed the associations between DPs and risk of AD or cognitive function in the elderly. Three patterning approaches have been most commonly used: (i) hypothesis-based that use dietary quality indexes or scores (e.g. Mediterranean pattern), (ii) data-driven that use factor or cluster analysis to derive DPs, (iii) reduced rank regression which combines characteristics of the former two approaches. Despite differences existing among the approaches, DPs characterized by higher intake of fruits, vegetables, fish, nuts and legumes, and lower intake of meats, high fat dairy, and sweets seemed to be associated with lower odds of cognitive deficits or reduced risk of AD. Overall, the inherent advantages as well as the existing evidence of DP analyses strongly suggest that this approach may be valuable in AD and aging research. Further studies are warranted, though, to confirm the findings in different population settings, to address some methodological issues, and possibly utilize the information for future clinical trial design.

Keywords

Alzheimer's disease; cognition; dementia; dietary patterns; nutrients

INTRODUCTION

An estimated 5.3 million Americans of all ages have Alzheimer's disease (AD), the most common type of dementia [1]. Due to the increasing longevity of the US population, the increasing incidence with age [2], and the lack of effective treatment options of AD, a dramatic rise in AD prevalence is expected. Thus, effective strategies for early prevention or delayed onset of AD, among them identifying risk-reducing modifiable environmental/lifestyle factors such as diet, are needed.

Although a great interest on the association between diet and AD has emerged, much of the efforts have been spent over the years on studying individual nutrients or food items. However, current literature regarding the impact of individual nutrients or food items on AD risk is inconsistent [3]. This could be partly due to the fact that humans eat meals with

complex combinations of nutrients or food items that are likely to be synergistic (or antagonistic) so that the action of the food matrix is different from the individual nutrients or food items [4]. In addition, nutrients or food items are highly correlated within foods, so it is difficult to examine their individual effects. Furthermore, the effect of a single nutrient may be too small to detect, or, a statistically significant association might be simply found by chance alone, due to an increased type I error in the case of multiple comparisons of a large number of nutrients [5].

Being able to represent complicated interactions and cumulative effects of diet, dietary pattern (DP) analysis has emerged in recent years to examine the relationship between diet and the risk of chronic diseases or conditions, including AD, cognitive impairment or cognitive decline [4–5]. In this review, published studies that evaluate the association between DPs and risk of AD or cognitive decline are summarized (Table 1), some general methodological issues in DP analysis are discussed, and finally, future directions of DP research in AD and cognitive aging area are suggested.

PATTERNING APPROACHES

DP (or food pattern, food combinations, dietary habit, dietary score, dietary index) is a combination of food components (food items, food groups, or nutrients) that summarizes an overall diet for a study population. Three approaches have been proposed in the literature to derive DPs [6]: hypothesis-driven, or *a priori*, approach; exploratory, or *a posteriori*, approach; and recently, reduced rank regression (RRR), which is a mix of an exploratory and hypothesis-driven approach since it not only uses available dietary data of the study but also incorporates prior information by using a set of variables (nutrients or biomarkers) that is known to predict disease [6].

Hypothesis-Driven, or *a Priori*, Approach

The hypothesis-driven, or *a priori*, approach aims to calculate a graded score or index that describes how well an individual adheres to a particular diet recommendation, which is based on prior knowledge concerning diet and diseases (i.e. the “hypothesis” underlying the approach) [7]. A variety of dietary indexes have been developed and their relationship with various diseases have been investigated [8]. There are two general methods to construct these dietary indexes, the first one being based on nutrition guidelines/recommendations i.e., Healthy Diet Indicator (HDI) [9], Healthy Eating Index [10–12], Healthy Food Index [13], Dietary Approaches to Stop Hypertension (DASH) [14], Dietary Guidelines Index [15], Diet Quality Index [16], Dietary Quality Score [17], Elderly Dietary Index [18], Recommended/non-recommended food score (RFS/nonRFS) [19–20], etc., and the second one being a diet style observed in Mediterranean populations - the Mediterranean DP (i.e., MeDi, Mediterranean Diet Scale, MedDietScore, etc.) [21–24].

To date, only a few studies investigated the association of *a priori* defined DPs with cognitive function or AD risk. Nevertheless, because of the availability of a variety of indexes, easiness for construction, and readiness for a potential comparison among studies using the same index, the *a priori* approach is relatively more common than the other two approaches (i.e. exploratory approach and RRR) used in the neurology field.

