



Lifetime occupational and leisure time physical activity and risk of Parkinson's disease



I-Fan Shih^a, Zeyan Liew^a, Niklas Krause^{a, b}, Beate Ritz^{a, c, *}

^a Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles, California, USA

^b Department of Environmental Health Sciences, Fielding School of Public Health, University of California at Los Angeles, California, USA

^c Department of Neurology, School of Medicine, University of California at Los Angeles, California, USA

ARTICLE INFO

Article history:

Received 3 February 2016

Received in revised form

6 April 2016

Accepted 2 May 2016

Keywords:

Parkinson's disease

Physical activity

Exercise

Occupations

ABSTRACT

Introduction: While regular exercise has been shown to alleviate the motor symptoms of Parkinson's disease (PD), it remains unclear whether a physically active lifestyle may prevent PD.

Methods: To examine physical activities across the lifespan and risk of PD, we relied on data from a population-based case-control study that enrolled 357 incident PD cases and 341 controls. We assessed physical activity levels via self-report of (1) overall physical activity (PA) over 4 age periods; (2) competitive sports; and (3) occupational histories.

Results: PD risks were lower comparing the overall PA highest quartile (moderate to vigorous activities ≥ 180 metabolic equivalent task-hours/week (MET-h/wk)) with the lowest quartile (<47.8 MET-h/wk) in age-period 18–24 years (adjusted odds ratio (OR) 0.64, 95% confidence interval (CI) 0.40–1.02), and 45–64 years (OR 0.50, 95%CI 0.31–0.83) but not in age-period 25–44. Individuals who consistently engaged in overall PA at high levels (before age 65 years) had a 51% lower PD risk than those with low levels. Also, having participated in competitive sports prior to age 25 was inversely associated with PD (OR 0.53, 95% CI 0.31–0.91 for high level versus never). There was no association for measures of occupational physical activity though.

Conclusion: The long prodromal stage of PD makes it difficult to conclude whether insidious disease leads to a reduction of physical activity years before motor symptom onset and PD diagnosis. However, sports activities and high levels of overall PA in youth appear protective unless they are markers for biologic or genetic factors that lower PD risk.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

Parkinson's disease (PD) is characterized by progressive motor and non-motor impairments leading to disability, a considerable decline in health related quality of life, and a large financial and caretaker burden in aging societies. Many clinical trials have shown beneficial effects of exercise therapies in people with PD as summarized in meta-analyses; for example, two recent meta-analyses found that aerobic exercise or physical therapy improved motor scores based on the Unified Parkinson's disease rating scale (UPDRS), as well as balance and gait compared with no intervention [1,2]. Even though there is some evidence from animal experiments

and PD intervention studies that intensive physical exercise induces neuroplasticity in the nigrostriatal dopaminergic system [3–6], less is known about the role lifetime physical activity may play for PD risk.

Some cohort studies (Supplementary Table 1) have suggested that those physically inactive or reporting prolonged daily TV viewing are more likely to develop PD [7–12]. However, many of these cohort studies relied on self-report of physical activity levels or recorded activity patterns at baseline only [11,12], accrued small numbers of incident PD cases or followed populations with a lifestyle different from the general population [10,11]. In addition, most previous studies focused on leisure time activities while only two considered work related activities [8,10]. Activities at work and during leisure time likely entail very different physical demands, in terms of intensity, frequency and duration, and are known to affect all-cause mortality and cardiovascular disease differently [13,14]. Our aim here is to examine whether the type and/or the timing of

* Corresponding author. Permanent address: Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772, USA.

E-mail address: britz@ucla.edu (B. Ritz).

physical activity throughout adulthood affects risk of PD.

2. Methods

Data collection and procedures described in this study have been approved by the University of California, Los Angeles (UCLA), Institutional Review Board for human subjects, and written informed consent has been obtained from all participants.

2.1. Study population

We conducted a population-based case-control study in largely agricultural counties in Central California. Details of the study have been provided elsewhere [15]. Briefly, we enrolled recently diagnosed PD patients (within 3 years of diagnosis) between 1998 and 2007, residing in Fresno, Kern, or Tulare counties, who at recruitment had lived in California for 5 years or more. Potential cases and controls were contacted by mail, by telephone, or both with eligibility criteria including: (1) being at least 35 years of age; (2) not too ill to participate; (3) currently living in one of the three designated counties; (4) having lived in California for five years or more; and (5) having PD for cases.

Of the 1167 PD patients who responded to invitations, we excluded 604 who had their initial PD diagnosis 3 years prior to contact or did not fulfill the above inclusion criteria. Of the 563 eligible cases, 90 were too ill to be examined, moved or died prior to exam. The remaining eligible cases were examined by movement disorder specialists from UCLA to confirm PD diagnoses while 94 did not meet published criteria for idiopathic PD [16], an additional 13 were reclassified as not having idiopathic PD during our follow-up study [17], and 6 withdrew between examination and interview. Of the remaining 360 cases, 357 provided complete information on physical activity.

Population controls 65 years or older were first identified from Medicare lists (in 2001). Later, due to implementation of the Health Insurance Portability and Accountability Act (HIPAA), we recruited around 70% of controls of all ages from residential parcel tax assessor records in the tri-county area. Of the 1212 potential controls, 457 were ineligible, and 409 declined participation due to illness or moving; a total of 341 individuals provided complete information on physical activity.

