REVIEW

Dietary Factors and Neurodegenerative Disorders: An Umbrella Review of Meta-Analyses of Prospective Studies

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ABSTRACT

Diet has been hypothesized to be associated with neurodegenerative disorders. The aim was to conduct an umbrella review to summarize and evaluate the current evidence of prospective associations between any dietary factors and the incidence of neurodegenerative disorders. We conducted a systematic search in PubMed, Embase, and Cochrane database up to November 2019 to identify systematic reviews with meta-analyses of prospective studies investigating the association between dietary factors (dietary patterns, foods and beverages, nutrients, and phytochemicals) and neurodegenerative disorders (cognitive decline, cognitive impairment, Alzheimer disease, all-cause dementia, and Parkinson disease). Summary risk ratios (SRRs) and 95% CIs were recalculated using a random effects model. We evaluated the risk of bias of identified meta-analyses and the quality of evidence for all associations. In total, 20 meta-analyses including 98 SRRs were identified. All original meta-analyses were rated as being at high risk of bias. Methodological concerns related mainly to the inappropriate synthesis, assessment, and discussion of the risk of bias of primary studies. For the recalculated meta-analyses, quality of evidence was moderate for inverse associations between higher adherence to the Mediterranean diet (SRR: 0.63; 95% CI: 0.48, 0.82; $n = 4$ primary studies) and higher fish intake (SRR: 0.72; 95% CI: 0.59, 0.89; $n = 6$) and Alzheimer disease, as well as for tea consumption and all-cause dementia (SRR: 0.74; 95% CI: 0.63, 0.88; $n = 2$) and Parkinson disease (SRR per 2 cups/d: 0.69; 95% CI: 0.54, 0.87; $n = 5$). This umbrella review provides a comprehensive overview of the available evidence on dietary factors and neurodegenerative disorders. The results indicate that the Mediterranean diet, fish, and tea could be inversely associated with neurodegenerative disorders. However, the quality of evidence was generally low, suggesting that further studies are likely to change the overall estimates. Thus, more well-conducted research, also investigating other dietary factors in association with neurodegenerative disorders, is warranted. *Adv Nutr* 2020;11:1161–1173.

Keywords: diet, cognitive decline, cognitive impairment, Alzheimer disease, dementia, Parkinson disease, umbrella review

Introduction

Neurodegenerative diseases, including Alzheimer disease, dementia, and Parkinson disease, have become important public health concerns worldwide due to aging populations. With regard to the most common neurodegenerative disease, it has been estimated that 43.8 million adults worldwide were living with dementia in 2016 (1). Moreover, cognitive decline and mild cognitive impairment (MCI) as potential precursors of Alzheimer disease or dementia can present early clinical indications of cognitive disorders (2). In a meta-analysis of studies investigating individuals aged ≥65 y with cognitive impairment followed for 2 y, the incidence of dementia was 14.9% (3). Furthermore, the prevalence of Parkinson disease was estimated to be ∼0.3% in adults or 1% in adults aged ≥60

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Abbreviations used: AHEI, Alternate Healthy Eating Index; ALA, α-linolenic acid; MCI, mild cognitive impairment; MDS, Mediterranean diet score; PI, prediction interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROBIS, risk of bias in systematic reviews; SRR, summary risk ratio.
This umbrella review provides an overview of the currently available evidence on dietary factors and neurodegenerative disorders derived from meta-analyses of prospective studies.

y (4). Thus, the prevention or delay of disease occurrence at an early stage is of high public health relevance.

Besides nonmodifiable risk factors such as advanced age and genetic predisposition, it has been suggested that modifiable risk factors could also play an important role in the prevention due to the long latency period of neurodegenerative diseases (5, 6). Research has been conducted to investigate environmental risk factors such as smoking, pesticides, and other toxins (7, 8). Moreover, some dietary factors have also been hypothesized to have some preventive potential. In fact, there are many reviews and meta-analyses investigating the association between dietary factors and neurodegenerative diseases. For instance, a number of studies have investigated the association between coffee or caffeine consumption and Parkinson disease (9–11). Furthermore, the Mediterranean diet has been shown to be inversely associated with the risk of cognitive disorders (12–14). Recently, a comprehensive review summarized the results of observational and intervention studies on the associations between dietary factors and cognitive impairment, and concluded that dietary patterns like the Mediterranean diet and its components could have a protective potential (15). These findings could be of importance for the prevention of neurodegenerative disorders. However, the strength of the associations, the quality of evidence, and the influence of potential bias of these systematic reviews and meta-analyses need to be clarified. Umbrella reviews provide a broad overview of the existing evidence by focusing on published systematic reviews and meta-analyses on a specific topic, and are helpful tools to evaluate the certainty of evidence (strength and precision of the estimates, and influence of potential bias regarding these associations) and the risk of bias in the process of the systematic review and the meta-analysis of the published reports (16). Umbrella reviews have summarized studies on environmental risk factors and dementia (17) and Parkinson disease (8), but these reviews did not include all dietary factors and focused on all study designs. Moreover, the methodological quality and the quality of evidence need to be assessed.

Thus, the aim of the present umbrella review was systematically to summarize and evaluate the current evidence of prospective associations between any dietary factors including dietary patterns, food groups, foods and beverages, macronutrients, micronutrients, and phytochemicals, and the incidence of neurodegenerative disorders including cognitive decline, cognitive impairment, Alzheimer disease, all-cause dementia, and Parkinson disease.

Methods

The present umbrella review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (18), and proposed methodology of conducting and reporting umbrella reviews (16). The umbrella review was registered a priori in PROSPERO—the International Prospective Register of Systematic Reviews (ID: CRD42018105892; available at: http://www.crd.york.ac.uk/PROSPERO/).

Search strategy

The systematic literature search was conducted by using predefined search terms in PubMed, Embase, and Cochrane. The search term consisted of terms of exposure such as "diet," "dietary," and outcome including "neurodegenerative," "dementia," "Parkinson," or "cognitive," as well as terms referring to the study design: "systematic review" or "meta-analysis." The full search strategy is shown in **Supplemental Table 1**. The terms were searched in title and abstract, and Mesh terms in PubMed and the Cochrane database as well as Emtree in Embase. The literature search was updated on November 6, 2019. Two researchers (JB and AWL) independently screened titles and abstracts according to predefined inclusion and exclusion criteria to identify potentially eligible studies. Full texts were retrieved and independently assessed for eligibility by 2 researchers. Any disagreements between the 2 reviewers were resolved by consensus. Reference lists of identified studies were screened for further relevant meta-analyses.

Eligibility criteria

We included meta-analyses if the following inclusion criteria were met: *1*) studies investigated the association of dietary factors (dietary patterns, food groups, foods, macronutrients, micronutrients, phytochemicals) and the following neurodegenerative disorders: cognitive decline, cognitive impairment, MCI, Alzheimer disease, all-cause dementia, or Parkinson disease; *2*) systematic reviews included a meta-analysis of ≥2 prospective cohort studies or randomized controlled trials investigating incident cases; *3*) general populations (including children, adolescents, adults, and elderly people) without prevalent cognitive disorders; *4*) an overall risk ratio was calculated; and *5*) articles were written in English or German and published in peer-reviewed scientific journals.

Studies were excluded based on the following exclusion criteria: *1*) no quantitative synthesis of the single study results was performed; *2*) meta-analysis was based on case-control or cross-sectional studies only; *3*) meta-analyses focused on pregnant or breastfeeding women and populations at risk (individuals with type 2 diabetes mellitus, cardiovascular diseases, or cancer); *4*) no risk ratio was calculated (correlation coefficients, regression coefficients were excluded); or *5*) duplicate publication on the same exposure and outcome. In the latter case, we included the most recent meta-analysis, the meta-analysis investigating dose–response relation, or the meta-analysis including the highest number of prospective studies. No restrictions based on publication date were applied.

Data extraction

Two review authors (JB and AWL) extracted the following data from each included meta-analysis using a standardized form: first author's last name, year of publication, type of exposure(s) and comparisons, type of outcome(s), number of prospective cohort studies or randomized controlled trials included in the meta-analysis, and the number of cases

and total sample size of the meta-analysis. One researcher extracted the data and a second researcher checked the data for accuracy. Any discrepancies were solved by consensus.

