Association of dietary niacin and tryptophan intake with the risk of Parkinson´s Disease in the EPIC4ND cohort

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Abstract

Background: Parkinson's disease (PD) is a disabling and currently incurable neurodegenerative disorder with a rapidly increasing global prevalence. Mitochondrial dysfunction is increasingly implicated in PD, with nicotinamide adenine dinucleotide (NAD) playing a crucial role. Given the growing number of clinical trials evaluating NAD augmentation therapies, we investigated whether dietary intake of niacin and tryptophan, major dietary precursors of NAD, is associated with incident PD.

Method: We investigated a sub-cohort of the EPIC study, EPIC4ND, comprising 494 incident PD cases among 130,622 participants. Dietary intakes were estimated by Food Frequency Questionnaires. Cox proportional hazards models, both crude and multivariable-adjusted, assessed potential associations between baseline dietary niacin and tryptophan intake and PD risk in all participants and in sex-stratified analyses.

Results: No significant associations were found in the unstratified cohort. In men, lower niacin intake (<20 mg/day) was associated with an increased risk of PD compared to higher intake (>32 mg/day) (HR_{Q1vsQ4} 1.52, 95% CI 1.04-2.24) in the multivariable model. In women, tryptophan intake in the lowest and third quartiles was associated with a lower risk of PD in the non- and age and center-adjusted models (HR_{Q1vsQ4}: 0.62, 95% CI: 0.41-0.95; HR_{Q3vsQ4}: 0.66, 95% CI: 0.44-0.97).

Conclusion: In the unstratified cohort, no associations were found. While a higher risk was observed in men with the lowest niacin intake, these findings were not dose-dependent nor robust to different censoring windows and should be interpreted with caution. More research is needed to confirm these findings and investigate potential sex-specific effects.

Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder and one of the most rapidly growing causes of neurological disability worldwide [1, 2]. Pathologically, PD is characterized by degeneration of the dopaminergic neurons of the substantia nigra pars compacta, as well as multiple other neuronal populations across the central and autonomic nervous systems, in the presence of intraneuronal α-synuclein-positive inclusions termed Lewy pathology [3, 4]. At molecular level, PD is associated with mitochondrial dysfunction, oxidative stress, aberrant proteostasis, and neuroinflammation [3, 5, 6]. Among these processes, mitochondrial impairment has emerged as an integral driver of neuronal vulnerability in PD [7–10].

Mitochondrial function is critically dependent on nicotinamide adenine dinucleotide (NAD), a key redox cofactor that constantly cycles between its oxidized (NAD^+) and reduced (NADH) states. Furthermore, NAD plays a key role in vital signaling processes, including DNA repair, histone and other protein deacylation, calcium homeostasis, and the generation of second messengers [11]. It has been shown that NAD levels decline with aging, the strongest risk factor for PD, and this age-dependent decline may be more pronounced in men [11–13].

These findings have stimulated considerable interest in NAD augmentation as a therapeutic strategy. Preclinical research indicates that increasing intracellular NAD levels can improve mitochondrial function and confer neuroprotection in models of aging and neurodegeneration [14]. Multiple clinical studies in healthy individuals have shown that treatment with oral nicotinamide riboside (NR), a biosynthetic precursor for NAD, increases NAD levels in blood and muscle and decreases levels of circulating inflammatory cytokines [15–18]. Moreover, clinical trials with NR in PD have confirmed target penetration and engagement, demonstrating augmentation of NAD metabolism in the patient's central nervous system, accompanied by changes in cerebral metabolism and signals of clinical improvement [19–21].

In humans, NAD is either produced de novo from the essential amino acid tryptophan via the kynurenine pathway or via salvage pathways from three NAD precursor compounds: nicotinamide, nicotinic acid, and NR [22]. Nicotinamide and nicotinic acid are collectively referred to as niacin, also known as vitamin B3, while NR is considered a vitamin B3-related precursor rather than a part of the classical niacin group. This precursor contribution is only part of the total NAD pool. Endogenous synthesis, salvage pathways, and tissue-specific regulation maintain NAD levels within relatively narrow ranges, which may limit the impact of habitual dietary intake on systemic NAD availability. Despite growing interventional evidence supporting NAD augmentation in PD, the potential role of habitual dietary intake of NAD precursors in PD risk remains largely unexplored. A retrospective case-control study from 1996 suggested an inverse association between niacin intake and PD [23], but prospective data are lacking.