2.2. Assessment of physical activity

Trained interviewers blinded to case/control status conducted structured telephone interviews to obtain demographic and physical activity information, including self-report of (1) overall physical activity level across four age periods; (2) history of participation in competitive sports; and (3) occupational histories to create a job exposure matrix (JEM) and estimate occupational physical activity.

2.2.1. Overall physical activity

Participants were asked to report average number of days per week and average number of hours per day during which they performed mild, moderate, or vigorous physical activity at work and leisure time, during 4 periods of adulthood: 18–24, 25–44, 45–64, and ≥ 65 years. Definitions and examples for intensity of activities were provided during interview. To account for both the effects of duration and intensity, we assigned metabolic-equivalent (MET) values to the activity intensities (vigorous activities as 8 and moderate activities as 4) [18] and created a cumulative physical activity measure — MET-hour per week (MET-h/wk) at each age period. Previous studies suggested that only moderate to vigorous activities were associated with PD risk and no effect was observed for mild activities [7,8]; therefore we set “mild” activities to a MET

value of zero to maximize the specificity of the physical activity measures. We also calculated the sum of the MET-hour per week for every year of adulthood before index date (PD onset in cases, interview date in controls) and divided by the total number of adult years to derive the average lifetime activity score.

2.2.2. Competitive sports history

If a participant reported ever having engaged in competitive sports, we collected information about type of sports, and ages at which they started and stopped. For every type of sport, a MET value was assigned according to published standard equivalents [19]. We then multiplied the MET value with the reported years for each sport, and summed those to derive cumulative sports measures (MET-year).

2.2.3. Occupational history

Participants were asked to report job titles, tasks, companies, industries, and duration (years) and frequency (hours per week) for all jobs in which they had worked for 6-months or more throughout their lifetime. We created a JEM to estimate occupational physical activity by coding information about jobs and industries based on the Integrated Public Use Microdata Series (IPUMS-USA) 2000 Occupation Code System [20], and assigned MET value to each job code [21]. We first multiplied the MET value with the reported years in each job, and summed those to derive cumulative occupational physical activity measures, and then calculated an average lifetime score by dividing the cumulative score by the total number of working years.

2.3. Statistical analyses

Logistic regression analysis were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina), with adjustment for age (continuous), gender, race (white, non-white), education (<12 years, 12 years, >12 years), smoking status (never, past, or current smoker), having a 1st degree family member with PD (yes, no), residential pesticide exposures (ever or never exposed) [22] and pesticide exposure estimates previously derived from a JEM (never, low, median or high exposure) [23]. We reported odds ratio (OR), 95% confidence intervals (95%CI), and p-values for trend based on the median of each exposure category.

We categorized the physical activity scores into quartiles based on the distribution of average lifetime MET scores in controls: <47.8, 47.8–93.0, 93.0–180.0, ≥ 180.0 MET-h/wk. Participants who never performed moderate and/or vigorous physical activities and those who fell in the 1st quartile of the MET distribution were considered less active and formed our reference group. Furthermore, we examined whether changes in overall physical activity over lifetime until age 64 were associated with PD risk. For each age period, participants were categorized as having high or low activity based on the overall median (93.0 MET-h/wk). We compared those who reported a consistently high activity, and those who reported either low-high or high-low trajectories to those who reported consistently low activity throughout life. For occupational physical activity measures, we categorized cumulative (MET-year) and average (MET) scores into quartiles based on the control distribution in each age period, and for cumulative sport activity scores, we considered those who never participated in any strenuous sport as reference and examined age periods specific tertiles (MET-year). We also included all three measures in the same model to mutually adjust for the different types of activity.

In sensitivity analyses we stratified by gender or excluded subjects with a PD diagnosis prior to age 60. Examining occupational physical activity, we also excluded participants with high occupational pesticide exposures, because we previously found pesticide

exposure to contribute to PD risk in this population [23]. To assess the potential influence of preclinical changes in physical activity due to insidious disease onset, we used exposure lagging and discounted activities within 10-years or 20-years prior to the index date for cumulative measures.

3. Results

Study participants were in average 68 years of age at eligibility screen and predominantly white (Table 1). Cases were more frequently male, less highly educated, never smokers, and residentially and occupationally more heavily exposed to pesticides. The mean score on the Hoehn and Yahr scale was 2.10 (range 1–5) at baseline (mean PD duration: 1.71 ± 1.18 years).

Higher levels of self-reported lifetime physical activity were inversely associated with PD risks (Table 2). Specifically, we found a 44% (OR 0.56, 95% CI = 0.34–0.92) lower risk of PD among those with moderate to vigorous physical activity of at least 180 MET-hours per week on average in adulthood compared with the less active reference group (<47.8 MET-h/wk). Similar results were obtained for all age periods except for activity during 25–44 years of age. Examining the influence of changes in physical activity from youth to later adulthood, those who remained highly active throughout their lifetime were at the lowest risk of PD (OR = 0.49, 95%CI 0.32–0.76), followed by those with a high-low or a low-high trajectory, compared with those who were consistently less active (Fig. 1).

Table 1
Sociodemographic characteristics of the study population in Central Valley of California, 2001–2007.