HDI

The HDI was developed by Huijbregts *et al.* [9] to measure the degree of accordance of a person's DP with the dietary recommendations for the prevention of chronic diseases [25]. To construct a HDI, firstly a dichotomous variable is generated for each food group or nutrient. If a person's intake is within the recommended borders, this variable is coded 1, and if the intake is outside these borders, it is coded 0. The recommended borders are as

following: saturated fatty acids (SFA) (≤ 10 percent of energy intake (en%)); polyunsaturated fatty acids (PUFA) (3 – 7 en%); protein (10 – 15 en%); polysaccharides / complex carbohydrates (50 – 70 en%); dietary fiber (27 – 40 grams per day); fruits and vegetables (> 400 grams per day); pulses, nuts and seeds (> 30 grams per day), oligosaccharides / mono- and disaccharides (≤ 10 en%); and cholesterol (≤ 300 milligrams per day). The HDI is then calculated as the sum of all these dichotomous variables (range 0 – 9).

Huijbregts *et al.* for the first time tested the hypothesis that a healthy and well-balanced diet might lead to good cognitive function. They investigated the association between DPs, measured as HDI, and cognitive performance, measured by the Mini-Mental State Examination (MMSE), in a population based cross-sectional study among elderly men in Finland, Italy and the Netherlands [26] (Table 1). The authors reported a tendency towards a lower prevalence of cognitive impairment (23 or lower in MMSE score) associated with increased HDI in four out of five study cohorts. After adjusting for age, education, cigarette smoking, alcohol consumption and energy intake, the association between HDI and the presence of impaired cognitive function was statistically significant [odds ratio (OR) per unit increase of HDI = 0.75; 95% CI = 0.58–0.97] in one cohort, and marginally significant in another [OR(95% CI) = 0.81(0.63–1.04)]. Thus, the results of the study suggested that a healthy diet can be associated with a better cognitive function in elderly men.

Later, Correa Leite *et al.* performed another population based cross-sectional study to replicate the work of Huijbregts *et al.*, with certain extensions in food intake and cognitive function assessments, in an Italian population of 1651 subjects aged 70 years or more (560 men and 1091 women) [27] (Table 1). A 0 – 70 point neuropsychological test was used to categorize cognitive function according to neuropsychological test scores (≥ 53 for normal cognition; 40–52 for mild cognitive deficit; 24–39 for moderate cognitive deficit; ≤ 23 or less for severe deficit). The cumulative OR for any level of cognitive deficit per unit increase of the HDI was 0.85 (95% CI = 0.77 – 0.93) after adjustment for age, education, energy intake, sex, cigarette smoking, alcohol consumption and physical activity. The findings were in line with those found by Huijbregts *et al.* [26], indicating that the consumption of a globally satisfactory diet was associated with better cognitive performance in the elderly.

RFS—The RFS, developed by Kant *et al.* [19], is a simple way to define DPs by summing the number of foods recommended by current Dietary Guidelines for Americans [28]. It is considered as a measure of dietary diversity.

In a recent report, Wengreen and coauthors examined associations of RFS with baseline cognitive function and cognitive decline over time among elderly men and women (age ≥ 65) of the Cache County Study on Memory and Aging in Utah, a population-based prospective study [29] (Table 1). Usual dietary intake was assessed using a 142-item FFQ. Consumption of any of the 57 recommended foods of the 6 categories (fruits, vegetables, whole grains, nuts, fish, and low-fat dairy products) in a frequency of at least 1–3 times/month led to assignment of 1 point; less frequent consumption led to assignment of 0 point. The RFS was calculated as the sum of points. Similarly, a non-RFS (23 non-recommended foods, coded as 1 point assignment for ≥ 3 times/wk) was calculated. The study found that mean baseline cognitive function, assessed by modified Mini-Mental State Examination (3MS) scores, increased across increasing quartiles of RFS: those in the highest quartile (Q4) of RFS scored 1.80 points higher on the baseline 3MS test than did those in the lowest quartile (Q1) of RFS ($P < 0.001$). Longitudinally, the difference was also noted: by the 11th year of follow-up, subjects with Q4 RFS declined (3.41-point decline) less than those with Q1 RFS (5.15-point decline) ($P = 0.0013$). The non-RFS was not associated with cognition.

Therefore, this study suggested that a DP with higher RFS score that provided a variety of recommended foods may provide benefits to cognitive function in late life.

MeDi—The MeDi, a diet high in plant foods (such as fruits, nuts, legumes, and cereals) and fish, with olive oil as the primary source of monounsaturated fat (MUFA) and low to moderate intake of wine, as well as low intake of red meat and poultry, is known to be one of the healthiest DPs in the world due to its protective effects on some chronic diseases [30]. The MeDi has been associated with a number of healthful outcomes including reduced risk of cardiovascular disease, cancer, and mortality [31–32].

