Vitamin A and Carotenoids and the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis

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Key Words

Vitamin A · Parkinson's disease · Meta-analysis · Carotenoids · Lutein

Abstract

Background: Vitamin A and carotenoids are involved in signalling pathways regulating gene expression in many organs, including the brain. The dopaminergic system is a target of retinoic acid action in the central nervous system. The aim of this review is to assess the epidemiological evidence on the association between blood levels or dietary intakes of vitamin A and carotenoids and risk of Parkinson's disease (PD). **Methods:** PubMed and ISI Web of Science were searched for relevant papers from 1990 to April 2013. Data reported in epidemiological studies assessing the association between vitamin A and/or carotenoids (α -carotene, β -carotene, β -cryptoxanthin, lutein, lycopene, zeaxanthin and canthaxanthin) and PD were extracted for a narrative synthesis and meta-analysis. **Results:** Thirteen papers were included out of a total of 362 potentially relevant; of these, eight contributed to the meta-analysis. No statistically significant pooled estimate between micronutrient and PD was detected. Forest plots suggest possible non-significant in-

verse pooled estimates of α -carotene and β -carotene and risk of PD. A significant association between lutein intake and PD risk was detected in case-control studies only. **Conclusions:** Data published to date are insufficient for drawing definite conclusions about the epidemiological evidence on the association between blood levels or dietary intakes of vitamin A and carotenoids and the risk of PD. Results should be interpreted particularly cautiously given the limitation of the present meta-analysis and the potential publication bias. Authors are urged to follow more closely the recommendations for reporting epidemiological studies in order to enhance the capacity for synthesising the evidence.

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Background

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease; its incidence rises steeply with age, reaching 93.1 per 100,000 person-years at ages 70–79 years [1]. While symptomatic treatment is currently available, no cure or drugs to slow disease progression have yet been found. Research in this field is hampered by the limited understanding of bio-

logical mechanisms underlying the degeneration of dopaminergic neurons and formation of Lewy bodies in the brain, hallmarks of the disease [1].

Historically, PD was considered a substantially sporadic disorder in which the environment played a dominant role, alongside some genetic forms caused by monogenetic mutations. Today this view has changed substantially, revealing a continuum of disease risk ranging from familial, early-onset forms to the so-called sporadic forms upon which age, environmental factors and additional genetic factors modulate the risk of manifesting the disease [2]. Despite the fact that the role of environmental factors is increasingly recognised, surprisingly few established risk/protective factors have been identified so far.

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 [3]. 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. Canthaxanthin, lutein, lycopene and zeaxanthin are carotenoids, but are not converted to vitamin A (fig. 1).

Vitamin A and carotenoids are involved in a complex signalling pathway that regulates gene expression in several organs including the brain and, in the central nervous system (CNS), controls neuronal differentiation and neural tube patterning [4]. Retinol-binding proteins have been found on the brain-blood barrier, probably regulating the access of retinol to the brain [5]; high concentrations of retinol and carotenoids are found in the postmortem human frontal lobe cortex [6]. 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 CNS [7]. The promoter of the D2 dopamine receptor gene contains a retinoic acid binding motif [8], and the expression pattern of dopamine D1 and D2 receptors is reduced in mice knocked out for the retinoic acid receptor [9]. The role of retinoid signal transduction in controlling dopaminergic neurotransmission is further strengthened by the presence of high levels of retinoic acid-synthesizing enzymes in the mesotelencephalic dopamine system [10] and by the fact that retinoic acid receptors are believed to critically control the survival, adaptation and homeostatic regulation of the dopaminergic system [11].

Since epidemiological studies have explored the inverse association between carotenoids and PD suggested by animal and in vitro studies, it is timely to synthesise

the available evidence in the form of a systematic review and meta-analysis. Although previous systematic reviews [12, 13] have addressed the epidemiological evidence on the association between nutritional factors and PD, with no clear-cut conclusions for vitamin A and carotenoids, they did not pool results for vitamin A in a meta-analysis. The aim of this paper was therefore to systematically review the available epidemiological evidence assessing the association between both blood levels or dietary intake of vitamin A and carotenoids and the risk of PD. Sound epidemiological evidence consistent with data coming from animal and in vitro studies would reinforce the notion of the suggested protective effect of these micronutrients on PD.

Methods

The protocol for this review has been developed a priori and agreed on by co-authors, but it has not been published in advance (documentation available upon request).

Search Strategy and Selection Criteria

In accordance with the protocol, two databases were searched. PubMed was searched for papers published between January 1st, 1990, and April 30th, 2013, using the following MeSH terms: ('vitamin A'[Mesh] OR retinol OR retinal OR retinaldehyde OR retinoic acid OR tretinoin OR 'tretinoin'[Mesh] OR 'carotenoids'[Mesh] OR 'beta-carotene'[Mesh] OR alpha-carotene OR beta-carotene OR cryptoxanthin OR 'retinoids'[Mesh] OR 'canthaxanthin'[Mesh] OR 'lutein'[Mesh] OR lycopene OR zeaxanthin) AND ('Parkinson disease'[Mesh] OR 'parkinsonian disorders'[Mesh]). Similarly, Web of Science was searched for articles published in the same date range using analogous key words and related synonyms. Two reviewers independently screened the titles and abstracts of the output of the search to identify potentially eligible studies. Full texts for potentially eligible papers were obtained where possible, and independently assessed for eligibility by two reviewers. All included papers were additionally scanned for references to other potentially relevant papers. In order to schematize the steps used for the selection of studies, a flowchart diagram was developed based on the PRISMA recommendations [14].