Given the growing biological rationale linking mitochondrial dysfunction, NAD metabolism, and PD, and emerging clinical interest in NAD augmentation therapies, we aimed to investigate whether dietary intake of niacin and tryptophan is associated with incident PD in the large, multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) cohort for neurodegenerative diseases (EPIC4ND), a sub-cohort of EPIC. Because of PD incidence and NAD biology differ by sex, we also prespecified sex stratified analysis.

Participants and Method

Study Population

The EPIC cohort is a multicenter study across ten European countries, which enrolled 521,323 participants between 1992 and 2000. The cohort study aims to investigate the association between nutrition, lifestyle, cancer, and other chronic diseases. At baseline, comprehensive questionnaires covering environmental and behavioral domains were administered, blood samples were collected, and anthropometry was assessed. Participants are actively and/or passively followed up for incident disease occurrence and deaths, with methods varying by study center. The EPIC study was ethically approved by the International Agency for Research on Cancer (IARC) and the respective participating centers, and written informed consent was obtained from the participants at baseline. Details can be found in the EPIC study populations and data collection reference [24].

To investigate the relationship between potential risk factors and the development of neurodegenerative diseases, including PD, the EPIC4ND was created as a sub-cohort of EPIC. The EPIC4ND cohort comprises 220,492 participants from 13 of the 23 EPIC centers across seven of the ten EPIC countries. For the present study, we included 130,622 participants from the Netherlands (Utrecht), Germany (Heidelberg), the UK (Cambridge), Spain (Navarra, San Sebastian, Murcia), and Italy (Turin, Varese, Florence, Naples), as participants from Greece (n = 27,514) and Sweden (n = 53,813) had to be excluded due to GDPR issues. The cohorts from Naples and Utrecht encompass females, whereas the other centers include both men and women. A total of 8,543 participants were excluded from the current project due to missing data on dietary variables or an implausible energy intake-to-energy requirement ratio (top and bottom 1%), as shown in Fig. 1.

Parkinson´s Disease Ascertainment

A PD template was developed for clinical data collection, based on which a final diagnosis of PD and related disorders were made. Ascertainment consisted of two phases. In Phase I, potential cases were identified through record linkage with at least one local source to minimize the likelihood of false negatives. Hospital discharge registries, drug databases, mortality records, questionnaires, and other sources were used for record linkage. Further in phase II, the potential cases were reviewed by specialists in movement disorders, and a final diagnosis was established. Each diagnosis was labelled with an EPIC4ND label (“definite”, “very likely”, “probable” or “possible”), which depended on the amount and data quality (“poor”, “good” or “excellent”) and the extent of confidence of the neurologist expert (“low”, “medium” and “high”). Details can be found in Gallo et al. [25].

Dietary Intake Assessments

At baseline, dietary data were collected using different assessment methods across the centers and countries. In Italy, the UK, the Netherlands, and Germany, semi-quantitative Food Frequency questionnaires (FFQs) were used to estimate intake frequency and individual portion size, which were self-administered. In Spain, a face-to-face dietary history structured by meals was administered [26].

Energy, Niacin and tryptophan intake were derived from the U.S. Department of Agriculture (USDA) food composition tables, which report on niacin (mg) and not niacin equivalents, and adapted for EPIC according to established ENDB procedures [29]. If foods were unavailable in the national databases, nutrient values were approximated using recipe calculations, adjusting for weight changes and vitamin/mineral losses [28].

Non-dietary variables

Standardized and validated questionnaires on education, socio-economic status, occupation, previous illness, disorders or surgeries; tobacco use, alcohol consumption, physical activity, menstrual and reproductive history, use of hormone contraception, and postmenopausal replacement therapy were administered. Height, weight, and waist-hip circumference were measured at baseline in all EPIC4ND

centers, expect for UK where they were self-reported, and the body mass index (BMI, in kg/m²) derived thereof [24].

Statistical analysis

All statistical analyses were performed using R software version 4.3.1 (R Project for Statistical Computing, RRID: SCR_001905). Statistical significance was set at $\alpha = 0.05$. Descriptive statistics were separately calculated for non-PD subjects and incident PD cases, with medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables.

A Cox proportional hazards model with age as the underlying time scale was used to estimate hazard ratios (HRs) for PD risk, with continuous or categorical niacin and tryptophan intake, in crude, basic, and multivariable-adjusted models. Niacin and tryptophan were modeled as continuous per standard deviation (SD) decrease and as categorical, with sex-specific quartiles based on non-cases, with the fourth quartile used as the reference.