Although slightly different methods have been used [24], the MeDi score is commonly constructed in the following way: For fruits, vegetables, legumes, cereals, fish, ratio of MUFA/SFA, and mild-moderate alcohol (beneficial components), individuals whose calorie-adjusted amount (grams) consumption is below the median are assigned a value of 0, and individuals whose calorie-adjusted consumption is at or above the median are assigned a value of 1. For meat and dairy products (components presumed to be detrimental), individuals whose consumption is below the median were assigned a value of 1, and individuals whose consumption is at or above the median were assigned a value of 0. The MeDi score is then generated for each participant by adding the scores in the food groups (theoretically ranging from 0–9). A higher score indicates greater adherence to a MeDi [22–23].

We evaluated the MeDi of over 2,000 participants of the Washington/Hamilton Heights-Inwood Columbia Aging Project (WHICAP), a cohort of nondemented elders aged 65 and older living in a multi-ethnic community of Northern Manhattan in the US [23] (Table 1). Detailed dietary information was collected with a validated FFQ. We found higher adherence to MeDi was significantly associated with prevalence of AD [33]. Furthermore, examining the association between MeDi and AD prospectively, we found those with higher MeDi scores at baseline had lower risk of incident AD over an average follow-up period of 4 years, even after adjustment for potential confounders [23]. This was the first study examining a DP in relation to incident AD risk. In addition, the risk of cognitive decline was also reduced with greater adherence. Later, we reported supporting evidence that higher adherence to the MeDi was associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD [34], and that the association between MeDi and risk of incident AD was independent of physical activity [35].

The multi-ethnic population of the WHICAP study may not strictly consume foods typical of the Mediterranean countries, and the “MeDi adherence” of this population may therefore be significantly lower as compared with Mediterranean populations. Psaltopoulou and colleagues [36] (Table 1) evaluated the relationship between MeDi at baseline and cognitive performance 6–13 years later in a population-based prospective study of 732 Greek men and women of 60 years or older, who ate a typical MeDi. No significant association between MeDi score and MMSE score was found in that study.

In another article, based on a population-based cohort from Bordeaux, France, a subsample of the Three-City cohort, Féart and colleagues [37] attempted to replicate the association of MeDi and cognitive decline or incident AD risk (Table 1). The authors used 4 neuropsychological tests to evaluate cognitive decline. After adjustment of covariates, individuals who had high adherence to the MeDi had slower decline in MMSE scores (as a continuous variable) over the 5-year follow-up period, supporting of the initial findings in the WHICAP study. However, the MeDi was not associated with other 3 neuropsychological tests measuring verbal episodic memory, immediate visual memory and semantic verbal fluency and there was no reduction in incident dementia in those with high adherence to the

MeDi, probably due to the limited power, as the number of AD patients was less than a quarter of that of the WHICAP study.

In summary, the current evidence provides moderately compelling evidence that adherence to the MeDi is linked to reduced risk of AD or cognitive decline in the elderly. Future studies are warranted to confirm these findings.

DASH—The DASH diet was one of the 3 diets prescribed in the Dietary Approaches to Stop Hypertension trial [14]. It is characterized by being rich in fruits, vegetables, and low-fat dairy foods and having reduced amounts of saturated fat, total fat, and cholesterol [14]. It is now included as an example of a healthy eating pattern in the 2005 Dietary Guidelines for Americans [28].

In a recent randomized clinical trial, 124 participants with elevated blood pressure who were sedentary and overweight or obese were randomized to the DASH diet alone, DASH+weight management (DASH+WM), or a usual diet control group [38]. Participants completed a battery of neurocognitive tests at baseline and again after the 4-month intervention. Compared with subjects on the usual diet, subjects on DASH+WM arm and the DASH diet alone arm both exhibited greater neurocognitive improvements. The study showed that combining aerobic exercise with the DASH diet and caloric restriction improves neurocognitive function among sedentary and overweight/obese individuals with high blood pressure [38] (Table 1).

A DASH diet score that reflects adherence to the DASH-style diet has been developed for observational studies to examine whether following a DASH-style DP is associated with risk of diseases such as cardiovascular disease and stroke [39–40]. However, no observational study has been done to examine the association between a DASH score and AD or cognitive decline.

Others—In another report from the Three-City cohort, Barberger-Gateau and colleagues constructed good or poor DPs according to the regular consumption of foods whose components were expected to be protective (sources of omega-3 PUFA such as fish or oils; sources of antioxidants such as fruits and vegetables) or conversely deleterious (intake of omega-6 PUFA not balanced by intake of omega-3 PUFA) based on previous knowledge (biologic mechanisms). The study found participants consuming diets high in fruits, vegetables, fish, and (omega -3) fatty acids had decreased incidence of all-cause dementia and AD compared with those with diets low in these foods and nutrients [41] (Table 1).

Exploratory, or a Posteriori, or Data-Driven Approach

The exploratory, or a *posteriori*, or data-driven approach uses statistical methods such as principal component analysis (PCA), factor analysis, or cluster analysis to derive DPs.