Additionally, 3 researchers (AWL, AS, and AL) extracted data from all primary studies included in every meta-analysis. Another author (JB) checked the data for accuracy. The following data were extracted from each primary study: first author's last name, year of publication, name of the study, country, sex and age of participants, duration of follow-up, type of exposure, exposure categories, type of outcome, person years, total number of participants and cases, number of participants and cases per category, multivariable adjusted RR, and corresponding 95% CIs. In case of missing data in primary studies, the data were extracted from the original meta-analysis. If a meta-analysis included both prospective and cross-sectional/retrospective studies, we only included primary studies with incident cases and excluded primary studies with prevalent cases at baseline. Furthermore, we excluded primary studies from the meta-analysis if only risk estimates for combined end points were available, for example, cognitive decline and dementia.

Risk of bias assessment and evaluation of the quality of evidence

The methodological quality was assessed using the risk of bias in systematic reviews (ROBIS) tool (19). The ROBIS tool consists of 4 domains: *1*) study eligibility criteria; *2*) identification and selection of studies; *3*) data collection and study appraisal; and *4*) synthesis and findings. For each domain, signaling questions help to judge the risk of bias in the systematic reviews. For the overall evaluation, the following issues were considered: *1*) the interpretation of findings addressed all the concerns identified in domains 1 to 4; *2*) the relevance of identified studies was adequately considered to the review's research question; and *3*) the reviewers avoided emphasizing the results on the basis of their statistical significance. A detailed description of the tool and judgment of potential risk of bias for each domain is given in **Supplemental Table 2**. Two researchers (JB and SS) independently assessed the risk of bias of each meta-analysis. Any discrepancies were identified and resolved by discussion.

The quality of evidence was evaluated using NutriGrade (20). This tool comprises the following items: *1*) risk of bias, study quality of the primary studies; *2*) precision of the estimate; *3*) heterogeneity; *4*) directness; *5*) publication bias; *6*) funding bias; *7*) effect size; and *8*) dose–response association. Information on risk-of-bias assessment and funding bias was extracted from the original meta-analyses, whereas the other items refer to the recalculated meta-analyses. The score could range between 0 and 10, and there were 4 categories to judge the meta-evidence: *1*) a score of $\geq$8 points was assigned to high quality of evidence and indicates that there was high confidence in the effect estimate and that further studies probably would not change the confidence in the effect estimate; *2*) a score of 6 to $<$8 points was assigned to moderate quality of evidence indicating that there was moderate confidence in the effect estimate and further research might change the effect estimate; *3*) a score of 4 to $<$6 was assigned to low quality of evidence indicating low confidence in the effect estimate and a likelihood that further studies would change the effect estimate; and *4*) a score of $<$4 was assigned to very low quality of evidence, indicating that there was very limited and uncertain meta-evidence (20). The rating was conducted independently by 2 authors (AS and AL) and any discrepancies were resolved by discussion. The quality of evidence was evaluated separately if a pairwise and dose–response meta-analysis was available.

Statistical analysis

We reanalyzed all meta-analyses to ensure that: *1*) only prospective studies (including prospective cohort studies, nested case-control studies, case-cohort studies, or randomized controlled trials) were pooled using the same methods; 2) summary risk ratios (SRRs) were calculated separately for different outcomes; and *3*) all relevant measures (e.g., heterogeneity measures) were consistently presented. If duplicate publications of the same study population were included in the original meta-analysis, we used the most recent primary study including the largest sample size. A meta-analysis was reanalyzed if $\geq$2 prospective studies on the same exposure and outcome were available. We estimated SRRs and corresponding 95% CIs by using a random effects model (21). For primary studies that reported RRs separately for men and women, or for different exposure groups (e.g., single foods instead of a food group), RRs were combined using a fixed effect model before entering the risk estimate into the overall meta-analysis. If RRs for different cohort studies were available in 1 primary study, we treated these as single studies. For pairwise meta-analyses (high compared with low meta-analysis), we excluded primary studies reporting continuous RRs. Furthermore, linear dose–response meta-analyses were reanalyzed using the method of Greenland and Longnecker (22). The following data were required for $\geq$3 exposure categories: a quantity of the exposure (e.g., grams per day), the effect estimate with the corresponding 95% CI, and the number of cases and person-years. If the number of cases in the categories or person-years was not reported, but information on the total number of cases and total person-years or the numbers of total participants plus follow-up period was available, the number of cases or person-years was calculated for specified categories as described previously (23). If a range of dietary intake was presented, the midpoint value was assigned as exposure level for the respective category. In addition, a nonlinear dose–response meta-analysis was performed by using restricted cubic spline regression models as described by Orsini et al. (24). A likelihood ratio test was used to test for nonlinearity. Statistical heterogeneity between studies was evaluated using τ^2 and prediction intervals (PIs) (25). We estimated PIs if $\geq$5 studies were available in a meta-analysis. The PI indicates which range of true effects can be expected from future research (25). Moreover, we calculated I^2 as a measure of inconsistency (26). We assessed publication and

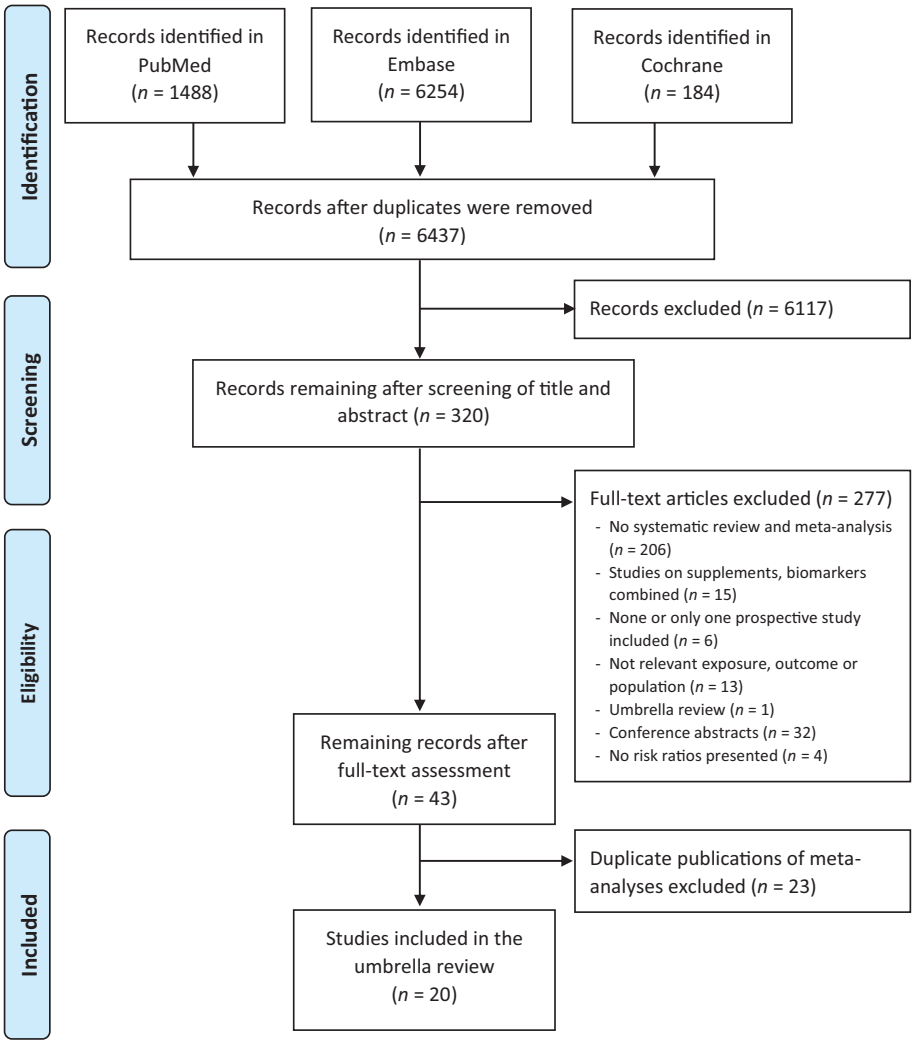

FIGURE 1 Flow chart illustrating the literature search process in the umbrella review.

small study effects visually by using the funnel plot, and statistically by using the Egger test for meta-analysis with ≥5 primary studies (27). All statistical analyses were performed using Stata (version 14; Stata-Corp).

