Systematic Review and Meta-Analysis

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# Dietary β-carotene and vitamin A and risk of Parkinson disease

## A protocol for systematic review and meta-analysis

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**Abstract**

**Background:** The beneficial effects of dietary β-carotene and vitamin A on Parkinson disease (PD) have been confirmed, but some studies have yielded questionable results. Therefore, this meta-analysis investigated the effect of dietary β-carotene and vitamin A on the risk of PD.

**Methods:** The following databases were searched for relevant paper: PubMed, Embase, Medline, Scopus, Cochrane Library, CNKI, Wanfang Med online, and Weipu databases for the relevant paper from 1990 to March 28, 2022. The studies included were as follows: β-carotene and vitamin A intake was measured using scientifically recognized approaches, such as food frequency questionnaire (FFQ); evaluation of odds ratios using OR, RR, or HR; β-carotene and vitamin A intake for three or more quantitative categories; and PD diagnosed by a neurologist or hospital records.

**Results:** This study included 11 studies (four cohort studies, six case–control studies, and one cross-sectional study). The high β-carotene intake was associated with a significantly lower chance of developing PD than low β-carotene intake (pooled OR = 0.83, 95%CI = 0.74-0.94). Whereas the risk of advancement of PD was not significantly distinctive among the highest and lowest vitamin A intake (pooled OR = 1.08, 95%CI = 0.91-1.29).

**Conclusions:** Dietary β-carotene intake may have a protective effect against PD, whereas dietary vitamin A does not appear to have the same effect. More relevant studies are needed to include into meta-analysis in the further, as the recall bias and selection bias in retrospective and cross-sectional studies cause misclassifications in the assessment of nutrient intake.

**Abbreviations:** CIs = 95% confidence intervals, FFQ = food frequency questionnaire, NOS = nine-point scale Newcastle Ottawa scale, OR = odds ratio, PD = Parkinson disease, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, REM = rapid eye movement, ROS = reactive oxygen species, SNc = substantia nigra pars compacta.

**Keywords:** meta-analysis, Parkinson disease, systematic review, vitamin A, β-carotene

## 1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease. The prevalence of PD is approximated to be 0.3% in the general population in industrialized countries, with incidence rates ranging between 8 and 18 per 100,000 person-years.[1] The Global Burden of Disease research indicated that the major reason for disabilities worldwide are neurological disorders, and PD is the fastest growing of these disorders. This population is expected to quadruple to almost 12 million by 2040, owing primarily to aging. Additional factors, such as longer life expectancy, lower smoking rates, and increased urbanization, might push the load to over 17 million people. A study of the global regional and national burden of PD (2016) showed that from 1990 to 2016, the global burden of PD rapidly increased from 2.5 to 6.1 million. The doubling of the number of people with PD between 1990 and 2016 is expected to happen again in the next generation as the population ages and life expectancy rises.[2,3]

PD manifests itself in both motor and non-motor symptoms. Tremor, stiffness, slowness, and imbalance are examples of motor symptoms that affect movement and physical tasks. Nonmotor symptoms can impact a variety of organ systems,

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including the gastrointestinal and genitourinary systems. Before movement symptoms appear in people who have PD, nonmotor symptoms usually develop gradually over years. Examples of prodromal nonmotor symptoms include rapid eye movement (REM) sleep behavior disorder, hyposmia, constipation, urine dysfunction, orthostatic hypotension, excessive daytime drowsiness, anxiety, and depression.[4]

Movement disorder in PD is brought on by the death of dopaminergic neurons in the substantia nigra pars compacta (SNc), reactive oxygen species (ROS) accumulation caused by mitochondrial malfunction or inflammation is still a prominent contributor to dopaminergic neuron degeneration. And there is evidence to suggest that a crucial factor of the complicated degenerative cascade underlying dopaminergic neurodegeneration is oxidative stress.[5]

Besides pharmacological treatments that exist to control PD, Parkinson patients frequently need extra care that is comprehensive to advance their daily life quality and well-being. Nutrition, in addition to influencing daily illness care, which is a possible disease-modifying component. Nutrition may help to slow the progression of neurodegeneration when it is fully utilized, and it can also aggravate it when nutrition is deficient. Previous epidemiologic research has revealed dietetic habits and risk for PD. Consumption of coffee and tea was found to be inversely related to the risk of PD. Also, smoking, exercise, and activity are protective factors. On the other hand, age, sex, genetic factors, and chemical exposure such as pesticides and high intake of dairy is related to the high risk of PD. Due to the inaccessibility of specific treatments to reduce the intensity or stop disease movement, the search for natural substances with neuroprotective and anti-inflammatory activities is a priority[6–9]

