Physical activity and Parkinson's disease: a two-sample Mendelian randomization study

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Funding agency: None.

Relevant conflicts of interests/financial disclosures: Nothing to report.

Word count: main text: 2,299**;** abstract: 175

ABSTRACT

Background: Observational studies reported an inverse association between physical activity and risk of Parkinson's disease (PD). However, the presence of early PD symptoms may have led to the avoidance of physical activity and induced reverse causation.

Objective: To assess the association between physical activity and PD risk using a two-sample Mendelian randomization (MR) design.

Methods: We used eight single nucleotide polymorphisms (SNPs) for accelerometer-measured 'average acceleration' and seven SNPs for vigorous physical activity ('fraction of accelerations >425 milligravities') from 91,084 UK Biobank participants and evaluated these in relation to risk of PD using 33,674 cases and 449,056 controls of European ancestry.

Results: The MR analysis suggested no effect of 'average acceleration' (inverse variance weighted odds ratio (OR) [95% confidence interval (CI)] = 0.97 [0.72-1.30], *P*-value = 0.824) and 'fraction of accelerations >425 milligravities' (OR = 0.78 [0.39; 1.54], *P*-value = 0.472) on PD. Sensitivity analysis to assess potential pleiotropy led to no substantive change in the estimate.

Conclusion: The current study does not support a protective association between physical activity and the risk of PD.

Key words: physical activity, Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition, after Alzheimer's disease [1]. The global burden of PD more than doubled since 1990 and is projected to double again by 2030 because of population aging [1]. Physical activity is known to be protective for a range of chronic conditions (such as cardiovascular disease and cancer) [2, 3], and the evidence for protection against PD has strengthened in the past two decades [4-6].

Several cohort studies have suggested that physically active individuals are less likely to develop PD [7-11]. This potential inverse association between physical activity and risk of PD has further been substantiated by two systematic reviews and meta-analyses [5, 11]. A recent umbrella review on environmental risk factors reported that constipation and physical activity presented with the most consistent evidence [12]. Also, evidence is accumulating that physical activity may postpone disease onset and slow its progression [13-15].

One concern that has not been adequately addressed in previous research is the potential for reverse causation. Early prodromal disease features may make individuals become less physically active and induce a spurious inverse association [16, 17]. Non-motor symptoms (hyposmia, constipation, sleep disorders) may precede diagnosis by up to two decades and could lower the propensity to engage in physical activity [18]. Previous studies relied on traditional observational epidemiological designs that can be subject to reverse causation and unmeasured confounding [19]. Mendelian randomization (MR) offers an alternative way to probe the issue of causality by using genetic variants as instrumental variables to account for observational study bias [20, 21]. We report on a summary-based MR study on the association of accelerometer-measured physical activity and risk of PD and age of disease onset.

Methods

Study design

We retrieved associations of single nucleotide polymorphisms (SNPs) with accelerometer-measured physical activity from a genome-wide association study (GWAS) [22] of UK Biobank

participants. SNP-outcome associations were derived from summary genetic association data on PD [23] and on disease age of onset [24] of the largest available GWAS meta-analyses.

Physical activity measurement in UK Biobank

UK Biobank recruited 502,641 individuals aged 37-73 years between 2006 and 2010 from across the UK [25]. This study has been described in full previously [26]. For objective assessment of physical activity, a subset of 103,712 participants wore an Axivity AX3 triaxial accelerometer on the wrist for a seven-day-period between 2013 and 2015 [27]. The mean age of study participants was 56.0 years (SD=7.9), and 54.5% were women. 100Hz raw triaxial acceleration data was used after calibration, removal of gravity and sensor noise, and identification of wear/non-wear episodes. Non-wear time was defined as consecutive stationary episodes lasting for at least 60 minutes where all three axes had a standard deviation of less than 13.0 mg. We used genetic variants proxying two accelerometer-based physical activity measures. 'Average acceleration' (mean acceleration in milli-gravities) and the 'fraction of accelerations >425 milli-gravities', the latter corresponding to an equivalent of vigorous physical activity (≥6 metabolic equivalent tasks (METs))[22].

