**Original article**

# A bi-directional Mendelian randomization study of glycemic and anthropometric traits and Parkinson's disease

**Running head:** Glucose, body weight and Parkinson's disease

Sandeep Grover[1], Ricarda Graf[2], Alastair Noyce[3], International Parkinson's Disease Genomics Consortium (IPDGC), Manu Sharma[1]

[1]Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Tübingen, Germany

[2]Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

[3]Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK.

**Corresponding Author:**

Dr Manu Sharma

E-Mail: manu.sharma@uni-tuebingen.de

Phone: 0049-7071-2978259

**Character count:**

Title: 96, Running head: 39

**Number of words:**

Abstract: 350, Body of the Manuscript: 2999 (Excluding abstract and references)

Number of Figures: 2; Number of Tables: 3

**Key points**

**Question:** Are glucose and obesity associated with Parkinson's disease?

**Findings:** Using bi-directional Mendelian randomization (MR) approach, and using Parkinson disease (PD) as an exposure, our study found that a 1-log odds increase in genetic predisposition to PD was associated with 0.0188 mmol/l increase in fasting glucose concentration. The genetic predisposition to PD was also associated with a 5.4% lower risk of type-2 diabetes (T2D). We found that a 1-SD increase in waist-hip ratio (WHR) was associated with a 26.5% lower risk of PD in the European population, likely to be mediated via body mass index.

**Meaning:** A strong genetic predisposition towards glucose tolerance was observed in PD patients. and PD patients are protective against T2D. Further, an increase in WHR lowers the risk of PD. Our study thereby suggests potential roles of body fat distribution and glycemic traits on PD symptomatology.

**Abstract**

**Importance:** Impaired glucose and obesity are known characteristics of patients with PD, although it is unclear whether the dysfunction precedes or results from the neurodegeneration.

**Objective:** To assess whether glycemic traits and anthropometric traits can influence the risk of PD in 33,674 cases and 449,056 healthy controls using Mendelian randomization (MR) framework.

**Design, setting, and participants:** We investigated causality with a two-sample bidirectional MR approach in the European population. We used the inverse variance-weighted (IVW), weighted median (WME), and weighted mode (MBE) methods to compute effect estimates with summary statistics from available meta-analyses of genome-wide association studies (GWAS) on glycemic and anthropometric traits that used discovery cohorts. We conducted sensitivity analyses with prioritized genetic instruments that used different study designs including employment of different study cohorts and body mass index (BMI) adjusted exposures, and exclusion of overlapping samples between risk factors and outcome datasets, and potential pleiotropic genetic instruments.

**Main outcome and measures**: PD, glycemic and anthropometric traits

**Results**: We observed a risky effect of PD on fasting glucose (FG) (IVW: $\beta = 0.0188$ per log-odds of PD; 95% CI 0.0062–0.0313, p-value = 0.0055). We further observed a protective effect of PD on type 2 diabetes (T2D) (WME: OR = 0.946 per log-odds of PD; 95% CI 0.929–0.983, p-value = 0.0051). A direct causal role of waist-hip ratio (WHR) was also observed in PD (IVW OR = 0.735; 95% CI = 0.622-0.868 per 1-SD of WHR, p = 0.0003). However, the association was lost after WHR was adjusted for body mass index (BMI) (IVW OR = 0.889; 95% CI = 0.779-1.037 per 1-SD of WHR adjusted for BMI, p = 0.1429) indicating that the observed association is mediated via BMI The associations were further retained after the exclusion of overlapping UK Biobank (UKB) samples in the PD dataset.

**Conclusions and relevance:** Our results showed that PD patients are glucose tolerant with protection against T2D. Furthermore, central obesity may be protective against PD development, independent of glucose levels. The implication of different indices of glycemic control and body fat distribution on the PD symptomatology deserves further investigation.

**Keywords:** Mendelian randomization, Causal inference, Neurodegenerative disorders, Parkinson's disease, Glycemic traits, Type 2 diabetes, body weight, anthropometric traits

## Introduction

The lack of neuroprotective or disease-modifying therapy has considerably hampered the management of PD. However, several recent preclinical and clinical studies have shown the potential beneficial effects of pharmacotherapy that promotes blood glucose-dependent insulin secretion and weight reduction on PD[1,2].

Traditionally, insulin has been implicated in the general hormonal regulation of glucose metabolism, as insulin crosses the blood-brain barrier to modulate brain energy homeostasis, with a minor contribution from internal neuronal secretion[3]. Several studies have demonstrated an association between impaired cortical glucose metabolism in specific brain regions and cognitive decline in patients with PD[4,5]. Preclinical studies in insulin-resistant models of neurodegeneration have shown the influence of insulin on dopaminergic cell death and dopamine expression, which induce severe motor and anxiety-like behavior[6-8]. Recently, T2D – characterized by high blood sugar, insulin resistance, and low insulin levels – was shown to be associated with higher motor scores in patients with PD [9]. Change in body weight is also long known to occur during the clinical course of Parkinson's disease (PD) and with the treatment of PD. A handful of observational studies with highly heterogeneous epidemiological study designs have investigated the association of body weight with PD, showing conflicting results[10-12].

Mendelian randomization (MR) has recently evolved as an alternative statistical approach that can, against potential confounding, judge potential causal relationships between risk factors (e.g. altered glucose metabolism or body mass index) and an outcome (e.g. PD)[13,14]. In principle, MR allows the use of genetic variants as proxy representatives of exposure from one population to test an association with an outcome in a completely independent population[15]. Genetic variants are randomly distributed at birth, and the process mimics the randomization of exposure in randomized controlled trials (RCTs) and, thereby, addresses hidden confounding factors[16].

To date, MR studies exploring the causal role of altered glucose or insulin homeostasis in PD are lacking. However, our previously published study explored the role of body mass index (BMI) on PD[17] and showed a protective role of body mass index (BMI) (OR = 0.82, 95% CI = 0.69-0.98)[17]. Most recently, the availability of GWAS datasets from the UK Biobank has further made possible to take advantage of increased power associated with a higher sample size by meta-analyzing it with previously existing large scale consortium datasets on various phenotypes of interest[18-20].

In the present study, we expanded the spectrum of assessing the impact and influence of several glycemic traits including 2-hour post-challenge glucose (2hrGlu), fasting glucose (FG), fasting insulin (FI), fasting insulin (FPI), homeostasis model assessment of β-cell function (HOMA-B); homeostasis model assessment of insulin resistance (HOMA-IR); glycated hemoglobin (HbA1c), Modified Stumvoll Insulin Sensitivity Index (ISI), and T2D and anthropometric traits include body metabolic index (BMI), waist-hip ratio (WHR), waist circumference (WC), hip circumference (HC), adult height (AH) and birth weight (BW) on PD. We used inverse variance-weighted (IVW), MR-Egger, weighted median (WME), and weighted mode methods (MBE) to investigate the direct causal role of glycemic traits and anthropometric traits on PD[18-30]. As a secondary analysis, we further employed a reverse directional MR to confirm our findings.

