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Association of Physical Activity and Parkinson Disease in Women: Long-term Follow-up of the E3N Cohort Study

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Abstract

Background and Objectives: Previous cohort studies reported that a single measure of physical activity (PA) assessed at baseline was associated with lower Parkinson's disease (PD) incidence, but a meta-analysis suggested that this association was restricted to men. Due to the long prodromal phase of the disease, reverse causation could not be excluded as a potential explanation. Our objective was to study the association between time-varying PA and PD using lagged analyses to address the potential for reverse causation, and to compare PA trajectories in patients prior to diagnosis and matched controls.

Methods: We used data from E3N (1990-2018), a cohort study of women affiliated with a national health insurance plan for persons working in education. PA was self-reported in six questionnaires over the follow-up. As questions changed across questionnaires, we created a time-varying latent PA (LPA) variable using latent-process mixed models. PD was ascertained using a multistep validation process based on medical records, or a validated algorithm based on drug claims. We set-up a nested case-control study to examine differences in LPA trajectories using multivariable linear mixed models with a retrospective time scale. Cox proportional hazards models with age as the timescale and adjusted for confounders were used to estimate the association between time-varying LPA and PD incidence. Our main analysis used a 10y-lag to account for reverse causation; sensitivity analyses used 5y, 15y, and 20y-lags.

Results: Analyses of trajectories (1,196 cases, 23,879 controls) showed that LPA was significantly lower in cases than in controls throughout the follow-up, including 29y before diagnosis; the difference between cases and controls started to increase ~10y before diagnosis (P-interaction=0.003). In our main survival analysis, of 95,354 women free of PD in 2000, 1,074 women developed PD over a mean follow-up of 17.2y. PD incidence decreased with increasing LPA (P-trend=0.001), with 25% lower incidence in those in the highest quartile compared to the lowest (adjusted hazard ratio=0.75, 95% confidence interval=0.63-0.89). Using longer lags yielded similar conclusions.

Discussion: Higher PA level is associated with lower PD incidence in women, not explained by reverse causation. These results are important for planning interventions for PD prevention.

Introduction

Parkinson's disease (PD) is the fastest growing neurological disorder in terms of prevalence, disability, and deaths, making prevention an urgent public health need in the absence of curative treatments.[1] Physical activity represents a modifiable health behavior with major benefits for multiple outcomes.[2] A few cohort studies examined the association between physical activity and PD incidence, with inconsistent results.[3-9] A meta-analysis of eight studies estimated that participants with the highest physical activity level, defined in different ways across studies, had 21% lower PD incidence.[10] This inverse association was statistically significant in men and weaker and not significant in women; however, only four studies examined this association in women. Determining whether physical activity plays a role in women is important for developing appropriate interventions.[11]

Reverse causation refers to situations in which the undiagnosed outcome precedes and leads to changes in exposures instead of the other way around.[12] It represents a key issue for the interpretation of the relation between physical activity and PD.[13] Non-motor symptoms (e.g., constipation, sleep disorders) and subtle motor signs (e.g., tremor, balance impairment, rigidity) can be present several years prior to PD diagnosis.[14,15] Hence, PD patients may reduce physical activity during the prodromal phase as a consequence of prodromal symptoms. To address this issue, some previous cohort studies excluded cases over the first 4-10y of the follow-up.[3,5-8] While findings were generally consistent with an inverse association, only one study reported a significant association.[7] Therefore, larger cohorts with longer follow-ups are needed to assess whether reverse causation contributes to the inverse association between physical activity and PD. Additionally, none of the previous studies used repeated physical activity measures, whereas analyses of physical activity trajectories prior to PD diagnosis would help understand the temporal relation between physical activity and PD.

Our aim is to examine the association between time-varying physical activity measures and PD incidence in women from the E3N cohort study over 29y of follow-up, while addressing the potential for reverse causation. We also used a nested case-control

design to compare physical activity trajectories in PD patients prior to diagnosis and matched controls.

Materials and methods

E3N study

We used data from E3N, an ongoing cohort study of 98,995 French women born between 1925-1950 and recruited in 1990, who were affiliated with a French national health insurance plan that covers mostly teachers (*Mutuelle Générale de l'Education Nationale*).[16]

After providing written informed consent (~20% of invited women), participants completed a self-administered questionnaire on lifestyle and medical history at baseline (Q1-1990). Follow-up questionnaires have been sent every 2-3y. Eleven waves of data collection are available at the present time (latest in 2014, Q11); the average response rate is of ~80% at each questionnaire. Since January 2004, women were also passively followed through healthcare databases (including drug and medical consultation claims). Causes of death were available.

Standard Protocol Approvals, Registrations, and Patient Consents

All women signed informed consent in compliance with the rules of the French National Commission for Data Protection and Privacy, from which approval was obtained. The study protocol is registered at clinicaltrials.gov (NCT03285230).

Ascertainment of Parkinson's disease patients

We provide a detailed description of PD ascertainment in E3N elsewhere.[17] Briefly, potential PD cases were identified through self-reported doctor-diagnoses of PD in follow-up questionnaires, antiparkinsonian drug claims until December 2018, and death certificates. Potential PD patients were contacted to confirm the PD diagnosis when possible by mail. For women who confirmed a diagnosis of PD or parkinsonism and for women who could not be contacted (e.g., deceased, contact refusal), we obtained from treating neurologists or general practitioners (GP) detailed medical documentation (year of PD onset and diagnosis, cardinal motor signs and other neurologic symptoms, use of neuroleptics, treatment, responsiveness to treatment, diagnosis). Finally, an expert panel adjudicated PD status (definite, probable, possible, no PD) based on all the medical documentation available.[17] Only definite and

probable PD patients were retained in the analyses. When medical documentation was not available, we used an algorithm based on antiparkinsonian drug claims and medical visits that was previously validated against a clinical diagnosis (94% sensitivity, 88% specificity).[17] Among women who were considered to have PD, the diagnosis was based on medical records for 62% (62% self-reported PD) and the algorithm for 38% (56% self-reported PD).[17]

Year of PD diagnosis was set as the year of diagnosis available in medical records or, in decreasing order of priority, self-reported year of diagnosis, year of first use of antiparkinsonian drugs, and year of the first questionnaire where PD was self-reported.