Types of Studies

The following inclusion criteria were used:

- Study type – all observational studies (cross-sectional, case control, nested case-control and cohort studies) investigating vitamin A (and/or carotenoids) levels – or their estimated dietary intake;
- Participants – PD cases and healthy controls/non-cases;
- Language – articles published in English.

Studies were excluded if they did not provide measures of vitamin A (and/or carotenoids) level (or dietary intake) in PD and controls/non-cases; the measures of vitamin A (and/or carotenoids) were carried out in human liquids different from serum or plasma (i.e. in cerebrospinal fluid); only case series of PD cases

Fig. 1. Chemical structure of retinol and carotenoids.

were included (or PD cases were compared with other neurological disease cases, i.e. amyotrophic lateral sclerosis or dementia); vitamin levels were compared across different PD treatments; the outcome was defined as a clinical characteristic of PD (i.e. PD dementia); or they were non-human studies (animal or in vitro studies).

Data Extraction and Quality Assessment

One reviewer used a standard data extraction form to extract relevant characteristics of the populations, exposures and outcome data of each study. A second reviewer checked the data and disagreements were resolved through consensus.

All studies were assessed for quality and potential risk of bias using a customised version of the Newcastle-Ottawa quality assessment scale for case-control and cohort studies [15]. The scale assesses the quality of the study in three main domains: selection (of cases and controls or of exposed and unexposed), comparability

(between cases and controls, or exposed and unexposed), and exposure assessment in case-control studies and outcome assessment in cohort studies. For each item, a few possible alternative degrees of quality are available to choose from, ranging from best quality to poor quality/not reported. Quality score was not used as exclusion criteria in the present review.

Greater consideration was given to potential for selection bias in case-control studies, and potential for loss to follow-up in cohort studies. A potential for selection bias was considered present if studies were judged as having 'potential for selection biases or not stated' as opposed to 'consecutive or obviously representative series of cases'. A potential for loss to follow-up was considered present if studies were judged as having 'follow-up rate <70% and no description of those lost' or 'no statement' as opposed to 'complete follow-up – all subjects accounted for' or 'subjects lost to follow-up unlikely to introduce bias – small number lost, >70%

Table 1. Results from the included papers divided by micronutrients investigated

	Study design	Cases, n	Total, n	Exposure assessment	OR/relative risk (95% CI)	Mean difference (cases – controls)	Median difference (cases – controls)	Potential for selection bias/lost to follow-up
<i>Vitamin A</i>								
Paraskevas [29], 2003	cross-sectional	44	72	serum measurement			0	yes
Paganini-Hill [17], 2001	nested case-control study in a population-based cohort of a retirement community	395	2,715	dietary estimate	high vs. low intake OR 1.16 (0.85–1.57)			yes
Johnson [18], 1999	population-based case-control study	126	558	dietary estimate	4th vs. 1st quartile OR 1.31 (0.75–2.30)		543 IU	no
Foy [30], 1999	hospital-based case-control study	41	82	serum measurement			0.17 µmol/l	yes
Anderson [24], 1999	population-based case-control study	103	259	dietary estimate	4th vs. 1st quartile OR 0.65 (0.29–1.45)			no
Jimenez-Jimenez [33], 1993	hospital-based case-control study	61	122	serum measurement		0.05 µg/dl		yes
Jimenez-Jimenez [36], 1992	hospital-based case-control study	42	84	serum measurement		0.02 µg/dl		yes
Adén [39], 2011	population-based case-control study	87	115	dietary estimate		36 µg		no
<i>α-Carotene</i>								
Miyake [19], 2011	hospital-based case-control study	249	617	dietary estimate	4th vs. 1st quartile OR 0.61 (0.36–1.02)	–8 µg		yes
Zhang [20], 2002	occupational cohort study (nurses and health professionals)	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.91 (0.64–1.29)		0 µmol/l	yes
Foy [30], 1999	hospital-based case-control study	41	82	serum measurement				yes
Scheider [21], 1997	hospital-based case-control study	57	107	dietary estimate	above vs. below median OR 1.39 (0.51–3.79)	–38 µg		no
Jimenez-Jimenez [33], 1993	hospital-based case-control study	61	122	serum measurement		–0.002 µg/dl		yes
<i>β-Carotene</i>								
Miyake [19], 2011	hospital-based case-control study	249	617	dietary estimate	4th vs. 1st quartile OR 0.56 (0.33–0.97)	–104.3 µg		yes
Zhang [20], 2002	occupational cohort study (nurses and health professionals)	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.90 (0.63–1.30)			yes
Johnson [18], 1999	population-based case-control study	126	558	dietary estimate	4th vs. 1st quartile OR 1.24 (0.70–2.21)		310 µg	no
Foy [30], 1999	hospital-based case-control study	41	82	serum measurement			0.01 µmol/l	yes
Scheider [21], 1997	hospital-based case-control study	57	107	dietary estimate	above vs. below median OR 1.67 (0.59–4.76)	365 µg		no
Hellenbrand [22], 1996	hospital-based case-control study	342	684	dietary estimate	4th vs. 1st quartile OR 0.67 (0.37–1.19)			yes
Jimenez-Jimenez [33], 1993	hospital-based case-control study	61	122	serum measurement		–0.14 µg/dl		yes
Adén [39], 2011	population-based case-control study	87	115	dietary estimate		–1,113 µg		no

