RESEARCH ARTICLE

Association of Body Mass Index and Parkinson Disease

A Bidirectional Mendelian Randomization Study

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Abstract

Background and Objectives

The role of body mass index (BMI) in Parkinson disease (PD) is unclear. Based on the Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in PD (Courage-PD) consortium, we used 2-sample Mendelian randomization (MR) to replicate a previously reported inverse association of genetically predicted BMI with PD and investigated whether findings were robust in analyses addressing the potential for survival and incidence-prevalence biases. We also examined whether the BMI-PD relation is bidirectional by performing a reverse MR.

Methods

We used summary statistics from a genome-wide association study (GWAS) to extract the association of 501 single-nucleotide polymorphisms (SNPs) with BMI and from the Courage-PD and international Parkinson Disease Genomics Consortium (iPDGC) to estimate their association with PD. Analyses are based on participants of European ancestry. We used the inverse-weighted method to compute odds ratios (OR_{IVW} per 4.8 kg/m^2 [95% CI]) of PD and additional pleiotropy robust methods. We performed analyses stratified by age, disease duration, and sex. For reverse MR, we used SNPs associated with PD from 2 iPDGC GWAS to assess the effect of genetic liability toward PD on BMI.

Results

Summary statistics for BMI are based on 806,834 participants (54% women). Summary statistics for PD are based on 8,919 (40% women) cases and 7,600 (55% women) controls from Courage-PD, and 19,438 (38% women) cases and 24,388 (51% women) controls from iPDGC. In Courage-PD, we found an inverse association between genetically predicted BMI and PD (OR_{IVW} 0.82 [0.70–0.97], p = 0.012) without evidence for pleiotropy. This association tended to be stronger in younger participants (≤67 years, OR_{IVW} 0.71 [0.55–0.92]) and cases with shorter disease duration (≤7 years, OR_{IVW} 0.75 [0.62–0.91]). In pooled Courage-PD + iPDGC analyses, the association was stronger in women (OR_{IVW} 0.85 [0.74–0.99], p = 0.032) than men (OR_{IVW} 0.92 [0.80–1.04], p = 0.18), but the interaction was not statistically significant (p-interaction = 0.48). In reverse MR, there was evidence for pleiotropy, but pleiotropy robust methods showed a significant inverse association.

Discussion

Using an independent data set (Courage-PD), we replicate an inverse association of genetically predicted BMI with PD, not explained by survival or incidence-prevalence biases. Moreover, reverse MR analyses support an inverse association between genetic liability toward PD and BMI, in favor of a bidirectional relation.

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Glossary

BMI = body mass index; **Courage-PD** = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in PD; **GWAS** = Genome-Wide Association Study; **iPDGC** = international Parkinson Disease Genomics Consortium; **IV** = instrumental variable; **IVW** = inverse variance-weighted; **LD** = linkage disequilibrium; **MAF** = minor allele frequency; **MR** = Mendelian randomization; **OR** = odds ratio; **PD** = Parkinson disease; **SNP** = single-nucleotide polymorphism.

Introduction

Previous epidemiologic studies on the relation between body mass index (BMI) and Parkinson disease (PD) provided inconsistent results.[1,2] Associations between BMI and PD may be affected by reverse causation because PD is characterized by a long prodromal phase[3]; cohort studies showed that weight loss begins 2–10 years before PD diagnosis.[4-6] Moreover, weight loss is common in patients with PD. On average, patients with PD have lower weight than controls, with a difference that increases with disease duration.[7] These observations raise the questions whether BMI has a causal effect on PD and whether the BMI-PD relation is bidirectional.

Mendelian randomization (MR) uses genetic variants associated with exposures as instrumental variables (IVs) to estimate their causal association with diseases.[8] Under several assumptions, this method provides findings not biased by confounding or reverse causation. Bidirectional MR allows examining whether diseases also has an effect on exposures.[9] In MR studies of age-related diseases, survival bias may distort MR estimates for exposures associated with mortality because study participants are a nonrandom subset of the population who survived long enough to be included into the study.[10] Incidence-prevalence bias may also occur in studies including prevalent cases, if genetic instruments are associated with survival after disease onset.[11]

A previous MR study examined the association of BMI with PD using data from the international Parkinson Disease Genomics Consortium (iPDGC) and 77 single-nucleotide polymorphisms (SNPs) associated with BMI. That study reported an inverse association (odds ratio [OR] per 5 kg/m^2 = 0.82, 95% CI 0.69–0.98).[12] Another study that used data from 23andMe and ∼700 BMI-associated SNPs also showed an inverse association (OR per 1 kg/m^2 = 0.99, 95% CI 0.98–1.00),[13] thus suggesting that higher BMI is associated with decreased PD risk. A follow-up iPDGC study reported an inverse association between other traits related to increasing adiposity and PD.[14]

As part of the Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in PD (Courage-PD) consortium, we used 2-sample MR to replicate the causal association of genetically predicted BMI with PD and investigated whether findings were robust in analyses addressing the potential for survival and incidence-prevalence biases. In addition, we used reverse MR to examine whether genetic liability toward PD also has a causal influence on BMI in favor of a bidirectional association.

Methods

Two-Sample MR

MR estimates the causal association between an exposure and an outcome by using SNPs associated with the exposure. These SNPs must verify 3 assumptions: they must be associated with the exposure (IV1), and not associated with the outcome (except through the exposure, IV2) or with unmeasured confounders of the exposure-outcome association (i.e., no horizontal pleiotropy, IV3).[8] In 2-sample MR, effect sizes and SEs of the SNP-exposure and SNP-outcome associations come from independent samples.

