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REVIEW

Effect of antioxidant intake patterns on risks of dementia and cognitive decline

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Key summary points

Aim This systematic review and meta-analysis aims to quantitatively investigate the relationships between the pattern of antioxidant intakes and risks of dementia and cognitive decline.

Findings For the risk of all-cause dementia, it is supplemental, not dietary, use of vitamin E or vitamin C that can significantly reduce the risk. For AD risk, dietary plus supplemental, not supplemental alone, intakes of vitamin E or vitamin C decrease markedly the risk. Furthermore, linear dose-response analyses further verified the positive effect of dietary plus supplemental intake of vitamin C on a reduced incidence of Alzheimer's dementia, with an association of every 20 mg/day increase in vitamin C and a 2% decrease in AD risk by diet plus supplement intake.

Message The findings support dietary guidelines that recommend increased intake of vitamin-C-rich foods accompanied by supplemental use of vitamin C which may be more beneficial to reduce the risk of Alzheimer-type dementia.

Abstract

Background Previous studies have suggested that increased antioxidant intakes might reduce risk of cognitive disorders including Alzheimer's disease (AD). Which avenue of antioxidant intake (vitamin E/C) is more effective for decreasing risk, however, is largely unknown.

Objectives To quantitatively investigate the relationships between the pattern of antioxidant intakes and risks of dementia and cognitive decline.

Methods We searched all related prospective cohort studies reporting antioxidant intakes (diet and/or supplement) from patients with cognitive disorders. We conducted dose–response meta-analyses to assess potential linear and non-linear dose–response relationships. Summary RRs and 95% CIs were calculated using a random- or fixed-effects model.

Results 73 eligible cohort studies totaling > 28,257 participants were included in the meta-analysis; the pooled relative risks of AD were 0.75 (95% CI 0.57–0.99; $I^2 = 59.9\%$) for the dietary only intake of vitamin E, 0.73 (95% CI 0.54–1.00; $I^2 = 0\%$) for the dietary plus supplemental intake of vitamin E, and 0.70 (95% CI 0.51–0.95; $I^2 = 0\%$) for the dietary plus supplemental intake of vitamin C. Moreover, pooled RRs of AD and vitamin C intake per 20 mg/day increase were 0.98 (95% CI 0.97–0.99) via dietary plus supplemental intake, 0.98 (95% CI 0.96–1.00) in the dietary only intake and 0.98 (95% CI 0.98–0.99) in the overall intake. There were no significant associations of all-cause dementia or cognitive impairment no dementia with the antioxidant intake.

Conclusions The risk of incident AD is significantly reduced by higher consumption of vitamin C by the intake avenue of diet plus supplement.

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Keywords Vitamin E · Vitamin C · Antioxidants · Alzheimer's disease · Dose–response

Introduction

Age-related cognitive decline is a major public health problem, affecting about 50% of people aged 60 years and older worldwide [1]. Experimental, clinical, neuropathological and epidemiological investigations have implicated oxidative stress, involving the accumulation of free radicals with resultant oxidative damage, as a possible factor in the pathogenesis of cognitive impairment. The prevalence of dementia, as a severe cognitive problem, increases with age, so that by the age of 80 years, about one in eight people are affected [2]. It has been suggested that all pathophysiological mechanisms involved in the onset and progression of AD are related to oxidative stress [3]. To find effective prevention and treatment strategies, it is important to identify the causes of cognitive deficit [4], and critical to develop an approach to treat or delay cognitive decline. Furthermore, novel preventive approaches focused on modifying risk factors [5] for cognitive disorders are urgently needed to combat this growing epidemic. As a promising measure for treating or preventing cognitive impairment, the role of antioxidants has caused great attention.

A previous meta-analysis suggested that the dietary intakes of vitamin E, vitamin C, and beta-carotene were associated with reduced incidence of AD. In recent years, a growing number of studies focused on the relationship between the antioxidant intake and the risks of cognitive disorders, providing results that might be of great importance for further understanding of the effect of the dietary or supplemental antioxidant intakes upon cognitive disorders. Furthermore, these studies varied with sample size, intake pattern, and other characteristics, thereby leading to apparent between-study inconsistencies. Therefore, we performed a comprehensive meta-analysis of all published prospective cohort studies to clarify the effects of distinct intake patterns of the antioxidants on the risks of incident all-cause, Alzheimer's dementia and cognitive impairment no dementia (CIND).

