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ORIGINAL ARTICLE

The Effect of Blood Lipids, Type 2 Diabetes, and Body Mass Index on Parkinson's Disease: A Korean Mendelian Randomization Study

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ABSTRACT

Objective Associations between various metabolic conditions and Parkinson's disease (PD) have been previously identified in epidemiological studies. We aimed to investigate the causal effect of lipid levels, type 2 diabetes mellitus (T2DM), and body mass index (BMI) on PD in a Korean population via Mendelian randomization (MR).

Methods Two-sample MR analyses were performed with inverse-variance weighted (IVW), weighted median, and MR-Egger regression approaches. We identified genetic variants associated with lipid concentrations, T2DM, and BMI in publicly available summary statistics, which were either collected from genome-wide association studies (GWASs) or from meta-analyses of GWAS that targeted only Korean individuals or East Asian individuals, including Korean individuals. The outcome dataset was a GWAS on PD performed in a Korean population.

Results From previous GWASs and meta-analyses, we selected single nucleotide polymorphisms as the instrumental variables. Variants associated with serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, as well as with T2DM and BMI, were selected (n = 11, 19, 17, 89, and 9, respectively). There were no statistically significant causal associations observed between the five exposures and PD using either the IVW, weighted median, or MR-Egger methods (p-values of the IVW method: 0.332, 0.610, 0.634, 0.275, and 0.860, respectively).

Conclusion This study does not support a clinically relevant causal effect of lipid levels, T2DM, and BMI on PD risk in a Korean population.

Keywords Body mass index; Hyperlipidemia; Hypertriglyceridemia; Mendelian randomization; Parkinson's disease; Type 2 diabetes mellitus.

Parkinson's disease (PD) is the most common neurodegenerative movement disorder worldwide and is characterized by resting tremors, rigidity, bradykinesia, and postural instability.[1] Globally, up to 10 million people are estimated to have PD. The prevalence is rapidly increasing in aging societies, including in South Korea.[2] Given the significant social and economic burden of PD on the next generation, research has focused on identifying modifiable risk factors that can be targeted to prevent the disease.[3]

Many epidemiological studies have suggested that metabolic conditions are related to PD.[4,5] Abnormal cholesterol levels, type 2 diabetes mellitus (T2DM), and obesity are risk factors that are

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actively being investigated for their association with PD.[6-8] However, the evidence is inconclusive, with some studies showing that these factors have a protective effect.[9] Observational studies are prone to various biases, including from unmeasured, confounding factors, which may explain the contradictory results. Mendelian randomization (MR) is a technique that can overcome these limitations;[10] specifically, by using genetic variants associated with each risk factor as proxy markers, the risk of confounding factors that can impact both the risk factor and outcome are minimized, thus enabling causality to be established.

Recently, a large-scale MR project studying more than 400 exposures as risk factors for PD was completed.[11] Exposures were derived from previous genome-wide association studies (GWASs); however, the majority of the GWASs targeted Europeans or their descendants.[12] Genetic variants are highly specific regarding ethnicity. Therefore, risk factors identified through MR studies of European populations cannot be generalized to other ethnicities. Moreover, due to the assessment of more than 400 exposures in the PD MR project, individual exposures without statistical significance were not fully discussed.[11] Given this background, we aimed to examine whether metabolic parameters (blood lipid levels, T2DM, and body mass index [BMI]) are causally related to PD development in a Korean population using MR.

MATERIALS & METHODS

Study design and data sources

MR utilizes one or more single nucleotide polymorphisms (SNPs) as the instrumental variable (IV) for the risk factor for interest (exposure) to explore the strength of association with the disease of interest (outcome).[10] Two-sample MR analyses were performed to investigate the causal relationship between three exposures (blood lipid levels, T2DM, and BMI) and the outcome (PD). Two-sample MR uses two different study results for the IV-exposure and IV-outcome associations to estimate a causal effect of the exposure on the outcome.[10]

For the exposure dataset, we searched for previously reported GWASs on the three exposures by using the following criteria: 1) SNPs were reported with a p-value $< 5.0 \times 10^{-8}$, 2) more than ten SNPs were associated with the given exposure to avoid a weak instrumental bias, and 3) the studied population was Korean. Ideally, the samples should be drawn from the same population for two-sample MR; however, if there were no existing Korean GWAS satisfying criteria 1 or 2, we expanded the search for the exposure dataset to GWAS targeting an East Asian population, within which Korean individuals were included.

For the outcome dataset, we used summary statistics from the Korean PD GWAS by our group (Park KW, Chung SJ [2021]. *Ethnicity- and Sex-Specific Genome-Wide Association Study on Parkinson's Disease.* Unpublished manuscript). The study included 1,050 sporadic Korean PD patients (age: 64.0 ± 9.7 years; 554 [53%] females; disease duration at sample collection: 5.3 ± 4.4 years) and 5,000 age- and sex-matched healthy controls (age: 64.0 ± 10.0 years; 2,610 [52%] females). All of the patients were diagnosed as having PD by movement disorder specialists via the United Kingdom Parkinson's Disease Brain Bank Criteria.

Assumptions and gene prioritization

Due to the fact that MR uses genetic variants as a proxy for exposure, three key assumptions should be met to avoid biasing the results and to define the chosen variants as valid IVs (Figure 1). The genetic variants should be associated with the exposure (IV assumption 1), should not be associated with confounders (IV assumption 2), and should only influence the outcome through the exposure (IV assumption 3). To satisfy these assumptions, the reported SNPs in the exposure dataset were further examined as follows. First, we only included SNPs with a strong association with the exposure by setting the p-value threshold as $< 5.0 \times 10^{-8}$. Second, if linkage disequilibrium (LD) between a pair of SNPs was confirmed ($R^2 > 0.25$ by using the LDlinkR package version 1.1.2),[13] one SNP of the pair was excluded, as including multiple SNPs in LD can lead to confounding effects. Third, not to violate the IV assumption 3, all of the SNPs were screened for previously reported associations with PD in the PDGene database (http://www.pdgene.org),[14] as well as in our Korean PD outcome dataset and through the identification of pathological associations via a literature search. Fourth, if a SNP was not available in our Korean PD GWAS dataset, we identified a proxy SNP in our dataset with the highest LD with the SNP (R^2 cutoff of 0.8) by using LDlinkR. Finally, SNPs with strand-ambiguous alleles were excluded to rule out strand mismatches.

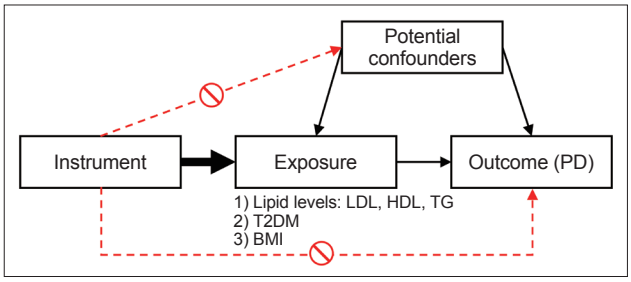

Figure 1. The framework of the Mendelian randomization analysis that was used in this study. The three key assumptions are denoted in the figure with the thick black arrow (instrument variable [IV] assumption 1) and the two red dashed line arrows with the general prohibition sign (circle with backslash in it) (IV assumptions 2 and 3). BMI, body mass index; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; PD, Parkinson's disease; T2DM, type 2 diabetes mellitus; TG, triglyceride.

