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Physical activity and risk of Parkinson's disease and parkinsonism in a prospective population-based study (NEDICES)

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ABSTRACT

To investigate whether physical activity (PA) is a protective factor for the incidence of Parkinson's disease (PD) and parkinsonism after three years of follow-up. All participants of this study were obtained from the Neurological Disorders in Central Spain (NEDICES), a prospective population-based cohort survey of older subjects (≥65 years) that comprised 5278 census-based participants at baseline (1994–1995). A modified version of Rosow-Breslau questionnaire was applied to categorize PA into active versus sedentary group. The final diagnosis of PD and parkinsonism was made by an expert neurologist. Cox regression models (CRM) adjusted for several covariates (sex, age, education, alcohol consumption, tobacco, stroke, hypertension and body mass index) were used to calculate the association between PA (active group vs. sedentary) and risk of PD and parkinsonism after three years. 22 incident PD and 25 incident parkinsonism cases were identified among 2943 participants with available PA information (57.1% female; mean age = 73.28 ± 6.24 years) after three years of follow-up. The CRM showed that the active group (vs. sedentary) showed a lower risk of parkinsonism (Hazard ratio (HR) = 0.18; 95% CI [0.07–0.51]; p = 0.0001). However, this effect was restricted to men (HR = 0.34; 95% CI [0.11–0.99], $p < 0.05$) for incident PD. PA may be a protective factor for incident parkinsonism, whereas this effect was only significant for men in the case of PD. The mechanisms implicated for brain maintenance in active individuals and the neurophysiological differences behind the role of sex on PD are discussed.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a slow progression that is clinically heterogeneous and involves motor and non-motor features (Kalia and Lang, 2015). The aetiology remains unknown but genetic, behavioural and environmental factors are implicated (Ascherio and Schwarzschild, 2016). Symptomatic treatments are available for PD, but are insufficient. Thus, many studies have focused on the prevention of PD over the last decade. Several factors, such as coffee and alcohol consumption, tobacco use and physical activity (PA), that could reduce the incidence of PD, or modify its development has been identified (Paul et al., 2019; Marras et al., 2019). Different studies, including a meta-analyses, have shown that PA clearly affects the improvement of symptoms in the progression of PD-principally in the motor symptoms – this is reflected in scores on the Unified Parkinson's Disease Rating Scale (UPDRS) (Shu et al., 2014). Whether PA modifies the incidence of PD and parkinsonism is not clear. It is difficult carry out prevention studies in diseases with such long prodromal phases, and such studies are scarce. However, a recent systematic review and meta-analysis reported an inverse dose-response relationship between PA and PD risk among men, particularly in those with moderate to vigorous activity (Fang et al., 2018). However, this observation was not robust in women (Fang et al., 2018; Shih et al., 2016). Furthermore, in the case of parkinsonism, two cohort studies have shown a protective effect of PA in

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both sexes (Buchman et al., 2016; Oveisgharan et al., 2020).

The aim of this study was to analyse whether PA is a protective factor against incident PD and parkinsonism in a population-based sample of older Spanish people after three years of follow-up. The main effect of PA on PD and parkinsonism was assessed after controlling for the effects of different covariates. In addition, in accordance with the recommendation of previous literature, stratified analysis by sex was performed to investigate for the differential effects of PA in men and women on both outcomes (PD and parkinsonism).

2. Methods

2.1. Design and participants

The Neurological Disorders in Central Spain (NEDICES) study is a population-based survey of older people's (age 65 years and older) main age-related conditions, including Parkinson's disease, essential tremor, stroke, and dementia. The details of the study (background, study population, and methods of the survey) were previously reported (Bermejo et al., 2001; Morales et al., 2004). Briefly, the NEDICES study was carried out in several areas of central Spain with different socioeconomic backgrounds: Las Margaritas, a working-class neighbourhood in Getafe (Greater Madrid); Lista, a professional-class neighbourhood in the Salamanca district (Central Madrid); and 38 villages from the agricultural region of Arévalo County (125 km northwest of Madrid). Participants were selected through population censuses of these areas.

Currently, two complete cross-sectional surveys have been performed: the baseline or first wave (1994–5) and the incidence or second wave (1997–8). A total of 5278 census-based older people (57.6% women with a mean age of 74.31 ± 6.97 years; 53.1% without a primary studies certificate) were interviewed face-to-face with a questionnaire that assessed demographic, medical and lifestyle data during the baseline period. All participants signed informed consent at the time of enrolment. Ethical standards committees on human research at the University Hospital "12 de Octubre" (Madrid) and "La Princesa" (Madrid) approved the protocol of the study as complying with the Declaration of Helsinki (World Medical Association, 1989).