The dietary β-carotene is a plant pigment and often found in orange and green vegetables.[10] β-Carotene is an antioxidant, which plays a part in coping with the oxidative stress that results from PD. Photosynthetic mechanisms of carotenoids can protect chlorophyl and mitochondria against oxidative damage. Carotenoids can be converted to vitamin A with the help of the enzyme carotene dioxygenase. Because of the existence of the β-ionone ring in its structure, dietary β-carotene is the most important precursor of vitamin A. During the previous decade, the ability of carotenoids to protect the nervous system has been illustrated.[11]

Vitamin A is a lipophilic chemical that can only be obtained from food. Preformed Vitamin A (mostly retinol and retinyl esters) is commonly found in animal-derived diets, while provitamin A (primarily β-carotene and carotenoids) is absorbed from plant-based diets.[10] As a nutrient, there are substantial linkages in the pathology of PD, and proteins participant in vitamin A metabolism. Also, altered vitamin A metabolism and bioavailability tend to result in an oxidative stress, neuroinflammation, dopaminergic cell passing, influence on biological rhythms, and endocrine homeostasis. Hence, vitamin A, as a nutritional factor perhaps at the crossroad of different environmental and hereditary element of PD.[12] Evidence from the preclinical stage demonstrated a variety of control by vitamin A and related pathways that have been implicated in the etiology of PD.[13–15]

A meta-analysis in 2014 showed available data are deficient for reaching firm conclusions on the epidemiological data on the link between vitamin A and β-carotene levels in the blood or dietary intakes and the risk of PD.[16] Considering the previous meta-analysis in 2013, new data from a large prospective cohort and case–control studies where the antioxidant impact of β-carotene and vitamin A was explored, and some studies inconsistent with the previous meta-analysis results..[17–19] After the meta-analysis in 2013, we included more studies conducted in our meta-analysis on the impact of dietary intakes of β-carotene and vitamin A in PD.

## 2. Methods

This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] This meta-analysis has already been registered in PROSPERO. Registration ID: CRD42022320314. The analysis was according to previous published articles, no ethical approval and patient consent are required.

### *2.1. Search strategy*

Our article searched the literature in the following databases: PubMed, Embase, Medline, SCOPUS, Cochrane Library, CNKI, Wanfang, and Weipu databases for research published before February 26, 2022. Our search terms are: [("Carotenoids" OR "Carotenoid" OR "Tetraterpenes" OR "Tetraterpene Derivatives" OR "Derivatives, Tetraterpene" OR "Carotenes" OR "Carotene") OR ("beta Carotene" OR "Carotene, beta" OR "Betacarotene" OR "beta-Carotene" OR "Carotaben" OR "Max-Caro" OR "Max Caro" OR "MaxCaro" OR "Solatene" OR "Vetoron" OR "BellaCarotin" OR "Provatene" OR "β-carotene") OR ("Vitamin A" OR "Aquasol A" OR "Retinol" OR "3,7-dimethyl-9-(2,6,6-tri-methyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol,(all-E)-Isomer" OR "All-Trans-Retinol" OR "All Trans Retinol" OR "Vitamin A1" OR "11-cis-Retinol")] AND ("Parkinson Disease" OR "Idiopathic Parkinson Disease" OR "Lewy Body Parkinson Disease" OR "Parkinson Disease, Idiopathic" OR "Parkinson Disease, Lewy Body" OR "Parkinson Disease, Idiopathic" OR "Parkinson Disease" OR "Idiopathic Parkinson Disease" OR "Lewy Body Parkinson Disease" OR "Primary Parkinsonism" OR "Parkinsonism, Primary" OR "Paralysis Agitans"). There were no restrictions on the language used in the publications. The references cited in the publications that were found to be relevant were also looked over to see if there were any new publications.

### *2.2. Study selection*

The title and abstract of each study were independently examined by two reviewers. The studies were chosen according to the following inclusion criteria: β-carotene and vitamin A intake was measured using scientifically recognized approaches, such as a food frequency questionnaire (FFQ); evaluation of odds ratios using OR, RR, or HR; β-carotene and vitamin A intake were converted to ordered categorical variables for three or more quantitative categories according to quartile points in the distribution of control; and PD diagnosed by a neurologist or hospital records. The following were the criteria for exclusion: reexaminations views or case reports; duplicate articles by identical articles; and no publications by the same cohort. Information from the OR, RR, or HR.