PD Genome-Wide Association Study

Courage-PD

SNP-PD associations come from a genome-wide association study (GWAS) using the NeuroChip[15] in 23 of 35 studies from the Courage-PD consortium (eMethods). We excluded (1) samples overlapping with iPDGC, (2) Asian studies so that both SNP-exposure and SNP-PD association estimates come from populations of European ancestry, (3) studies with cases only, and (4) studies including less than 50 cases and 50 controls.

We compared the frequency of SNPs in cases and controls in each study under an additive model using logistic regression adjusted for sex and the first 4 principal components. We performed a meta-analysis of the 23 GWAS using a fixed ($I^2 \leq$ 25%) or random ($I^2 >$ 25%) effects model (eMethods). We estimated and compared the mean (95% CI) pooled age of cases and controls using random effects meta-analysis.

iPDGC

We used data from the iPDGC (nonoverlapping with Courage-PD) that performed a sex-stratified GWAS to study sex-specific genetic factors associated with PD (European ancestry).[16] We used sex-specific summary statistics that did not include UK Biobank participants to avoid overlap with the summary statistics for BMI.[8] We also pooled summary statistics from women and men to obtain summary statistics that combined both sexes.

GWAS of Exposures

Body Mass Index

We selected SNPs associated with BMI at a genome-wide significant threshold ($p < 5 \times 10^{-8}$) and with a minor allele frequency (MAF) ≥1% using summary statistics (βs, SEs) provided by a GWAS in participants of European ancestry

(GIANT consortium and UK Biobank).[17] We retained independent SNPs after clumping based on European ancestry reference data (1000 Genomes Project; $r^2 > 0.001$; genomic region = 10,000 kb). For SNPs not available in Courage-PD, we used proxies in high linkage disequilibrium (LD) with the index SNP ($r^2 > 0.8$) according to LDlink[18] or SNIPA.[19] We harmonized summary statistics on alleles positively associated with exposures; ambiguous palindromic SNPs (i.e., A/T or C/G with MAF >0.42) were discarded.[8]

We selected 543 SNPs from the BMI GWAS (eMethods) of which 5 were not available in Courage-PD and 37 were excluded (ambiguous palindromic SNPs, MAF <0.01, available in less than 17 studies in Courage-PD), leaving 501 SNPs for the analysis (*F*-statistic = 85.4).[8]

For sex-stratified, we used SNPs associated with BMI in women (299 SNPs used in the analysis) and men (248 SNPs used in the analysis) and corresponding sex-specific summary statistics.[17]

PD (Reverse MR)

We used 2 iPDGC GWASs to identify SNPs associated with PD; the associations of these SNPs with BMI come from the GWAS of BMI described above:

1. Using the same approach as described above for BMI, we selected SNPs associated with PD at a genome-wide significant threshold ($p < 5 \times 10^{-8}$) and with a minor allele (MAF) ≥1% from an iPDGC GWAS.[20] After clumping (1000 Genomes Project; $r^2 > 0.001$; genomic region, 10,000 kb), we selected 38 SNPs; we excluded 1 SNP that was not available in the BMI GWAS, 1 ambiguous SNP, and 3 SNPs associated with BMI at a genome-wide significant level ($p < 5 \times 10^{-8}$),[9] leaving 33 SNPs for the analysis.
2. We did not use the most recent iPDGC GWAS[21] because it included UK Biobank participants and overlapped with the BMI GWAS, which can induce bias in 2-sample MR studies.[8] However, a sex-stratified analysis of a subset of this GWAS made available sex-specific summary statistics without UK Biobank participants.[16] Therefore, we pooled summary statistics from men and women to obtain pooled estimates and retained 24 SNPs associated with PD at the GWAS significance level in analyses of men and women combined.

Statistical Analyses

We performed statistical analyses using *TwoSampleMR*, *MendelianRandomisation*, *MRPRESSO*, *simex*, and *phenoscanner* R packages (R Foundation for Statistical Computing, Vienna, Austria). *p* Values are 2-sided.

Mendelian Randomization

Wald ratio estimates (exponentiated ratio of SNP-outcome to SNP-exposure association estimates) and R^2 (proportion of BMI variance explained) were computed for each SNP.[8]

For our main analyses, we used the random-effects inverse variance-weighted (IVW) method that provides valid estimates for SNPs that verify IV assumptions. We tested heterogeneity across SNPs with the Cochran's *Q*-statistic.[8]

We also used additional methods that relax some IV assumptions to examine the robustness of our findings. The *MR-Egger method* provides an estimate corrected for directional pleiotropy.[22] However, this method has lower power than IVW. To be valid, the strength of the gene-exposure association should not correlate with the strength of bias due to potential pleiotropy if IVs correlate with confounders of the exposure-outcome association (InSIDE assumption).[22] The I^2_{GX} statistics quantifies the strength of regression dilution bias of SNP-exposure associations. Values <90% indicate a violation of the No Measurement Error assumption. In this case, we used the *SIMEX* method, which corrects MR-Egger estimates.[23] The *weighted median method* provides consistent estimates if ≥50% of IVs are valid.[24] *The weighted mode-based method* calculates the modal estimate using the causal estimate from each SNP so that the largest group of variants with the same causal estimate in the asymptotic limit contains valid IVs.[25] *MR-PRESSO* allows testing for horizontal pleiotropy and to identify outliers (*p*-global test), to compute corrected estimates by removing outliers (when *p*-global test <0.05), and to test whether the difference between uncorrected and corrected estimates is statistically significant (distortion test).[26] The contamination mixture approach involves 2 steps: first, it identifies groups of genetic variants with similar causal estimates; second, it performs MR robustly and efficiently in the presence of invalid IVs.[27] Finally, we performed leave-one-out analyses, by removing one-by-one each SNP from the analysis and re-estimating the causal effect, to assess whether MR findings were explained by specific variants.[8]

We computed the proportion of variance explained by IVs, the *F*-statistic (as a measure of instrument strength),[8] and statistical power for a type-I error rate of 5%.[28]

LD Score Regression

We investigated the genetic correlation between BMI and PD using cross-trait LD score regression[29] using the same filters as in previous studies.[30] Genetic correlations were estimated separately for Courage-PD and iPDGC and were then meta-analyzed using an inverse variance-weighted model.

