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Review

Adherence to Healthy Diet Can Delay Alzheimer's Diseases Development: A Systematic Review and Meta-Analysis

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ABSTRACT: A healthy diet has long been indicated to be protective against Alzheimer's diseases (AD). We carried out a systematic review and meta-analysis of published observational studies to explore the relationship between healthy and unhealthy diets and risk of ADs. We screened PubMed, Scopus, Web of Sciences, Google Scholar, Science Direct, and Embase, and screened manually to identify relevant articles published in English and non-English until Jun 2020. We classified the studied dietary patterns into two groups: healthy and unhealthy diets. The pooled weighted mean difference and 95% confidence interval (95% CI) was used to analyze the data using a random-effects model. The data were extracted manually and the preferred reporting items for systematic review and meta-analysis checklist was used to appraise the risk of bias and quality of data. Of the 1,813 articles identified, 21 met the inclusion criteria and were included in the quantitative analysis. A healthy diet was related to a lower risk of AD [odds ratio (OR): 0.45, 95% CI: 0.23 to 0.86, I^2=99.7%; n=17 studies]. Moreover, high adherence to an unhealthy diet was not associated with increased risk of AD (OR: 0.99, 95% CI: 0.98 to 0.99, I^2=0.0%; n=6 studies). However, the etiology of AD is uncertain and it is difficult draw conclusions about dietary healthy patterns. We concluded that adherence to a healthy diet is associated with a lower risk of AD, but were unable to find evidence that an unhealthy diet increases the risk of AD.

Keywords: Alzheimer's disease, dietary pattern, healthy diet, meta-analysis, systematic review

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease associated with progressive memory and cognitive impairment (Niu et al., 2017). Although the etiology of AD is unclear, evidence suggests that damage to nerve cells involved in cognitive functions may promote AD development (Alzheimer's Association, 2015). Extracellular amyloid-β (Aβ) plaques accumulate in the brain, which cause synapse dysfunction and results cell death (Querol-Vilaseca et al., 2019). In 2017, approximately 6.08 million persons in the United States were suffering from clinical or mild cognitive impairment due to AD; this figure is estimated to increase to 15 million by 2060 (Brookmeyer et al., 2018). There is an increasing prevalence of AD worldwide, associated with the rapidly aging population (Niu et al., 2017).

Diet can have a protective role on cognitive function in human aging. In animal models dietary restriction without malnutrition extends life span and decreases the incidence of neurodegenerative disorders by protecting against brain atrophy (Cox et al., 2019; Pifferi and Aujard, 2019). Many studies have evaluated one type of diet and risk of AD (Scarmeas et al., 2006b; Gu et al., 2010a; Eskelinen et al., 2011; Gu et al., 2011; Gardener et al., 2012; Liu et al., 2016). A healthy diet is reflected by adequate consumption of whole grains, nuts, legumes, fruits, vegetables, low-fat dairy, poultry, and fish, and by low consumption of red meat, processed meat, and added sugar foods (Pasdar et al., 2019; Pasdar et al., 2020a). For example, Mediterranean diets (MDs), which emphasizes higher intakes of whole grains, vegetables, nuts, fish, olive, olive oil, and lower intakes of red meat and processed meat, and wine as the main source of alcohol, are con-

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sidered healthy diets (Scarmeas et al., 2006b; Pasdar et al., 2020b). In contrast, unhealthy diets, such as Western diets, are high in saturated fat, trans-fatty acids, refined grains, red meat, processed meat, and added sugar, promote obesity and many chronic diseases, such as cardiovascular disease, diabetes, depression, and cancer (Pasdar et al., 2019; Moludi et al., 2020).

Dietary components such as vitamin C, vitamin E, flavonoids, and unsaturated fatty acids can delay the degeneration of neurons and nerve tissue (Scarmeas et al., 2006a). Some epidemiological studies have stated protective role of diet on incidence of AD (Scarmeas et al., 2006a; Scarmeas et al., 2006b; Devore et al., 2009; Gu et al., 2010b; Morris et al., 2015). However, no studies have yet categorized or summarized this evidence. In our recent systematic review, we qualitatively summarized the association between diet and risk of AD. These results indicated that high adherence to a healthy diet can decrease the incidence of AD and that an unhealthy diet has neurodegenerative effects (Samadi et al., 2019).

To the best of our knowledge, there no meta-analyses and systematic reviews have quantified the association between diet and risk of AD. Therefore, we carried out a meta-analysis and systematic review of the association between diet and risk of AD, expanding on the results of our previous meta-analysis by exploring the association between a healthy diet and risk of AD.

MATERIALS AND METHODS

Design

This systematic review and meta-analysis was carried out by following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (Moher et al., 2015) until Jun 2020. The meta-analysis was registered in PROSPERO (ID: CRD42020171361).

Search strategy

We designed the systematic search terms using related medical subject headings (MeSH) and non-MeSH keywords (Table 1). Two independent researchers searched online electronic databases, including PubMed, Scopus, Web of Sciences, Google Scholar, Science Direct, and Embase. In addition, we manually searched the references of the relevant review articles to identify any additional relevant articles. Also, we did not filter articles by publication time, location of the study or language.

Inclusion and exclusion criteria

Eligible studies were performed on adults and evaluated the relationship between dietary patterns and risk of AD. We considered all observational studies, including case-control, cross-sectional, prospective, and retrospective studies. Interventional studies were not included to this study because the duration of exposure is generally short. Overall, we identified 1,813 articles in the initial search. We excluded duplicate studies (n=103) and the remaining studies were screened based on topic, following which a further 1,554 studies were excluded. An additional, 40 studies were excluded based on study type. We reviewed the full texts of the remaining 116 studies. Of these, 89 studies were excluded: 20 did not assess dietary patterns and 69 did not evaluate the outcome "Alzheimer's disease". In addition, 6 studies were excluded as they did not determine an effect size (Gustaw-Rothenberg, 2009; Mosconi et al., 2014; Berti et al., 2015; Liu et al., 2016; Pase et al., 2017; Calil et al., 2018). In total, 21 eligible studies were identified (Fig. 1).