Table 1 (continued)

Study design	Cases, n	Total, n	Exposure assessment	OR/relative risk (95% CI)	Mean difference (cases – controls)	Median difference (cases – controls)	Potential for selection bias/lost to follow-up
Powers [23], 2003	250	638	dietary estimate	4th vs. 1st quartile OR 1.2 (0.8–1.9)			no
<i>β-Cryptoxanthin</i> Miyake [19], 2011	249	617	dietary estimate	4th vs. 1st quartile OR 1.16 (0.71–1.89)	125.4 µg		yes
Zhang [20], 2002	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.74 (0.53–1.02)			yes
Scheider [21], 1997	57	107	dietary estimate	above vs. below median OR 1.38 (0.62–3.06)	8 µg		no
<i>Lutein</i> Zhang [20], 2002	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.78 (0.56–1.08)			yes
Johnson [18], 1999	126	558	dietary estimate	4th vs. 1st quartile OR 2.52 (1.32–4.84)		281 µg	no
Scheider [21], 1997	57	107	dietary estimate	above vs. below median OR 3.04 (1.04–8.89)	580 µg		no
Powers [23], 2003	250	638	dietary estimate	4th vs. 1st quartile OR 1.4 (0.9–2.3)			no
<i>Lycopene</i> Zhang [20], 2002	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.87 (0.63–1.21)			yes
Foy [30], 1999	41	82	serum measurement			–0.1 µmol/l	yes
Scheider [21], 1997	57	107	dietary estimate	above vs. below median OR 0.69 (0.30–1.57)		–37 µg	no
Jimenez-Jimenez [33], 1993	61	122	serum measurement		–0.11 µg/dl		yes
Powers [23], 2003	250	638	dietary estimate	4th vs. 1st quartile OR 1.6 (1.0–2.6)			no
<i>Zeaxanthin</i> Zhang [20], 2002	371	124,221	dietary estimate	5th vs. 1st quintile RR 0.78 (0.56–1.08)			yes

Fig. 2. Flowchart describing the process of selection and inclusion of papers in the systematic review.

follow-up or description for those lost provided'. For each micro-nutrient, relevant studies with relative sample size, mean and/or median of intake among cases and controls/non-cases, and measure of association with PD risk were extracted for a narrative synthesis and meta-analysis.

Statistical Analysis

The included studies used different definitions for their exposure categories (i.e. quartiles, quintiles, below/above the median, etc.), so it would have been appropriate to derive the estimated dose-response trend using the method recommended by Greenland and Longnecker [16]. However, since data was presented without enough detail (e.g. boundaries of quartiles) in the majority of the included studies [17–23], this was not possible. As a consequence, meta-analyses were carried out using the odds ratio (OR) and hazard ratio (HR) comparing the most extreme categories in each study (4th vs. 1st quartile [18, 19, 22–24], 5th vs. 1st quintile [20], above vs. below the median [21], high vs. low intake [17]; table 1). In order to allow for heterogeneity introduced by using this approach, random-effect models were used to pool the studies. RevMan (version 5.2) software from the Cochrane Collaboration [25] was used to obtain a pooled OR using the generic inverse variance method, where studies' log OR were weighted by the inverse of their variances.

In each meta-analysis, subgroup analysis distinguished between case-control and cohort studies. In the event of sufficient studies being included, sensitivity analyses were considered to investigate possible differences in results depending on: (1) exposure assessment method (dietary questionnaire vs. biomarkers); (2) region of the world (due to potential dietary differences), and (3) quality of study.

Results

After removing duplicates, 362 potentially suitable papers were identified from the two sources. A total of 21 papers passed the title and abstract screening and were assessed for eligibility [17–22, 24, 26–39]. Of these, two were excluded because the exposure measurement was not available [26, 27], four because they did not provide original data [28, 32, 38] and three because the full text was not available [31, 34, 37]. One additional paper was added after screening all relevant references of the included papers [23] (fig. 2). Data was extracted by micronutrient (table 1). Of the 13 studies which reported data, eight studies contributed to the meta-analyses.