### *2.3. Data extraction*

Two reviewers separately extracted all relevant papers and identified studies that were eligible. Based on a thorough examination of the title and abstract, the studies were evaluated for eligibility, and conflicts were addressed through consensus. The following information from each included study, includes the initial author name, the date of publication, kind of study, patients' number, mean age of the participants, gender, duration of follow-up, adjusted variables, and outcome data: the odds ratio (OR) and 95% confidence intervals (CIs), for the development of PD was extracted. After the enrolled participants were sorted into five quintiles (Q1-Q5) based on dietary β-carotene and vitamin A intake, we selected the outcome data of the participants in Q1 (lowest intake group) and Q5 (highest intake group) in this study. If the participants were divided into four

quartiles (Q1-Q4) or three tertiles (Q1-Q3), participants in Q1 were deemed the reference group, while those in Q4 or Q3 were considered the highest intake group.

### 2.4. Quality assessment

The research studies' methodological quality was assessed using the nine-point scale Newcastle Ottawa scale (NOS), which was according to three criteria: subject selection, group comparability, and measurement of outcomes or exposures.[21] Each study's quality was rated as low (0-3), moderate (4-6), or high (7-9). The consensus was used to resolve any conflicts.

### 2.5. Statistical analyses

The statistical analysis was completed with Revman5.4 software. The $I^2$ statistics were used to perform the heterogeneity test to determine the degree of discrepancy between the outcomes. If $I^2 < 50\%$, showed the statistical heterogeneity non-existent between these researches, and the fixed effects model was employed in the calculation of the combined effect OR and 95% CI; $I^2 \geq 50\%$ was thought to imply significant heterogeneity, and the random effects model was utilized. OR and 95% CIs was used to analyze and investigate the rate of change in examining the disparity in the rate at which PD develops between the two groups with high and low β-carotene and vitamin A intake. A *P*-value of less than .05 was used to determine statistical significance. To assess the possibility of publication bias, funnel plots were utilized.

## 3. Results

### 3.1. Literature search

There were a total number of 4128 studies found, with 991 duplicates deleted. After deleting duplicates, there were a total of 3137 articles found in Figure 1, a total of 21 papers were eligible after passing the title and abstract screening, studies characteristics in Table 1. Following a thorough examination, 10 studies were excluded.[22–31] Three studies were excluded for inadequate outcomes were recorded, one article had no specific dietary β-carotene and vitamin A intake,[23] and 2 reported insufficient outcome data (OR and 95% CIs).[22,25] Six studies were excluded for β-carotene and vitamin A intake was measured by serum levels.[24,26–28,30,31] One study was excluded for β-carotene and vitamin A intake not for three or more quantitative categories.[29] Resulting in 11 articles were excluded and 10 articles were included in our meta-analysis.[17–19,32–39] Nine studies analyzed the effect of dietary β-carotene and the risk of PD.[17–19,33–36,38,39] Four researches examined the impact of dietary vitamins A in relation to the possibility of PD.[19,32,35,37] Besides, research showed data for both sexes independently.[18] As a result, we considered the individual outcomes in our meta-analysis. Moreover, 7 studies categorized the research data into four quintiles according to the taking in levels of β-carotene or vitamins A.[18,19,32,34–36,38] One study categorized the research data into five quartiles;[40] and three studies categorized the exposure variables into tertiles.[17,33,37]

### 3.2. Study characteristics

The sum amount of 240,166 participants in the 11 studies and 4205 instances of PD were identified. Of the 11 included studies, 5 were done in the United States,[32,35,37–39] 2 were conducted in Sweden,[17,18] also 1 research each was carried out in Germany,[34] the Netherlands,[33] Singapore, and Japan,[36] respectively. In addition, nine studies (4 case–control, 4 cohort, and 1 cross-sectional) offered information on dietary β-carotene intake and 4 studies (3 case–control, and 1 cohort) offered information on dietary vitamin A intake. All researches within the investigation of β-carotene and vitamin A are considered to be dietary intake. The features of each research are displayed in Table 2.

### 3.3. Risk of bias

The considers included in our study the NOS was used to conduct the survey in Table 3. All of the literature were high quality and appraised 8 to 9 points.

### 3.4. Meta-analysis results

***3.4..1. Dietary β-carotene and PD*** Nine studies with a total of 237,192 participants and 3707 PD cases were included in our analysis of dietary β-carotene and PD risk. The high β-carotene

