Dietary antioxidants and risk of Parkinson's disease: a systematic review and dose-response meta-analysis of observational studies

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Abbreviations: PD: Parkinson's disease, RR: relative risks, CI: confidence interval, TAC: total antioxidant capacity, FFQ: food frequency questionnaire, RNS: reactive nitrogen species, ROS: reactive oxygen species, RDA: recommended dietary allowance.

Abstract

The aim of the current review was to explore the association between various dietary antioxidants and the risk of developing Parkinson's disease (PD). PubMed, Scopus, Web of Science, and Google Scholar were searched up to March 2021. Prospective, observational cohort studies, nested case-control, and case-control designs that investigated the association between antioxidants and PD risk were included. A random-effects model was used to pool the relative risks (RR). The certainty of the evidence was rated using the GRADE scoring system. In addition, a dose-response relationship was examined between antioxidant intake and PD risk. Six prospective cohort studies and two nested case-control (total n= 448,737 with 4654 cases), as well as six case-control studies (1948 controls, 1273 cases) were eligible. The pooled RR was significantly lower for the highest compared to the lowest intake categories of vitamin E (0.84, 95% CI 0.71, 0.99, n = 7), and anthocyanins (0.76, 95% CI: 0.61, 0.96, n = 2) in cohort studies. Conversely, a significantly higher risk of PD was observed for higher lutein intake (1.86, 95% CI: 1.20, 2.88, n = 3) among case-control studies. Dose-response meta-analyses indicated a significant association between a 50 mg/d increase in vitamin C (RR: 0.94, 95% CI: 0.88, 0.99, n = 6), a 5 mg/d increment in vitamin E (RR: 0.84, 95% CI: 0.70, 0.99, n = 7), a 2 mg/d increment in β-Carotene (RR: 0.94, 95% CI: 0.89, 0.99, n=6), and a 1 mg/d increment in zinc (OR: 0.65, 95% CI: 0.49, 0.86; n = 1) and

the reduced risk of PD. Overall, higher intake of antioxidant-rich foods may be associated with a lower risk of PD. Future, well-designed prospective studies are needed to validate the present findings.

Keywords: Antioxidants, Parkinson, Meta-analysis, Observational studies

Statement of Significance: Based on the literature, although previous meta-analyses have reviewed the association between specific types of dietary antioxidants and PD risk, several restrictions may distort these results. Notably, this is the first study to assess whether there is a dose-response relationship between the amount of consumed dietary antioxidants and the risk of PD.

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterized by rigidity, bradykinesia, slowness of movement, and tremors (1). It has been estimated that 0.3% of the general population in industrialized countries, and 1% of those above the age of 60 years are prone to the degeneration of dopaminergic neurons, the hallmark of PD (2). The exact underlying cause of this neurodegenerative disorder is still unknown. Nonetheless, it has been suggested that oxidative stress, neuroinflammation, and mitochondrial dysfunction are involved in PD pathogenesis (3).

Given that oxidative stress is involved in dopaminergic neurotoxicity (4), it has been hypothesized that the consumption of antioxidants-rich foods may represent a promising approach to protect against neuronal damage by scavenging reactive oxygen species (5). Accordingly, attention has been placed on the neuroprotective effects of dietary antioxidants

on PD outcomes. A large Swedish cohort that followed up participants for 17 years showed that higher dietary vitamin E and C consumption was associated with a lower risk of PD (6). Moreover, several epidemiological studies have reported an inverse relationship between dietary carotenoids and the risk of PD (7, 8). However, results from the Nurses' Health Study and Health Professionals Follow-Up Study did not support this association (9). Consequently, it remains inconclusive which specific antioxidants are related to the risk of PD.

Two previous meta-analyses have reviewed the association between specific types of dietary antioxidants and PD risk (10, 11). However, several major limitations may have distorted the generated outcomes. The reviews comprised of a limited number of studies, and included both, a cross-sectional study (12) and a study that assessed whole foods containing vitamins (13). In addition, both meta-analyses failed to assess whether there may be a dose-response relationship between the amount of consumed dietary antioxidants and the risk of PD. Expanding from these previous reviews, we identified six new relevant population-based cohort studies (6, 8, 9, 14, 15). This systematic review and dose-response meta-analysis of observational studies summarized the available findings relating to the potential associations between dietary intake of numerous antioxidants and the risk of developing PD. These antioxidants included vitamin C, vitamin E, vitamin A, α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, flavonoids, selenium, zinc, and overall antioxidant capacity. Where possible, the dose-response relationship was also examined.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16) was used to conduct this systematic review and meta-analysis. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO, CRD42021242511).

Search Strategy

Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched up to March 2021. No filters or restrictions were applied to publication time or language. Detailed information relating to the search strategy of databases as well as keywords relating to dietary intake of various antioxidants, PD, and study design are described in **Supplementary Table 1**. The reference lists of selected publications were also searched manually in an effort to avoid missing any relevant articles.

Eligibility and study selection

Two reviewers (ST and HM) independently selected eligible articles that met the following criteria: (1) observational studies with a prospective cohort, nested case-control, or case-control design; (2) conducted on adults (≥18 years); (3) reported the consumption of the following dietary antioxidants: vitamin C, vitamin E, vitamin A, selenium, zinc, α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, flavonoids, and antioxidant capacity; (4) reported the risk estimate of PD as an outcome variable; and (5) reported odds ratios (OR), relative risk (RR) or hazard ratios (HR) along with 95% confidence intervals (CIs). Studies with a cross-sectional design, intervention studies, review articles, case reports, letters to the editor and those conducted on children or patients with specific diseases were not included. When multiple publications used duplicate or overlapping data, the most recent publication with the longest follow-up time was included.

Data extraction

The following characteristics from selected eligible studies were recorded: first author's name, the country where the study was conducted, publication year, gender, age-range and/or mean age (year), study follow-up duration, number of participants/cases, dietary assessment method, type of exposure, method of outcome assessment, dietary intake categories (high vs

low), and adjusted covariates. Reported effect sizes in the form of OR, RR or HR and the 95% CI of risk of PD were also recorded. The process of data extraction was performed individually by three authors (ST, AJ, and HM).

Quality Assessment

The quality of included studies was assessed by two independent researchers (ST and AJ), using the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (17). This checklist examined whether study bias related to seven potential domains: confounding, selection of participants, exposure assessment, misclassification of exposure during follow-up, missing data, measurement of the outcome, and selective reporting of the results. According to this scale, the overall quality of studies was categorized as a low, moderate, or serious risk of bias (**Supplementary Table 2**).

Data synthesis and statistical analysis

RR and their 95% CI constituted the effect sizes of the pooled cohort studies. The reported ORs from nested case-control and HRs from cohort studies were considered the equivalent to RRs (18). Furthermore, OR (and 95% CIs) were used as the effect sizes in the analysis of case-control studies. Separate analyses were carried out for cohort and case-control studies.

Reported risk estimates of PD for the highest compared to the lowest category of dietary antioxidant intake were pooled using DerSimonian and Laird random-effects model (19). Cochrane's Q test of heterogeneity and the I^2 statistic ($P < 0.05$) were conducted to evaluate heterogeneity across studies (20). To detect potential heterogeneity, subgroup analyses stratified by sex, follow-up duration, number of participants/cases, country of study, and adjustment for confounding variables including vitamin and mineral supplement use, physical activity, and alcohol intake were used. A sensitivity analysis was also performed to determine

the influence of each individual study on the overall effect size. Publication bias was evaluated using Egger's regression test (21) and Begg's test (22).

Second, the linear dose-response relationship was tested using generalized least-squares trend estimation, according to the methods developed by Greenland and Longnecker (23, 24). Finally, the shape of the dose-response relationships was examined using studies that reported sufficient information (25). The correlation within each category of relative risk was taken into account and the study-specific estimates were combined using a one-stage linear mixed-effects meta-analysis (26). This method estimates the study-specific slope lines and combines them to find an overall average slope (27, 28). This single stage approach has been shown to be more precise, flexible, and efficient than the traditional two-stage method (26). The best fitting, second order fractional polynomial was used to perform the dose-response meta-analysis when only two studies were available. Statistical analyses were conducted using STATA version 14 software (Stata Corp, College Station, Texas, USA). In addition, Grading of Recommendations Assessment, Development and Evaluations (GRADE) was applied to evaluate the quality of the evidence for each relationship (29).