## Methods

### Study design and identification of datasets

We conducted a two-sample MR study through the use of summary estimates to examine the lifelong effect of glycemic and anthropometric traits on the risk of PD in the European population. We reviewed the most recent meta-analyses of discovery GWAS datasets in the literature and identified genetic instruments that influence glycemic traits including 2hGlu, FG, FI, HOMA-B, HOMA-IR, HbA1c, ISI, T2D and anthropometric traits including BMI, WHR, WC, HC, AH, and BW [18,20-30] (**Table 1)**. With respect to the outcome dataset, we used the discovery cohort of a recent meta-analysis of GWAS on

33674 PD cases and 449056 controls[19]. We further identified genetic variants representing proxy markers of PD by using the same study to conduct a reverse directional MR.

**Prioritization of genetic variants**

We extracted significant SNPs from each GWAS dataset by employing a cutoff of $5\times10^{-8}$. All SNPs with F-statistics <10 were further excluded for a possible violation of MR Assumption I[31]. Loci known to be directly involved in PD were also excluded for a possible violation of MR Assumption III, based on the existing evidence from previously published GWAS studies and relevant literature[32].A clumping window of 10,000 kb and linkage disequilibrium (LD; i.e. $r^2$) cutoff of 0.001 was applied in the European population in the 1000Genome Phase 3v5 dataset to identify the leading SNP that represents each significantly associated locus[33]. If a specific leading SNP was not available in the PD dataset, a proxy SNP ($r^2 > 0.8$) was identified by using the European population in the 1000Genome Phase 3v5 dataset, when possible. The statistical power to detect a causal association was calculated by the method described by Brion et al [34]. Based on the method, we used a sample size of outcome dataset of 482750 with a 7.498% as proportion of PD patients in the dataset, a continuous exposure with a variance ≥1% and a threshold p-value of $3.3 \times 10^{-3}$ (see the section below).

**Effect estimation using MR and test of pleiotropy**

The IVW effect method with second-order weights was employed as the primary method to compute causal effect estimates[35]. We applied a conservative Bonferroni correction to account for 15 independent tests (threshold p-value = $3.3 \times 10^{-3}$, i.e. 0.05/15). We used Cochrane Q-statistics and $I^2$ for the IVW method as well as Rucker's Q-statistics and the Intercept deviation test with MR-Egger's method [36-39].

**Sensitivity analysis**

We employed MR-Egger, WME, and MBE methods to check the reliability of estimates with varying proportions of pleiotropic variants, as previously explained[37,39-42]. We further compared the results with genetic instruments from studies that reported discovery, replication, and pooled cohorts. The BMI has been shown to influence the role of glycemic and anthropometric traits on several diseases, including PD[43]. Therefore, we estimated the effect of genetic instruments adjusted for BMI for 2hrGlu, FG, FI, ISI,

T2D, and WHR to identify their overall influence on the causal effect estimates for PD. A summary of GWAS datasets used to study the influence of GWAS study design and BMI adjusted datasets is provided in **Supplementary Table 1**. We employed a leave-one and leave-one-group-out cross-validation approach to check the influence of outlier variants as well as that of variants known to be associated with confounders of the relationship between glycemic, and anthropometric traits and PD. In addition, we employed graphical approaches, including a scatter plot of individual SNP-level effect estimates among exposure and outcome datasets and a funnel plot of the spread of inverse of the standard error of individual SNP-level effect estimates, around the effect estimates computed by various MR methods. We used the Phenoscanner database to identify potential pleiotropic genetic instruments that are known to be associated with potential confounders[44]. To avoid the overlapping of samples from UK Biobank, which has been included in recently published GWAS, we computed casual effect estimates by using PD datasets without UK biobank samples, as used in the previous study (9,581 PD cases and 33,245 controls)[32,45,46].

## Results

### Prioritization of genetic instruments and power analysis

The depth of genomic coverage and number of individuals in different discovery GWAS datasets on have been provided in **Table 1**. The table further shows variance explained by genetic instruments for different exposure datasets and availability of genetic instruments in the PD dataset.

Our power analysis suggest that our study has ≈80% power to detect a true OR of 1.210 or 0.789 for PD per SD of the continuous phenotype assuming that the proportion of the continuous phenotype explained by the genetic instrument is ≥1% at a type 1 error rate of $3.3 \times 10^{-3}$.

### Effect estimation and sensitivity analysis

The direct and reverse causal effect estimates of glycemic traits and anthropometric traits with PD are shown in **Tables 2** and **3**, both of which also provides various measures to evaluate the robustness of the effect estimates. Overall summary data used to compute effect estimates and sensitivity analysis are presented in **Supplementary Table 2**

Using a bidirectional MR approach, we observed a risky casual effect of PD on FG using IVW and MR Egger methods (**Table 3**). We observed a protective role of PD on T2D with the WME and MBE methods (**Table 3**). We observed high heterogeneity (76.8%) in the association of PD with T2D which could be attributed to the small number of genetic variants used as instruments for PD. However, the pleiotropic tests demonstrated there was a negligible effect on the overall results (MR-Egger intercept p-value = 0.4711 and Rucker's test statistic/Cochrane Q-statistic = 0.9685). The distribution of individual SNP-level effect estimates along with the effect estimates computed through different MR methods for the effect of PD on FG and T2D are shown as scatter and funnel plots in **Figure 1**. Our sensitivity analysis excluding individual SNPs in the causal effect estimation of PD on both FG and T2D failed to show the influence of outlier or potential pleiotropic SNP, thereby confirming the robustness of our findings (**Supplementary Table 3**).

The observed findings were further confirmed by the absence of the causal effect of any of the glycemic traits, including FG and T2D on PD. This lack of association further persisted when we used genetic instruments that were prioritized from a small proportion of moderately associated SNPs which were followed up in a pooled cohort for 2hGlu, FG, FI, and FPI (**Supplementary Table 4**). Similarly, no association was observed for HOMA-B and HOMA-IR where genetic instruments were available for the replication cohorts. In addition, we did not observe any influence of the BMI-adjusted instruments that were available for 2hrGlu, FG, FI, and T2D, regardless of the GWAS study cohort that was used to extract the instrument (**Supplementary Table 4**). With respect to other glycemic traits, we could not find genetic instruments for ISI. However, we were able to evaluate the causality using the genetic instruments for BMI adjusted ISI phenotype. We observed association using genetic instruments prioritized from the discovery cohort only. However, the observed association could not withstand the Bonferroni's correction.

Among all the anthropometric traits, we observed a significant protective effect of WHR on PD (**Table 2**). However, we observed loss of association when we used genetic instruments for WHR, which was adjusted for BMI, suggesting that the role of BMI in influencing genetic predisposition to PD. Using

the phenoscanner database, out of 357 SNPs WHR associated SNPs employed in causal effect analysis; we further identified a total of 127 pleiotropic SNPs that have been previously shown to be associated with non-anthropometric traits such as blood cell count, glycemic traits, lipid levels, and respiratory capacity (Data not shown). Our sensitivity analysis by excluding these pleiotropic SNPs demonstrated existence of protective trend in the effect estimate (OR = 0.801, 95% CI = 0.640-1.00, p = 0.052). However, the loss of association may be attributed to the overall loss of variance in the genetic instrument used for the sensitivity analysis.