Sensitivity Analyses

1. There is some evidence of sex dimorphism in genetic susceptibility of BMI,[17] and male sex is associated with increased PD risk. We performed sex-stratified analyses in Courage-PD based on sex-specific summary statistics, for both BMI and PD, and compared MR estimates from both strata (interaction test). As sex-stratified analyses in Courage-PD had insufficient power to detect weak associations (eTable 1), we leveraged publicly available sex-specific summary statistics from

iPDGC[16] to increase the sample size by performing a pooled analysis of Courage-PD and iPDGC.

2. As PD is a disease of old age, selection by survival may distort MR estimates when exposures (such as BMI) are associated with survival into old age (eFigure 1).[10] Bias may be in any direction, increases with age, and is expected to be more pronounced in 2-sample compared with 1-sample MR. We performed analyses stratified by median-age at study of cases and controls (67 years) and examined whether MR estimates observed overall were consistent with those seen in younger participants with lower mortality rates and in whom survival bias is therefore unlikely.[31,32]
3. The consortium included prevalent and incident patients. Genetic associations may be biased if genetic variants have a different effect on survival in patients with PD and controls.[11] We assessed whether MR estimates in cases with shorter disease duration (median ≤7 years) were consistent with those obtained overall.
4. As the role of environmental factors may be different in carriers of Mendelian PD mutations, we repeated the analyses after excluding participants with *GBA*/*LRRK2* mutations or with positive PD family history among first-degree relatives.
5. To examine the influence of pleiotropy, we used the PhenoScanner database-V2[33] to identify SNPs associated with PD or environmental exposures that are associated with PD (physical activity, lipid fractions, uric acid, vitamin D, cigarette smoking, alcohol drinking, and coffee drinking) and repeated our analyses after excluding them; we also removed SNPs associated with depression/anxiety/neuroticism to examine their influence if these exposures had a causal role in PD. Of the BMI-associated SNPs, one is associated with milk intake (rs4988235)[34]; we also excluded this SNP because milk intake is associated with PD.[35,36]
6. We applied Steiger filtering to exclude SNPs that have a disproportionately large effect on the outcome compared with the exposure.[8] We did not use this approach for our main analyses because it can produce erroneous results under some scenarios (differential measurement error, unmeasured confounding), and large differences in sample sizes between the exposure and outcome GWAS may also affect the efficacy of this approach.[9]

Reverse MR

Using the same approaches as described above, we estimated the causal effect of genetic liability toward PD on BMI to examine whether PD has a causal effect on BMI. Note that several authors recommended that MR investigations based on a rare binary exposure (i.e., PD in reverse MR in this article) should only test the causal null hypothesis, rather than attempt to calculate a causal estimate; therefore, for these analyses, we will consider whether associations are significant but we do not discuss the value of the estimates.[37]

Because there was high heterogeneity across SNPs and evidence for outliers in reverse MR analyses, we used an additional outlier-robust method, MR-Lasso, to examine the robustness of our findings.[38] An intercept term that represents the pleiotropic effect of SNPs on the outcome is added for each SNP. The causal estimate is obtained by the IVW method using the SNPs with a null intercept, while those with an intercept different from 0 are excluded. ORs are scaled to 1-unit increase in log odds of liability to PD.[37] We also performed leave-one-out analyses for reverse MR.

Standard Protocol Approvals, Registrations, and Patient Consents

Individual studies that contributed data to the Courage-PD–received approval from an institutional review board from their country, and informed signed consent was obtained from the participants.

Data Availability

All the results reported in the article can be reproduced using the data available in eTables.

Results

Summary statistics for BMI are based on 806,834 participants (54% women). Summary statistics for PD are based on 8,919 (40% women) cases and 7,600 (55% women) controls from Courage-PD, and 19,438 (38% women) cases and 24,388 (51% women) controls from iPDGC.

Causal Effect of Genetically Predicted BMI on PD

Courage-PD participant's characteristics are given in eTable 2. The pooled mean ages (in years) of PD cases (68.5, 95% CI 64.4–72.6, I^2 = 0%, p-heterogeneity = 0.99) and controls (66.9, 95% CI 62.5–71.1, I^2 = 0%, p-heterogeneity = 0.99) were similar (p = 0.58).

The proportion of the variance of BMI explained by all SNPs was 5.03%. In Courage-PD, the statistical power to detect an OR (per 4.8 kg/m^2) of 0.8 at a type-1 error of 5% was 90% overall (eTable 1).

SNPs-BMI and SNPs-PD (Courage-PD) associations are given in eTable 3 (overall), eTable 4 (by sex), and eTable 5 (by median age and disease duration).