Methods

Search strategy

Following the guidelines by the MOOSE (meta-analysis of observational studies in epidemiology) statement[6], we searched the electronic databases (PubMed and EMBASE) from inception to June 18, 2018 using the following terms: vitamin E, vitamin C, beta-carotene, flavonoids; intake, use, dietary; dementia, Alzheimer*, cognit*; prospective, cohort, follow-up, inciden*, longitudinal, "nested case–control", and so on (Details of search strategies are shown in eTable S1 in Supplemental material). A list of the excluded studies is provided in eTable S2 in Supplemental material. No language restrictions were imposed. Bibliographies of eligible studies and relevant meta-analyses were hand-searched for potential missing studies (Fig. 1).

Study selection

Studies were included if they were prospective cohort or prospective nested case–control studies, investigated an association between the antioxidant intake and the risks of all-cause, Alzheimer's dementia or cognitive impairment no dementia, classified the antioxidant intake into two or more categories, and reported crude or adjusted risk estimates with corresponding 95% CIs or results allowed calculation of risk ratios or odds ratios (ORs). For the dose–response analysis, the level-specific case numbers and person-years or sufficient data for deriving these numbers were required. The inclusion decisions were made independently by two reviewers (Zhou FT and Zhang HZ) and any disagreements were resolved by consensus after discussion.

Data extraction and quality evaluation

For each study included, we extracted the first author's last name, publication year, region (or country), cohort name, mean age or age range, mean follow-up duration, sample size, number of cases, and person-years stratified by antioxidant intake doses, cognitive outcome, exposure assessment method, range of intake dose, adjusted covariates, and multivariable-adjusted effect sizes (RR, OR or HR and corresponding 95% CI) for each exposure category. The study quality was evaluated with the Newcastle–Ottawa Quality Assessment Scale (NOS), the quality score ranged from 0 to 9. Details of how the criteria were applied are shown in Supplementary eTable S3.

Statistical methods

In this meta-analysis, all associations were estimated as RRs and 95% CIs; HRs were considered equivalent to the RRs [7]. Some studies reported the odds ratio (OR) or hazard ratio (HR) in each category, and the OR (or HR) was considered equivalent to the RR in cohort studies if the value of P_0 was small [8]. The ORs were transformed into RRs by use of the formula $RR = OR/[(1 - P_0) + (P_0 \times OR)]$, where P_0 is the incidence of the outcome in the non-exposed group. To unify the units of exposure as milligram, one International

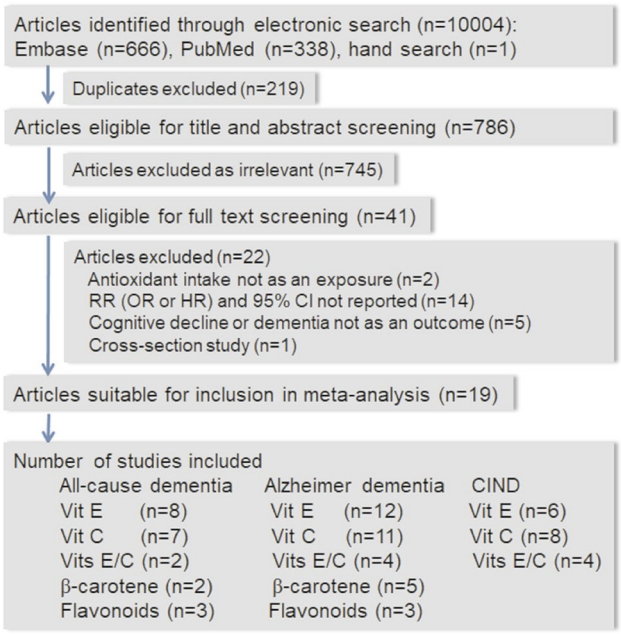

Fig. 1 Screening and selection process of studies of antioxidant intakes and risk of cognitive disorders

Unit (IU) of vitamin E is defined as 0.667 mg α-Tocopherol equivalents [9], and of vitamin C as 0.74 mg according to the international criteria. For each of the studies included, the reported median or mean intake of each category was considered as the category of the antioxidant intakes [8]. When a study reported only the range of the antioxidants intake dose for a category, we obtained the average value of the lower and upper bounds. If the highest category was open-ended, the lower end value of the category multiplied by 1.2 was assigned. The risk estimate from the most fully adjusted models in the analysis of the pooled RR was used. If the number of cases/non-cases in each category was not available and the authors did not give their reply, a method [10] was used to provide approximate data based on the total number and RRs of each category. We excluded the studies without the number of participants and/or cases in the whole cohort, also not providing RRs (ORs) and 95% CI.