Results

In total, we identified 7926 publications. The flow chart illustrating the study selection process is shown in **Figure 1**. After retrieving 320 full-text articles, 43 studies were eligible for inclusion and we excluded 277 articles according to our exclusion criteria. Furthermore, we identified >1 meta-analysis for the same topic for most exposures. In most cases, they included similar articles, but mostly different types of study design (prospective cohort, case-control, and cross-sectional studies). We included the most recent meta-analyses comprising the most prospective cohort studies. Thus, we excluded 23 articles due to duplicate publication of the same meta-analysis. In total, we finally included 20 meta-analyses (11, 14, 28–45) investigating in total 98 SRRs on dietary factors and cognitive decline ($n = 5$) (32, 34, 37, 42, 43), cognitive impairment/MCI ($n = 3$) (14, 34, 42), Alzheimer disease ($n = 10$) (14, 28–30, 35–38, 44, 45), all-cause dementia ($n = 11$) (14, 28, 29, 32, 35, 37–39, 42, 44, 45), and Parkinson disease ($n = 6$) (11, 31, 33, 39–41).

The characteristics and recalculated results of the original meta-analyses are presented in **Supplemental Table 3**. The meta-analyses included 2–8 primary studies. All meta-analyses were published between 2012 and 2018. All meta-analyses included primary studies based on adult populations.

We identified meta-analyses on the following dietary factors: Alternate Healthy Eating Index (AHEI) (39), Mediterranean diet score (MDS) (14), fruit and vegetables (32), fish (28, 44, 45), total dairy and specific dairy products (31, 33, 43), coffee (11, 35, 42), tea and specific types of tea (11, 37), total energy (41), total carbohydrates (41), total protein (41), total fat and specific types of fat (including SFAs, cholesterol, MUFAs, PUFAs, n–3 PUFAs, n–6 PUFAs, arachidonic acid, linoleic acid, α-linolenic acid (ALA), EPA, DHA (38, 41, 44,

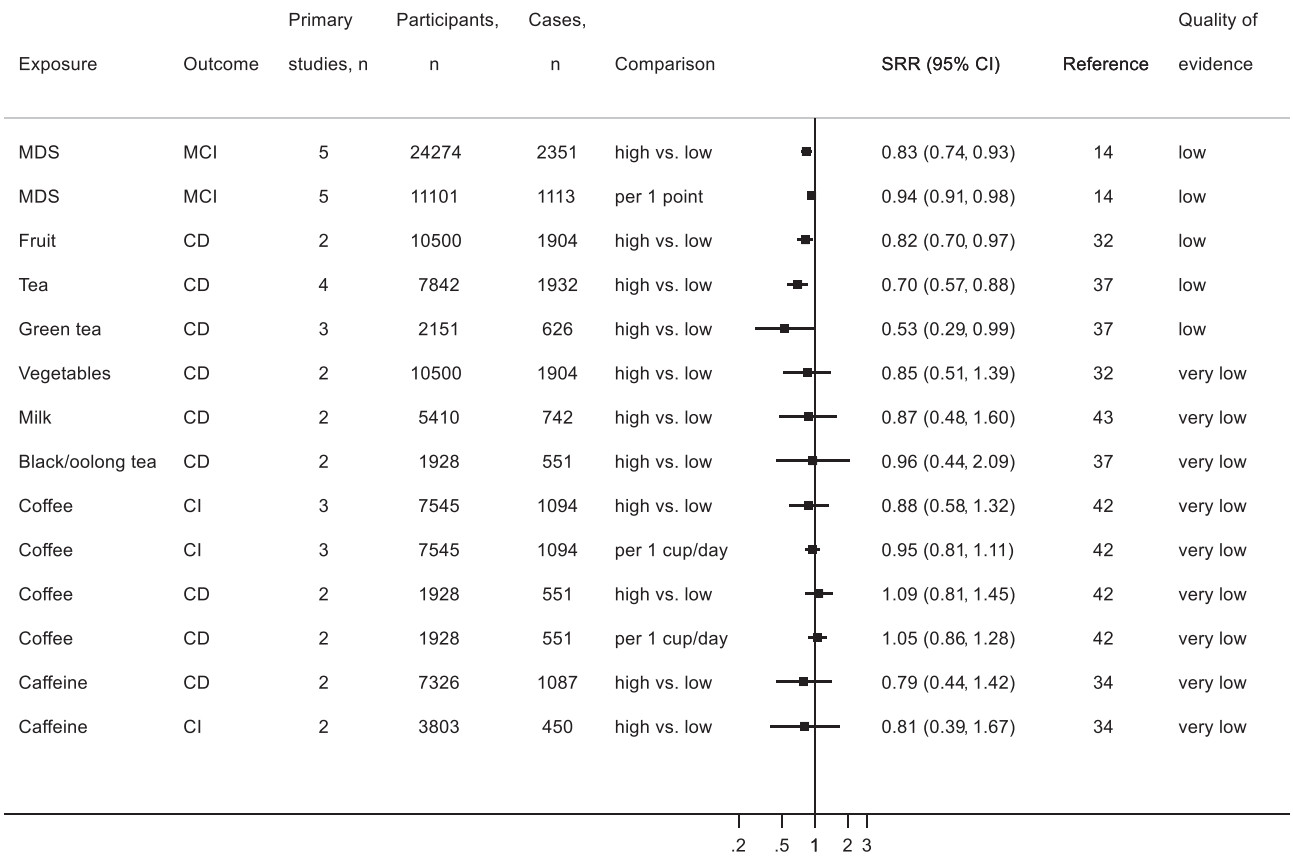

FIGURE 2 Associations between dietary factors and cognitive decline (CD), cognitive impairment (CI), or mild cognitive impairment (MCI). Summary risk ratios (SRRs) with corresponding 95% CIs have been estimated using random effects models, and quality of evidence for each association has been evaluated using NutriGrade. MDS, Mediterranean diet score.

45), vitamin B-6 (29, 40), vitamin B-12 (29, 30, 40), vitamin C (29, 36), vitamin E (29, 36), folate (29, 40), β-carotene (36), flavonoids (29), and caffeine (11, 34).

Methodological quality of the included meta-analyses

The results of the methodological quality assessment of the included meta-analyses are presented in Supplemental Table 3. Overall, all studies were rated as being at high risk of bias. In detail, less than half of the studies ($n = 9$) (11, 14, 28, 30, 35, 38, 39, 41, 42) were rated as low risk in the first domain assessing the appropriateness of the study eligibility criteria. Evaluating the second domain on identification and selection of studies revealed that only 3 meta-analyses (14, 38, 42) were rated as low risk of bias. This was mainly due to the insufficient search strategies that could have missed potentially relevant studies. Seven meta-analyses (14, 30, 37, 39, 42, 43, 45) were rated as being at low risk in the third domain (data collection and study appraisal). The Newcastle-Ottawa Scale was used for quality assessment of primary studies in 11 meta-analyses (14, 28, 32, 34, 35, 37–39, 42, 44, 45), 2 meta-analyses (30, 43) applied other tools, and 7 meta-analyses (11, 29, 31, 33, 36, 40, 41) had not evaluated the risk of bias. Furthermore, all studies were regarded as high risk of bias in the "synthesis and findings" domain, which was mainly due to the pooling of study results derived from different study designs, different exposures or outcomes, and the lack of sensitivity analyses or addressing the risk of bias in the synthesis.

Associations and quality of evidence between dietary factors and incidence of cognitive decline or MCI

Figure 2 shows the SRRs and the respective quality of evidence for the associations between dietary factors and incidence of cognitive decline or MCI. None of the associations was graded with high or moderate quality of evidence. An inverse association was found between the adherence to the MDS and incidence of MCI for both, high compared with low and dose–response meta-analysis and graded as low quality of evidence. There was no indication for nonlinearity for the association between MDS and MCI (P for nonlinearity = 0.28; **Supplemental Figure 1**).

Moreover, an inverse association was found for intake of fruit, green tea, and total tea and incidence of cognitive decline from evidence graded as low quality.

