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Micronutrients and Risk of Parkinson's Disease: A Systematic Review

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Although the precise pathogenetic mechanisms of PD remain undetermined, there appears to be both genetic and environmental factors that contribute to the risk of developing PD. With regard to environmental risk factors, there has been significant interest related to the role of diet, nutrition, and nutrients on the onset and progression of PD. As the current treatments are predominantly focused on symptomatic management, efforts must be directed toward prevention of the PD and identification of potentially modifiable risk and preventive factors. This comprehensive review gives an overview of studies examining the role of micronutrients in PD, and provides guidance on the value of the reported outcomes.

Keywords

Parkinson's disease, micronutrients, prevention

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with a prevalence of about 1% in adults above the age of 60 and approximately 3% in elderly adults above the age of 80 in industrialized countries (de Lau & Breteler, 2006). As the population ages, the importance of PD as a public health issue is expected to increase. Based on published prevalence studies of the world's most populous nations, it is projected that between 2005 and 2030, the number of individuals with PD will double to 9.3 million cases (Dorsey et al., 2007). In the Unites States, annual medical costs associated with PD including doctor visits, medications, physical and speech therapies, and comorbidities of the disease (such as depression and often eventual dementia) are significant burden to the health care system with US$23,101 per patient, and total cost to the nation is projected to be US$23 billion annually (Huse et al., 2005).

Although the precise pathogenetic mechanisms causing the progressive loss of dopaminergic cells in the substantia nigra of patients with PD remain undetermined, there appears to be both genetic and environmental factors that contribute to the risk of developing PD (Tanner & Goldman, 1996). At the time of clinical diagnosis, it is estimated that more than 70% of dopaminergic cells in the substantia nigra have already been damaged. Therefore, as current treatments are predominantly focused on symptomatic management, efforts must be directed toward prevention of the disease and identification of potentially modifiable risk and preventive factors.

Several non-genetic factors have been associated with increased (i.e., aging, male gender, head traumas, particular occupations, exposure to certain metals, pesticides or solvents) or reduced risk of developing PD (i.e., smoking, coffee, anti-inflammatory drugs, exercise, certain vitamins). Among environmental risk factors, there has been significant interest related to the role of individual foods and nutrients on the onset and progression of PD (Gao

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et al., 2007). In particular, several studies have focused on micronutrients, defined as organic substances that are present in plasma at low concentrations, are essential for the brain's proper functioning and are not readily synthesized in the brain. Implicit in this definition is the fact that these micronutrients come exclusively from the human diet. Albeit limited by inconsistent methodology and the multitude of micronutrients and their proposed mechanisms of action, research in the association of micronutrients and PD risk has provided a wealth of information, which the scientific community has struggled to merge into evidence-based recommendations for PD prevention by nutrition (Suchowersky et al., 2006). The aim of this work is to conduct a comprehensive review of studies examining the role of micronutrients in PD and provide guidance on the value of the reported outcomes.

Method

To identify epidemiologic studies pertaining to risk of PD and nutrition, specifically micronutrients, a systematic literature search review was conducted using PubMed, CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature), and the Web of Science databases. Initial search terms included "Parkinson's Disease" and "Nutrition," "Parkinson's Disease" and "Nutrients," and "Parkinson's Disease" and "Food." We also looked for a combination of "Parkinson's Disease" and "Supplements" and included specific micronutrients, such as vitamins A, B, C, D, E, α-carotene, β-carotene, riboflavin, flavonoids, calcium, urate, iron, copper, manganese, and zinc as search terms. According to these criteria, we screened 168 articles. We excluded articles examining plasma nutrient levels and the risk of PD, non-human studies, articles in languages other than English, and included those addressing dietary consumption of the micronutrients. In all, 23 studies were identified that met the inclusion criteria. Each journal article was reviewed and the following information was extracted: study population, study design, nutrients analyzed, results, and conclusions (Table 1).

We organized the micronutrients as vitamins, minerals, and vitamin-like substances. Furthermore, we start each section by introducing the most widely discussed vitamins and elements with robust supporting data concerning neuroprotection, followed by less robust studies.

For each micronutrient of interest, results from studies were summarized, and the evidence was aggregated to determine whether they supported a positive, negative, or no association with PD risk. Particular attention was directed to possible sex-specific effects of micronutrients on PD. When possible, the strengths and weaknesses of each study were considered, and recommendations were made toward future research projects.