Genetically predicted BMI was inversely associated with PD (OR_{IVW} per 1 SD = 0.82, 95% CI 0.70–0.97, p = 0.012; Table 1, Figure 1, eFigure 2) without heterogeneity across SNPs (p-heterogeneity = 0.20). The weighted median approach also showed an inverse association although with a wider CI, while no association was observed using the

Table 1 Causal Effect of Genetically Predicted BMI on PD in Courage-PD

Exposure	Odds ratio (95% CI)	*p* Value
BMI (501 SNPs, per 1 SD = 4.8 kg/m^2)		
IVW (*p*-heterogeneity = 0.20)	0.82 (0.70–0.97)	0.012
Weighted median	0.87 (0.66–1.15)	0.34
Weighted mode	1.06 (0.59–1.94)	0.84
MR Egger (*p*-pleiotropy = 0.84; I^2_{GX} = 0.90)	0.79 (0.50–1.26)	0.32
MR-PRESSO (*p*-pleiotropy = 0.15)	—	—
Contamination mixture (number of valid SNPs, 407)	0.83 (0.66–1.14)	0.21

Abbreviations: BMI = body mass index; Courage-PD = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in PD; IVW = inverse variance-weighted; MR = Mendelian randomization; PD = Parkinson disease; SNP = single-nucleotide polymorphism.

weighted mode approach. The MR-Egger and MR-PRESSO methods did not show pleiotropy. Leave-one-out analyses showed consistent results after removing SNPs one-by-one (eTable 6).

The association tended to be stronger in younger individuals (OR_{IVW} = 0.71, 95% CI 0.55–0.92, p = 0.009) than in older ones (OR_{IVW} = 0.89, 95% CI 0.69–1.15, p = 0.39), but the difference was not statistically significant (p-interaction = 0.22; Figure 1, eTable 7). The association also tended to be stronger in patients with shorter disease duration (OR_{IVW} = 0.75, 95% CI 0.62–0.91, p = 0.003) compared with those with longer disease duration (OR_{IVW} = 0.92, 95% CI 0.75–1.13, p = 0.45; Figure 1, eTable 7). The inverse association was confirmed in participants without a family history of PD (OR_{IVW} = 0.84, 95% CI 0.71–1.00, p = 0.047).

In analyses stratified by sex in Courage-PD (Figure 1, eTable 7), the inverse association was stronger in women (OR_{IWV} = 0.81, 95% CI 0.64–1.03, p = 0.087) than men (OR_{IVW} = 0.95, 95% CI 0.75–1.21, p = 0.67), but the sex difference was not statistically significant (p-interaction = 0.36). In iPDGC, the association was of a similar size in women (OR_{IWV} = 0.88, 95% CI 0.73–1.05, p = 0.17) and men (OR_{IWV} = 0.90, 95% CI 0.77–1.05, p = 0.18; p-interaction = 0.86). In pooled sex-stratified analyses, the association was statistically significant in women (OR_{IWV} = 0.85, 95% CI 0.74–0.99, p = 0.032) but not in men (OR_{IWV} = 0.92, 95% CI 0.80–1.04, p = 0.18); however, the difference between the 2 ORs was not statistically significant (p-interaction = 0.48).

Using PhenoScanner, we identified 1 SNP associated with PD, 13 SNPs with lipid fractions (8 for high-density lipoprotein cholesterol, 5 for low-density lipoprotein cholesterol, 4 for triglycerides), 1 with uric acid, 3 with smoking initiation, 10 with alcohol drinking, 1 with coffee drinking, and 4 with neuroticism, depression, or anxiety (eTable 8). After excluding these SNPs and 1 SNP associated with milk intake, results were consistent with those seen overall (OR_{IVW} = 0.79, 95% CI 0.67–0.94, p = 0.008; Figure 2).

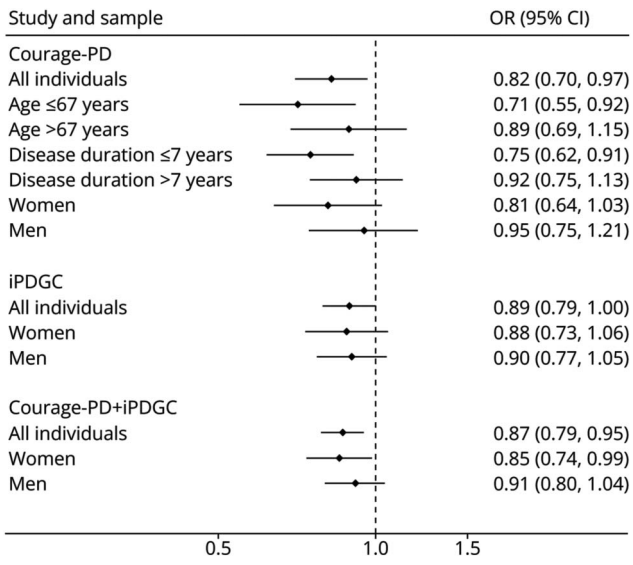
Steiger filtering did not identify significant outliers.

Causal Effect of Genetic Liability Toward PD on BMI

eTable 9 shows SNPs retained for reverse MR analyses, associations with PD (in 2 iPDGC GWAS) and BMI, and corresponding Wald-ratio MR estimates.