Statistical analyses

We used an inverse-variance weighted (IVW) fixed-effect method, the MR-Egger method, and a weighted median method for MR estimates. The IVW method uses a meta-analysis approach to combine the causal effect of multiple genetic variants; however, it has the potential to include pleiotropic genetic variants. The MR-Egger method provides less biased effect estimates in the presence of directional pleiotropy. Both the IVW and MR-Egger methods further assume that the pleiotropic effects of genetic variants are independent of their associations with the exposure. The weighted median method provides consistent effect estimates even when this assumption is violated.

We used Cochran's Q-statistics and funnel plots to assess heterogeneity among the SNPs. We also performed a leave-one-out analysis to investigate whether a disproportionate influence of individual SNPs occurred in the effect estimate.

The MendelianRandomization R package version 0.6.0 was used to perform the MR estimates and sensitivity analyses.[15] All of the statistical analyses were performed with R version 4.1.2 (R Core Team [2021], R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). *p*-values under 0.05 were considered to be statistically significant. The study was approved by the Institutional Review Board of Uijeongbu Eulji Medical Center (IRB #: NON2021-002). Informed consent was waived due to the fact that the study utilized publicly available summary statistics.

RESULTS

Lipid levels

We adopted IVs for lipid levels based on a previous two-sample MR study on lipid levels and ischemic heart disease in a Korean population.[16] The study performed GWAS on three serum lipid fractions (low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride [TG]) measured in 35,000 Korean participants. Details of the data sources and IV prioritization process are summarized in Supplementary Table 1 (in the online-only Data Supplement). To evaluate their association with PD, we selected 11, 19, and 17 SNPs as IVs for LDL, HDL, and TG, respectively; the SNPs are listed in Supplementary Tables 2-4 (in the online-only Data Supplement).

The IVW method yielded no evidence to support a causal association between LDL levels and PD (beta = 0.009, standard error [SE] = 0.010, $p = 0.332$) (Table 1 and Figure 2A). The MR-Egger test also failed to show a causal association between LDL levels and PD (beta = 0.006, SE = 0.013, $p = 0.682$) (Table 1 and Figure 2A) without evidence of directional pleiotropy, which can be represented by the intercept deviation from zero (beta = 0.020, SE = 0.054, $p = 0.712$). Likewise, the weighted median approach yielded no causal association between LDL levels and PD (beta = 0.007, SE = 0.011, $p = 0.518$) (Table 1 and Figure 2A). Moreover, the Cochran's Q-test showed no evidence of heterogeneity between IV estimates (Table 1), which was supported by a symmetric funnel test (Supplementary Figure 1A in the online-only Data Supplement), thus indicating no heterogeneity. The leave-one-out analysis demonstrated that no single SNP drove the

Table 1. MR estimates of the causal effect of exposure to adverse metabolic and anthropometric conditions on Parkinson's disease

Exposure	Method	Beta	SE	*p*-value	Number of SNPs	Cochran's Q statistic	Heterogeneity *p*-value
LDL	IVW	0.009	0.010	0.332	11	2.35	0.999
	MR-Egger	0.006	0.013	0.682	11	2.21	0.988
	Weighted median	0.007	0.011	0.518	11	NA	NA
HDL	IVW	0.011	0.021	0.610	19	4.00	1.000
	MR-Egger	-0.022	0.041	0.594	19	3.14	1.000
	Weighted median	0.010	0.028	0.723	19	NA	NA
TG	IVW	0.002	0.004	0.634	17	3.86	0.999
	MR-Egger	0.005	0.006	0.403	17	3.39	0.999
	Weighted median	0.002	0.005	0.656	17	NA	NA
T2DM	IVW	-0.208	0.190	0.275	89	26.40	1.000
	MR-Egger	-0.098	0.422	0.817	89	26.61	1.000
	Weighted median	0.021	0.287	0.943	89	NA	NA
BMI	IVW	0.193	1.098	0.860	8	0.92	0.996
	MR-Egger	-1.878	3.834	0.624	8	0.60	0.996
	Weighted median	-0.259	1.347	0.848	8	NA	NA

MR, Mendelian randomization; SE, standard error; SNP, single nucleotide polymorphism; LDL, low-density lipoprotein cholesterol; IVW, inverse-variance weighted method; NA, not applicable; HDL, high-density lipoprotein cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; BMI, body mass index.