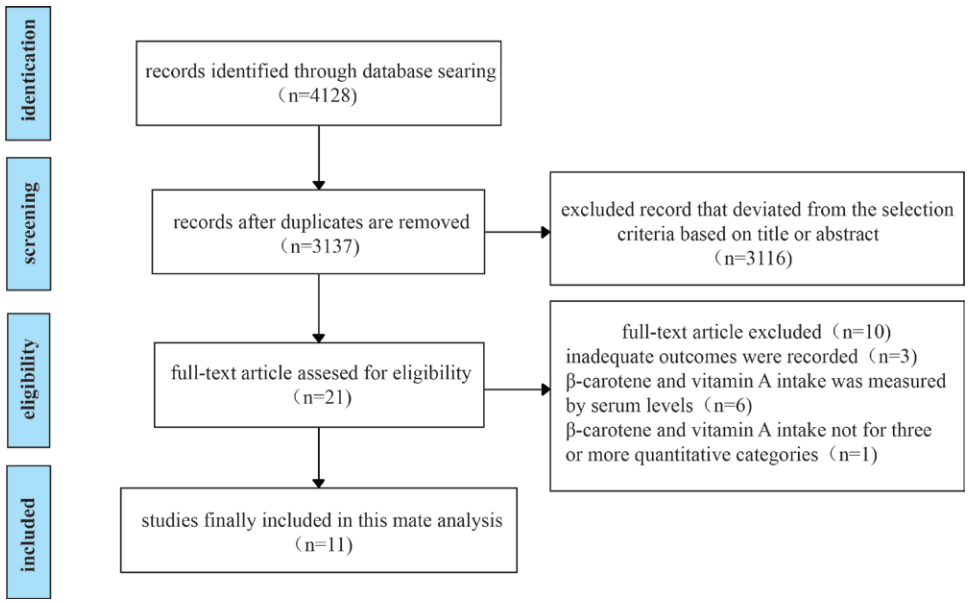


**Figure 1.** Flow chart showing the search results of the meta-analysis.

**Table 1**

**Characteristics of full text reviewed studies.**

| Study | Study type | Exposure assessment | Main results | | Causes of exclusion |
|---|---|---|---|---|---|
| | | | β-Carotene | Vitamin A | |
| Anderson (1999) | Case–control study | FFQ | | OR 0.65 (0.29–1.45) | Include |
| de Rijk. (1997) | Cross-sectional study | FFQ | OR 0.6 (0.3–1.2) | | Include |
| Hantikainen (2021) | cohort study | FFQ | HR 1.05 (0.78–1.39) | | Include |
| Hellenbrand (1996) | Case–control study | FFQ | OR 0.67 (0.37–1.19) | | Include |
| Johnson (1999) | Case–control study | FFQ | OR 1.16 (0.64–2.12) | OR 1.15v (0.62–2.11) | Include |
| Miyake (2011) | Case–control study | DHQ | OR 0.56 (0.33–0.97) | | Include |
| Paganini-Hill (2001) | Nested Case–control study | FFQ | | OR 1.21 (0.94–1.57) | Include |
| Powers (2003) | Case–control study | FFQ | OR 1.2 (0.8, 1.9) | | Include |
| Yang (2017) | Cohort study | FFQ | HR (men) 0.91 (0.84–0.99) HR(women) 0.86 (0.78–0.95) | | Include |
| Ying (2020) | Cohort study | FFQ | HR 1.02 (0.78–1.32) | HR 1.01 (0.78–1.32) | Include |
| Zhang (2002) | Cohort study | FFQ | RR 0.90 (0.63–1.30) | | Include |
| Agarwal (2022) | Cohort study | FFQ | β = -0.04(-0.08–0.0021) | | Using different outcome data |
| Hughes (2016) | Cohort study | FFQ | RR = 0.92 | | Short of 95% CIs |
| Ayuso-Peralta (1997) | Case–control study | FFQ | | | No exposure assessment and outcome data |
| Scheider (1997) | Case–control study | Health Habits and History Questionnaire | OR 1.67(0.59-4.76) | | β-Carotene intake not for three or more quantitative categories |
| Jiménez (1992) | Case–control study | Serum levels | | Mean ± SD PD (μg/dl): 0.59 ± 0.03 Control (μg/dl): 0.57 ± 0.03 | Exposure assessment using serum levels |
| Kim (2017) | Case-control study | Serum levels | Median (25–75th percentile) PD (μmol/L): 1.08(0.60-1.71) Control (μmol/L): 2.39(1.52-3.28) | | Exposure assessment using serum levels |
| Larumbe (2001) | Case-control study | Serum levels | $P > .05$ | | Exposure assessment using serum levels |
| Jiménez (1993) | Case-control study | Serum levels | Mean ± SD PD (μg/dl): 0.87 ± 0.08 Control (μg/dl): 1.01 ± 0.12 | | Exposure assessment using serum levels |
| Tan (2009) | Case-control study | Serum levels | | $P < .05$ | Exposure assessment using serum levels |
| Molina (1999) | Case-control study | Serum levels | $P > .05$ | $P > .05$ | Exposure assessment using serum levels |

CIs = 95% confidence intervals, DHQ = diet history questionnaire, FFQ = food frequency questionnaire, PD = Parkinson's disease.

intake appeared a significantly lower chance of development of PD than the low β-carotene intake (pooled OR = 0.86, 95%CI = 0.77-0.96, Z-value = 2.70, $P = .007 < .05$). The fixed-effect mode was utilized according to the results of $I^2 = 36\%$, with moderate evidence of heterogeneity in the data in Figure 2.