We first summarized the RRs for the highest versus lowest category of antioxidants dose in the included studies using the random effects ($I^2 > 50\%$, the DerSimonian–Laird method) or fixed effects ($I^2 \leq 50\%$, the Mantel–Haenszel method) meta-analysis (high versus low meta-analysis). For the dose–response meta-analysis, the two-stage generalized least-squares trend estimation method was used to estimate the study-specific slope lines first and then to derive an overall average slope using the method described by Greenland and Longnecker [11]. Dose–response meta-analyses were performed to examine a potential nonlinear relationship between antioxidants intake and risk of dementia using restricted cubic splines. Restricted cubic spline models with 3 knots were fitted in each study taking into account the covariance among log RR, and the regression coefficients were then combined using multivariate meta-analysis. A test for a non-linear relation was calculated by making the coefficient of the second spline equal to zero, as described previously [12]. To generate a linear dose–response curve, data on antioxidant intake categories, the distribution of cases and person-years, and RRs plus 95% CIs for 3 or more categories were extracted. First, specific linear trends and 95% CIs were estimated from the natural logs of RRs across categories of dose by the generalized least-square models method. For studies that reported continuous risk estimates per certain units these risk estimates were converted to a risk estimate per 20-unit by first taking the natural logarithm of the RR (95% CI), then dividing the ln(RR, 95% CI) by the increment reported, multiplying by 20. Then, the estimated linear trends were pooled with fixed- or random-effects meta-analysis, depending on the absence or presence of statistical heterogeneity.

Study heterogeneity was assessed using the Q test and I^2 statistic, $P < 0.10$ and $I^2 > 50\%$ indicated evidence of heterogeneity. If the I^2 statistic was 50% or less, a meta-analysis based on a fixed-effect model was conducted, otherwise the random-effects model was used. Sensitivity analyses excluding one study at a time were conducted to explore whether the results were strongly influenced by a specific study. Potential publication bias was assessed by the application of contour-enhanced funnel plots [13], as well as by the Egger's/Begg's tests. All statistical analyses were conducted with two-tailed test at the $P < 0.05$ level for statistical significance using STATA v14.0 (Stata Corp, College Station, TX, USA).

Results

Study characteristics

The initial search identified 338 records from PubMed, 666 records from EMBASE and 1 record [14] from hand search. We identified 786 articles for review of title and abstract. After the initial screening, full text of potentially eligible articles was retrieved for detailed assessment. After full text reviews, 22 articles were excluded (see Fig. 1 and eTable S2 in Supplemental material), and 75 eligible cohort studies from 19 eligible articles were included for meta-analysis, with a total of 28,257 participants and 2,557 AD patients [9, 14–25], 1035 cases of all-cause dementia [14, 16–18, 22, 24, 26–28] and 6197 cases of cognitive impairment no dementia [14, 22, 24, 29–31]. All the studies included have been published as full manuscripts and are of high quality (see Supplementary eTable S4). Figure 1 shows a flowchart

of study selection. In addition, the characteristics of the included studies are summarized in detail in eTable S3 in the supplemental material.

Main associations of AD risk with antioxidant intakes

AS shown in Fig. 2 and eTables 9–12 in Supplemental material, the pooled RRs of AD in the overall intakes of high versus low category were 0.76 (95% CI 0.65–0.89, $I^2 = 20.9\%$, $P_{\text{heterogeneity}} = 0.238$; $n = 10$) for vitamin E, 0.81 (95% CI 0.70–0.94; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.573$; $n = 11$) for vitamin C, 0.97 (95% CI 0.79–1.19; $I^2 = 25.2\%$, $P = 0.254$; $n = 5$) for beta-carotene, 1.18 (95% CI 0.95–1.46; $I^2 = 0\%$, $P = 0.475$) for flavonoids. There were significant associations between AD risk and vitamin E intake from diet alone (RR = 0.75; 95% CI 0.57–0.99; $I^2 = 59.9\%$, $P_{\text{heterogeneity}} = 0.041$; $n = 5$) and from diet plus supplement (RR = 0.73; 95% CI 0.54–1.00; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.843$; $n = 3$). For the intake of vitamin C, there was a significantly lower RR of AD in dietary plus supplemental intake (RR = 0.70; 95% CI 0.51–0.95; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.887$; $n = 3$). In contrast, the distinct intake patterns of beta-carotene and flavonoids yielded non-significant estimates.