	PD cases		Controls	
	N = 357	%	N = 341	%
Mean age (years) [SD]	68.29	± 10.22	68.20	± 11.42
Gender				
Male	205	57	176	52
Female	152	43	165	48
Race				
White	287	80	279	82
Non-white	70	20	62	18
Education				
< 12 years	66	18	38	11
12 years	96	27	64	19
> 12 years	195	55	239	70
Cigarette smoking status				
Never	187	52	146	43
Former	150	42	161	47
Current	20	6	34	10
PD Family History				
Yes	52	15	37	11
No	305	85	281	82
Residential pesticide exposure				
Dithiocarbamates				
Never	198	55	228	67
Ever	159	46	113	33
Organochlorines				
Never	148	41	159	47
Ever	209	59	182	53
Organophosphorus				
Never	60	17	83	24
Ever	297	83	258	76
Paraquat				
Never	128	36	139	41
Ever	229	64	202	59
Occupational Pesticide exposure				
None	227	64	242	71
Low	23	6	25	7
Medium	56	16	47	14
High	51	14	27	8

Having participated in competitive sports was inversely associated with PD risk (Table 3, Supplementary Table 2). Compared with individuals who never participated in competitive sports, for those who reported a high sports activity level prior to 25 years of age, we estimated a 47% lower risk of PD (OR 0.53, 95%CI 0.31–0.91; p for trend = 0.04). Cumulative or average scores for occupational physical activity were not associated with PD risk (Table 3).

In sensitivity analyses, no apparent gender specific effect was found for overall physical activity or competitive sports measures, and higher levels of occupational physical activity did not reduce PD risk overall or in males only (Supplementary Table 3). Results from lagged analyses that excluded physical activity 10-years or 20-years prior to PD diagnosis (Supplementary Table 4) for cumulative measures were similar to unlagged estimates. Excluding participants with high occupational pesticide exposure (Supplementary Table 5) or excluding PD cases diagnosed prior to age 60 also did not substantially change all physical activity estimates (results not shown).

4. Discussion

In this population-based case-control study, we examined three different measures of physical activity and found that higher lifetime moderate to vigorous activity, especially consistently high level of such activities throughout adulthood, reduced the risk of developing PD. Controls who did not develop PD had more often engaged in strenuous competitive sports in their youth. However, occupational physical activity did not influence PD risk.

Our findings agree with a meta-analysis of five prospective studies reporting that being physically active reduces PD risk with a 34% lower risk estimated for the highest versus the lowest activity levels [10]. Some of these studies, however, only examined leisure time physical activity at baseline (between age 50–60) [7,9,24], and did not account for other types of physical activity (e.g. occupational, household and commuting activities). A Swedish study [10], reported an inverse association with PD risk for the sum of household, commuting and leisure time exercise and total physical activity, but no associations for occupational activity or leisure time exercise when analyzed separately. Similarly, our overall physical activity measure included activities at work and leisure time, and higher activities according to this overall measure were inversely associated with PD risk. Our occupational measure covered all lifetime job-related activities and considered intensity and duration while the Swedish study only asked about job intensity in the past year [10]. Both studies do not support a protective role for occupational activities. Interestingly, the lack of beneficial effects for job-related physical activity in cardiovascular disease and all-cause mortality [13,14] has recently been coined the 'health paradox' of physical activity [25].

We collected physical activity data according to age periods, and found inverse association with PD in all except the 25–44 year period. Careers and child rearing demands may restrict leisure time or sports activities in this period such that occupational activity may be the main activity to overall physical activity. The only other paper [8] that examined physical activity during several age periods reported only on leisure time activity and reported inverse associations with PD during 35–39 years and 50–60 years of age but not in young adulthood (ages 15–29). Yet, our evaluation of activity trajectories throughout adulthood is consistent with this study's findings suggesting that individuals who remain highly active throughout life are at lowest risk of PD [8].

Similar to previous study, we cannot dismiss the possibility of reverse causation because decreasing physical activity before disease onset might be a prodromal PD symptom. However, our estimates did not substantially change after excluding physical activity

Table 2

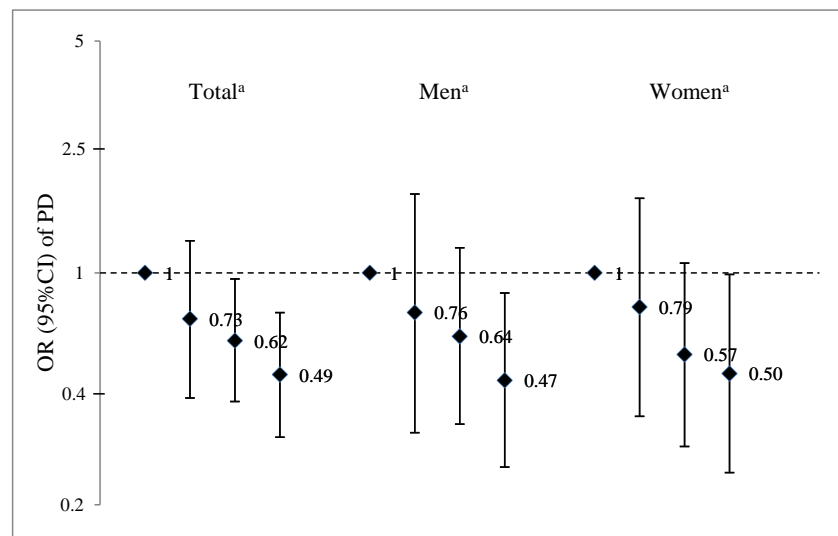
Multivariable-adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-for-trend for Parkinson's disease (PD) risk by four age periods of self-reported overall moderate to vigorous physical activity.^a