***3.4..2. Dietary vitamin A and PD*** Four studies involving a total of 63,781 participants with 962 cases were included in our analysis of dietary vitamin A and the risk of PD. Whereas the risk of advancement of PD was not significantly distinctive among the highest and the lowest vitamin A intake (pooled OR = 1.08, 95%CI = 0.91-1.29, Z-value = 0.93, $P = .35$).

**Table 2**

**Characteristics of studies in meta-analysis.**

| Study | Year of publication | Study type | Sample size (cases, controls) | Mean age | Male: Female (%) (cases: controls) | | Country | Source of β-carotene or vitamin A | Classification of β-carotene or vitamin A intake | Exposure assessment | Intake of β-carotene (μg/d) | | Intake of vitamin A (IU/d) | | Variables in risk adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Lowest intake | Highest intake | Lowest intake | Highest intake | |
| Anderson | 1999 | Case-control study | 259 (103, 156) | 72 | 59:41 | 62:38 | USA | Dietary | Quartiles | FFQ | | | - | - | Age, sex, caloric intake, smoking, having lived on a farm |
| de Rijk. | 1997 | Cross-sectional study | 5342 (31,5311) | 71 | 52:48 | 41:59 | The Netherlands | Dietary | Tertiles | FFQ | - | - | | | Age, sex, smoking, energy intake |
| Hantikainen | 2021 | Prospective cohort study | 43,865 | - | - | | Sweden | Dietary | Tertiles | FFQ | ≤1600 (men) ≤2100 (women) | 2700–19100 (men) 3800–26000 (women) | | | Age, sex, BMI, education, smoking, total physical activity, coffee, alcohol, dairy intake, energy intake, vitamin and mineral supplement use |
| Hellenbrand | 1996 | Case-control study | 684 | 56 | 65:35 | 65:35 | Germany | Dietary | Quartiles | FFQ | - | - | | | Caloric intake, smoking, education |
| Johnson | 1999 | Case-control study | 558 (342, 342) | - | 62:38 | 63:37 | USA | Dietary | Quartiles | FFQ | - | - | - | - | Age, sex, race, smoking, BMI |
| Miyake | 2011 | Case-control study | 617 (126, 432) | 68.5 | 37:63 | 38:62 | Japan | Dietary | Quartiles | DHQ | <1836.1 | ≥4080.9 | | | sex, age, region of residence, smoking, education, BMI, intake of cholesterol, alcohol, total dairy products, coffee, dietary glycemic index |
| Paganini-Hill | 2001 | Nested case-control study | 2715 (249,368) | 75 | - | | USA | Dietary | Tertiles | FFQ | | | - | - | Age, sex |
| Powers | 2003 | Case-control study | 638 (395, 2320) | 71 | 62:38 | 62:38 | USA | Dietary | Quartiles | FFQ | - | - | | | Age, sex, education, ethnicity, caloric intake, smoking |
| Yang_men | 2017 | Prospective cohort study | 45,837 (250, 388) | - | 100:0 | | Sweden | Dietary | Quartiles | FFQ | 1100 ± 400 | 5300 ± 1900 | | | Age, smoking, alcohol, coffee, education, BMI, total energy intake, multivitamin supplement use |
| Yang_ women | 2017 | Prospective cohort study | 38,937 | - | 0:100 | | Sweden | Dietary | Quartiles | FFQ | 1400 ± 500 | 6200 ± 2100 | | | Age, smoking, alcohol, coffee, education, BMI, total energy intake, multivitamin supplement use |
| Ying | 2020 | Prospective cohort study | 60249 | 59.7 | 50.5:49.4 | 44.4:55.6 | Singapore | Dietary | Quartiles | FFQ | <1358 | >2674 | <3322 | >6180 | Age, year of interview, sex, dialect group, education, energy, BMI, smoking, black tea intake, caffeine intake, cholesterol intake, monounsaturated fat intake. |
| Zhang | 2002 | Prospective cohort study | 124,221 | - | 38:62 | | USA | Dietary | Quartiles | FFQ | - | - | | | Age, length of follow-up, cigarette smoking, alcohol, coffee intake, BMI, physical activity, total energy. |

BMI = body mass index, DHQ = diet history questionnaire, FFQ = food frequency questionnaire.

