Assessment of causal effects of physical activity on neurodegenerative diseases: A Mendelian randomization study

Peng-Fei Wu a,b, Hui Lu c,*, Xiaoting Zhou d, Xuchen Liang e, Ruizhuo Li f, Wan Zhang b,g, Danyang Li g, Kun Xia a,h,*

a Center for Medical Genetics & Hunan Provincial Key Laboratory of Medical Genetics, School of Life Sciences, Central South University, Changsha 410008, China
b Department of Neurology, Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, MA 02115, USA
c Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China
d Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, China
e School of Physical Education, Henan University, Kaifeng 475001, China
f School of Medicine, South China University of Technology, Guangzhou 510006, China
g Department of Biology, College of Arts & Sciences, Boston University, Boston, MA 02215, USA
h CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai 200031, China

Received 6 July 2020; revised 13 October 2020; accepted 17 December 2020
Available online 27 January 2021

Abstract

Background: Physical activity has been hypothesized to play a protective role in neurodegenerative diseases. However, effect estimates previously derived from observational studies were prone to confounding or reverse causation.

Methods: We performed a two-sample Mendelian randomization (MR) analysis to explore the causal association of accelerometer-measured physical activity with 3 common neurodegenerative diseases: Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS). We selected genetic instrumental variants reaching genome-wide significance (p < 5 × 10^{-8}) from 2 largest meta-analyses of about 91,100 UK Biobank participants. Summary statistics for AD, PD, and ALS were retrieved from the up-to-date studies in European ancestry led by the international consortia. The random-effect, inverse-variance weighted MR was employed as the primary method, while MR pleiotropy residual sum and outlier (MR-PRESSO), weighted median, and MR-Egger were implemented as sensitivity tests. All statistical analyses were performed using the R programming language (Version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results: Primary MR analysis and replication analysis utilized 5 and 8 instrumental variables, which explained 0.2% and 0.4% variance in physical activity, respectively. In each set, one variant at 17q21 was significantly associated with PD, and MR sensitivity analyses indicated them as an outlier and source of heterogeneity and pleiotropy. Primary results with the removal of outlier variants suggested odds ratios (ORs) of neurodegenerative diseases per unit increase in objectively measured physical activity were 1.52 for AD (95% confidence interval (95%CI): 0.88–2.63, p = 0.13) and 3.35 for PD (95%CI: 1.32–8.48, p = 0.01), while inconsistent results were shown in the replication set for AD (OR = 1.06, 95%CI: 1.01–1.12, p = 0.02) and PD (OR = 0.99, 95%CI: 0.88–0.12, p = 0.97). Similarly, the beneficial effect of physical activity on ALS (OR = 0.51, 95%CI: 0.29–0.91, p = 0.02) was not confirmed in the replication analysis (OR = 0.96, 95%CI: 0.91–1.02, p = 0.22).

Conclusion: Genetically predicted physical activity was not robustly associated with risk of neurodegenerative disorders. Triangulating evidence across other studies is necessary in order to elucidate whether enhancing physical activity is an effective approach in preventing the onset of AD, PD, or ALS.

Keywords: Alzheimer’s disease; Amyotrophic lateral sclerosis; Genetic epidemiology; Mendelian randomization; Parkinson’s disease; Physical activity

1. Introduction

Neurodegenerative diseases have become a major health burden around the world. Despite numerous advances and progress in the field of molecular biology, genetics, and pharmaceutical research, there are still no effective drugs to halt or...
Physical activity and neurodegenerative disorders

physical activity and PD risk. However, another study suggested that exercise has a negative or beneficial effect on the risk of PD and ALS and whether exercise affects motor performance, but thus far this research has failed to draw convincing conclusions.

AD is the most common neurodegenerative disease among the elderly. Emerging evidence demonstrates the potential protective effect that physical activity can have on AD. A large cohort study that included 404,840 cases found that physical inactivity was associated with increased incidence of different kinds of dementia, including AD. However, the study found that the relationship no longer existed when the measurement of physical activity occurred less than 10 years before the dementia diagnosis. Another prospective cohort study that included 10,308 cases and an average 27-year follow-up found no evidence of neuroprotective effects of physical activity on the risk of AD.

As early as 1992, a clinical report showed exercise was associated with a lower risk of PD diagnosis later in their life in a male university cohort, and more recent evidence shows that exercise greatly reduces the risk of PD. The famous National Institutes of Health-American Association of Retired Persons Diet and Health Study cohort, which recruited 213,701 participants with a wide age range, showed that those who had moderate-to-vigorous physical activity had significantly reduced the risk of PD. Likewise, a recent meta-analysis revealed an inverse dose–response association between physical activity and PD risk. However, another study suggested that this neuroprotective effect of physical activity was more prominent in males than females.