PD incidence rates in E3N are in agreement with those in women from Western Europe (1992-2018) according to the Global Burden of Disease, which supports the validity of our case ascertainment strategy.[17]

Physical activity

Six questionnaires included physical activity-related questions (1990-Q1, 1993-Q3, 1997-Q5, 2002-Q7, 2005-Q8, 2014-Q11; eTable 1). Physical activity related to different recreational and household activities was assessed over the follow-up in different ways and units, and 11 types of activities were included in at least one questionnaire. MET (metabolic equivalent of task) values were attributed to each activity based on a compendium and expert opinion (eTable 1). For each activity, METs were multiplied by their frequency and duration to obtain a physical activity score (MET-h/week).

The baseline questionnaire (1990-Q1) included six closed-ended questions on recreational physical activity: usual distance walked daily (<500/500-2000/>2000 meters), average number of flights of stairs climbed daily (0/1-4/>5), weekly average time spent in light household activities (0/1-4/5-13/≥14 hours), weekly average time spent in heavy household activities (0/1-4/≥5 hours), weekly average time spent in moderate recreational activity (e.g., light gardening, sports of moderate intensity; 0/1-4/5-13/≥14 hours), and weekly average time spent in vigorous recreational activities (e.g., vigorous sports; 0/1-4/≥5 hours).[18]

In subsequent questionnaires (1993-Q3, 1997-Q5, 2002-Q7, 2014-Q11), physical activity-related questions were derived from a modified version of the Baecke questionnaire.[19,20] The questions assessed the duration (hours/week) that participants spent walking (including walking to work, shopping, and leisure time), cycling (including cycling to work, shopping, and leisure time), and engaging in sports during 2 typical weeks over the past year, one in summer and one in winter. These questionnaires used open-ended questions, allowing women

to provide more detailed information on frequency and duration of each activity than at Q1. In addition, the number of hours practicing each activity was ascertained in the winter and summer, and durations were averaged over the summer and winter. The questionnaire from 2005-Q8 was similar to Q1 but asked open-ended rather than closed-ended questions.

There were five questions in common for Q3, Q5, and Q7; Q5 and Q7 included the same questions; Q8 had four matching questions with Q1; Q11 had four identical questions with Q5 and Q7 (eTable1).

Covariates

Participants' characteristics were collected through follow-up questionnaires. Birth date, education level (</≥ high School), region of residence (French commune categorized into rural/urban according to the French *Institut national de la statistique et des études économiques*),[21] age at menarche (≤11y/12-13y/≥14y), and parity (nulliparous/one child/two children/≥three children) were assessed at baseline (Q1). Menopausal status (premenopausal/natural/artificial/unknown type of menopause) and weight were determined at all waves; height was determined at Q1, Q4 (1994), and Q6-Q11 (2000-2014) and standardized by using the most frequent value. BMI was computed as weight divided by height squared (kg/m²) and categorized into four categories (underweight: <18.5/normal weight: 18.5-24.9/overweight: 25.0-29.9/obese: ≥30.0kg/m²). Information on smoking status (never/ex/current) was collected from Q1 to Q8. Diet, including adherence to the Mediterranean diet, total intake of caffeine (in mg), and daily intake of lactose (in g), was assessed at Q3 (1993) using a validated dietary questionnaire and categorized in quartiles.[22] We used self-reports in E3N questionnaires throughout the follow-up to ascertain comorbidities, including history of hypercholesterolemia, cardiovascular diseases (ischemic heart disease/stroke), and high blood pressure. Type 2 diabetes was ascertained using self-reports in questionnaires before 2004 and antidiabetic drug claims thereafter.

Nested case-control study

In order to compare physical activity trajectories in PD cases and matched controls, we set-up a nested case-control study. Each incident PD case was individually matched to 20 controls using incidence density sampling.[23] To be selected as controls, women had to be alive and at risk of PD at the date of diagnosis of the matched case (index date, T_0) and have the same exact age (rounded to the nearest integer without decimals) at T_0.

Statistical analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC), the lcmm R package (R Foundation for Statistical Computing, Vienna, Austria),[24] and Stata 15.1 (StataCorp, College Station, TX).

Latent physical activity process

When measurement tools of a risk factor change over the follow-up, latent process mixed models (LPMM) allow to include observations from different measurement tools and to define trajectories of a latent process, provided that the tools measure the same quantity. This latent process represents the unmeasured common factor underlying the observations obtained through different tools.[25,26] We aimed at predicting a latent physical activity process for all the participants from the cohort with at least one physical activity assessment (N=98,766) using LPMMs.

In order to link repeated individual physical activity measures (in MET-h/week) obtained from different questionnaires to their common underlying latent process and correct the departure of each activity from a normal distribution, we first selected the best activity-specific parameterized link function (among quadratic I-splines link functions with 2-, 3-, 4-, and 5-knots) according to the Akaike information criterion (AIC) in activity-specific LPMMs. We then included the 11 activities (with the shapes of activity-specific link functions previously determined) in the same LPMM for multivariate longitudinal outcomes, in order to model the latent physical activity trajectory according to age. Age was centered at its mean at Q1 (49y) and change over age was approximated by natural cubic splines with two internal knots (lower AIC). The within-participant correlation was captured by independent random intercept and slopes on the three functions of age.

We finally obtained subject-specific latent physical activity predictions for each subject at each visit based on the best fitting LPMM, which were used in subsequent trajectories and survival analyses.

As it relies on maximum likelihood estimation, the LPMM allows to handle missing values of physical activity under the assumption of missingness at random, i.e., missing values at a given time point can be predicted by the observed values of physical activity and other covariates (age).[27]

Trajectories of latent physical activity in cases and controls

Latent physical activity trajectories from the index time T_0 to the beginning of the study (retrospective timescale) were examined in cases and controls over 29y of follow-up using a linear mixed model. The latent physical activity trajectory was modeled as a function of retrospective time and time squared, and was adjusted for PD status, age at T_0, and two-way interactions of time with PD status and age; it was further adjusted for confounders associated with physical activity and PD, including parity,[28] age at menarche,[28] rural residence,[29] and time-varying smoking[29] and menopausal status.[28] The within participant correlation was captured by correlated random intercept and slopes on time and time squared.

Survival Analysis

We used Cox proportional hazard models for time-varying variables with age as the timescale to estimate hazard ratios (HR), 95% confidence intervals (CI), and two-tailed *P*-values (α=0.05).