Overall physical activity [MET-hour/week] ^b	PD/Control	aOR	95%CI	P-for-trend ^c
Lifetime Average				
<47.8	107/84	1 (Reference)		
47.8–93.0	75/79	0.68	0.43–1.07	
93.0–180.0	73/79	0.68	0.43–1.07	
≥180.0	81/78	0.56	0.34–0.92	0.05
18–24 years				
<47.8	86/68	1 (Reference)		
47.8–93.0	82/69	1.00	0.62–1.62	
93.0–180.0	63/79	0.64	0.39–1.05	
≥180.0	105/104	0.64	0.40–1.02	0.03
25–44 years				
<47.8	111/93	1 (Reference)		
47.8–93.0	67/73	0.78	0.49–1.22	
93.0–180.0	53/62	0.73	0.45–1.19	
≥180.0	105/92	0.82	0.53–1.28	0.33
45–64 years				
<47.8	136/112	1 (Reference)		
47.8–93.0	65/67	0.82	0.52–1.29	
93.0–180.0	63/58	0.97	0.60–1.56	
≥180.0	65/72	0.50	0.31–0.83	0.01
≥65 years				
<47.8	145/112	1 (Reference)		
47.8–93.0	51/48	0.89	0.54–1.46	
93.0–180.0	24/35	0.50	0.27–0.92	
≥180.0	18/21	0.65	0.31–1.37	0.08

^a Logistic regression models adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.

^b Overall Physical Activity (MET-h/wk) = 8 × vigorous activity hour/week + 4 × moderate activity hour/week; quartiles according to the average lifetime physical activity distribution in controls.

^c Linear trend was tested using the midpoint of each exposure category as a continuous variable in the regression model.



^a Left to right:

Low-Low trajectory (reference group): low activity at 18-24, 25-44 and 45-64 age periods.

Low-High trajectory: low activity at 18-24, and high activity at either 25-44 or 45-64 or both age periods.

High-Low trajectory: high activity at 18-24, and low activity at either 25-44 or 45-64 or both age periods.

High-High trajectory: high activity at 18-24, 25-44 and 45-64 age periods.

Fig. 1. Multivariable-adjusted odds ratios (OR) with 95% confidence intervals (CI) of Parkinson's disease (PD) according to changes of overall moderate to vigorous physical activities before age 65. The analysis adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.

reported during 10- or 20-years before diagnosis. We also found that those who were consistently active throughout life or active in at least one of the age periods were at lower risk of PD, compared

with those maintaining low physical activity levels throughout life. This suggests that staying or becoming active in adulthood may protect against PD. Further, the protective associations found for

Table 3Multivariable-adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-for-trend for Parkinson's disease (PD) risk by competitive sports and occupational activity.^a

Cumulative physical activity [MET-year] ^b	PD/Control	aOR	95%CI	P-for-trend ^c
Competitive Sports				
Lifetime				
Never	184/160	1 (Reference)		
<42	69/61	0.99	0.63–1.56	
42–105	58/59	0.94	0.58–1.52	
≥105	40/58	0.62	0.37–1.04	0.06
18–24 years				
Never	192/168	1		
<40	63/59	0.97	0.61–1.52	
40–91	66/56	1.06	0.67–1.70	
>91	30/55	0.53	0.31–0.91	0.04
Occupational Activity				
Lifetime				
<56.7	89/85	1 (Reference)		
56.7–89.3	69/86	0.76	0.47–1.22	
89.3–130.8	86/84	0.85	0.51–1.43	
≥130.8	109/85	0.78	0.44–1.39	0.49
18–24 years				
<12.0	122/113	1 (Reference)		
12.0–22.5	70/76	0.92	0.60–1.43	
22.0–37.6	66/74	0.76	0.47–1.21	
≥37.6	94/76	0.97	0.59–1.59	0.86
25–44 years				
<30.7	90/102	1 (Reference)		
30.7–50.0	94/83	1.46	0.92–2.33	
50.0–65.8	62/75	0.87	0.52–1.46	
≥65.8	106/79	1.21	0.70–2.08	0.72
45–64 years				
<22.5	121/126	1 (Reference)		
22.5–36.5	71/68	0.97	0.61–1.55	
36.5–52.5	69/73	0.86	0.53–1.39	
≥52.5	91/72	0.86	0.52–1.42	0.51

^a Logistic regression models were adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.^b Competitive Sports = sum of sport MET value × year of participation (MET-year); tertiles – age periods specific. Occupational Activity = sum of job MET value × year of participation (MET-year); quartiles – age periods specific.^c Linear trend was tested using the midpoint of each exposure category as a continuous variable in the regression model.

high physical activity and sports activities in youth would not be affected by reverse causation unless an active lifestyle depends on genetic factors that also lower PD risk.