The relationship between physical activity and the risk of ALS has not been fully elucidated yet. In the beginning, people noticed a positive correlation between ALS and strenuous exercise for the reason that ALS is quite common in professional athletes. Although this study found that ALS patients had slightly higher levels of physical exercise, there is no evidence that an extremely increased duration or level of physical activity is associated with ALS. A recently published study using instrumental variables for self-reported physical activity showed that the risk of ALS was negatively correlated with light levels of physical activity, but it was positively correlated with more strenuous moderate levels of physical activity. Inconsistent results from longitudinal studies indicate that better methodologies are desperately needed in order to elucidate the relationship between physical activity and neurodegenerative diseases.

Traditional measurement of physical activity based on self-reported exercise patterns incurs bias to some extent. Self-reported questionnaires may represent what individuals should do in terms of exercise rather than how routinely they actually exercise. However, advancing technologies, such as wearable trackers and statistical machine learning, provide an opportunity to implement a relatively objective measure of physical activity in free-living environments. Elucidating causal associations when using traditional observational designs, even in randomized clinical trials, is indeed prone to various biases due to restricted sample sizes and ethical and financial challenges. Therefore, high-quality evidence is still largely warranted. Recently, genome-wide association studies (GWAS) have been conducted by large international consortia to identify significant loci for objectively measured physical activity and neurodegenerative diseases. Meanwhile, Mendelian randomization (MR) design utilizing valid instrumental variants has been applied as a robust approach to making causal inference. In our study, we implemented a two-sample MR design to investigate the role of physical activity in 3 common neurodegenerative diseases: AD, PD, and ALS.

2. Methods

2.1. Summary-level data for physical activity

We constructed 2 sets of instrumental variables for accelerometer-measured physical activity (Table 1 and Supplementary Table 1). For the primary analysis, summary statistics for physical activity were obtained from a recent GWAS, which identified 5 single nucleotide polymorphisms (SNPs) associated with objectively measured physical activity reaching genome-wide significance \( p < 5 \times 10^{-8} \). For the replication analysis, 8 genome-wide significant SNPs from another GWAS (Klintemård et al.) were utilized. Two original GWAS were conducted independently with approximately 91,100 European participants in the UK Biobank. One of the 2 GWAS measured overall activity level as average acceleration per each 30-s epoch, while the other measured it in a 5-s window. Both instrumental sets for genetically predicted physical activity have been validated and employed in several recent MR studies. Raw data for physical activity were initially collected from activity sensors for a 7-day period; measurement on free-living ambient conditions should be well representative of daily exercise routine of individuals to some extent. A statistical machine-learning model has been validated and employed to integrate sleep, sedentary behavior, and various levels of exercise intensity and yields an indicator for overall physical activity: average acceleration (milligravity). The GWAS results were adjusted for principal covariates like sex, age, sex squared, and season; effect size was interpreted as unit change in standard deviation of physical activity per additional risk allele, which is roughly equal to 75 min of moderate activity (i.e., fast walking) each day in place of sedentary behaviors.
2.2. Instrumental variable selection

Selected instrumental SNPs were examined to determine whether they satisfied 3 MR assumptions (Fig. 1). Briefly, these assumptions were that genetic variants should (1) be robustly associated with physical activity, (2) be unrelated to factors confounding the exposure-outcome relationship, and (3) influence the risk of neurodegenerative diseases only via its effects on physical activity. First, 2 sets of SNPs were associated with accelerometer-measured physical activity at genome-wide significance, thus conforming to the relevance assumption. They were also validated to be independent and not in linkage disequilibrium (threshold set at $r^2 = 0.001$ within the window of 10 mega base pairs). Second, compared to randomized controlled trials, a similar randomized allocation in MR studies is realized, mediated by genetic proxies in which a set of alleles is associated with higher or lower physical activity levels. Genetic variants, which are set in gamete formation, are an ideal tool for randomization of exposure of interest; and confounding factors and reverse causation, which are often found in traditional observational studies, hardly exists here. Additionally, our MR study only incorporated European-ancestry samples, and population stratification could be excluded from violating the independence assumption. Lastly, we looked up these instrumental SNPs in the GWAS catalog. Considering the limited number of instrumental SNPs in our study, we initially included all of them into the liberal analyses and then implemented several sensitivity analyses to investigate horizontal pleiotropic effects and the robustness of the MR findings.