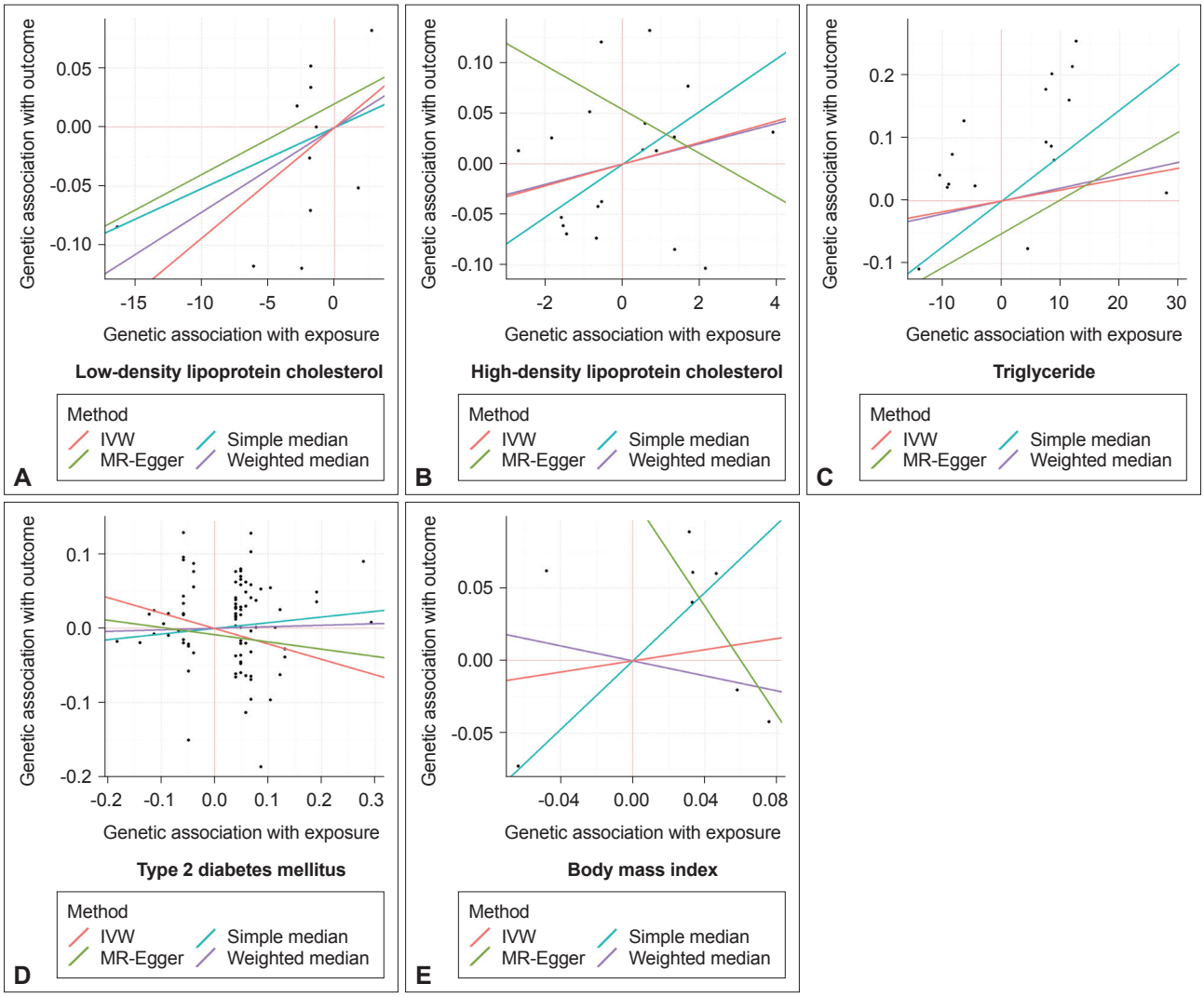

Figure 2. Scatter plots visualizing the Mendelian randomization (MR) estimates of the different exposures with the outcome (Parkinson's disease). The exposures are as follows; A: Low-density lipoprotein cholesterol, B: High-density lipoprotein cholesterol, C: Triglyceride. D: Type 2 diabetes mellitus, and E: Body mass index. Inverse-variance weighted (IVW), MR-Egger, and weighted median methods are the main estimators of the analysis; a simple median estimate is shown as a reference.

IVW estimate (Supplementary Figure 1B in the online-only Data Supplement).

Neither the IVW, MR-Egger, nor weighted median methods demonstrated evidence of a causal association between HDL levels and PD (IVW, beta = 0.011, SE = 0.021, $p = 0.610$; MR-Egger, beta = -0.022, SE = 0.041, $p = 0.594$; weighted median, beta = 0.010, SE = 0.028, $p = 0.723$) or between TG levels and PD (IVW, beta = 0.002, SE = 0.004, $p = 0.634$; MR-Egger, beta = 0.005, SE = 0.006, $p = 0.403$; weighted median, beta = 0.002, SE = 0.005, $p = 0.656$) (Table 1, Figure 2B and C). The heterogeneity tests and leave-one-out analysis showed no significant heterogeneity among the IV estimates (Supplementary Figure 1C-F in the online-only Data Supplement).

T2DM

We identified a meta-analysis that combined 23 GWASs on T2DM in 433,540 individuals from an East Asian population, which included 97,676 Korean individuals from three datasets.[17] From the summary statistics, 171 SNPs associated with T2DM with $p < 5 \times 10^{-8}$ (unadjusted for BMI) were initially identified as IV candidates. A total of 89 SNPs were finally selected as the IVs after the IV prioritization process (Supplementary Tables 1 and 5 in the online-only Data Supplement). The SNP rs7983505 was excluded because the proxy SNP rs2858980 (R^2 with rs7983505 = 0.960) showed an association with PD in our Korean PD GWAS ($p = 0.0005$), although it was not associated with PD in the PD-Gene database.

The IVW, MR-Egger, and weighted median methods that were

performed to estimate the causal relationship between T2DM and PD showed no statistically significant associations (IVW, beta = -0.208, SE = 0.190, p = 0.275; MR-Egger, beta = -0.098, SE = 0.422, p = 0.817; weighted median, beta = 0.021, SE = 0.287, p = 0.943) (Table 1 and Figure 2D). Similarly, the heterogeneity tests and leave-one-out analysis showed no significant heterogeneity among the IV estimates (Supplementary Figure 1G and H in the online-only Data Supplement).

BMI

We identified a meta-analysis that combined 21 GWASs on BMI in 134,548 individuals from an East Asian population, which included 19,325 Korean individuals from five datasets.[18] From the summary statistics, 12 SNPs associated with BMI were initially identified, and eight SNPs were included as IVs (Supplementary Tables 1 and 6 in the online-only Data Supplement).

The IVW, MR-Egger, and weighted median methods that were performed to estimate the causal relationship between BMI and PD showed no significant associations (IVW, beta = 0.193, SE = 1.098, p = 0.860; MR-Egger, beta = -1.878, SE = 3.834, p = 0.624; weighted median, beta = -0.259, SE = 1.347, p = 0.848) (Table 1 and Figure 2E). The heterogeneity tests and leave-one-out analysis also showed no significant heterogeneity among the IV estimates (Supplementary Figure 1I and J in the online-only Data Supplement).

DISCUSSION

In this study, we applied MR methods to determine the causal effect of metabolic conditions (including lipid levels, T2DM, and BMI) on PD and found that these conditions are not risk factors in a Korean population.

We found that none of the lipid markers (specifically, LDL, HDL, or TG) were associated with sporadic PD in a Korean population. Given the functional rationale and genetic evidence that brain cholesterol homeostasis is altered in neurodegenerative disorders, numerous epidemiological studies have investigated the association between serum lipid levels and PD.[19] Although earlier studies have reported mixed results with both deleterious and protective associations,[20-22] a recent meta-analysis that combined 13 case–control and eight cohort studies with 980,180 subjects (including 11,188 PD patients) suggested that elevated serum levels of LDL, TG, and total cholesterol may protect against PD.[23] Lipids have been implicated in various aspects of PD pathogenesis; specifically, dysfunctional lipid binding with α-synuclein, which is the key protein involved in PD, affects the folding, aggregation, and distribution of the protein.[24] GWAS for PD validated numerous hits in lipid-associated pathways, which is represented by variants in two well-known lipid pathway genes (*GBA* and *LRRK2*). The hits in the two genes exhibit differences in prevalence and types according to the ethnicity of the target population.[25-27] In contrast to our MR results, European-targeted MR studies have shown that higher levels of LDL, TG, and total cholesterol are associated with a lower future risk of PD.[6] Such discrepancies in MR results may also support the significance of ethnicity for genetic contributions to PD in the context of lipid regulation, but more supporting evidence from East Asian populations is encouraged.

There has long been debate about the association between T2DM and PD, which share several common features. These diseases are two of the most common chronic degenerative diseases in humans, and they arise from the destruction of specific cells (such as nigrostriatal dopaminergic neurons in PD and pancreatic beta cells in T2DM). The fact that some drugs targeting T2DM seem to protect against PD has led to several epidemiological investigations.[28] One large cohort study found an increased rate of PD diagnosis following T2DM.[29] In addition, a recent comprehensive study using both meta-analyses of traditional observational studies and MR methods observed that the presence of T2DM increases PD risk.[30] However, the authors highlighted an important limitation of the study; specifically, they stated that the majority of observational data and all of the genetic data were derived from patients of European ancestry. Both T2DM and PD exhibit differences between East Asian and European descendants; for example, T2DM develops in East Asian patients at a lower BMI and a younger age and requires earlier insulin treatment compared with European descendants.[31] In Western studies, the prevalence and incidence rates of PD are higher, and male predominance is more obvious.[32] In support of these differences in a clinical context, our study suggests that the association between T2DM and PD should be investigated more thoroughly in the Eastern regions.