Lastly, to rule out the effect of week instrument bias on account of overlapping UKB samples, we used PD dataset without UKB samples. The protective effect of PD on T2D as well as the risky effect of WHR on PD were retained suggesting the reliability of the observed findings (PD on T2D: WME: OR = 0.954, 95% CI = 0.938–0.970, p = 0.0094; MBE: OR=0.949, 95% CI = 0.916–0.983, p-value=0.0084) (Data not shown).

**Additional analysis**

Our findings further motivated us to explore the triangulation relationship between the traits shown to be related to PD using MR approach. We observed a bidirectional causal relationship between T2D and FG as well as T2D and WHR (**Figure 2**) (Data not shown). We further observed WHR as a risk factor for a higher FG with the absence of any effect of FG on WHR (**Figure 2**).

**Discussion**

The present study using a bi-directional MR aimed to understand the role of glycemic and anthropometric on PD, and observed that PD patients showed higher glucose tolerance, strong protective effect against T2D. Furthermore, an increase in WHR showed protection against PD; the observed effect is mediated via BMI.

The results observed in our present study provided further evidence regarding the role of glucose metabolism in PD, and and data obtained herein is in agreement with the previously published epidemiological studies. For example, a recent study reported significantly higher blood glucose at T90 (p = 0.04) and T150 (p = 0.01) in 50 non-diabetic PD patients compared to 50 healthy controls during a 75g

oral glucose tolerance test, with no significant increase in insulin levels[43]. The study also reported that higher blood glucose levels were associated with higher BMI ($p<0.0001$). Another recent longitudinal study identified high blood glucose as a risk marker for PD progression[47]. The 48 month follow-up study exploring the role of 44 clinical variables in 135 patients with early PD, identified high FG levels ($p=0.013$) and T2D ($p=0.033$), among several other factors as significant predictors of annual cognitive decline in PD. The study further observed significant differences in the baseline levels of glucose when compared to 109 healthy controls. Our results are henceforth consent with these results suggesting that PD promotes dysregulation of glucose metabolism.

Several cohort studies have previously explored the influence of pre-existing T2D on the predisposition to PD with contradictory results. A prospective follow-up of 147,096 predominantly Caucaisn participants in the Cancer Prevention Study II Nutrition Cohort from the United States found no association of the history of diabetes with PD risk (RR 0.88; 95% CI 0.62–1.25)[48]. Another study that comprised two large US cohorts – the Nurses' Health Study (121,046 women) and the Health Professionals Follow-up Study (50,833 men) – observed similar results (RR 1.04, 95% CI 0.74–1.46)[49]. In contrast, a follow-up study in 51,552 Finnish individuals demonstrated an increased incidence of PD among patients with T2D (HR 1.85, 95% CI 1.23–2.80)[50]. Most recently, a meta-analysis of four cohort studies (3284 PD cases and 32, 695 diabetes cases) confirmed the finding that the onset of diabetes was a risk factor for PD (RR 1.37, 95% CI 1.21–1.55)[51]. However, the same study reported the absence of an association in pooled populations of five case-control studies (6487 PD cases and 1387 diabetes cases; OR 0.75, 95% CI 0.50–1.11). In summary, the findings of the association between T2D and PD have been highly heterogeneous and could be attributed to variables such as different study populations and epidemiological study designs. Our MR study further suggests that the onset of T2D has no lifetime risk in the predisposition to PD. On the other hand, we show that a genetic predisposition to PD could lower the lifetime risk to T2D by 4–5%. In conclusion, our study suggests that individuals with PD are less likely to develop T2D when compared to the general population.

Dopamine neurotransmission in human brain is known to modulate rewarding properties of food. Previous studies have further shown that dopamine receptors are under-expressed in obese individuals, thereby initiating a feedback look to compensate for lower dopamine secretion [52]. It is however not known whether an altered dopaminergic metabolism in overweight individuals could influence the onset of PD. Numerous observational studies have previously explored the association between obesity and PD with mixed results. A recent meta-analysis of ten cohort studies with 2706 PD cases showed absence of association of BMI with PD[11]. In contrast, a recent nationwide health check-up data for the whole South Korean population comprising 44,205 incident cases identified risky association of abdominal obesity with PD (HR: 1.13, 95% CI: 1.10-1.16)[10]. In our study, we observed a risk reduction of 26.5% with every one standard deviation (SD) increase in WHR. Our results are in contrast with a previously reported protective causal association of BMI with PD, which observed a risk reduction of 18%. However, since the publication of last MR study, both exposure and outcome datasets have seen an enormous addition of new samples with increased genomic coverage. The observation of a protective role of WHR henceforth adds novelty to our results.

Despite our inability to stratify patients by age, our study has several strengths. We adopted a comprehensive approach that included several known markers of insulin metabolism, including FG, FI, 2hrGlu, FPI, HOMA-B, HOMA-IR, HbA1c, ISI, and T2D. However, we observed that the genetic instruments for FI, HOMA-B, and HOMA-IR explained a very low amount of variance and, therefore, potential causation with PD might not be completely ruled out. Although we demonstrated a consistent reverse causal association of T2D with PD using different MR methods, we did not observe similar results with HbA1C, which is a known biomarker for prediabetes or diabetes. One of the reasons for this could be that the GWAS on HbA1c with 123,491 individuals from the general population was underpowered when compared to the GWAS on T2D that included 898,129 individuals[22,23]. Another important limitation of this study could be the unavailability of individual-level data, which could have enabled us to confirm the absence of pleiotropic variants by using various potential confounding variables

between PD and T2D. The possibility of a lack of pre-existing GWAS on some of the potential confounding variables cannot be ruled out. Lastly, we could not conduct a causal association analysis among different glycemic traits within PD patients. Nevertheless, our study suggest importance of collection of such data in near future.

Despite these limitations, to the best of our knowledge, our study represents one of the most comprehensive studies, to date, that has explored the potential causal role of glycemic and anthropometric traits on PD. An extensive sensitivity analysis demonstrated the role of PD in altered glucose metabolism independent of insulin activity. Furthermore, we showed that despite high fasting glucose levels, PD patients are protective against T2D. On the contrary, anthropometric traits mainly WHR and BMI may play a role in conferring protection against PD. We further suggest the adoption of a cautionary approach when drawing clinical interpretations from the results of the current study, because additional lines of evidence may be generated, including the potential complex relationship of anthropometric, glycemic and PD with other unexplored traits.

**Author contributions**

| Name | Location | Role | Contributions |
|---|---|---|---|
| Sandeep Grover | University of Tübingen, Tübingen, Germany | Author | Designed and conceptualized the study; conducted data extraction; analyzed the data; drafted the manuscript; and revised the final draft |
| Ricarda Graf | Universität zu Lübeck, Germany | Author | Contributed to preliminary statistical analysis |
| Alastair Noyce | Queen Mary University of London | Author | Revised the final draft. |
| Manu Sharma, | University of Tübingen, Tübingen, Germany | Author | Supervised the overall study and revised the final draft. |

## Acknowledgements

Data on PD GWAS was contributed by IPDGC team and downloaded from https://pdgenetics.org/. Data on glycemic traits were contributed by MAGIC investigators and downloaded from www.magicinvestigators.org. Data on T2D were contributed by DIAGRAM investigators and downloaded from www.diagram-consortium.org. Data on BMI, WHR,WC, HC and height were provided by GIANT consortium and downloaded from https://portals.broadinstitute.org/collaboration/giant/. Data on birth weight was provided by EEG consortium and downloaded from https://egg-consortium.org/.