In the linear dose–response analysis, as shown in Fig. 4 and eTables 19–22 in Supplemental material, every 20 mg/day increase in vitamin C intake reduced the risk of incident AD through diet alone (RR = 0.98; 95% CI 0.96–1.00; $I^2 = 41.9\%$; $n = 4$), diet plus supplement (RR = 0.98; 95% CI 0.97–0.99; $I^2 = 0$; $n = 3$) and the overall intake pattern (RR = 0.98; 95% CI 0.98–0.99; $I^2 = 34.2\%$; $n = 9$). For every 20 mg/day increase in vitamin E intake, every 1 mg/day increase in beta-carotene intake and every 10 mg/day increase in dietary flavonoids intake, there were no significant statistical relationships between AD risk and any of intakes.

Antioxidant intakes and risk of all-cause dementia

AS shown in Fig. 3 and eTables 5–8 in Supplemental material, the pooled RRs of all-cause dementia in the overall intakes of high versus low category were 0.84 (95% CI 0.72–0.92; $I^2 = 36.1\%$, $P_{\text{heterogeneity}} = 0.141$; $n = 8$) for vitamin E, 0.88 (95% CI 0.78–0.99; $I^2 = 24.3\%$, $P_{\text{heterogeneity}} = 0.244$; $n = 7$) for vitamin C, 1.21 (95% CI 0.98–1.49; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.481$; $n = 2$) for beta-carotene, and 0.99 (95% CI 0.64–1.54; $I^2 = 74.0\%$, $P_{\text{heterogeneity}} = 0.021$; $n = 3$) for flavonoids. There were significant associations between risk of all-cause dementia and the supplemental intakes of vitamin E (RR = 0.80; 95% CI 0.70–0.92; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.480$; $n = 6$) and of vitamin C (RR = 0.81; 95% CI 0.70–0.93; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.647$; $n = 5$). In contrast, there were no significant effects of the intakes of beta-carotene, flavonoids and the combination use of vitamins E and C on risk of all-cause dementia. In the linear dose–response analysis, there were no significant statistical relationships between risk of all-cause dementia and any of the antioxidant intakes and any of the intake patterns (see Fig. 4 and eTables 15–18 in Supplemental material).

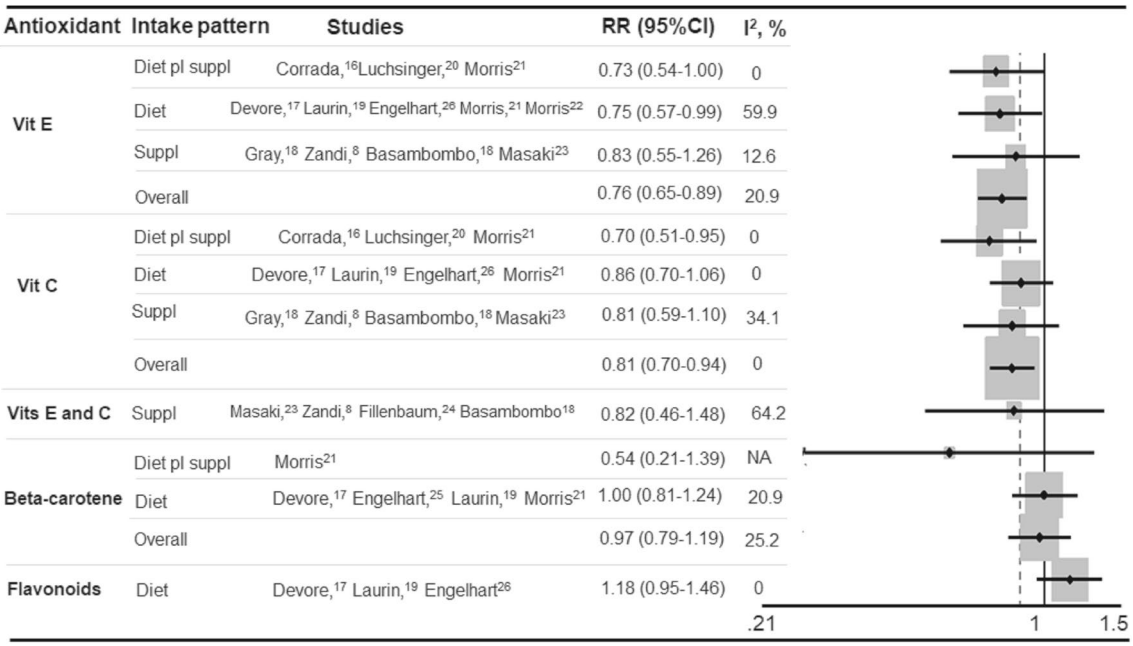

Fig. 2 Subgroup analyses within AD risk based on intake pattern in high versus low antioxidant intakes (*pl* plus, *suppl* supplement)