Cluster Analysis—Cluster analysis is a statistical method in which individuals are placed into distinct mutually exclusive groups/clusters on the basis of similarity/difference of dietary intake, so that diets of the individuals within the same cluster are relatively homogeneous, while diets of the individuals differ between clusters [42]. A cluster-belonging indicator is assigned to each subject. Thus, the indicator variable can be used in subsequent analysis to estimate risk of diseases.

Only one study has investigated the association between cluster analysis-derived DPs and cognitive function (Table 1). In this study [43], 1724 elderly community subjects of a subgroup of the Three-City cohort were grouped into five dietary clusters for each sex, and their relationship with cognitive function was investigated. Five clusters were identified:

“Small”, “Biscuits and snacking”, “Healthy”, “Charcuterie, meat, and alcohol” and “pasta eaters” (in men)/“pizza and sandwich” (in women). A “healthy” DP characterized by higher consumption of fish in men and fruits and vegetables in women was related to better cognitive performance measured by MMSE cross-sectionally.

Factor Analysis and PCA—The aim of factor analysis is to reduce the dimensionality of the data by transforming many (usually correlated) original dietary variables (nutrients, food items, or food groups) into a smaller set of uncorrelated variables, i.e. DPs [44]. The most common factor analysis applied in nutritional epidemiology is PCA. The PCA-derived DPs are optimized linear combinations of the standardized dietary variables constructed to represent the most of the variation among these dietary variables. The weights (loadings) of a linear combination (representing a DP) correspond to the importance of each dietary variable to that DP, as each loading is proportional to the correlation coefficient between dietary variable and the DP. In this way, each individual gets score values for each of the identified DPs, indicating the degree to which the individual’s diet conforms to the DP. The DP scores can then be applied in traditional epidemiological studies as a continuous (or transformed to categorical) exposure variables to assess their associations with disease risk.

In a recent cross-sectional study of 4693 white, middle-aged (35–55 years old) participants of the Whitehall II study, PCA was used to derive DPs which were then examined in relation to cognitive function, assessed using 5 standard cognitive tasks covering memory, reasoning, vocabulary, phonemic fluency, and semantic fluency domains [45] (Table 1). Cognitive deficit was defined as performance in the worst quintile for each cognitive test. The results suggest that a ‘whole food’ pattern (rich in fruit, vegetables, dried legume and fish) is associated with lower while a ‘processed food’ pattern (rich in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products) is associated with greater odds of cognitive deficit in all 5 domains. Nevertheless, education, through its role as a powerful confounder, shapes the relationship between DPs and cognitive deficit in this study [45]. No study using PCA-derived DP has been performed to study the cognition or AD risk among elderly subjects (aged 65 and older).

RRR (or Maximum Redundancy Analysis)—RRR has been recently introduced to nutritional epidemiology by Hoffman *et al.* as a third option to derive DPs [46]. RRR determines linear combinations (i.e., DPs) of a set of predicting variables (food groups) by maximizing the explained variation of a set of response variables (disease-related nutrients, biomarkers, etc.). Briefly, the RRR procedure is implemented in the following 2 steps (although it is somewhat more sophisticated and efficient than this 2-step procedure [47]). First a PCA on nutrients (or other response variables such as biomarkers) constructs a linear function of nutrients called response score. Second, a linear regression of this response score on food groups produces a DP score. A higher DP score indicates a stronger adherence of a subject’s diet to the particular DP. The DP scores can then be applied as the exposure variables to assess disease risk.

RRR can be viewed as a combination of two approaches: a hypothesis-oriented approach using prior information of nutrients-disease association existing in literature (i.e. selection of nutrients and biomarkers to be considered), and an exploratory approach using study-specific data (use of nutrients, biomarkers, food group information from the particular study) [46]. In contrast to the classic exploratory methods, the RRR method has an etiologic advantage because it incorporates prior knowledge of the relationship between nutrients (or other factors such as biomarkers) and AD. As compared to *a priori* methods such as MeDi, the RRR method identifies DPs that naturally exist in the study population, and thus less limited by the fixed structure of a certain *a priori* pattern.

Only one study has investigated the association between RRR-derived DPs and incident AD risk. We recently applied the RRR methods in the WHICAP population. In this study, 30 food groups were created and searched for the existence of DPs that can explain variation in 7 AD-related nutrients. A DP that was positively correlated with omega-3, omega-6, folate, and vitamin E, and negatively correlated with SFA and vitamin B12 intakes was identified. It was characterized by higher intakes of oil and vinegar based salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high-fat dairy products, meat and butter. This DP was strongly associated with lower incident AD risk: when compared to the lowest DP score tertile, AD hazard ratio (95% CI) for the middle and highest tertiles were 0.81(0.59–1.12) and 0.62 (0.43–0.89), respectively (p for trend = 0.01) [48] (Table 1).