Associations between intake of vegetables, milk, and black/oolong tea and cognitive decline, and between coffee

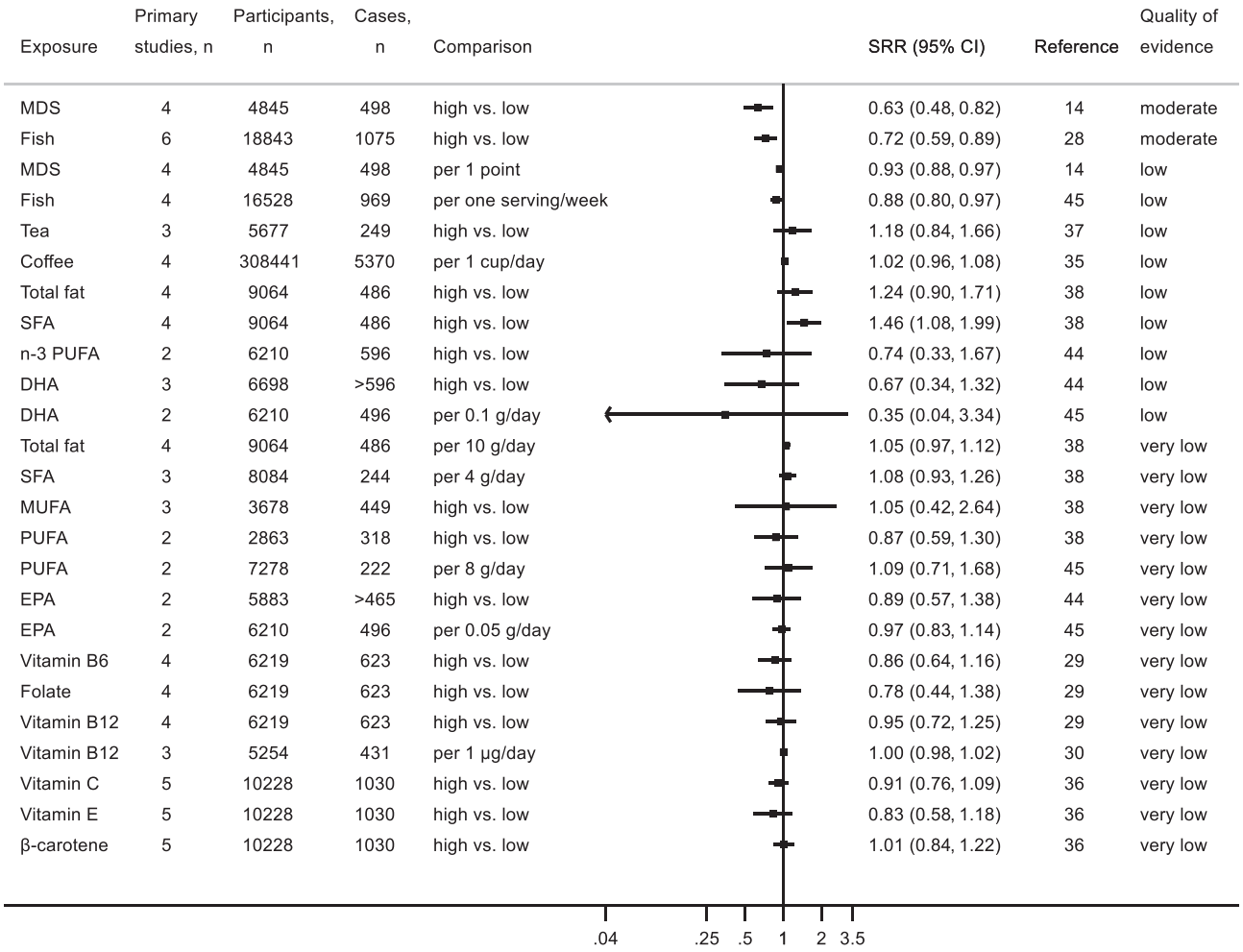

FIGURE 3 Associations between dietary factors and Alzheimer disease. Summary risk ratios (SRRs) with corresponding 95% CIs have been recalculated using random effects models, and quality of evidence for each association has been evaluated using NutriGrade. MDS, Mediterranean diet score; SAFA.

and caffeine intake and both cognitive decline and cognitive impairment were evaluated as very low quality of evidence, and SRRs were imprecisely estimated.

Potential publication bias was identified for the association between MDS and MCI as presented in the funnel plot (**Supplemental Figure 2**) indicating that ≥2 studies with a null result or a small positive association are missing. This is also supported by the Egger test ($P = 0.04$).

Associations and quality of evidence between dietary factors and incidence of Alzheimer disease

The SRRs and the respective quality of evidence for the associations between dietary factors and incidence of Alzheimer disease are presented in **Figure 3**. None of the associations was graded with high quality of evidence. We found an inverse association between the MDS and incidence of Alzheimer disease in high compared with low meta-analysis (SRR: 0.63; 95% CI: 0.48, 0.82; $\tau^2 = 0.00$; $I^2 = 0.0\%$; 4 primary studies) graded with moderate quality of evidence. However, the dose–response meta-analysis was graded with low quality of evidence. We found no indication for nonlinearity (P for nonlinearity $= 0.48$; **Supplemental Figure 3**). Moreover, compared with no or low consumption, a higher consumption of fish was associated with decreased incidence of Alzheimer disease (SRR: 0.72; 95% CI: 0.59, 0.89; $\tau^2 = 0.02$; $I^2 = 42.5\%$; PI = 0.43–1.22; 6 primary studies) with moderate quality of evidence. The corresponding dose–response meta-analysis also indicated an inverse association between fish consumption and Alzheimer disease, but was only graded with low quality of evidence. Moreover, we found a positive association between SFA intake and incidence of Alzheimer disease in high compared with low meta-analysis, with low quality of evidence. However, the SRR in the dose–response analysis for an increment of 4 g/d was also imprecisely estimated (very low quality of evidence).

Associations between the intake of total fat, n–3 PUFAs, DHA, and folate and Alzheimer disease were imprecisely estimated and evaluated as low or very low quality of

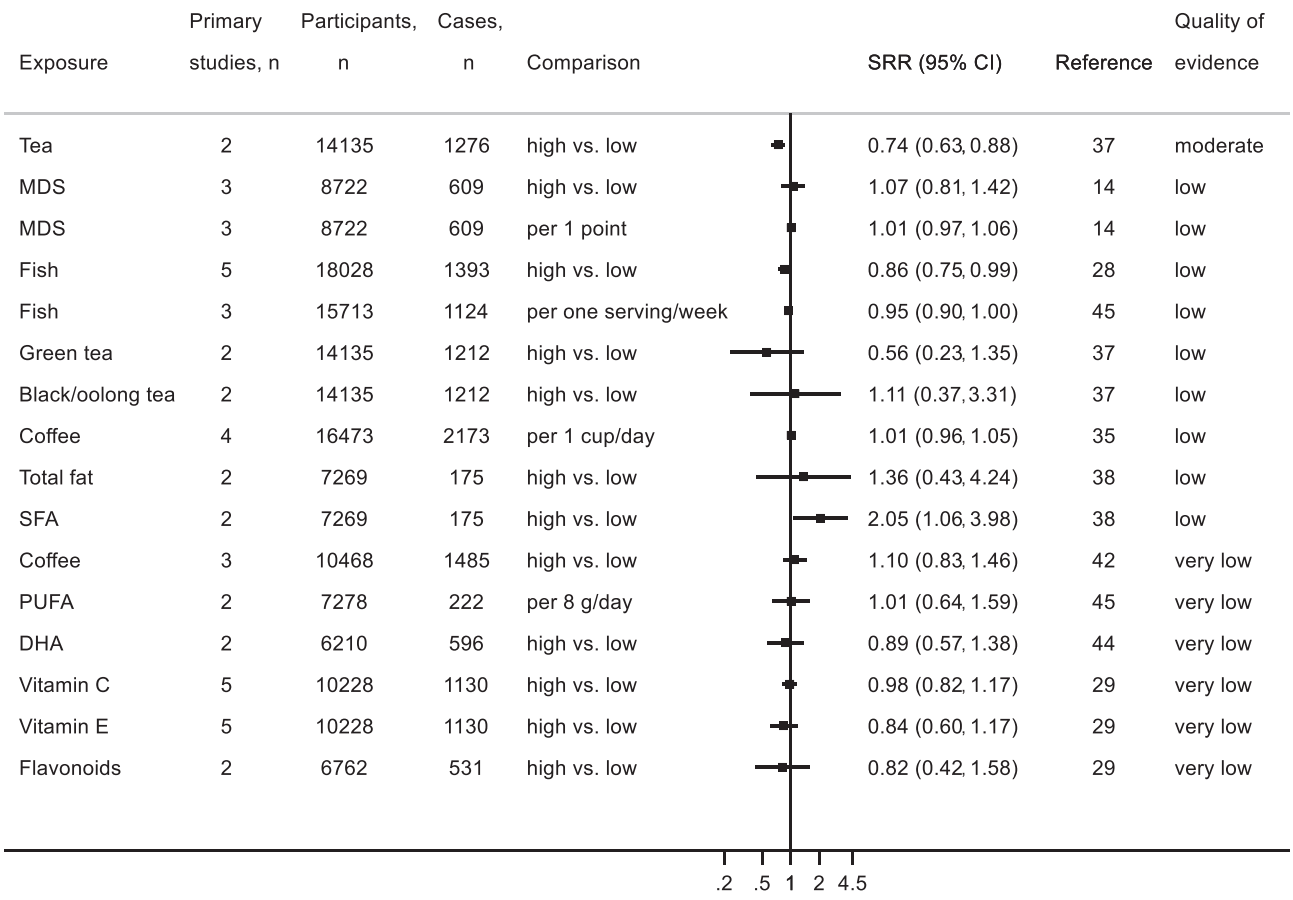

FIGURE 4 Associations between dietary factors and all-cause dementia. Summary risk ratios (SRRs) with corresponding 95% CIs have been recalculated using random effects models, and quality of evidence for each association has been evaluated using NutriGrade. MDS, Mediterranean diet score; SAFA.