Table 1. Medical subject headings (MeSH) and non-MeSH keywords used to search relevant publications

Concept 1	"diet" OR "food" OR "dietary" OR "dietary pattern" OR "food pattern"
Concept 2	"Alzheimer's disease" OR "Alzheimer's 's disease"
Concept 3	"Cohort studies" OR "Prospective studies" OR "Retrospective studies" OR "Cross sectional" OR "Case control" OR "Cohort" OR "Prospective" OR "Retrospective"

The combination of keywords was used to search online databases as follows: ("concept 1" AND "concept 2" AND "concept 3").

Quality assessment

The strengthening the reporting of observational studies in epidemiology (STROBE) guidelines was used to evaluate the quality of the studies. STROBE guidelines include a checklist of 22 items that are considered essential for good reporting of observational studies, including for the title, abstract, introduction, methods, results, and discussion. Of these, 18 items were common across all observational studies and the other items were specific for case-control, cohort, and cross-sectional studies (PLoS Medicine at http://www.plosmedicine.org/). This list is liberally available on the PLoS medicine website, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/ (Vandenbroucke et al., 2007). Evidence on the STROBE Initiative is accessible at www.strobe-statement.org. The scores of the methods sections of the included studies are presented in Table 2.

Data extraction and quality assessment

Data were extracted by two independent investigators (SM and JM) using a data collection checklist. Any disagreement during quality assessment and data extraction were discussed and resolved accordingly. This checklist included first author name, study population, study year,

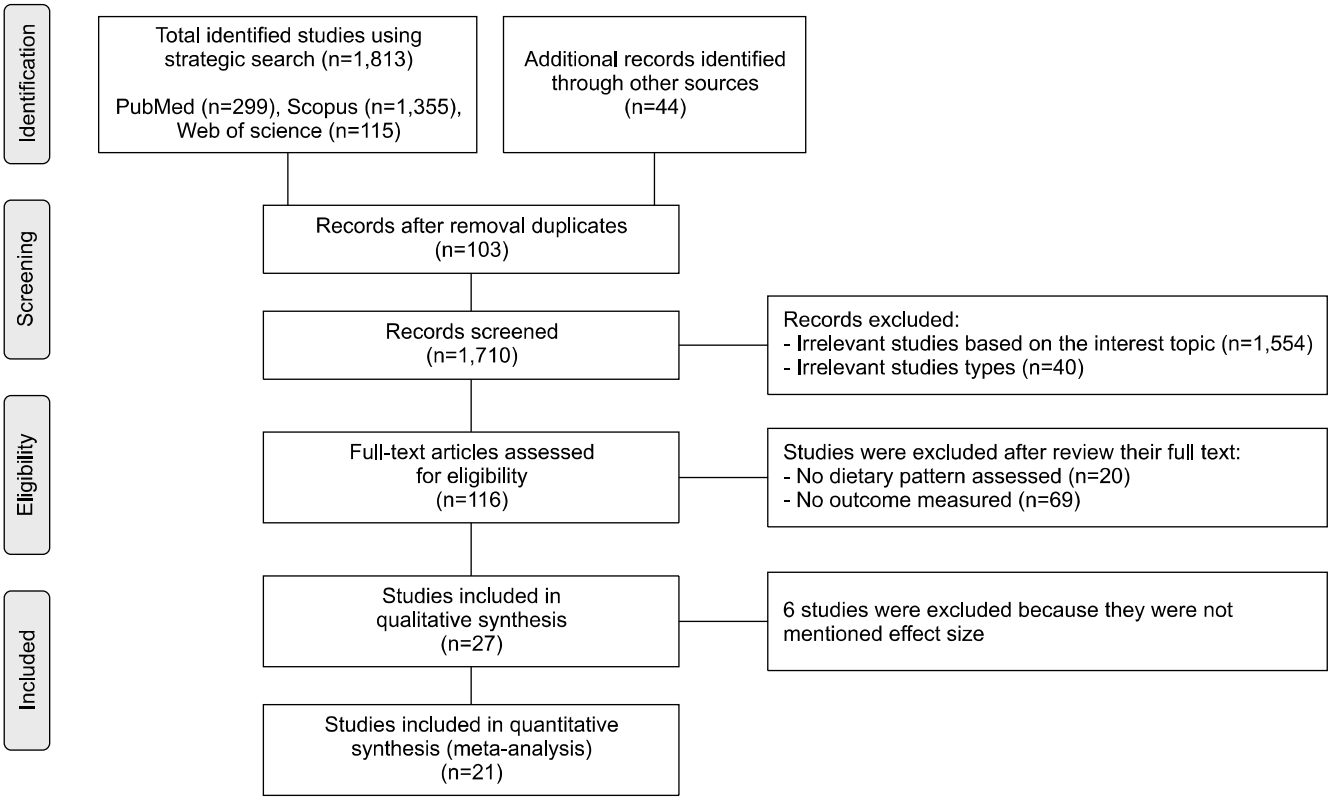

Fig. 1. Flow diagram of the literature search.

study design, study country, sample size, age, dietary assessment instruments, and type of dietary pattern.

Definition of adherence to a healthy diet

Based on the reviewed studies, we categorized dietary patterns as healthy and unhealthy. Healthy dietary patterns were related to intake of fiber, vegetables, fruits, sea foods, poultry, low fat dairy, and whole grains, and a high intake of antioxidants and polyunsaturated and monounsaturated fatty acids (PUFA and MUFA, respectively). Unhealthy dietary patterns included a high intake of sugar-sweetened beverages, processed and red meat, refined grains, and fatty foods (Lyros et al., 2014). By these definitions, 16 of the identified articles evaluated healthy dietary patterns and five evaluated unhealthy dietary patterns. All data are presented in the RESULTS.