## References

1. Kim DS, Choi HI, Wang Y, Luo Y, Hoffer BJ, Greig NH. A New Treatment Strategy for Parkinson's Disease through the Gut-Brain Axis: The Glucagon-Like Peptide-1 Receptor Pathway. *Cell Transplant.* 2017;26(9):1560-1571.
2. Katout M, Zhu H, Rutsky J, et al. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. *Am J Hypertens.* 2014;27(1):130-139.
3. Kuwabara T, Kagalwala MN, Onuma Y, et al. Insulin biosynthesis in neuronal progenitors derived from adult hippocampus and the olfactory bulb. *EMBO Mol Med.* 2011;3(12):742-754.
4. Hosokai Y, Nishio Y, Hirayama K, et al. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. *Mov Disord.* 2009;24(6):854-862.
5. Firbank MJ, Yarnall AJ, Lawson RA, et al. Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. *J Neurol Neurosurg Psychiatry.* 2017;88(4):310-316.
6. Jones KT, Woods C, Zhen J, Antonio T, Carr KD, Reith ME. Effects of diet and insulin on dopamine transporter activity and expression in rat caudate-putamen, nucleus accumbens, and midbrain. *J Neurochem.* 2017;140(5):728-740.
7. Kleinridders A, Cai W, Cappellucci L, et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc Natl Acad Sci U S A.* 2015;112(11):3463-3468.
8. Wang L, Zhai YQ, Xu LL, et al. Metabolic inflammation exacerbates dopaminergic neuronal degeneration in response to acute MPTP challenge in type 2 diabetes mice. *Exp Neurol.* 2014;251:22-29.
9. Pagano G, Polychronis S, Wilson H, et al. Diabetes mellitus and Parkinson disease. *Neurology.* 2018;90(19):e1654-e1662.
10. Nam GE, Kim SM, Han K, et al. Metabolic syndrome and risk of Parkinson disease: A nationwide cohort study. *PLoS Med.* 2018;15(8):e1002640.
11. Wang YL, Wang YT, Li JF, Zhang YZ, Yin HL, Han B. Body Mass Index and Risk of Parkinson's Disease: A Dose-Response Meta-Analysis of Prospective Studies. *PLoS One.* 2015;10(6):e0131778.
12. Wills AM, Perez A, Wang J, et al. Association Between Change in Body Mass Index, Unified Parkinson's Disease Rating Scale Scores, and Survival Among Persons With Parkinson Disease:

336 Secondary Analysis of Longitudinal Data From NINDS Exploratory Trials in Parkinson Disease
337 Long-term Study 1. *JAMA Neurol.* 2016;73(3):321-328.
338 13. Grover S, Del Greco MF, Stein CM, Ziegler A. Mendelian Randomization. *Methods Mol Biol.*
339 2017;1666:581-628.
340 14. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to
341 understanding environmental determinants of disease? *Int J Epidemiol.* 2003;32(1):1-22.
342 15. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple
343 genetic variants using summarized data. *Genet Epidemiol.* 2013;37(7):658-665.
344 16. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using
345 genes as instruments for making causal inferences in epidemiology. *Stat Med.* 2008;27(8):1133-
346 1163.
347 17. Noyce AJ, Kia DA, Hemani G, et al. Estimating the causal influence of body mass index on risk of
348 Parkinson disease: A Mendelian randomisation study. *PLoS Med.* 2017;14(6):e1002314.
349 18. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for
350 body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet.*
351 2019;28(1):166-174.
352 19. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and
353 heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies.
354 *Lancet Neurol.* 2019;18(12):1091-1102.
355 20. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for
356 height and body mass index in approximately 700000 individuals of European ancestry. *Hum*
357 *Mol Genet.* 2018;27(20):3641-3649.
358 21. Scott RA, Lagou V, Welch RP, et al. Large-scale association analyses identify new loci influencing
359 glycemic traits and provide insight into the underlying biological pathways. *Nat Genet.*
360 2012;44(9):991-1005.
361 22. Wheeler E, Leong A, Liu CT, et al. Impact of common genetic determinants of Hemoglobin A1c
362 on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-
363 wide meta-analysis. *PLoS Med.* 2017;14(9):e1002383.
364 23. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant
365 resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet.*
366 2018;50(11):1505-1513.
367 24. Manning AK, Hivert MF, Scott RA, et al. A genome-wide approach accounting for body mass
368 index identifies genetic variants influencing fasting glycemic traits and insulin resistance. *Nat*
369 *Genet.* 2012;44(6):659-669.
370 25. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose
371 homeostasis and their impact on type 2 diabetes risk. *Nat Genet.* 2010;42(2):105-116.
372 26. Walford GA, Gustafsson S, Rybin D, et al. Genome-Wide Association Study of the Modified
373 Stumvoll Insulin Sensitivity Index Identifies BCL2 and FAM19A2 as Novel Insulin Sensitivity Loci.
374 *Diabetes.* 2016;65(10):3200-3211.
375 27. Strawbridge RJ, Dupuis J, Prokopenko I, et al. Genome-wide association identifies nine common
376 variants associated with fasting proinsulin levels and provides new insights into the
377 pathophysiology of type 2 diabetes. *Diabetes.* 2011;60(10):2624-2634.
378 28. Saxena R, Hivert MF, Langenberg C, et al. Genetic variation in GIPR influences the glucose and
379 insulin responses to an oral glucose challenge. *Nat Genet.* 2010;42(2):142-148.
380 29. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin
381 biology to body fat distribution. *Nature.* 2015;518(7538):187-196.
382 30. Horikoshi M, Beaumont RN, Day FR, et al. Genome-wide associations for birth weight and
383 correlations with adult disease. *Nature.* 2016;538(7624):248-252.