A priori power analyses were performed using recently validated methods (30, 31). We found matching RR and average sample sizes across all outcomes in the previous meta-analyses (10, 11). In line with this, we anticipated to detect a small statistically significant effect size with an alpha of 5%, a statistical power of 80%. The present analyses including the minimum number of studies required to obtain power using a random-effects model (**Supplementary Table 3)**.

Results

Literature search

We identified 2230 publications through initial electronic searches. Of those, 622 articles were eliminated based on duplicates, animal studies, and non-original articles. 1566 records were removed following the title and abstract screening. Out of 42 full text publications, 29 were excluded for either of the following reasons: irrelevant outcomes (*n* = 3), insufficient information (*n* = 11), irrelevant exposure (*n* = 11), cross-sectional design (*n* = 2), and duplicated reports (*n* = 2). Detailed reasons for study exclusion are described in **Supplementary Table 4**. Ultimately, 6 prospective cohort studies (5 publications) (6, 8, 9, 14, 15), 2 nested case-control (32, 33), and 6 case-control studies (7, 34-38) met the inclusion criteria. The flow diagram of the study selection process is provided in **Figure 1**.

Study characteristics

In total, 448737 participants, consisting of 4654 cases with PD formed the analyses of prospective cohort studies (6, 8, 9, 14, 15, 32, 33). 1948 controls and 1273 cases made up the analysis for the case-control studies (7, 34-38). These studies were conducted from 1996 to 2021 in Sweden (6, 8), Singapore (14), USA (9, 15, 33, 35-37), Japan (7, 32, 38), and Germany (34). Four studies (three prospective cohort and one case-control) included only men (8, 9, 15, 32, 35), two prospective cohort studies enrolled only women (8, 9, 15), while other studies were conducted on both genders (6, 7, 14, 33, 34, 36-38). The follow-up duration among cohort studies ranged form 14 (8) to 28 years (32). All cohort studies measured dietary antioxidant intakes using a validated food frequency questionnaire (FFQ) (6, 8, 9, 14, 15, 32, 33). Among case-control studies, four used FFQs (34-37), and two used a diet history questionnaire to assess dietary intakes (7, 38). All effect sizes were adjusted for

by smoking status. Some studies controlled for additional confounding variables which included age (n = 8), body mass index (n = 7), alcohol consumption (n = 6), coffee consumption (n = 9), energy intake (n = 9), and vitamin and mineral supplement use (n = 3). The general characteristics of cohort and case-control studies are summarized in **Supplementary Tables 5 and 6**, respectively.

Among thirteen studies, the dietary intake of various antioxidants were evaluated. These included vitamin C (cohort n = 7, case-control n = 5), vitamin E (cohort n = 7, case-control n = 5), vitamin A (cohort n = 2, case-control n = 1), α-Carotene (cohort n = 3, case-control n = 2), β-Carotene (cohort n = 6, case-control n = 5), β-Cryptoxanthin (cohort n = 3, case-control n = 2), total carotenoids (cohort n = 3, case-control n = 1), lycopene (cohort n = 3, case-control n = 2), lutein (cohort n = 3, case-control n = 3), total flavonoids (cohort n = 2), flavonols (cohort n = 2), flavones (cohort n = 2), flavanones (cohort n = 2), flavan-3-ols (cohort n = 2), polymers (cohort n = 2), anthocyanins (cohort n = 2), total antioxidant capacity (cohort n = 2), non enzymatic antioxidant capacity (cohort n = 1), zinc (case-control n = 2), selenium (case-control n = 1), total xanthophylls (case-control n = 1). These antioxidants were included into the highest vs. lowest category meta-analysis (6-9, 14, 15, 32-38). Among these studies, eight had sufficient information to be included into the linear dose-response meta-analysis (6-9, 14, 15, 32, 38). However, the nonlinear dose-response meta-analysis was conducted only on six prospective cohort studies (6, 8, 9, 14, 15) (**Table 1**).

Risk of bias assessment

Based on the ROBINS tool, nine studies were categorized as being at moderate risk of bias (6-9, 14, 15, 35, 36, 38), and four studies had a serious risk of bias due to the possibility of

residual confounding or insufficient information regarding the selection of participants (32-34, 37) (**Supplementary Table 2**).

Findings from the meta-analysis

Association between dietary vitamin C intake and risk of PD

A total of seven prospective cohort studies (total *n* = 318,784) with 4570 cases (6, 8, 9, 14, 33), and 5 case-control studies (7, 34-37) were included in the analysis of dietary vitamin C intake. The risk estimate of PD was similar for the highest compared to the lowest category of dietary vitamin C intake (RR: 0.95, 95% CI: 0.77, 1.18; I^2 = 75.9%, CI: 49, 89; $P_{\text{heterogeneity}}$ = < 0.001; **Supplementary Figure 1**) among cohort studies, and for the vitamin C intake category (OR: 0.92, 95% CI: 0.72, 1.18; I^2 = 0.0%, 95% CI: 0, 79; $P_{\text{heterogeneity}}$ = 0.41; **Supplementary Figure 2**) among case-control studies (**Table 1**).

The subgroup analysis of dietary vitamin C intake and risk of PD for cohort studies showed that the association was significant only in studies with women participants (RR: 0.77, 95% CI: 0.62, 0.95; *n* = 2), those that controlled for physical activity (RR: 0.75, 95% CI: 0.63, 0.79; *n* = 3), and those not controlling for alcohol intake (RR: 1.31, 95% CI: 1.10, 1.58; *n* = 2) (**Supplementary Table 7**).

Six prospective cohort studies (4 publications) presented sufficient data for vitamin C dose-response meta-analyses (6, 8, 9, 14). The results demonstrated that each 50 mg/d increment in dietary vitamin C consumption was associated with a 6% lower risk of PD (RR: 0.94, 95% CI: 0.88, 0.99; I^2 = 55.2%, $P_{\text{heterogeneity}}$= 0.06, *n* = 6) (**Supplementary Figure 3**, **Table 1**). However, no association was observed in the analysis of one case-control study (7) (OR: 0.99, 95% CI: 0.76, 1.29; I^2 = 0.0%, $P_{\text{heterogeneity}}$ = 0.47) **(Table 1**). There was evidence of departure from linearity between dietary vitamin C intake and risk of PD ($P_{\text{nonlinearity}}$= 0.01, $P_{\text{dose-response}}$= 0.23; *n* = 7; **Figure 2A**).

Association between dietary vitamin E intake and risk of PD

Seven prospective cohort studies (6, 8, 9, 14, 32) with 316,405 participants, comprising of 3444 cases of PD and five case-control studies (1024 cases, 1580 controls) (7, 34-37) were considered eligible for the analysis of dietary vitamin E intake and risk of PD. The highest compared to the lowest category of dietary vitamin E intake was associated with a 16% lower risk of PD in the analysis of cohort studies (RR: 0.84, 95% CI: 0.71, 0.99; I^2 = 51.9%, 95% CI: 0, 80; $P_{\text{heterogeneity}}$ = 0.05; **Supplementary Figure 4**) but not in case-control studies (OR: 0.80, 95% CI: 0.57, 1.12; I^2 = 23.4%, 95% CI: 0, 69; $P_{\text{heterogeneity}}$ = 0.26; **Supplementary Figure 5**) (**Table 1**).

Findings from the subgroup analyses of cohort studies suggested that follow-up duration, number of participants, geographical region and adjustment for vitamin and mineral supplement use and alcohol intake could explain the observed heterogeneity (**Supplementary Table 8**).

A linear dose-response meta-analysis of prospective cohort studies indicated that each 5 mg/d increment in vitamin E consumption was associated with a 16 % lower risk of PD (RR: 0.84, 95% CI: 0.70, 0.99, P=0.049; I^2= 58.3%, $P_{\text{heterogeneity}}$= 0.02, n = 7) (**Supplementary Figure 6, Table 1**), with no evidence of departure from linearity ($P_{\text{nonlinearity}}$= 0.48, $P_{\text{dose-response}}$= 0.11; n = 7; **Figure 2B**).