Statistical analysis

Data analysis was performed using STATA (ver. 15.1) software (StataCorp LLC, College Station, TX, USA). Differences between results were considered significant at $P<0.05$. The relationship between dietary patterns and risk of AD was expressed in odds ratios (ORs). To combine the results of the different studies, OR logarithms were employed for each study, and I^2 indexes and Cochran Q tests were used to measure study heterogeneities (Higgins and Green, 2019). Furthermore, we used a popular method by Zhang and Yu (1998) for converting risk ratios to OR. The I^2 index can be categorized as slight heterogeneity (less than 25%), moderate heterogeneity (25% to 75%), and intense heterogeneity (more than 75%). Since the fixed effects model is used for low heterogeneity and the random effects model is used for high heterogeneity, we used a random effects model (I^2=99.7%). In addition, we used Egger's regression asymmetry test and visual inspection of funnel plots to evaluate potential publication bias.

RESULTS

Literature search

Of the 1,813 articles identified, 21 met the eligibility criteria and were involved in the quantitative analysis. Details of the meta-analysis selection process are shown in Fig. 1.

Study characteristics

Sample sizes ranged from 115 and 5,395, with studies had durations of follow-up ranging from 3.7 to 18 years. The outcome of interest was risk of AD. Only six of the 21 studies were carried out in Mediterranean populations. The other cohorts included populations in the US and Northern Europe, and a cohort of Europeans living in Australia. The overall number of subjects in the included studies was 50,506. All but four prospective studies used

Table 2. Quality assessment of studies included in the systematic review and meta-analysis based on strengthening the reporting of observational studies in epidemiology statement

	Morris et al. (2003a)	Morris et al. (2003b)	Scarmeas et al. (2006a)	Scarmeas et al. (2006b)	Laitinen et al. (2006)	Luchsinger et al. (2007)	Scarmeas et al. (2009a)	Devore et al. (2009)	Gu et al. (2010a)	Gu et al. (2010b)	Gu et al. (2011)
Study design	*	*	*	*	*	*	*	*	*	*	*
Study location and date	*	*	*	*	*	*	*	*	*	*	*
Study sittings: periods of recruitment, exposure, and follow-up	*	*	*	*	*	*	*	*	*	*	*
Sampling method and adequate sample size	*	*	*	*	*	*	*	*	*	*	*
Inclusion and exclusion criteria and demographic characteristics	*	*	*	*	*	*	*	*	*	*	*
Data sources - measurements	*	*	*	*	*	*	*	*	*	*	*
Outcome data	*	*	*	*	*	*	*	*	*	*	*

	Eskelinen et al. (2011)	Gardener et al. (2012)	Ozawa et al. (2013)	Morris et al. (2015)	Olsson et al. (2015)	Morris et al. (2016)	Ylilauri et al. (2017)	Vassilaki et al. (2018)	Fernando et al. (2018)	Hill et al. (2018)
Study design	*	*	*	*	*	*	*	*	*	*
Study location and date	*	*	*	*	*	*	*	*	*	*
Study sittings: periods of recruitment, exposure, and follow-up	*	*	*	*	*	*	*	*	*	*
Sampling method and adequate sample size	*	*	*	*	*	*	*	*	*	*
Inclusion and exclusion criteria and demographic characteristics	*	*	*	*	*	*	*	*	*	*
Data sources - measurements	*	*	*	*	*	*	*	*	*	*
Outcome data	*	*	*	*	*	*	*	*	*	*

a food frequency questionnaire (FFQ) for dietary assessment; these 4 studies used food records and dietary habit questionnaires (Laitinen et al., 2006; Eskelinen et al., 2011; Olsson et al., 2015; Ylilauri et al., 2017). General study characteristics are summarized in Table 3 and 4. Based on the STROBE statement, all studies included in this meta-analysis were of adequate quality (Table 2).

Publication bias

We investigated the heterogeneity of the included studies using chi-square tests. The random-effect model was used due to high heterogeneity (Higgins and Green, 2011). Egger's linear regression investigations did not identify evidence of publication bias for the healthy (P=0.24, Fig. 2) or unhealthy (P=0.066, Fig. 3) groups.

Diet and risk of AD

In this updated systematic review and meta-analyses, data of new studies were combined with data included in former reports. Overall risk of AD was reported in 18 prospective studies, 2 cross-sectional studies, and 1 case-control study.

Using the random effects model, we observed that maximum adherence to a healthy diet was inversely associated with lower risk of AD [OR: 0.45, 95% confidence interval (CI): 0.23 to 0.86, I^2=99.7%; n=17 studies] (Fig. 4, Table 5). Moreover, high adherence to an unhealthy dietary pattern was not associated with risk of AD (OR: 0.99, 95% CI: 0.98 to 0.99, I^2=0.0%; n=6 studies) (Fig. 5, Table 6).