evidence. Additionally, no association was found between the intake of coffee, tea, total fat (per 10 g/d), MUFAs, PUFAs, EPA, vitamin C, vitamin E, vitamin B-6, vitamin B-12, and β-carotene and Alzheimer disease, with low or very low quality of evidence.

A small study effect could be present for the association between fish consumption and Alzheimer disease according to the funnel plot (**Supplemental Figure 4**) indicating that 3 studies with a null result or a small positive association are missing, but not according to the Egger test ($P = 0.46$).

Associations and quality of evidence between dietary factors and incidence of all-cause dementia

Figure 4 shows the SRRs with the corresponding 95% CIs and the respective quality of evidence for the associations between dietary factors and incidence of all-cause dementia. None of the associations was graded with high quality of evidence. The association between higher compared with lower tea consumption and decreased incidence of dementia (SRR: 0.74; 95% CI: 0.63, 0.88; $\tau^2 = 0.00$; $I^2 = 0.0\%$; 2 primary studies) was graded with moderate quality of evidence.

Moreover, we found inverse associations between the intake of fish and green tea and dementia, with low or very low quality of evidence, and SRRs were imprecisely estimated. There was no indication of nonlinearity for the association of fish intake and dementia (P for nonlinearity $= 0.83$; **Supplemental Figure 5**). We found a positive association between intake of total fat and of SFAs and incidence of dementia, with low quality of evidence, and SRRs were imprecisely estimated.

No association was found for adherence to the MDS, intake of coffee, black/oolong tea, PUFAs, DHA, vitamin E, vitamin C, or flavonoids, with low or very low quality of evidence.

We found a slight asymmetry in the funnel plot for the association between vitamin E intake and dementia (**Supplemental Figure 6**), indicating that $\geq$1 study with a positive association could be missing. However, the analysis comprised only 5 primary studies and potential publication bias was not indicated by the Egger test ($P = 0.64$).

Exposure	Primary studies, n	Participants, n	Cases, n	Comparison	SRR (95% CI)	Reference	Quality of evidence
Tea	5	343345	1322	high vs. low	0.65 (0.51, 0.83)	11	moderate
Tea	5	343345	1322	per 2 cup/day	0.69 (0.54, 0.87)	11	moderate
Milk	5	272238	1637	high vs. low	1.57 (1.30, 1.88)	31	low
Milk	4	190223	811	per 200 g/day	1.20 (1.10, 1.32)	33	low
Cheese	3	182719	683	per 10 g/day	1.11 (1.04, 1.19)	33	low
Coffee	8	785300	2452	high vs. low	0.61 (0.44, 0.85)	11	low
Coffee	8	785300	2452	per 2 cups/day	0.87 (0.80, 0.95)	11	low
MUFA	5	207386	742	high vs. low	0.88 (0.69, 1.12)	41	low
MUFA	4	141608	499	per 10 g/day	0.77 (0.57, 1.04)	41	low
PUFA	5	207386	742	high vs. low	0.81 (0.64, 1.02)	41	low
n-3 PUFA	4	141608	499	per 1 g/day	0.58 (0.44, 0.77)	41	low
Caffeine	5	340630	927	high vs. low	0.61 (0.44, 0.85)	11	low
Caffeine	5	340630	927	per 200 mg/day	0.71 (0.54, 0.91)	11	low
AHEI	2	34285	5443	high vs. low	0.87 (0.49, 1.55)	39	very low
Dairy	4	264734	1509	high vs. low	1.28 (1.06, 1.55)	31	very low
Yogurt	2	178195	598	high vs. low	1.06 (0.74, 1.51)	33	very low
Butter	2	49467	251	high vs. low	0.76 (0.51, 1.13)	33	very low
Energy	3	136319	448	high vs. low	1.09 (0.82, 1.46)	41	very low
Energy	3	161301	447	per 1000 kcal/day	0.97 (0.75, 1.24)	41	very low
Carbohydrates	3	198955	516	high vs. low	1.16 (0.87, 1.54)	41	very low
Carbohydrates	2	135894	359	per 100 g/day	0.96 (0.67, 1.39)	41	very low
Total fat	6	338250	1130	high vs. low	0.85 (0.68, 1.05)	41	very low
Total fat	5	272472	887	per 20 g/day	0.87 (0.72, 1.06)	41	very low
Protein	4	329819	904	high vs. low	1.14 (0.85, 1.52)	41	very low
SFA	5	207386	742	high vs. low	0.85 (0.63, 1.16)	41	very low
SFA	4	141608	499	per 10 g/day	0.92 (0.74, 1.16)	41	very low
PUFA	4	141608	499	per 5 g/day	0.82 (0.72, 0.92)	41	very low
Arachidonic acid	2	135894	359	high vs. low	0.65 (0.47, 0.91)	41	very low
EPA	2	135894	359	high vs. low	0.91 (0.66, 1.26)	41	very low
EPA	3	141183	410	per 0.1 g/day	1.01 (0.87, 1.18)	41	very low
DHA	2	135894	359	high vs. low	0.84 (0.60, 1.18)	41	very low
DHA	3	141183	410	per 0.1 g/day	0.98 (0.88, 1.09)	41	very low
Linoleic acid	4	144325	585	high vs. low	0.80 (0.61, 1.04)	41	very low
Linoleic acid	4	141608	499	per 5 g/day	0.83 (0.73, 0.93)	41	very low
Linolenic acid	4	144325	585	high vs. low	0.80 (0.56, 1.15)	41	very low
Linolenic acid	4	141608	499	per 0.5 g/day	0.82 (0.69, 0.97)	41	very low
n-3 PUFA	4	199380	605	high vs. low	0.83 (0.59, 1.16)	41	very low
n-6 PUFA	2	63486	246	high vs. low	0.75 (0.51, 1.12)	41	very low
Cholesterol	2	135894	359	high vs. low	0.95 (0.67, 1.34)	41	very low
Cholesterol	2	135894	359	per 100 mg/day	0.95 (0.84, 1.08)	41	very low
Vitamin B6	3	141346	487	high vs. low	0.85 (0.53, 1.36)	40	very low
Folate	3	141346	487	high vs. low	1.10 (0.81, 1.50)	40	very low
Vitamin B12	3	141346	487	high vs. low	1.02 (0.79, 1.32)	40	very low