Results

Vitamin A

Several studies have examined the effect of vitamin A on PD. Vitamin A and its active derivatives, retinoids (among which retinoic acid is the most active form), have been shown to have antioxidant properties in animal studies (Trumbo, Yates, Schlicker, & Poos, 2001) In the human diet, two forms of vitamin A are available: preformed vitamin A (in food from animal sources including dairy products, fish, and meat) and pro-vitamin carotenoids (plant pigments): β-carotene, α-carotene, and β-cryptoxanthin. Vitamin A and carotenoids are involved in a complex signaling pathway that regulates gene expression in the central nervous system (CNS; Tafti & Ghyselinck, 2007). The dopaminergic system, which constitutes a well-documented pathway involved in PD, is one of the best-established targets of retinoic acid action in the brain. High levels of retinoid acid-synthesizing enzymes have been detected in the mesotelencephalic dopamine system (Smith, Wagner, Koul, McCaffery, & Drager, 2001), and retinoid acid receptors are believed to critically control the integrity and homeostatic regulation of the dopaminergic system (Levesque & Rouillard, 2007). However, in epidemiological studies, the antioxidative property of vitamin A has not been found to reduce the risk of PD in any of the studies so far (Hellenbrand et al., 1996; Logroscino et al., 1996; Miyake, 2011b; Zhang et al., 2002). On the contrary, a large case-control study including 395 PD cases and 2,320 controls found that the risk of PD was significantly increased among individuals with a high intake of dietary total vitamin A (odds ratio [OR] = 1.31, 95% confidence interval [CI] = [1.01, 1.71]). However, after adjusting for other variables, the relationship lost its statistical significance (Paganini-Hill, 2001). Similarly, another study found that the use of vitamin A supplements increased the risk of PD, but only the trend was statistically significant (for >0 tablets/day vs. 0, OR = 2.85, 95% CI = [0.91, 8.93], p for trend = .05)(Anderson et al., 1999).

α- and β-Carotene

Carotenoids are the inactive forms of vitamin A and are known to have antioxidant activity. A case-control study (N = 249 PD cases, 368 controls) demonstrated that the intake of β-carotene was associated with lower risk of PD (OR = 0.56, 95% CI = [0.33, 0.97], p for trend = .03), while no significant relationship was established between PD risk and intake of α-carotene (Miyake, Fukushima, et al., 2011). There is no additional data that support the protective effect of carotenoids with regard to PD risk. In a large prospective study of two cohorts, the Nurses Health Study and the Health Professionals' Follow-Up Study, dietary intake of carotenoids was not associated with PD risk (Zhang et al., 2002). In a case-control study of dietary factors and PD risk (N = 342 cases, 342 controls), statistical significance was not reached for β-carotene (β-carotene: OR = 0.67, 95% CI = [0.37, 1.19], p = .06; Hellenbrand et al., 1996). Similarly, a small cross-sectional study in the Rotterdam study population (PD cases = 31) failed to show statistically significant inverse relationship between β-carotene

Table 1. Characteristics of the included studies.