2.2. Measures and testing procedure

2.2.1. Assessment of PD and parkinsonism

The NEDICES study was carried out in two phases: 1) the door-to-door screening (phase 1) of eligible people; and 2) examination by a neurologist for those who screened positive (phase 2). The methods for the diagnosis of parkinsonism were similar in both waves, at baseline for detecting prevalent cases and for diagnosing incident cases (PD and other parkinsonism) in the second wave.

In phase 1, the questionnaire included 3 questions to screen for parkinsonism (that is, previous diagnosis of PD, presence of tremor and presence of bradykinesia). If at least one of these was present, an individual was considered to have screened positive for parkinsonism. To assess the performance of these questions, a random sample of 183 subjects who had screened negative for parkinsonism were selected. A neurologist examined these patients, and all the cases were also negative for the diagnosis of PD. In phase 2, every person who screened positive for parkinsonism underwent a neurological examination by a neurologist, including the motor items of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). The diagnosis of parkinsonism was made when at least two core signs (resting tremor, rigidity, bradykinesia, and impaired postural reflexes) were present. PD was diagnosed in subjects without atypical characteristics or secondary causes of parkinsonism (in such cases, they are classified as parkinsonism). Stages of PD were classified according to the Hoehn and Yahr scale (Hoehn and Yahr, 1967). Incident PD and parkinsonism cases were defined as those subjects who were free of parkinsonism at the first wave but who developed PD or parkinsonism during the follow-up. The total incidence rate of parkinsonism (PD [N = 30] and other parkinsonism [N = 38]) in the NEDICES study was 534.6 (95% CI 415.2–677.8) per 100,000 person-years. More details about the participants characteristics and the methodology have earlier been published (Benito-Leon et al., 2004).

2.2.2. Assessment of daily physical activity

At baseline (1994–1995), an adapted modified version of the Rosow-Breslau physical function measure (Rosow and Breslau, 1966) was used to collect data on the PA of the participants. This questionnaire's test–retest reliability (r = 0.81) has been assessed in the Established Populations for Epidemiologic Studies of the Elderly (Smith et al., 1990).

In this survey, trained interviewers asked the participants "*How many hours do you dedicate daily to…..*" (a) sedentary lifestyle (i.e., only minimal house chores or short walks at home); (b) slight physical activity (i.e., regular house chores, walks independently at home); (c) moderate physical activity (i.e., regular house chores, walks up to one kilometre per day); and (d) high activity (i.e., performs heavy housework, walks more than one kilometre or practices any sport regularly). The level of intensity of the PA based on the number of hours spent was weighted by multiplying the sedentary category by 1; slight PA by 1.2; moderate PA by 1.4; and high PA by 1.8. Next, different cut off points were calculated based on the quartile distribution to classify the subjects as follows: ≤15.6 hr (sedentary group), ≤17.6 hr (light PA group), ≤19.4 hr (moderate PA group), and >19.4 hr (high PA group). Eventually, PA was classified for consecutive statistical analyses using two ways: sedentary, light, moderate and high PA groups; or active (light + moderate + high) and sedentary groups. Details of the measurement of physical activity in the NEDICES study have been reported elsewhere (Llamas-Velasco et al., 2015, 2016).

2.3. Statistical analysis

Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., 2012). All descriptive data were presented as mean ± standard deviation, and categorical variables were expressed as absolute numbers or relative frequencies. Analysis of variance (ANOVA) tests for numerical variables and $\chi 2$ tests for categorical variables were used for comparing baseline characteristics of the groups, respectively. Moreover, we explored the effect of independent variables associated with PD and parkinsonism using univariate Cox proportional hazards regression analysis. All variables that exhibited a significant univariate association ($p < 0.10$) and other variables considered relevant according to previous scientific literature [6], were included in the models to test the association between PA and the risk of PD or parkinsonism at three years follow-up: sex, age, education, alcohol consumption, tobacco, stroke, HTA and BMI. A sensitivity analysis was carried out excluding cases diagnosed during the first year. A global and gender analysis was performed. For all analyses, a $p < 0.05$ was considered statistically significant.

