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

Parkinson's disease (PD) is the second most common neurodegenerative condition, and the number of people living with PD is projected to double by 2030. Physical activity is known to be protective for a wide range of chronic conditions (such as cardiovascular disease and cancer), and the evidence for protection against PD has strengthened in the past two decades. Meta-analysis of cohort studies has suggested that physical activity lowers the risk of PD.[1] However, the causality of this association has not been established because conventional observational studies are susceptible to the effects of confounding and reverse causation. Of particular concern is the potential for reverse causation. Early prodromal disease features may make individuals become less physically active and induce a spurious inverse association. Nonmotor symptoms (hyposmia, constipation, sleep disorders) may precede diagnosis by up to two decades and could lower the propensity to engage in physical activity. We conducted a Mendelian randomisation (MR) study to examine the effect of accelerometer-measured physical activity on the risk of PD. MR exploits genetic variants as instrumental variables that affect the disease outcome through the exposure and allows to determine whether the exposure is a cause of the disease.[2] The MR method diminishes confounding by environmental factors because alleles are randomly allocated when passed from parents to offspring at conception and avoids reverse causation because disease cannot affect genotype.

We leveraged data from 91 084 UK Biobank participants[3] for whom genome-wide genotyping and measurements of physical activity were available, and then combined this information with genome-wide association (GWAS)[4] summary statistics for 33 674 PD cases and 449 056 controls of European ancestry. Physical activity was measured over 7 days using a wrist-worn Axivity AX3 triaxial accelerometer.[3] 'Average acceleration' (mean acceleration in milli gravities) and the 'fraction of accelerations >425 milli gravities' (vigorous physical activity) served as exposures.[3] Eight single-nucleotide polymorphisms (SNPs) associated with 'average acceleration' at $p<5\times10^{-8}$ and seven SNPs associated with vigorous physical activity at $p<5\times10^{-7}$ were selected as instruments, after applying a PLINK clumping algorithm (r^2 threshold=0.001 and window size=10 mB). PD 'age of onset' was used as a secondary outcome from a genome-wide meta-analysis[5] of 28 568 cases. We estimated the effect of physical activity on PD and age of onset using a multiplicative random effects inverse-variance weighted (IVW) method.[2] Key assumptions of MR require that the instrument is independent of confounders of the exposure–outcome association; and that the instrument is independent of the outcome conditional on the exposure and confounders.[2] The presence of pleiotropy (whereby the instruments influence the outcome independent of the exposure) was investigated by examining heterogeneity (Cochran's Q) and by MR Egger intercept test.[2] We also checked for previously reported associations with smoking (confounding between physical activity and PD), applied pleiotropy-robust methods (weighted median, robust adjusted profile score, radial regression, MR-Pleiotropy Residual Sum and Outlier) and performed leave-one-out analysis.[2]

In the standard MR analysis (IVW method), average acceleration was not associated with PD (ORs per 1SD: 0.97; 95% CI: 0.72 to 1.30; p value=0.824, figure 1). Vigorous physical activity was inversely related to PD, although the CI was wide and contained the null effect (OR: 0.78; 95% CI: 0.39 to 1.54; p value=0.472). Similarly, average acceleration and vigorous physical activity showed little association with age of PD onset (figure 1). None of the selected instruments was associated with smoking. There was substantial heterogeneity for average acceleration and PD, and low heterogeneity for the remaining IVW estimates.