The 'basic' model was adjusted for age at recruitment in years, sex, and center. Covariates for the multivariable model were selected based on epidemiological risk factors from the literature or their relation to niacin and tryptophan. In addition, the fully adjusted model was adjusted for continuous variables, age at recruitment, BMI, coffee consumption (g/day) and energy intake (kcal/day), and dummy-coded variables sex, highest education level (none, primary school, technical/professional school, secondary school, longer education, or not specified), physical activity (inactive, moderately inactive, moderately active, active, or not specified), smoking history (never, current (1-15cig/day), current (16-25cig/day), current (+ 26 cig/day), former (quit < = 10years), former (quit 11-20years), former (quit > 20 + years), current (pipe, cigar/occasionally), current/former missing or unknown), alcohol consumption (g/d).

To reduce potential reverse causation bias, PD cases diagnosed within the first five and ten years after baseline were censored. To account for sex differences in associations, we also ran analyses stratified by sex.

Results

Baseline Characteristics

Selected baseline characteristics of EPIC4ND participants are displayed in **Table 1**. The median time from baseline to PD diagnosis was 14 years (IQR, 12-16), with a median age at diagnosis of 76 years. Of the 130,622 participants, 494 (0.4%) were diagnosed with PD during that time, 61 had a definite diagnosis, 205 were very likely to have PD, 73 were probable, and 155 had a possible diagnosis. Sixty-six percent of the EPIC4ND study population were women, reflecting the inclusion of two female-only centers. PD cases nevertheless showed a slight male predominance (55%), in line with the diseases

known sex distribution. On average, niacin intake met the recommended intake in men (16–18 mg/d) and women (13–14 mg/d). Similarly, tryptophan intake met the daily recommended intake in men (360–450 mg/d) and women (310–385 mg/d).

Associations of niacin and tryptophan intake with risk of PD

In the unstratified cohort, neither niacin nor tryptophan intake was associated with Parkinson's disease (PD) risk in the basic or multivariable-adjusted models (Table 2). This null finding was consistent in both the continuous and quartile-based analyses.

For niacin, the continuous model showed no association with PD after adjustment. Crude analyses suggested lower PD risk in the first and second quartiles and per-SD decrease, but these patterns did not persist after accounting for confounders and did not indicate a dose–response relationship.

For tryptophan, crude models showed inverse associations across lower quartiles and per-SD decrease. After adjusting for age, sex, and center, only the lowest quartile and a one-SD increase remained statistically significant, but all associations disappeared in the fully adjusted model, and the quartile pattern did not suggest a consistent dose–response.

Sensitivity analyses excluding PD cases diagnosed within five and ten years after recruitment showed only minimal changes in HR (**Online Resource, Table S1 and S2).**

Associations of niacin and tryptophan intake with risk of PD, stratified by sex

In the sex-stratified analyses, we observed several associations between niacin and tryptophan intake and PD risk in unadjusted models; however, these patterns did not persist after multivariable adjustment, except for a higher PD risk among men in the lowest niacin quartile (Table 3).

Among men, the fully adjusted model showed that those in the lowest niacin quartile had a higher PD risk than those in the highest quartile (HRQ1 vs Q4: 1.52; 95% CI, 1.04–2.24), and no dose–response pattern was observed across the intermediate quartiles. No adjusted associations remained for tryptophan.

Among women, lower niacin and tryptophan intake were associated with reduced PD risk in crude analyses, both in the continuous and quartile models. These associations weakened after basic adjustment, and in the multivariable model, there was no evidence of independent associations for either nutrient.

Sensitivity analyses excluding PD cases diagnosed within five years of baseline abolished the association between niacin intake and PD risk in men (**Online Resource, Table S3)**. However, the association re-emerged when excluding cases diagnosed within ten years, with a higher HR compared to the primary analysis (**Online Resource, Table S4**).

Discussion

In this large prospective cohort study, we found no significant association between dietary niacin or tryptophan intake and incident PD in the overall population. However, some sex-specific patterns were observed, but these were not fully consistent and should be interpreted with caution and not be viewed as conclusive. In men, lower niacin intake (< 20 mg/day) was associated with a 52% higher risk of PD in fully adjusted models, whereas no consistent associations were observed in women. For tryptophan, associations observed in unadjusted and minimally adjusted models did not survive after multivariable adjustment.