Table 3. Characteristics of studies that assessed healthy dietary patterns and risk of Alzheimer's diseases

	Study name	Study design	Country	Sample size	Age (years)	Dietary pattern assessment tools	Kind of diet	Diet components
Morris et al. (2003b)	Chicago health and aging project	Prospective study	USA	815 (101 men and 713 women)	≥65	FFQ	Seafood rich diet	Tuna sandwich, fish sticks, cakes; or sandwich, fresh fish as a main dish, and shrimp, lobster, or crab
Morris et al. (2003a)							Dietary vegetable oil	Dairy products, removal fat, or poultry skin, specified brand name products for cereals, margarine, oil, and multivitamins
Scarmeas et al. (2006a)	WHICAP 1992 and WHICAP 1999	Case-control	USA	1,984 (630 men and 1,354 women)	76.3 (mean)	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
Scarmeas et al. (2006b)	WHICAP 1992 and WHICAP 1999	Prospective study	USA	2,226 (720 men and 1,506 women)	77.2 (mean)	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
Scarmeas et al. (2009a)	WHICAP 1992 and WHICAP 1999	Prospective study	USA	1,880 (587 men and 1,293 women)	77.2 (mean)	FFQ	MD	Dairy, meat, fruits, vegetables, legumes, cereals, and fish
Devore et al. (2009)	Ommoord cohort study	Prospective study	The Netherlands	5,395 (2,211 men and 3,184 women)	≥55	FFQ	Seafood rich diet	Total fish intake and intake of different fish types (e.g., salmon)
Gu et al. (2010a)	WHICAP II	Prospective study	USA	1,219 (407 men and 812 women)	≥65	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
Gu et al. (2010b)	WHICAP 1992 and WHICAP 1999	Prospective study	USA	2,148 (691 men and 1,457 women)	≥65	FFQ	MD	Higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables, and a lower intake of high fat dairy products, red meat, organ meat, and butter
Eskelinen et al. (2011)	The cardiovascular risk factors, aging, and dementia (CAIDE) study	Prospective study	Sweden	525 (201 men and 324 women)	65~79	Dietary habits question-naire	HEI	Beneficial components (vegetables and roots, berries, and fruits, bread, fish, coffee drinking, MUFAs, and PUFAs from milk products and spreads) and unhealthy (sausage foods, eggs, candies, sweet soft drinks, sugar lumps in coffee, salty fish, and SFAs from milk products, and spreads)
Gardener et al. (2012)	The Australian imaging, biomarkers, and lifestyle study of ageing (AIBL)	Prospective study	Australia	970 (402 men and 568 women)	≥60	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
Ozawa et al. (2013)	Hisayama study	Prospective study	Japan	1,006 (433 men and 573 women)	60~79	FFQ	Soy based food and diary	High intake of soybeans and soybean products, vegetables, algae, and milk and dairy products, and a low intake of rice

Table 3. Continued

	Study name	Study design	Country	Sample size	Age (years)	Dietary pattern assessment tools	Kind of diet	Diet components
Olsson et al. (2015)	The Uppsala longitudinal study of adult men (ULSAM)	Prospective study	Sweden	1,602 men	60~70	Food record	HEI	WHO dietary guidelines
							MD	PUFA/SFA (ratio), fruits, vegetables, legumes, cereals, fish, meat, dairy products and alcohol
							LCHP	Carbohydrate and protein intake
Morris et al. (2015)	Rush memory and aging project	Prospective study	USA	923 (232 men and 691 women)	58~98	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
							DASH	7 food groups and 3 dietary components (total fat, saturated fat, and sodium)
							MIND	Ten brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter, and stick margarine, cheese, pastries, and sweets, and fried/fast food)
Morris et al. (2016)	Rush memory and aging project	Cross-sectional	USA	286 (93 men and 193 women)	89.9 (mean)	FFQ	Seafood rich diet	Tuna sandwich; fish sticks, cakes, or sandwich; fresh fish as a main dish; and shrimp, lobster, or crab
							DHA + EPA Food sources	
							α-Linolenic 18:3 n-3	
Vassilaki et al. (2018)	Mayo clinic study of aging (MCSA)	Prospective study	USA	278 (155 men and 123 women)	70~89	FFQ	MD	Fruits, vegetables, legumes, cereals, fish, meat, and dairy products
Fernando et al. (2018)	The Australian imaging, biomarkers and lifestyle study of ageing (AIBL)	Cross-sectional	Australia	541 (222 men and 319 women)	≥60	FFQ	High protein and high fiber	Grams per day intake of protein and fiber
Hill et al. (2018)	The women's health aging project	Prospective study	Australia	115 men	45~55	FFQ	MD	Whole grains, vegetables, nuts, fish, and wine as the main source of alcohol
							low fat	Low-fat dairy products, vegetables, and unsaturated spreads

FFQ, food frequency questionnaire; MD, Mediterranean diet; HEI, healthy eating index; LCHP, low carbohydrate high protein; DASH, dietary approaches to stop hypertension; MIND, Mediterranean-DASH intervention for neurodegenerative delay; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Table 4. Characteristics of studies that assessed an unhealthy dietary pattern and risk of Alzheimer's diseases

	Study name	Study design	Country	Sample size	Age (year)	Dietary pattern assessment	Kind of diet	Diet components
Morris et al. (2003a) Morris et al. (2003b)	Chicago health and aging project	Prospective study	USA	815 (101 men and 713 women)	≥65	FFQ	High fat diet and high animal fat diet	Dairy products, removal fat or poultry skin, specified brand name products for cereals, margarine, oil, and multivitamins
Laitinen et al. (2006)	The cardiovascular risk factors, aging and incidence of dementia (CAIDE) study	Prospective study	Finland	1,449 (549 men and 900 women)	65~80	Dietary habit question-naire	High fat diet	Milk, sour milk, eggs, coffee, tea, and sugar in tea/coffee
Luchsinger et al. (2007)	—	Prospective study	USA	939 (549 men and 390 women)	≥65	FFQ	High glycemic diet	Carbohydrate and sugary food intake
Gu et al. (2011)	WHICAP 1992 and WHICAP 1999	Prospective study	USA	2,258 (1,526 men and 732 women)	≥65	FFQ	DII	Amount and type of fat, essential fatty acids, vitamins, minerals and antioxidants, glycemic index, and anti-inflammatory compounds
Ylilauri et al. (2017)	The Kuopio ischemic heart disease risk factor study	Prospective study	Finland	2,497 men	42~60	Food record	Dietary choles-terol	Cholesterol from all component of diet
							Dietary choles-terol from egg intake	Cholesterol from egg
Hill et al. (2018)	The women's health aging project	Prospective study	Australia	115 women	45~55	FFQ	High fat	High-fat diet loaded heavily on food groups such as processed meats, fried fish, red meats, fried potatoes, and poultry
							Junk food	High consumption of takeaway foods, added sugar, confectionary and cakes, biscuits, and sweet pastries

FFQ, food frequency questionnaire; DII, dietary inflammatory index.