31. Pichler I, Del Greco MF, Gogele M, et al. Serum iron levels and the risk of Parkinson disease: a Mendelian randomization study. *PLoS Med.* 2013;10(6):e1001462.
32. Lill CM, Roehr JT, McQueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. *PLoS Genet.* 2012;8(3):e1002548.
33. Consortium GP, Auton A, Brooks LD, et al. A global reference for human genetic variation. *Nature.* 2015;526(7571):68-74.
34. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol.* 2013;42(5):1497-1501.
35. Bowden J, Del Greco MF, Minelli C, et al. Improving the accuracy of two-sample summary data Mendelian randomization: moving beyond the NOME assumption. *bioRxiv.* 2017.
36. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. *Stat Med.* 2015;34(21):2926-2940.
37. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015;44(2):512-525.
38. Rucker G, Schwarzer G, Carpenter JR, Binder H, Schumacher M. Treatment-effect estimates adjusted for small-study effects via a limit meta-analysis. *Biostatistics.* 2011;12(1):122-142.
39. Grover S, Del Greco M F, Kasten M, Klein C, Lill CM, Koenig IR. Risky behaviors and Parkinson's disease: A Mendelian randomization study in up to 1 million study participants. *bioRxiv.* 2018.
40. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol.* 2016;40(4):304-314.
41. Burgess S BJ. Integrating summarized data from multiple genetic variants in Mendelian randomization: bias and coverage properties of inverse-variance weighted methods. *arXiv:151204486* 2015.
42. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol.* 2017;46(6):1985-1998.
43. Marques A, Dutheil F, Durand E, et al. Glucose dysregulation in Parkinson's disease: Too much glucose or not enough insulin? *Parkinsonism Relat Disord.* 2018;55:122-127.
44. Staley JR, Blackshaw J, Kamat MA, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics.* 2016;32(20):3207-3209.
45. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet.* 2014;46(9):989-993.
46. Grover S, Lill CM, Kasten M, Klein C, Del Greco MF, Konig IR. Risky behaviors and Parkinson disease: A mendelian randomization study. *Neurology.* 2019;93(15):e1412-e1424.
47. Mollenhauer B, Zimmermann J, Sixel-Doring F, et al. Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). *Mov Disord.* 2019;34(1):67-77.
48. Palacios N, Gao X, McCullough ML, et al. Obesity, diabetes, and risk of Parkinson's disease. *Mov Disord.* 2011;26(12):2253-2259.
49. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology.* 2007;69(17):1688-1695.
50. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care.* 2007;30(4):842-847.
51. Cereda E, Barichella M, Pedrolli C, et al. Diabetes and risk of Parkinson's disease: a systematic review and meta-analysis. *Diabetes Care.* 2011;34(12):2614-2623.

52. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet.* 2001;357(9253):354-357.

**List of figures and tables**

**Figure 1.** Graphical representation of causal association analysis and assessment of pleiotropy

**A.** Scatterplot showing causal effect estimates computed using various MR methods for the association of Parkinson disease (PD) as exposure with Fasting glucose (FG) as an outcome.

**B.** Funnel plot showing the extent of heterogeneity among the individual Wald ratio estimates for the association of Parkinson disease (PD) as exposure with Fasting glucose (FG) as an outcome.

**C.** Scatterplot showing causal effect estimates computed using various MR methods for the association of Parkinson disease (PD) as exposure with type 2 disease (T2D) as an outcome.

**D.** Funnel plot showing the extent of heterogeneity among the individual Wald ratio estimates for the association of Parkinson disease (PD) as exposure with type 2 disease (T2D) as an outcome.

**E.** Scatterplot showing causal effect estimates computed using various MR methods for the association of Parkinson disease (PD) as exposure with Waist Hip Ratio (WHR) as an outcome.

**F.** Funnel plot showing the extent of heterogeneity among the individual Wald ratio estimates for the association of Parkinson disease (PD) as exposure with Waist Hip Ratio (WHR) as an outcome.

**Figure 2.** Graphical representation of causal relationship between Parkinson's disease, glycemic and anthropometric traits. (Effect estimates of significant causal relationships have been written as red text).

**Table 1.** Details of the discovery GWAS datasets that explored and prioritized genetic instruments used for direct and reverse casual analysis in the present study. The direct analysis was done using Parkinson's disease (PD) as an outcome, and reverse was done using glycemic traits and modifiable anthropometric traits as an outcome.

**Table 2.** Causal effect estimates using different Mendelian randomization (MR) methods and heterogeneity analysis of causal effect estimates for Parkinson's disease (PD) by using various (a) glycemic traits as exposures. (b) anthropometric traits as exposures.

**Table 3.** Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for various (a) glycemic traits and (b) modifiable anthropometric traits by using Parkinson's disease as an exposure.

**Supplementary Table 1a.** Details of follow-up genetic variants in the replication and pooled exposure GWAS datasets and prioritized genetic instruments used for the secondary analysis

**Supplementary Table 1b.** Details of exposure GWAS datasets adjusted for BMI and prioritized genetic instruments used for the sensitivity analysis

**Supplementary Table 2.** Harmonized summary effect estimates from exposure and outcome datasets used for the conduct of Mendelian randomization (MR)

**Supplementary Table 3.** Sensitivity analysis of causal effect estimates using leave one out method (a) Parkinson's disease (PD) as exposure and fasting glucose (FG) as an outcome (b) Parkinson’s disease (PD) as exposure and type 2 diabetes (T2D) as an outcome.

**Supplementary Table 4.** Sensitivity analysis exploring the (a) influence of GWAS study design (b) BMI adjusted traits on causal effect estimates

**Table 1.** Details of discovery GWAS datasets explored and prioritized instruments used for direct and reverse causal analysis in the present study. Direct analysis was done using PD as an outcome and reverse was done using glycemic traits and modifiable anthopometric traits as outcome.

| S.No. | Phenotype | Source study | Maximum sample size | P | # of SNPs analyzed | # of significant SNPs | # of significant SNPs (post-clumping) ($R^2 < 0.001$) | # of proxy SNPs | # of SNPs in the genetic instrument | Average F-statistics (Median (Range) | $R^2$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Glycemic traits** | | | | | | | | | | | |
| 1 | 2 hour glucose (2hGlu) | Saxena et al. 2010, Scott et al. 2012* | 15234, 42854 | $5 \times 10^{-8}$ | 2401708 | NA | 4 | 0 | 3 | 48.9 (44.8-67.4) | 1.05 |
| 2 | Fasting glucose (FG) | Manning et al. 2012 | 58074 | $5 \times 10^{-8}$ | 2628879 | 505 | 22 | 0 | 22 | 41.8 (29.8-455.9) | 4.80 |
| 3 | Fasting insulin (FI) | Manning et al. 2012 | 51750 | $5 \times 10^{-8}$ | 2627848 | 34 | 4 | 0 | 4 | 35.6 (32.7-40.2) | 1.20 |
| 4 | Fasting proinsulin (FPI) | Strawbridge et al. 2011 | 10701 | $5 \times 10^{-8}$ | 2496073 | 407 | 8 | 0 | 8 | 53.7 (31.7-189) | 1.92 |
| 5 | Hemoglobin A1c (HbA1c) | Wheeler et al. 2017 | 123491 | $5 \times 10^{-8}$ | 2586698 | 821 | 38 | 0 | 38 | 46.7 (28.7-288) | 0.48 |
| 6 | Homeostasis model assessment of β-cell function (HOMA-B) | Dupuis et al. 2010 | 36466 | $5 \times 10^{-8}$ | 2456945 | 119 | 4 | 0 | 4 | 69.8 (33.4-123) | 0.17 |
| 7 | Homeostasis model assessment of insulin resistance (HOMA-IR) | Dupuis et al. 2010 | 37037 | $5 \times 10^{-8}$ | 2458073 | 0 | NA | NA | NA | NA | NA |
| 8 | Modified stumvoll insulin sensitivity index (ISI) | Walford et al. 2016 | 16753 | $5 \times 10^{-8}$ | 2423410 | 0 | NA | NA | NA | NA | NA |
| 9 | Type 2 Diabetes (T2D) | Mahajan et al. 2018 | 74123 cases/82 4006 controls | $5 \times 10^{-8}$ | 23465132 | 19227 | 202 | NA | 202 | 47.6 (29.2-2018) | NA |
| **Anthopoimetric traits** | | | | | | | | | | | |
| 1 | Body mass index (BMI) | Pulit et al. 2019 | 694649 | $5 \times 10^{-8}$ | 27381302 | 85104 | 548 | 2 | 548 | 49.0 (28.4-2030.6) | 5.77 |
| 2 | Waist hip ratio (WHR) | Pulit et al. 2019 | 694649 | $5 \times 10^{-8}$ | 27376273 | 39705 | 358 | 2 | 357 | 44.0 (29.0-820.0) | 3.28 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Waist circumference (WC) | Shungin et al. 2015 | 210088 | 5 x $10^{-8}$ | 2565407 | 1105 | 42 | 0 | 42 | 38.1 (29.3-447.0) | 1.18 |
| 4 | Hip circumference (HC) | Shungin et al. 2015 | 210088 | 5 x $10^{-8}$ | 2559738 | 1238 | 52 | 0 | 52 | 39.4 (27.8-378.1) | 1.36 |
| 5 | Adult height (AH) | Yengo et al. 2018 | 693529 | 5 x $10^{-8}$ | 2334001 | 130933 | 832 | 0 | 831 | 92.2 (28.4-2209.0) | 24.6 |
| 6 | Birth weight (BW) | Horikoshi et al. 2016 | 153781 | 5 x $10^{-8}$ | 16245523 | 2278 | 50 | 3 | 49 | 36.9 (30.4-179.8) | 2.00 |
| | | | **Disease trait** | | | | | | | | |
| 1 | Parkinson's disease (PD) | Nalls et al. 2019 | 33,674 cases, 449056** | 5 x $10^{-8}$ | 175,137,73 | 3465 | 23 | 0-11 | 18-23 | 43.6 (30.0-181.5) | NA |