Authors	Study design	Population name	Sample size	Factors studied	Findings
Vitamin A, vitamin C, vitamin E					
1. Paganini-Hill (2001)	Case-control study	The Leisure World Cohort Study	Cases: 395 Controls: 2,320	Vitamin A and C	No relationship detected
2. Zhang et al. (2002)	Prospective cohort HPFS: 1986-1998 NHS: 1980-1998	NHS HPFS	HPFS (*N* = 47,331), NHS (*N* = 76,890) Cases: 371	Supplemental vitamin E Supplemental vitamin C Dietary vitamin C Nuts (vitamin E) Carotenoids	No relationship detected No relationship detected No relationship detected Decreased risk No relationship detected
3. Hellenbrand et al. (1996)	Case-control study	9 German neurologic clinics	Cases: 342 Controls: 342	Vitamin B β-carotene ascorbic acid niacin	Decreased risk Decreased risk Decreased risk Decreased risk
4. Miyake et al. (2011b)	Hospital-based case-control	Japanese population	Cases: 249 Control: 368	Vitamin E β-carotene α-carotene	Decreased risk Decreased risk No relationship detected
5. Logroscino et al. (1996)	Population-based case-control study 5-year follow-up	Community study	Cases: 110 Controls: 287	Vitamin A Vitamin C Vitamin E	No relationship detected No relationship detected No relationship detected
6. Anderson et al. (1999)	Case-control	DATATOP	Cases: 103 Controls: 156	Dietary vitamins D Supplements: Vitamin D Vitamin A Vitamin C Vitamin E	Increased risk Increased risk No relationship detected No relationship detected No relationship detected
7. Morens et al. (1996)	Case-control	Honolulu Heart Study	Cases: 83 Controls: 336	Vitamin E	No relationship detected
8. Scheider et al. (1997)	Case-control	DATATOP	Cases: 57 Controls: 50	Vitamins E Vitamin C	No relationship detected No relationship detected
9. de Rijk et al. (1997)	Cross-sectional study, 3 years	Rotterdam Study	*N* = 5,342 Cases: 31	Vitamin E	Decreased risk
Folate, vitamin B12, vitamin B6, Riboflavin					
10. Gao et al. (2012)	Prospective cohort, 20-22 years	HPFS NHS	Cases: 438	Flavonoids	Increased risk
11. Murakami et al. (2010)	Multicenter hospital-based case-control study, 4 years	11 collaborating hospitals in Japan	Cases: 249 Controls: 368	Folate Vitamin B6 Vitamin B12 Riboflavin	No relationship detected Increased risk No relationship detected No relationship detected
12. Chen et al. (2004)	Prospective cohort: HPFS: 24 years NHS: 18 years	HPFS NHS	Cases: 248	Folate Vitamin B6 Vitamin B12	No relationship detected No relationship detected No relationship detected
13. Ueki and Otsuka (2004)	Case-control study Retrospective	DATATOP	Cases: 94 Controls: 69	Vitamin B2 Niacin Vitamin C	Decreased risk Decreased risk Decreased risk
14. de Lau et al. (2006)	Prospective cohort, 13 years	Rotterdam Study	Cases: 72	Folate Vitamin B6 Vitamin B12	No relationship detected Increased risk No relationship detected
Urate					
15. Gao et al. (2008)	Prospective cohort, 14 years	HPFS	Cases: 1,387 men	Urate	Decreased risk
Iron, copper, zinc, magnesium, manganese					
16. Powers et al. (2009)	Population-based case-control	Group Health Cooperative	Cases 430 Controls 560	Iron	Increased risk
17. Logroscino et al. (2008)	Prospective Cohort	HPFS NHS	Cases: 422	Total Iron Non-heme iron Supplement iron	No relationship detected Increased risk (with low vitamin C intake) Increased risk (borderline)
18. Powers et al. (2003)	Population-Based Case-Control	Group Health Cooperative health maintenance organization	Cases: 250 Control: 388	Iron Manganese	Increased risk Increased risk (joint effect)

(continued)

Table 1. (continued)

Authors	Study design	Population name	Sample size	Factors studied	Findings
19. Miyake et al. (2011a)	Hospital-based case-control	Japanese population	Cases: 249 Control: 368	Iron Copper Zinc Manganese Magnesium	Decreased risk No relationship detected Decreased risk No relationship detected Decreased risk
20. Johnson et al. (1999)	Prospective cohort	Detroit population	Cases: 126 Controls: 432	Iron	Decreased risk
Vitamin D, calcium					
21. Miyake et al. (2011b)	Hospital-based case-control	Japanese population	Cases: 249 Controls: 368	Dairy calcium and vitamin D	No relationship detected
22. Chen et al. (2002)	Prospective follow-up	HPFS: *N* = 47,331 NHS: *N* = 88,563	NHS Cases: 184 HPFS Cases: 210	Dairy calcium and vitamin D Non-dairy calcium and vitamin D	Increased risk (among men only) No relationship detected
23. Park et al. (2005)	Prospective follow-up, 1965-1998	Honolulu Heart Program	Cases: 128	Calcium	No relationship detected

HPFS = Health Professionals Follow-up Study; NHS= Nurses Health Study; DATATOP= Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism.

and PD risk (OR = 0.6, 95% CI = [0.3, 1.3] per 1-mg β-carotene intake; de Rijk et al., 1997).

Some studies show that carotenoids may increase the risk of PD. A large prospective study studied the relationship between dietary intake of antioxidants in 110 PD cases and 287 controls (Logroscino et al., 1996). After adjustment for age, sex, race, education, and total energy measured in calories, only carotenoids showed a marginal linear trend (p = .095), with increased risk of PD for the highest quartiles (Logroscino et al., 1996). Similarly, a small case-control study of 57 PD cases and 50 controls demonstrated that higher intake of carotenoids was associated with increasing trend toward PD risk (Scheider et al., 1997).

Vitamin C

Despite having a reputation as a strong antioxidant, multiple studies have failed to establish an association between vitamin C intake and PD risk (Anderson et al., 1999; Logroscino et al., 1996; Scheider, 1997; Zhang et al., 2002), which is not consistent with the oxidative stress hypothesis. Its neuroprotective potential may be limited because it is water-soluble and requires active transport at the choroid plexus to enter the CNS (Rice, 2000). Vitamin C has been shown to promote lipid peroxidation in in-vitro rat nigrostriatal tissue (Heikkila & Manzino, 1987). In addition, a possible risk of PD with high dietary vitamin C intake may be due to lifestyle of behavior related to vitamin C intake, such as sweets and other processed foods that contain vitamin C additives, which are associated with high PD risk (Scheider et al., 1997).