Vitamin A

Vitamin A or retinoic acid was assessed in eight studies [17, 18, 24, 29, 30, 33, 36, 39], of which only one was a case-control nested in a cohort study [17]. Estimates of the association between dietary vitamin A intake and risk of PD were not consistent: two good-quality, powered population-based case-control studies estimated a non-significant OR comparing the 4th versus the 1st quartile of distribution in the opposite direction [18, 24] (fig. 3). The pooled estimate for case-control studies is OR 0.92 (95% CI 0.53–1.59). Another good-quality population-based case-control study reported only the mean intake

Fig. 3. Forest plot of vitamin A (retinol) from dietary intake and risk of PD in cohort and case-control studies.

difference showing a higher intake among cases, albeit of small magnitude [39]. The cohort nested case-control study showed a non-significant increased risk comparing high versus low intake of vitamin A [17] (fig. 3). Overall, the pooled estimate of the association between vitamin A and PD is close to null OR 1.09 (95% CI 0.84–1.42). None of the four studies measuring vitamin A in serum reported a measure of association with PD. They all reported mean or median differences only and, although in three studies differences favour cases compared to controls, differences are so small that these could be assumed to be negligible [30, 33, 36]; in another cross-sectional study the same median in cases and controls was reported [29].

α -Carotene

Five studies reported the association between α -carotene and PD [19–21, 30, 33]. A large cohort study analysing α -carotene dietary intake in relation to the risk of PD found a non-significant inverse association comparing the 5th versus the 1st quintile of distribution [20] (fig. 4). A large population-based case-control study in Japan reported an estimated mean of dietary intake of α -carotene that was higher in controls compared to cases, with a borderline significant inverse OR comparing the 4th versus the 1st quartile of distribution [19]. Another hospital-based case-control study also reported mean α -carotene intakes that were higher in controls than cases, but there appeared to be an error in the paper. In fact,

authors also reported a positive association between α -carotene and PD comparing values above and below the median giving an OR of ‘11.39 (95% CI 0.51–3.79)’ [21]. We interpreted this as a typographical error and assumed that the reported OR of 11.39 should be 1.39; however, we excluded this last study from the meta-analysis given the incoherence between the two sets of results (fig. 4). The overall pooled estimate of the association between α -carotene and PD is OR 0.78 (95% CI 0.54–1.14). The same meta-analysis also including the study by Scheider et al. [21] led to a pooled estimate for case-control studies of 0.82 (95% CI 0.38–1.78) and an overall pooled estimate of 0.84 (95% CI 0.59–1.18). The only two hospital-based case-control studies measuring serum levels of α -carotene reported either the same estimates in cases and controls [30], or values slightly higher in controls [33].

β -Carotene

A total of nine studies reported data on β -carotene and PD [18–23, 30, 33, 39]. A large cohort study investigating the association between dietary intake of β -carotene and risk of PD found a non-significant inverse association comparing the 5th versus the 1st quartile of distribution [20]. Similar inverse associations were reported by two other large hospital-based case-control studies [19, 22] which compared the 4th versus 1st quartile of distribution of dietary intake, in one case reaching statistical sig-

Fig. 4. Forest plot of α -carotene from dietary intake and risk of PD in cohort and case-control studies.

Fig. 5. Forest plot of β -carotene from dietary intake and risk of PD in cohort and case-control studies.

Fig. 6. Forest plot of β -cryptoxanthin from dietary intake and risk of PD in cohort and case-control studies.

nificance [19]. Another good-quality population-based case-control study reported β -carotene values higher in controls than in cases, although no measure of association was given [39]. However, two additional good quality large population-based and one hospital-based case-control studies reported non-significant positive associations between β -carotene and PD in quartiles of distribution [18, 23], or comparing dietary estimated values above and below the median [21]. As a consequence, the pooled estimated association between β -carotene and risk of PD suggest an inverse, non-significant association (OR 0.92, 95% CI 0.64–1.33) for case-control studies, for the single cohort study (OR 0.90, 95% CI 0.63–1.29) and for all studies (OR 0.91, 95% CI 0.70–1.20; fig. 5). The two hospital-based case-control studies reporting values of serum measurements of β -carotene in cases and controls show inconsistent small differences in means [33] and medians [30].

β -Cryptoxanthin

Three studies reported data on β -cryptoxanthin in relation to PD [19–21]. One large cohort study reported a borderline significant inverse association between β -cryptoxanthin and PD comparing the 5th versus 1st quintile of distribution [20]. However, the two hospital-based case-control studies reporting dietary estimates of

β -cryptoxanthin in relation to PD risk reported higher mean values in cases than controls, and non-significant positive associations comparing the 4th versus the 1st quartile of distribution [19], and values above versus below the median [21]. As a consequence, the pooled estimate is far from being significant (OR 0.96, 95% CI 0.66–1.40; fig. 6). No biomarker studies on the association between serum levels of β -cryptoxanthin and PD were found.