3. Results

Fig. 1 shows the flow chart of this survey. Of the 5278 subjects screened for neurological disorders at baseline (1994–95), we detected 118 patients with prevalent parkinsonism (PD and other parkinsonism) who were excluded from further analyses. Therefore, the cohort consisted of 5160 participants without parkinsonism at baseline. 828 participants died before they were contacted the second time, and 3,685 completed the screening procedure. A total of 3813 subjects had adequate information during the second wave (1997 to 1998), which was followed from baseline (1994–1995) for an interval of 3.4 years (range = 1.5–6.6). In this final cohort 2943 participants had available PA information. This comprised of 22 incident PD cases, 25 subjects with parkinsonism (14 drug-induced parkinsonism (56%), 3 parkinsonism with associated dementia (12%), 3 vascular parkinsonism (12%), 1 progressive supranuclear palsy (4%) and 4 cases (16%) classified as

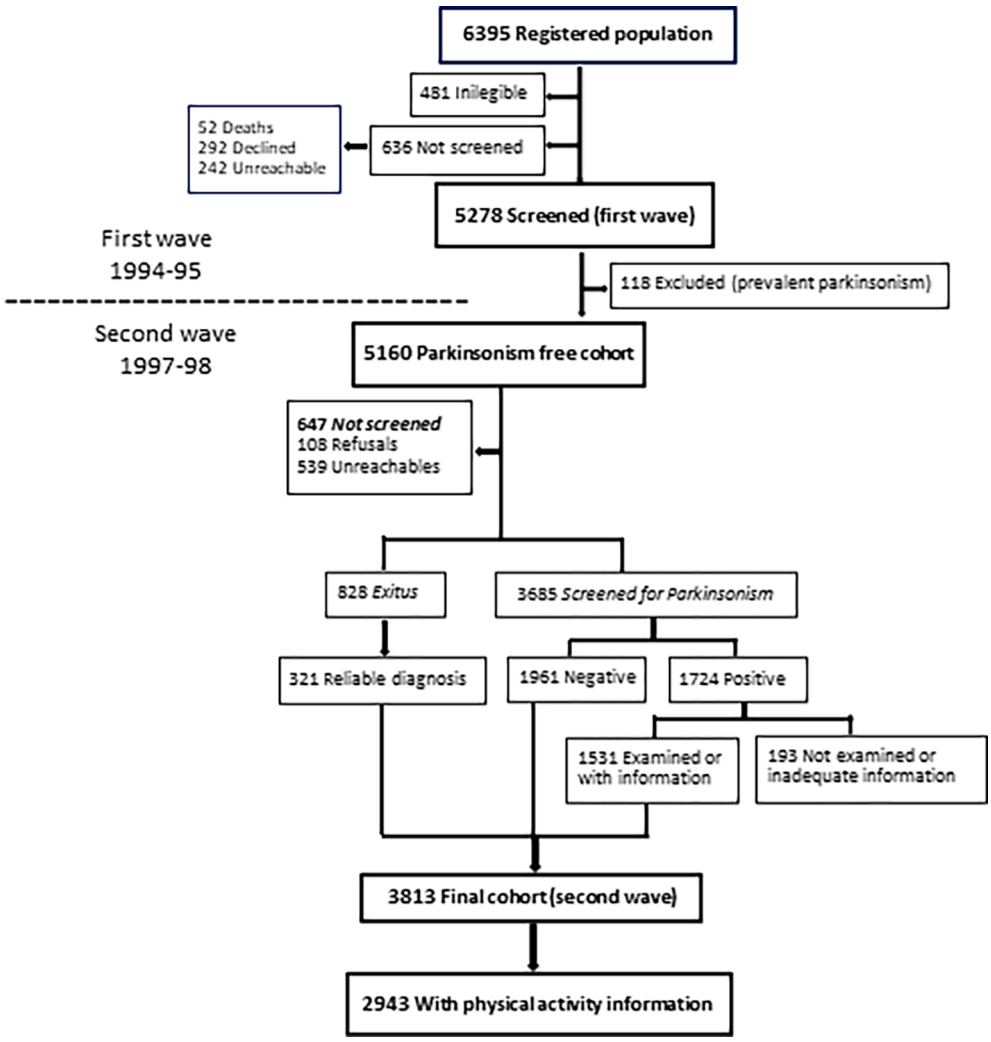

Fig. 1. Flow chart of the survey.

unspecified parkinsonism), and 2896 without parkinsonism. Significant differences were found between the final sample and the excluded participants (N = 870) without PA assessment. Also, the proportion of women was lower in the group with PA information (57.1% vs. 60.9%, p = 0.04), they were slightly younger (73.28 ± 6.24 vs. 73.98 ± 7.04, p = 0.04), but they had higher alcohol consumption (34.9% vs. 27.6%, p = 0.02). No significant differences existed in terms of educational level (p = 0.5), tobacco use (p = 0.41) or history of previous stroke (p = 0.8) in the group with PA information.