There are also conflicting results about the association between BMI and PD. Epidemiological studies have shown that being overweight may be a risk factor for PD,[33] whereas other studies have suggested that being underweight is a risk factor for PD.[8] Moreover, the determination of the causal effect of BMI on PD is difficult due to various potential biases. For example, the presence of PD can lower BMI due to the hyposmia, change in appetite, and physical inactivity resulting from having the disease. Such a complex relationship between BMI and PD could result in the conflicting results that have been reported from traditional observational studies. Therefore, MR could be a useful method in delineating a causal association. A previous two-sample MR study focusing on European descendants found that higher BMI leads to a lower risk of PD.[34] Another large MR study investigating PD reported an inverse relationship between adiposity mea-

sures (arm fat percentage, leg fat percentage, and trunk fat mass, among other measures) and PD risk.[11] In contrast, we found no evidence to support a causal effect of BMI on PD in a Korean population. Such contradictory results may suggest that in an Asian population, body composition is not a pathogenic mechanism in PD. However, obesity is more severe in Western than East Asian societies, and individuals who have higher BMI have a higher risk of early mortality in the West; therefore, individuals with lower BMI may be overrepresented in populations with PD because of the late appearance of the disease in their lifespan. Due to the fact that the causal relationship between BMI and PD is still unclear even with MR methods, further studies to functionally clarify the relationship between adiposity and neurodegeneration are warranted.

Due to the fact that PD is one of the most common global neurodegenerative disorders, with increased social and economic burdens, efforts to identify and modify the risk factors associated with the disease have been undertaken. The most well-established risk factors for sporadic PD include age, male sex, and family history of PD, which are uncorrectable.[3] The potential effects of the three metabolic factors on PD that were investigated in our study pose great importance, due to the fact that these factors are modifiable through lifestyle and medication. Although our results do not support the causal effect of abnormal lipid levels, glucose levels, or BMI on the risk of PD in the Korean population, these conditions should be properly managed to avoid their inherent negative impacts on health. However, our study justifies the idea that these comorbid conditions do not need to be strictly adjusted in epidemiological studies on risk factors for PD in the Korean population.

There were several limitations in our study. First, the number of individuals included in the outcome database was small compared with those individuals in meta-analyses worldwide. Hence, the power of the study was relatively low, which could lead to false-negative results. However, this scenario is inevitable for genetic studies targeting a small genetic group, such as the Korean population. Further larger-scale MR targeting Korean or East Asian populations should be encouraged, along with functional studies. Second, our results showed that the presence of the investigated exposures does not alter the risk of PD, but conclusions about whether controlling the metabolic conditions in those individuals who already have the conditions would lower the risk of PD or slow the progression of PD cannot be drawn.

In conclusion, our MR analysis does not support the causal effects of abnormal lipid levels, T2DM, and BMI on the risk of PD in a Korean population. When considering the different genetic backgrounds between Eastern and Western world populations, larger MR studies targeting East Asia should be encouraged to elucidate their risk factors for PD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22175.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Kye Won Park, Sun Ju Chung. Data curation: Kye Won Park. Formal analysis: Kye Won Park. Funding acquisition: Sun Ju Chung. Investigation: Kye Won Park, Yun Su Hwang. Methodology: Kye Won Park, Yun Su Hwang. Project administration: Kye Won Park, Sun Ju Chung. Resources: Sun Ju Chung. Software: Kye Won Park. Supervision: Sun Ju Chung. Validation: Yun Su Hwang, Seung Hyun Lee. Visualization: Kye Won Park. Writing—original draft: Kye Won Park. Writing—review & editing: Yun Su Hwang, Seung Hyun Lee, Sungyang Jo, Sun Ju Chung.

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REFERENCES

1. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers 2017;3:17013.
2. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd-Allah F, Abdelalim A, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:939-953.
3. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15:1257-1272.
4. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. Mov Disord 2020;35:55-74.
5. Kummer BR, Diaz I, Wu X, Aaroe AE, Chen ML, Iadecola C, et al. Associations between cerebrovascular risk factors and Parkinson disease. Ann Neurol 2019;86:572-581.
6. Fang F, Zhan Y, Hammar N, Shen X, Wirdefeldt K, Walldius G, et al. Lipids, apolipoproteins, and the risk of Parkinson disease. Circ Res 2019;125:643-652.
7. Labandeira CM, Fraga-Bau A, Arias Ron D, Muñoz A, Alonso-Losada G, Koukoulis A, et al. Diabetes, insulin and new therapeutic strategies for Parkinson's disease: focus on glucagon-like peptide-1 receptor agonists. Front Neuroendocrinol 2021;62:100914.
8. Jeong SM, Han K, Kim D, Rhee SY, Jang W, Shin DW. Body mass index, diabetes, and the risk of Parkinson's disease. Mov Disord 2020;35:236-244.
9. Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. Total cholesterol and the risk of Parkinson disease. Neurology 2008;70:1972-1979.
10. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, et al. Mendelian randomization. Nat Rev Methods Primers 2022;2:6.
11. Noyce AJ, Bandres-Ciga S, Kim J, Heilbron K, Kia D, Hemani G, et al. The Parkinson's disease Mendelian randomization research portal. Mov Disord 2019;34:1864-1872.
12. Mills MC, Rahal C. A scientometric review of genome-wide association studies. Commun Biol 2019;2:9.