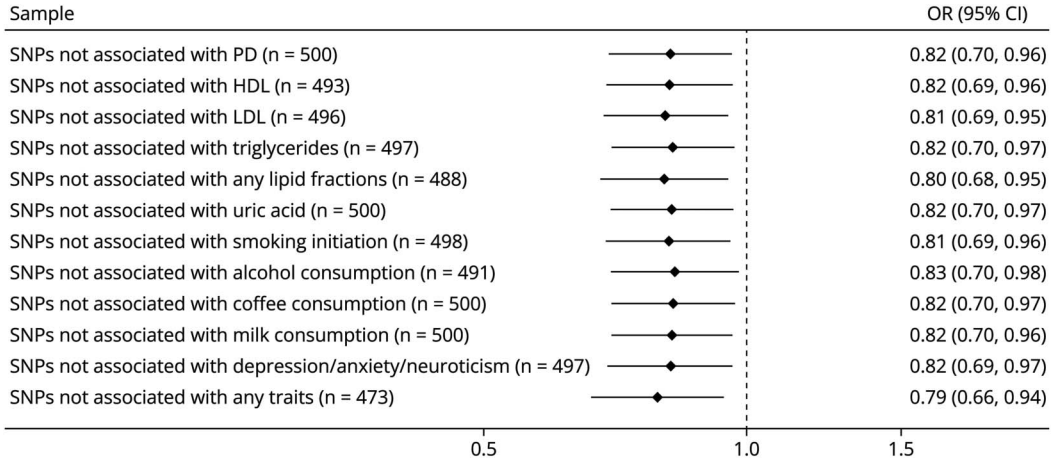
Results of reverse MR analyses are presented in Table 2 and eFigure 2. Based on 33 SNPs from an iPDGC GWAS,[20] the IVW method yielded an inverse association that was not statistically significant, but there was evidence of large heterogeneity (p-heterogeneity <0.001), thus suggesting the

Figure 1 Mendelian Randomization Estimates for Association Between BMI and PD, Overall and After Stratification by Age at Study, Disease Duration, and Sex



BMI = body mass index; iPDGC = international Parkinson Disease Genomics Consortium; OR = odds ratio per 4.8 kg/m^2; PD = Parkinson disease.

Figure 2 Mendelian Randomization Estimates for Association Between BMI and PD After Excluding SNPs Associated With Traits Related to PD



BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio per 4.8 kg/m^2; PD = Parkinson disease; SNP = single-nucleotide polymorphism.

potential for pleiotropy. The MR-Egger approach did not detect directional pleiotropy ($p = 0.92$), but there was strong evidence for horizontal pleiotropy based on the MR-PRESSO approach ($p < 0.001$) that detected 7 outliers. After excluding these outliers, there was an inverse association between genetic liability toward PD and BMI (OR = 0.99, 95% CI 0.97–1.00, $p = 0.013$). The MR-Lasso detected 21 valid and 12 invalid instruments, and there was an association based on valid instruments (OR = 0.99, 95% CI 0.98–1.00, $p = 0.038$). There was an association of the same magnitude using the weighted median and mode approaches ($p < 0.002$). Leave-one-out analyses showed consistent results after removing SNPs one-by-one (eTable 10).

Similar findings were obtained based on 24 SNPs from another iPDGC GWAS,[16] except that MR-PRESSO did not show a significant association; however, other robust methods showed significant inverse associations (Table 2, eFigure 2).

Steiger filtering did not identify significant outliers.

Genetic Correlation Between BMI and PD

Analyses using LD score regression showed similar negative correlations in Courage-PD and iPDGC, with a pooled estimate of −0.087 (95% CI −0.132 to −0.042, $p < 0.001$) without heterogeneity ($I^2 = 0.0\%$, $p = 0.969$) (Table 3).

Discussion

Using data from Courage-PD, after excluding samples overlapping with iPDGC, our results support an inverse causal association between genetically predicted BMI and PD. In addition, although there was evidence for pleiotropy, our findings also suggest that genetic liability toward PD may be inversely associated with lower BMI.

A meta-analysis of 10 prospective studies showed no association between BMI and PD (relative risk per 5 kg/m^2 = 1.00, 95% CI 0.89–1.12), but there was significant heterogeneity across studies ($I^2 = 64.5\%$, p-heterogeneity = 0.003).[1] By contrast, another meta-analysis of 3 prospective studies showed that persons with underweight (BMI <18.5 kg/m^2) had a ∼20% increased risk of developing PD, while there was no association between obesity and PD based on 4 studies.[2] However, the association between BMI and PD may be biased by reverse causation because previous studies showed that BMI starts declining a few years before diagnosis.[5,39,40] Hence, large observational studies with very long follow-up and repeated BMI measures are needed to assess whether midlife BMI is associated with PD incidence in older age. In the E3N cohort study in 96,702 French women 40–65 years old at baseline and followed for ∼29 years with 11 BMI measures, the frequency of obesity started to decreased in PD cases 5–10 years before diagnosis, showing the importance of analyses that include an exposure lag to address reverse causation; in addition, incidence was lower among women with obesity compared with those with normal BMI, even when BMI was assessed more than 20 years before diagnosis.[6]

Weight loss is also common in patients with PD after diagnosis. On average, patients with PD have lower weight than controls, with a difference that increases with disease duration and severity.[7] A variety of factors are involved in weight loss in PD.[41] Metabolic studies suggest that increased energy expenditure related to rigidity, tremor, and dyskinesias play a role. Appetite loss, nausea, vomiting, and gastrointestinal function impairment are also involved.