Lutein

A total of four studies reported data on lutein and PD [18, 20, 21, 23]. Interestingly, while the only cohort study investigating dietary lutein intake in relation to PD risk reported a non-significant inverse association comparing the 5th versus the 1st quintile [20], the three case-control studies consistently reported positive associations that were statistically significant [18, 21], or borderline so [23] (fig. 7). As a consequence, although the pooled estimate from case-control studies showed a significant increased risk of PD for higher lutein intake (OR 1.85, 95% CI 1.19–2.87), this falls short of statistical significance overall (OR 1.49, 95% CI 0.83–2.68). No biomarker data are available for supporting the evidence of association between dietary intake of lutein and PD.

Fig. 7. Forest plot of lutein from dietary intake and risk of PD in cohort and case-control studies.

Fig. 8. Forest plot of lycopene from dietary intake and risk of PD in cohort and case-control studies.

Lycopene

Five studies reported data on lycopene and PD [20, 21, 23, 30, 33]. The only cohort study from these reported a non-significant inverse association between quintiles of lycopene intake and risk of PD [20]. Similar results were

also reported by a good-quality hospital-based case-control study investigating estimates of dietary intake above versus below the median in relation to PD [21]. These findings are also consistent with higher levels of lycopene detected in controls compared to cases in two hospital-

based case-control studies reporting serum measurement of lycopene [30, 33]. Only one good-quality population-based case-control study reported a significant positive association between dietary lycopene estimate and PD comparing the 4th versus the 1st quartile of intake [23]. As a consequence, the pooled estimate of lycopene is close to unity (OR 1.03, 95% CI 0.64–1.65; fig. 8).

Zeaxanthin

Only one cohort study reported the association between dietary estimates of zeaxanthin and PD risk, showing a non-significant inverse association comparing the 5th versus the 1st quintile of distribution of the nutrient (HR 0.78, 95% CI 0.56–1.08) [20].

Discussion

To our knowledge, this is the first systematic review addressing the association between dietary intake or blood levels of vitamin A and carotenoids in relation to PD in such detail; also, it is the first review attempting to pool results from published studies. Results come from a total of 13 papers published since 1990 reporting findings from epidemiological studies investigating either the association between dietary intake of target micronutrients [17–24, 39] or their serum levels [29, 30, 33, 36] in relation to PD. Only two studies carried out in the USA were prospective, a cohort study [20] and a case-control study nested in a cohort [17]. Apart from a cross-sectional study [29], the others were either population-based [18, 23, 24, 39] or hospital-based case-control studies [19, 21, 22, 30, 33, 36]. The assessment of the quality of the studies, using the Newcastle-Ottawa quality assessment scale, was particularly focussed on the potential for selection bias in case-control studies and for incomplete follow-up for cohort studies. This summary quality assessment led to the identification of five studies with relatively low potential for specific bias [18, 21, 23, 24, 39] out of all 13 included studies.

From the analysis of pooled data there is a suggestion that both α - and β -carotene might be inversely associated with PD. Although the risk reductions are small and do not reach statistical significance (OR 0.78, 95% CI 0.54–1.14 and OR 0.91, 95% CI 0.70–1.20, respectively), pooled estimates from case-control studies are in the same direction as results obtained from the cohort study investigating these associations. Cohort studies using pre-diagnostic information are generally considered superior to case-control studies given they are recall bias free. All studies

reporting these associations might be underpowered for detecting a true association with a relatively small effect size, especially considering the effect of the measurement error coming from estimating these micronutrients from dietary intake assessed with a wide range of questionnaires. The scattered results from biomarker measurements in serum are not inconsistent with this notion for both α - and β -carotene (although they do show very small differences between case and control levels).

Results from the analysis of the evidence on β -cryptoxanthin, lutein and lycopene, on the contrary, showed a substantial inconsistency between results from case-control studies and from cohort studies. While the associations tended to be positive in case-control studies, reaching a pooled significant positive association for lutein (OR 1.85, 95% CI 1.19–2.87), they are consistently non-statistically significantly inversely associated with PD in the only cohort study included [20]. This is a sound and well-conducted large cohort analysis including 371 PD cases coming from two large cohorts in the USA: the Nurse's Health Study and the Health Professional Follow-Up Study. One possible interpretation of this pattern is that case-control studies are affected by the potential for reverse causality and might be measuring a healthier dietary pattern changed as a result of the disease onset more than a pre-morbid dietary habit. However, studies in which the definition of incident case was more relaxed (within 5 [18] or 6 [19] years from diagnosis) did not yield more extreme estimates compared to those using a more stringent definition [21, 23]. The analyses of vitamin A and zeaxanthin are more difficult to interpret given the paucity of data available and estimates consistently close to unity found in the included papers. Data on canthaxanthin were not available.

The main limitations hampering the interpretation of results are: the small number of suitable studies; the heterogeneity of estimates included in meta-analyses; the measurement error introduced by estimating micronutrient levels via dietary questionnaires and to what extent these reflect the actual levels in the brain, and potential publication bias.