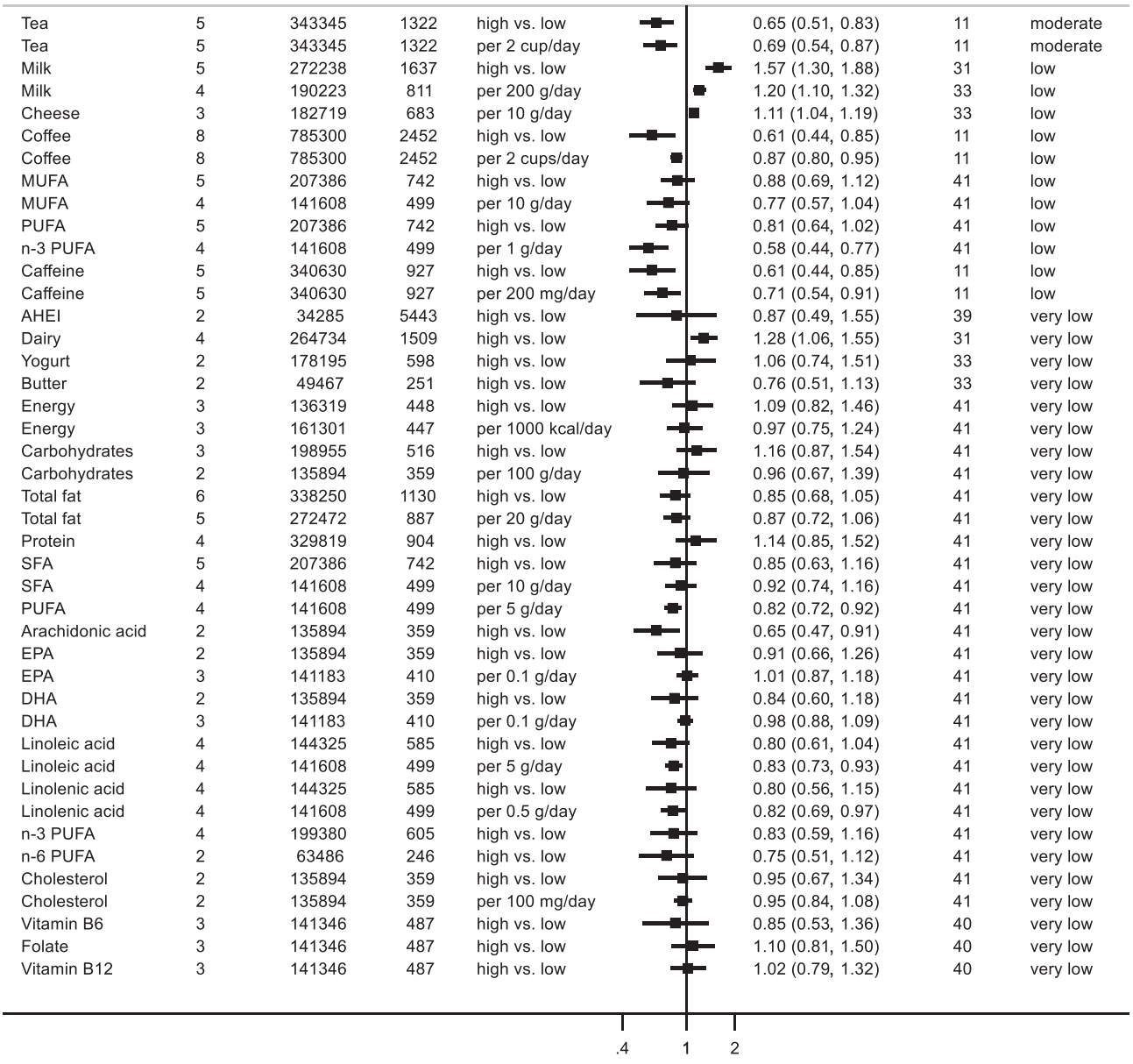

FIGURE 5 Associations between dietary factors and Parkinson disease. Summary risk ratios (SRRs) with corresponding 95% CIs have been recalculated using random effects models, and quality of evidence for each association has been evaluated using NutriGrade. AHEI, Alternate Healthy Eating Index; SAFA.

Associations and quality of evidence between dietary factors and incidence of Parkinson disease

The SRRs and the corresponding 95% CIs for the associations between dietary factors and incidence of Parkinson disease with the respective quality of evidence are presented in **Figure 5**.

None of the associations was graded with high quality of evidence. We found an inverse association between tea consumption and incidence of Parkinson disease (in high compared with low, and in dose–response meta-analyses), graded with moderate quality of evidence. Higher consumption of tea was associated with a lower incidence of Parkinson disease, with moderate quality of evidence (SRR: 0.65; 95% CI: 0.51, 0.83; $\tau^2 = 0.00$; PI = 0.44–0.97; $I^2 = 0.0\%$; 5 primary studies) compared with no or low consumption. Moreover, an increment of 2 cups/d was associated with a decreased incidence of Parkinson disease of 31% (SRR: 0.69; 95% CI: 0.54, 0.87; $\tau^2 = 0.00$; $I^2 = 0.0\%$; PI = 0.47–1.00; 5

primary studies) with moderate quality of evidence. There was no indication for nonlinearity (P for nonlinearity = 0.64; **Supplemental Figure 7**).

The majority of associations were graded as low ($n = 11$) and very low ($n = 30$) quality of evidence. Inverse associations were found between caffeine and coffee consumption, n–3 PUFAs (per 1 g/d), and total PUFA intake and Parkinson disease, with low quality of evidence. An increased incidence of Parkinson disease was found for higher intakes of cheese and milk, with low quality of evidence, and for intake of dairy products, with very low quality of evidence.

We found inverse associations between intakes of butter, MUFAs, ALA, arachidonic acid, linoleic acid, and n–6 PUFAs and incidence of Parkinson disease, with low or very low quality of evidence, and the SRRs were imprecisely estimated. We found no association for the adherence to the AHEI, intake of yogurt, energy intake, most macronutrients [intake of carbohydrates, protein, total fat, SFAs, n–3 PUFAs (high compared with low), DHA, EPA, cholesterol] and vitamin B-6, vitamin B-12, and folate, with low or very low quality of evidence.

Potential publication bias indicated by an asymmetry in the funnel plots, was found for the associations between milk, coffee, caffeine, and PUFAs and Parkinson disease (**Supplemental Figures 8–11**). According to the Egger test, small study effects were found for caffeine ($P = 0.06$) and PUFAs ($P = 0.07$), but not for milk ($P = 0.17$) and coffee ($P = 0.34$).

Discussion

In the present umbrella review, we provided a comprehensive overview of the currently available meta-analyses investigating dietary factors and the neurodegenerative disorders Parkinson disease, all-cause dementia, Alzheimer disease, and cognitive impairment or decline. To our knowledge, we are the first to evaluate the methodological quality of the meta-analyses and quality of evidence for all these associations.

We identified 20 systematic reviews and meta-analyses comprising in total 98 SRRs. None of these associations were rated as high quality of evidence. The quality of evidence was moderate for the inverse associations between the Mediterranean diet and fish intake and Alzheimer disease, as well as for tea consumption and all-cause dementia and Parkinson disease. All other associations were graded with low or very low quality of evidence, and thus further research could likely change the overall summary estimates. Moreover, all published meta-analyses were assessed as being at high risk of bias.

Comparison with other studies and possible explanations

The findings of the present umbrella review are in agreement with general dietary guidelines recommending a Mediterranean-like diet including a diet high in fruit and vegetables, legumes, nuts, cereals, fish, and olive oil and low or moderate intake of red meat and dairy products (46, 47). Several chronic diseases, including type 2 diabetes and cardiovascular diseases, as well as risk factors for these diseases have been linked to an increased risk of cognitive decline and dementia (6, 48). Additionally, a meta-analysis combining 7 cohort studies found an increased risk of Parkinson disease in individuals with diabetes (49). It has been hypothesized that the pathogenesis of neurodegenerative diseases shares some mechanistic pathways with other chronic diseases such as type 2 diabetes and cardiovascular diseases (50, 51). Although the pathophysiology is not yet fully clarified, common risk factors could include chronic low-grade inflammation, oxidative stress, glycemia/insulinemia, and dyslipidemia. Thus, guidelines for the primary prevention of type 2 diabetes or cardiovascular disease could also be beneficial for the prevention of cognitive disorders. The WHO (6) proposed a Mediterranean-like diet to reduce the risk of cognitive decline and dementia based on intervention studies and graded with moderate quality of evidence. However, these intervention studies investigated the effect of the Mediterranean diet on cognitive performance, rather than the hard end points investigated in the present umbrella review. In the present umbrella review, we excluded systematic reviews and meta-analyses that reported no risk ratio. A meta-analysis focusing on intervention studies found a weak correlation between adherence to the Mediterranean diet and global cognitive performance (52). However, adherence to the Mediterranean diet has been shown to be associated with decreased concentrations of inflammatory markers and lower oxidative stress (53). A Mediterranean diet supplemented with 1 L olive oil/wk has been shown to improve cognitive function in older adults compared with the control group advised to reduce dietary fat intake (54, 55). This could be attributable to the higher consumption of fruit, vegetables, vegetable oils, and fish, and thus the higher content of MUFAs, PUFAs, vitamins, and polyphenols in the Mediterranean diet compared with a diet low in overall dietary fat. In the present umbrella review, the evidence for associations between intake of fruit, vegetables, MUFAs, PUFAs, vitamins, and polyphenols and neurodegenerative disorders was limited. This could be due to the small number of studies included in these meta-analyses. Nevertheless, SFAs were positively associated with Alzheimer disease and dementia. A diet high in SFAs and low in unsaturated fatty acids is associated with higher blood concentrations of LDL cholesterol. Hypercholesterolemia has been shown to be a risk factor for amyloid accumulation in the human brain (56). High serum concentrations of total cholesterol have been hypothesized to increase the risk of Alzheimer disease, but this relation is still debatable (57).