To address the potential for reverse causation, we included a lag of increasing duration (5y, 10y, 15y, 20y) between time-varying variables (including latent physical activity) and PD incidence. Given results of the analyses of trajectories described above, we used a 10y-lag for our main analyses: latent physical activity was lagged by 10y and we started the follow-up in 2000 (i.e., 10y after the baseline assessment), so that participants who developed PD before 2000 (prevalent cases) were excluded. Women were followed from 2000 until PD diagnosis or end of follow-up (maximum of the date of the last questionnaire and last drug reimbursement). The same approach was used for other lags.

Latent physical activity was included as time-varying quartiles in the models, and linear trends in HRs were tested through ordinal variables defined by the median of each quartile. We also used restricted cubic splines to test for departures from linearity for continuous latent physical activity. Analyses were adjusted for confounders associated with physical activity and PD, including baseline parity,[28] age at menarche,[28] and rural residence,[29] and time-varying smoking[29] and menopausal status.[28] Missing values were coded as specific categories to retain the same number of participants in all analyses.

We used the Fine-Gray subdistribution hazard model to estimate the cumulative incidence function (CIF) of PD over time in the presence of the competing risk of death.[30] For this analysis, we estimated the CIF of PD as a function of the quartiles of latent physical activity at Q1, with time since the beginning of the follow-up as the time scale and a 10y-lag.

Analyses are adjusted for the same covariates described above and for age at the beginning of the follow-up (restricted cubic splines with 3 knots).

We performed several sets of sensitivity analyses:

- We constructed an alternative latent physical activity variable by excluding the baseline physical activity questions (1990-Q1) that were less precise than subsequent measures.
- In order to examine whether our findings may have been confounded by diet, we performed analyses based on physical activity assessed at Q5 (1997) and adjusted for dietary exposures associated with PD risk that were assessed earlier during the follow-up (1993-Q3; Mediterranean diet, caffeine, dairy intake).[31] Analyses with a lag longer than 10y were not possible due to an insufficient number of cases.
- We performed analyses stratified by median age (72.8y) in order to examine whether associations were similar for PD patients who developed PD before or after that age.
- To examine the influence of the case definition on our findings, we excluded PD patients predicted by the algorithm and performed analyses restricted to cases validated based on medical documentation (definite or probable; definite only). Because we were concerned that the reduced sample size would lead to insufficient statistical power, we performed additional analyses in which, in addition to validated cases, we also retained cases predicted based on a more specific version of the algorithm (90% sensitivity; 90% specificity).[17] For these analyses, we compared PD incidence in the fourth quartile to that in the other three quartiles combined.
- Higher physical activity is associated with lower risk of several comorbidities, including obesity, high blood pressure, dyslipidemia, and cardiovascular disease.[2] Hence, comorbidities may be potential mediators of the association between physical activity and PD. We ran sensitivity analyses adjusted for time-varying BMI, high blood pressure, hypercholesterolemia, diabetes, and cardiovascular disease to examine their contribution to the association between physical activity and PD.

Data availability

Data on E3N cohort participants are available to bona fide researchers for all type of health-related research, which is in the public interest. Data are made available under managed access owing to governance constraints and need to protect the privacy of study participants. Raw data requests should be submitted through the E3N website (www.e3n.fr) or sent to contact@e3n.fr; requests will be reviewed by the E3N Access Committee. Further information is available at https://www.e3n.fr/node/78.

Results

Figure 1 shows a flowchart for inclusion of participants into the study. We excluded 50 possible PD cases, 13 cases without a diagnosis date, 31 prevalent cases at Q1 and 229 women who did not answer physical activity questions at any questionnaire; among the remaining E3N participants, 90% had three measures or more of physical activity during the follow-up, and of these, 80% had five or six measures available.

The number of participants available for survival analyses decreased with increasing lags. For instance, for our main survival analysis (10y-lag), we further excluded 3,193 women whose follow-up ended before 2000 and 125 prevalent PD patients, leaving 95,354 women followed for 19y (mean=17.2, SD=3.3) of whom 1,074 developed PD. Compared to previous studies, our study included the largest number of PD patients and had the longest follow-up (eTable 2).

Table 1 describes baseline (1990-Q1) participant's characteristics. Mean age was 49.3y (SD=6.6) and mean physical activity level was 45.3 (SD=30.1) METs-h/week. Women with later age of menarche, ≥3 children, and who lived in rural areas had higher latent physical activity levels than their counterparts. Women with incident PD were older, less frequently smokers, more frequently postmenopausal, and had later age of menarche and more often ≥3 children than those who remained PD-free (eTable 3).

Trajectories of physical activity preceding Parkinson's disease

Among 25,200 women (1,200 cases, 24,000 age-matched controls) included in the nested case-control study, we excluded 45 women (4 PD cases) for whom physical activity was missing at all visits before T_0, and 80 controls matched to these 4 PD cases, leading to a final sample of 25,075 women (1,196 PD cases, 23,879 controls); 1,156 cases where matched to 20 controls, 39 cases to 19 controls, and 1 case to 18 controls.

eTable 4 describes the characteristics of cases and controls at the index date (T_0). The mean (SD) age of cases and controls was 71.9y (SD=7.8). Compared to controls, PD cases were less often smokers and obese, had more frequently menarche ≤11y or ≥14y and artificial menopause, and had more children.

Figure 2 shows latent physical activity trajectories in cases and controls for the most common profile of covariates and three ages at T_0; eTable 5 presents estimates from the corresponding model.

After an initial increase of latent physical activity in cases and controls, it decreased with a steeper decline in cases than in controls in the 10y before T_0, due to a significant interaction between PD status and time (*P-interaction*=0.003). Cases had a significantly lower physical activity level at T_0 than controls (difference, -0.164, 95% CI, -0.230 to -0.097); this difference decreased over the 10y before T_0, but it remained significant throughout the follow-up, and latent physical activity was significantly lower in than controls 29y before T_0; hence, the difference in latent physical activity between cases and controls was larger at the index date than at the beginning of the study. Based on these findings, we used a 10y-lag for our main survival analysis.

In addition, latent physical activity level decreased with age, increased with the number of children, and it was lower in smokers than non-smokers, in urban compared to rural regions, and in post-menopausal compared to pre-menopausal women.

Physical activity and Parkinson's disease incidence

Figure 3 show the CIF of PD over the follow-up, while taking the competing risk of death into account; the CIF was reduced by 22% (95% CI=7%-34%, P=0.007) in women in the highest quartile of latent physical activity compared to those in the lowest quartile.