Written informed consent was obtained from UK Biobank study participants and ethics approval of UK Biobank was given by the North West Multicentre Research Ethics Committee, the National Information Governance Board for Health & Social Care and the Community Health Index Advisory Group. The GWAS studies [22] were covered by the general ethical approval of the UK Biobank studies from the NHS National Research Ethics Service on June 17, 2011 (Ref 11/NW/0382).

Selection of genetic instrumental variables for physical activity

Data from 91,084 UK Biobank participants with valid accelerometer measurements were genotyped using the UK BiLEVE array and the UK Biobank axiom array. We selected 8 SNPs associated with 'average acceleration' at a genome-wide significance level ($P < 5 \times 10^{-8}$) and eight SNPs associated with 'fraction of accelerations >425 milli-gravities' at $P < 5 \times 10^{-7}$, using a PLINK clumping algorithm (r^2 threshold = 0.001 and window size = 10mB) (Supplementary

Table 1). After removing one SNP that was associated with PD in previous GWAS (Supplementary Table 3), 7 SNPs were retained as instruments for 'fraction of accelerations >425 milligravities'.

GWAS summary statistics for Parkinson's disease and age of disease onset

We derived SNP-outcome associations from the largest GWAS meta-analysis [23] to date. The meta-analysis by Nalls et al. [23] included three previously published GWAS [28, 29], and 13 new datasets. All samples underwent similar standardized quality control for inclusion and clinical case definition. Recruitment, genotyping quality control, and diagnostic criteria are described elsewhere in detail [23]. We extracted log odds ratios (OR) per additive allele dosages and standard errors from the meta-analysis of 33,674 cases and 449,056 controls of European ancestry. Genetic summary data for PD 'age of onset' of 28,568 cases was obtained from 19 studies contributing to the International Parkinson's Disease Genomics Consortium (IPDGC) reported in the GWAS by Blauwendraat and colleagues [24]. 'Age of onset' was defined based on patient report of initial manifestation of parkinsonian motor signs (tremor, bradykinesia, rigidity, or gait impairment) or, where this information was not available, age of diagnosis was used as a proxy for onset age. For all SNPs used as instruments for accelerometer-measured physical activity, harmonized SNP-PD and SNP-'age of onset' associations are provided in Supplementary Table 2.

Data availability

The summary statistics for the physical activity GWAS [22] are available at https://klimentidis.lab.arizona.edu/content/data. The PD GWAS summary data are available upon request (for details see Nalls et al.[23]). 'Age of onset'[24] summary data are available at https://t2m.io/WLhfhcA7.

Statistical power

The a priori statistical power was calculated according to Brion et al. [30]. The accelerometer-measured physical activity SNPs explained 0.1% of the phenotypic variance. Given a type 1

error of 5%, we had sufficient statistical power (≥80%) when the expected OR per 1-SD for PD was ≤0.68 in genetically instrumented accelerometer-measured physical activity.

Statistical analyses

Harmonization was performed to rule out strand mismatches and to ensure alignment of effect sizes. Wald ratios were calculated by dividing the per-allele log OR (or beta coefficient) for each SNP from the PD GWAS (and 'age of onset' GWAS) by the corresponding log OR (or beta) of the same SNP in the physical activity GWAS. We estimated the effect of physical activity on PD by performing a multiplicative random effects inverse-variance weighted (IVW) meta-analysis [20, 31] of Wald ratios. Results are presented as mean OR for PD or mean beta for 'age of onset' per 1-SD increment in 'average acceleration' and for comparing engagement in vigorous physical activity ('fraction accelerations >425 milli-gravities') and no engagement in vigorous physical activity ('fraction accelerations ≤425 milligravities'), respectively. One SD of 'average acceleration' in the UK Biobank Study is approximately 8 milligravities (or 0.08 m/s^2) of acceleration in a mean 5-second window [22].