Table 1 compares the baseline characteristics of the PD, parkinsonism and non-parkinsonism groups. Higher age, lower educational level, history of stroke and sedentarism were associated with the incidence of PD and parkinsonism.

According to the level of PA, 787 individuals were classified as "sedentary group" and 2156 as "active group" (see Table 2). As shown, the sedentary group was significantly older, had more men, diabetes mellitus, history of stroke, lower educational level and alcohol consumption than the active group.

The Cox regression model (CRM) showed that the active PA group had a lower risk of PD incidence at 3 years compared with the sedentary lifestyle group (see Table 3). When the Cox model was adjusted by controlling for all covariates (age, sex, education, current alcohol consumption, tobacco, previous stroke and body mass index [BMI]), being in the active versus sedentary group remained a protective factor against PD only among men (HR = 0.34; 95% CI [0.11, 0.99]; p < 0.05). In subgroup analysis men had a slightly stronger effect that overall effect, while there was no or less effect in the group of women, probably due to lack of statistical power. Also, no significant differences were observed in the Cox regression model with different levels of PA (light, moderate, high versus sedentary). In contrast to BMI, tobacco and alcohol consumption; older age, lower educational level and previous history of stroke remained independent risk factors of PD in the sample.

Regarding parkinsonism, the CRM showed a lower incidence risk in the active PA group versus the sedentary group, which remained significant after adjustments were made for several covariates (sex, age, education, alcohol consumption, tobacco, stroke, hypertension and BMI), in all participants (HR = 0.18, 95% CI [0.07, 0.51]; p = 0.001) and sex independent samples (HR = 0.17, 95% CI [0.03, 0.90]; p < 0.05) in the men's group; and (HR = 0.22, 95% CI [0.06, 0.82]; p < 0.05) in the women's group.

4. Discussion

Our findings show a protective effect of PA on the incidence of PD after three years follow-up. However, after controlling for the effect of all covariates, the CRM showed a gender-specific inverse preventive effect between active PA vs. sedentary men and PD risk. Sasco et al. (Sasco et al., 1992) firstly suggested in a case-control study that physical activity could be a potential protective factor against PD. Since then, several prospective cohort studies have identified this inverse association between the level of PA and the development of PD with different results regarding sex, level of physical activity or age of the subjects

Table 1
Characteristics of participants at baseline: statistical comparisons.

Characteristic	Incident PD (N = 22)	Incident parkinsonism (N = 25)	Non parkinsonism (N = 2896)	p
Age (years)	76.0 ± 6.31	79.8 ± 6.61	73.20 ± 6.45	<0.001
Sex (female)	8 (36.4%)	14 (56%)	1658 (57.3)	0.14
Education (years)	6.50 ± 4.20	5.55 ± 4.38	6.89 ± 5.26	<0.001
Illiterates/read-write (%) Primary school/ higher (%)	12 (54.6%) 10 (45.5%)	15 (60%) 10 (40%)	1585 (54,7%) 1311 (45,3%)	
Current alcohol	6 (27.3)	4 (16%)	1014 (35.1%)	0.10
Tobacco	1 (4.6%)	1 (4%)	336 (11.6%)	0.29
Previous stroke	3 (13.6%)	3 (12%)	131 (4.5%)	0.03
Hypertension	12 (54.6%)	13 (52%)	1464 (50.6%)	0.93
Physical activity				
- Sedentary	9	18 (72%)	760 (26.2%)	<0.001
Light	(40,9%)	5 (20%)	796 (27.5%)	
Moderate	6	2 (8%)	632 (21.8%)	
High	(27.3%)	0 (0%)	708 (24.5%)	
- Active *(light + moderate + high)*	3 (13.6%) 4 (18.2%) 13 (59.1%)	7 (28%)	2136 (73.8%)	
BMI	26.72 ± 4.76	25.39 ± 3.46	27.58 ± 5.75	0.001
Diabetes Mellitus	5 (22.7%)	2 (8.3%)	479 (16.6%)	0.41

PD: Parkinson's disease; BMI: Body mass index.
Note: Data are given as Mean ± SD and frequency (%).

Table 2
Characteristics of participants stratified by levels of physical activity.