In the Leisure World Laguna Hills cohort, the risk of PD was significantly increased among individuals with a high intake of dietary vitamin C (OR = 1.33, 95% CI = [1.02, 1.73]), but this relationship did not reach statistical significance after adjusting for other variables (Paganini-Hill, 2001). The only inverse relation between vitamin C and PD risk was documented in a case-control study investigating past dietary habits in relation to PD risk among 342 cases and 342 controls (cases = 224 male and 118 female) and calculating specific nutrient intake from the reported food intakes on questionnaire. After adjusting for total energy intake, educational status, and cigarette smoking, an inverse relationship was found between PD risk and intake of vitamin C (vitamin C: OR = 0.60, 95% CI = [0.33, 1.09], p = .04; Hellenbrand et al., 1996). However, higher intake of vitamin C (179 ± 80 mg/day) showed a trend toward increased PD risk, although it was not statistically significant (OR = 2.13, 95% CI = [0.89, 5.11]; Scheider et al., 1997).

Vitamin E

Vitamin E is one of the most important naturally occurring antioxidant and has been studied extensively with regard to neurovascular and neurodegenerative studies. The largest study that investigated the association between vitamin E and PD risk was performed within the Nurses Health Study and the Health Professionals' Follow-Up Study cohorts (Zhang et al., 2002). The risk of PD was significantly reduced among individuals with high intake of dietary vitamin E (pooled multivariate Relative Risk = 0.68 [highest vs. lowest quintile], 95% CI = [0.49, 0.93]). However, no significant association was noted between PD and total or supplemental vitamin E (Zhang et al., 2002).

The relationship between specific dietary antioxidant vitamins and PD risk was investigated in a hospital-based case-control study of 249 PD cases and 368 controls (Miyake, Fukushima, et al., 2011). After adjusting for confounders such as gender, age, region of residence, pack-years of smoking, years of education, body mass

index (BMI), dietary intake of cholesterol, alcohol usage, intake of total dairy products, coffee intake, and dietary glycemic index, higher intake of vitamin E was significantly associated with lower risk of PD (OR = 0.45, 95% CI = [0.25, 0.79], p for trend = .009). After further stratification by gender, the inverse relationships were statistically significant only for women (Miyake, Fukushima, et al., 2011).

Several other epidemiological studies have not been able to detect a statistically significant association between vitamin E intake and PD risk (Anderson et al., 1999; Logroscino et al., 1996; Morens et al., 1996; Scheider et al., 1997). After adjustment for age, sex, race, education, and total energy measured in calories, a prospective study including 110 PD cases and 287 controls failed to show a statistically significant association between PD risk and dietary intake of vitamin E (Logroscino et al., 1996). A nested case-control study of 84 PD cases and 336 age-matched controls, part of the Honolulu Heart Study cohort, evaluated the effect of total dietary vitamin E on PD. Three dietary data sets for vitamin E and vitamin E-containing foods were examined, and significant protective associations were found with some vitamin E-containing foods, such as legumes (OR = 0.27, 95% CI = [0.09, 0.78]). However, there was no evidence of difference in prior consumption of vitamin E among individuals with and without PD (Morens et al., 1996).

Another case-control study, including 57 men with at least two cardinal signs of PD compared with 50 age-matched friend controls, examined the effect of dietary antioxidants on PD risk. After adjusting for age, education, smoking, rural living, and total energy intake, vitamin E was not associated with reduced PD risk (vitamin E: OR = 1.18, 95% CI = [0.47, 2.98]; Scheider et al., 1997).

B Vitamins

The B vitamins are involved in regulation of homocysteine metabolism, which has been associated with accelerating dopaminergic cell death in PD (Duan et al., 2002; Obeid, McCaddon, & Herrmann, 2007). Both epidemiological and interventional studies (by direct injection of homocysteine into the brain) have been linked to enhanced dopaminergic cell death through its neurotoxic effects. Hyperhomocysteinaemia, which has been linked to higher risk for PD (Kuhn, Roebroek, Blom, Van Oppenraaij, & Müller, 1998), has been associated with low plasma levels and insufficient dietary intake of folate, vitamin B6 and vitamin B (Refsum, Guttormsen, Fiskerstrand, & Ueland, 1998; Selhub et al., 1999). Thus, increased vitamin B may be associated with decreased risk of PD, by reducing plasma homocysteine (Obeid et al., 2007).