MR is based on the assumption that SNP-outcome effects are mediated solely through the exposure [20, 32]. Violations of this assumption through horizontal pleiotropy, whereby the instruments exert an effect on the outcome independent of the exposure, can introduce bias. To examine possible violations of this assumption, we checked each candidate SNP and its proxies (r^2>0.8) in PhenoScanner [33] for previously reported associations ($P<5x10^{-8}$) with confounders. Of the potential risk factors [4, 18, 34, 35] judged to have sufficient evidence for association with PD, we considered smoking [36] to be the only common cause of physical activity and PD. Furthermore, statistical sensitivity analyses more robust to the inclusion of potentially pleiotropic variants can be used to help establish the validity of causal inference from MR analysis. Valid genetic instruments should furnish similar estimates of effect [32]. This can be assessed using the Cochran's Q statistic [32]. If Q detects heterogeneity among ratio estimates, this points to pleiotropy. If the pleiotropy is 'balanced' (i.e., pleiotropic effects are independent of magnitude of the SNP-exposure associations; and if the mean pleiotropic effect is zero), the effect can be

reliably estimated by the multiplicative random effects IVW method [31, 32]. However, if the mean pleiotropic effect is non-zero, as shown by the presence of a deviation from a zero intercept of an MR Egger regression [20], robust meta-analytic methods are indicated [32, 37]. Classes of robust methods each relying on different sets of assumptions can assist in protecting against pleiotropy. We followed Slob and Burgess [37] to report estimates from at least one method of three classes of robust methods: (1) consensus class (weighted median [20]), (2) outlier robust class (MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) [37], Radial regression [38]), and (3) modeling methods class (Robust Adjusted Profile Score [37]). We also performed leave-one-out analysis to assess whether the IVW estimate was driven or biased by a single SNP. Selective survival is another potential source of bias in MR studies truncated by death, which is of particular relevance in our study because PD is a strong predictor of death, physical activity influences death, and death rates are high in older adults included in the PD GWAS [39]. As suggested by Vansteeland et al.[40], we performed IVW to check for an association of physical activity with longevity using data from a GWAS on longevity [41]. Analyses were performed using the meta (4.11.0), TwoSampleMR (0.5.2) [42], and MRPRESSO (1.0) packages in R (version 3.6.3).

Results

The OR from the IVW-MR for the magnitude of the effect of 1-SD increment in 'average acceleration' on PD was 0.97 (95% CI: 0.72-1.30. P-Value = 0.824) (Table 1). Likewise, 'fraction accelerations >425 milli-gravities' was unrelated to PD (IVW OR: 0.78, 95% CI: 0.39-1.51, P-Value = 0.472). 'Average acceleration' and 'fraction accelerations >425 milli-gravities' were not associated with age of disease onset (Table 1). None of our selected instruments or its proxies was associated with smoking in PhenoScanner (Supplementary Table 3). There was substantial heterogeneity between Wald ratios for 'average acceleration' and PD, and low heterogeneity for the association of 'average acceleration' and 'fraction accelerations >425 milli-gravities' and disease onset age (Supplementary Table 4). The intercept from the MR Egger regression was not statistically significant for the two considered outcomes but it might have been underpowered 32 and pointed to possible directional pleiotropy for the physical activity-

PD association (Supplementary Table 5). However, the estimates were similar when using models that are more robust to directional pleiotropy (Tables 1). Furthermore, leave-one-out analysis revealed that no single SNP drove the results (Supplementary Table 6). 'Average acceleration' physical activity was unrelated to the odds of surviving the 90th percentile of age (IVW OR per 1-SD: 1.01, 95% CI: 0.92-1.12, P-value = 0.794) in a sensitivity analysis to assess potential survival bias.

Discussion

Using genetic instruments for accelerometer-measured physical activity from 91,000 UK Biobank participants and 30,000 cases of PD, we examined the relationship between physical activity and PD and age of disease onset. Th current study provides no evidence for a role of physical activity in the development of PD or the delay of disease onset.

Several observational studies have investigated the association between moderate to vigorous self-reported physical activity and risk of PD [7-11], which according to a recent meta-analysis was 29% (hazard ratio: 0.71; 95% CI: 0.58-0.87) lower among individuals with the highest level of activity compared to those with the lowest [5]. Exercise may also prevent conditions associated with PD, including lower the progression of motor disability and reducing the risk of non-motor features such as depression and cognitive impairment [13, 43-45].