The heterogeneity of measures of associations found across studies is a main concern when pooling data in the meta-analyses and synthesising the available evidence. Although data analysis and presentation should be decided on a case-to-case basis depending on various factors (e.g. study size), more detail on the process leading to grouping of data – such as the boundaries of quartiles – should be given, as also stated in the STROBE recommendations (item 11: explain how quantitative vari-

ables were handled in the analyses; if applicable, describe which groupings were chosen and why) [40]. This would allow estimation of the dose-response trend [16] and overcome the problems of heterogeneity encountered in this review. As a possible alternative, once the linearity of the association is checked, authors could provide estimates of association (ORs or HRs) for doubling concentration of the biomarker/estimation of the exposure alongside the statistical models they have chosen, to allow more agile pooling ability.

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 did not show entirely consistent results. In one study, conducted to assess the association between individual plasma carotenoid levels (α -carotene, β -carotene, lycopene, β -cryptoxanthin, lutein, zeaxanthin) and fruit and vegetable intakes recorded by food frequency questionnaires (FQ) and 24-hour dietary recall records (24 HDR) in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [41], β -cryptoxanthin was most strongly correlated with total fruits (FQ $r = 0.52$, 24 HDR $r = 0.39$), lycopene with tomato and tomato products (FQ $r = 0.38$, 24 HDR $r = 0.25$), and α -carotene with intake of root vegetables ($r = 0.39$) and of total carrots ($r = 0.38$) for FQ only. Based on the diet measured by FQ and adjusting for possible confounding by body mass index, age, gender, smoking status, alcohol intake and energy intake, the strongest predictors of individual plasma carotenoid levels were fruits ($R^2_{\text{partial}} = 17.2\%$) for β -cryptoxanthin, total carrots ($R^2_{\text{partial}} = 13.4\%$) and root vegetables ($R^2_{\text{partial}} = 13.3\%$) for α -carotene, and tomato products ($R^2_{\text{partial}} = 13.8\%$) for lycopene. For 24 HDR, the highest R^2_{partial} was for fruits in relation to β -cryptoxanthin (7.9%) [41]. However, in a previous study on gastric cancer in the EPIC study [42], in a sample of 244 gastric cancer cases and 645 matched controls, the correlations between the plasma and dietary values of β -carotene and retinol were judged as modest ($r = 0.28$, $p < 0.001$ and $r = 0.20$, $p < 0.001$, respectively).

Estimates of the validity of dietary assessment in approximating serum levels in another study in pregnant women found that there were statistically significant correlations for α -carotene (0.32), β -carotene (0.22), lutein-zeaxanthin (0.29) and β -cryptoxanthin (0.26), but non-significant correlations were also observed for retinol and lycopene ($r \leq 0.12$) [43]. On the other hand, some evidence investigating the correlation between serum and brain levels of carotenoids showed how, among all the carotenoids, lutein concentrations had the highest se-

rum-brain correlation ($p < 0.0001$). Serum lutein, zeaxanthin, cryptoxanthin, lycopene and β -carotene were positively associated with brain lutein (0.283, $p < 0.0001$), zeaxanthin (0.503, $p < 0.0001$), cryptoxanthin (0.468, $p < 0.0001$), lycopene (0.348, $p < 0.0001$) and β -carotene (0.515, $p < 0.0001$) [44].

In the present review, only dietary estimates of micronutrients contributed to the meta-analyses as no studies reporting serum measurement levels were able to provide an estimate of the measure of association with PD case-control status. Only for α -carotene and lutein were the median and mean differences consistent with the pooled OR (albeit not significant for α -carotene).

Although most cohort studies rely on a single blood measurement, giving rise to spurious risk estimates due to misclassification of exposure due to within-subject variation of blood levels, measuring serum levels of vitamins and carotenoids for investigating the association with a disease outcome reduces substantially the intrinsic measurement error of the dietary measurements.

However, dietary estimates of micronutrient intake can capture a mean intake over a longer period of time (typically 1 year), while the biomarker measurement reflects the level of that micronutrient according to its half-life (on average 1–3 months for carotenoids [45]), although some studies suggest a shorter half-life of 1 week to 2 months [46]. However, given relatively stable dietary intake, even a short half-life may be consistent with a level of reliability that is sufficient for appropriate ranking of participants.

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 confidence intervals.

Moreover, the considerations made for the statistical handling of data apply also to biomarker studies (see STROBE-ME recommendations, item ME-12: describe how biomarkers were introduced into statistical models) with some extra addition about specific bias potentially introduced in molecular epidemiological studies [47]. Ideally, consistency between micronutrient dietary measurement and their blood measurement would reinforce the notion of a true association between dietary intake and the outcome considered. Absence of an association

with dietary intake in the presence of an association with blood levels could still point to a true underlying association of the marker of interest with risk due to, for instance, between-subject differences in bioavailability and absorption.

The lack of reporting of measures of associations in some studies might introduce a publication bias as these studies might have been more likely to have found results of the association between micronutrient and risk of PD closer to unity compared to studies reporting a risk estimate. We deliberately chose not to pool crude estimates of means as these are unadjusted for potential confounders and therefore not directly comparable with adjusted OR and HR.