DISSCUSION

The current meta-analysis evaluating >50,506 subjects showed a significant relationship between adherence to a healthy diet and decreased risk of AD. Indeed, adhering to a healthy diet was associated with a significantly lower overall risk of AD (by approximately 55%). However, we showed an unhealthy diet had a minimal effect on risk of AD.

A healthy diet can improve overall health by providing fluids, macronutrients, micronutrients and adequate calories (Swain et al., 2008), and helps protect against many chronic diseases, including heart disease, cancer, and diabetes (de Ridder et al., 2017). Our results suggest the combination of food groups considered a healthy diet exerts benefits for the brain (Olsson et al., 2015). However, it ultimately remains challenging to define a healthy diet (Tangney et al., 2017). A healthy diet may contain fruits, vegetables, whole grains and white meat (fish and poultry), and little or no sweetened beverages and processed food (Swain et al., 2008). Whereas unhealthy diets, constituting refined grains, sweetened desserts, high fat dairy products, and processed/red meat, have been associated with a higher risk of AD (Olsson et al., 2015;

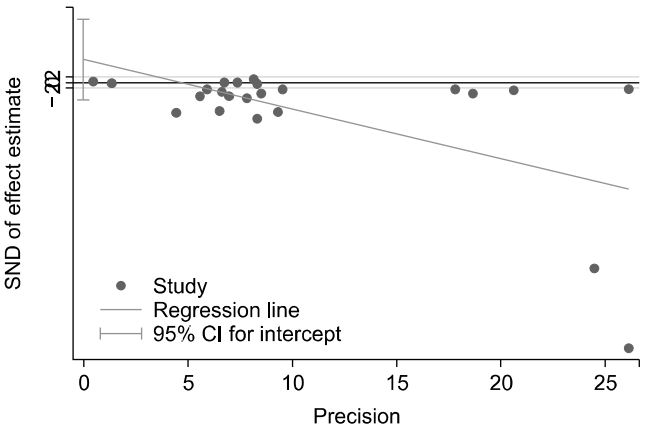

Fig. 2. Publication bias for articles on healthy dietary pattern and risk of Alzheimer's diseases. SND, standard normal distribution; CI, confidence interval.

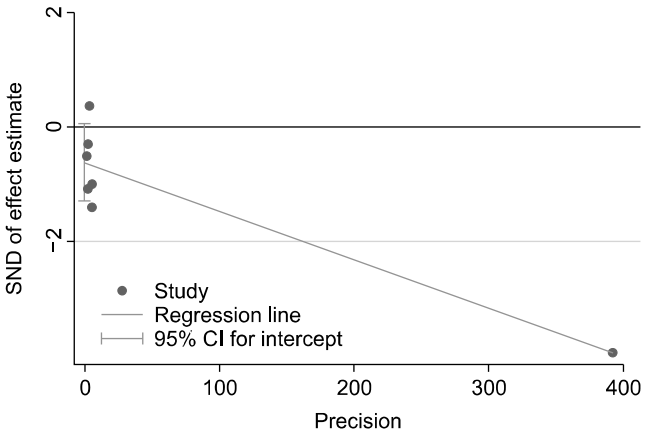

Fig. 3. Publication bias for articles on unhealthy dietary pattern and risk of Alzheimer's diseases. SND, standard normal distribution; CI, confidence interval.

Samadi et al., 2020). The main healthy dietary patterns identified in respect to risk of AD, include the MD (Scarmeas et al., 2006a; Scarmeas et al., 2006b; Scarmeas et al., 2009b; Gu et al., 2010a; Gu et al., 2010b; Gardener et al., 2012; Morris et al., 2015; Olsson et al., 2015; Hill et al., 2018; Vassilaki et al., 2018), dietary approaches to stop hypertension (DASH) diet (Morris et al., 2015), Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet (Morris et al., 2015), healthy eating index (HEI) diet (Eskelinen et al., 2011; Olsson et al., 2015), seafood-rich diet (Morris et al., 2003b; Devore et al., 2009; Morris et al., 2016), soy-based diet (Ozawa et al., 2013), and low-fat diet and high-protein diet (Olsson et al., 2015; Fernando et al., 2018; Hill et al., 2018).

Our findings indicate that healthy dietary patterns decrease the incidence of AD. This is not unpredicted because all components of a healthy diet (e.g., vegetables, fruits, plants proteins, and polyunsaturated-to-saturated fat ratio) have protective roles against AD (Devore et al., 2009; Holt et al., 2009; Farooqui, 2012; Berti et al., 2015; Calil et al., 2018). The health-related benefits of foods consumed together are additive or even synergistic. The