However, the observed inverse association between physical activity and PD in available studies could be due to reverse causation [16, 17]. Previous cohort studies have sought to reduce the impact of reverse causation by excluding cases that occurred during the first few years of follow-up. The recent meta-analysis [5] considered the possibility of reverse causation between early PD with decreased levels of physical activity by conducting time-lag analyses only considering studies that excluded the first 10 years of follow-up. The results of this sensitivity analysis suggested that estimates were unaffected by reverse causation. However, PD has a long prodromal phase characterized by symptoms such as hyposmia, constipation, and sleep disorders that might be present up to 20 years before the manifestation of the characteristic motor symptoms, and it is likely that such preclinical nonmotor symptoms affect

several lifestyle factors, including physical activity [18]. There is also the possibility that early dopaminergic loss may cause less participation in physical activity [46]. Recently, large-scale prospective observational studies [47, 48] and a MR [49] study have provided convincing evidence that the previously reported observed inverse association between physical activity and Alzheimer's disease might have been due to reverse causation and the interpretation of the authors was that the association with Alzheimer's disease was likely non-causal.

Notable strengths of the present study are the large sample size of the outcomes GWAS that enabled considerable statistical precision and the use of genetic proxies for accelerometer-measured physical activity, which is less prone to measurement bias and pleiotropy[50]. The study had sufficient statistical power to detect the previous observationally reported effect sizes for self-reported physical activity and PD [5, 7]. Limitations that should be considered are the age-ranges of the exposure and outcome GWAS. To ensure the validity of the analysis, the two sets represent samples taken from the same underlying population. If this was not the case, the MR estimate can be biased towards the observational estimate [20]. Another potential weakness of the current study is that PD samples consisted of a non-random subset of the population that had to survive before being included and survival bias may have distorted estimates [39]. We tested sensitivity to survival bias and found that physical activity was unrelated to longevity. Additionally, MR models employed assumed no interaction (e.g., gene-environment), and a linear relationship between physical activity and PD.

In conclusion, the association patterns between physical activity levels and lower risk of PD seen in previous observational studies were not replicated when applying an MR design. The observed inverse relationship between physical activity and PD might be due to reverse causation.

Study funding

The authors did not receive funding for this study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Author's Contribution

Conception and design: Sebastian E. Baumeister, Christa Meisinger, Michael F. Leitzmann, Andé Karch, Hansjörg Baurecht

Development of methodology: Sebastian E. Baumeister, Alexander Teumer, Hansjörg Baurecht

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Sebastian E. Baumeister

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Sebastian E. Baumeister, Alexander Teumer, Hansjörg Baurecht

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Table 1 Mendelian randomization estimates for the relationship between accelerometer-measured physical activity and Parkinson's disease and age of disease onset

Outcomes	Exposure	Method	OR [a]	(95% CI)	P-value
Parkinson's disease	Average acceleration	Inverse variance weighted	0.97	(0.72;1.30)	0.824
		Weighted median	1.06	(0.95;1.18)	0.297
		Robust adjusted profile score	1.01	(0.85;1.19)	0.951
		IVW radial	0.97	(0.72;1.3)	0.823
		MR PRESSO	1.03	(0.97;1.09)	0.447
	Fraction accelerations >425 milli-gravities	Inverse variance weighted	0.78	(0.39;1.54)	0.472
		Weighted median	0.71	(0.28;1.76)	0.456
		Robust adjusted profile score	0.77	(0.37;1.6)	0.486
		IVW radial	0.78	(0.41;1.48)	0.444
		MR PRESSO	0.78	(0.41;1.48)	0.472
			Beta [b]	(95% CI)	P value
Age of onset	Average acceleration	Inverse variance weighted	-0.028	(-0.44;0.39)	0.894
		Weighted median	0.165	(-0.35;0.68)	0.532
		Robust adjusted profile score	-0.029	(-0.47;0.41)	0.899
		IVW radial	-0.028	(-0.34;0.28)	0.857

Fraction accelerations >425 milli-gravities	Inverse variance weighted	-1.015	(-5.48;3.45)	0.656
	Weighted median	-3.498	(-9.09;2.09)	0.220
	Robust adjusted profile score	-1.070	(-5.85;3.71)	0.661
	IVW radial	-1.015	(-5.48;3.45)	0.656

MR PRESSO, MR Pleiotropy RESidual Sum and Outlier. [a] OR (odds ratio) per one standard deviation increment in 'mean accelerations' (in milli-gravities).
[b] Increment in 'Age of onset' (years) per one standard deviation increment in 'mean accelerations' (in milli-gravities).