Table 2 shows the association between time-varying latent physical activity and PD incidence. In our main analysis (10y-lag), the hazard of PD decreased with increasing physical activity (*P*-trend=0.001), with 25% lower incidence in those in the highest quartile compared to the lowest (HR=0.75, 95% CI=0.63-0.89). The hazard of PD decreased linearly with increasing physical activity level; analyses based on splines showed no departure from linearity (*P*=0.25; Figure 4). Using longer lags yielded similar associations (Table 2); the inverse association was borderline significant for the 20y-lag based on a smaller number of PD cases (*P*-trend=0.06).

Sensitivity analyses adjusted for Mediterranean diet, and caffeine and dairy intake (Table 3) or excluding baseline physical activity assessments (eTable 6) yielded similar results. Analyses stratified by median age showed similar associations in both age groups (eTable 7). In analyses using alternative PD definitions, associations were similar to those from our main analyses (eTable 8). In analysis adjusted for comorbidities that represent potential mediators (BMI, high blood pressure, hypercholesterolemia, diabetes, cardiovascular diseases), the association between physical activity and PD remained unchanged after adjusting for these

covariates that explained a small proportion of the association between physical activity and PD (5.5%) (eTable 9).

Discussion

In this cohort study of ~100,000 French women with six physical activity measures over 29y of follow-up, increasing physical activity was associated with reduced PD incidence, while taking into account the potential for reverse causation. Analyses of physical activity trajectories showed that PD cases had lower physical activity levels than controls 29y before the index date, and that case-control differences in physical activity level increased ~10y prior to diagnosis in agreement with the hypothesis that prodromal PD leads to a reduction in physical activity.

Previous cohort studies on the relation between physical activity and PD yielded inconsistent findings (eTable 2). One meta-analysis (eight studies, 2,192 PD patients) with a median follow-up period of 12y (range=6.1-22.0) showed that physical activity was associated with lower PD incidence in analyses of men and women combined.[10] This association was statistically significant in men and weaker and not significant in women; however, only four studies examined women only (604 PD patients),[3,5-7] and did not adjust for characteristics of reproductive life associated with PD. In addition, no previous study used repeated physical activity measures to take into account changes in physical activity over the follow-up. Five studies performed sensitivity analysis using a lag between physical activity assessment and PD incidence (4y-lag, *n*=3; 8y-lag, *n*=1; 10y-lag, *n*=1), and only one with a 4y-lag showed a significant inverse association, overall and in sex-stratified analyses (198 women with PD).[7] One study showed that moderate-to-vigorous physical activity at ages 35-39 was associated with lower PD risk in men and women,[7] while another found a significant inverse association between higher physical activity level in early adulthood and PD in men but not in women.[3]

The main difference between previous studies and ours is that we identified a considerably larger number of women with incident PD over a longer follow-up allowing us to perform analyses with longer lags while retaining a sufficient number of PD patients. Physical activity trajectories in controls were consistent with decreasing physical activity levels in the elderly.[32] This decline was steeper in cases, with a case-control difference that started to increase ~10y before PD diagnosis, emphasizing the importance of performing lagged analyses to estimate associations between physical activity and PD not biased by reverse causation. Analyses with lags ≥10y confirmed an inverse association between physical activity and PD incidence that was significant for a 15y-lag and borderline significant for a

20y-lag, likely due to the smaller number of cases. Therefore, our findings suggest that reverse causation is unlikely to explain the inverse association between physical activity and PD.

Converging evidence from studies in PD patients, including observational studies[33] and randomized controlled trials,[34,35] suggests that physical activity improves PD motor and non-motor symptoms. In PD patients, aerobic exercise stabilizes disease progression in the cortico-striatal sensorimotor network and enhances cognitive performance.[36] Our results extend these findings and suggest that physical activity may help prevent or delay PD onset, possibly by slowing PD pathological processes, in agreement with one study that showed a reduced prevalence of PD prodromal symptoms in individuals more physically active in midlife.[37] These findings have triggered interest in elucidating the mechanisms that explain beneficial effects of physical activity for PD. Exercise induces recovery of motor function and neuroprotection of dopaminergic neurons in animal models of PD, regulates dopaminergic and glutamatergic transmission, mobilizes neurotrophic factors (BDNF/GDNF), modulates neuro-inflammatory mechanisms, attenuates mitochondrial dysfunction and oxidative stress, and enhances brain plasticity.[38-41] In humans, physical activity has been associated with brain structural and functional changes until late adulthood.[42] In postmenopausal women, higher fitness levels were associated with higher antioxidant enzyme activity and lower levels of oxidative stress.[43]

We examined whether a set of potential mediators (BMI, high blood pressure, hypercholesterolemia, diabetes, cardiovascular diseases) explained part of the relation between physical activity and PD. Our findings are not in favor of this hypothesis because the association between physical activity and PD was little attenuated after adjusting for these covariates. Hence, the potential mediators examined do not seem to be in the causal pathway between physical activity and PD. These findings suggest that the mechanisms involved in the relation between physical activity and PD are independent of these variables and are in favor of a direct protective effect of physical activity, for instance through motor reserve.[44,45]

The main strengths of our study are its large size and long follow-up which allowed us to perform lagged analyses in order to address the potential for reverse causation. We used repeated physical activity measures rather than a single measure, and a method specifically designed to allow longitudinal analyses when measurement tools change over the follow-up.[25] Our approach to ascertain PD patients yielded incidence rates comparable to those in

women from Western Europe, in favor of its validity.[17] Finally, few studies specifically examined the relation between physical activity and PD in women, possibly because PD is more frequent in men than women, while our study focused on this understudied population,[46] and analyses were adjusted for the characteristics of reproductive life.