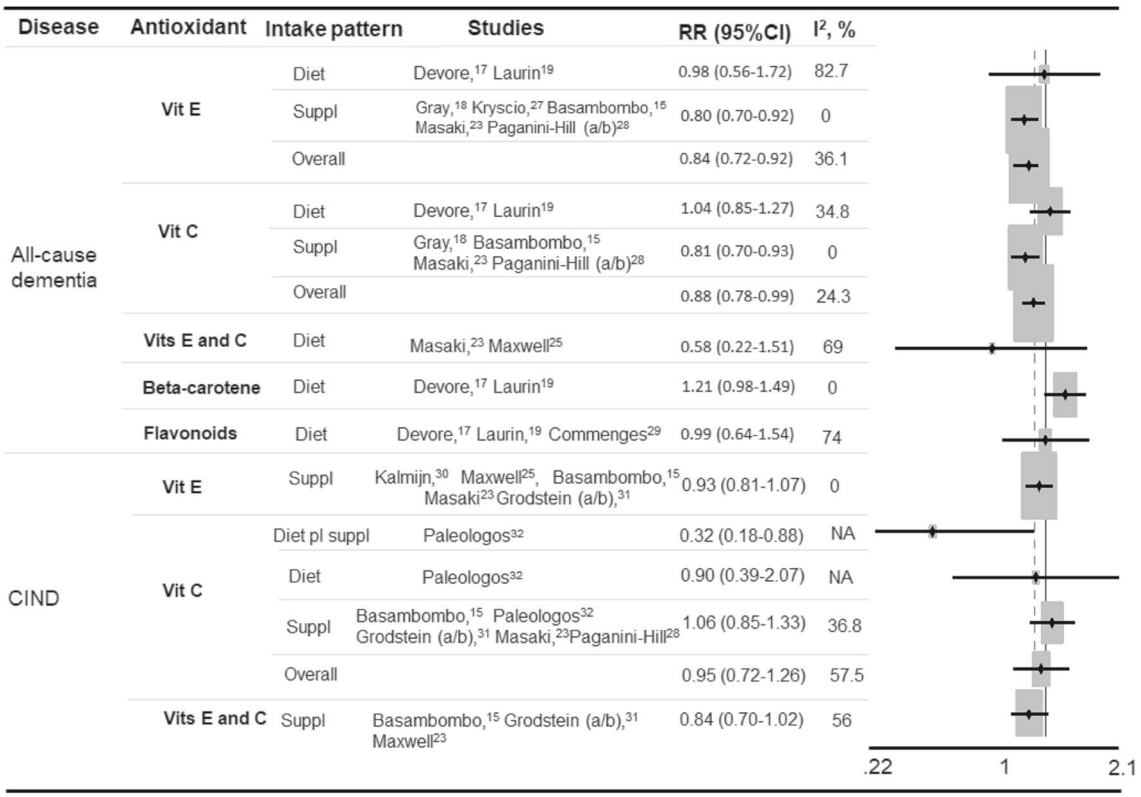

Fig. 3 Subgroup analyses within risks of all-cause dementia and cognitive impairment no dementia based on intake pattern in high versus low antioxidant intakes (*pl* plus, *suppl* supplement)

Antioxidant intakes and risk of incident cognitive impairment no dementia

As shown in Fig. 3 and eTables 13–18 in Supplemental material, the pooled RRs of all-cause dementia in the overall intakes of high versus low category were 0.93 (95% CI 0.81–1.07; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.765$; $n = 6$) for vitamin E, 0.95 (95% CI 0.72–1.26; $I^2 = 57.5\%$, $P_{\text{heterogeneity}} = 0.021$; $n = 8$) for vitamin C. There was an association between risk of CIND and the dietary plus supplemental intake of vitamin C (RR = 0.32; 95% CI 0.18–0.88; $n = 1$). When considering the use of the combination of vitamins E and C, the pooled RR was 0.84 (95% CI 0.70–1.02; $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.078$; $n = 4$). In the linear dose–response analysis, similarly, there were no significant statistical relationships between risk of CIND and any of the antioxidant intakes and any of the intake patterns (see Fig. 4 and eTables 23–24 in Supplemental material).

Non-linearity dose–response analysis, study quality, publication bias and sensitivity analyses

Using a restricted cubic splines model, it was shown that there were no significant non-linear relationships between AD risk and the intakes of vitamin E or C ($P > 0.05$ for non-linearity; Fig. 5). Begg's and Egger's tests indicated no publication bias in most of the pooled studies (eTable 25 in Supplemental material).