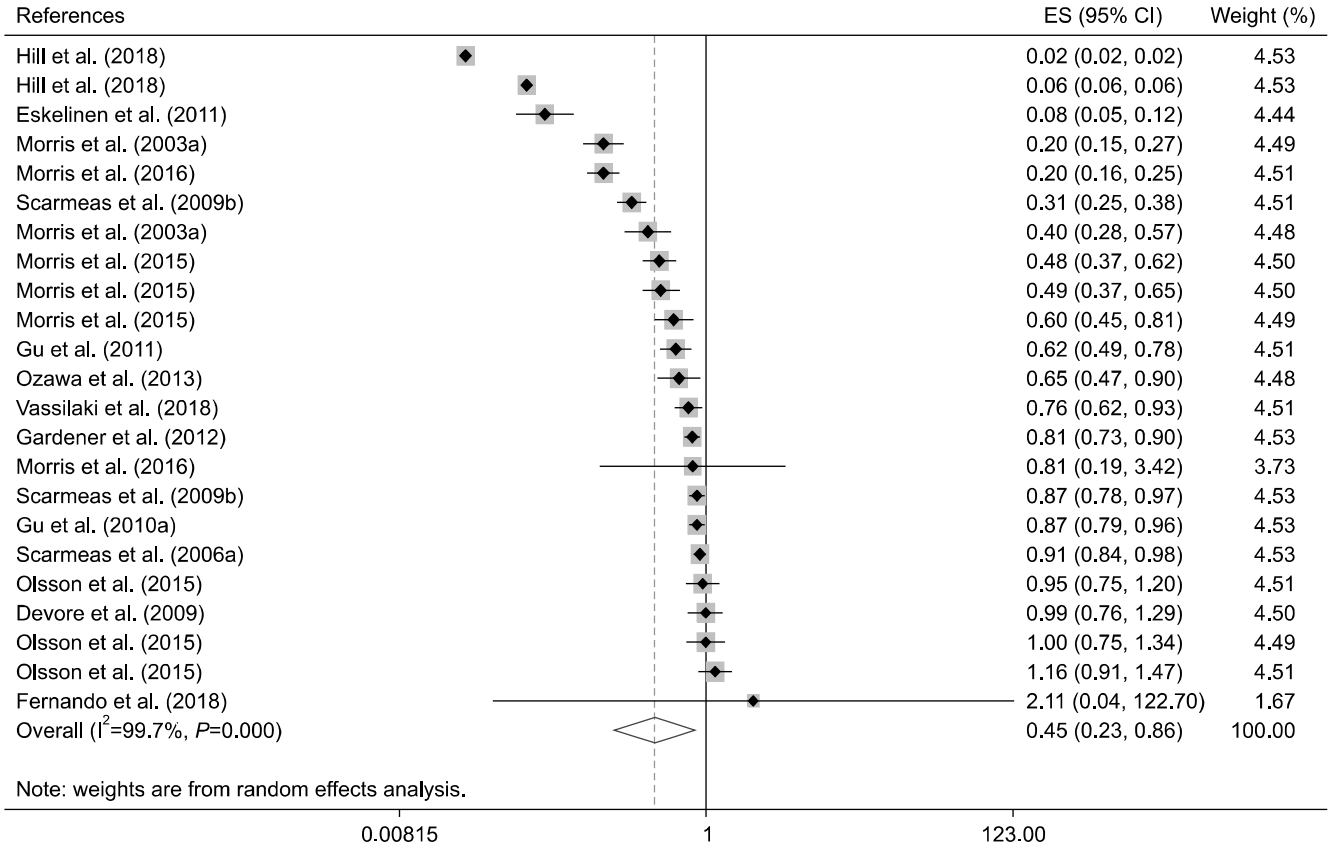

Fig. 4. Forest plot of healthy dietary pattern and risk of Alzheimer's diseases. ES, effect size; CI, confidence interval.

Table 5. Studies that investigated the association between a healthy dietary pattern and Alzheimer's diseases

	Kind of diet	Comparison	Effect size	Confidence interval	Outcome[1)]
Morris et al. (2003b)	Seafood-rich diet	Q4 vs. Q1	RR: 0.4	0.2~0.9	1, 2, 3, 4, 7, 28
Morris et al. (2003a)	Dietary vegetable oil		RR: 0.6	0.3~1.3	1, 2, 3, 4, 7, 27, 28
Scarmeas et al. (2006a)	MD	Continuous	HR: 0.91	0.83~0.98	1, 2, 3, 4, 8, 10, 12, 13, 28
Scarmeas et al. (2006b)	MD	T3 vs. T1	OR: 0.31	0.16~0.58	1, 2, 3, 4, 8, 10, 11, 12, 13, 24, 25, 28
Devore et al. (2009)	Seafood-rich diet	T3 vs. T1	HR: 0.99	0.76~1.29	1, 2, 3, 4, 21, 22, 23
Scarmeas et al. (2009a)	MD	Continuous	HR: 0.87	0.77~0.99	1, 2, 3, 4, 5, 8, 10, 12, 14, 16, 17, 18, 28
Gu et al. (2010a)	MD	Continuous	HR: 0.87	0.78~0.97	–
Gu et al. (2010b)	MD	T3 vs. T1	HR: 0.62	0.43~0.89	1,2, 4, 11, 12, 17, 28
Eskelinen et al. (2011)	HEI	High adherence vs. low	OR: 0.08	0.01~0.89	1, 2, 4, 12
Gardener et al. (2012)	MD	Continuous	OR: 0.806	0.71~0.92	–
Ozawa et al. (2013)	Soy-based food and dairy	Q4 vs. Q1	HR: 0.65	0.40~1.06	1, 2, 3, 4, 8, 10, 12, 13, 14, 16, 17, 18, 19, 28
Olsson et al. (2015)	HEI	Continuous	HR: 0.95	0.75~−1.22	–
	MD		HR: 1	0.75~1.33	
	LCHP		HR: 1.16	0.95~1.43	
Morris et al. (2015)	MD	T3 vs. T1	HR: 0.48	0.29~0.79	1, 2, 4, 8, 9, 10, 12, 14, 15, 16, 30
	DASH		HR: 0.6	0.37~0.96	
	MIND		HR: 0.49	0.29~0.85	
Morris et al. (2016)	Seafood-rich diet	Continuous	Beta: 0.2	−0.04~0.43	1, 2, 4, 5, 10, 12, 28
	DHA+EPA food sources		Beta: 0.81	−0.63~2.25	
	α-Linolenic 18:3 n-3		Beta: −0.37	−0.93~0.18	
Vassilaki et al. (2018)	MD	Continuous	OR: 0.76	0.58~0.99	1, 2, 4, 8, 10, 11, 12, 14, 16, 18, 26
Fernando et al. (2018)	High protein	T1 vs. T3	OR: 12.594	1.70~93.01	1, 2, 3, 4, 8, 10, 12, 13, 28
	High fiber		OR: 2.106	0.51~8.64	
Hill et al. (2018)	MD		Coefficient: 0.06	−0.02~0.14	1, 4, 17, 18
	Low fat	Liner	Coefficient: 0.023	−0.05~0.1	