The main limitation of our study is that we used self-reported physical activity rather than objective measures (e.g., accelerometer) that are considered more valid, although they do not capture all types of physical activity (underestimating, for example, cycling and carrying a load). They are however difficult and costly to implement on a large scale, and only capture physical activity over a few days. Measurement error is inevitable for self-reported physical activity, but is reduced through the estimation of the latent process by the LPMM[26] and is likely to be non-differential and lead to underestimated associations. Recent studies showed that both self-reported and objectively measured physical activity were associated with outcomes such as all-cause and cardiovascular mortality or self-rated health.[47] Second, there was an insufficient number of questions for vigorous and moderate physical activity to generate separate latent variables. Third, our analyses based on time-varying physical activity were not adjusted for diet as it was not recorded at baseline; we performed sensitivity analyses adjusted for dietary characteristics associated with PD, showing that diet was not a strong confounder of the association between physical activity and PD. Fourth, E3N participants are mostly educated and health-conscious teachers who are not representative of the general population. However, it is generally considered that representativeness is not essential for estimating associations, and associations in occupational cohorts are not necessarily different compared to those estimated in the general population.[48,49] Fifth, we did not obtain medical records for all potential PD patients, and used an algorithm based on drug claims with high sensitivity and specificity for those participants to determine PD status. We confirmed the robustness of our main findings using alternative and stricter PD definitions. Last, all the persons who accepted to participate into the study were assigned female at birth; in addition, they accepted to participate to a study aimed at investigating the risk factors associated with cancer and other major non-communicable diseases in women. Our findings cannot be extended to persons who were assigned intersex at birth and to men assigned female at birth.

In conclusion, our findings reinforce the evidence in favor of the health benefits of physical activity and provide stronger evidence than previous studies in favor of an inverse association between physical activity and PD in women not explained by reverse causation. These results

are important for planning interventions for PD prevention,[50] and warrant further studies to understand which type and level of physical activity are beneficial.

WNL-2023-000262_etab --- http://links.lww.com/WNL/C801

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Table 1 Participant's characteristics at baseline (1990-Q1).

		Latent physical activity at baseline[a]			
Baseline characteristics, *n* (%)	**Total 96,665**	**Quartile 1** 24,166 (25.0)	**Quartile 2** 24,166 (25.0)	**Quartile 3** 24,166 (25.0)	**Quartile 4** 24,167 (25.0)
PA (METs-h/wk), M (SD)[a,b]	45.3 (30.1)	27.0 (15.7)	37.3 (18.7)	46.0 (21.7)	70.8 (38.7)
Age (y), M (SD)	49.3 (6.6)	49.9 (6.5)	48.5 (6.4)	48.5 (6.4)	50.5 (7.0)
≤49	56,279 (58.2)	11,035 (53.1)	17,129 (63.3)	16,993 (63.5)	11,122 (50.3)
50-59	31,825 (32.9)	7,804 (37.6)	7,986 (29.6)	7,847 (29.3)	8,188 (37.0)
≥60	8,561 (8.9)	1,941 (9.3)	1,910 (7.1)	1,920 (7.2)	2,790 (12.7)
Education					
<High school diploma	12,815 (13.8)	3,703 (16.0)	2,970 (12.8)	2,807 (12.1)	3,335 (14.4)
≥High school diploma	79,814 (86.2)	19,373 (84.0)	20,210 (87.2)	20,362 (87.9)	19,869 (85.6)
Missing	4,036	1,090	986	997	963
Smoking					
Never	52,014 (53.9)	12,822 (53.1)	12,580 (52.2)	12,850 (53.2)	13,762 (57.0)
Ex	29,911 (31.0)	7,298 (30.2)	7,659 (31.8)	7,707 (32.0)	7,247 (30.0)
Current	14,564 (15.1)	4,012 (16.7)	3,852 (16.0)	3,565 (14.8)	3,135 (13.0)
Missing	176	34	75	44	23
Age at menarche (y), M (SD)	12.8 (1.4)	12.8 (1.4)	12.8 (1.4)	12.8 (1.4)	12.9 (1.4)
≤11	19,761 (20.9)	5,030 (21.4)	4,963 (21.0)	4,942 (21.0)	4,826 (20.4)
12-13	47,656 (50.5)	11,942 (50.7)	12,118 (51.2)	11,892 (50.4)	11,704 (49.5)
≥14	27,002 (28.6)	6,564 (27.9)	6,573 (27.8)	6,734 (28.6)	7,131 (30.1)
Missing	2,246	630	512	598	506
Menopausal status					
Premenopausal	53,531 (57.5)	12,620 (53.7)	14,166 (61.7)	14,568 (62.9)	12,177 (51.6)
Natural menopause	32,520 (34.9)	8,841 (37.6)	7,119 (31.1)	7,058 (30.5)	9,502 (40.2)
Artificial menopause	6,410 (6.9)	1,810 (7.7)	1,436 (6.3)	1,382 (6.0)	1,782 (7.5)
Unknown type of menopause	694 (0.7)	217 (1.0)	200 (0.9)	129 (0.6)	148 (0.7)
Missing	3,510	678	1,245	1,029	558
Parity					
Nulliparous	11,586 (12.1)	3,705 (15.5)	2,865 (11.9)	2,549 (10.6)	2,467 (10.3)
One child	15,571 (16.2)	4,405 (18.4)	4,067 (17.0)	3,701 (15.4)	3,398 (14.2)
Two children	40,724 (42.5)	9,632 (40.3)	10,617 (44.2)	10,722 (44.7)	9,753 (40.6)
≥ 3 children	28,011 (29.2)	6,168 (25.8)	6,449 (26.9)	7,030 (29.3)	8,364 (34.9)
Missing	773	256	168	164	185
Place of residence					
Rural	13,089 (14.8)	2,138 (9.7)	2,844 (12.9)	3,525 (16.0)	4,582 (20.7)
Urban	75,327 (85.2)	19,939 (90.3)	19,233 (87.1)	18,570 (84.0)	17,585 (79.3)
Missing	8,249	2,089	2,089	2,071	2,000
BMI (kg/m^2), M (SD)	22.6 (3.2)	22.9 (3.5)	22.5 (3.1)	22.4 (3.0)	22.6 (3.0)
<18.5	3,995 (4.2)	1,100 (4.7)	1,006 (4.3)	1,011 (4.3)	878 (3.7)
18.5-24.9	73,801 (78.3)	17,537 (74.7)	18,648 (79.0)	18,832 (79.7)	18,784 (79.4)
25-29.9	13,658 (14.5)	3,767 (16.1)	3,247 (13.8)	3,221 (13.6)	3,423 (14.5)
≥30.0	2,860 (3.0)	1,046 (4.5)	693 (2.9)	555 (2.4)	566 (2.4)
Missing	2,351	716	572	547	516
Hypercholesterolemia[c]	36,574 (37.8)	10,763 (38.6)	7,694 (36.4)	7,727 (36.6)	10,390 (39.2)
High blood pressure[c]	28,843 (29.8)	8,966 (32.1)	6,113 (28.9)	6,085 (28.8)	7,679 (29.0)
Diabetes[c]	2,651 (2.7)	1,010 (3.6)	551 (2.6)	497 (2.4)	593 (2.2)
Cardiovascular disease[c]	2,743 (2.8)	1,011 (3.6)	573 (2.7)	527 (2.5)	632 (2.4)

PA, physical activity; M, mean; SD: Standard deviation; BMI, body mass index.