**Table 3**

**Quality assessment of included studies using the Newcastle Ottawa Quality Assessment Scale.**

| Author | Study design | Quality criteria | | | Overall quality |
|---|---|---|---|---|---|
| | | Selection | Comparability | Outcome/exposure | |
| Anderson | Case–control | **** | ** | ** | 8 |
| de Rijk. | Case–control | **** | ** | ** | 8 |
| Hellenbrand | Case–control | **** | ** | ** | 8 |
| Johnson | Case–control | **** | ** | ** | 8 |
| Miyake | Case–control | **** | ** | *** | 9 |
| Paganini-Hill | Case–control | **** | ** | *** | 9 |
| Powers | Case–control | **** | ** | ** | 8 |
| Hantikainen | Cohort | **** | ** | *** | 9 |
| Yang | Cohort | **** | ** | *** | 9 |
| Ying | Cohort | **** | ** | *** | 9 |
| Zhang | Cohort | **** | ** | *** | 9 |

*one point.

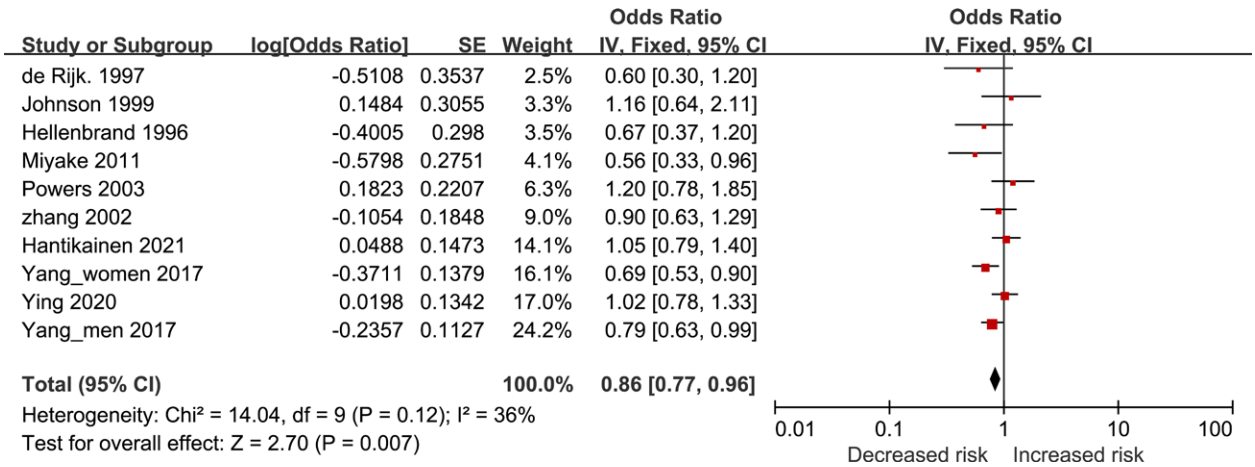


**Figure 2.** Results of the meta-analysis of the rate of the development of Parkinson's disease in the low and high β-carotene intake groups.

The fixed-effect mode was utilized according to the results of $I^2 = 0\%$ in Figure 3.

### *3.5. Publication bias*

The funnel plot showed no publication bias in Figure 4, and Figure 5.

## 4. Discussions

Our meta-analysis summarized data about the association of dietary β-carotene and vitamin A intake with the risk of PD. The findings from the study suggested that higher dietary β-carotene intake was both significantly and inversely related to the likelihood of PD, whereas higher dietary intake of vitamin A did not show such protective effects.

The dietary carotenoids are discovered in red, orange, yellow, and leafy green vegetables as well as red and orange fruit. Research showed carotenoids helps reduces these oxidative biochemical indicators and combat oxidative stress and as an antioxidant in the food that may help to slow or stop the course of PD.[40] β-Carotene has also been found to have anti-inflammatory properties which are important in the prevention of many degenerative diseases caused by oxidative stress, including neurological diseases such as PD.[11] Although this article only discussion the connection between dietary β-carotene intake and the possibility of PD, some studies also studied the relationship between serum β-carotene levels and the risk of PD. A study explained serum β-carotene levels are all significant reduction in PD patients ($P < .001$).[26] And three studies suggest that serum levels of β-carotene did not differ significantly between PD patients and control groups.[27,28,31] Two former meta-analyses done by Takeda et al[16] and Etminan et al[41] researched about intake of β-carotene and the risk of PD. The two former meta-analyses did not suggest any defensive impacts related to β-carotene. However, our study finds intake of β-carotene reduced the risk of PD. Among the 9 articles about β-carotene included in our meta-analysis, 3 studies showed the consumption of β-carotene has been linked to the development of PD. Two studies (1 cohort study and 1 case–control study) showed higher consumption of dietary β-carotene was significantly linked to a lower incidence of PD[18,36] and 1 cross-sectional study showed Intake of β-carotene was oppositely related to PD but this association was not significant.[33] Three new prospective cohort studies were included in our study.[17–19] One study showed that β-carotene consumption was linked to a decreased risk of PD.[18] Also, a study published recently was excluded from our meta-analysis for different outcome measures were recorded, which showed dietary β-carotene intake was inversely associated with the progression of PD.[22] But 3 studies containing dietary β-carotene intake were excluded for short of the outcome data,[23,25,29] those studies did not provide support for high dietary β-carotene intake can decrease the risk of PD.