MD, Mediterranean diet; HEI, healthy eating index; LCHP, low carbohydrate high protein; DASH, dietary approaches to stop hypertension; MIND, Mediterranean-DASH intervention for neurodegenerative delay; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RR, relative risk; HR, hazard ratio; OR, odd ratio.

[1)]Age (1), gender (2), race/ ethnic (3), education (4), country (5), enrollment time (6), follow-up time (7), smoking status (8), alcohol drinking (9), body mass index (10), physical activity (11), caloric intake (12), medical comorbidity index (13), diabetes (14), history of myocardial infarction (15), stroke (16), coronary heart diseases (17), hypertension (18), dyslipidemia (19), serum total cholesterol (20), high sensitivity C-reavtive protein (21), fasting insulin (22), adiponectin level (23), depression (24), dementia (25), cholesterol intake (26), other fat (27), apolipoprotein E ε4 allele (28), cognition (29), supplement use (30).

current study showed that the inverse link between adherence to a healthy diet and AD risk is not as a result of a lone constituent of this diet but rather the whole dietary pattern. Similarly, to our results, beneficial trends have been identified between AD and fruits and vegetables, fish, dairy, and nuts (Morris et al., 2003a; Swain et al., 2008; Olsson et al., 2015; Pifferi and Aujard, 2019). A healthy diet is recognized to have beneficial anti-inflammatory, antioxidant, and metabolic effects, which may in turn induce anti-neurodegenerative benefits (Seeram, 2006; Berti et al., 2015). Therefore, healthy diets (including DASH, MD, MIND, seafood-rich, HEI, soy-based, capsaicin-rich, and low-fat and high-protein diets) may reduce oxidative stress, chronic inflammation and accumulation of amyloid-β (Morris et al., 2003a; Morris et al., 2003b; Scarmeas et al., 2006a; Scarmeas et al., 2006b; Devore et al., 2009; Scarmeas et al., 2009b; Gu et al., 2010a; Gardener et al., 2012; Ozawa et al., 2013; Olsson et al., 2015; Morris et al., 2015; Morris et al., 2016; Fernando et al., 2018; Hill et al., 2018; Vassilaki et al., 2018). Moreover, few studies have focused on the ability of unhealthy diets, particularly diets high in fat and sugar-sweetened beverages, to promote oxidative stress, inflammation, and the developing of amyloid-β and, consequentially, AD (Morris et al., 2003b; Laitinen et al., 2006; Luchsinger et al., 2007; Gu et al., 2011; Ylilauri et al., 2017; Hill et al., 2018).

The present study did not show a relationship between an unhealthy diet (i.e. high in refined grains, sweetened puddings, full-fat dairy products, and processed/red

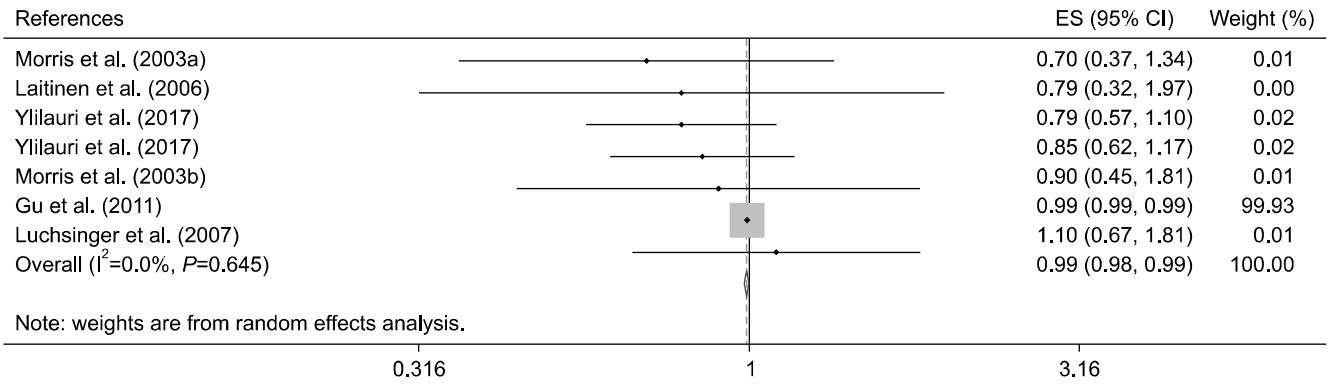

Fig. 5. Forest plot of unhealthy dietary pattern and risk of Alzheimer's diseases. ES, effect size; CI, confidence interval.