Baseline characteristics are shown for participants available for survival analyses based on a 5y-lag.

[a] Physical activity was not available at baseline for 1,169 women (1.2%); therefore we used the first latent physical activity value available over the follow-up for these women (95% at Q3-1993 or Q5-1997).

[b] Total PA assessed at the baseline questionnaire (1990-Q1).

[c] Assessed at the end of the follow-up.

Table 2 Association of time-varying physical activity with Parkinson's disease incidence.

Latent physical activity	Cases (*n*)	IR	Age-adjusted HR (95% CI)	*P*-value	Multivariable HR (95% CI)[a]	*P*-value
5y-lag (FU 1995-2018; N=96,665)	**1,163**					
Quartile 1	316	0.60	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	304	0.60	1.01 (0.86-1.18)	0.95	0.99 (0.85-1.16)	0.94
Quartile 3	289	0.56	0.96 (0.81-1.12)	0.58	0.94 (0.80-1.11)	0.49
Quartile 4	254	0.45	0.76 (0.64-0.89)	<0.001	0.75 (0.63-0.88)	<0.001
			P-linear trend	<0.001	*P*-linear trend	<0.001
10y-lag (FU 2000-2018; N=95,354)	**1,074**					
Quartile 1	286	0.73	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	274	0.69	0.95 (0.80-1.12)	0.57	0.94 (0.80-1.11)	0.50
Quartile 3	268	0.67	0.93 (0.78-1.10)	0.37	0.92 (0.77-1.08)	0.30
Quartile 4	246	0.55	0.76 (0.64-0.90)	0.002	0.75 (0.63-0.89)	0.001
			P-linear trend	0.002	*P*-linear trend	0.001
15y-lag (FU 2005-2018; N=93,755)	**901**					
Quartile 1	237	0.80	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	229	0.74	0.93 (0.78-1.12)	0.44	0.92 (0.77-1.10)	0.37
Quartile 3	222	0.72	0.90 (0.75-1.08)	0.27	0.89 (0.74-1.07)	0.20
Quartile 4	213	0.63	0.79 (0.66-0.95)	0.01	0.78 (0.64-0.94)	0.008
			P-linear trend	0.01	*P*-linear trend	0.008
20y-lag (FU 2010-2018; N=90,407)	**662**					
Quartile 1	166	0.88	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	178	0.85	0.97 (0.78-1.20)	0.78	0.96 (0.78-1.19)	0.71
Quartile 3	167	0.81	0.92 (0.74-1.14)	0.44	0.90 (0.73-1.12)	0.36
Quartile 4	151	0.73	0.83 (0.67-1.04)	0.11	0.82 (0.65-1.02)	0.08
			P-linear trend	0.09	*P*-linear trend	0.06

FU, follow-up; IR, age-standardized incidence rate of Parkinson's disease per 1,000 person-years.
Hazard ratios (HR) and 95% confidence intervals (CI) calculated using Cox proportional hazards models for time-varying variables with age as the timescale.
[a] Models are adjusted for baseline place of residence (rural/urban), age at menarche (≤11/12-13/≥14 years), parity (nulliparous/one child/two children/≥three children), and time-varying smoking (never/ex/current) and menopausal status (premenopausal/natural menopause/artificial menopause/unknown type of menopause).

Table 3 Association of physical activity (assessed at Q5 in 1997) with Parkinson's disease incidence: analyses adjusted for diet (assessed at Q3 in 1993).

PA (METs-h/week) in 1997 (Q5)	Cases (*n*)	IR	Age-adjusted HR (95% CI)	*P*-value	Model 1 HR (95% CI)[a]	*P*-value	Model 2 HR (95% CI)[b]	*P*-value
5y-lag (FU 2002-2018; N=81,777)	**881**							
Quartile 1	235	0.79	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	207	0.68	0.85 (0.70-1.02)	0.09	0.85 (0.70-1.02)	0.08	0.84 (0.70-1.01)	0.07
Quartile 3	225	0.69	0.86 (0.72-1.03)	0.10	0.85 (0.70-1.02)	0.07	0.84 (0.70-1.01)	0.06
Quartile 4	214	0.61	0.77 (0.64-0.92)	0.005	0.75 (0.62-0.90)	0.002	0.74 (0.62-0.90)	0.002
			P-linear trend	0.01	*P*-linear trend	0.005	*P*-linear trend	0.004
10y-lag (FU 2007-2018; N=79,836)	**685**							
Quartile 1	176	0.87	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-
Quartile 2	160	0.77	0.87 (0.71-1.08)	0.22	0.87 (0.70-1.08)	0.20	0.86 (0.70-1.07)	0.18
Quartile 3	182	0.83	0.94 (0.77-1.16)	0.57	0.93 (0.75-1.14)	0.47	0.92 (0.74-1.13)	0.41
Quartile 4	167	0.72	0.82 (0.66-1.01)	0.07	0.80 (0.65-0.99)	0.04	0.79 (0.64-0.98)	0.04
			P-linear trend	0.11	*P*-linear trend	0.07	*P*-linear trend	0.06

PA, physical activity; FU, follow-up; IR, age-standardized incidence rate of Parkinson's disease per 1,000 person-years.

Hazard ratios (HR) and 95% confidence intervals (CI) calculated using Cox proportional hazards models with age as the timescale.

86,824 women participated to the Q5 wave of data collection of whom 83,574 had information on PA; we further excluded 46 participants who were possible PD cases, 7 participants who had no date of PD diagnosis and 83 prevalent PD cases at Q5 (*n*=136). Of the remaining 83,438 women, 94 developed PD and 1,567 were censored free of PD within the first 5y of follow-up, leaving 81,777 (881 PD) women for the analyses based on a 5y-lag; 290 developed PD and 3,312 were censored free of PD within the first 10y of follow-up, leaving 79,836 (685 PD) women for the analyses based on a 10y-lag. Analyses with lags longer than 10y were not possible due to an insufficient number of cases.