2.3. Outcome data sources

Summary data on genetic associations with the 3 neurodegenerative diseases were extracted from 3 GWAS meta-analyses in which Europeans were the dominant participants. AD summary statistics were retrieved from the most recent GWAS of clinically diagnosed, late-onset AD patients; the GWAS incorporated 21,982 cases and 41,944 controls. PD datasets were released by the International Parkinson’s Disease Genomics Consortium (https://pdgenetics.org); these datasets consisted of 33,674 cases and 449,056 controls. AD summary statistics were retrieved from the most recent GWAS incorporating 21,982 cases and 41,944 controls. PD = Parkinson’s disease; SNPs = single-nucleotide polymorphisms.

Fig. 1. Schematic of the Mendelian randomization study and key assumptions. First, genetic instrumental variants associated with accelerometer-measured physical activity at genome-wide significance ($p < 5 \times 10^{-8}$) all satisfied the relevance assumption. Second, there scarcely existed any factors confounding the natural randomization in gamete formation to violate the independence assumption. Lastly, potential horizontal pleiotropic effects violating the exclusion-restriction assumption were inspected. AD = Alzheimer’s disease; ALS = amyotrophic lateral sclerosis; PD = Parkinson’s disease; SNPs = single-nucleotide polymorphisms.

2.4. Statistical analysis

We conducted a two-sample MR using the R programming language (Version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria), with the TwoSampleMR (Version 0.4.26) and MR pleiotropy residual sum and outlier (MR-PRESSO; Version 1.0.0) packages. First, the Wald ratio for each instrumental SNP was derived by dividing the outcome-association effect size ($\beta$ per additional risk allele) by the corresponding exposure-association coefficient. Then, the pooled estimates were calculated by 1 primary MR approach, the inverse-variance weighted method, and 3 sensitivity tests, MR-PRESSO, weighted median, and MR-Egger. The inverse-variance weighted estimate was based on a request from the consortia (Table 1). For instrumental SNPs whose equivalent variants were not present in the outcome GWAS datasets, proxy SNPs ($r^2 > 0.9$, according to the European panel, 1000 Genomes Project Phase 3) were searched in LDlink and adopted for MR analyses (Supplementary Table 2). Several variants were palindromic, yet they were not excluded since their minor allele frequency was lower than 0.36, which wouldn’t incur ambiguity when inferring the strand. Finally, we harmonized the exposure and outcome datasets for subsequent analysis.
random-effect meta-analysis to integrate the causal effects of individual SNPs, whereas Cook’s distance (Cook’s $D > 4/\text{number of SNPs}$ indicates significant heterogeneity) and Cochran’s $Q$ test were employed to evaluate heterogeneous effects within instrumental SNPs. The weighted median estimator pooled the effects of individual variants efficiently under the prerequisite that more than 50% of the weight came from valid instrumental variables. MR-PRESSO was capable of identifying pleiotropic effects and outlier SNPs, which yielded overall estimates adjusted for them. The MR-Egger regression intercept and MR-PRESSO global test were also implemented to examine horizontal pleiotropy. Lastly, we used the web-tool mRnd \[^{15}\] (https://shiny.cnsgenomics.com/mRnd\) to calculate a priori power for a given odds ratio (OR) scenario.

### 3. Results

For the primary analysis, instrumental variables from Doherty et al.
\[^{19}\] collectively explained about 0.2% of the variance in accelerometer-measured physical activity. For the 8 SNPs in the replication analysis, the variables from Klementidis et al.
\[^{20}\] explained about 0.4% of the variance (Supplementary Table 1). The strength of instrumental SNPs was measured by the $F$-statistic ($<10$, deemed as a weak instrument), and no weak strength bias ($F$-statistic ranged from 27 to 60) seemingly presented. Notably, rs2696625 in the primary instrument set and rs55657917 in the replication both are located at 17q21.31, a previously identified locus for PD.
\[^{36}\] To minimize the distortion to MR estimates due to heterogeneity and pleiotropy, we conducted analyses after removal of the outlier in each instrument set. Look-up in the GWAS catalog (Supplementary Table 3) indicated no pleiotropy for primary instrumental SNPs. Three SNPs in the replication analysis were associated with other traits; nevertheless, we didn’t preclude them from the instrument set. Instead, we examined their pleiotropic effects and effects on causal estimates, also through MR sensitivity analyses. After inputting required parameters in mRnd,
\[^{35}\] the minimum detectable OR was roughly estimated (Supplementary Table 4). Specifically, our study would be underpowered to detect the OR intervals of 0.57–1.61 for AD, 0.66–1.36 for PD, and 0.57–1.56 for ALS.