Data on PD risk and dietary source of these vitamins are limited. The relationship between PD risk and dietary flavonoid intake was studied in the Health Professional Follow-Up Study (N = 49,287 men) and the Nurses Health Study (N = 80,336 women), who were followed for 20 to 22 years (Gao, Cassidy, Schwarzschild, Rimm, & Ascherio, 2012). After adjustment for age, smoking status, BMI, use of nonsteroidal anti-inflammatory drugs, intake of total energy (kcal/d), caffeine, alcohol, and lactose, the highest quintile of total flavonoids was associated with lower PD risk when compared with the lowest quintile among men only (HR = 0.60, 95% CI = [0.43, 0.83], p for trend = .001; Gao et al., 2012).

A multicenter Japanese hospital-based case-control study, enrolling 249 PD cases and 368 controls, examined dietary intake of folate, vitamin B6, vitamin B12, and riboflavin and its relationship to PD risk (Murakami et al., 2010). After adjusting for potential dietary and non-dietary confounding factors, the authors found that low intake of vitamin B6 (highest quartile vs. lowest quartile) was independently associated with increased risk of PD (OR = 0.58, 95% CI = [0.36, 0.94], p = .052). On the contrary, increased intake of vitamin B12, riboflavin, and folate were not associated with increased risk of PD (Murakami et al., 2010). Another case-control study found that a higher intake of folate, vitamin B6, and vitamin B12, but not of riboflavin, was associated with a lower risk of PD when intakes were adjusted for total energy intake. Niacin showed a strong inverse relationship with PD risk even in the absence of energy adjustment (OR = 0.15, 95% CI = [0.06, 0.36], p for trend < .00005; Hellenbrand et al., 1996). A long-term prospective study evaluated the relationship between folate, vitamin B6, vitamin B12 intake, and PD risk as part of the Rotterdam Study (de Lau, Koudstaal, Witteman, Hofman, & Breteler, 2006). Diet was assessed at baseline and at intervals among 5,289 patients (3,122 women and 2,167 men), who were followed for 9.7 years. At the end of the follow-up, 72 participants were diagnosed with PD. Their analysis revealed a significant decrease in risk of PD among individuals with higher intake of vitamin B6 (Hazard Ratio = 0.69, 95% CI = [0.50, 0.96], p = .048; for highest vs. lowest tertile, HR = 0.46, 95% CI = [0.22, 0.96]). However, no association was observed for dietary folate or vitamin B12 intake and PD risk (de Lau et al., 2006).

Negative results, after adjusting for confounding factors and on comparing the highest quintile of intake with the lowest quintile, emerged from a prospective study in 248 men and 167 women with PD participating in the HPFS and the NHS, which found no association between high intake of folate, vitamin B6, or B12 and PD risk in either men or women (Chen et al., 2004). Similar results emerged from another case-control study (N = 94 cases, 69 controls), which explored the temporal relationship between constipation, nutrients, and the appearance of motor symptoms, showing that vitamin B2, niacin, and vitamin C intake in PD patients was not different from the controls prior to disease onset (Ueki & Otsuka, 2004).

Vitamin D and Calcium

There are conflicting results regarding the association of PD risk with dietary vitamin D and calcium. A multicenter hospital-based case-control study, including 249 PD patients and 368 controls and adjusting for sex, age, region of residence, pack-years of smoking, years of education, BMI, and dietary factors (i.e., cholesterol, dietary glycemic index, vitamin E, β-carotene, vitamin B6, caffeine, iron, and alcohol) found no association between calcium or vitamin D intake with PD risk (Miyake et al., 2011b).

Other studies appear to suggest a relationship between dairy intake and risk of PD. Two large prospective cohorts, with 210 incident PD cases in men and 184 in women, found a positive association between dairy intake and PD risk in men (RR comparing extreme categories = 1.8; p for trend = .004) but not in women (RR = 1.1; p for trend = .9). Further analyses among men showed significant positive associations with PD risk for intakes of several dairy foods as well as dairy calcium (RR = 1.5; p for trend = .02) and dairy vitamin D (RR = 1.6; p for trend = .004). Intakes of calcium and vitamin D from other dietary or supplemental sources were not related to PD risk in men. The results suggest that higher intake of dairy products may increase the risk of PD in men (Chen, Zhang, Hernán, Willett, & Ascherio, 2002). Similar results emerged from a study of 7,504 men aged 45 to 68 years, enrolled in the Honolulu Heart Program and followed for 30 years. During follow-up, 128 individuals developed PD. After adjusting for age, incidence of PD increased with milk intake from 6.9/10,000 person-years (non-milk users) to 14.9/10,000 person-years in men who consumed > 16 ounce/day (p = .017). Further adjustment for other dietary confounders increased the odds of having PD 2.3 folds in the highest intake group, defined as intake of more than 16 ounces of milk per day (OR = 2.3, 95% CI = [1.3, 4.1]), compared with non-milk users. After adjusting for milk consumption, calcium intake from dairy sources had no effect on the risk of PD (age-adjusted PD incidence = 9.0/10,000 person-year, p = .046), as well as calcium intake from nondairy sources (age-adjusted PD incidence = 5.6/10,000 person-year, p = 0.704; Park et al., 2005).