METHODOLOGICAL ISSUES IN DP ANALYSIS

Subjectivity

Exploratory approaches and RRR involve arbitrary choices such as consolidation of food items into food groups, number of DPs to be retained, selection of response variables in RRR, applied rotation method in factor analysis, and naming of the DPs [49]. While for the hypothesis-based approaches the inclusion of the selected nutrients or foods largely depends on their presence in the dietary recommendations utilized to define the score, they may also depend on the investigator's arbitrary selection of dietary components, weightings and cutoff points of them. McCann *et al.* reported that the choice of food groups had only a small impact on the observed associations between PCA-identified DPs and endometrial cancer [50]. In another study, we examined the effect of different combinations of response variables on RRR-derived DPs and their relationship with AD risk, and the results showed a "common" DP, with very similar food components, can be identified and its association with AD risk was quite stable [48]. Although these two studies suggest that the obtained DPs are independent of parameter selections involved, more studies are warranted to test the reproducibility of the results.

External Reproducibility

Thus, DPs may not be reproducible across studies because of the above-mentioned differences in analytics decisions. In addition, cautions are also warranted when results across studies or populations are to be compared, since reproducibility may also be affected by population characteristics, in particular, history or cultural influence on eating habits, food availability, ethnicity, etc. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found the first country-specific RRR-derived DPs that explained a considerable proportion of 23 key nutrients intake variation in 24-h dietary recalls are very similar across the 10 countries in terms of food group combinations. The study shows that, despite the large variability in food and nutrient intakes reported in the EPIC countries, the variance of intake of important nutrients is explained, to a large extent, by similar food group combinations across countries [51]. Nevertheless, a recent study conducted confirmatory RRR and found RRR-derived DPs that predict type 2 diabetes mellitus risk in one population may not be generalizable to different populations, with noticeable differences seen in the characteristic of food components and the associations with disease risk [52]. It is of notice, though, that the latter study involves comparison among three populations from US, Europe (including UK), and UK, while the former one includes European populations only.

Internal Reproducibility

Meanwhile, use of dietary patterning methods in epidemiologic studies also requires evaluation of the internal reproducibility of the derived DPs in the specific study population.

Internal reproducibility of the DPs has been examined in a few studies, including DPs derived from hypothesis-driven [23], factor analysis [53–55], and RRR approaches [48]. In one study, using confirmatory factor analysis, Newby *et al.* found correlations between two DPs, derived from two diet assessments that were 10 years apart, ranged from 0.27 for the Western/Swedish pattern to 0.54 for the Alcohol pattern, suggesting that DPs measured by the use of confirmatory factor analysis are reproducible over time [53]. Analysis of shorter-term, 1 year apart, reproducibility of factor analysis-derived DPs showed much higher correlations in two studies [54–55]. The reliability correlations for the factor scores between the two 1 year apart FFQs were 0.70 for a prudent pattern and 0.67 for a Western pattern in a subsample of the Health Professionals Follow-up Study [54]. Another study found similar high correlation coefficients between two factor analysis-derived DPs that were 1 year apart (ranging from 0.63 for healthy pattern, to 0.73 for drinker pattern) [55]. In the WHICAP study, both MeDi and an RRR-derived DP were found to be stable over a period of approximately 7 years [23, 48].

Internal Validity

Román-Viñas [56] recently conducted a systematic review of the literature on the value of the methods used to assess DPs for measuring nutrient intake adequacy in the population. Both the hypothesis-driven approach and factor analysis approach showed moderate to good validity results for measuring the adequacy of intakes for a variety of nutrients, supporting the internal validity of these DP analysis approaches for characterizing dietary exposures in epidemiological research.

Biological Mechanisms

Different from individual nutrient analysis in which the underlying biological mechanism is by nature self-explaining, the mechanism of the association between DP and outcome variable is difficult to explain, since a typical DP consists of a variety of foods or nutrients that are likely to have multi-dimensional biological effects. Nevertheless, the RRR method has the advantage of incorporating existing scientific evidence about nutrients-AD relationship in constructing pattern variables. For instance, in the WHICAP study [48], by taking into account seven responses nutrients (SFA, MUFA, omega-3 PUFA, omega-6 PUFA, vitamin E, vitamin B12, and folate) in the RRR analysis, the strong and significant association between DP and AD might be explained via pathways such as reducing circulating homocysteine levels (vitamin B12 and folate), anti-oxidation (vitamin E), as reducing atherosclerosis, thrombosis, inflammation, as affecting membrane functioning, or via beta-amyloid (fatty acids). If RRR analysis involves more specific response variables, i.e. variables representing a single mediating pathway, whether this particular pathway explains the association between diet and disease outcome can be tested.