Association between dietary vitamin A intake and risk of PD

Two cohort studies (14, 33) (939 cases, 62,964 participants) and one case-control study (36) analyzed the association between dietary vitamin A intake and risk of PD. The highest category of vitamin A intake did not significantly reduce the risk of PD in cohort studies (RR: 1.11, 95% CI: 0.92, 1.33; I^2 = 0.0%, 95% CI: 0, 90; $P_{\text{heterogeneity}}$ = 0.33, n = 3; **Supplementary Figure 7**) or in one case-control study (OR: 1.15, 95% CI: 0.62, 2.11) (**Table 1**).

Based on the dose-response analysis on one prospective cohort study (14), a 1000 IU/d increment in dietary vitamin A intake was not associated with a reduced risk of PD (RR: 1.00, 95% CI: 0.94, 1.06) (**Table 1**). Due to only one of the studies reporting categorical data, we could not perform a non-linear dose-response meta-analysis.

Association between dietary α-Carotene intake and risk of PD

Three cohort studies (total n = 189,671) with 1580 cases (9, 14) and 2 case-control studies (controls n = 418) with 306 cases (7, 35) were included in the α-Carotene analyses. Higher dietary α-Carotene intake was not significantly associated with the risk of PD in the analysis of three cohort studies (RR: 1.06, 95% CI: 0.89, 1.25; I^2 = 0.0%, 95% CI: 0, 90; $P_{\text{heterogeneity}}$ = 0.46; **Supplementary Figure 8**), and two case-controls (OR: 0.82, 95% CI: 0.38, 1.78; I^2 = 55%, $P_{\text{heterogeneity}}$ = 0.15; **Supplementary Figure 9**) (**Table 1**).

This was confirmed by a linear dose-response meta-analysis, which suggested that each 0.5 mg/d increase in α-Carotene intake was not associated with the risk of PD in cohort (9, 14) (RR: 0.98, 95% CI: 0.92, 1.04; I^2= 0.4%, $P_{\text{heterogeneity}}$= 0.36, n = 3) and case control studies (7) (OR: 0.65, 95% CI: 0.41, 1.02, n = 1) (**Supplementary Figure 10, Table 1**), with no evidence of departure from linearity ($P_{\text{nonlinearity}}$= 0.14, $P_{\text{dose-response}}$= 0.60; n = 4; **Figure 3A**).

Association between dietary β-Carotene intake and risk of PD

Six prospective cohort studies with 3370 cases of PD among a total of 316,069 participants (6, 8, 9, 14) and 5 case-control studies (1024 cases, 1580 controls) (7, 34-37) were included in the analysis of dietary β-Carotene intake. The highest category of β-Carotene intake compared with the lowest category was not associated with the risk of PD in the analysis of cohort studies (RR: 0.88, 95% CI: 0.76, 1.03; I^2 = 45.2%, $P_{\text{heterogeneity}}$ = 0.10, 95% CI: 0, 78; n = 6; **Supplementary Figure 11**), and analysis of case-control studies (OR: 0.92, 95% CI:

0.64, 1.33; I^2 = 47.8%, 95% CI: 0, 81; $P_{heterogeneity}$ = 0.10, n = 5; **Supplementary Figure 12**) (**Table 1**).

Moreover, each 2 mg/d increase in dietary β-Carotene intake was weakly associated with a 6% lower risk of PD based on 6 prospective cohort studies (6, 8, 9, 14) (RR: 0.94, 95% CI: 0.89, 0.99, P= 0.049; I^2= 58%, $P_{heterogeneity}$= 0.03, n = 6) and 30 % lower risk from one case-control study (7) (OR: 0.70, 95% CI: 0.51, 0.94; n = 1) (**Supplementary Figure 13, Table 1**). Evidence of nonlinearity ($P_{nonlinearity}$= 0.43, $P_{dose\text{-}response}$= 0.09; n = 7; **Figure 3B**) was not observed in the analysis of cohort studies that presented sufficient information for the non-linear dose-response meta-analysis (6, 8, 9, 14).

Association between dietary lycopene intake and risk of PD

A total of three prospective cohort studies, derived from 2 publications (total n = 189,671) with 1580 cases (9, 14) and two case-control studies (35, 37) were considered eligible for the analysis that examined the association between dietary lycopene intake and risk of PD. In comparison to the lowest category of dietary lycopene intake, the highest intake category was not associated with a reduced risk of PD in cohort (RR: 1.04, 95% CI: 0.88, 1.24; I^2 = 15.9%, 95% CI: 0, 91; $P_{heterogeneity}$ = 0.30; **Supplementary Figure 14**) and case-control studies (OR: 1.13, 95% CI: 0.50, 2.54; I^2 = 66.6%, $P_{heterogeneity}$ = 0.08; **Supplementary Figure 15**) (**Table 1**).

Three prospective cohort studies were included in the dose-response meta-analyses (9, 14). Findings revealed no significant association between an increase of 2 mg/d dietary lycopene intake and risk of PD (RR: 1.01, 95% CI: 0.97, 1.04; I^2 = 0.0%, $P_{heterogeneity}$ = 0.44; n = 3) (**Supplementary Figure 16, Table 1**). There was no evidence of non-linearity from cohort studies ($P_{nonlinearity}$= 0.52, $P_{dose\text{-}response}$= 0.72; n = 4; **Figure 3C**).

Association between dietary total carotenoids intake and risk of PD

Three cohort studies (total n = 189,671) with 1580 cases (9, 14) and one case-control study (35) were included in the analysis of total dietary carotenoid intake. There was no significant difference in the risk of developing PD between high and low categories of total dietary carotenoid intake in cohort studies (RR: 0.98, 95% CI: 0.81, 1.19; I^2 = 32.1%, $P_{\text{heterogeneity}}$ = 0.22; n = 3) (**Supplementary Figure 17, Table 1**).

Findings from a linear dose-response meta-analysis of cohort studies (9, 14) indicated that a 5 mg/d increase in the dietary total carotenoid intake was not associated with a reduced risk of PD (RR: 0.99, 95% CI: 0.91, 1.08; I^2 = 48.9%, $P_{\text{heterogeneity}}$ = 0.14; n = 3) (**Supplementary Figure 18, Table 1**), with no evidence of departure from linearity ($P_{\text{nonlinearity}}$= 0.95, $P_{\text{dose-response}}$= 0.93; n = 4; **Figure 3D**).

Association between dietary lutein intake and risk of PD

The association between dietary lutein intake and risk of PD was estimated by three prospective cohort studies (total n = 189,671) with 1580 cases (9, 14) and three case-control studies (870 controls, 433 cases) (35-37). The overall effect size indicated that higher lutein intake was associated with increased risk of PD in case-control studies (OR: 1.86, 95% CI: 1.20, 2.88; I^2 = 23.4%, 95% CI: 0, 79; $P_{\text{heterogeneity}}$ = 0.27; **Supplementary Figure 19**) but not in cohort studies (RR: 1.00, 95% CI: 0.82, 1.21; I^2 = 34.5%, 95% CI: 0, 92; $P_{\text{heterogeneity}}$ = 0.21; **Supplementary Figure 20**) (**Table 1**).

There was no significant association for a 1 mg/d increment in lutein consumption and risk of PD (RR: 1.00, 95% CI: 0.94, 1.06; I^2 = 44.2%, $P_{\text{heterogeneity}}$ = 0.16; n = 3) (**Supplementary Figure 21, Table 1**). We found no evidence of departure from linearity between dietary lutein intake and the risk of PD ($P_{\text{nonlinearity}}$= 0.45, $P_{\text{dose-response}}$= 0.91; n = 4; **Figure 4A**).

Association between dietary β-Cryptoxanthin intake and risk of PD

Three cohort studies (1580 cases, 189,671 participants) (9, 14) and two case-control studies (306 cases, 418 controls) (7, 35) focused on β-Cryptoxanthin and the risk of PD. The relative risk of PD was lower for the highest compared to the lowest category of dietary β-Cryptoxanthin intake among both, cohort studies (RR: 1.03, 95% CI: 0.88, 1.22; I^2 = 0.0%, 95% CI: 0, 90; $P_{heterogeneity}$ = 0.87; n = 3; **Supplementary Figure 22**), and case-control studies (OR: 1.22, 95% CI: 0.80, 1.85; I^2 = 0.0%, $P_{heterogeneity}$ = 0.71; n = 2; **Supplementary Figure 23**) (**Table 1**).