Assessment of study quality yielded an average score of 6.8 (9 representing the highest quality), and 11 publications had scores of ≥ 7 (eTable S4 in Supplemental material). Sensitivity analyses demonstrated that the estimates were not substantially altered for all-cause dementia, Alzheimer-type dementia and CIND (eTables 26–36 in Supplemental material).

Discussion

To our best knowledge, this is the first meta-analysis assessing the relationships between patterns of antioxidant intake and incident risks of cognitive disorders. For risk of all-cause dementia, it was supplemental, not dietary, use of vitamin E or vitamin C that significantly reduced the risk. In contrast, it was dietary plus supplemental, not supplemental alone, intakes of vitamin E or vitamin C that decreased dramatically AD risk. Furthermore, linear dose–response analyses further verified the positive effect of dietary plus supplemental intake of vitamin C on a reduced incidence of Alzheimer's dementia, with an association of every 20 mg/

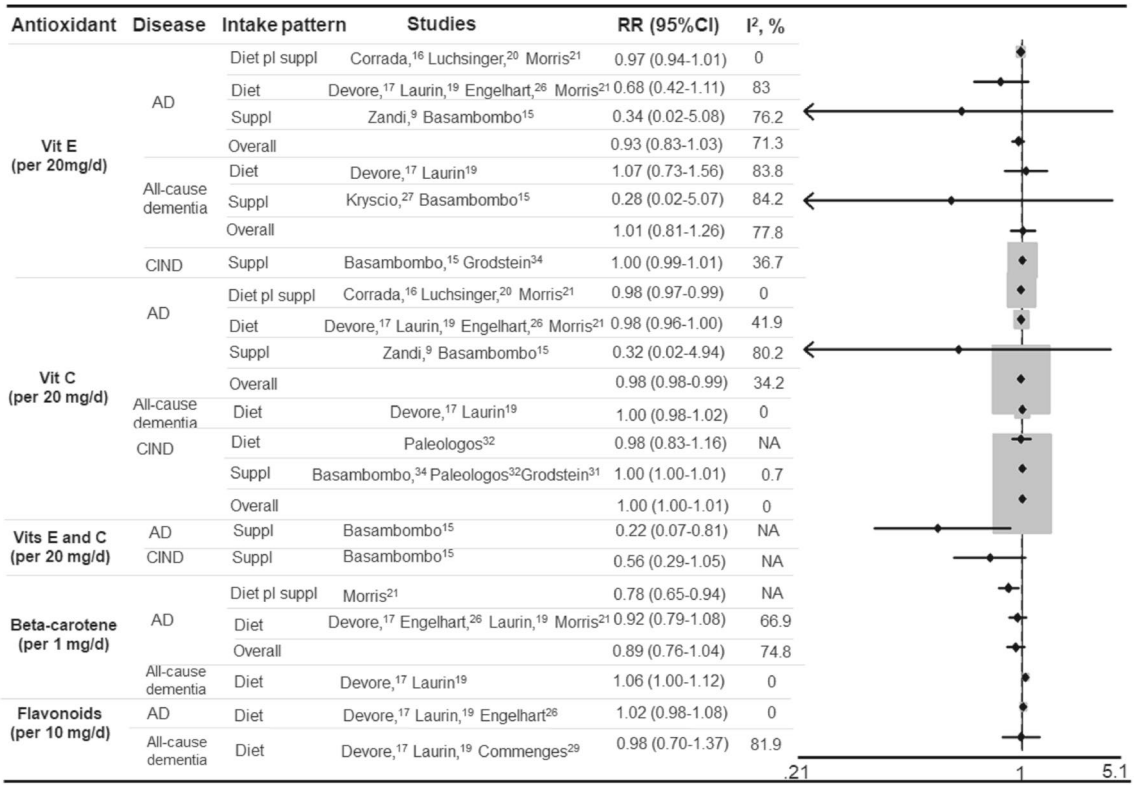

Fig. 4 Estimates of relative risk associated with intakes of antioxidant per unit increment (*pl* plus, *suppl* supplement)

day increase in vitamin C and a 2% decrease in AD risk by diet plus supplement intake. Nevertheless, this meta-analysis did not find linear associations of vitamin E intake with AD risk, of vitamin E/C intakes with risk of all-cause dementia; there were also none of the significant relationships for cognitive impairment without dementia.