*Discovery cohort (Saxena et al. 2010) was used to identify the SNPs, while effect estimates were taken from pooled cohort (Scott et al. 2012).
** The significant SNPs were identified from the Nalls et al. 2014 but the effect estimates were derived from a sub-population (without 23andMe cohort). Two SNPs were not available in the available GWAS dataset.

**Table 2a.** Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for Parkinson' disease using various glycemic traits as exposures.

| Trait* | MR methodology | # of SNPs | Direct causal effect estimates | | | Tests of heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | OR | 95% CI | p | | |
| 2 hour glucose (2hGlu) | Inverse variance weighted (2nd order weights) | 3 | 0.9260 | 0.563-1.523 | 0.5749 | MR-Egger intecept (p-value) | 0.8253 |
| | MR Egger | | 0.7160 | nd | 0.7786 | I square (IVW) | 0.0% |
| | Weighted median method | | 0.8930 | 0.786-1.016 | 0.4738 | Cochrane Q-test (IVW) (p-value) | 0.7984 |
| | Weighted mode method (NOME assumptions) | | 0.8850 | 0.650-1.204 | 0.5173 | Rucker's Q-test (p-value) | 0.5427 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.8229 |
| Fasting glucose (FG) | Inverse variance weighted (2nd order weights) | 22 | 1.1810 | 0.858-1.624 | 0.2910 | MR-Egger intecept (p-value) | 0.5647 |
| | MR Egger | | 1.0000 | 0.510-1.963 | 0.9992 | I square (IVW) | 29.4% |
| | Weighted median method | | 1.1390 | 0.952-1.363 | 0.4758 | Cochrane Q-test (IVW) (p-value) | 0.0970 |
| | Weighted mode method (NOME assumptions) | | 1.0520 | 0.752-1.473 | 0.7706 | Rucker's Q-test (p-value) | 0.0834 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9823 |
| Fasting insulin (FI) | Inverse variance weighted (2nd order weights) | 4 | 2.4399 | 0.053-112.905 | 0.5128 | MR-Egger intecept (p-value) | 0.1768 |
| | MR Egger | | nd | nd | 0.2085 | I square (IVW) | 79.0% |
| | Weighted median method | | 1.7492 | 0.895-3.417 | 0.1867 | Cochrane Q-test (IVW) (p-value) | 0.0025 |
| | Weighted mode method (NOME assumptions) | | 1.4995 | 0.155-14.481 | 0.2864 | Rucker's Q-test (p-value) | 0.0637 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.3851 |
| Fasting proinsulin (FPI) | Inverse variance weighted (2nd order weights) | 8 | 1.0200 | 0.811-1.283 | 0.8437 | MR-Egger intecept (p-value) | 0.1311 |
| | MR Egger | | 0.7356 | 0.445-1.218 | 0.1865 | I square (IVW) | 16.7% |
| | Weighted median method | | 0.8703 | 0.775-0.978 | 0.2710 | Cochrane Q-test (IVW) (p-value) | 0.2984 |
| | Weighted mode method (NOME assumptions) | | 0.9213 | 0.706-0.202 | 0.5641 | Rucker's Q-test (p-value) | 0.4654 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.6705 |
| Hemoglobin A1c (HbA1c) | Inverse variance weighted (2nd order weights) | 38 | 0.9441 | 0.625-1.500 | 0.8005 | MR-Egger intecept (p-value) | 0.1183 |
| | MR Egger | | 1.7000 | 0.712-4.056 | 0.2242 | I square (IVW) | 24.4% |
| | Weighted median method | | 1.1540 | 0.879-1.517 | 0.6022 | Cochrane Q-test (IVW) (p-value) | 0.0905 |
| | Weighted mode method (NOME assumptions) | | 1.1920 | 0.686-2.070 | 0.5368 | Rucker's Q-test (p-value) | 0.1206 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9422 |
| Homeostasis model assessment of β-cell function (HOMA-B) | Inverse variance weighted (2nd order weights) | 4 | 1.0250 | 0.397-2.645 | 0.9392 | MR-Egger intecept (p-value) | 0.7166 |
| | MR Egger | | 0.6348 | 0.004-103.727 | 0.7382 | I square (IVW) | 0.0% |
| | Weighted median method | | 1.1970 | 0.853-1.680 | 0.6328 | Cochrane Q-test (IVW) (p-value) | 0.8413 |
| | Weighted mode method (NOME assumptions) | | 1.2447 | 0.514-3.011 | 0.6605 | Rucker's Q-test (p-value) | 0.7187 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.7921 |
| Type 2 Diabetes (T2D) | Inverse variance weighted (2nd order weights) | 202 | 1.0333 | 0.974-1.093 | 0.2780 | MR-Egger intecept (p-value) | 0.9723 |
| | MR Egger | | 1.0300 | 0.911-1.165 | 0.6330 | I square (IVW) | 31.5% |
| | Weighted median method | | 1.0010 | 0.963-1.042 | 0.9700 | Cochrane Q-test (IVW) (p-value) | <0.0001 |
| | Weighted mode method (NOME assumptions) | | 1.0140 | 0.928-1.109 | 0.7580 | Rucker's Q-test (p-value) | <0.0001 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 1.0000 |

nd: Not defined

*No significant SNPs were identified for Homeostasis model assessment of insulin resistance (HOMA-IR) and Modified stumvoll insulin sensitivity index (ISI).