Physical activity may reduce the risk of PD by increasing cerebrovascular circulation and improving the production of neurotransmitters, including neurotrophic substances [3,4]. In rodent models of PD, animals forced to exercise before or after toxin treatments had more remaining dopaminergic neurons and terminals as well as less motor deficits than immobilized animals [26,27]. Forced exercise was found to stimulate neurotrophic factors and downregulation of the dopamine transporter, which may contribute to neuroplasticity and reduce vulnerability to neurotoxicants [3,4]. In early stages of PD, 8 weeks of high-intensity treadmill training (MET ≥3 or 60–80% age-adjusted maximal heart rate) has been shown to induce cortico-motor excitability and an increase in dopamine D2 receptor binding potential in the dorsal striatum, along with motor function improvement [5,6]. Alternatively, high intensity exercise may induce elevations in plasma urate [28], an anti-oxidant, and high urate levels have been associated with lower PD risk and slower disease progression [29].

Compared with other studies, we measured physical activity levels more comprehensively using multiple approaches. First, we accounted for the two most important sources of physical activity – occupation and leisure time sports activity – by age periods. This allowed us to evaluate the effect of changes in physical activity levels, reflecting a life course perspective and possibly identify periods of importance for interventions. Second, to overcome some of the recall problems in our case-control design, we asked participants to report their lifetime history of competitive sports and job-related activities. Based on the latter, we created an

exposure matrix for which raters assigned physical activity levels to job titles and tasks while blinded to case status. To our knowledge, we are the first PD study that used a JEM to examine occupational physical activity. Though the possibility exists that cases spent more effort to recall details of their job histories, we found that the reported number of occupations and work years was similar for cases and controls [23].

Our study with nearly 360 PD cases enrolled a substantially larger number of PD affected participants than most previous studies [10,11,24,30]. Moreover, ours is the only epidemiologic population-based study in which movement disorder specialists examined 71% of patients multiple times over almost a decade to confirm a diagnosis of idiopathic PD, minimizing disease misclassification potential. PD ascertainment in prospective cohort studies is generally based on self-reported PD diagnoses and medical records review that relies heavily on a patients' access to quality health care [7,8,24,30]. PD diagnoses strongly depends on clinical evaluations, thus diagnostic and reporting errors may be differential for those who are more health conscious and thus more physically active.

The present study has several limitations. Our JEM approach assumes that everyone with the same job title/tasks had a similar level of physical activity and thus was given the same MET value. This inevitably introduces non-differential misclassification errors because of likely within-job variability. Moreover, female participants may simply report housewife/homemaker, and this category is hard to judge in terms of physical activity. In our farming population, 'housework' may also be physically intensive for women who engaged in farming or gardening but do not consider this a job – these activities, however, would have been captured by our

overall physical activity measure. Furthermore, our study was conducted in largely agricultural counties in Central California, which may limit the generalizability of our findings. Given the high correlation between active manual labor on farms and occupational pesticide exposure, controlling for pesticide exposure was important. Also, sensitivity analyses excluding participants with high occupational pesticide exposure did not change our results for occupational physical activity. An advantage of our rural study population is that our study included a wide range of occupational PA including physically demanding farm labor that should have increased our ability to detect associations. Although non-differential exposure misclassification remains a concern and may have biased our results towards the null, our findings indicate that the beneficial effects of overall physical activity and leisure time sports activity are not observed for occupational physical activity in this agricultural population.

In conclusion, we found that lifetime overall physical activity, and participation in competitive sports during young ages were negatively associated with PD risk, but found no beneficial role for occupational physical activity. Our results provide further support for a previous meta-analysis of 5 studies that concluded higher leisure-time physical activity levels are associated with lower PD risk [10].

Funding

Research reported in this publication was supported by the NIEHS of the National Institutes of Health under award number R01ES10544; pilot funding for the study was received from the SCEHSC# 5P30 ES07048 and The American Parkinson Disease Association.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

We thanks Dr. Bronstein and Dr. Bordelon, all study participants, and the Parkinson's disease support groups in the California central valley for their support and contributions.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2016.05.007>.