The paucity of studies included in the meta-analysis meant that the pre-specified sensitivity analyses were not feasible. Restriction of the studies to those less likely to be subject to bias did not yield a clearer picture, with the exception of reducing the magnitude of the inverse association between β -carotene and PD in case-control studies

after excluding the studies by Miyake and al. [19] and Hellenbrand et al. [22] (results not shown).

It was not possible to draw definitive conclusions on the role of vitamin A and carotenoids on PD from the current evidence. High-quality, large-cohort studies (and ideally case-control studies nested in these cohorts using pre-diagnostic exposure measurements) and population-based case-control studies recruiting incident cases are needed in order to epidemiologically assess these biologically plausible associations. The use of biomarkers for validating specific dietary tools for estimating vitamin intake should be particularly encouraged as it would allow the correction for measurement error and increase the chances of detecting modest, but important associations.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Lees AJ, Hardy J, Revesz T: Parkinson's disease. *Lancet* 2009;373:2055–2066.
- 2 Shulman JM, De Jager PL, Feany MB: Parkinson's disease: genetics and pathogenesis. *Annu Rev Pathol* 2011;6:193–222.
- 3 Trumbo P, Yates AA, Schlicker S, Poos M: Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc* 2001;101:294–301.
- 4 Tafti M, Ghyselinck NB: Functional implication of the vitamin A signaling pathway in the brain. *Arch Neurol* 2007;64:1706–1711.
- 5 MacDonald PN, Bok D, Ong DE: Localization of cellular retinol-binding protein and retinol-binding protein in cells comprising the blood-brain barrier of rat and human. *Proc Natl Acad Sci USA* 1990;87:4265–4269.
- 6 Craft NE, Haitema TB, Garnett KM, Fitch KA, Dorey CK: Carotenoid, tocopherol, and retinol concentrations in elderly human brain. *J Nutr Health Aging* 2004;8:156–162.
- 7 Borrelli E, Chambon P: Control of transcription and neurological diseases. *Mol Psychiatry* 1999;4:112–114.
- 8 Samad TA, Krezel W, Chambon P, Borrelli E: Regulation of dopaminergic pathways by retinoids: activation of the D2 receptor promoter by members of the retinoic acid receptor-retinoid X receptor family. *Proc Natl Acad Sci USA* 1997;94:14349–14354.
- 9 Krezel W, Ghyselinck N, Samad TA, Dupe V, Kastner P, Borrelli E, Chambon P: Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. *Science* 1998;279:863–867.
- 10 Smith D, Wagner E, Koul O, McCaffery P, Drager UC: Retinoic acid synthesis for the developing telencephalon. *Cereb Cortex* 2001;11:894–905.
- 11 Levesque D, Rouillard C: Nur77 and retinoid X receptors: crucial factors in dopamine-related neuroadaptation. *Trends Neurosci* 2007;30:22–30.
- 12 Ishihara L, Brayne C: A systematic review of nutritional risk factors of Parkinson's disease. *Nutr Res Rev* 2005;18:259–282.
- 13 Etminan M, Gill SS, Samii A: Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. *Lancet Neurol* 2005;4:362–365.
- 14 Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *J Clin Epidemiol* 2009;62:1006–1012.
- 15 Wells GA, B Shea, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- 16 Greenland S, Longnecker MP: Methods for trend estimation from summarized dose-response data, with applications to metaanalysis. *Am J Epidemiol* 1992;135:1301–1309.
- 17 Paganini-Hill A: Risk factors for Parkinson's disease: the leisure world cohort study. *Neuroepidemiology* 2001;20:118–124.
- 18 Johnson CC, Gorell JM, Rybicki BA, Sanders K, Peterson EL: Adult nutrient intake as a risk factor for Parkinson's disease. *Int J Epidemiol* 1999;28:1102–1109.
- 19 Miyake Y, Fukushima W, Tanaka K, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M: Dietary intake of antioxidant vitamins and risk of Parkinson's disease: a case-control study in Japan. *Eur J Neurol* 2011;18:106–113.
- 20 Zhang SM, Hernan MA, Chen H, Spiegelman D, Willett WC, Ascherio A: Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. *Neurology* 2002;59:1161–1169.
- 21 Scheider WL, Hershey LA, Vena JE, Holmlund T, Marshall JR, et al: Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease. *Mov Disord* 1997;12:190–196.
- 22 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;47:644–650.