13. Myers TA, Chanock SJ, Machiela MJ. Ldlinkr: an R package for rapidly calculating linkage disequilibrium statistics in diverse populations. Front Genet 2020;11:157.
14. PDGene. PDGene [Internet]. Munich, Germany: The Max Planck Society for the Advancement of Science; [accessed on 2022 Apr 26]. Available at: http://www.pdgene.org/.
15. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol 2017;46:1734-1739.
16. Lee SH, Lee JY, Kim GH, Jung KJ, Lee S, Kim HC, et al. Two-sample Mendelian randomization study of lipid levels and ischemic heart disease. Korean Circ J 2020;50:940-948.
17. Spracklen CN, Horikoshi M, Kim YJ, Lin K, Bragg F, Moon S, et al. Identification of type 2 diabetes loci in 433,540 East Asian individuals. Nature 2020;582:240-245.
18. Wen W, Zheng W, Okada Y, Takeuchi F, Tabara Y, Hwang JY, et al. Meta-analysis of genome-wide association studies in East Asian-ancestry populations identifies four new loci for body mass index. Hum Mol Genet 2014;23:5492-5504.
19. Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. EMBO Rep 2014;15:1036-1052.
20. Johnson CC, Gorell JM, Rybicki BA, Sanders K, Peterson EL. Adult nutrient intake as a risk factor for Parkinson's disease. Int J Epidemiol 1999;28:1102-1109.
21. Tan LC, Methawasin K, Tan EK, Tan JH, Au WL, Yuan JM, et al. Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study. J Neurol Neurosurg Psychiatry 2016;87:86-92.
22. Huang X, Chen H, Miller WC, Mailman RB, Woodard JL, Chen PC, et al. Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. Mov Disord 2007;22:377-381.
23. Fu X, Wang Y, He X, Li H, Liu H, Zhang X. A systematic review and meta-analysis of serum cholesterol and triglyceride levels in patients with Parkinson's disease. Lipids Health Dis 2020;19:97.
24. Fanning S, Selkoe D, Dettmer U. Parkinson's disease: proteinopathy or lipidopathy? NPJ Parkinsons Dis 2020;6:3.
25. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol 2020;19:170-178.
26. Pang SY, Lo RCN, Ho PW, Liu HF, Chang EES, Leung CT, et al. LRRK2, GBA and their interaction in the regulation of autophagy: implications on therapeutics in Parkinson's disease. Transl Neurodegener 2022;11:5.
27. Foo JN, Chew EGY, Chung SJ, Peng R, Blauwendraat C, Nalls MA, et al. Identification of risk loci for Parkinson disease in Asians and comparison of risk between Asians and Europeans: a genome-wide association study. JAMA Neurol 2020;77:746-754.
28. Vaccari C, Grotto D, Pereira TDV, de Camargo JLV, Lopes LC. GLP-1 and GIP receptor agonists in the treatment of Parkinson's disease: translational systematic review and meta-analysis protocol of clinical and preclinical studies. PLoS One 2021;16:e0255726.
29. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: a record-linkage cohort study. Neurology 2018;91:e139-e142.
30. Chohan H, Senkevich K, Patel RK, Bestwick JP, Jacobs BM, Bandres Ciga S, et al. Type 2 diabetes as a determinant of Parkinson's disease risk and progression. Mov Disord 2021;36:1420-1429.
31. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013;1281:64-91.
32. Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease-East versus West. Mov Disord Clin Pract 2018;5:14-28.
33. Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. Body mass index and the risk of Parkinson disease. Neurology 2006;67:1955-1959.
34. Noyce AJ, Kia DA, Hemani G, Nicolas A, Price TR, De Pablo-Fernandez E, et al. Estimating the causal influence of body mass index on risk of Parkinson disease: a Mendelian randomisation study. PLoS Med 2017;14:e1002314.

Supplementary Table 1. Data source informations and instrument selection process

	Lipid levels			DM	BMI
	LDL	HDL	TG		
Reference		1		2	3
Population		Korean		East Asians	East Asians
Study design		GWAS for MR		Meta-analysis of GWAS	Meta-analysis of GWAS
Data source		Korean Genome and Epidemiology Study (KoGES)		23 GWAS	21 GWAS
Sample size		35,000		433,540	134,548
Instrument inclusions & exclusions					
Number of SNPs with $p < 5.0 \times 10^{-8}$ (a)	20	29	20	171	12
SNPs in LD ($R^2 > 0.25$) (b)	0	0	0	0	0
SNPs with direct influence on PD (c)	0	1	0	1	0
Proxy SNPs unidentifiable (d)	9	7	3	58	1
Pallindromic SNPs or ambiguous strand information (e)	0	2	0	23	3
Final number of SNP {a-(b+c+d+e)}	11	19	17	89	8

LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; DM, diabetes mellitus; BMI, body mass index; GWAS, genome-wide association study; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; LD, linkage disequilibrium; PD, Parkinson's disease.

REFERENCES

1. Lee SH, Lee JY, Kim GH, Jung KJ, Lee S, Kim HC, et al. Two-sample Mendelian randomization study of lipid levels and ischemic heart disease. Korean Circ J 2020;50:940-948.
2. Spracklen CN, Horikoshi M, Kim YJ, Lin K, Bragg F, Moon S, et al. Identification of type 2 diabetes loci in 433,540 East Asian individuals. Nature 2020;582:240-245.
3. Wen W, Zheng W, Okada Y, Takeuchi F, Tabara Y, Hwang JY, et al. Meta-analysis of genome-wide association studies in East Asian-ancestry populations identifies four new loci for body mass index. Hum Mol Genet 2014;23:5492-5504.

Supplementary Table 2. List of instrumental SNPs to calculate the effect estimates of LDL level for PD

Intrumental SNP	Effect alelle	CHR	Gene	Exposure (LDL)			Outcome (PD)			
				Beta	SE	MAF	Proxy-SNP used	Beta	SE	MAF
rs1034601	T	12	*CUX2*	-1.383	0.256	0.401	Yes	0.000	0.128	0.405
rs1053878	A	9	*ABO*	2.779	0.288	0.249	No	0.082	0.201	0.245
rs10987824	A	9	*FAM102A*	1.783	0.323	0.182	Yes	-0.051	0.112	0.205
rs11134475	A	5	*TIMD4, HAVCR1*	-1.786	0.296	0.233	Yes	0.033	0.172	0.232
rs12740374	T	1	*CELSR2*	-6.085	0.530	0.059	No	-0.118	0.176	0.062
rs3846661	A	5	*HMGCR*	-2.827	0.249	0.477	Yes	0.018	0.136	0.482
rs6129731	A	20	*TOP1*	-1.894	0.321	0.188	Yes	-0.026	0.142	0.184
rs737337	C	19	*DOCK6*	-1.798	0.278	0.278	No	0.052	0.175	0.279
rs7394579	G	11	*FADS1, FADS2*	-1.827	0.268	0.315	Yes	-0.070	0.079	0.318
rs7412	T	19	*APOE*	-16.330	0.505	0.064	No	-0.084	0.194	0.065
rs7588415	A	2	*LOC101928271, APOB, C2orf43*	-2.488	0.377	0.124	No	-0.119	0.104	0.119

SNP, single nucleotide polymorphism; LDL, low-density lipoprotein cholesterol; PD, Parkinson's disease; SE, standard error; MAF, minor allele frequency; CHR, chromosome.