Moreover, intake of coffee was inversely associated with Parkinson disease, whereas tea was associated with a lower incidence of cognitive decline, dementia, and Parkinson disease. Regular intake of tea has been hypothesized to reduce biomarkers of oxidation and inflammation due to the antioxidative properties of polyphenols, especially of catechins. Moreover, phenolic compounds are discussed to prevent amyloid deposition and therefore, might reduce the

risk of Alzheimer disease (58). Green tea showed a stronger association in the present umbrella review compared with black tea; this might be explained by the higher concentration of catechins in green tea, which might improve cognitive function (59, 60) and protect against neurodegenerative diseases (61). Furthermore, green tea extract supplementation has also been shown to reduce elevated blood pressure and LDL cholesterol concentrations (62) and thus might lower the risk of cardiovascular diseases. Because cardiovascular risk factors are associated with increased risk of Alzheimer disease, tea consumption could also be beneficial for cognitive health. Other compounds in tea comprise caffeine and L-theanine, which have been discussed to possess neuroprotective effects and improve cognitive performance (59). This could also explain the inverse association between tea and coffee consumption and Parkinson disease presented in the present umbrella review.

Surprisingly, milk and dairy consumption was positively associated with Parkinson disease; however, the association was graded as low or very low quality of evidence and further research is likely to change these results. Thus, there is a need for further research in this area to investigate the direction of this association and potential mechanism.

Finally, lifestyle per se could explain the observed associations. Participants adhering to a more health-promoting diet (e.g., Mediterranean diet) could also be more active, less often smokers, and more likely to maintain a normal body weight than individuals consuming a Western-like diet, which is characterized by high intakes of meat and processed meat, refined grains, and high-fat and energy-dense foods. However, the primary studies included in the meta-analyses conducted multivariable-adjusted regression models and adjusted for a range of potential confounders.

Limitations of the included meta-analyses and future research directions

In the present umbrella review, we were able to identify research gaps and the need for well-conducted meta-analyses. We found no meta-analysis investigating, for example, the association of neurodegenerative disorders with intake of meat, whole grain/cereals, nuts, or minerals. Because these dietary factors have been shown to be associated with the risk of other chronic diseases, there could be a potential effect on neurodegenerative disorders as well. The included meta-analyses were mostly based on a small number of primary studies. As a consequence, the quality of evidence was low or very low for the majority of the associations. Most meta-analyses included only 2–4 primary studies, and some meta-analyses including >5 studies indicated small study effects or potential publication bias. It is possible that primary studies published after the original meta-analyses were undertaken might not be included. In this context, we found that several search strategies were potentially insufficient to retrieve all eligible studies; however, most systematic reviews also scanned reference lists of included articles to potentially identify further relevant studies. Furthermore, 7 meta-analyses did not evaluate the risk of bias of the included studies, which also resulted in a downgrading of the quality of evidence.

Methodological quality assessment of the identified meta-analyses showed that all were rated as being at high risk of bias. Foremost in the methodological weaknesses was the statistical synthesis of findings, such as the inclusion of different study designs, pooling different outcomes or exposures, or including the same study population in 1 meta-analysis. Thus, future studies should take the similarity of the primary study results into account and carry out the meta-analysis with caution. If relevant data are available, authors should conduct linear and nonlinear dose–response meta-analyses. Another major limitation of the meta-analyses is the lack of or insufficient assessment of the risk of bias of the included studies. Some authors used the Newcastle-Ottawa Scale to evaluate the quality of the primary studies, but did not interpret the results based on the quality or relevance of the identified studies. Moreover, the Newcastle-Ottawa Scale is regarded as insufficiently assessing the quality of observational studies, such as assessing selection bias (63). Thus, future studies should focus more on the risk of bias assessment using valid tools, such as the Cochrane risk of bias in nonrandomized studies of interventions (ROBINS-I) tool (64), or risk of bias in nonrandomized studies of exposures (ROBINS-E) tool (65), and interpret the relevance of the studies more carefully in the context of the research question.

Only 9 of the meta-analyses conducted a linear dose–response meta-analysis (11, 14, 30, 33, 35, 38, 41, 42, 45), and 7 conducted a nonlinear dose–response meta-analysis (11, 14, 33, 35, 41, 42, 45). Thus, future meta-analyses should investigate the association between dietary factors and neurodegenerative disorders not only in high compared with low meta-analyses, but also in linear and nonlinear dose–response meta-analyses.

It is highly recommended that authors register a protocol (e.g., PROSPERO) and adhere to standardized methods or guidelines such as the PRISMA (18) or the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (66) guidelines to ensure high methodological quality and a complete report of the conduct of the systematic review and meta-analysis.

Strengths and limitations

The main strength of the present umbrella review is the comprehensive overview of the published meta-analyses on the association of any dietary factors and the incidence of neurodegenerative disorders. Moreover, we recalculated all meta-analyses including only prospective studies and using random effects meta-analysis. Two investigators independently conducted several steps of the review process to minimize bias in the umbrella review. We evaluated the methodological quality of all included meta-analyses as well as the quality of evidence for all identified associations. Because the evaluation of the quality of evidence was mainly based on recalculated meta-analyses, we were able to minimize the risk of bias of original meta-analyses with regard to the inappropriate synthesis of the findings. Moreover, we

were able to identify research gaps and provided potential future research directions.

Our umbrella review has also some limitations. First, we identified meta-analyses based on observational studies only. We found no meta-analysis that included >1 intervention study and provided an SRR. However, it is rare that intervention studies investigate hard end points. Second, confounding is of major concern in observational studies. Although we used data from multivariable-adjusted models from the primary studies, residual confounding cannot be ruled out due to the observational design of the studies. Third, most observational studies assessed the diet at baseline only; changes in dietary behavior and misclassification due to the self-reported dietary intake could have affected the results. Nevertheless, we expect that misclassification was nondifferential due to the prospective design of the studies. Fourth, although we included the most recent published meta-analysis or the study based on the highest number of prospective studies, recent primary studies published after the systematic reviews and meta-analyses were conducted might be missing, for example, results from the large Ohsaki cohort 2006 study on fish consumption and incident dementia (67), or from an Australian longitudinal cohort study on the Mediterranean diet and Mediterranean-DASH diet Intervention for Neurological Delay (MIND) diet and cognitive impairment (68).

Finally, although we analyzed different outcomes and exposures separately as far as possible, there was substantial heterogeneity in some meta-analyses. We conducted or recalculated no sensitivity analyses to investigate sources of heterogeneity. Moreover, because some studies performed no sensitivity analyses, we might have missed other relevant factors (e.g., carrier of the apoEε4 allele) that could have influenced the associations.

Conclusion

The present umbrella review provided a comprehensive overview of the currently available meta-analyses investigating dietary factors and neurodegenerative disorders. We found inverse associations between the Mediterranean diet and fish intake and Alzheimer disease, as well as for tea consumption and all-cause dementia and Parkinson disease, with moderate quality of evidence. We additionally identified several systematic reviews and meta-analyses for the intake of fruit and vegetables, dairy products, coffee, macronutrients and vitamins, but the quality of evidence was rated as low or very low for most associations, mainly due to the low number of primary studies included in the meta-analyses. Thus, further studies are likely to change the overall estimates. Methodological concerns regarding original meta-analyses relate mainly to the inappropriate synthesis, and assessment and discussion of the risk of bias of primary studies. Therefore, more well-conducted research, investigating other dietary factors also, into the association with neurodegenerative disorders is warranted.