- 23 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;60:1761–1766.
- 24 Anderson C, Checkoway H, Franklin GM, Beresford S, Smith-Weller T, Swanson PD: Dietary factors in Parkinson's disease: the role of food groups and specific foods. *Mov Disord* 1999;14:21–27.
- 25 RevMan, 2013. <http://ims.cochrane.org/revman>.
- 26 Tanaka K, Miyake Y, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M: Intake of Japanese and Chinese teas reduces risk of Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:446–450.
- 27 Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M: Lack of association of dairy food, calcium, and vitamin D intake with the risk of Parkinson's disease: a case-control study in Japan. *Parkinsonism Relat Disord* 2011;17:112–116.
- 28 Abbott RD, Ross GW, White LR, Sanderson WT, Burchfiel CM, Kashon M, Sharp DS, Masaki KH, Curb JD, Petrovitch H: Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia aging study. *J Neurol* 2003;250(suppl 3):III30–III39.
- 29 Paraskevas GP, Kapaki E, Petropoulou O, Anagnostouli M, Vagenas V, Papageorgiou C: Plasma levels of antioxidant vitamins C and E are decreased in vascular parkinsonism. *J Neurol Sci* 2003;215:51–55.
- 30 Foy CJ, Passmore AP, Vahidassr MD, Young IS, Lawson JT: Plasma chain-breaking antioxidants in Alzheimer's disease, vascular dementia and Parkinson's disease. *QJM* 1999; 92:39–45.
- 31 de Rijk MC, Breteler MM, den Breeijen JH, Launer LJ, Grobbee DE, van der Meche FG, Hofman A: Dietary antioxidants and Parkinson disease: the Rotterdam study. *Arch Neurol* 1997;54:762–765.
- 32 Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R: Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. *Ann Neurol* 1996; 39:89–94.
- 33 Jimenez-Jimenez FJ, Molina JA, Fernandez-Calle P, Vazquez A, Cabrera-Valdivia F, Catalan MJ, Garcia-Albea E, Bermejo F, Codoceo R: Serum levels of beta-carotene and other carotenoids in Parkinson's disease. *Neurosci Lett* 1993;157:103–106.
- 34 Abbott RA, Cox M, Markus H, Tomkins A: Diet, body size and micronutrient status in Parkinson's disease. *Eur J Clin Nutr* 1992;46: 879–884.
- 35 King D, Playfer JR, Roberts NB: Concentrations of vitamins A, C and E in elderly patients with Parkinson's disease. *Postgrad Med J* 1992;68:634–637.
- 36 Jimenez-Jimenez FJ, Molina JA, Fernandez-Calle P, Vazquez A, Pondal M, del Ser T, Gomez-Pastor A, Codoceo R: Serum levels of vitamin A in Parkinson's disease. *J Neurol Sci* 1992;111:73–76.
- 37 Durrieu G, ME LL, Rascol O, Senard JM, Rascol A, Montastruc JL: Parkinson's disease and weight loss: a study with anthropometric and nutritional assessment. *Clin Auton Res* 1992; 2:153–157.
- 38 Okubo H, Miyake Y, Sasaki S, Murakami K, Tanaka K, Fukushima W, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Shimada H, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M, et al: Dietary patterns and risk of Parkinson's disease: a case-control study in Japan. *Eur J Neurol* 2012;19:681–688.
- 39 Aden E, Carlsson M, Poortvliet E, Stenlund H, Linder J, Edstrom M, Forsgren L, Haglin L: Dietary intake and olfactory function in patients with newly diagnosed Parkinson's disease: a case-control study. *Nutr Neurosci* 2011;14:25–31.
- 40 von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–349.
- 41 Al-Delaimy WK, Ferrari P, Slimani N, et al: Plasma carotenoids as biomarkers of intake of fruits and vegetables: individual-level correlations in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Clin Nutr* 2005;59:1387–1396.
- 42 Jenab M, Riboli E, Ferrari P, et al: Plasma and dietary carotenoid, retinol and tocopherol levels and the risk of gastric adenocarcinomas in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 2006; 95:406–415.
- 43 Vioque J, Navarrete-Munoz EM, Gimenez-Monzo D, Garcia-de-la-Hera M, Granado F, Young IS, Ramon R, Ballester F, Murcia M, Rebagliato M, Iniguez C: Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. *Nutr J* 2013;12:26.
- 44 Johnson EJ, R Vishwanathan, Scott TM, Schalch W, Witwer J, Hausman DB, Davey A, Johnson MA, Green RC, Gearing M, Poon LW: Serum carotenoids as a biomarker for carotenoid concentrations in the brain. *FASEB J* 2011;25:344.2.
- 45 Burri BJ, Neidlinger TR, Clifford AJ: Serum carotenoid depletion follows first-order kinetics in healthy adult women fed naturally low carotenoid diets. *J Nutr* 2001;131:2096–2100.
- 46 Jansen MC, Van Kappel AL, Ocke MC, Van 't Veer P, Boshuizen HC, Riboli E, Bueno-de-Mesquita HB: Plasma carotenoid levels in Dutch men and women, and the relation with vegetable and fruit consumption. *Eur J Clin Nutr* 2004;58:1386–1395.
- 47 Gallo V, Egger M, McCormack V, Farmer PB, Ioannidis JP, Kirsch-Volders M, Matullo G, Phillips DH, Schoket B, Stromberg U, Vermeulen R, Wild C, Porta M, Vineis P: Strengthening the Reporting of Observational Studies in Epidemiology – Molecular Epidemiology (STROBE-ME): an extension of the STROBE statement. *PLoS Med* 2011; 8:e1001117.