Supplementary Table 3. List of instrumental SNPs to calculate the effect estimates of HDL level for PD

Intrumental SNP	Effect alelle	CHR	Gene	Exposure (HDL)			Outcome (PD)			
				Beta	SE	MAF	Proxy-SNP used	Beta	SE	MAF
rs11570891	T	8	*LPL*	2.148	0.141	0.125	Yes	-0.103	0.110	0.124
rs1180333	T	1	*PPIEL*	-0.841	0.151	0.109	Yes	0.052	0.233	0.111
rs12832859	T	12	*LOC105370051*	0.705	0.116	0.208	Yes	0.132	0.248	0.212
rs1532085	G	15	-	-1.531	0.094	0.485	No	-0.061	0.077	0.488
rs1883025	T	9	*ABCA1*	-1.439	0.108	0.252	No	-0.069	0.092	0.251
rs2289891	C	11	*SIK3*	1.700	0.214	0.051	Yes	0.077	0.338	0.047
rs28679685	G	8	-	1.345	0.117	0.202	No	0.027	0.175	0.196
rs2876971	G	22	*UBE2L3*	-0.543	0.095	0.422	Yes	0.120	0.214	0.427
rs289745	C	16	-	0.882	0.094	0.484	No	0.013	0.132	0.486
rs2925979	T	16	*CMIP*	-0.534	0.097	0.367	No	-0.037	0.099	0.370
rs4149310	A	9	*ABCA1*	-0.674	0.104	0.287	No	-0.073	0.084	0.276
rs4244229	G	7	-	0.531	0.094	0.430	Yes	0.014	0.133	0.422
rs429358	C	19	*APOE*	-1.831	0.160	0.095	No	0.026	0.226	0.099
rs4360631	G	10	-	0.588	0.098	0.360	Yes	0.040	0.159	0.351
rs4983387	A	14	*ZBTB42*	-0.631	0.098	0.351	No	-0.042	0.098	0.349
rs651821	C	11	*APOA5*	-2.683	0.101	0.299	Yes	0.013	0.145	0.300
rs74436333	G	20	*PCIF1, LOC107985388*	-1.574	0.192	0.065	Yes	-0.053	0.214	0.062
rs769446	C	19	*APOE*	1.356	0.189	0.067	Yes	-0.084	0.194	0.065
rs821840	G	16	*CETP*	3.895	0.123	0.171	Yes	0.031	0.190	0.163

SNP, single nucleotide polymorphism; HDL, high-density lipoprotein cholesterol; PD, Parkinson's disease; SE, standard error; MAF, minor allele frequency; CHR, chromosome.

Supplementary Table 4. List of instrumental SNPs to calculate the effect estimates of TG level for PD

Intrumental SNP	Effect alelle	CHR	Gene	Exposure (TG)			Outcome (PD)			
				Beta	SE	MAF	Proxy-SNP used	Beta	SE	MAF
rs113103943	A	6	*HLA-DQB1, HLA-DQA2*	12.630	1.569	0.054	Yes	0.254	0.455	0.050
rs113988682	G	8	*LPL, SLC18A1*	-13.980	1.069	0.124	Yes	-0.108	0.108	0.123
rs114815710	A	6	*MUC22*	8.538	1.390	0.070	Yes	0.202	0.403	0.055
rs115697023	G	6	*HLA-DOA, HLA-DPA1*	12.020	1.698	0.046	Yes	0.213	0.455	0.042
rs1260326	C	2	*GCKR*	-10.480	0.713	0.449	No	0.041	0.154	0.451
rs174541	C	11	*FADS1, FADS2*	4.428	0.758	0.319	Yes	-0.076	0.076	0.318
rs1865063	T	19	*DOCK6*	-4.459	0.794	0.273	Yes	0.024	0.154	0.275
rs28780106	A	6	*TRIM40*	7.526	1.350	0.074	Yes	0.177	0.352	0.076
rs2954021	A	8	*TRIB1, LINC00861*	7.537	0.712	0.430	Yes	0.093	0.193	0.417
rs34859606	G	8	*LPL, SLC18A1*	-8.908	0.885	0.201	Yes	0.027	0.175	0.196
rs4938355	G	11	*PCSK7*	8.457	1.189	0.098	Yes	0.087	0.265	0.104
rs58542926	T	19	*TM6SF2*	-9.184	1.338	0.076	No	0.022	0.250	0.073
rs651821	C	11	*APOA5, APOA4*	27.960	0.757	0.299	Yes	0.013	0.145	0.300
rs7798357	C	7	*MLXIPL*	-8.347	1.161	0.103	Yes	0.074	0.252	0.103
rs79589473	A	6	*LY6G6F*	11.460	1.603	0.051	Yes	0.160	0.388	0.052
rs9261547	G	6	*HCG17*	8.946	1.373	0.072	Yes	0.065	0.281	0.073
rs9436224	C	1	*DOCK7*	-6.335	0.903	0.190	Yes	0.128	0.252	0.176

SNP, single nucleotide polymorphism; TG, triglyceride; PD, Parkinson's disease; SE, standard error; MAF, minor allele frequency; CHR, chromosome.

Supplementary Table 5. List of instrumental SNPs to calculate the effect estimates of T2DM level for PD