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References

1. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(1):88–106.
2. Levey A, Lah J, Goldstein F, Steenland K, Bliwise D. Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease. Clin Ther 2006;28(7):991–1001.
3. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, et al. Practice guideline update summary. Mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90(3):126–35.
4. Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harb Perspect Biol 2018;10(4):a033118.
5. Lista S, Dubois B, Hampel H. Paths to Alzheimer's disease prevention: from modifiable risk factors to biomarker enrichment strategies. J Nutr Health Aging 2015;19(2):154–63.
6. World Health Organization. Risk reduction of cognitive decline and dementia. Geneva: WHO Guidelines; 2019.
7. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. Neurotoxicology 2017;61:143–87.
8. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord 2016;23:1–9.
9. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52(3):276–84.
10. Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. J Alzheimers Dis 2010;20(Suppl 1):S221–38.
11. Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. Geriatr Gerontol Int 2014;14(2):430–9.
12. Gardener H, Caunca MR. Mediterranean diet in preventing neurodegenerative diseases. Curr Nutr Rep 2018;7(1):10–20.
13. Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv Nutr 2016;7(5):889–904.
14. Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: an updated systematic review and meta-analysis of prospective cohort studies. Sci Rep 2017;7:41317.
15. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol 2018;17(11):1006–15.
16. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13(3):132–40.
17. Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between

environmental risk factors and dementia: an umbrella review of systematic reviews and meta-analyses. Alzheimers Dement 2017;13(4):406–18.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
19. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R, ROBIS group. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;69:225–34.
20. Schwingshackl L, Knuppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopantelis E, Iqbal K, et al. Perspective: NutriGrade: a scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research. Adv Nutr 2016;7(6):994–1004.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45(Pt A):139–45.
22. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135(11):1301–9.
23. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, Cade JE, Burley VJ, Norat T. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23(4):843–52.
24. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175(1):66–73.
25. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 2016;6(7):e010247.
26. Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. Res Synth Methods 2017;8(1):5–18.
27. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
28. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, Danat IM, Zhou W, Schofield P, Clifford A, et al. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. Public Health Nutr 2018;21(10): 1921–32.
29. Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Lu H, Tan MS, Yu JT. Dietary patterns and risk of dementia: a systematic review and meta-analysis of cohort studies. Mol Neurobiol 2016;53(9):6144–54.
30. Doets EL, van Wijngaarden JP, Szczecinska A, Dullemeijer C, Souverein OW, Dhonukshe-Rutten RA, Cavelaars AE, van 't Veer P, Brzozowska A, de Groot LC. Vitamin B12 intake and status and cognitive function in elderly people. Epidemiol Rev 2013;35:2–21.
31. Hughes KC, Gao X, Kim IY, Wang M, Weisskopf MG, Schwarzschild MA, Ascherio A. Intake of dairy foods and risk of Parkinson disease. Neurology 2017;89(1):46–52.
32. Jiang X, Huang J, Song D, Deng R, Wei J, Zhang Z. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. Front Aging Neurosci 2017;9:18.
33. Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 2014;29(9):613–9.
34. Kim YS, Kwak SM, Myung SK. Caffeine intake from coffee or tea and cognitive disorders: a meta-analysis of observational studies. Neuroepidemiology 2015;44(1):51–63.
35. Larsson SC, Orsini N. Coffee consumption and risk of dementia and Alzheimer's disease: a dose-response meta-analysis of prospective studies. Nutrients 2018;10(10):E1501.
36. Li FJ, Shen L, Ji HF. Dietary intakes of vitamin E, vitamin C, and beta-carotene and risk of Alzheimer's disease: a meta-analysis. J Alzheimers Dis 2012;31(2):253–8.
37. Liu X, Du X, Han G, Gao W. Association between tea consumption and risk of cognitive disorders: a dose-response meta-analysis of observational studies. Oncotarget 2017;8(26):43306–21.
38. Ruan Y, Tang J, Guo X, Li K, Li D. Dietary fat intake and risk of Alzheimer's disease and dementia: a meta-analysis of cohort studies. Curr Alzheimer Res 2018;15(9):869–76.
39. Schwingshackl L, Bogensberger B, Hoffmann G. Diet quality as assessed by the healthy eating index, alternate healthy eating index, dietary approaches to stop hypertension score, and health outcomes: an updated systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2018;118(1):74–100 e11.
40. Shen L. Associations between B vitamins and Parkinson's disease. Nutrients 2015;7(9):7197–208.
41. Wang A, Lin Y, Wu Y, Zhang D. Macronutrients intake and risk of Parkinson's disease: a meta-analysis. Geriatr Gerontol Int 2015;15(5):606–16.
42. Wu L, Sun D, He Y. Coffee intake and the incident risk of cognitive disorders: a dose-response meta-analysis of nine prospective cohort studies. Clin Nutr 2017;36(3):730–6.
43. Wu L, Sun D. Meta-analysis of milk consumption and the risk of cognitive disorders. Nutrients 2016;8(12):E824.
44. Zeng LF, Cao Y, Liang WX, Bao WH, Pan JK, Wang Q, Liu J, Liang HD, Xie H, Chai YT, et al. An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. Oncotarget 2017;8(24):39877–95.
45. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr 2016;103(2):330–40.
46. Montagnese C, Santarpia L, Buonifacio M, Nardelli A, Caldara AR, Silvestri E, Contaldo F, Pasanisi F. European food-based dietary guidelines: a comparison and update. Nutrition 2015;31(7-8):908–15.
47. Montagnese C, Santarpia L, Iavarone F, Strangio F, Sangiovanni B, Buonifacio M, Caldara AR, Silvestri E, Contaldo F, Pasanisi F. Food-based dietary guidelines around the world: eastern Mediterranean and Middle Eastern countries. Nutrients 2019;11(6):E1325.
48. Ninomiya T. Epidemiological evidence of the relationship between diabetes and dementia. Adv Exp Med Biol 2019;1128:13–25.
49. Yue X, Li H, Yan H, Zhang P, Chang L, Li T. Risk of Parkinson disease in diabetes mellitus: an updated meta-analysis of population-based cohort studies. Medicine (Baltimore) 2016;95(18):e3549.
50. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. Mov Disord 2020;35(1):55–74.
51. Kubis-Kubiak AM, Rorbach-Dolata A, Piwowar A. Crucial players in Alzheimer's disease and diabetes mellitus: friends or foes? Mech Ageing Dev 2019;181:7–21.
52. Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME. The impact of the Mediterranean diet on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. Adv Nutr 2017;8(4):571–86.
53. Tosti V, Bertozzi B, Fontana L. Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. J Gerontol A Biol Sci Med Sci 2018;73(3):318–26.
54. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, Martinez-Lapiscina EH, Fito M, Perez-Heras A, Salas-Salvado J, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med 2015;175(7):1094–103.
55. Mazza E, Fava A, Ferro Y, Rotundo S, Romeo S, Bosco D, Pujia A, Montalcini T. Effect of the replacement of dietary vegetable oils with a low dose of extravirgin olive oil in the Mediterranean diet on cognitive functions in the elderly. J Transl Med 2018;16(1):10.
56. Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, et al. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurology 2003;61(2):199–205.

57. Wood WG, Li L, Muller WE, Eckert GP. Cholesterol as a causative factor in Alzheimer's disease: a debatable hypothesis. J Neurochem 2014;129(4):559–72.
58. Polito CA, Cai ZY, Shi YL, Li XM, Yang R, Shi M, Li QS, Ma SC, Xiang LP, Wang KR, et al. Association of tea consumption with risk of Alzheimer's disease and anti-beta-amyloid effects of tea. Nutrients 2018;10(5):E655.
59. Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: a systematic review. Phytomedicine 2017;34:26–37.
60. Ide K, Matsuoka N, Yamada H, Furushima D, Kawakami K. Effects of tea catechins on Alzheimer's disease: recent updates and perspectives. Molecules 2018;23(9):E2357.
61. Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y. Beneficial effects of green tea catechins on neurodegenerative diseases. Molecules 2018;23(6):E1297.
62. Onakpoya I, Spencer E, Heneghan C, Thompson M. The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014;24(8):823–36.
63. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
64. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
65. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE, Goldstone AE, Ross P, Guyatt G, Schunemann HJ. Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the 'target experiment' concept in studies of exposures: rationale and preliminary instrument development. Environ Int 2018;120: 382–7.
66. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.
67. Tsurumaki N, Zhang S, Tomata Y, Abe S, Sugawara Y, Matsuyama S, Tsuji I. Fish consumption and risk of incident dementia in elderly Japanese: the Ohsaki cohort 2006 study. Br J Nutr 2019;122(10):1182–91.
68. Hosking DE, Eramudugolla R, Cherbuin N, Anstey KJ. MIND not Mediterranean diet related to 12-year incidence of cognitive impairment in an Australian longitudinal cohort study. Alzheimers Dement 2019;15(4):581–89.