There was no linear association between dietary β-Cryptoxanthin intake and risk of PD in cohort studies (9, 14) (RR: 1.01, 95% CI: 0.96, 1.06; I^2= 0.0%, $P_{heterogeneity}$= 0.47, n = 3) as well as case-control studies (7) (OR: 1.05, 95% CI: 0.95, 1.17; n = 1) (**Supplementary Figure 24, Table 1**), with no evidence of departure from linearity ($P_{nonlinearity}$= 0.30, $P_{dose-response}$= 0.70; n = 4; **Figure 4B**).

Association between dietary flavonoid intake and risk of PD

Two prospective cohort studies from one publication, which consisted of 805 PD cases among a total of 129,617 participants were included in the pooled analysis of total dietary flavonoid intake and their subclasses (flavanones, anthocyanin's, flavan-3-ols, flavonols, flavones, and polymers) (15). The summary RR of PD for the highest flavonoid intake was lower in comparison to the lowest intake (RR: 0.77, 95% CI: 0.46, 1.29; I^2 = 77.1%, $P_{heterogeneity}$ = 0.03) (**Supplementary Figure 25, Table 1**). Comparing the highest and lowest categories for the subclasses showed that high dietary intake of anthocyanins was significantly associated with a lower risk of PD (RR $_{anthocyanins}$: 0.76, 95% CI: 0.61, 0.96; I^2 = 0.0%, $P_{heterogeneity}$ = 0.54) (**Table 1**).

In the linear dose-response meta-analysis based on two cohorts, no significant association was found between a 100 mg/d increment of dietary total flavonoid intake and risk of PD (RR: 0.95, 95% CI: 0.86, 1.04; I^2 = 83.4%, $P_{heterogeneity}$ = 0.01; n = 2) (**Supplementary Figure 26, Table 1**). No evidence of departure from linearity was seen between dietary total flavonoid intake and risk of PD ($P_{nonlinearity}$= 0.93; n = 2; **Figure 4C**).

Association between dietary antioxidant capacity intake and risk of PD

Two cohort studies (1329 cases, 84,837 participants) (8) and one cohort study (461 cases, 41,624 participants) (6) were included in the analyses of total antioxidant capacity (TAC) and non-enzymatic antioxidant capacity (NEAC), respectively. No significant differences in the risk of PD were observed between the highest and lowest intake categories of both, TAC (RR: 0.93, 95% CI: 0.78, 1.11; I^2 = 0.0%, $P_{heterogeneity}$ = 0.67) and NEAC (RR: 0.79, 95% CI: 0.60, 1.04) **(Table 1**).

The results of the linear dose-response meta-analysis illustrated that per 2000 Trolox equivalents/d increase in TAC (RR: 0.98, 95% CI: 0.94, 1.02; I^2 = 0.0%, $P_{heterogeneity}$ = 0.47; n = 2), was not associated with a lower risk of PD **(Table 1**), with no evidence of departure from linearity ($P_{nonlinearity}$= 0.21, $P_{dose\text{-}response}$= 0.34; n = 2; **Figure 4D**).

Association between dietary zinc intake and risk of PD

Two case-control studies (37, 38) analyzed the association between dietary zinc intake and risk of PD. The relative risk of PD was lower for the highest compared with the lowest category of dietary zinc intake (OR: 0.64, 95% CI: 0.31, 1.31; I^2 = 68.8%, $P_{heterogeneity}$ = 0.07). In addition, a 1 mg/d increment in dietary zinc intake was associated with a significantly lower risk of PD (OR: 0.65, 95% CI: 0.49, 0.86; n = 1) **(Table 1**).

Sensitivity analyses and Publication bias

The sensitivity analysis for the association between dietary vitamin E intake and risk of PD showed that the exclusion of various studies changed the pooled RRs. These studies included the Hantikainen study (6) (RR: 0.87, 95% CI: 0.73, 1.04), the SMC study by Yang et al. (8) (RR: 0.87, 95% CI 0.73, 1.04), the COSM study by Yang et al. (8) (RR: 0.83, 95% CI: 0.68, 1.03), the NHS study by Hughes et al. (9) (RR: 0.84, 95% CI: 0.69, 1.02), and the Morens study (32) (RR: 0.85, 95% CI: 0.72, 1.01). Moreover, excluding the study by Hughes et al. (9) altered the overall effect of dietary β-Carotene intake and risk of PD (RR: 0.85, 95% CI: 0.72, 0.99). Moreover, findings from the sensitivity analysis for the association between dietary total flavonoid intake and zinc intake with risk of PD indicated that excluding the NHS study by Gao et al. (15) (RR: 0.59, 95% CI: 0.43, 0.83) and the Powers study (37) (RR: 0.43, 95% CI: 0.23, 0.80) altered the pooled effect size. However, other effect sizes were not influenced by one particular study. No evidence of publication bias, based on Begg's and Egger's tests was found in the analyses of cohort and case-control studies.

Grading the evidence

The certainty of the evidence was rated using the GRADE approach. GRADE evidence tables for cohort and case-control studies are presented in **Supplementary Tables 9** and **10**, respectively. The quality of the assessed evidence was rated as very low or low for all outcomes, with various downgrades for serious risk of bias, inconsistency, indirectness, and imprecision.

Discussion

The present meta-analysis indicated that dietary intake of vitamin E and anthocyanins can significantly reduce the risk of PD. Furthermore, higher lutein intake was associated with an

increased risk of PD in case-control studies, a finding that was not confirmed by cohort studies. Dose-response meta-analyses showed that an increased daily consumption of 50 mg of vitamin C, 5 mg of vitamin E, 2 mg of β-carotene, and 1 mg of zinc could be associated with lower risk of PD. The certainty of the evidence was graded between very low to low for all outcomes.

Several possible mechanisms have been suggested to explain the relationship between the mentioned antioxidants and PD. Increased consumption of antioxidants is associated with a decreased risk of chronic diseases including cardiovascular diseases (39), diabetes (40), Alzheimer's disease (41), and cancer (42). The brains of patients with PD have low levels of endogenous antioxidants (glutathione and coenzyme Q10) (43), increased dopamine oxidation (44), and high iron levels (45). Based on the evidence, oxidative stress can be an important factor in the neurodegeneration associated with PD (46, 47). Thus, free radicals are believed to be involved in neuronal loss (48). According to several epidemiological studies, antioxidant-rich diets can prevent and protect from oxidative damage and neurodegeneration (49, 50).

Vitamin E has displayed neuroprotective actions against free radical-mediated injury. This is exemplified by vitamin E protecting neurons in the locus coeruleus (the principal site for norepinephrine synthesis) from death in an early model of PD (51, 52), preventing the toxin-induced destruction of striatal dopaminergic terminals (53), and controlling the levels of antioxidant defenses such as glutathione and superoxide dismutase (SOD) (54, 55). Like vitamin E, vitamin A and C have also demonstrated neuroprotective effects alone or in combination with CoQ10 (56, 57). The antioxidant activity of these vitamins leads to their neuroprotective roles in neurodegenerative diseases. Additionally, vitamin A and β-carotene prevent the constitution of fibrillar alpha-synuclein aggregates and destabilize the generated

alpha-synuclein aggregates. As a result, vitamin A and β-carotene can prevent synucleinopathies like PD (56).

Polyphenols are a group of chemical compounds that have demonstrated the ability to reduce oxidative stress (58, 59). The cellular and molecular mechanisms by which polyphenols, particularly flavonoids, protect neurons from oxidative damage and degeneration are poorly understood. However, it has been suggested that flavonoids operate by scavenging reactive nitrogen species (RNS) and reactive oxygen species (ROS) (58, 60). This is achieved through the control of signaling pathways associated with cell survival (61-63).

Previous studies have reported conflicting findings regarding the association between dietary antioxidants and PD risk. A meta-analysis of six observational studies found that a moderate intake of vitamin E was inversely associated with PD, whereas no association was seen for vitamin C and β-carotene (11). Another meta-analysis indicated a non-significant, inverse association between both, α and β-carotene and PD risk (10). These previous non-significant associations are in line with a number of non-significant findings generated from the present review. Extending these previous findings, is the observed significant relationship between higher lutein intake and increased risk of PD in case-control studies.