Table 2 Reverse Mendelian Randomization Using SNPs Associated With PD From 2 GWAS From iPDGC

Exposure	Odds ratio (95% CI)	*p* Value
Chang et al. 2017; 33 SNPs		
IVW (*p*-heterogeneity <0.001)	1.00 (0.98–1.01)	0.49
Weighted median	0.98 (0.97–0.99)	0.002
Weighted mode	0.98 (0.97–0.99)	<0.001
MR Egger (*p*-pleiotropy = 0.92; I^2_{GX} = 0.94)	0.99 (0.96–1.02)	0.69
MR-PRESSO (*p*-pleiotropy <0.001, *p*-distortion = 0.53)[a]	0.99 (0.97–1.00)	0.013
Contamination mixture (number of valid SNPs, 18)	0.98 (0.98–0.99)	<0.001
MR-Lasso (number of valid SNPs, 21; lambda = 0.44)	0.99 (0.98–1.00)	0.038
Blauwendraat et al. 2021; 24 SNPs		
IVW (*p*-heterogeneity <0.001)	1.00 (0.99–1.01)	0.91
Weighted median	0.99 (0.98–1.00)	0.031
Weighted mode	0.98 (0.97–0.99)	0.004
MR Egger (*p*-pleiotropy = 0.47; I^2_{GX} = 0.94)	0.99 (0.96–1.02)	0.48
MR-PRESSO (*p*-pleiotropy <0.001, *p*-distortion = 0.12)[b]	1.00 (0.99–1.01)	0.87
Contamination mixture (number of valid SNPs, 11)	0.98 (0.98–0.99)	0.003
MR-Lasso (number of valid SNPs, 9; lambda = 0.38)	0.99 (0.98–1.00)	0.014

Abbreviations: IVW = inverse variance-weighted; MR = Mendelian randomization; PD = Parkinson disease; SNP = single-nucleotide polymorphism.
[a] Outliers: rs11158026, rs11343, rs12456492, rs12637471, rs1474055, rs4073221, rs6430538.
[b] Outliers: rs10513789, rs1692821, rs356182, rs4588066, rs6741007, rs823116.

MR may contribute to better understand the association between BMI and PD. Based on data from iPDGC (13,708 PD cases, 95,282 controls), one MR study used 77 BMI-associated SNPs and reported an inverse association of genetically predicted BMI with PD (OR per 5 kg/m^2 = 0.82, 95% CI 0.69–0.98).[12] A split-sample MR analysis of 23andMe data (19,924 cases, 2,413,087 controls) also showed an inverse association (OR per 1 kg/m^2 = 0.99, 95% CI 0.98–1.00) using 729 and 693 SNPs in subsamples 1 and 2; the OR scaled to an increase of 5 kg/m^2, as in iPDGC, was 0.94, therefore suggesting a weaker association in this sample.[13] However, cases and controls from both GWAS were not matched on age, and BMI is strongly associated with age; for instance, in 23andMe, cases were 20 years older on average than controls, and this difference may lead to issues related to differential cohort effects on the exposure or residual confounding even after age adjustment. In iPDGC, the authors performed simulations to assess whether findings might have been explained by age differences between cases and controls. They concluded that survivor bias could have contributed to the inverse association but did not explain all the effect. Another analysis of iPDGC (26,035 PD cases, 403,190 controls) showed an inverse association between several traits related to increasing adiposity and PD[14]; there was also an inverse association between BMI and PD using the same genetic instrument as in the previous study (77 SNPs, OR per 5 kg/m^2 = 0.81; p = 0.037) or another instrument (273 SNPs, OR per 4.8 kg/m^2 = 0.81, p = 0.03).[14] By contrast, there was no association between genetically predicted BMI and PD among clinically diagnosed cases from a smaller iPDGC

Table 3 Genetic Correlations Between BMI and PD

Study	No. of SNPs	G_{corr}	95% CI	*p* Value	I^2 (%)	*p*-het.
Courage-PD	1,051,136	−0.086	−0.157 to −0.015	0.0178		
iPDGC	756,723	−0.088	−0.146 to −0.030	0.0029		
Pooled	—	−0.087	−0.132 to −0.042	<0.001	0.0	0.969

Abbreviations: BMI = body mass index; Courage-PD = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in PD; G_{corr} = genetic correlation; iPDGC = international Parkinson Disease Genomics Consortium; PD = Parkinson disease; *p*-het. = Cochran *Q* test for heterogeneity across studies; SNP = single-nucleotide polymorphism.

GWAS (5,851 cases, 5,866 controls),[14] and in an analysis of a Korean data set (1,050 cases, 5,000 control; 9 SNPs).[42] Finally, one study pooled results of 2 MR studies, one based on the FinnGen consortium (305 SNPs, 2,162 cases, 216,630 controls; OR = 0.76, 95% CI 0.60–0.96) and the other using a smaller iPDGC study in clinically diagnosed cases (300 SNPs, 5,851 cases, 5,866 controls; OR = 0.96, 95% CI 0.83–1.12); it showed an inverse but nonsignificant association (OR per ~4.8 kg/m^2 = 0.90, 95% CI 0.83–1.02).[43]

We used a large number of BMI-associated SNPs to replicate the inverse association of genetically predicted BMI with PD, with an OR of the same size as reported by the iPDGC.[12] In our study, cases and controls were of a similar age; therefore, age differences between the 2 groups could not explain the observed association. However, more complex scenarios of selection by death could be involved.[10] To address this issue, we performed analyses stratified by age and examined whether associations observed overall were replicated in younger participants. The stronger inverse association in younger participants compared with older participants is against the hypothesis that differential survival explains the inverse association between BMI and PD. Similarly, the stronger inverse association in cases with shorter disease duration suggests that incidence-prevalence bias does not explain our findings.

There is some evidence of sex dimorphism in genetic susceptibility of BMI,[17] and sex is associated with PD risk. In pooled sex-stratified analysis of Courage-PD and iPDGC data sets, the association between genetically predicted BMI and PD was significant in women only and tended to be stronger in women than men, although the difference was not statistically significant. It is possible that sex-stratified analyses lacked statistical power to detect weak associations and interactions, and larger studies will be needed to estimate more precisely the association in men.