#### 3.1. Physical activity and AD

Overall, there was no causal relationship between accelerometer-measured physical activity and AD. MR analysis (Table 2, Fig. 2, and Supplementary Table 4) indicated that risk for AD was 1.03 (95% confidence interval (95%CI): 0.48–2.21, $p = 0.94$) per one-unit increase in genetically predicted physical activity level in the primary analysis and 1.03 (95%CI: 0.96–1.10, $p = 0.32$) in the replication analysis. Cochran’s $Q$ test ($p_{\text{het}} = 0.04$), MR-PRESSO global test ($p_{\text{Res}} = 0.03$), MR-Egger regression intercept ($p_{\text{int}} = 0.06$), and Cook’s $D$ (62.10, >4/number of SNPs indicates heterogeneity) consistently showed that rs2696625 unproportionally exerted an influence on the overall MR estimate in the primary analysis (Supplementary Tables 5–8). After removal of the outlier SNP, heterogeneity within the remaining instrumental SNPs ($p_{\text{het}} = 0.80; p_{\text{Res}} = 0.80; p_{\text{int}} = 0.65$) went down, but it didn’t support the effect of objectively measured physical activity on AD (OR = 1.52, 95%CI: 0.88–2.63, $p = 0.13$). Likewise, heterogeneity incurred by rs55657917 in the replication instrument set was investigated through sensitivity analyses (Supplementary Tables 5–8 and Supplementary Table 9).

### Table 2

Mendelian randomization estimates for the effects of physical activity on 3 neurodegenerative diseases.

| Instrumental variables | Outcome | Inverse variance weighted OR (95%CI) | $p$ | Weighted median OR (95%CI) | $p$ | MR-PRESSO naive estimate OR (95%CI) | $p$ | MR-PRESSO outlier-corrected estimate OR (95%CI) | $p$ |
|------------------------|---------|--------------------------------------|-----|---------------------------|-----|--------------------------------------|-----|------------------------------------------|-----|
| **Primary analysis** (SNPs from the GWAS by Doherty et al. 2018)\(^{19}\)** |         |                                      |     |                           |     |                                     |     |                                          |     |
| 5 SNPs at              | AD      | 1.03 (0.48–2.21)                     | 0.94| 1.25 (0.61–2.56)          | 0.53| 1.03 (0.48–2.21)                    | 0.94| 1.52 (1.11–2.09)                        | 0.08|
|                        | PD      | 0.81 (0.43–1.50)                     | 0.51| 2.10 (0.80–5.51)          | 0.13| 0.81 (0.03–17.27)                    | 0.90| 1.50 (1.32–1.71)                        | 0.10|
|                        | ALS     | 0.45 (0.27–0.74)                     | <0.001| 0.42 (0.23–0.78)         | 0.01| 0.45 (0.29–0.69)                     | 0.02| NA                                        | NA  |
| 4 SNPs at              | AD      | 1.52 (0.88–2.63)                     | 0.13| 1.49 (0.79–2.78)          | 0.21| 1.52 (1.11–2.09)                     | 0.08| NA                                        | NA  |
|                        | PD      | 3.35 (1.32–8.48)                     | 0.01| 2.77 (1.07–7.15)          | 0.03| 3.35 (1.32–8.48)                     | 0.08| NA                                        | NA  |
|                        | ALS     | 0.51 (0.29–0.91)                     | 0.02| 0.46 (0.22–0.94)          | 0.03| 0.51 (0.31–0.85)                     | 0.08| NA                                        | NA  |
| **Replication analysis** (SNPs from the GWAS by Klementidis et al. 2018)\(^{20}\)** |         |                                      |     |                           |     |                                     |     |                                          |     |
| 8 SNPs at              | AD      | 1.03 (0.96–1.10)                     | 0.32| 1.04 (0.98–1.11)          | 0.17| 1.03 (0.96–1.10)                     | 0.36| NA                                        | NA  |
|                        | PD      | 1.11 (0.88–1.40)                     | 0.37| 1.05 (0.95–1.17)          | 0.30| 1.11 (0.88–1.40)                     | 0.40| 1.06 (0.97–1.15)                        | 0.20|
|                        | ALS     | 0.95 (0.90–1.00)                     | 0.06| 0.94 (0.88–1.00)          | 0.08| 0.95 (0.90–1.00)                     | 0.10| NA                                        | NA  |
| 7 SNPs at              | AD      | 1.06 (1.01–1.12)                     | 0.02| 1.06 (1.00–1.14)          | 0.05| 1.06 (1.02–1.11)                     | 0.02| NA                                        | NA  |
|                        | PD      | 0.99 (0.88–1.12)                     | 0.97| 1.03 (0.93–1.14)          | 0.48| 0.99 (0.88–1.12)                     | 0.97| 1.02 (0.96–1.08)                        | 0.43|
|                        | ALS     | 0.96 (0.91–1.02)                     | 0.22| 0.98 (0.92–1.05)          | 0.73| 0.96 (0.91–1.02)                     | 0.26| NA                                        | NA  |