**Table 2b.** Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for Parkinson' disease using various anthropometric traits as exposures.

| Trait* | MR methodology | Number of SNPs | Direct causal effect estimates | | | Tests of heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | OR | 95% CI | p | | |
| Body mass index (BMI) | Inverse variance weighted (2nd order weights) | 548 | 0.920 | 0.802-1.054 | 0.2418 | MR-Egger intecept (p-value) | 0.3961 |
| | MR Egger | | 0.807 | 0.579-1.125 | 0.2046 | I square (IVW) | 25.9% |
| | Weighted median method | | 0.957 | 0.856-1.069 | 0.6906 | Cochrane Q-test (IVW) (p-value) | <0.0001 |
| | Weighted mode method (NOME assumptions) | | 1.002 | 0.756-1.329 | 0.9875 | Rucker's Q-test (p-value) | <0.0001 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9988 |
| Waist hip ratio (WHR) | Inverse variance weighted (2nd order weights) | 357 | 0.735 | 0.622-0.868 | 0.0003 | MR-Egger intecept (p-value) | 0.1508 |
| | MR Egger | | 1.012 | 0.635-1.614 | 0.9602 | I square (IVW) | 22.0% |
| | Weighted median method | | 0.810 | 0.721-0.911 | 0.0737 | Cochrane Q-test (IVW) (p-value) | 0.0003 |
| | Weighted mode method (NOME assumptions) | | 0.872 | 0.580-1.311 | 0.5098 | Rucker's Q-test (p-value) | 0.0003 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9947 |
| Waist circumference (WC) | Inverse variance weighted (2nd order weights) | 42 | 0.890 | 0.678-1.169 | 0.3965 | MR-Egger intecept (p-value) | 0.8559 |
| | MR Egger | | 0.946 | 0.461-1.943 | 0.8770 | I square (IVW) | 29.9% |
| | Weighted median method | | 0.944 | 0.797-1.118 | 0.7361 | Cochrane Q-test (IVW) (p-value) | 0.0378 |
| | Weighted mode method (NOME assumptions) | | 0.985 | 0.695-1.396 | 0.9318 | Rucker's Q-test (p-value) | 0.0289 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 1.0030 |
| Hip circumference (HC) | Inverse variance weighted (2nd order weights) | 52 | 0.904 | 0.719-1.136 | 0.3776 | MR-Egger intecept (p-value) | 0.7351 |
| | MR Egger | | 0.987 | 0.471-2.069 | 0.9727 | I square (IVW) | 34.2% |
| | Weighted median method | | 0.952 | 0.823-1.102 | 0.7402 | Cochrane Q-test (IVW) (p-value) | 0.0097 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Weighted mode method (NOME assumptions) | | 1.009 | 0.715-1.424 | 0.9581 | Rucker's Q-test (p-value) | 0.0072 |
| | | | | | | Cochrane Q-staitics/Rucker's test statistic | 1.0029 |
| Adult height (AH) | Inverse variance weighted (2nd order weights) | 49 | 1.024 | 0.952-1.101 | 0.5237 | MR-Egger intecept (p-value) | 0.9183 |
| | MR Egger | | 1.031 | 0.885-1.201 | 0.6974 | I square (IVW) | 19.4% |
| | Weighted median method | | 0.965 | 0.911-1.021 | 0.5302 | Cochrane Q-test (IVW) (p-value) | 0.0000 |
| | Weighted mode method (NOME assumptions) | | 0.883 | 0.721-1.082 | 0.2302 | Rucker's Q-test (p-value) | 0.0000 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 1.0000 |
| Birth weight (BW) | Inverse variance weighted (2nd order weights) | 831 | 1.198 | 0.926-1.549 | 0.1643 | MR-Egger intecept (p-value) | 0.3284 |
| | MR Egger | | 1.779 | 0.784-4.040 | 0.1641 | I square (IVW) | 38.0% |
| | Weighted median method | | 1.291 | 1.100-1.514 | 0.1164 | Cochrane Q-test (IVW) (p-value) | 0.0045 |
| | Weighted mode method (NOME assumptions) | | 1.518 | 0.919-2.507 | 0.1093 | Rucker's Q-test (p-value) | 0.0052 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9759 |

*No significant SNPs were identified for Homeostasis model assessment of insulin resistance (HOMA-IR) and Modified stumvoll insulin sensitivity index (ISI).

**Table 3a.** Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for various glycemic traits using Parkinson's disease as an exposure.