To our knowledge, this is the first prospective cohort study to have investigated the association between dietary niacin and tryptophan and the risk of PD. In contrast to the only case-control study from 1996 [23] reporting a universal association between niacin intake and PD, our study found an association only in men. This discrepancy may reflect differences in study design, as the case-control study relied on retrospective self-reported intake among already-diagnosed participants. A prospective design generally reduces the risk of reverse causality, which is particularly relevant in PD, due to prodromal symptoms, medication use, and disease-related lifestyle changes influencing dietary habits. Furthermore, a prospective assessment minimizes the risk of differential exposure misclassification.

Our data suggest that the role of niacin intake in PD may be sex-dependent, preferentially affecting men and that the preventive effect of niacin at standard diet levels may be limited to certain thresholds. The mechanisms underlying this observation remain unknown and merit preclinical and prospective clinical research. It is possible that the absence of estrogen-mediated neuroprotection in men renders them more susceptible to the metabolic benefits of niacin-derived NAD [30, 31], a notion supported by experimental evidence indicating that men exhibit a steeper age-related decline in NAD levels and greater oxidative and metabolic stress than women [32–34].

Although associations between tryptophan intake and PD risk were not statistically significant in fully adjusted models, we observed trends in crude analyses suggesting higher risk with higher intake. One potential mechanistic explanation involves the kynurenine pathway and the hypothesis that a high-tryptophan environment may fuel neuroinflammation via increased flux through the kynurenine pathway, leading to accumulation of neurotoxic metabolites, such as quinolinic acid and 3-hydroxykynurenine.Accumulation of such compounds may outweigh the potential neuroprotective benefits of NAD [35, 36] At the same time, it is important to note that dietary tryptophan is strongly regulated by intestinal transport, first-pass liver metabolism, and modulation by the gut microbiota. Therefore, dietary intake may be a relatively crude proxy for the relevant central kynurenine dynamics.

Strengths and limitations

This study provides new prospective evidence on the association between dietary NAD precursors and risk of PD, conducted in a multinational European cohort with over 130,000 participants and ~ 500 incident PD cases. Case ascertainment was based on validated PD diagnoses following standardized procedures [25], which strengthens confidence in outcome classification. The long follow-up period (median 13.8 years to diagnosis, with up to 30 years of follow-up) enhances temporal separation between exposure assessment and diagnosis, although it does not fully eliminate concerns about prodromal influences.

However, this study also has several limitations. First, although the follow-up is long, the prodromal phase of PD may extend 20 years or more, meaning that reverse causation cannot be fully excluded. The prospective design, exclusion of early follow-up, and large sample size reduce these concerns, but do not eliminate them.

Second, dietary data were obtained only from the baseline dietary assessment. Dietary habits likely change over time, including due to early nonmotor symptoms of PD, and we were unable to capture such changes. We also lacked information on supplements containing niacin or tryptophan, limiting the analysis to food-derived nutrient intakes. However, given the period of baseline assessment and the limited focus on niacin at that time, we expect supplement use to be low, and amino acid supplements were not widely consumed [37].

Third, nutrient intake was based on self-reported FFQs, even though they were validated, and the intake was calculated using the USDA database rather than a European database, which may have led to over- or underestimation. Further, dietary intake data may include outliers that distort results, though we have excluded participants with implausible energy intake.

Conclusion

These findings suggest no overall association between dietary niacin or tryptophan intake and PD risk. However, lower niacin intake was associated with higher PD risk in men, suggesting possible sex-specific effects. Although this finding was neither dose-dependent across quartiles nor robust to different censoring windows, it should be interpreted with caution. Further studies should focus on stratifying by sex and intake levels of niacin and tryptophan, and should account for dietary supplements.

Declarations

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Ethical approval: The studies involving human participants were reviewed and approved by the IARC Ethics Committee (IEC).

Consent to participate: The patients/participants provided their written informed consent to participate in this study.

Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of International Agency for Research on Cancer / World Health Organization.

Data availability EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of the International Agency for Research on Cancer (IARC), WHO, and the EPIC centres. The primary responsibility for accessing the data, obtained in the frame of the present publication, belongs to the EPIC centres that provided them. Access to EPIC data can be requested to the EPIC Steering Committee, as detailed in the EPIC-Europe Access Policy.