Findings from a number of previous studies that assessed the association between antioxidants and other neurodegenerative diseases contradict the finding from the current review. One case-control study demonstrated no associations between vitamin E, lycopene, and coenzyme Q10 with dementia, while compromised vitamin C and β-carotene intake was associated with dementia (64). This may be due to certain antioxidants having no effect on cerebrospinal fluid (CSF) biomarkers related to amyloid or tau pathology in patients with Alzheimer's Disease (65).

Based on intervention studies, the progression of PD may be slowed by vitamin E and vitamin C (66). Due to the increasing incidence rates of worldwide PD (67), raising the consumption of antioxidant-rich diets seems to be a viable recommendation to prevent PD. Furthermore, multiple cohort studies revealed a mean daily intake well below the recommended dietary allowance (RDA) for different types of antioxidants (68, 69), confirming the need to increase the consumption of antioxidant-rich foods.

The present meta-analysis has numerous strengths. The inclusion of six new cohort studies in addition to performing dose-response analyses are key strengths of the present review relative to previous meta-analyses. A nonlinear dose-response association between dietary antioxidants and the risk of PD was assessed for the first time. Notably, the GRADE system was adopted to evaluate the overall quality of the evidence. Given that the included studies consisted of long, prospective cohort designs, this minimized the risk of recall and selection biases. Most of the included studies adjusted for important confounders. The large study sample sizes, as confirmed by a power analysis, ensure high statistical power and increase the generalizability of results. In an effort to examine sources of potential heterogeneity, a range of subgroup analyses were performed. Moreover, the most recently developed statistical method was applied to conduct nonlinear dose-response analyses.

There are a number of limitations that need to be considered. Due to the observational nature of studies, causality cannot be elicited from the results. During long-term follow-up periods within cohort studies, possible changes in dietary intakes may occur, which were not taken into account amongst a majority of included studies. A high degree of heterogeneity between studies and significant study bias reduces the confidence in the estimated effect sizes. Higher antioxidant intakes are associated with higher consumption of other neuroprotective nutrients, greater compliance with dietary guidelines and lower intakes of unhealthy foods. Most of the included studies did not assess the dietary intake of these other nutrients/foods, failing to

adequately adjustment for this potential confounding factor. Moreover, the majority of included studies have been conducted in developed countries. Thus, the obtained results may not be applicable to a range of countries/societies. Due to the use of FFQs to assess the dietary antioxidant intake, the reported values may not be precise and account for antioxidant absorption. FFQs can lead to recall bias and the overestimated intake of fruits, vegetables, and consequently, water-soluble antioxidants. They may further underestimate the intake of fats and oils, which are linked to fat-soluble antioxidants (70).

Conclusion

The present dose-response meta-analysis revealed that higher consumption of dietary antioxidants, specifically vitamin E, vitamin C and polyphenols such as anthocyanins are associated with a lower risk of PD. Importantly, the quality rating of the meta-evidence indicated that there is low confidence in the generated effect size estimates across a number of examined dietary antioxidants. Future well-designed prospective cohort studies may be needed to reliably determine whether the dietary consumption of antioxidants may be a plausible option for the prevention of PD.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

Author Contribution

S.T, A.J, and H.M contributed to the conception of research, searched databases, data extraction, and performed the statistical analysis. S.T and S.M.G wrote the manuscript. H.M, AJ and NT critically revised the manuscript. All authors have read and approved the final manuscript.

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References

1. Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease. Journal of Neural Transmission 2017;124(8):901-5.
2. De Rijk Md, Launer L, Berger K, Breteler M, Dartigues J, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C. Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54(11 Suppl 5):S21-3.
3. He J, Zhu G, Wang G, Zhang F. Oxidative Stress and Neuroinflammation Potentiate Each Other to Promote Progression of Dopamine Neurodegeneration. Oxidative Medicine and Cellular Longevity 2020;2020.
4. Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR. Oxidative stress and Parkinson's disease. Frontiers in neuroanatomy 2015;9:91.
5. Duarte-Jurado AP, Gopar-Cuevas Y, Saucedo-Cardenas O, Loera-Arias MdJ, Montes-de-Oca-Luna R, Garcia-Garcia A, Rodriguez-Rocha H. Antioxidant Therapeutics in Parkinson's Disease: Current Challenges and Opportunities. Antioxidants 2021;10(3):453.
6. Hantikainen E, Trolle Lagerros Y, Ye W, Serafini M, Adami HO, Bellocco R, Bonn S. Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort. Neurology 2021;96(6):e895-e903. doi: 10.1212/wnl.0000000000011373.
7. Miyake Y, Fukushima W, Tanaka K, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, et al. Dietary intake of antioxidant vitamins and risk of Parkinson's disease: a case-control study in Japan. European journal of neurology 2011;18(1):106-13. doi: 10.1111/j.1468-1331.2010.03088.x.
8. Yang F, Wolk A, Hakansson N, Pedersen NL, Wirdefeldt K. Dietary Antioxidants and Risk of Parkinson's Disease in Two Population-Based Cohorts. Movement Disorders 2017;32(11):1631-6. doi: 10.1002/mds.27120.
9. Hughes KC, Gao X, Kim IY, Rimm EB, Wang M, Weisskopf MG, Schwarzschild MA, Ascherio A. Intake of antioxidant vitamins and risk of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2016;31(12):1909-14. doi: 10.1002/mds.26819.
10. Takeda A, Nyssen OP, Syed A, Jansen E, Bueno-de-Mesquita B, Gallo V. Vitamin A and carotenoids and the risk of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 2014;42(1):25-38.
11. Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. The Lancet Neurology 2005;4(6):362-5.
12. de Rijk MC, Breteler MM, den Breeijen JH, Launer LJ, Grobbee DE, van der Meché FG, Hofman A. Dietary antioxidants and Parkinson disease: the Rotterdam Study. Archives of neurology 1997;54(6):762-5.
13. Anderson C, Checkoway LH, Franklin GM, Beresford S, Smith-Weller T, Swanson PD. Dietary factors in Parkinson's disease: The role of food groups and specific foods. Movement Disorders 1999;14(1):21-7. doi: 10.1002/1531-8257(199901)14:1<21::aid-mds1006>3.0.co;2-y.
14. Ying AF, Khan S, Wu Y, Jin AZ, Wong ASY, Tan EK, Yuan JM, Koh WP, Tan LCS. Dietary Antioxidants and Risk of Parkinson's Disease in the Singapore Chinese Health Study. Movement Disorders 2020;35(10):1765-73. doi: 10.1002/mds.28173.

15. Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology 2012;78(15):1138-45. doi: 10.1212/WNL.0b013e31824f7fc4.
16. Moher D, Liberati A. A., Tetzlaff, J., & Altman, DG (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed);339:b2535.
17. Jüni P, Loke Y, Pigott T, Ramsay C, Regidor D, Rothstein H, Sandhu L, Santaguida P, Schünemann H, Shea B. Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance. Br Med J 2016.
18. Symons M, Moore D. Hazard rate ratio and prospective epidemiological studies. Journal of clinical epidemiology 2002;55(9):893-9.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials 1986;7(3):177-88.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed) 2003;327(7414):557-60.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed) 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088-101.
23. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology (Cambridge, Mass) 1993;4(3):218-28. doi: 10.1097/00001648-199305000-00005.
24. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. The stata journal 2006;6(1):40-57.
25. Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis: Springer, 2015.
26. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Statistical methods in medical research 2019;28(5):1579-96. doi: 10.1177/0962280218773122.
27. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology 1992;135(11):1301-9. doi: 10.1093/oxfordjournals.aje.a116237.
28. 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. American journal of epidemiology 2012;175(1):66-73. doi: 10.1093/aje/kwr265.
29. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2008;336(7650):924-6.
30. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. Psychological methods 2001;6(3):203.
31. Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. Journal of Educational and Behavioral Statistics 2010;35(2):215-47.
32. Morens DM, Grandinetti A, Waslien CI, Park CB, Ross GW, White LR. Case-control study of idiopathic Parkinson's disease and dietary vitamin E intake. Neurology 1996;46(5):1270-4. doi: 10.1212/wnl.46.5.1270.
33. Paganini-Hill A. Risk factors for parkinson's disease: the leisure world cohort study. Neuroepidemiology 2001;20(2):118-24. doi: 10.1159/000054770.
34. Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study. Neurology 1996;47(3):644-50. doi: 10.1212/wnl.47.3.644.
35. Scheider WL, Hershey LA, Vena JE, Holmlund T, Marshall JR, Freudenheim. Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease. Movement