Several meta-analyses [32–34] of prospective cohort studies have reported the relationships of antioxidant intakes with incident risk of cognitive disorders, and the results of these studies were, by and large, consistent with the findings of our overall analysis. All the reviews reached the conclusion that vitamin E or C intakes were significantly negative associated with risk of dementia [33, 34]. More comprehensively, our current meta-analysis examined the relationships between the intake patterns (including diet and supplemental use) of antioxidant (including vitamins E and C, beta-carotene and flavonoids) and incident cognitive disorders (a broad range of cognitive outcomes including all-cause dementia, Alzheimer's dementia, and CIND), providing greater statistical power and more precise estimates because of pooling of multiple studies. Importantly, there was a clear linear, but no curvilinear, dose–response relationship between the dietary plus supplemental intake of vitamin C and risk of incident Alzheimer dementia. Our results support the notion that increased vitamin C intake (diet plus supplement) is an effective preventive measure for Alzheimer's disease.

The endogenous capacity of antioxidant vitamins, such as vitamins E [35] and C [36] to prevent neuronal damage and death induced by oxidative stress, has been well-recognized for their beneficial influence on cognitive performance [37, 38]. The current founding demonstrated that there was a linear dose–response effect of the intake of vitamin C, rather than vitamin E, on AD risk, which might be attributed to the fact that many different biological mechanisms were believed to be linked to the effect of vitamin C on AD pathology. In fact, the neuroprotective role of ascorbic acid (vitamin C) is based not only on its general free radical trapping, but also on the chelation of iron, copper and zinc, as well as the reduction of amyloid-beta peptide production [36, 39]. Oxidative stress has a key role in the etiology of AD, according to a growing body of research. Oxidative stress is found to interact with the processes related to AD pathogenesis, including APP processing, mitochondrial dysfunction, and metal buildup [40]. Vitamin C has been demonstrated to protect SH-SY5Y cells from Aβ-mediated apoptosis, lowering the rate of endogenous amyloid production [41]. In rat hippocampal brains, oral vitamin C treatment reduced oxidative stress and neuroinflammation mediated by Aβ