Author contributions

Conceptualization: Sina-Isabel Warz, Jutta Dierkes and Charalampos Tzoulis. Methodology: Sina-Isabel Warz, Verena A. Katzke and Jutta Dierkes. Formal analysis and Writing – original draft: Sina-Isabel Warz. Interpretation: Sina-Isabel Warz, Verena A. Katzke, Jutta Dierkes, Christina M. Lill and Charalampos Tzoulis. Supervision: Jutta Dierkes, Verena A. Katzke and Charalampos Tzoulis. Writing – review and editing: All authors

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Figures

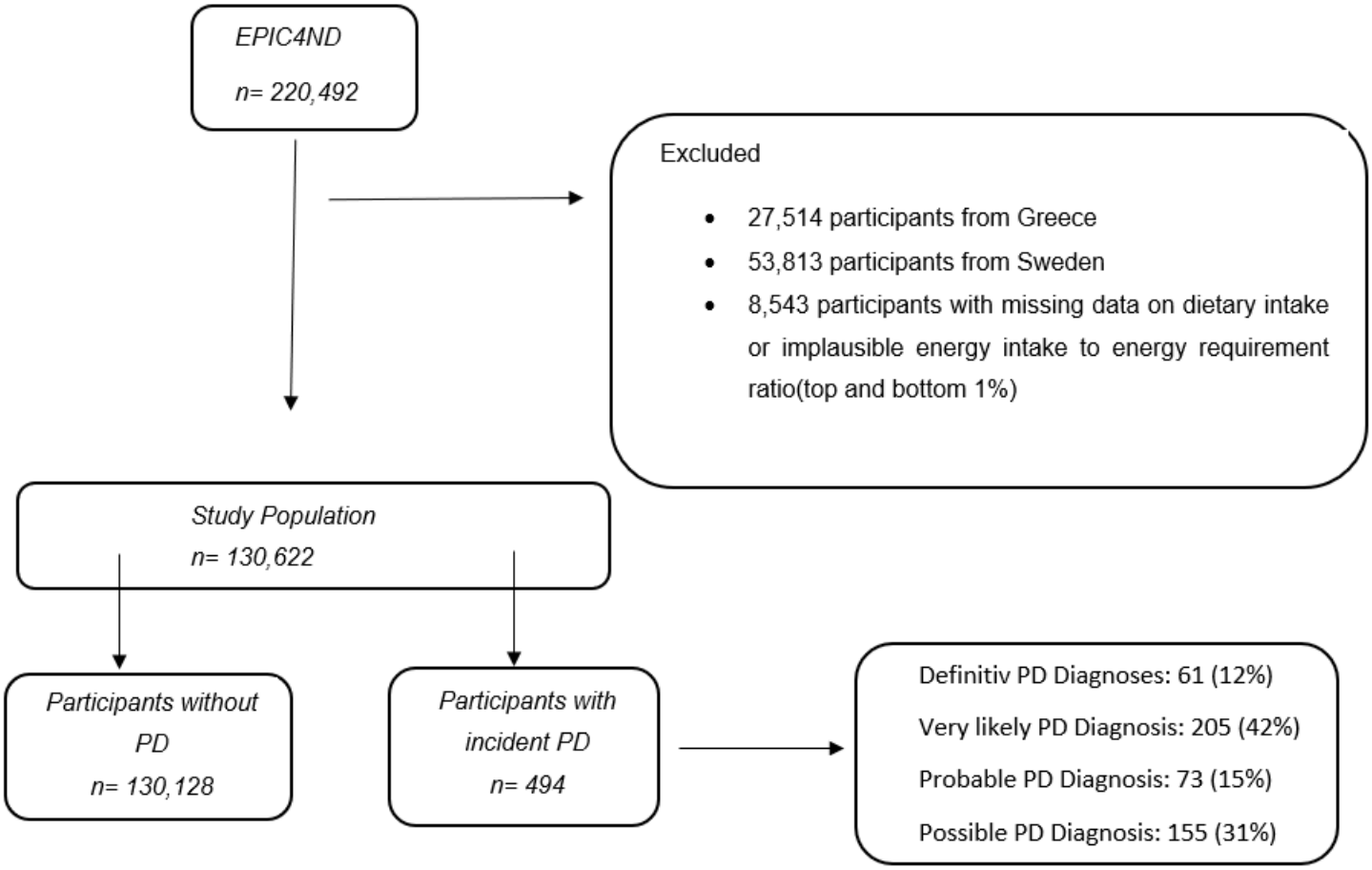

Figure 1

Flowchart of cohort participants included in the study

Supplementary Files

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