[a] Multivariable Model 1 is adjusted for baseline place of residence (rural/urban), age at menarche (≤11/12-13/≥14 years), parity (nulliparous/one child/two children/≥three children), smoking (never/ex/current), and menopausal status (premenopausal/natural menopause/artificial menopause/unknown type of menopause).

[b] Multivariable Model 2 is further adjusted for caffeine intake (mg, quartiles), adherence to Mediterranean diet (quartiles), and dairy intake (g, quartiles) assessed in 1993 (Q3).

Figure legends

Figure 1 Flow chart for inclusion into the study using 5y, 10y, 15y, and 20y-lags between physical activity and Parkinson's disease incidence in survival analyses.

Q, questionnaire; FU, follow-up; SD, standard deviation.

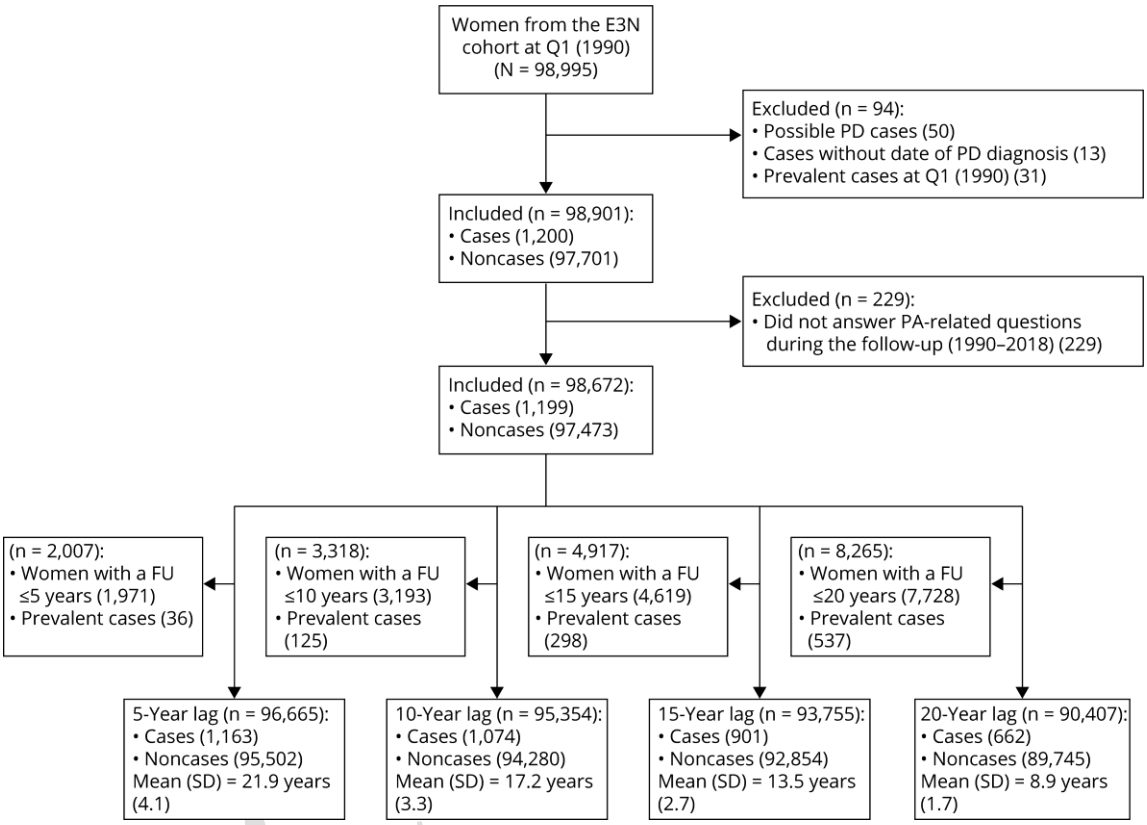


Figure 2 Trajectories of latent physical activity in cases with Parkinson's disease and matched controls up to 29y before the index date.

Figures A.a, B.a, and C.a show the trajectories (95% confidence interval, CI) of mean latent physical activity (LPA) in 1,196 PD cases and 23,879 matched controls based on a linear mixed model with a quadratic function of retrospective time; the model's coefficients are shown in eTable5.

Figures A.b, B.b, and C.b show the differences (95% CI) between the mean trajectories of latent physical activity in PD cases and controls. Differences whose CI do not include 0 (horizontal dashed line) are statistically significant.

We used a retrospective timescale, with T0 (time=0) representing the year of PD diagnosis in cases and the index date in controls. The model was adjusted for PD status, age at T 0 , and two-way interactions of time with PD status and age at T0 . It was further adjusted for baseline parity, place of residence, age at menarche, and time-varying smoking and menopausal status.

Given the significant interaction between age at T0 and time, trajectories were plotted for three different ages at T0 (63y, 73y, 83y) and the most common profile of E3N participants (never smokers, age at menarche at 12-13y, natural menopause, two children, and living in urban areas).