References

- [1] H.-F. Shu, T. Yang, S.-X. Yu, H.-D. Huang, L.-L. Jiang, J.-W. Gu, et al., Aerobic exercise for Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials, *PLoS One* 9 (2014) e100503.
- [2] C.L. Tomlinson, S. Patel, C. Meek, C.P. Herd, C.E. Clarke, R. Stowe, et al., Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis, *BMJ* 345 (2012) e5004.
- [3] M. Hirsch, B. Farley, Exercise and neuroplasticity in persons living with Parkinson's disease, *Eur. J. Phys. Rehabil. Med.* 45 (2009) 215–229.
- [4] J.E. Ahlskog, Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology* 77 (2011) 288–294.
- [5] B.E. Fisher, Q. Li, A. Nacca, G.J. Salem, J. Song, J. Yip, et al., Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease, *Neuroreport* 24 (2013) 509–514.
- [6] B.E. Fisher, A.D. Wu, G.J. Salem, J. Song, C.-H.J. Lin, J. Yip, et al., The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease, *Arch. Phys. Med. Rehabil.* 89 (2008) 1221–1229.
- [7] E.L. Thacker, H. Chen, A.V. Patel, M.L. McCullough, E.E. Calle, M.J. Thun, et al., Recreational physical activity and risk of Parkinson's disease, *Mov. Disord.* 23 (2008) 69–74.
- [8] Q. Xu, Y. Park, X. Huang, A. Hollenbeck, A. Blair, A. Schatzkin, et al., Physical activities and future risk of Parkinson disease, *Neurology* 75 (2010) 341–348.
- [9] H. Chen, S. Zhang, M. Schwarzschild, M. Hernan, A. Ascherio, Physical activity and the risk of Parkinson disease, *Neurology* 64 (2005) 664–669.
- [10] F. Yang, Y.T. Lagerros, R. Belloc, H.-O. Adami, F. Fang, N.L. Pedersen, et al., Physical activity and risk of Parkinson's disease in the Swedish national march cohort, *Brain* 138 (2015) 269–275.
- [11] K. Sääksjärvi, P. Knekt, S. Männistö, J. Lyytinen, T. Jääskeläinen, N. Kanerva, et al., Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity, *Eur. J. Epidemiol.* 29 (2014) 285–292.
- [12] S.K. Keadle, S.C. Moore, J.N. Sampson, Q. Xiao, D. Albanes, C.E. Matthews, Causes of death associated with prolonged TV viewing: NIH-AARP diet and health study, *Am. J. Prev. Med.* 49 (2015) 811–821.
- [13] L.B. Andersen, P. Schnohr, M. Schroll, H.O. Hein, All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work, *Arch. Intern. Med.* 160 (2000) 1621–1628.
- [14] N. Krause, Physical activity and cardiovascular mortality-disentangling the roles of work, fitness, and leisure, *Scand. J. Work Environ. Health* (2010) 349–355.
- [15] S. Costello, M. Cockburn, J. Bronstein, X. Zhang, B. Ritz, Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California, *Am. J. Epidemiol.* 169 (2009) 919–926.
- [16] A.J. Hughes, Y. Ben-Shlomo, S.E. Daniel, A.J. Lees, What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study, *Neurology* 57 (2001) S34–S38.
- [17] B. Ritz, S.L. Rhodes, Y. Bordelon, J. Bronstein, alpha-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease, *PLoS One* 7 (2012) e36199.
- [18] Committee IR, Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)—short and long forms, *Retriev. Sept.* 17 (2005) 2008.
- [19] B.E. Ainsworth, W.L. Haskell, M.C. Whitt, M.L. Irwin, A.M. Swartz, S.J. Strath, et al., Compendium of physical activities: an update of activity codes and MET intensities, *Med. Sci. Sports Exerc.* 32 (2000) S498–S504.
- [20] Public Use Microdata Series (IPUMS-USA) Occupation Code System 2000. <http://usa.ipums.org/usa/volii/00occup.shtml>. Accessed June 2010.
- [21] C. Tudor-Locke, B.E. Ainsworth, T.L. Washington, R. Troiano, Assigning metabolic equivalent values to the 2002 census occupational classification system, *J. Phys. Act. Health* 8 (2011) 581–586.
- [22] A. Wang, S. Costello, M. Cockburn, X. Zhang, J. Bronstein, B. Ritz, Parkinson's disease risk from ambient exposure to pesticides, *Eur. J. Epidemiol.* 26 (2011) 547–555.
- [23] Z. Liew, A. Wang, J. Bronstein, B. Ritz, Job Exposure Matrix (JEM)-derived estimates of lifetime occupational pesticide exposure and the risk of Parkinson's disease, *Arch. Environ. Occup. Health* 69 (2014) 241–251.
- [24] G. Logroscino, H.D. Sesso, R. Paffenbarger, I.-M. Lee, Physical activity and risk of Parkinson's disease: a prospective cohort study, *J. Neurol., Neurosurg. Psychiatry* 77 (2006) 1318–1322.
- [25] A. Holtermann, J. Hansen, H. Burr, K. Sjøgaard, G. Sjøgaard, The health paradox of occupational and leisure-time physical activity, *Br. J. Sports Med.* 46 (2012) 291–295.
- [26] A.D. Cohen, J.L. Tillerson, A.D. Smith, T. Schallert, M.J. Zigmond, Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF, *J. Neurochem.* 85 (2003) 299–305.
- [27] J. Tillerson, W. Caudle, M. Revere, G. Miller, Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease, *Neuroscience* 119 (2003) 899–911.
- [28] H.J. Green, I. Fraser, Differential effects of exercise intensity on serum uric acid concentration, *Med. Sci. Sports Exerc.* 20 (1988) 55–59.
- [29] S. Cipriani, X. Chen, M.A. Schwarzschild, Urates: a novel biomarker of Parkinson's disease risk, diagnosis and prognosis, *Biomark. Med.* 4 (2010) 701–712.
- [30] A. Kyrozi, A. Ghika, P. Stathopoulos, D. Vassilopoulos, D. Trichopoulos, A. Trichopoulou, Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece, *Eur. J. Epidemiol.* 28 (2013) 67–77.