Abbreviations: 95%CI = 95% confidence interval; AD = Alzheimer’s disease; ALS = amyotrophic lateral sclerosis; GWAS = genome-wide association study; MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier; NA = not applicable; OR = odds ratio; PD = Parkinson’s disease; SNPs = single-nucleotide polymorphisms.

\[^{15}\] https://shiny.cnsgenomics.com/mRnd
Figs. 1–3), but it was not as significant ($p_{Het} = 0.08$; $p_{Rss} = 0.08$; and $p_{Int} = 0.58$) as rs2696625 in the primary analysis. With the removal of rs55657917 in the replication analysis, a weak association between physical activity and AD (OR = 1.06, 95%CI: 1.01–1.12, $p = 0.02$) was shown.

3.2. Physical activity and PD

Genetically predicted physical activity was not associated with PD either in the primary analysis (OR = 0.81, 95%CI: 0.43–1.50, $p = 0.51$) or replication analysis (OR = 1.11, 95%CI: 0.88–1.40, $p = 0.37$). Notably, rs2696625 and rs55657917 were strongly associated with PD ($p = 2.95 \times 10^{-19}$ and $p = 9.63 \times 10^{-20}$, respectively) in the dataset (Table 2, Fig. 3, and Supplementary Table 2). They showed evident heterogeneity both in the primary and replication analysis ($p_{Het} < 0.001$ and $p_{Rss} < 0.001$, respectively). Cook’s $D$ for rs2696625 and rs55657917 (Supplementary Table 9) denoted that they are potential outliers ($>4/5$ number of instrumental SNPs) as well. A causal association between physical activity and PD was present in the primary analysis after excluding rs2696625 (OR = 3.35, 95%CI: 1.32–8.48, $p = 0.01$), whereas the non-null effect was not shown in the replication analysis after excluding s55657917 (OR = 0.99, 95%CI: 0.88–1.12, $p = 0.97$).

3.3. Physical activity and ALS

On the whole, the association of genetically predicted physical activity with ALS was not consistently verified in our MR study (Table 2 and Fig. 4). Accelerometer-measured physical activity was related to risk of ALS in the primary analysis (OR = 0.45, 95%CI: 0.27–0.74, $p < 0.001$), but this was not confirmed in the replication analysis (OR = 0.95, 95%CI: 0.90–1.00, $p = 0.06$). Sensitivity analyses (Supplementary Tables 5–8) did not indicate heterogeneous or pleotropic effects of rs2696625 and rs55657917 in the primary and replication analysis ($p_{Het}$, $p_{Rss}$, and $p_{Int}$, all $> 0.29$). Cook’s $D$ was 0.33 (<4/5) for rs2696625 and 0.32 (<4/8) for rs55657917 (Supplementary Table 10), which indicates that there were no outlying effects, even though some outlying effects were found in the analysis of physical activity on AD and PD. After the removal of rs2696625 in the primary analysis, the protective effect of physical activity on ALS existed (OR = 0.51, 95%CI: 0.29–0.91, $p = 0.02$). However, in the replication analysis without rs55657917, the association was not confirmed (OR = 0.96, 95%CI: 0.91–1.02, $p = 0.22$).

4. Discussion

Neurodegenerative diseases, including AD, PD, and ALS, have largely unknown etiologies and thus are deemed as incurable chronic diseases. However, researchers are nonetheless dedicated to seeking potential disease-modifying treatments. Many observational studies seeking to establish the relationship between physical activity and neurodegenerative diseases have yielded inconsistent results. Establishing associations using a clinical-trial design is indeed prone to various biases brought about by restricted sample sizes and ethical and financial challenges. To strengthen the causal inference, we therefore conducted an MR study. Our results suggest that physical activity might act as a protective factor for ALS, but no causal associations were found between physical activity and AD or PD.
Physical activity was first considered as a risk factor for ALS based on the observation of its higher incidence among top athletes. Other studies have supported this hypothesis in that their results showed that more top athletes were diagnosed with ALS than healthy controls. For example, a study showed more weight loss and leaner figures during the premorbid stage among varsity athletes. However, a population-based study involving 636 patients with sporadic ALS and 2166 controls failed to support the hypothesis that an excess of extreme exercise such as marathon running or that occupations requiring extreme energy use increased the incidence of ALS, although some participants with ALS had slightly higher levels of leisure-time physical activity.