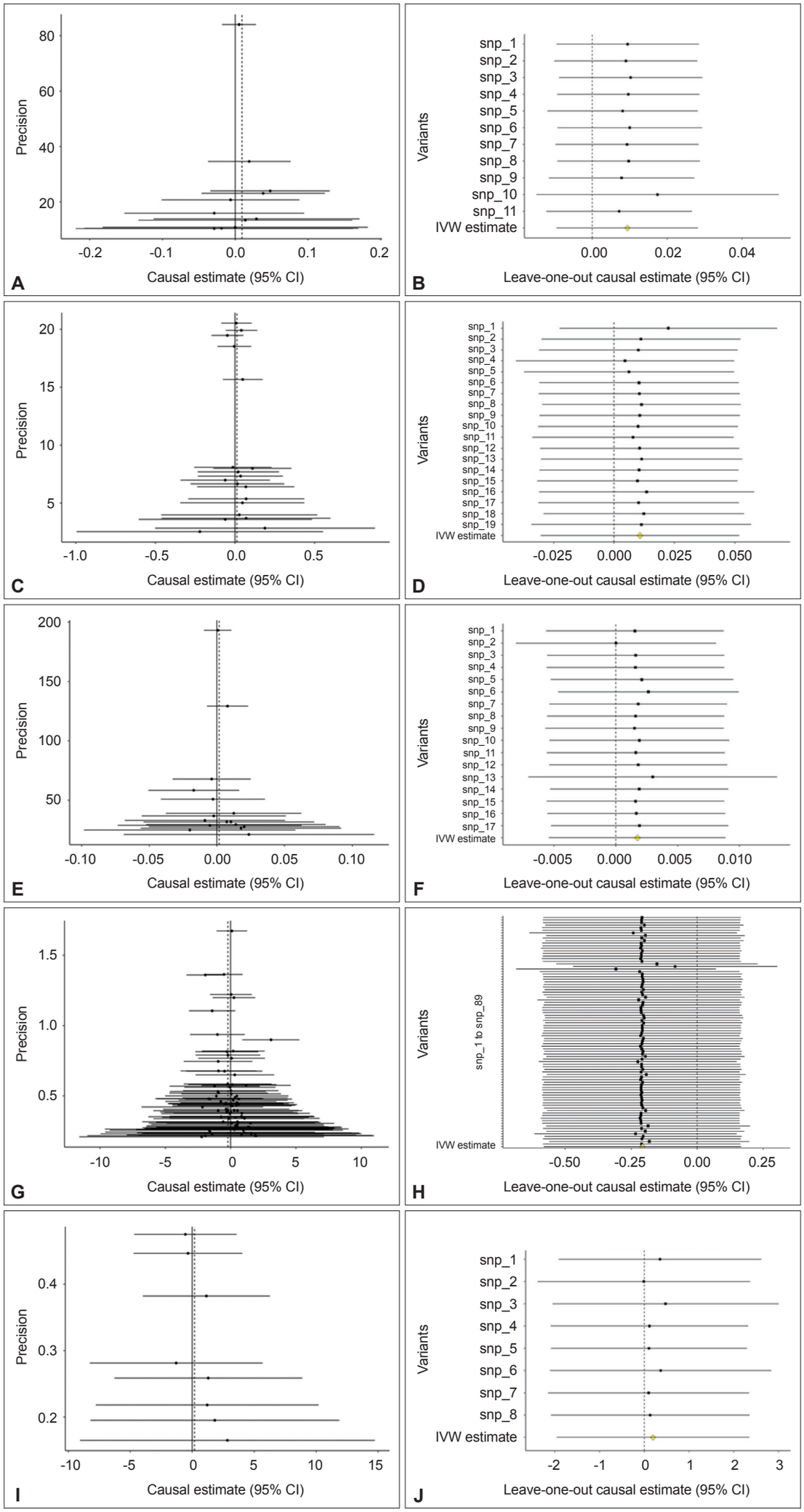
Intrumental SNP	Effect alelle	CHR	Gene	Exposure (T2DM)			Outcome (PD)			
				Beta	SE	MAF	Proxy-SNP used	Beta	SE	MAF
rs1016565	A	9	*DMRT2, DMRT3, LINC01230*	0.039	0.007	0.421	Yes	0.003	0.127	0.433
rs10736116	C	10	*ARHGAP19, ARHGAP19-SLIT1*	0.049	0.007	0.306	Yes	0.025	0.154	0.298
rs10830963	G	11	*MTNR1B*	0.039	0.007	0.421	No	0.029	0.143	0.435
rs10852123	A	15	*AP3S2, C15orf38-AP3S2*	0.058	0.010	0.201	No	-0.064	0.116	0.182
rs10886863	G	10	*LINC01153, FGFR2, MIR5694*	-0.058	0.007	0.336	Yes	-0.020	0.120	0.296
rs10938398	A	4	*GNPDA2, GABRG1*	0.049	0.007	0.292	Yes	0.058	0.182	0.281
rs10965248	A	9	*CDKN2B-AS1, DMRTA1*	-0.182	0.006	0.437	Yes	-0.018	0.109	0.435
rs11043003	C	11	*ASCL2, MIR4686*	0.104	0.012	0.082	Yes	-0.097	0.154	0.084
rs11205766	A	1	*CDKN2C, MIR4421*	-0.086	0.012	0.097	Yes	-0.010	0.201	0.095
rs112820281	C	10	*PLEKHA1*	0.049	0.007	0.410	Yes	-0.048	0.092	0.358
rs117267808	A	16	*GP2*	0.104	0.014	0.078	Yes	0.054	0.264	0.080
rs118074491	G	12	*SPPL3*	0.191	0.019	0.032	Yes	0.035	0.405	0.027
rs11926494	C	3	*UBE2E2, MIR548AC*	-0.113	0.009	0.180	Yes	-0.008	0.147	0.199
rs1215468	T	13	*SPRY2, LINC00382, LINC01080*	-0.086	0.007	0.281	Yes	0.020	0.148	0.300
rs1236816	A	10	*PTEN*	0.039	0.007	0.499	No	0.062	0.169	0.465
rs12600132	T	16	*PKD1L3*	0.039	0.005	0.432	Yes	0.076	0.181	0.421
rs1260326	C	2	*GCKR*	0.068	0.007	0.456	No	0.041	0.154	0.451
rs12625671	C	20	*HNF4A*	0.068	0.007	0.442	Yes	-0.004	0.120	0.459
rs12698877	G	7	*AUTS2*	0.068	0.005	0.336	Yes	-0.096	0.061	0.342
rs12712928	C	2	*SIX3, SIX2*	0.058	0.007	0.402	Yes	-0.113	0.043	0.379
rs13086331	A	3	*BCL6, LPP-AS2*	-0.049	0.010	0.189	Yes	-0.150	0.054	0.176
rs13092876	A	3	*IGF2BP2*	0.122	0.007	0.312	Yes	0.025	0.149	0.312
rs13266634	G	8	*SLC30A8*	-0.113	0.007	0.414	Yes	0.024	0.143	0.410
rs1328412	A	9	*LOC101927450, TLE4*	-0.095	0.014	0.055	Yes	0.006	0.255	0.064
rs1421085	C	16	*FTO*	0.131	0.009	0.167	No	-0.039	0.161	0.122
rs148928116	A	10	*JMJD1C*	-0.058	0.010	0.205	Yes	0.095	0.226	0.190
rs149265787	G	8	*JPH1*	0.131	0.020	0.024	Yes	-0.028	0.330	0.033
rs16902871	G	5	*RANBP3L*	0.058	0.010	0.149	No	0.030	0.196	0.140
rs1850421	A	3	*P2RY1, MBNL1*	0.049	0.007	0.278	Yes	-0.036	0.106	0.313
rs186568031	T	17	*SLC16A11*	0.113	0.011	0.094	Yes	0.001	0.211	0.093
rs201018682	A	3	*SLC2A2*	-0.058	0.010	0.184	Yes	0.033	0.184	0.187
rs2074120	A	7	*CALCR*	0.039	0.007	0.323	Yes	-0.066	0.082	0.328
rs2233580	T	7	*PAX4*	0.293	0.011	0.086	No	0.008	0.239	0.073
rs2269245	C	1	*PGM1*	-0.058	0.007	0.185	Yes	0.092	0.238	0.147
rs243018	C	2	*MIR4432, LOC101927285*	-0.058	0.007	0.334	Yes	0.020	0.143	0.337
rs2583934	T	12	*HMGA2, LOC100129940*	0.058	0.007	0.340	Yes	0.049	0.164	0.344
rs28599782	A	4	*MOB1B*	0.068	0.010	0.209	Yes	0.058	0.192	0.221
rs28637892	T	22	*WNT7B, ATXN10*	0.049	0.007	0.215	Yes	0.077	0.206	0.213
rs2925979	T	16	*CMIP*	0.039	0.007	0.364	No	-0.037	0.099	0.370
rs3135911	A	5	*FGFR4*	0.049	0.005	0.432	Yes	-0.045	0.094	0.389
rs328301	T	8	*FGFR1, C8orf86*	0.039	0.007	0.328	Yes	0.017	0.144	0.328
rs34204798	G	10	*ZMIZ1*	-0.058	0.007	0.432	Yes	0.128	0.220	0.415
rs349359	C	8	*KCNB2*	0.039	0.007	0.242	Yes	0.003	0.148	0.237
rs3731600	G	2	*SCTR*	-0.122	0.023	0.032	No	0.019	0.360	0.032
rs3735567	C	7	*JAZF1*	-0.058	0.010	0.222	Yes	0.018	0.151	0.277
rs3751236	G	12	*KLHL42, PTHLH*	-0.068	0.007	0.328	Yes	-0.003	0.131	0.316
rs4148646	C	11	*KCNJ11*	0.077	0.007	0.385	Yes	0.037	0.154	0.392
rs4237150	C	9	*GLIS3*	0.068	0.007	0.426	Yes	-0.032	0.100	0.414
rs4273712	G	6	*RSPO3, MIR588*	0.049	0.007	0.469	No	-0.017	0.110	0.475
rs475002	G	19	*SNAPC2*	0.039	0.007	0.518	No	0.015	0.136	0.482
rs476828	C	18	*MC4R, PMAIP1*	0.086	0.007	0.243	Yes	0.053	0.180	0.242
rs4776970	A	15	*MAP2K5*	0.039	0.007	0.221	No	0.032	0.175	0.216
rs4922793	T	11	*BDNF*	-0.039	0.007	0.434	Yes	0.076	0.181	0.442
rs532504	A	1	*LOC101928778, SEC16B*	0.058	0.007	0.213	Yes	-0.020	0.130	0.246
rs56687477	A	8	*KCNU1, MIR1268A*	0.049	0.007	0.323	Yes	-0.060	0.086	0.350
rs58524310	G	14	*IRF2BPL,LRRC74*	0.049	0.007	0.327	Yes	0.001	0.127	0.394
rs60054445	G	3	*ADCY5*	-0.049	0.007	0.336	Yes	-0.058	0.085	0.356
rs6021276	T	20	*NFATC2*	0.039	0.007	0.410	Yes	0.027	0.144	0.437
rs602652	T	11	*CCND1, LOC101928292*	-0.058	0.007	0.191	Yes	-0.016	0.147	0.184
rs60573766	G	1	*LINC01141*	-0.039	0.007	0.355	Yes	0.055	0.171	0.346
rs61021634	A	15	*RGMA, LOC101927153*	0.049	0.007	0.438	No	0.070	0.176	0.414
rs610930	A	7	*AUTS2*	0.068	0.007	0.287	Yes	-0.065	0.091	0.289
rs62405419	T	6	*TFAP2B*	0.049	0.007	0.268	Yes	0.029	0.156	0.310
rs62469016	C	7	*STEAP2*	0.068	0.007	0.223	Yes	0.103	0.221	0.222
rs6416749	C	16	*HCCAT5, ZFHX3*	0.049	0.007	0.375	No	-0.021	0.109	0.388
rs6556925	C	5	-	0.039	0.005	0.416	Yes	0.038	0.153	0.431
rs6806156	A	3	*ZBTB20, GAP43*	-0.049	0.007	0.389	Yes	-0.021	0.112	0.370
rs7109575	G	11	*ARAP1*	-0.140	0.015	0.055	Yes	-0.020	0.241	0.064
rs7307263	G	12	*LINC01234*	0.039	0.007	0.427	Yes	0.020	0.140	0.411
rs73085586	C	20	*LOC284788, LINC00261*	-0.039	0.007	0.356	Yes	-0.033	0.104	0.360
rs7313668	T	12	*PTPRR, TSPAN8*	0.049	0.007	0.374	Yes	0.018	0.140	0.377
rs73708054	C	8	*EFR3A, ADCY8*	0.039	0.007	0.252	Yes	0.012	0.151	0.242
rs74334916	C	5	*PARP8*	0.068	0.012	0.075	Yes	0.128	0.309	0.086
rs75990271	T	7	*FAM185A, POLR2J2*	-0.068	0.010	0.185	Yes	-0.004	0.152	0.202
rs76704029	T	15	*HERC2*	-0.058	0.010	0.278	Yes	0.043	0.165	0.299
rs77065181	A	10	*C10orf115*	0.086	0.016	0.047	Yes	-0.186	0.204	0.036
rs7739842	G	6	*ENPP3, MED23*	0.049	0.007	0.356	No	0.066	0.175	0.367
rs7787720	T	7	*ETV1, ARL4A*	0.058	0.007	0.421	Yes	0.062	0.171	0.396
rs7901695	C	10	*TCF7L2*	0.278	0.017	0.038	Yes	0.090	0.427	0.029
rs8038760	T	15	*PTPN9, SIN3A*	-0.049	0.007	0.392	Yes	-0.024	0.108	0.384
rs8043085	T	15	*RASGRP1*	0.049	0.007	0.449	Yes	0.080	0.184	0.431
rs8064454	A	17	*HNF1B*	0.122	0.007	0.305	Yes	-0.063	0.090	0.296
rs896852	G	8	*TP53INP1, NDUFAF6*	0.039	0.007	0.300	Yes	0.041	0.164	0.291
rs9316706	A	13	*LINC00424, LINC00540*	0.039	0.007	0.351	Yes	-0.061	0.082	0.385
rs9350271	A	6	*CDKAL1*	0.191	0.006	0.423	Yes	0.049	0.159	0.474
rs9376382	G	6	*ECT2L*	-0.039	0.005	0.401	Yes	0.087	0.188	0.419
rs9515905	A	13	*MIR17, MIR17HG, LINC00379*	0.077	0.009	0.831	Yes	0.001	0.176	0.146
rs952472	C	15	*HMG20A*	0.068	0.007	0.395	Yes	-0.069	0.072	0.419
rs9859381	G	3	*CASR*	0.039	0.005	0.486	Yes	0.028	0.146	0.449

SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus; PD, Parkinson's disease; SE, standard error; MAF, minor allele frequency; CHR, chromosome.

Supplementary Table 6. List of instrumental SNPs to calculate the effect estimates of BMI for PD

Intrumental SNP	Effect alelle	CHR	Gene	Exposure (BMI)			Outcome (PD)			
				Beta	SE	MAF	Proxy-SNP used	Beta	SE	MAF
rs11030104	T	11	*BDNF, BDNF-AS*	-0.048	0.005	0.45	Yes	0.062	0.170	0.449
rs12463617	G	2	*TMEM18, FAM150B*	-0.063	0.009	0.09	Yes	-0.073	0.166	0.086
rs1558902	A	16	*FTO*	0.076	0.007	0.15	Yes	-0.042	0.159	0.122
rs2237892	T	11	*KCNQ1*	0.033	0.005	0.36	No	0.061	0.171	0.379
rs2535633	G	3	*ITIH4, MUSTN1*	0.031	0.006	0.41	Yes	0.089	0.191	0.439
rs574367	T	1	*LOC101928778, SEC16B*	0.058	0.006	0.21	Yes	-0.020	0.130	0.246
rs591166	A	18	*MC4R, PMAIP1*	0.046	0.006	0.24	Yes	0.060	0.179	0.278
rs6545814	G	2	*ADCY3*	0.033	0.005	0.45	Yes	0.040	0.152	0.446

SNP, single nucleotide polymorphism; BMI, body mass index; PD, Parkinson's disease; SE, standard error; MAF, minor allele frequency; CHR, chromosome.



Supplementary Figure 1. Funnel plots (left column) and leave-one-out analysis (right column) of the MR analyses exposures. LDL (A and B), HDL (C and D), TG (E and F), T2DM (G and H), and BMI (I and J). MR, Mendelian randomization; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; BMI, body mass index; CI, confidence interval; IVW, inverse-variance weighted method.