Characteristic	Sendentary (N = 787)	Active (N = 2156)	p
Age (years)	75.06 ± 7.29	72.63 ± 6.03	<0.001
Sex (female)	402 (51.08%)	1278 (59.28)	<0.001
Education (years)	6.06 ± 5.15	7.16 ± 5.25	<0.001
Illiterates/read-write (%)	490 (62.26%)	1122 (52.04%)	
Primary school/higher (%)	297 (37.74%)	1034 (47.96%)	
Current alcohol	246 (31.38%)	778 (36.14%)	0.02
Tobacco	96 (12.24%)	242 (11.23%)	0.45
Previous stroke	60 (7.62%)	77 (3.57%)	<0.001
Hypertension	414 (52.74%)	1075 (49.88%)	0.17
BMI	27.3 ± 5.40	27.62 ± 5.83	0.11
Diabetes Mellitus	158 (20.20%)	328 (15.3%)	0.002

Note: Data are given as Mean ± SD and frequency (%).
BMI: Body mass index.

(Shih et al., 2016; Chen et al., 2005; Yang et al., 2015; Xu et al., 2010; Thacker et al., 2008). A recent meta-analysis (Fang et al., 2018) evaluated eight prospective studies with a total of 554,336 participants and identified 2192 patients with PD during follow-up (median of 12 years). The relative risk of PD was 0.79 (95% CI, 0.68–0.91) when they compared the highest category of physical activity with the lowest, 0.71 (95% CI, 0.58–0.87) for moderate to vigorous physical activity level versus lowest, and there was no association for light physical activity level. Stronger effects among men than among women were found, with a linear dose–response association in the first group. In this cohort, age and previous history of stroke remained independent risk factors for PD and parkinsonism, whereas unlike previous reports, BMI and tobacco

Table 3
Cox regression models: risk of PD and parkinsonism (sedentary group as reference).

	General model			Adjusted *		
	HRs	95% HR CI	p	HRs	95% HR CI	p
PD						
. *Active group (global)*	**0.42**	0.18–0.98	<0.05	0.42	0.17–1.04	0.06
sensitivity	**0.41**	0.17–0.96	0.042	0.42	0.16–1.04	0.06
- *Men*	**0.27**	0.09–0.77	0.01	**0.34**	0.11–0.99	<0.05
- *Women*	1.73	0.21–14.05	0.61	1.08	0.12–9.30	0.95
Parkinsonism						
. *Active group (global)*	**0.11**	0.05–0.27	<0.001	**0.18**	0.07–0.51	0.001
sensitivity	**0.19**	0.09–0.56	< 0.001	**0.21**	0.08–0.79	< 0.05
- *Men*	**0.08**	0.02–0.37	0.001	**0.17**	0.03–0.90	<0.05
- *Women*	**0.14**	0.05–0.42	<0.001	**0.22**	0.06–0.83	<0.05

HRs = Hazad ratios; PD = Parkinson's disease; Sensitivity analysis: 1015 subjects were excluded for PD (12 events) and 1014 for parkinsonism (11 events).
* PD adjusted by: Sex, age, education, alcohol consumption, tobacco, stroke and BMI; Parkinsonism adjusted by: Sex, age, education, alcohol consumption, tobacco, stroke, BMI and HTA.

did not show such effect (Marras et al., 2019; Buchman et al., 2016).

As previously noted by Chen et al. (2005) and Yang et al. (2015), no association was found between PA and PD for women. However, this discovery is not conclusive given that a previous meta-analysis (Xu et al., 2010) did not find sex-differences, and some prospective studies did not show a protective effect of PA on the incidence of PD (Roos et al., 2018). Differences in the biological response, in particular, resting metabolic rate (i.e., the number of calories required to keep your body functioning at rest) between sexes has been proposed as an underlying physiological mechanism (LaHue et al., 2016). Moreover, our findings did not show statistical association when analysing different levels of PA (light, moderate and high) vs. sedentarism and risk of PD, and when dichotomizing high activiy group vs. all others yields and moderate-high vs sedentary-light, probably due to the limitation of few individuals in each group. As in the Swedish National March cohort (Yang et al., 2015), this study not only reported exercise, PA also consisted of short walks and household chores. This fact suggests that minor changes in lifestyle could be relevant in PD prevention (LaHue et al., 2016).