Vitamin A is entirely provided by food like liver, meat, eggs, fish, dairy fat, and margarine. Vitamin A can be obtained from food in a variety of ways: directly as retinol-esters, or indirectly as β-carotene, which is partially converted to retinol. Same as β-carotene, dietary vitamin A is also an antioxidant, which exhibits neuroprotective properties against neurodegeneration. Vitamin

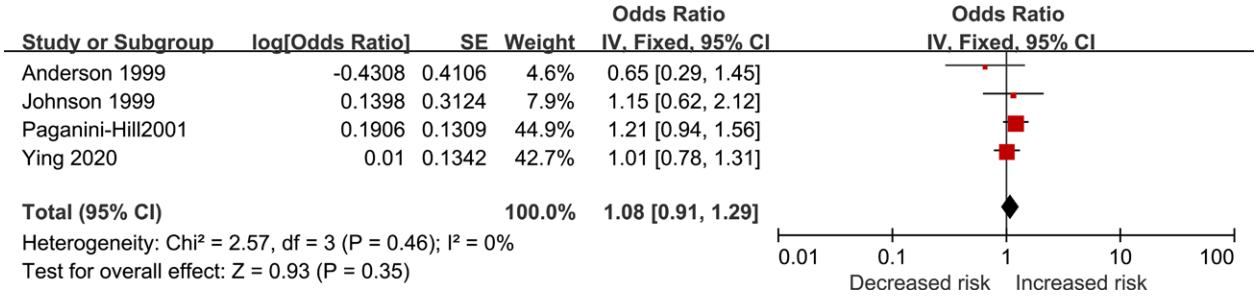


**Figure 3.** Results of the meta-analysis of the rate of the development of Parkinson's disease in the low and high vitamin A intake groups.

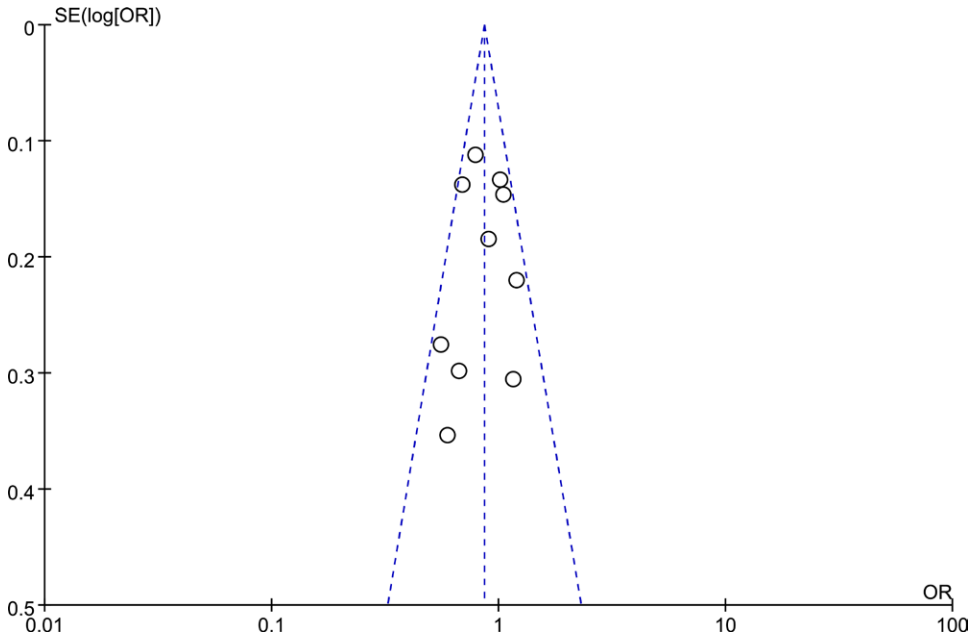


**Figure 4.** Graphic funnel plots of the included studies for evaluating the effects of β-carotene on the risk of Parkinson's disease.