On the contrary, since exploratory approaches are data-driving and entirely empirical, ignoring key-nutrients which are likely to be implicated in the physiopathology, the identified DPs may not be the best predictors of disease risk and biological mechanisms are difficult to explain [5]. As for hypothesis-driven approaches, although some dietary recommendations are considered for construction of DPs, the recommendations are somehow non-specific. For these studies, potential biological mechanisms may be explored by examining their effects on biomarkers or other biological outcomes, or even better, through a mediating effect analysis. In one of our previous studies, we investigated whether there was attenuation of the association between MeDi and AD when vascular variables (stroke, diabetes mellitus, hypertension, heart disease, lipid levels) were simultaneously introduced in the models (which would constitute evidence of mediation). We found that introduction of the vascular variables in the model did not change the magnitude of the association, suggesting that the association between MeDi and AD risk may not be mediated

by vascular comorbidity (or measurement error of vascular comorbidity may be the reason for failing mediation models) [33]. Nevertheless, such analysis can only explore one or few pathways each time and is thus subject to inflated type I error if a large number of pathways are tested.

Contribution of Individual Dietary Components

In DP studies, the interpretation of the effect of a single food or nutrient component should always be confined to the context of a dietary pattern, because a high or low intake of a single food/nutrient may reveal little information without taking into account other foods/nutrients, especially those that are highly correlated to it. A protective DP in general most likely represents a diet rich in “healthy” and lower in “bad” dietary components, but it is also possible that certain “healthy” dietary components, by being highly correlated with “bad” ones, are poorly presented in this DP. An example of such a case is the low contribution of vitamin B12 (usually considered as a protective nutrient for cognition) in the RRR-derived protective DP in the WHICAP population [48]. This DP reflects a diet rich in omega-3 PUFA, omega-6 PUFA, vitamin E and folate, but with lower in SFA and vitamin B12. An examination of the food sources of these nutrients indicate that it is the high correlation between SFA (a believed risk factor for AD) and vitamin B12, both mainly from meats and dairy, that contribute the paradoxical position of vitamin B12 in these findings. However, such issue may only be a concern for RRR and exploratory approaches but not for the hypothesis-driven approaches, since index-based DPs clearly identify the food component’s role in the DP by assigning either a positive (if “healthy”) or a negative (if “bad”) value according to dietary recommendations/hypotheses.

Nevertheless, because most hypothesis-driven approaches usually weigh dietary components equally, the relative contributions of the components thus may not be able to identify. To the contrary, some exploratory approaches like PCA and RRR are able to identify the relative contributions to a certain extent by examining the factor loadings of food components.

Study Design

All of the exploratory studies [43, 45] and some hypothesis-driven studies [26–27] have been solely cross-sectional studies. These studies have in general suggested that a healthy diet (e.g. fruits, vegetables, and fish) can be associated with a better cognitive function. However, although these cross-sectional studies are useful for hypothesis generation, they are not useful for causal inference, because they cannot establish whether AD or cognitive decline is a result of dietary habits or a primary event leading to dietary changes. In addition, most of the studies [26–27, 29, 43] examined the overall cognitive performance, while the association between DP and specific cognitive domains was explored in only one study [45].

Several prospective studies, including the studies of MeDi [23, 33–34, 36–37], the RSF study [29], and the study using RRR method [48] have been conducted and they are generally considered to be more useful (although still tentative) for causal inference. However, it needs to be shown that the association between DPs and AD or cognitive decline can be consistently observed in different populations under different circumstances [57]. In addition, prospective studies with longer follow-up time are preferred since they are less likely to be subject to the possibility of reverse causality, i.e., changes in diet being secondary to the preclinical disease process.

The ultimate evidence to support dietary recommendations would come from clinical trial data [58]. However, to date only one clinical trial has examined the effects of DPs on cognitive functioning [38]. Since AD is a chronic disease with a long latency period, such clinical trials pose practical limitations since they would require long follow-up and large

sample sizes [58]. Advances in AD biomarker identification (either as selection tools of high risk groups or as outcomes) may greatly facilitate such interventional dietary approaches.

CONCLUSION

This article reviewed the current evidence of DPs and AD risk or cognitive impairment/decline. All three types of patterning approaches have been explored, and the results in general suggest that higher intake of fruits, vegetables, fish, nuts, and legumes, lower intake of meats, high fat dairy, and sweets, seem to be associated with lower odds of cognitive deficits or reduced risk of AD. Further studies are needed, to confirm the findings, especially considering that very few studies have been done for each of the patterning approaches. In particular, more prospective studies and clinical trials are necessary to better elucidate the temporal relationship between diet and AD development or cognitive function and to establish cause-effect relations with higher confidence. The relationship between DPs and functions in specific cognitive domains in healthy aging needs to be explored. Some methodological issues, such as the reproducibility of DPs, needs to be, and can be, addressed. Overall, the inherent advantages as well as the existing evidence of DP analyses strongly suggest that this approach may be valuable in AD and cognitive aging research.