Supplementary Table 1
7 Cohort studies of lifetime physical activity and risk of developing Parkinson's disease

Author (year)	Cohort name, Country, Gender	Baseline/Age (year)/Follow-up (years)	Case N/ Cohort N	Activity measure	Case identification	Covariates Adjustment	Main results
Yang (2014)	National March Cohort, Sweden, Male and female	1997 / mean=50.3 / mean=12.6	286 / 43,368	Total PA: 24-h EE questionnaire, tertiles (MET-hours/day) Household and commuting: <2, 3-4, 5-6, >6 hours/week (h/wk) Leisure time exercise: tertiles (MET-hours/day) Occupational PA: sedentary, moving little, strenuous General PA: sum of household and commuting, leisure time and occupational, tertiles (MET-hours/day)	Swedish national patient register, primary and secondary PD diagnoses	Age, gender, education, smoking, alcohol, caffeine, BMI	Total PA medium vs. low: HR=0.55 (95%CI 0.35-0.87), male Household and commuting >6 vs. <2h/wk: HR=0.57 (95%CI 0.39-0.83), all; HR=0.50(95%CI 0.31-0.81), male Occupational PA strenuous vs. sedentary: HR=0.74(95%CI 0.45-1.22), all General PA high vs. low: HR=0.72 (95%CI 0.53-0.99), all; HR=0.53(95%CI 0.33-0.85), male
Sääksjärvi (2014)	Mobile Clinic Health Examination Survey, Finland, Male and female	1973-1976 / 50-79 / max=22	101 / 6,715	Leisure-time PA: none, light activity ≥4 h/wk, heavy activity ≥3 h/wk	Nationwide register of prescription drug reimbursement	Age, gender, education, alcohol, caffeine, smoking, BMI, community density, occupation	Leisure-time PA heavy vs. none: RR=0.27(95%CI 0.08-0.90), all; RR=0.25(95%CI 0.06-1.09), excluded the first 10 years of follow-up*
Kyrozis (2013)	EPIC-Greece population-based cohort, Greek, Male and female	1993-1999 / 20-86 / mean=8.45	88 / 25,407	Self-reported both occupational and leisure-time PA, and calculated as daily MET-hours (continuous)	Self-report PD diagnosis or medication use with phone validation	Age, gender, marital status, education, farming, smoking, caffeine, BMI, energy intake	HR=0.95 (95%CI 0.90-1.00)
Xu (2010)	NIH-AARP (American Association of Retired Persons) Diet and Health Study cohort, United States, Male and	1996-1997 / 50-71 / max=10	767 / 213,701	Moderate to vigorous leisure time PA at ages 15-18, 19-29, 35-39 and in past 10 years: never, <1, 1-3, 4-7, >7 h/wk Occupational PA: sitting, standing, walking, light or heavy lifting Sports at ages 15-18: <1, 1-2, 3-4, ≥5 times/wk	Self-report with confirmed medical record	Age, gender, race, education, smoking, caffeine	Leisure time PA Moderate to vigorous activities >7 vs. <1h/wk: Ages 35-39: OR=0.62 (95%CI 0.48-0.81) Past 10y: OR=0.65; 95%CI 0.51-0.83) Occupational PA heavy lifting vs. sitting: OR= 0.63 (95%CI 0.39-1.02)

Thacker (2008)	female	1992-1993 / mean=63 / max=10	413 / 14,325	Leisure-time PA: self-reported frequency/duration of light, moderate and vigorous activities (MET-h/wk) at baseline and at age 40.	Self-report with confirmed medical record	Age, education, caloric intake, dairy intake, smoking, alcohol, caffeine, BMI, pesticide, ibuprofen	Moderate to vigorous activities $\geq 16(M)$ or $\geq 11.5(F)$ MET- h/wk vs. none or light activities only at baseline: RR=0.6 (95%CI 0.4-1.0) Moderate to vigorous activity at age 40 was not associated with PD risk.
Logrosino (2006)	Harvard Alumni Health Study, United States, Male only	1988 / mean=67.6 / 10	101 / 10,714	Leisure time PA: self-reported frequency/duration; quartiles EE (≤ 1000 to >3000 kcal/wk) Sports participation during college: <5 , ≥ 5 , unknown h/wk, varsity athlete	Self-report and death certificates	Age, smoking, tea, caffeine, history of CVD, cancer	EE >3000 vs. <1000 kcal/wk: RR=0.64 (95%CI 0.36-1.13); p for trend=0.12
Chen (2005)	Health Professionals Follow-Up Study (male) and Nurses' Health Study (female), United States	1986 / HPFS: 40-75; NHS: 30-55 / max=14	252 / 48,574 (M) / 135 / 77,254 (F)	Leisure time PA: self-reported frequency/duration; quintile (MET-h/wk) Youth strenuous exercise: self-reported months per year spent ≥ 2 days/wk on strenuous exercises	Self-report with medical record confirmation	Age, smoking, energy, caffeine, lactose and alcohol intake, BMI	Leisure time PA highest vs. lowest quintile: RR=0.7 (0.5-1.1); vigorous only: RR=0.5 (0.3-0.9), male Youth strenuous exercise ≥ 10 vs. ≤ 2 months/year: 0.4 (95%CI 0.2-0.7), male; RR=0.5 (95%CI 0.2-1.4), female

PD, Parkinson's disease; PA, physical activity; MET, metabolic equivalent tasks; EE, energy expenditure; h/wk, hours per week; BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio; RR, relative risk; OR, odds ratio; CI, confidence interval.