It is possible that other constituents of dairy foods may have a detrimental effect on risk of PD. Anderson et al. (1999) detected an increase in PD risk with increasing intake of foods containing vitamin D and vitamin D supplements, but this relationship was rendered statistically insignificant after adjustment for animal fat intake. Therefore, the association may have been secondary to animal fat intake rather than the vitamin (Anderson et al., 1999).

Urate

Diet is an important determinant of serum urate levels, a metabolic breakdown product of dietary purines. It has been proposed that urate is a potent antioxidant, iron chelator, and ascorbate stabilizer, which can prevent oxidative damage in the human brain (Ascherio et al., 2009), and a relationship between dietary urate index and reduced risk of PD was established (De Vera et al., 2008). Given the high metabolic demand of the neurons and their susceptibility to oxidative damage, it has been proposed that urate may prevent oxidative stress and subsequently neurodegeneration (Xu et al., 2002). A large body of evidence has revealed increased risk of PD among those with lower levels of plasma and CNS urate, with oxidative stress consistently implicated as a central pathogenic mechanism (Chen, Mosley, Alonso, & Huang, 2009; Jain et al., 2011; O'Reilly et al., 2010; Schwarzschild et al., 2008; Weisskopf, O'Reilly, Chen, Schwarzschild, & Ascherio, 2007). Studies have consistently reported low PD risk among those with higher serum or cerebrospinal fluid urate levels in PD patients compared with healthy controls (Tohgi, Abe, Takahashi, & Kikuchi, 1993). Other groups explored the relationship between gout and PD, finding a lower risk of PD among prospectively followed men (Alonso, Rodriguez, Logroscino, & Hernán, 2007; De Vera et al., 2008; Kutzing & Firestein, 2008). Furthermore, high urate has been associated with reduced rate of clinical progression of PD, as well as improved neuropsychological performance among PD patients (Annanmaki, Pessala-Driver, Hokkanen, & Murros, 2008).

Only one study examined the relationship of urate with PD risk. Out of a subsample of 1,387 men in the Health Professionals Follow-Up Study, 248 incident PD cases were documented after 14 years of follow-up. Dietary urate index was calculated by a stepwise regression model, with plasma urate as a dependent variable and intake of foods and nutrition known to affect uricemia as potential predictors. After adjusting for age, smoking, and caffeine intake, an inverse relationship with PD was detected among those in the highest quintile of dietary urate intake, pointing to a potential protective effect of urate (RR = 0.47, 95% CI = [0.30, 0.74], p = .001). The relative risk remained significant after adjustment for other variables such as vitamin C, dairy protein, fructose, and alcohol intake (Gao et al., 2008).

Iron and Manganese

The alteration of iron metabolism in the brain has been observed and extensively studied in multiple neurodegenerative diseases and PD in particular (Dusek, Jankovic, & Le, 2012; Pichler et al., 2013; Sian-Hülsmann, Mandel, Youdim, & Riederer, 2011). The elevated nigral iron levels observed in PD may reflect a dysfunction of brain iron homeostasis (Li et al., 2013). Two prospective studies and three case-control studies examined the relationship of dietary sources of iron, as well as other metals such as manganese, copper, magnesium, and zinc in PD.

In the 422 incident PD cases recorded in the Health Professional Follow-Up Study cohort (N = 47,406 men)

and Nurses Health Study cohort (N = 76,947 women), total iron intake was not associated with PD risk (RR = 1.10, 95% CI = [0.74, 1.65], p for trend = .84), but high dietary non-heme iron intake from food was associated with a 30% increased risk of PD as compared with low non-heme iron intake (RR = 1.27, 95% CI = [0.92, 1.76], p for trend = .02). A secondary analysis revealed that PD risk was significantly increased among individuals with combined high non-heme iron and low vitamin C intakes (RR = 1.92, 95% CI = [1.14, 3.32], p for trend = .002). Among male participants, supplemental iron intake was associated with a borderline increase in PD risk (Logroscino, Gao, Chen, Wing, & Ascherio, 2008).