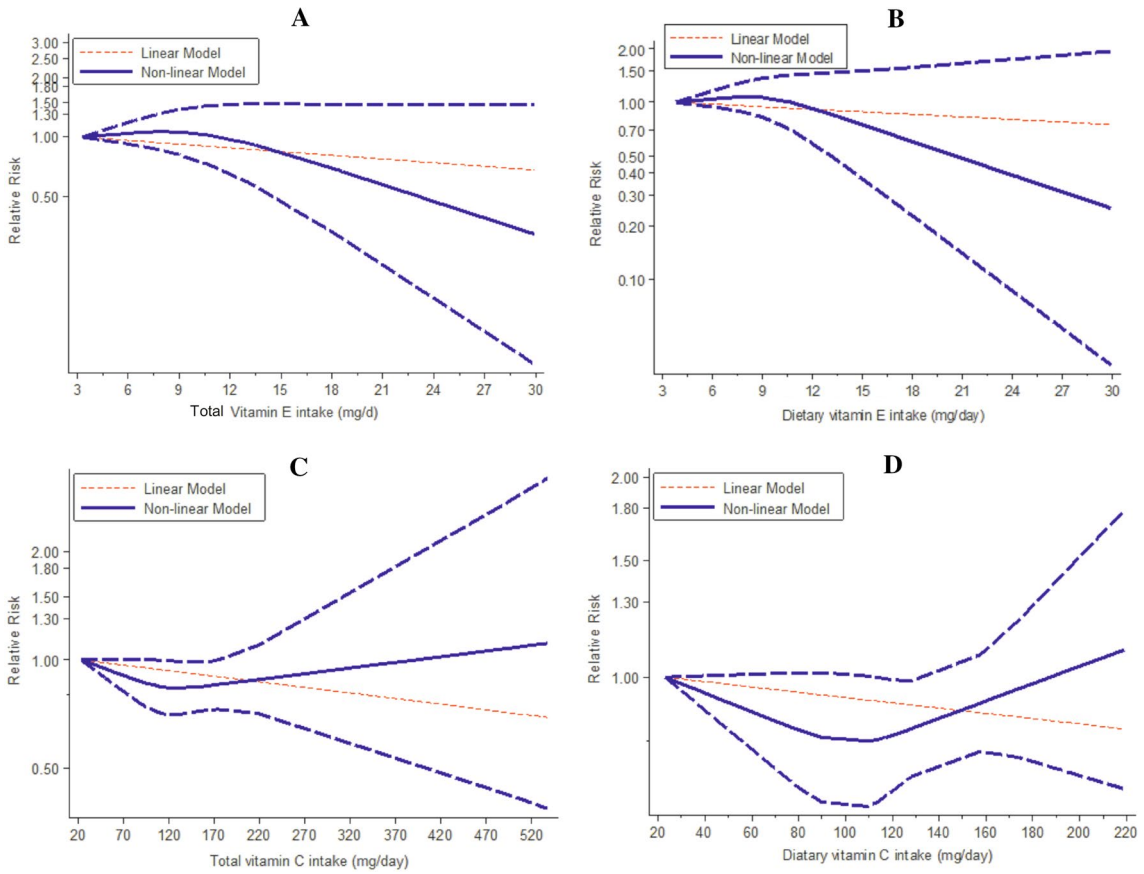

Fig. 5 Dose–response analyses of the non-linear association between ad risk and antioxidant intakes (**A** total intake of vitamin E; **B** dietary intake of vitamin E; **C** total intake of vitamin C; **D** dietary intake of vitamin C)

fibrils [42]. Furthermore, new data have emerged recently regarding potentially dangerous adverse effects (including increased mortality) of vitamin E [43].

Vitamin C has also been suggested to prevent neurodegenerative changes by protecting blood–brain barrier (BBB) integrity [39]. Many studies have reported that BBB disruption precedes neurodegeneration and cognitive decline in both AD patients and AD model animals [44]. It was shown that there was the substantially increased permeability of BBB at a very early stage of AD, and the extent of BBB leakage was positively associated with the severity of cognitive decline measured by Mini-Mental State Examination [45]. Kook et al. [46] recently reported that high dose supplementation of vitamin C reduced amyloidosis in the cortex and hippocampus of KO-Tg AD mice (cross-breeding of 5 familial Alzheimer's disease mutation mice with iotagulono-gamma-lactone oxidase knockout mice, which were unable to synthesize their own vitamin C) via attenuation of BBB disruption and mitochondrial alteration, with substantial reduction of amyloid plaque burden. These findings help to explain the cause of why vitamin C intake is more effective in preventing the incidence of Alzheimer dementia.

One important unresolved question is why dietary plus supplemental intake of vitamin C could reduce AD risk, but neither dietary alone nor supplemental alone intake of vitamin C did. Riviere et al. [47] found that plasma ascorbate levels were lower in Alzheimer's disease individuals in proportion to the degree of cognitive impairment, despite adequate ascorbic acid intake, suggesting that diet alone might not correct the imbalance in pro-oxidant and antioxidant activities. It was reported that vitamin C showed an antioxidant effect at lower doses, but resulted in a pro-oxidant effect at higher dose levels in colchicine-induced AD rats [48]. One possibility is that a pro-oxidant effect of vitamin C supplementation [49] might occur in some studies due to higher supplement use. Further investigations are needed to better understand the underlying mechanism that accounts for the effect of the intake patterns of antioxidants on incident AD.

Strengths of this study include the comprehensive, linear and non-linear dose–response, sensitivity and influence analyses; having a large number of participants and a complete quality assessment. The estimates from the fully adjusted models per study were used in our analyses

to reduce the potential of confounding. This can help to quantify the associations and test their shapes.

Despite these strengths, there are several limitations in the current study. First, antioxidants treatment would be efficient, but inefficient or even pro-oxidant in individuals with a high or low level of reactive oxygen species (ROS), respectively [36]. Because not all of the participants in the included studies were dementia-free at baseline, the dementia-preventive effect of antioxidants might depend partly on their initial ROS levels or baseline total antioxidant capacity [50], which was, however, not available for almost all the included studies. Therefore, the baseline antioxidant capacity should be measured before intake of antioxidants for the purpose of reducing the effect of the endogenous antioxidant activity. This helps reduce the potential bias. Second, differential adjustment for confounders across studies could potentially influence our study findings. Given the observational nature of this and other previous studies, it is still possible that unmeasured factors may be responsible for potential bias risk. Third, our meta-analysis was conducted with summary statistics, rather than individual data, which allowed more precise delineation for the dose–response relationship and controlled potential residual confounding.

Conclusions

There is significant meta-analytic evidence that it exists a markedly negative relationship of antioxidant intakes with risk of all-cause and Alzheimer's dementia, but not with risk of CIND. Our dose–response meta-analysis shows that every 20 mg/day increased intake of vitamin C from diet plus supplement is linearly associated with a 2% decreased risk for Alzheimer-type dementia. These findings support dietary guidelines that recommends increased intake of the consumption of vitamin C rich foods accompanied with supplemental use of vitamin C may be more beneficial to reduce the risk of Alzheimer-type dementia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41999-022-00720-7.

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Data availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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