The mechanisms underlying an inverse association between BMI and PD remain poorly understood. It is argued that neuroprotective benefits may arise in participants with higher BMI, in particular for the preservation of cognitive function and neural networks.[44] In addition, BMI affects levels of circulating and central insulin that could play a beneficial role against neurodegeneration.[45] Insulin crosses the blood-brain barrier, and there is evidence to suggest that it influences a multitude of pathways in the brain including the promotion of neuronal survival and dopaminergic transmission.[46] The insulin/IGF-1 signaling pathway contributes to the control of neuronal excitability, and growing evidence suggests that its dysfunction contributes to the progressive loss of neurons in PD.[47] Further studies are needed to understand the mechanisms underlying the inverse association between BMI and PD.

Our reverse MR analysis supports an effect of genetic liability to PD on BMI, although the results are more difficult to interpret due to large heterogeneity across SNPs and evidence for horizontal pleiotropy. However, MR-PRESSO showed an inverse association after excluding outliers, and the weighted median and mode approaches also yielded inverse associations. Although they need to be replicated, these findings suggest that genetic susceptibility to PD may predispose to lower BMI. Bidirectional relations, where each of the variables causes the other, may reflect variation in causal effects of the variables across different periods of the lifespan[48]; the effect of BMI on PD may reflect the role of midlife BMI, while the effect of PD on BMI may reflect its role later in life. The mechanisms involved are likely to be multifactorial, including disruption of both peripheral and central regulatory mechanisms of body weight, increased energy expenditure, appetite loss, nausea, vomiting, and gastrointestinal function impairment.[41,49] Alternatively, bidirectional relations may reflect a shared cause and a departure from the exclusion-restriction assumption underlying MR.[50] We found a negative genetic correlation between BMI and PD; although the correlation was weak, it was consistent in 2 large independent data sets. Additional analyses at a SNP, gene, or pathway level may help better understand the mechanisms underlying the association between BMI and PD.

Strengths of this study include it large size and careful clinical assessment by movement disorder specialists. Another strength relates to the MR design whose findings are not biased by reverse causation and confounding under 3 main validity assumptions.[8] Our sample size was sufficient to detect an association of the size reported previously in iPDGC with a statistical power of >80%.[12] Our findings are unlikely to be affected by weak instrument bias because the *F*-statistic was >10 and weak genetic instruments are expected to lead to bias toward the null in 2-sample MR studies.[8] Pleiotropy is one of the main issues for MR analyses, and to assess the robustness of their findings, researchers are advised to use multiple methods that rely on different assumptions.[8] We used several approaches developed to address pleiotropy such as the weighted median and mode, MR-Egger, MR-PRESSO, contamination mixture, and MR-Lasso. Since we restricted analyses to individuals of European descent, our findings are unlikely to be affected by population stratification; in addition, cases were compared with controls from the same study site, and analyses were adjusted for principal components. Another strength of our approach is that we performed analyses stratified by age and diseased duration. We compared our main findings with associations in younger participants and those with shorter disease duration. Selection by survival may lead to bias for PD genetic associations studies; however, bias is unlikely in younger persons with lower mortality rates.[10]

One limitation of our analysis is that 2-sample MR assumes linear relations between exposure and disease, and do not allow examining nonlinear relations. There are several examples of nonlinear associations between BMI and health-related outcomes, although reverse causation probably

accounts for some of the departures from linearity (e.g., low BMI and increased mortality). In addition, our findings cannot be generalized to Asian populations because GWAS summary statistics were derived from populations of European origin.

In conclusion, using an independent data set, our study replicates previous MR findings in favor of a causal protective effect of BMI on PD and shows that this association is not explained by survival or incidence-prevalence bias. In addition, our reverse MR analysis supports an inverse association between genetic liability to PD and BMI. Additional studies are needed to elucidate the mechanisms underlying the bidirectional relation between BMI and PD.