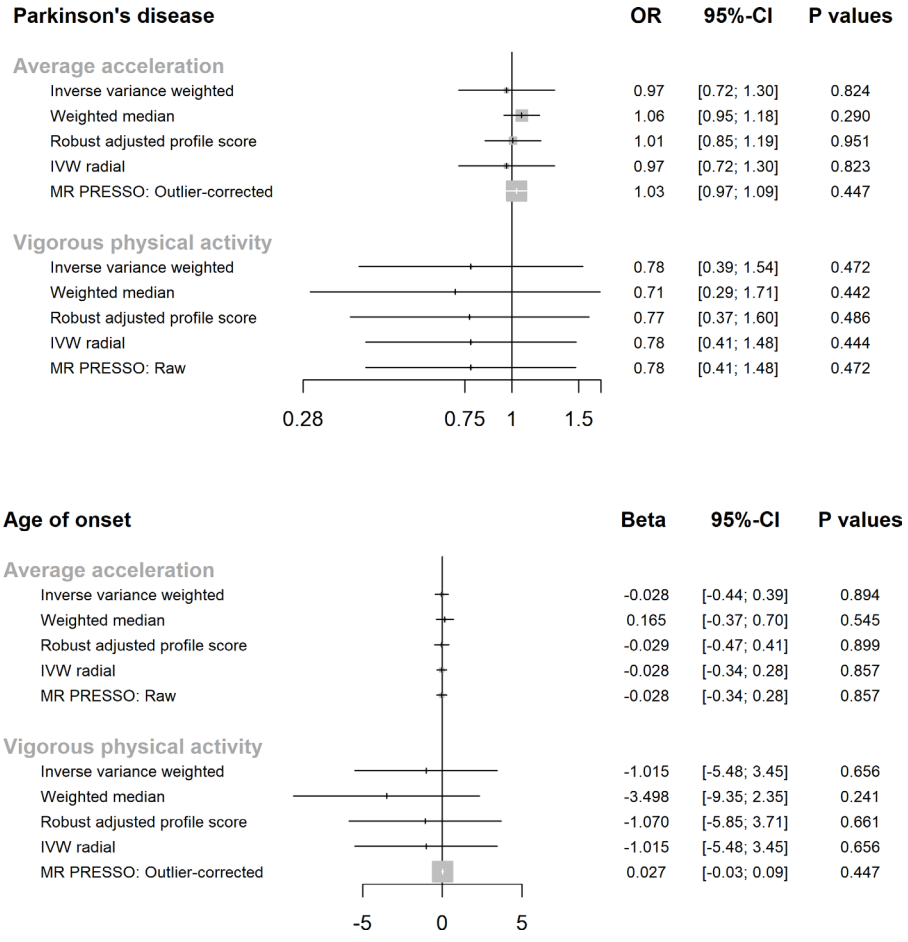

Figure 1 Estimates for the relationship between accelerometer-measured physical activity and PD and age of disease onset MR PRESSO. ORs per 1SD increment in 'mean accelerations' (in milli gravities), and for comparing vigorous physical activity (fraction accelerations >425 milli gravities) versus no vigorous physical activity (fraction accelerations ≤425 milli gravities). Beta coefficient for increment in 'age of onset' (years) per 1SD increment in 'mean accelerations' (in milli gravities), and for comparing vigorous physical activity versus no vigorous physical activity. IVW, inverse-variance weighted; MR PRESSO, Mendelian randomisation Pleiotropy RESidual Sum and Outlier; PD, Parkinson's disease.

MR Egger intercept tests did not reveal directional pleiotropy. The estimates were similar when using models that are more robust to directional pleiotropy (figure 1). Leave-one-out analysis revealed that no single SNP drove the results.

Several observational studies have investigated the association between self-reported physical activity and the risk of PD. According to a recent meta-analysis,[1] the risk of PD was 29% (HR: 0.71; 95% CI: 0.58 to 0.87) lower when comparing high and low activity levels. The meta-analysis[1] considered the possibility of reverse causation between early PD and decreased levels of physical activity by conducting time-lag analysis, 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 characterised 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 such preclinical non-motor symptoms likely affect several lifestyle factors, including physical activity. There is also the possibility that early dopaminergic loss may cause less participation in physical activity. In addition to reverse causation, previous observational estimates could have been subject to unobserved confounding (eg, by mental health, coexisting neurological disorders, medication use, time-varying health behaviours). The study has some limitations. First, the SNPs for vigorous physical activity explained only a small fraction of the phenotypic variability, and the precision of the results was low in analyses of vigorous physical activity. Second, the PD GWAS[4] included cases from the UK Biobank, which could bias the IVW estimate.[2] However, if genetic associations with physical activity levels were estimated in non-cases only, then this sample overlap would not lead to bias or type 1 error inflation. We therefore additionally analysed PD age of onset using a GWAS[5] without sample overlap. Another potential weakness is that PD samples consisted of a non-random subset of the population that had to survive before being included. Thus, survival bias may have distorted estimates.

In conclusion, the association between physical activity levels and lower risk of PD seen in previous observational studies was not replicated when applying MR. The previously observed inverse relationship between physical activity and PD may have been due to reverse causation and unobserved confounding.

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