Regarding the risk of parkinsonism, a clear inverse significant association was observed between the active group versus the sedentary group in the global sample (82% lower risk). This effect remained significant after adjusting for several covariates and stratification by sex (men 83% lower risk, women 78% lower risk). There is hardly any literature on this topic. In this survey (NEDICES), the incidence rate of parkinsonism per 100,000 person-years was 534.6 (CI 95%; 415.2–677.8) (Benito-Leon et al., 2004). This was similar to the rate described in the study of Baldereschi et al., (560/100,000 person-years) (Baldereschi et al., 2000), but lower than others, e.g., approximately 89.9/1000 person-years by Buchman et al., 2016 (Buchman et al., 2016). Cross-sectional studies have calculated the prevalence of parkinsonism to range from 15% to 50% in elderly people (Buchman et al., 2016). Regarding the protective role of PA on the risk of parkinsonism, Buchman et al., found a HR = 0.97 (95% CI [0.94–0.99]), $p < 0.01$) when comparing the highest PA group with the lowest PA group (Buchman et al., 2016), and Oveisgharan et al. found a HR = 0.79 (95% CI [0.70–0.88], $p < 0.001$) after objectively measuring physical activity (Oveisgharan et al., 2020). More epidemiological studies are required to confirm these observations.

The physiological mechanism underlying the effect of PA as a preventive factor of PD and parkinsonism remains unclear. PA is believed to stimulate neurotrophic factors that act on dopamine neurons reducing vulnerability to toxins and reconstituting the function of the basal ganglia (Zigmond and Smeyne, 2014; Paillard et al., 2015). In rat

models, PA has been shown to improve mitochondrial function and shows how astrocytes could contribute by increasing the expression of glial fibrillary acidic protein (GFAP) in the dorsal striatum (Paillard et al., 2015). Also, PA influences cardiovascular risk factors linked to vascular parkinsonism such as hypertension, diabetes, and cholesterol (Murtagh et al., 2015).

This study has several limitations. The first and main weakness is a possible bias due to reverse causation over a follow-up of three years. Prodromal features such as depressive symptoms and body pain (not assessed at baseline) may have direct effects on physical activity associated with a lower PA level at baseline. Additionally, possible early dopaminergic loss can lead to subtle stiffness or bradykinesia that makes exercise difficult, as well as a reduced response to the dopamine-based reward system (Hughes et al., 2019). To mitigate this possible bias, a sensitivity analysis was performed excluding incident cases during the first year, without showing relevant changes (see Table 3). Second, although a longer follow-up period (>three years) would be suitable, the follow-up period in this study was long enough to identify a significant effect of PA on the incidence of PD and parkinsonism. Third, a self-reported questionnaire was used to collect PA information, whereas objective measurements, such as actigraphy, have been used in other studies (Oveisgharan et al., 2020). Fourth, the results should be interpreted with caution due to the low number of of participants with incident PD and parkinsonism. This low number is consistent with the low incidence of this disease i.e., approximately 37.55 per 100,000 person-years (95% CI 26.20–53.83) in females, and 61.21 per 100,000 person-years (95% CI 43.57–85.99) in males (Hirsch et al., 2016). Finally, approximately 22.8% of participants who were reachable in the second wave did not have available PA information. The group without PA information were slightly older and had a higher percentage of women and alcohol consumption. These limitations may affect the internal validity of the study, but it should be noted that the findings remained stable after adjustments were made for these covariates

There are also different strengths of this study. First, it is a prospective population-based study aimed at assessing neurological disorders in older participants. This is the first study that compares the association of PA with the risk of PD and parkinsonism, in a sample representative of a broad spectrum of socioeconomic and sociocultural status in the Spanish population. Furthermore, PD and parkinsonism were diagnosed by expert neurologists based on standardised clinical evaluation to reduce the chance of misclassification. Finally, adjustments were made for an important group of covariates in the analysis.

In summary, this work supports PA as a protective factor against PD and against parkinsonism among older people (65 years or older). Therefore, an active lifestyle in aged people should be promoted in health prevention programs. More studies are needed to determine the type and level of PA required. Future investigations should add novel neurophysiological markers to explain interaction effects of PA on the incidence of PD.

CRediT authorship contribution statement

Sara Llamas-Velasco: Data curation, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Israel Contador:** Investigation, Visualization, Writing - review & editing. **Antonio Méndez-Guerrero:** Investigation, Software, Writing - review & editing. **Carmen Romero Ferreiro:** Formal analysis, Writing - review & editing. **Julián Benito-León:** Data curation, Investigation, Writing - review & editing. **Alberto Villarejo-Galende:** Supervision, Writing - review & editing. **Félix Bermejo-Pareja:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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