Higher iron intake was associated with increased PD risk also in a population-based nested case-control study, which enrolled 126 PD cases and 432 controls and compared highest and lowest quartiles of iron intake (OR = 1.88, 95% CI = [1.05, 3.38], p = .034) after adjusting for age, sex, smoking, and BMI, but not total kilocalories (Johnson, Gorell, Rybicki, Sanders, & Peterson, 1999). Similar results were reported in two studies from the same group (Powers et al., 2003, 2009). The first, a population-based case-control study (N = 250 PD patients and 388 controls) investigated whether PD risk is associated with dietary iron, manganese and intake of other nutrients (Powers et al., 2003). After adjusting for age, sex, education, ethnicity, kilocalories, and smoking status, the highest quartile of iron intake had an increased PD risk compared with the lowest quartile (OR = 1.7, 95% CI = [1.0, 2.7], p = .016). The odds of developing PD was further increased for combination of both iron and manganese intake compared with lower intake of each nutrient (OR = 1.9, 95% CI = [1.2, 2.9]; Powers et al., 2003). The same authors replicated this finding in another population-based case-control study, evaluating the association between dietary fats, cholesterol, and iron as risk factors for PD (N = 20 PD cases and 560 controls; Powers et al., 2009). The results indicated that the highest quartile of iron intake was associated with an increased risk of PD when compared with the lowest quartile. The significance was only shown in men and not in women (Men: OR = 1.82, 95% CI = [1.11, 2.99], p = .013; women: OR = 1.12, 95% CI = [0.59, 2.12], p = .314; Powers et al., 2009).

Opposite results were reported by a Japanese hospital-based, case-control study that investigated whether dietary intake of metals such as iron, copper, zinc, magnesium, and manganese are associated with risk of PD. After adjustment for sex, age, region of residence, pack-years of smoking, years of education, BMI, and dietary factors, including cholesterol, dietary glycemic index, vitamin E, β-carotene, vitamin B6, caffeine, and alcohol, an inverse relationship was detected between higher intake of iron (OR = 0.24, 95% CI = [0.10, 0.57]), magnesium (OR = 0.33, 95% CI = [0.13, 0.81], p = .007), and zinc (OR = 0.50, 95% CI = [0.26, 0.95], p = .055) and PD risk. No association was found between copper or manganese intake and PD risk (Miyake et al., 2011a).

Discussion

This comprehensive review of the relationship between individual micronutrients and PD suggests that dietary intake of essential elements for the proper functioning of the CNS, not readily synthesized in our organism, can be associated with both decreased and increased risk of PD. The strongest association with a reduced risk of PD risk is present for dietary vitamin E whereas a role of supplemental vitamin E in reducing PD risk has not been established. In fact, the use of supplemental vitamin E in early PD failed to delay the need for starting levodopa in a large-scale prospective clinical study, possibly due to inferior bioactivity of the racemic tocopherol as compared with the alpha tocopherol found in natural foods (Parkinson Study Group, 1993). Studies examining the effects of vitamin E administration in animal models of PD have been controversial, as some authors report a protective effect of vitamin E (Dexter et al., 1994; Lan & Jiang, 1997; Ren et al., 2006), while others dispute these results (Mihatsch, Russ, Gerlach, Riederer, & Przuntek, 1991; Parkinson Study Group, 1993). Vitamin E deficient mice were more susceptible to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity than controls, leading to dopamine metabolite deletion in substantia nigra (Odunze, Klaidman, & Adams, 1990). In another mouse model, striatal degeneration secondary to MPTP was inhibited with oral administration or vitamin E (Ren et al., 2006). However, daily oral administration of vitamin E, following a large dose of MPTP, did not deplete dopamine in the mice striatum (Gong, Daigneault, Acuff, & Kostrzewa, 1991). Given that more than half of the dopaminergic neurons might have degenerated by the time the first signs and symptoms of PD appear, the differential response to supplemental versus dietary vitamin E may be related to timing and duration of use (Fearnley & Lees, 1991). One could surmise that dietary vitamin E may be influencing PD risk during early disease, as it is usually a lifelong habit, as compared with supplemental vitamin E, which is usually consumed later in life when the neurodegenerative process may have already started.

With regard to vitamin A, the available data do not indicate a significant association between dietary vitamin A intake and PD risk. A recent meta-analysis of pooled data suggested a weak and statistically insignificant inverse association between PD and both α- and β-carotene. This may have been due to the small number of studies that included data on dietary intake of α- and β-carotene. In addition, the studies reporting these associations might have been underpowered for detecting a true association with a relatively small effect size, considering the effect of the measurement error stemming from estimating these micronutrients from dietary intake assessed with a wide range of questionnaires. Previous studies attempting to estimate the extent to which food frequency questionnaires and other dietary estimates of vitamin A and carotenoid intake reflected true biomarker

levels in blood showed only modest correlations between plasma and dietary values of β-carotene and retinol (r = .28, $p < .001$ and r = .20, $p < .001$, respectively).