![Figure 3](image1.png)

*Fig. 3. Mendelian randomization analysis of the effect of physical activity on PD. Scatter plots depict the genetic variant—physical activity effect (point and horizontal line) vs. the genetic variant—PD effect (point and horizontal line). The fitted line denotes the overall estimate given by the IVW method with all instrumental variants included (solid line) or after the removal of certain variant (dashed line). Both in the primary (A) and replication (B) analysis, each variant at 17q21.3 manifested significant heterogeneity (rs2696625, Cook’s D = 42.36; Cochran’s P < 0.001; and rs55657917, Cook’s D = 0.53; Cochran’s P < 0.001). Cook’s D = Cook’s distance; IVW = inverse-variance weighted; OR = odds ratio; PD = Parkinson’s disease; SNP = single-nucleotide polymorphism.*

![Figure 4](image2.png)

*Fig. 4. Mendelian randomization analysis of the effect of physical activity on ALS. Scatter plots depict the genetic variant—physical activity effect (point and horizontal line) vs. the genetic variant—ALS effect (point and horizontal line). The fitted line denotes the overall estimate given by the IVW method with all instrumental variants included (solid line) or after the removal of certain variant (dashed line). Either in the primary (A) or replication (B) instrumental set, the 17q21.3 variant showed negligible heterogeneity (rs2696625, Cook’s D = 0.33; Cochran’s P = 0.55; and rs55657917, Cook’s D = 0.32; Cochran’s P = 0.29). ALS = amyotrophic lateral sclerosis; Cook’s D = Cook’s distance; IVW = inverse-variance weighted; OR = odds ratio; SNP = single-nucleotide polymorphism.*
Recall bias, of course, is one of the most important factors to consider. It is hard to conclude that exercise simply leads to a higher risk of ALS since multiple injuries, such as head trauma, are inevitable during strenuous exercise. One recent community-based study exploring the incidence of developing ALS among varsity high school football players from 1956 to 1970 failed to find an increased risk of ALS. One recent MR study exploring the causal relationship between different self-reported types of physical activity and ALS revealed that light-intensity physical activity was negatively associated with the risk of ALS. However, the subjective nature of the participants’ self-reported physical activity was subject to heterogeneity and measurement errors due to the fact that the study did not use clearly defined measures of exercise, like strength and frequency. In our study, we did find a protective effect on ALS risk from objectively measured physical activity based on measurements from wearable accelerometers and our evaluation system using 5 SNPs as instrumental variables. Our results are also supported by a recent prospective cohort study, which found that total physical activity was inversely associated with ALS mortality, with those who were physically active being 33% less likely to die from ALS compared to those who were inactive, although the results were borderline statistically significant across categories ($p = 0.042$). However, we failed to replicate these results using the 8 SNPs as instrumental variables. The conflicting results may have occurred because the 8 SNPs involved the use of devices that were worn by participants for only 72 h, which may be less accurate than devices worn for 7 days. Therefore, it is still not possible to firmly conclude that there is an association between physical activity and the risk of ALS.

Our study did not confirm a causal relationship between physical activity and PD or AD. Although we used a primary MR method and sensitivity analyses, we found consistent evidence for a null association of physical activity with PD or AD, and significant heterogeneity and inadequate power were issues that undermined the findings of our study. Additional studies are warranted in order to elucidate whether an increase in physical activity is an effective approach to preventing the onset of PD or AD.

The SNPs rs2696625 and rs55657917 were identified as outlier SNPs that led to increased pleiotropy in the overall MR estimate. Both of the SNPs are located at 17q21.31, a previously reported significant locus for various kinds of neurodegenerative diseases. The 17q21.31 locus was unusual because of its pattern of long-range linkage disequilibrium. This major genetic risk factor is an extended H1 haplotype on chromosome 17q21.31, which includes microtubule-associated protein tau (MAPT). Recently, a large GWAS study revealed 3 independent regions associated with PD ($p < 5 \times 10^{-8}$), one of which is the 17q21/MAPT. Another chromosome region has been strongly correlated with the 17q21/MAPT region and is associated with the onset of PD. This may partially explain the role of rs2696625 and rs55657917 in neurodegenerative diseases. However, their biological functions are still largely unknown.