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Table 1
Studies Reporting DPs and Their Association with AD Risk, Cognitive Impairment or Cognitive Decline in the Elderly*

Reference	Study Design	Subjects	Cognition Assessment or AD Diagnosis	Food Intake Assessment	DP Construction	Results	Conclusion
Huifregts <i>et al.</i> 1998 [26]	Cross-sectional	1049 men aged 70–91 years; the Seven Countries Study	MMSE: A score of 23 or lower was used to indicate cognitive impairment.	Cross-check dietary history	HDI	After multivariable adjustment, OR (95% CI) for cognitive impairment per unit increase of HDI =0.75 (0.58–0.97) and 0.81(0.63–1.04) in two cohorts.	A healthy diet (higher HDI) might be associated with a better cognitive function in elderly men.
Corrêa Leite <i>et al.</i> 2001 [27]	Cross-sectional	560 men and 1091 women aged ≥65 years; Italy.	Neuropsychological test score (≥53 for normal cognition; 40–52 for mild cognitive deficit; 24–39 for moderate cognitive deficit; <= 23 or less for severe deficit).	180-item FFQ	HDI	After multivariable adjustment, OR (95% CI) for any level of cognitive deficit per unit increase of HDI = 0.85 (0.77–0.93).	A better HDI was associated with a lower prevalence of cognitive deficit in the elderly.
Wengreen <i>et al.</i> 2009 [29]	Prospective	3634 subjects ≥ 65 years of age followed up for an average ~11 years; Cache County Study on Memory and Aging in Utah.	3MS	142-item FFQ	RFS	Subjects in the highest quartile (Q4) of RFS scored 1.80 points higher on the baseline 3MS test than did those in the Q1 (P < 0.001). Subjects with Q4 RFS declined less (3.41 points) than those with Q1 RFS (5.15 points) (P = 0.0013) over 11 years.	Consuming a diverse diet that includes a variety of recommended foods may help to attenuate age-related cognitive decline among the elderly.
Scarmeas <i>et al.</i> 2006a [35]	Prospective	2,258 nondemented subjects ≥ 65 years old followed up for an average 4 years; WHICAP.	Comprehensive Neuropsychological test battery. Physicians screened subjects for potential AD by neurologists and neuropsychologists.	61-item FFQ	MeDi	Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a HR(95%CI)=0.85 (0.63–1.16) and in the highest tertile 0.60 (0.42– 0.87) for AD (p-for-trend=0.007).	MeDi is associated with a reduction in risk for incident AD.
Scarmeas <i>et al.</i> 2006b [33]	Case-control	194 patients with AD and 1790 nondemented participants of WHICAP.	As Scarmeas N 2006a.	61-item FFQ	MeDi	Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had an OR(95% CI) of 0.47(0.29–0.76) and those at the highest tertile an OR(95% CI) of 0.32 (0.17–0.59) for AD (p-for-trend=0.001).	Higher adherence to the MeDi is associated with a reduced risk for AD.
Scarmeas <i>et al.</i> 2009 [34]	Prospective	1393 cognitively normal	As Scarmeas N 2006. MCI diagnosis	61-item FFQ	MeDi	Compared with subjects in the lowest MeDi tertile,	Higher adherence to the MeDi is