Table 6. Studies that investigated the association between an unhealthy dietary pattern and Alzheimer's diseases

	Kind of diet	Comparison	Effect size	Confidence interval	Adjustments[1)]
Morris et al. (2003a)	High fat diet	Q5 vs. Q1	RR: 0.9	0.4~1.8	1, 2, 3, 4, 6, 17, 18
Morris et al. (2003b)	High animal fat diet	Q5 vs. Q1	RR: 0.7	0.3~1.6	
Laitinen et al. (2006)	High fat diet	Q4 vs. Q1	OR: 0.79	0.29~2.12	1, 2, 5, 7, 9, 12, 13, 14, 15, 16, 17, 18
Luchsinger et al. (2007)	High-glycemic diet	Q4 vs. Q1	HR: 1.1	0.7~1.7	1, 2, 3, 4, 12, 18
Gu et al. (2011)	DII	Continuous	HR: 0.99	0.99~1	–
Ylilauri et al. (2017)	High cholesterol diet	Q4 vs. Q1	HR: 0.79	0.53~1.19	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 18
	High dietary egg	Q4 vs. Q1	HR: 0.85	0.59~1.23	
Hill et al. (2018)	High fat	Liner	Coefficient: −0.007	−0.09~0.07	1, 4, 18, 19
	Junk food	Liner	Coefficient: −0.09	−0.18~−0.008	

DII, dietary inflammatory index; ES, effect size; CI, confidence interval; RR, relative risk; OR, odd ratio; HR, hazard ratio.
[1)]Age (1), gender (2), race/ethnic (3), education (4), enrollment time (5), follow-up time (6), smoking status (7), alcohol drinking (8), body mass index (9), caloric intake (10), medical comorbidity index (11), diabetes (12), history of myocardial infarction (13), stroke (14), midlife systolic blood pressure (15), cholesterol (16), other fat (17), apolipoprotein E ε4 allele (18), cognition (19).

meat) and risk of AD. However, our results highlights that little is known about the relationship between an unhealthy diet and risk of AD. To our knowledge, few previous studies has investigated the relationship between Western diets, risk of AD, and the possible mechanism of action (Graham et al., 2016). Although we did not find a significant relationship between an unhealthy diet and risk of AD, we are unable to draw conclusions. For example, if the sample size increases, the statistical power is increased and may reach a false level of significance. Although the relationship between an unhealthy diet and risk of AD was not statically significant (approximately 1%), it may be clinically important (Filho et al., 2013; Gholizadeh et al., 2018). However, the constituents of an unhealthy diet, in contrast to a healthy diet, do not have a clear definition. The constituents of Western and unhealthy diets regularly include a high intake of high-fat dairy products, butter, processed meat, saturated- and trans-fat, and refined sugar, which may lead to inflammation and oxidative stress and play an important role in the etiology of AD (Gu et al., 2010a; Graham et al., 2016; Ylilauri et al., 2017).

The MD diet was the most frequently investigated healthy diet in this study (Scarmeas et al., 2006a; Scarmeas et al., 2006b; Scarmeas et al., 2009b; Gu et al., 2010a; Gardener et al., 2012; Vassilaki et al., 2018) regarding the decrease in risk of AD. Morris et al. (2015) demonstrated that high adherence to a DASH diet or MD, and moderate adherence to a MIND diet could reduce the incidence of AD. Other diets do not necessarily show positive results in all studies; for example, some studies have demonstrated that intake of seafood may decrease risk of AD, whereas Devore et al. (2009) did not detect any association between moderate consumption of fish and omega-3 PUFAs and AD. We speculate that this may be due to the MD containing a higher or more diverse nutrient content than seafood and/or soy-based foods, and high protein diets. With regard to the possible mechanisms of action, there appears to be a close relationship between inflammation, endothelial dysfunction, oxidative stress, and AD (Lyros et al., 2014). Healthy diet constituents, including green leafy vegetables, nuts, berries, and fish as well as unhealthy food such as butter and red meats are contain a high content

of flavonoids, beta carotene, n-3 fatty acids, folate, and carotenoids (Solfrizzi et al., 2017). These components of healthy diets, may contribute synergistically to reducing oxidative stress and inflammation, leading to reduced risk of AD (Holt et al., 2009).

What constitutes a healthy diet is complex problem and understanding requires development of exact dietary pattern. Morris (Morris et al., 2015) developed a new diet highlighting intake of natural and plant-based foods and restriction of saturated fat and animal foods. The MIND diet, has 15 components, including 10 food groups beneficial for the brain [green leafy vegetables, other vegetables, berries, nuts, whole grains, beans, white meat (fish and poultry), olive oil, and limited intake of wine] and recommends decreasing intake of 5 unhealthy food groups, including stick margarine and butter, pastries and sweets, red meats, cheese, and fried/fast food. The MIND diet it thought to help prevent dementia and loss of brain function (Morris et al., 2015).

Possible mechanisms for the effect of a healthy diet on AD are related to high intake of n-3 fatty acids from fish consumption, leading to a decrease in oxidative stress, inflammation and Aβ development (Farooqui, 2012). Furthermore, complications related to AD are improved with a high intake of beta carotene, flavonoids, folate and carotenoids, such as consumption of green leafy vegetables (Holt et al., 2009).

The limitations of this meta-analysis is inclusion of studies that use a FFQ to assess diet, which may might not unavoidably signify a dietary pattern. Furthermore, in some included studies confounders were not taken into account. Furthermore, the meta-analysis combined results from studies that had different definitions of healthy and unhealthy diets. In addition, since there was an inadequate number of studies investigation the relationship between AD and diet, characterization of healthy and unhealthy diet is too detailed. Further well-designed clinical studies are required to identify healthy diets in adults with AD.

Our systematic review and meta-analysis provides evidence that high adherence to a healthy diet is related to a lower risk of AD. In addition, we show that greatest adherence to a healthy diet is associated with a decrease in risk of AD of 55%. These findings may be clinically applicable for public health, in order to decrease the risk of disability in the general population. However, it is difficult to draw conclusions about regional healthy diets. The main healthy diets investigated in relation to the risk of AD included DASH, MD, MIND, seafood-rich, HEI, soy-based diet, high-protein and low-fat diets. Future studies should consider the potential effects of total diet scores more carefully, for example, to assess the extent of a healthy diet by HEI scores.

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