One major advantage of our study lies in its two-sample MR design, which helps circumvent measurement errors, residual confounding, and reverse causation. But our study also has several limitations. First, the exposure data from wrist-worn accelerometers used for only 1 week may not well represent regular or lifelong physical activity patterns. Second, there are only a few SNPs associated with physical activity. These were used as instrumental variables and only accounted for a relatively small proportion of variance, which may have caused distortion to the MR estimate. Third, several proxy SNPs were utilized, and the biological implications of these SNPs are largely unknown. Thus, the strength of evidence given by the MR analysis is undermined. Lastly, given that our findings are mainly restricted to participants having European ancestry, caution should be used in interpreting our results and generalizing them to other populations.

5. Conclusion

Genetically predicted physical activity was not robustly associated with risk of neurodegenerative disorders. Triangulating evidence across other studies is necessary to elucidate whether enhancing physical activity is an effective approach in preventing the onset of AD, PD, and ALS.

Acknowledgments

The authors gratefully thank Dr Aiden Doherty, Dr Yann Klimentidis, Dr Brian Kunkle, Dr Aude Nicolas, Dr Mike Nalls, and all investigators and related consortia for sharing GWAS summary statistics on physical activity, Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis.

This work was supported by the Natural Science Foundation of China (81525007 and 81730036) and Key R&D Program of Hunan Province (2019SK2051). PFW and XZ received a visiting PhD scholarship from the China Scholarship Council.

Authors’ contributions

PFW played a role in conceiving and designing the study, overseeing and performing data collection, project administration, formal analysis, and drafting and editing this manuscript; HL played a role in conceiving and designing the study, project administration, and funding acquisition; XZ played a role in conceiving and designing the study and drafting and editing this manuscript; XL played a role in performing data collection and drafting this manuscript; RL played a role in performing data collection and drafting this manuscript; RL played a role in formal analysis and drafting this manuscript; WZ played a role in performing data collection and editing this manuscript; DL played a role in formal analysis and editing this manuscript; KX played a role in conceiving and designing the study, funding acquisition, and drafting and editing this manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.
Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jshs.2021.01.008.

References

1. Revi M. Alzheimer’s disease therapeutic approaches. Adv Exp Med Biol 2020;1935:105–16.
2. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson’s disease. N Engl J Med 2004;351:2498–508.
3. Dorst J, Ludolph AC, Huerbers A. Disease-modifying and symptomatic treatment of amyotrophic lateral sclerosis. Ther Adv Neurol Disord 2017;11:1756285617734734. doi:10.1177/1756285617734734.