disorders : official journal of the Movement Disorder Society 1997;12(2):190-6. doi: 10.1002/mds.870120209.
36. Johnson CC, Gorell JM, Rybicki BA, Sanders K, Peterson EL. Adult nutrient intake as a risk factor for Parkinson's disease. International journal of epidemiology 1999;28(6):1102-9. doi: 10.1093/ije/28.6.1102.
37. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT, Jr., Swanson PD, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology 2003;60(11):1761-6. doi: 10.1212/01.wnl.0000068021.13945.7f.
38. Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, et al. Dietary intake of metals and risk of Parkinson's disease: a case-control study in Japan. Journal of the neurological sciences 2011;306(1-2):98-102. doi: 10.1016/j.jns.2011.03.035.
39. Farbstein D, Kozak-Blickstein A, Levy AP. Antioxidant vitamins and their use in preventing cardiovascular disease. Molecules (Basel, Switzerland) 2010;15(11):8098-110.
40. Scott JA, King GL. Oxidative stress and antioxidant treatment in diabetes. Annals of the New York Academy of Sciences 2004;1031(1):204-13.
41. Chang Y-T, Chang W-N, Tsai N-W, Huang C-C, Kung C-T, Su Y-J, Lin W-C, Cheng B-C, Su C-M, Chiang Y-F. The roles of biomarkers of oxidative stress and antioxidant in Alzheimer's disease: a systematic review. BioMed research international 2014;2014.
42. Collins AR. Antioxidant intervention as a route to cancer prevention. European Journal of Cancer 2005;41(13):1923-30.
43. Götz M, Gerstner A, Harth R, Dirr A, Janetzky B, Kuhn W, Riederer P, Gerlach M. Altered redox state of platelet coenzyme Q 10 in Parkinson's disease. Journal of neural transmission 2000;107(1):41-8.
44. Berman SB, Hastings TG. Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria: implications for Parkinson's disease. Journal of neurochemistry 1999;73(3):1127-37.
45. Lan J, Jiang D. Excessive iron accumulation in the brain: a possible potential risk of neurodegeneration in Parkinson's disease. Journal of neural transmission 1997;104(6):649-60.
46. Prasad KN, Cole WC, Hovland AR, Prasad KC, Nahreini P, Kumar B, Edwards-Prasad J, Andreatta CP. Multiple antioxidants in the prevention and treatment of neurodegenerative disease: analysis of biologic rationale. Current opinion in neurology 1999;12(6):761-70.
47. Beal MF. Mitochondria, oxidative damage, and inflammation in Parkinson's disease. ANNALS-NEW YORK ACADEMY OF SCIENCES 2003;991:120-31.
48. Jesberger JA, Richardson JS. Oxygen free radicals and brain dysfunction. International Journal of Neuroscience 1991;57(1-2):1-17.
49. Obrenovich ME, Nair NG, Beyaz A, Aliev G, Reddy VP. The role of polyphenolic antioxidants in health, disease, and aging. Rejuvenation research 2010;13(6):631-43.
50. Wolfe K, Wu X, Liu RH. Antioxidant activity of apple peels. Journal of agricultural and food chemistry 2003;51(3):609-14.
51. Cadet JL, Katz M, Jackson-Lewis V, Fahn S. Vitamin E attenuates the toxic effects of intrastriatal injection of 6-hydroxydopamine (6-OHDA) in rats: behavioral and biochemical evidence. Brain research 1989;476(1):10-5.
52. Pasbakhsh P, Omidi N, Mehrannia K, GHOLI SA, Ragerdi KI, ABASI M, Kord VA. THE PROTECTIVE EFFECT OF VITAMIN E ON LOCUS COERULEUS IN EARLY MODEL OF PARKINSON'S DISEASE IN RAT: IM-MUNOREACTIVITY EVIDENCE. 2008.
53. Ungerstedt U. Postsynaptic supersensitivity after 6-hydroxy-dopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiologica Scandinavica 1971;82(S367):69-93.
54. Perumal A, Gopal V, Tordzro W, Cooper T, Cadet J. Vitamin E attenuates the toxic effects of 6-hydroxydopamine on free radical scavenging systems in rat brain. Brain research bulletin 1992;29(5):699-701.
55. Allan Butterfield D, Castegna A, Drake J, Scapagnini G, Calabrese V. Vitamin E and neurodegenerative disorders associated with oxidative stress. Nutritional neuroscience 2002;5(4):229-39.

56. Ono K, Yamada M. Vitamin A potently destabilizes preformed α-synuclein fibrils in vitro: implications for Lewy body diseases. Neurobiology of disease 2007;25(2):446-54.
57. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Archives of neurology 2002;59(10):1541-50.
58. Jimenez-Del-Rio M, Guzman-Martinez C, Velez-Pardo C. The effects of polyphenols on survival and locomotor activity in Drosophila melanogaster exposed to iron and paraquat. Neurochemical research 2010;35(2):227-38.
59. Vauzour D, Vafeiadou K, Rodriguez-Mateos A, Rendeiro C, Spencer JP. The neuroprotective potential of flavonoids: a multiplicity of effects. Genes & nutrition 2008;3(3-4):115-26.
60. Vauzour D, Ravaioli G, Vafeiadou K, Rodriguez-Mateos A, Angeloni C, Spencer JP. Peroxynitrite induced formation of the neurotoxins 5-S-cysteinyl-dopamine and DHBT-1: implications for Parkinson's disease and protection by polyphenols. Archives of biochemistry and biophysics 2008;476(2):145-51.
61. Levites Y, Youdim MB, Maor G, Mandel S. Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-κB) activation and cell death by tea extracts in neuronal cultures. Biochemical pharmacology 2002;63(1):21-9.
62. Levites Y, Amit T, Youdim MB, Mandel S. Involvement of protein kinase C activation and cell survival/cell cycle genes in green tea polyphenol (−)-epigallocatechin 3-gallate neuroprotective action. Journal of biological chemistry 2002;277(34):30574-80.
63. Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. European journal of pharmacology 2006;545(1):51-64.
64. von Arnim CA, Herbolsheimer F, Nikolaus T, Peter R, Biesalski HK, Ludolph AC, Riepe M, Nagel G, Group AUS. Dietary antioxidants and dementia in a population-based case-control study among older people in South Germany. Journal of Alzheimer's disease 2012;31(4):717-24.
65. Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Archives of neurology 2012;69(7):836-41.
66. Fahn S. An open trial of high-dosage antioxidants in early Parkinson's disease. The American journal of clinical nutrition 1991;53(1):380S-2S.
67. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement disorders 2014;29(13):1583-90.
68. Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. Critical reviews in food science and nutrition 2020:1-14.
69. Hemilä H. Vitamin E and mortality in male smokers of the ATBC study: implications for nutritional recommendations. Frontiers in nutrition 2020;7:36.
70. Stepaniak U, Micek A, Grosso G, Stefler D, Topor-Madry R, Kubinova R, Malyutina S, Peasey A, Pikhart H, Nikitin Y. Antioxidant vitamin intake and mortality in three Central and Eastern European urban populations: the HAPIEE study. European journal of nutrition 2016;55(2):547-60.