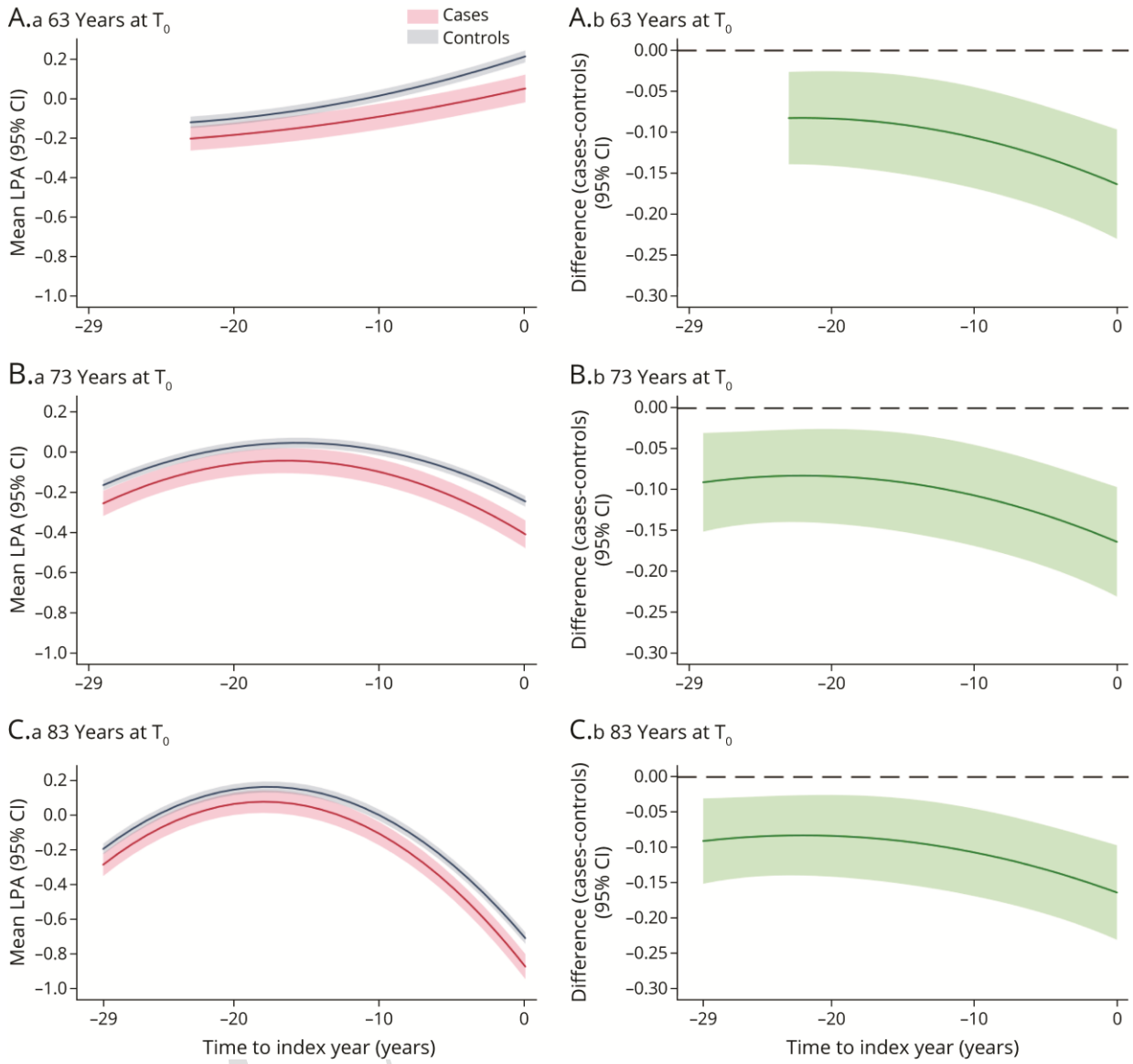


Figure 3 Cumulative incidence function of Parkinson's disease over the follow-up (2000-2018) according to latent physical activity assessed at Q1 (1990).

The cumulative incidence function (CIF) of PD as a function of the quartiles of latent physical activity assessed at Q1 (1990) is predicted by a Fine-Gray regression model for competing risks, with time since the beginning of the follow-up as the time scale and a 10y-lag (follow-up, 2000-2018). The model was adjusted for age (restricted cubic spline with 3 knots), parity, place of residence, age at menarche, smoking, and menopausal status (all assessed at the beginning of the follow-up).

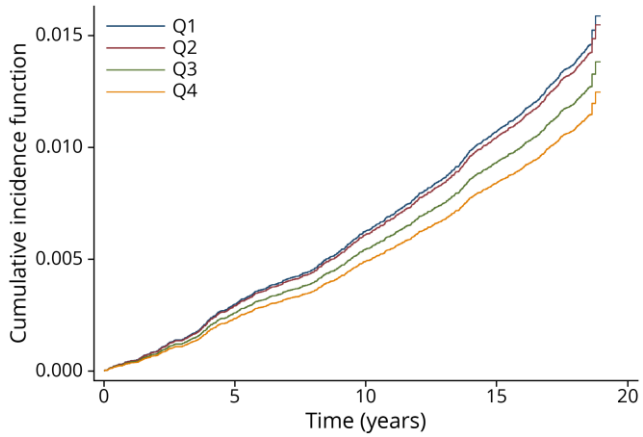


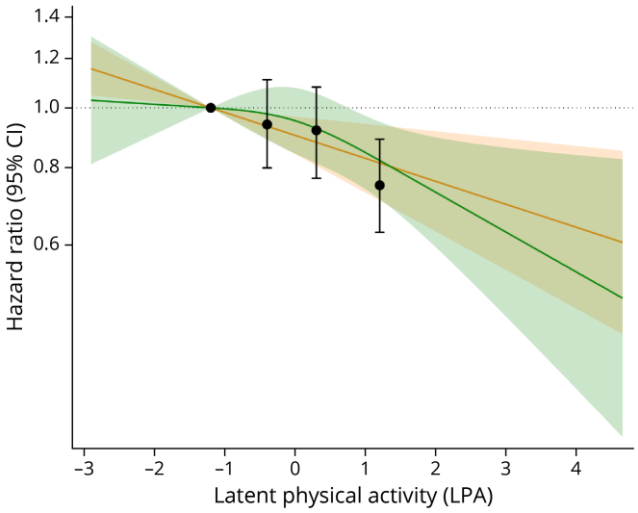
Figure 4 Hazard ratios of Parkinson's disease in relation to latent physical activity (10y-lag).

Hazard ratios (HR) and 95% confidence intervals (CI) calculated using Cox proportional hazards models for time-varying variables with age as the timescale, and adjusted for baseline place of residence (rural/urban), age at menarche (≤11/12-13/≥14 years), parity (nulliparous/one child/two children/≥three children), and time-varying smoking (never/ex/current) and menopausal status (premenopausal/natural menopause/artificial menopause/unknown type of menopause).

The dots correspond to HRs for quartiles of latent physical activity (LPA) compared to the reference quartile (Table 2) together with their 95% confidence intervals (CI, vertical bars); HRs are plotted at the median of each quartile.

The orange solid line represents the HR of PD for continuous latent physical activity modelled as a linear variable and the shaded area corresponds to the 95% CI. The HR of PD decreased linearly with increasing level of latent physical activity.

The green solid line represents the HR of PD for continuous latent physical activity modelled with restricted cubic splines and the shaded area corresponds to 95% CI; 3 knots provided the best fit (lower AIC values). There was no significant departure from linearity (P=0.25).



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