4. Brasure M, Desai P, Davila H, et al. Physical activity interventions in preventing cognitive decline and Alzheimer-type dementia: A systematic review. Ann Intern Med 2018;168:30–8.
5. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. Lancet Neurol 2017;16:377–89.
6. Xu Q, Park Y, Huang X, et al. Physical activities and future risk of Parkinson disease. Neurology 2010;75:341–8.
7. Yang F, Trolle Lagerros Y, Bellocco R, et al. Physical activity and risk of Parkinson’s disease in the Swedish National March cohort. Brain 2015;138:269–75.
8. Huisman MH, Seelen M, de Jong SW, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2013;84:976–81.
9. Gallo V, Vanacore N, Bueno-de-Mesquita HB, et al. Physical activity and risk of amyotrophic lateral sclerosis in a prospective cohort study. Eur J Epidemiol 2016;31:255–66.
10. Kivimäki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardio-metabolic disease, and risk of dementia: An individual-participant meta-analysis. BMJ 2019;365:l41495. doi:10.1136/bmj.l41495.
11. Sabia S, Dugravot A, Dartigues JF, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of the Whitehall II cohort study. BMJ 2017;357:j2709. doi:10.1136/bmj.j2709.
12. Sasco AJ, Paffenbarger Jr RS, Gendre L, Wing AL. The role of physical exercise in the occurrence of Parkinson’s disease. Arch Neurol 1992;49:360–5.
13. Fang X, Han D, Cheng Q, et al. Association of levels of physical activity with risk of Parkinson disease: A systematic review and meta-analysis. JAMA Netw Open 2018;1:e182421. doi:10.1001/jamanetworkopen.2018.2421.
14. Bandres-Ciga S, Noyce AJ, Hemani G, et al. Shared polygenic risk and causal inferences in amyotrophic lateral sclerosis. Ann Neurol 2019;85:470–81.
15. Chen T, Honda T, Chen S, Narazaki K, Kumagai S. Dose—response association between accelerometer-assessed physical activity and incidence of functional disability in older Japanese adults: A 6-year prospective study. J Gerontol A Biol Sci Med Sci 2020;75:1763–70.
16. Papadimitriou N, Dimou N, Tsilidis KK, et al. Physical activity and risks of breast and colorectal cancer: A Mendelian randomisation analysis. Nat Commun 2020;11:597. doi:10.1038/s41467-020-14389-8.
17. Lynch BM, Dixon-Suen SC, Ramirez Varela A, et al. Approaches to improve causal inference in physical activity epidemiology. J Phys Act Health 2020;17:80–4.
18. Choi KW, Chen C-Y, Stein MB, et al. Assessment of bidirectional relationships between physical activity and depression among adults: A 2-sample Mendelian randomization study. JAMA Psychiatry 2019;76:399–408.
19. Doherty A, Smith-Byrne K, Ferreira T, et al. GWAS identifies 14 loci for device-measured physical activity and sleep duration. Nat Commun 2018;9:5257. doi:10.1038/s41467-018-07434-3.
20. Klimentidis YC, Raichlen DA, Bea J, et al. Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including CADM2 and APOE. Int J Obes (Lond) 2018;42:1161–76.
21. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer’s disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet 2019;51:414–30.
22. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer’s disease risk. Nat Genet 2019;51:404–13.
23. Marioni RE, Harris SE, Zhang Q, et al. GWAS on family history of Alzheimer’s disease. Transl Psychiatry 2018;8:899. doi:10.1038/s41398-018-0150-6.
24. Nalls MA, Blauwendraat C, Vallega CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson’s disease: A meta-analysis of genome-wide association studies. Lancet Neurol 2019;18:1091–102.
25. Nicolas A, Kenna KP, Renton AE, et al. Genome-wide analyses identify KIF5A as a novel ALS Gene. Neuron 2018;97:1268–83.
26. Zhuang Z, Gao M, Yang R, et al. Association of physical activity, sedentary behaviours and sleep duration with cardiovascular diseases and lipid profiles: A Mendelian randomization analysis. Lipids Health Dis 2020;19:86. doi:10.1186/s12944-020-01257-z.
27. Pan Y, Wang Y, Wang Y. Investigation of causal effect of atrial fibrillation on Alzheimer disease: A Mendelian randomization study. J Am Heart Assoc 2020;9:e014889. doi:10.1161/JAHA.119.014889.
28. Li GF, Ge GM, Cheung CL, et al. Evaluation of causality between ADHD and Parkinson’s disease: Mendelian randomization study. Eur Neuropsychopharmacol 2020;37:49–63.
29. Yu X, Wang T, Chen Y, et al. Alcohol drinking and amyotrophic lateral sclerosis: An instrumental variable causal inference. Ann Neurol 2020;88:195–8.
30. Larsson SC, Roos PM. Serum 25-hydroxyvitamin D in amyotrophic lateral sclerosis: Mendelian randomization study. Neurobiol Aging 2020;87:140.e1–3.
31. Baumeister SE, Leitzmann MF, Bahls M, et al. Physical activity does not lower the risk of lung cancer. Cancer Res 2020;80:3765–9.
32. Buniello A, MacArthur JAL, Cercato M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res 2019;47:D1005–12.
33. Machiela MJ, Chanock SJ. LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics 2015;31:5555–7.
34. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7:e34408. doi:10.7554/eLife.34408.
35. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50:693–8.
36. International Parkinson Disease Genomics Consortium, Nalls MA, Pagnol V, et al. Imputation of sequence variants for identification of genetic risks for Parkinson’s disease: A meta-analysis of genome-wide association studies. The Lancet 2011;377:641–9.
37. Lewis M, Gordon PH, Lou Gehrig, rawhide, and 1938. Neurology 2007;68:615–8.
38. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and variability in ALS. Neurology 2002;59:773–8.
39. Janssen PH, Mandrekar J, Mielke MM, et al. High school football and late-life risk of neurodegenerative syndromes, 1956–1970. Mayo Clin Proc 2017;92:66–71.
40. Razquin C, Ortega-Cubero S, Rojo-Bustamante E, et al. Target-enriched sequencing of chromosome 17q21.31 in sporadic tauopathies reveals no candidate variants. Neurobiol Aging 2018;66:177. doi:10.1016/j.neurobiolaging.2017.12.026.
41. Chen JA, Chen Z, Won H, et al. Joint genome-wide association study of progressive supranuclear palsy identifies novel susceptibility loci and genetic correlation to neurodegenerative diseases. Mol Neurodegener 2018;13:41. doi:10.1186/s13234-018-0270-8.
42. The UK Parkinson’s Disease Consortium and The Wellcome Trust Case Control Consortium 2. Dissection of the genetics of Parkinson’s disease identifies an additional association 5’ of SNCA and multiple associated haplotypes at 17q21. Hum Mol Genet 2011;20:345–53.