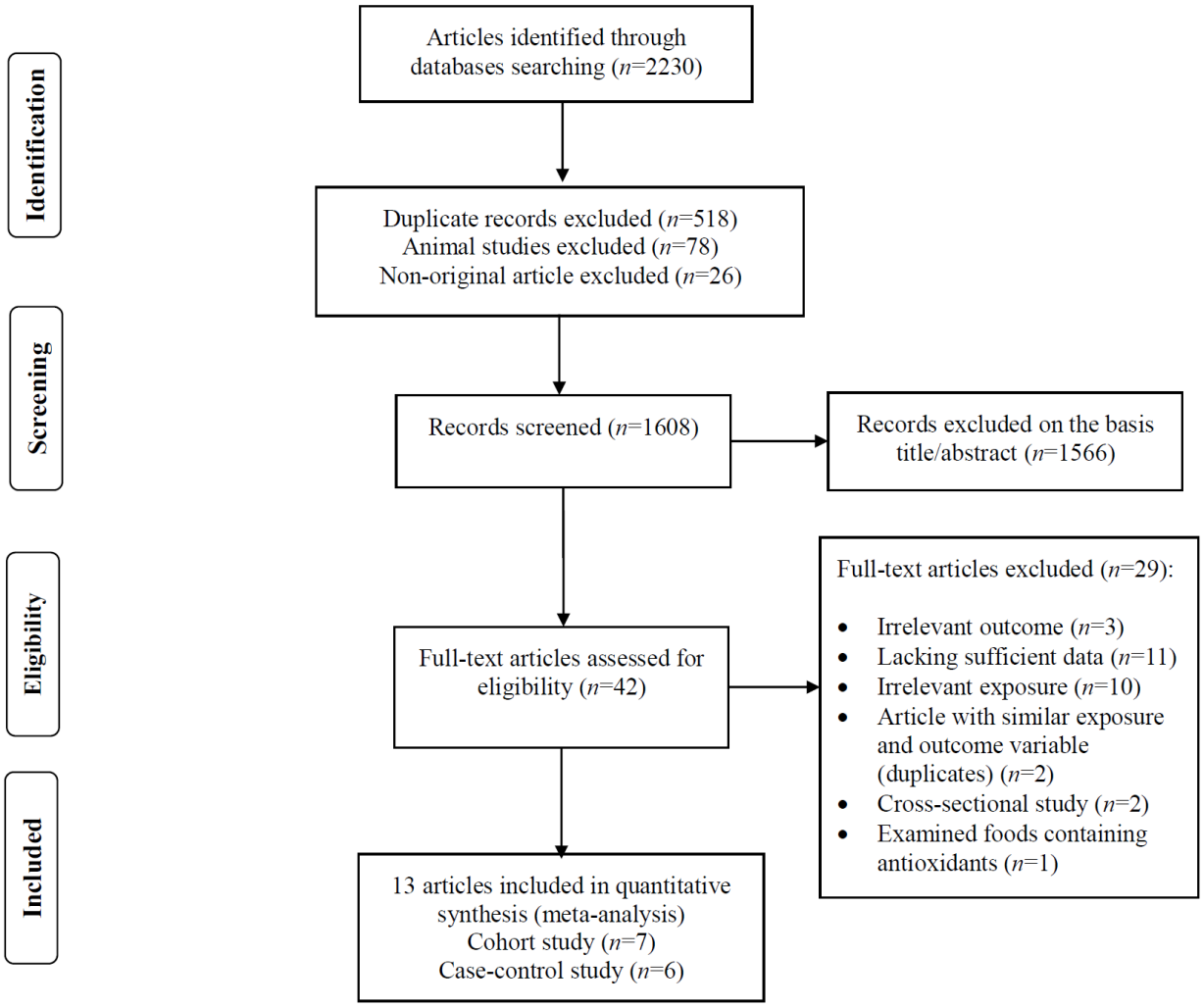

Figure 1: Flow diagram of study selection.

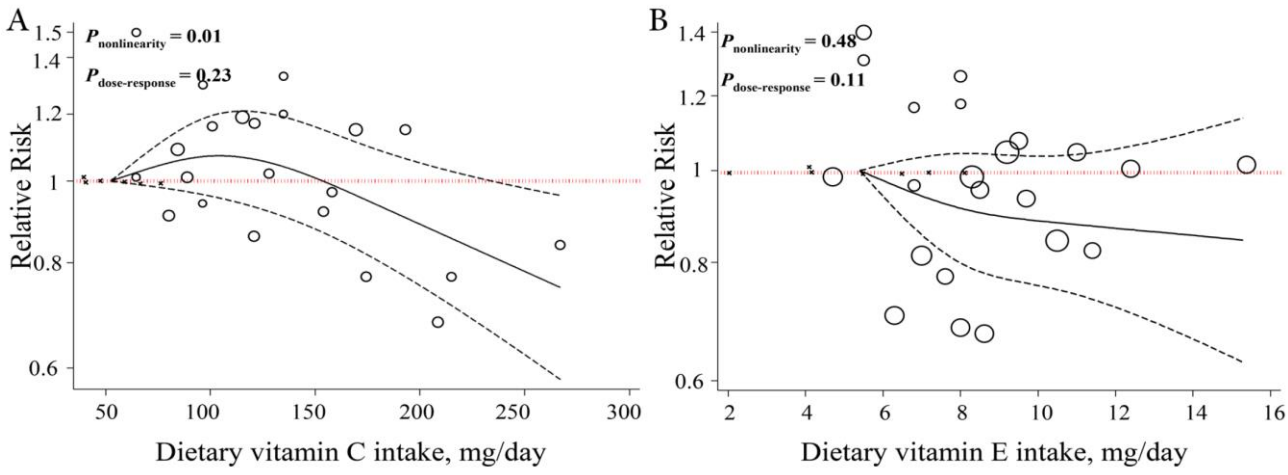

Figure 2: Dose-response associations of dietary vitamin intake and risk of Parkinson's disease. (A) vitamin C, (B) vitamin E in random-effects models. Solid lines represent the relative risk of the association between dietary vitamin intake and PD; dashed lines represent 95% CI.

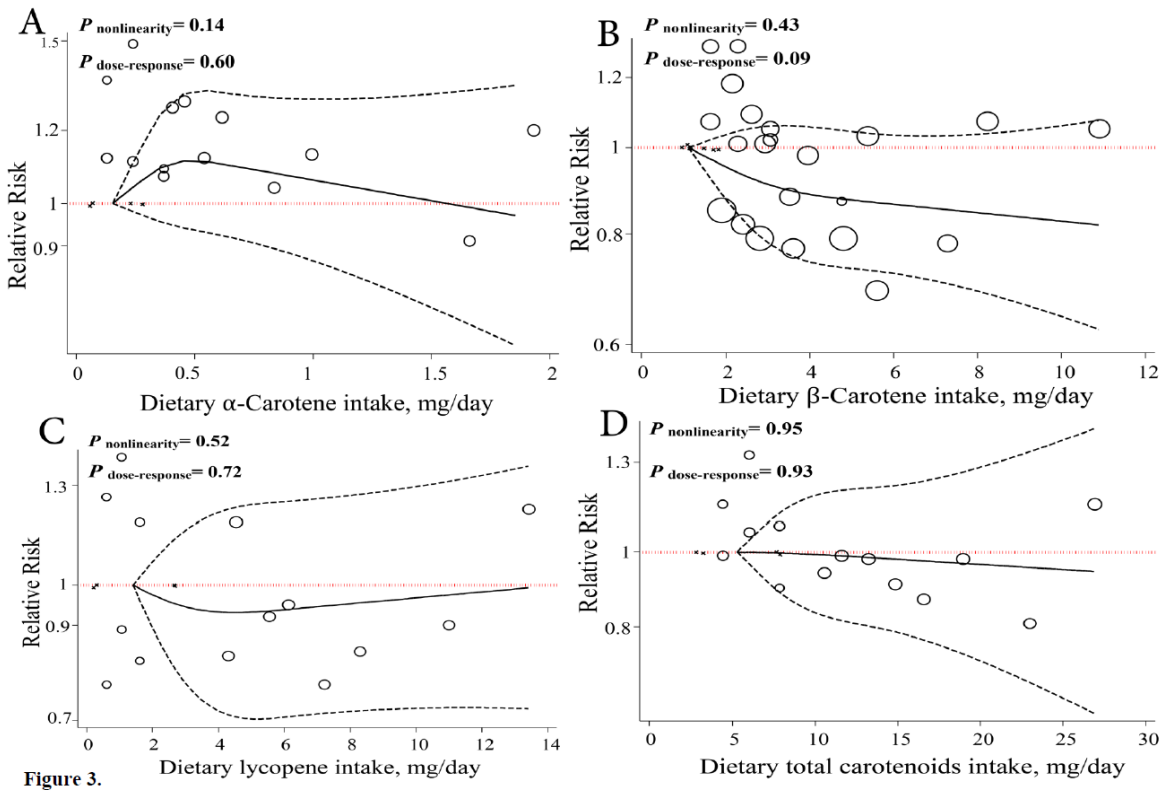

Figure 3.