Reference	Study Design	Subjects	Cognition Assessment or AD Diagnosis	Food Intake Assessment	DP Construction	Results	Conclusion
		participants (≥ 65 years old) of WHICAP followed up for 4.5 years				subjects in the middle and highest MeDi tertile had HR = 0.83(0.62–1.12) and 0.72(0.52–1.00) of developing MCI (p-for-trend = 0.05), respectively. Compared with subjects in the lowest MeDi tertile, HR of MCI conversion to AD for middle and highest tertiles = 0.55(0.34–0.90) and 0.52(0.30–0.91), respectively, p for trend = 0.02	associated with reduced risk of developing MCI and with reduced risk of MCI conversion to AD.
Psaltopoulou <i>et al.</i> 2008 [36]	Prospective	732 subjects ≥ 60 years old followed up for 6–13 years; EPIC–Greece cohort	MMSE	61-item FFQ	MeDi	Adherence to the MeDi exhibited weakly positive (multiple regression for 1 unit increase of MeDi $\beta=0.05$) but not significant ($p=0.485$) associations.	Adherence to the MeDi was very weakly positively and not significantly associated with MMSE score.
Feart <i>et al.</i> 2009 [37]	Prospective	1410 adults (≥ 65 years) from Bordeaux, France, included in the Three-City cohort in 2001–2002. Median followed up time was 4.1 years.	MMSE for global cognitive performance, IST for semantic verbal fluency and speed of verbal production, BVRT for immediate visual memory, FCSRT for verbal episodic memory.	FFQ	MeDi	Higher MeDi score associated with fewer MMSE errors ($\beta = -0.006$; 95% CI, -0.01 to -0.0003 ; $P = 0.04$ for 1 point increase of the MeDi score). MeDi was not associated with the risk for incident dementia: HR (95% CI) = 1.12 (0.60–2.10) comparing the highest to the lowest tertile; $P = 0.72$.	Higher adherence to MeDi was associated with slower MMSE cognitive decline but not consistently with other cognitive tests. Higher adherence was not associated with risk for incident dementia or AD.
Smith <i>et al.</i> 2010 [38]	Randomized clinical trial	124 participants with elevated blood pressure who were sedentary and over-weight or obese	A battery of neurocognitive tests at baseline and again after the 4-month intervention.	N/A	DASH	Compared with subjects on the usual diet, subjects on DASH+ weight management arm and the DASH diet alone arm both exhibited greater neurocognitive improvements.	Combining aerobic exercise with the DASH diet and caloric restriction improves neurocognitive function among sedentary and overweight/obese individuals with pre-hypertension and hypertension.
Barberger-Gateau <i>et al.</i> 2007 [41]	Prospective	8,085 participants (≥ 65 years) of the Three-City cohort study in France. Median	3 steps: neuropsychological tests; neurologists screened subjects for potential AD patients;	FFQ	Good and Poor DP's	A poor DP (infrequent consumption of fish, fruits and vegetables, and no regular use of omega-3 rich oils) was associated with an increased risk for dementia:	A combination of dietary sources of omega-3 PUFA and antioxidants seems therefore necessary

Reference	Study Design	Subjects	Cognition or AD Diagnosis	Food Intake Assessment	DP Construction	Results	Conclusion
		followed up time was 3.7 years.	consensus diagnosis by neurologists.			HR(95% CI)=1.51(1.04–2.20) and AD 1.63(1.04–2.56). Having either of the two good DPs “fish (≥1/week) & fruits and vegetables daily” or “0-3 rich oils and fruits and vegetables daily”) had a decreased risk of dementia: HR=0.72 (0.54–0.97). “Having a single good DP” was not associated with risk of dementia.	for a protective effect against dementia.
Samieri <i>et al.</i> 2008 [43]	Cross-sectional	1,724 subjects aged ≥65 years; the Three-City cohort in France.	MMSE	FFQ	Cluster analysis	Mean MMS score was higher in the “healthy” cluster and lower in the “biscuits and snacking” cluster in both sexes.	A “healthy” dietary pattern characterized by higher consumption of fish in men and fruits and vegetables in women was related to better cognitive performance.
Akbaraly <i>et al.</i> 2009 [45]	Cross-sectional	4,693 aged 35–55 years white European participants of the Whitehall II study	Cognitive test battery consisted of 5 standard tasks.	127-item FFQ	PCA	The ‘whole food’ pattern was associated with lower (OR=0.5–0.9, $p<0.05$ for all 5 domains) and the ‘processed food’ pattern with increased (OR=1.0–1.8, $p<0.05$ for all domains except memory) odds of cognitive deficit.	A diet rich in fruits, vegetable and fish (‘whole food’ pattern) is associated with lower odds of cognitive deficit while ‘processed food’ DP rich in processed meat, chocolates and sweeteners, desserts, fried food, refined grains and high fat dairy products is associated with greater odds of cognitive deficit. Education shapes the relationships.
Gu <i>et al.</i> 2010 [48]	Prospective	2148 nondemented individuals ≥ 65 years old followed up for an average 4 years; WHICAP.	As Scarmeas N 2006a.	61-item FFQ	RRR	A DP was identified and it was strongly associated with lower AD risk: compared to subjects in the lowest tertile of adherence to this pattern, AD HR (95% CI) for subjects in the highest DP tertile was 0.62 (0.43–0.89) after multivariable	Higher consumption of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, dark- and green-leafy vegetables and lower of high fat dairy, red meat, organ meat, and butter may be

Reference	Study Design	Subjects	Cognition Assessment or AD Diagnosis	Food Intake Assessment	DP Construction	Results	Conclusion
						adjustment, p for trend = 0.01.	associated with decreased risk of AD via a more favorable profile of nutrients (i.e. lower ingestion of SFA and higher ingestion of PUFA, Vitamin E and folate).

* Except for one study [45] that included younger participants.
Abbreviations: Benton Visual Retention Test (BVRT); Dietary Approaches to Stop Hypertension (DASH); Free and Cued Selective Reminding Test (FCSRT); Healthy diet indicator (HDI); Isaacs Set Test (IST); Mediterranean diet (MeDi); Modified Mini-Mental State Examination (3MS); Mini-Mental State Examination (MMSE); Recommended food score (RFS), Washington Heights-Inwood Columbia Aging Project (WHICAP).