* Less than 5 PD cases in the heavy group

Supplementary Table 2
 Distribution of competitive sports history (reported as ever participated) case status among study participants in Central Valley of California, 2001–2007

Competitive sports (MET)	All subjects (N=698)		PD cases (N=357)		Controls (N=341)	
	N	%	N	%	N	%
Basketball (7)	144	20.63	69	19.33	75	21.99
Baseball (5)	126	18.05	59	16.53	67	19.65
Football (8)	126	18.05	60	16.81	66	19.35
Track and field (7)	87	12.46	40	11.20	47	13.78
Softball (5)	58	8.31	26	7.28	32	9.38

a. We show only the top 5 most commonly reported competitive sports.

b. Note: Participants may have participated in more than one sports.

Supplementary Table 3
 Gender stratified multivariable-adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-for-trend for Parkinson's disease (PD) risk by overall moderate to vigorous physical activity, competitive sports and occupational activity^a.

Physical activity ^b	Men			Women				
	PD/Control	aOR	95%CI	P-for-trend ^c	PD/Control	aOR	95%CI	P-for-trend ^c
Overall Physical Activity								
<47.8	43/30	1 (Reference)			64/54	1 (Reference)		
47.8-93.0	41/38	0.73	0.37-1.47		34/41	0.63	0.34-1.17	
93.0-180.0	48/42	0.74	0.38-1.45		25/37	0.56	0.28-1.12	
≥180.0	58/53	0.50	0.25-1.02	0.07	23/25	0.68	0.32-1.44	0.25
Competitive Sports								
Never	75/53	1 (Reference)			109/107	1 (Reference)		
<42	44/37	0.89	0.48-1.66		25/24	1.16	0.58-2.31	
42-105	47/39	0.98	0.53-1.82		11/20	0.70	0.29-1.71	
≥105	34/45	0.60	0.33-1.12	0.10	6/13	0.63	0.22-1.85	0.32
Occupational Activity								
<56.7	12/11	1 (Reference)			77/74	1 (Reference)		
56.7-89.3	29/35	0.86	0.31-2.39		40/51	0.81	0.46-1.45	
89.3-130.8	63/61	1.17	0.44-3.13		23/23	1.02	0.48-2.16	
≥130.8	101/69	1.37	0.49-3.82	0.24	8/16	0.37	0.11-1.21	0.22

^a Logistic regression models were adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.

^b Overall Physical Activity (MET-h/wk) = 8*vigorous activity hour/week + 4*moderate activity hour/week; quartile cutoff.

Competitive Sports (MET-year) = sum of sport MET value*year of participation; tertile cutoff.

Occupational Activity (MET-year) = sum of job MET value*year of participation; quartile cutoff.

^c Linear trend was tested using the midpoint of each exposure category as a continuous variable in the regression model.

Supplementary Table 4
Lag analysis of multivariable-adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-for-trend for Parkinson's disease (PD) risk by competitive sports and occupational activity^a.

	Exclusion of Last 10 years Prior to Diagnosis			Exclusion of Last 20 years Prior to Diagnosis			
	PD/Control	aOR	95%CI	PD/Control	aOR	95%CI	P-for-trend ^c
Cumulative physical activity [MET-year]^b							
Never	185/160	1 (Reference)		186/160	1 (Reference)		
<42	74/68	0.98	0.64-1.52	75/71	0.96	0.62-1.48	
42-105	52/52	0.93	0.57-1.54	54/54	0.94	0.57-1.54	
≥105	40/58	0.62	0.37-1.03	36/53	0.59	0.34-0.99	0.09
Occupational Activity							
< 56.7	111/113	1 (Reference)		140/149	1 (Reference)		
56.7-89.3	66/76	0.83	0.52-1.33	74/75	1.08	0.68-1.72	
89.3-130.8	79/75	0.88	0.52-1.49	73/59	1.05	0.61-1.80	
≥130.8	96/72	0.87	0.47-1.60	64/46	1.04	0.55-1.96	0.93

^a Logistic regression models were adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.

^b Competitive Sports (MET-year) = sum of sport MET value*year of participation; tertile cutoff.

Occupational Activity (MET-year) = sum of job MET value*year of participation; quartile cutoff.

^c Linear trend was tested using the midpoint of each exposure category as a continuous variable in the regression model.

Supplementary Table 5
Multivariable-adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-for-trend for Parkinson's disease (PD) risk and occupational activity, excluding highly occupational pesticide exposed individuals^a

Occupational activity (MET-year) ^b	Men and Women			Men			Women					
	case/control	aOR	95% CI	p for trend ^c	case/control	aOR	95% CI	p for trend ^c	case/control	aOR	95% CI	p for trend ^c
< 56.7	88/85	1	(Reference)		11/11	1	(Reference)		77/74	1	(Reference)	
56.7-89.3	66/84	0.78	0.48-1.26		27/33	0.84	0.30-2.38		39/51	0.80	0.45-1.42	
89.3-130.8	80/79	0.91	0.54-1.56		57/57	1.14	0.42-3.10		23/22	1.09	0.51-2.35	
≥ 130.8	68/65	0.75	0.41-1.39	0.42	64/53	1.21	0.42-3.48	0.44	4/12	NA	NA	0.23

^a Logistic regression model adjusted for age, gender, race, education, smoking, family history of PD, and residential and occupational pesticide exposures.

^b Occupational Activity = sum of job MET value*year of participation (MET-year); quartile cutoff.

^c Linear trend was tested using the midpoint of each exposure category as a continuous variable in the regression model.