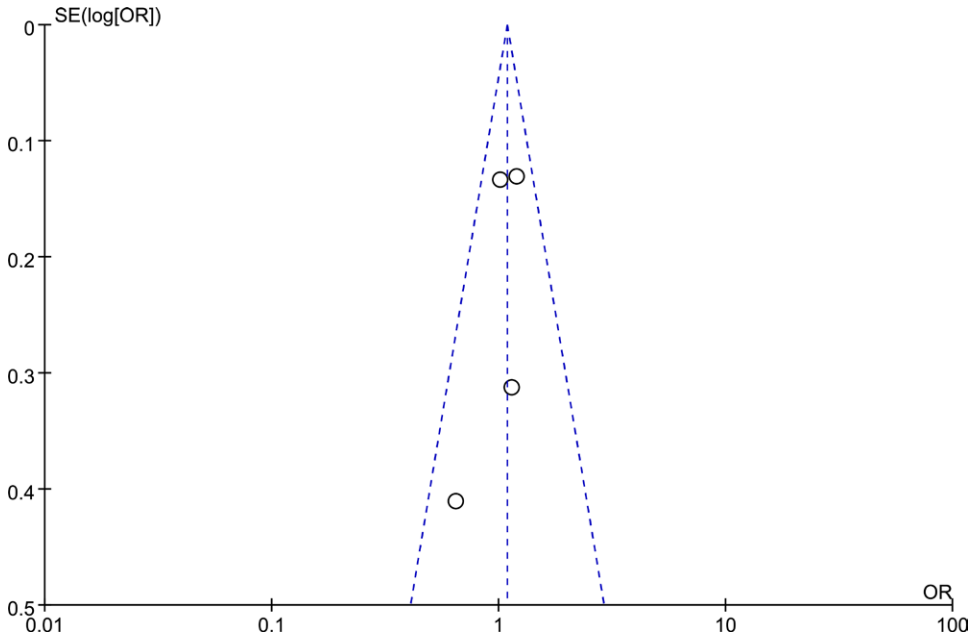


**Figure 5.** Graphic funnel plots of the included studies for evaluating the effects of vitamin A on the risk of Parkinson's disease.

A plays a role in coping with the oxidative stress that results in PD.[12] Retinoic, the main metabolite of vitamin A controls brain advancement by controlling neuronal separation, engine axonal development, and neural patterning.[13] Retinoic acid encourages GABAergic neurons to express dopamine receptors differentiate, also alterations in PD that inhibition of retinoic acid-mediated neuronal differentiation.[40] There is substantial contact between the PD pathogenesis and vitamin A and retinoid metabolism-related proteins. A variety of manipulations of vitamin A and its pathways have been used to determine vitamin A in the pathogenesis of PD: diet supplementation, diet inadequacy, knockout rats for retinoid receptors, and therapies using vitamin A derivatives in vivo or in vitro.[13–15] Three articles elucidated the relationship between serum vitamin A levels and the pathogenesis of PD. One study explained serum vitamin A was decreased in PD patients ($P < .05$).[30] And 2 studies suggested that serum vitamin A levels do not play a role in the pathogenesis of PD.[24,31] In 2014, Takeda et al conducted the first meta-analysis focus on vitamin A and carotenoids and the risk of PD.[16] For vitamin A, Takeda study included 8 papers: 7 case–control studies and 1 cross-sectional study. Takeda study showed current data have been insufficient to draw firm conclusion about the association between vitamin A levels in the blood or dietary intakes and the risk of PD. This is the same with the outcomes of our meta-analysis, though vitamin A intake was measured only using a FFQ or a diet history. Four studies included in our study about vitamin A with the risk of PD (3 case–control studies and 1 cohort study): all showed there were no preventive benefits of dietary vitamin A to PD.[19,32,35,37]

Our study's strength is that it included not just current large-scale observational studies published after the previous meta-analysis, but also two Asian studies, resulting in a more ethnically diverse sample.[19,36] Furthermore, the research included in this analysis had a high overall quality. However, we must also acknowledge the study's potential limitations. Different studies we included evaluated dietary intake using the different FFQs, also the semi-quantitative instrument is possible to lead to underestimate true intake levels of dietary β-carotene and vitamin A.

## 5. Conclusion

Our meta-analysis indicated that dietary β-carotene intake might have a protective impact against PD. In addition, we found that dietary vitamin A appears not to have protective effects on PD. More relevant studies are needed to include into meta-analysis in the further, as the recall bias and selection bias in retrospective and cross-sectional studies cause misclassifications in the assessment of nutrient intake.

## Declaration statement

All authors declare that they have no competing interest.

## Author contributions

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