Despite being the most potent antioxidant, vitamin C was not found to be associated with reduced risk for PD in most of the studies, possibly as an effect of the water-soluble nature of vitamin C and the need for active transport at the blood brain barrier (Heikkila, Manzino, Cabbat, & Hanly, 1983). In addition, the strong effect on lowering uric acid levels (which may reduce risk for PD) could possibly counteract vitamin C beneficial relationship with PD risk (Heikkila et al., 1983).

We found conflicting results regarding the association of vitamin D and calcium with PD. The lack of associations could be due to changes in dietary habits after PD onset. Some of the non-motor symptoms such as constipation and hyposmia might precede the onset of noticeable motor signs and symptoms, which could affect food choices (Abbott, Waites, Lillywhite, & Jackson, 2010; Ponsen et al., 2004). Thus, pre-symptomatic and/or post-symptomatic PD could influence dietary habits in some cases, which would lead to misclassification of their true long-term dietary exposure.

Although evidence supporting the role of dietary metal intake in PD risk is limited, a number of studies suggested a direct relationship between dietary iron intake and risk of PD. The exact mechanisms of iron accumulation in the substantia nigra are unclear, but there is evidence of free radical formation in the substantia nigra of PD patients (Dexter et al., 1989; Sofic, Paulus, Jellinger, Riederer, & Youdim, 1991). There is evidence that the small amount of iron that crosses the blood brain barrier remains unbound and reacts with hydrogen peroxide through Fenton's reaction, leading to increased oxidative stress (Dusek et al., 2012). It remains unknown whether this is an effect of increased dietary intake or other confounders. More research is needed regarding iron consumption and PD prevention before any recommendation can be made.

Oxidative stress has been at the center of many proposed mechanisms underlying cell death in PD (Fahn & Cohen, 1992; Olanow, 1990) and it may represent a common pathway for genetic and environmental factors leading to PD, contributing to dopaminergic degeneration in the substantia nigra pars compacta (Tse, McCreery, & Adams, 1976). So far, there is no dispute in the fact that oxidative stress is present in PD patients, and therefore, the focus of nutritional epidemiology in PD has been mainly on antioxidants due to the long-standing presumed central role of dopamine oxidative stress hypothesis in PD. However, the inconsistencies of the studies suggest that dopamine metabolism may not be the only trigger and that neurodegenerative process may start in noncatecholaminergic neurons (Braak et al., 2002; Iwanaga et al., 1999; Wakabayashi, Takahashi, Takeda, Ohama, & Ikuta, 1988). Other processes, such as inflammation, infections, or aberrant neurotransmitter system have been proposed to contribute to the pathogenesis as well (Beal, 2003; Jenner, 2003). There is a dire need for further studies to identify environmental risk factors, in light of recent developments in PD. It is, therefore, critical to address PD as a much more complex disease, and at the very least, not consider oxidative stress as the only mechanism of disease progression.

Variations in the influence of the micronutrients may be attributed to the complex synergistic nature of food components that may modify their biologic action. Often, observational studies may identify a particular nutrient to be associated with increased risk for a particular disease, however, randomized trials have not been able to duplicate the finding (McCracken, 2010). The complex nature of measuring dietary intake or biological markers in epidemiological studies cannot be ignored (Mayne, 2003). Dietary estimates from food intake questionnaires may be subject to inaccuracies, both in terms of recall (actual vs. perceived intake, for example, portion size or content of meal) and considerations such as different cooking methods, which may result in differences in the nutrient content of the same food items. Such inaccuracies leading to measurement error are likely to occur in both cases and controls (i.e., non-differential) and should be incorporated in the calculations when estimating the CIs.

Moreover, food preparation can change the quality and quantity of the nutrient (Freeland-Graves, Nitzke, & Academy of Nutrition and Dietetics, 2013). Despite these limitations, we believe this review provides valuable overview of the complex relationship between micronutrients and their relationship with risk for PD. It also serves as a platform for future studies that could better elucidate these relationships.

In conclusion, there is some consensus regarding a relationship between dietary vitamin E intake and decreased PD risk. The protective effects of other micronutrients such as vitamin C and D, as well as the negative influence of metals such as iron and copper were not as robust and often inconsistent. Thus, no conclusions can currently be drawn with regard to potential interventions. There are, of course, several crucial micronutrients not covered in this review because of insufficient information. Future studies will need to focus on better designed, large prospective studies with appropriate biomarkers to validate the findings. Although the biologic mechanisms of particular micronutrients and PD risk have been studied, a better understanding of nutrient interactions and physiologic/biologic factors that account for these differences is needed. Future studies should also consider differences in gender-specific physiological mechanisms that might modify the action of some micronutrients and ensure use of the most reliable method of nutrient intake exposure.

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