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Continued

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Pei-Chen Lee, PhD	Department of Public Health, National Cheng Kung University, Tainan	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Peter Lichtner, PhD	Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrew B. Singleton, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, and Center for Alzheimer's and Related Dementias, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Dena Hernandez, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Connor Edsall, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
George D. Mellick, PhD	Griffith Institute for Drug Discovery, Griffith University, Nathan, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Alexander A. Zimprich, MD	Department of Neurology, Medical University of Vienna, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Walter Pirker, MD	Department of Neurology, Wilhelminenspital, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Ekaterina A. Rogaeva, PhD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Anthony E. Lang, MD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto; Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN; Division of Neurology, University of Toronto; Krembil Brain Institute, Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Sulev Koks, MD, PhD	Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Australia; Perron Institute for Neurological and Translational Science, Nedlands, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Pille Taba, MD, PhD	Department of Neurology and Neurosurgery, University of Tartu; Neurology Clinic, Tartu University Hospital, Estonia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Suzanne Lesage, PhD	Department of Neurologie, Institut du Cerveau—Paris Brain Institute—ICM, INSERM, CNRS, Assistance Publique Hôpitaux de Paris, Sorbonne Université, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Alexis Brice, MD	Department of Neurologie, Institut du Cerveau—Paris Brain Institute—ICM, INSERM, CNRS, Assistance Publique Hôpitaux de Paris, Sorbonne Université, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Jean-Christophe Corvol, MD, PhD	Department of Neurologie, Institut du Cerveau—Paris Brain Institute—ICM, INSERM, CNRS, Assistance Publique Hôpitaux de Paris, Sorbonne Université; Assistance Publique Hôpitaux de Paris, Department of Neurology, CIC Neurosciences, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Marie-Christine Chartier-Harlin, PhD	Univ. Lille, Inserm, CHU Lille, UMR-S 1172—LilNCog-Centre de Recherche Lille Neurosciences & Cognition, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Eugenie Mutez, MD	Univ. Lille, Inserm, CHU Lille, UMR-S 1172—LilNCog-Centre de Recherche Lille Neurosciences & Cognition, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Kathrin Brockmann, MD	Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen; German Center for Neurodegenerative Diseases (DZNE), Tubingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Angela B. Deutschlander, MD, PhD	Department of Neurology, Ludwig Maximilians University of Munich; Department of Neurology, Max Planck Institute of Psychiatry, Munich, Germany; Department of Neurology and Department of Clinical Genomics, Mayo Clinic Florida, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Georgios M. Hadjigeorgiou, MD	Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Greece; Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Efthimios Dardiotis, MD	Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Greece	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Leonidas Stefanis, MD, PhD	1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens; Center of Clinical Research, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Greece	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Athina Maria Simitsi, MD, PhD	1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Greece	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Enza Maria Valente, MD, PhD	Department of Molecular Medicine, University of Pavia; Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Simona Petrucci, PhD	UOC Medical Genetics and Advanced Cell Diagnostics, S. Andrea University Hospital, Rome; Department of Clinical and Molecular Medicine, University of Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Letizia Straniero, PhD	Department of Biomedical Sciences, Humanitas University, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Anna L. Zecchinelli, MD	Parkinson Institute, Azienda Socio Sanitaria Territoriale (ASST) Gaetano Pini/CTO, Milano	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Gianni Pezzoli, MD	Parkinson Institute, Fontazione Grigioni—Via Zuretti, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Laura Brighina, MD, PhD	Department of Neurology, San Gerardo Hospital, Monza; Department of Medicine and Surgery and Milan Center for Neuroscience, University of Milano Bicocca, Milano, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Carlo Ferrarese, MD, PhD	Department of Neurology, San Gerardo Hospital, Monza; Department of Medicine and Surgery and Milan Center for Neuroscience, University of Milano Bicocca, Milano, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Grazia Annesi, PhD	Institute for Biomedical Research and Innovation, National Research Council, Cosenza, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrea Quattrone, MD	Institute of Neurology, Magna Graecia University, Catanzaro, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Monica Gagliardi, PhD	Institute of Molecular Bioimaging and Physiology National Research Council, Catanzaro, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Hirotaka Matsuo, MD, PhD	Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Akiyoshi Nakayama, MD, PhD	Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Nobutaka Hattori, MD, PhD	Department of Neurology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Kenya Nishioka, MD, PhD	Department of Neurology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Sun Ju Chung, MD, PhD	Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Yun Joong Kim, MD, PhD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Pierre Kolber, MD	Neurology, Centre Hospitalier de Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Bart P.C. Van De Warrenburg, MD, PhD	Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Radboud University Medical Centre, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Bastiaan R. Bloem, MD, PhD	Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Radboud University Medical Centre, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Mathias Toft, MD, PhD	Department of Neurology, Oslo University Hospital, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Lasse Pihlstrøm, MD, PhD	Department of Neurology, Oslo University Hospital, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Leonor Correia Guedes, MD, PhD	Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa; Department of Neurosciences and Mental Health, Neurology, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte (CHULN), Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Joaquim J. Ferreira, MD, PhD	Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa; Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Soraya Bardien, PhD	Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Jonathan Carr, PhD	Division of Neurology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Eduardo Tolosa, MD, PhD	Parkinson's disease & Movement Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED: CB06/05/0018-ISCIII), Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Mario Ezquerra, PhD	Lab of Parkinson Disease and Other Neurodegenerative Movement Disorders, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Institut de Neurociències, Universitat de Barcelona, Catalonia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Pau Pastor, MD, PhD	Fundació per la Recerca Biomèdica i Social Mútua Terrassa; Movement Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Monica Diez-Fairen, MSc	Fundació per la Recerca Biomèdica i Social Mútua Terrassa; Movement Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Karin Wirdefeldt, MD, PhD	Department of Clinical Neuroscience, and Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Nancy L. Pedersen, PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Caroline Ran, PhD	Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrea C. Belin, PhD	Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andreas Puschmann, MD, PhD	Department of Clinical Sciences Lund, Neurology, Skåne University Hospital, Lund University, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Clara Hellberg, MD, PhD	Department of Clinical Sciences Lund, Neurology, Skåne University Hospital, Lund University, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Carl E. Clarke, MD	University of Birmingham and Sandwell and West Birmingham Hospitals NHS Trust, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Karen E. Morrison, MD,	Faculty of Medicine, Health and Life Sciences, Queens University, Belfast, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Manuela M. Tan, PhD	Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Dimitri Krainc, MD, PhD	Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Lena F. Burbulla, PhD	Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL; Metabolic Biochemistry, Biomedical Center (BMC), Faculty of Medicine, Ludwig-Maximilians-Universität München; Munich Cluster for Systems Neurology (SyNergy); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Matthew Farrer, PhD	Department of Neurology, McKnight Brain Institute, University of Florida, Gainesville	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Name	Location	Contribution
Rejko Kruger, MD	Translational Neuroscience, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-Belval; Neurology, Centre Hospitalier de Luxembourg; Parkinson's Research Clinic, Centre Hospitalier de Luxembourg; Transversal Translational Medicine, Luxembourg Institute of Health (LIH), Strassen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Thomas Gasser, MD	Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen; German Center for Neurodegenerative Diseases (DZNE), Tubingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Manu Sharma, PhD	Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Alexis Elbaz, MD, PhD	Université Paris-Saclay, UVSQ, Inserm, Gustave Roussy, CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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