Figure 3: Dose-response associations of dietary carotenoid intake and risk of Parkinson's disease. (A) α-carotene, (B) β-Carotene, (C) lycopene, (D) total carotenoids in random-effects models. Solid lines represent the relative risk of the association between dietary carotenoid intake and PD; dashed lines represent 95% CI.

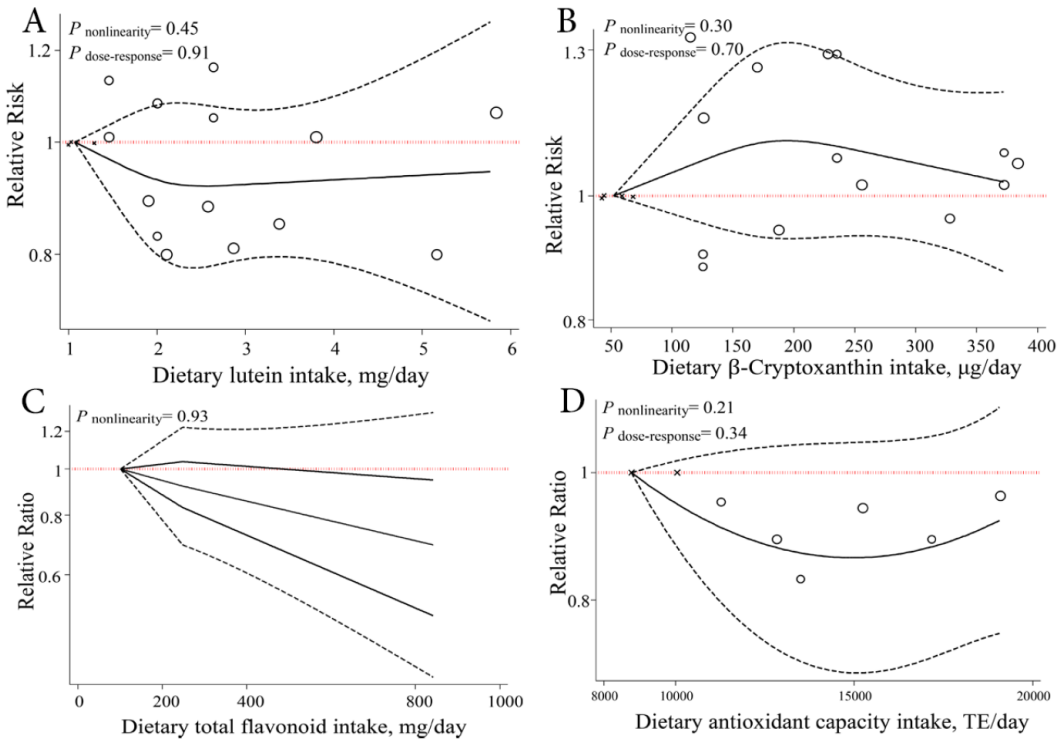

Figure 4.

Figure 4: Dose-response associations of dietary antioxidant intake and risk of Parkinson's disease. (A) lutein, (B) ***β***-Cryptoxanthin, (C) total flavonoid, (D) total antioxidant capacity in random-effects models. Solid lines represent the relative risk of the association between dietary carotenoid intake and PD; dashed lines represent 95% CI.

Table 1. Dietary antioxidants and risk of Parkinson's disease

	Highest vs. lowest category meta-analysis				Dose-response meta-analysis				
	Studies, *n*	**RR (95% CI)**	**I^2, % (95% CI)**	**$P_{heterogeneity}$**	**Dose, unit**	**Studies, *n***	**RR (95% CI)**	**I^2, %**	**$P_{heterogeneity}$**
Cohort studies									
Vitamin C	7	0.95 (0.77, 1.18)	75.9 (49, 89)	<0.001	50 mg/d	6	0.94 (0.88, 0.99)	55.2	0.06
Vitamin E	7	0.84 (0.71, 0.99)	51.9 (0, 80)	0.05	5 mg/d	7	0.84 (0.70, 0.99)	58.3	0.02
Vitamin A	2	1.11 (0.92, 1.33)	0.0 (0, 90)	0.33	1000 IU/d	1	1.00 (0.94, 1.06)	-	-
α-Carotene	3	1.06 (0.89, 1.25)	0.0 (0, 90)	0.46	0.5 mg/d	3	0.98 (0.92, 1.04)	0.4	0.36
β-Carotene	6	0.88 (0.76, 1.03)	45.2 (0, 78)	0.10	2 mg/d	6	0.94 (0.89, 0.99)	58	0.03
β-Cryptoxanthin	3	1.03 (0.88, 1.22)	0.0 (0, 90)	0.87	100 µg/d	3	1.01 (0.96, 1.06)	0.0	0.47
Total carotenoids	3	0.98 (0.81, 1.19)	32.1 (0, 93)	0.22	5 mg/d	3	0.99 (0.91, 1.08)	48.9	0.14
Lycopene	3	1.04 (0.88, 1.24)	15.9 (0, 91)	0.30	2 mg/d	3	1.01 (0.97, 1.04)	0.0	0.44
Lutein	3	1.00 (0.82, 1.21)	34.5 (0, 79)	0.21	1 mg/d	3	1.00 (0.94, 1.06)	44.2	0.16
Total flavonoids	2	0.77 (0.46, 1.29)	77.1	0.03	100 mg/d	2	0.95 (0.86, 1.04)	83.4	0.01
Flavonols	2	0.80 (0.63, 1.00)	0.0	0.44	-	-	-	-	-
Anthocyanins	2	0.76 (0.61, 0.96)	0.0	0.54	-	-	-	-	-
Flavones	2	0.86 (0.68, 1.07)	0.0	0.95	-	-	-	-	-
Flavanones	2	0.88 (0.63, 1.24)	52.8	0.14	-	-	-	-	-
Flavan-3-ols	2	0.89 (0.61, 1.30)	61.2	0.10	-	-	-	-	-
Polymers	2	0.79 (0.48, 1.31)	77.2	0.03	-	-	-	-	-
TAC	2	0.93 (0.78, 1.11)	0.0	0.67	2000 TE/d	2	0.98 (0.94, 1.02)	0.0	0.47
NEAC	1	0.79 (0.60, 1.04)	-	-	5 mg/d	1	0.96 (0.90, 1.03)	-	-
Case-Control studies									
Vitamin C	5	0.92 (0.72, 1.18)	0.0 (0, 79)	0.41	50 mg/d	1	0.99 (0.76, 1.29)	-	-
Vitamin E	5	0.80 (0.57, 1.12)	23.4 (0, 69)	0.26	5 mg/d	1	0.34 (0.16, 0.69)	-	-
Vitamin A	1	1.15 (0.62, 2.11)	-	-	-	-	-	-	-
α-Carotene	2	0.82 (0.38, 1.78)	51	0.15	0.5 mg/d	1	0.65 (0.41, 1.02)	-	-
β-Carotene	5	0.92 (0.64, 1.33)	47.8 (0, 81)	0.10	2 mg/d	1	0.70 (0.51, 0.94)	-	-
β-Cryptoxanthin	2	1.22 (0.80, 1.85)	0.0	0.71	100 µg/d	1	1.05 (0.95, 1.17)	-	-
Total carotenoids	1	1.17 (0.49, 2.81)	-	-	-	-	-	-	-
Lycopene	2	1.13 (0.50, 2.54)	66.6	0.08	-	-	-	-	-
Lutein	3	1.86 (1.20, 2.88)	23.4 (0, 92)	0.27	-	-	-	-	-
Zinc	2	0.64 (0.31, 1.31)	68.8	0.07	1 mg/d	1	0.65 (0.49, 0.86)	-	-
Selenium	1	1.01 (0.60, 1.70)	-	-	-	-	-	-	-
Total xanthophylls	1	3.16 (1.08, 9.30)	-	-	-	-	-	-	-

Abbreviations: RR: relative risk; TAC, total antioxidant capacity; NEAC, non enzymatic antioxidant capacity; TE, Trolox equivalents.