| Trait* | MR methodology | # of SNPs | Reverse causal effect estimate | | | Tests of heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | β or OR** | 95% CI | p | | |
| Fasting glucose (FG) | Inverse variance weighted (2nd order weights) | 19 | 0.0188 | 0.0062-0.0313 | 0.0055 | MR-Egger intecept (p-value) | 0.0957 |
| | MR Egger | | 0.0422 | 0.0117-0.0728 | 0.0097 | I square (IVW) | 0.0% |
| | Weighted median method | | 0.0150 | 0.0071-0.0228 | 0.0710 | Cochrane Q-test (IVW) (p-value) | 0.4555 |
| | Weighted mode method (NOME assumptions) | | 0.0161 | -0.0046-0.0368 | 0.1454 | Rucker's Q-test (p-value) | 0.5934 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.8349 |
| Fasting insulin (FI) | Inverse variance weighted (2nd order weights) | 19 | 0.0099 | -0.0059-0.0258 | 0.2035 | MR-Egger intecept (p-value) | 0.1686 |
| | MR Egger | | 0.0325 | -0.0039-0.0690 | 0.0775 | I square (IVW) | 35.7% |
| | Weighted median method | | 0.0122 | 0.0041- 0.0203 | 0.1423 | Cochrane Q-test (IVW) (p-value) | 0.0621 |
| | Weighted mode method (NOME assumptions) | | 0.0190 | 0.0014-0.0366 | 0.0404 | Rucker's Q-test (p-value) | 0.1102 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.8698 |
| Fasting proinsulin (FPI) | Inverse variance weighted (2nd order weights) | 19 | 0.0230 | -0.0106-0.0566 | 0.1672 | MR-Egger intecept (p-value) | 0.5022 |
| | MR Egger | | 0.0503 | -0.0408-0.1416 | 0.2590 | I square (IVW) | 30.7% |
| | Weighted median method | | 0.0276 | 0.0079-0.0472 | 0.1770 | Cochrane Q-test (IVW) (p-value) | 0.1062 |
| | Weighted mode method (NOME assumptions) | | 0.0138 | -0.0689-0.0967 | 0.7456 | Rucker's Q-test (p-value) | 0.0946 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9698 |
| Hemoglobin A1c (HbA1c) | Inverse variance weighted (2nd order weights) | 19 | 0.0005 | -0.0086-0.0096 | 0.9059 | MR-Egger intecept (p-value) | 0.4788 |
| | MR Egger | | 0.0082 | -0.0160-0.0325 | 0.4846 | I square (IVW) | 37.8% |
| | Weighted median method | | 0.0023 | -0.0024-0.0071 | 0.6483 | Cochrane Q-test (IVW) (p-value) | 0.0492 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Weighted mode method (NOME assumptions) | | 0.0016 | -0.0118-0.0151 | 0.8094 | Rucker's Q-test (p-value) | 0.0416 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9782 |
| Homeostasis model assessment of insulin resistance (HOMA-IR) | Inverse variance weighted (2nd order weights) | 19 | 0.0086 | -0.0081-0.0254 | 0.2917 | MR-Egger intecept (p-value) | 0.1701 |
| | MR Egger | | 0.0335 | -0.0066-0.0738 | 0.0960 | I square (IVW) | 15.7% |
| | Weighted median method | | 0.0142 | 0.0040-0.0244 | 0.2279 | Cochrane Q-test (IVW) (p-value) | 0.2654 |
| | Weighted mode method (NOME assumptions) | | 0.0262 | -0.0072- 0.0598 | 0.1429 | Rucker's Q-test (p-value) | 0.3390 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.8796 |
| Homeostasis model assessment of β-cell function (HOMA-B) | Inverse variance weighted (2nd order weights) | 18 | -0.0035 | -0.0159-0.0088 | 0.5530 | MR-Egger intecept (p-value) | 0.2189 |
| | MR Egger | | 0.0122 | -0.0167-0.0413 | 0.3827 | I square (IVW) | 0.0% |
| | Weighted median method | | 0.0034 | -0.0046-0.0115 | 0.6900 | Cochrane Q-test (IVW) (p-value) | 0.7384 |
| | Weighted mode method (NOME assumptions) | | 0.0093 | -0.0120-0.0308 | 0.4035 | Rucker's Q-test (p-value) | 0.7860 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.8770 |
| Modified stumvoll insulin sensitivity index (ISI) | Inverse variance weighted (2nd order weights) | 18 | -0.0491 | -0.1062-0.0078 | 0.0866 | MR-Egger intecept (p-value) | 0.4443 |
| | MR Egger | | -0.0915 | -0.2200-0.0368 | 0.1501 | I square (IVW) | 43.6% |
| | Weighted median method | | -0.0228 | -0.0511-0.0055 | 0.4516 | Cochrane Q-test (IVW) (p-value) | 0.0252 |
| | Weighted mode method (NOME assumptions) | | -0.0260 | -0.0996- 0.0475 | 0.5017 | Rucker's Q-test (p-value) | 0.0238 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9622 |
| Type 2 Diabetes (T2D) | Inverse variance weighted (2nd order weights) | 23 | 0.9735 | 0.9211-1.029 | 0.3258 | MR-Egger intecept (p-value) | 0.4711 |
| | MR Egger | | 1.0180 | 0.886-1.170 | 0.7901 | I square (IVW) | 76.9% |
| | Weighted median method | | 0.9460 | 0.929-0.963 | 0.0051 | Cochrane Q-test (IVW) (p-value) | <0.0001 |
| | Weighted mode method (NOME assumptions) | | 0.9430 | 0.904-0.983 | 0.0116 | Rucker's Q-test (p-value) | <0.0001 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9685 |

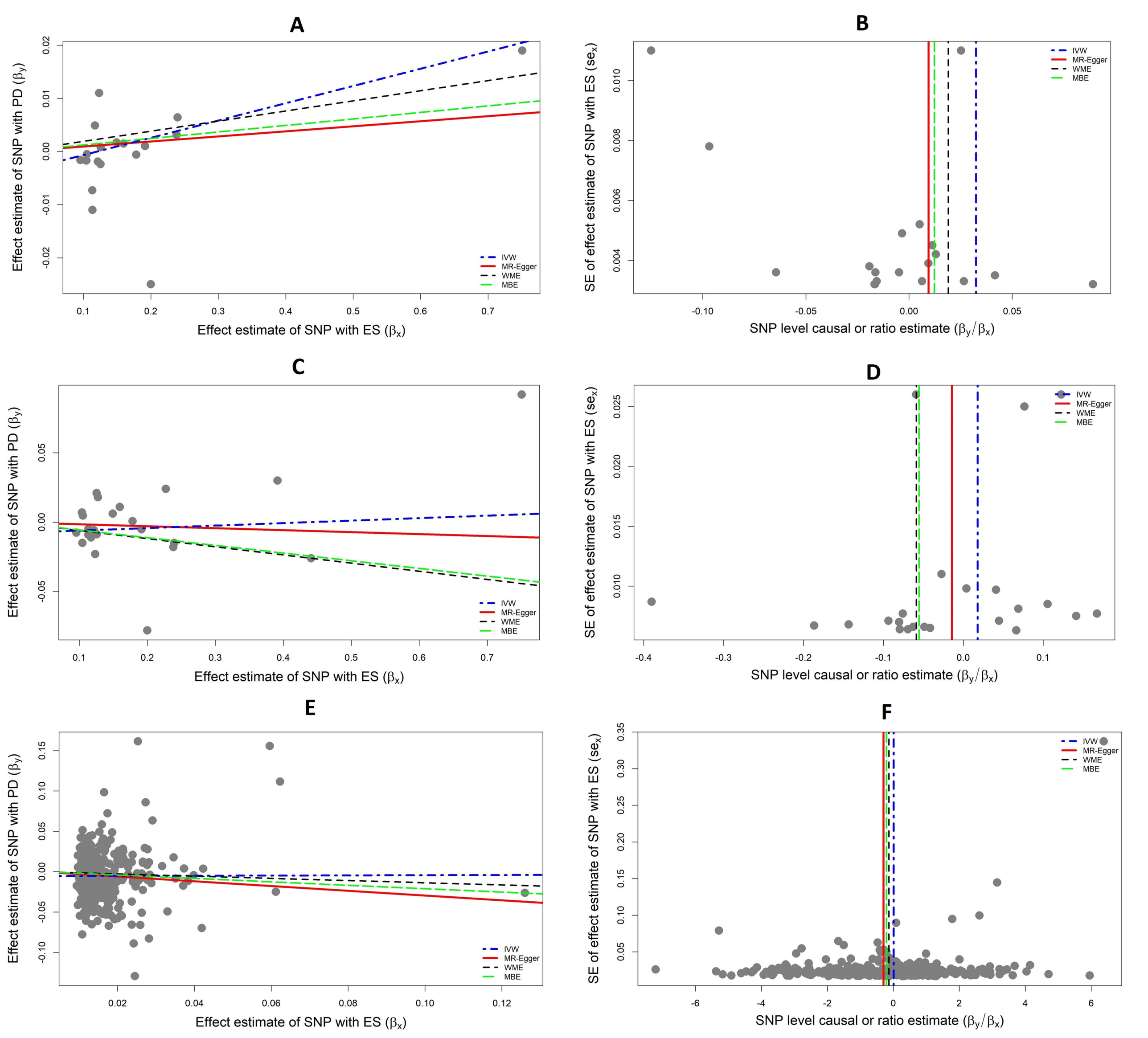
*Discovery cohort for 2 hour glucose (2hGlu) was not available.

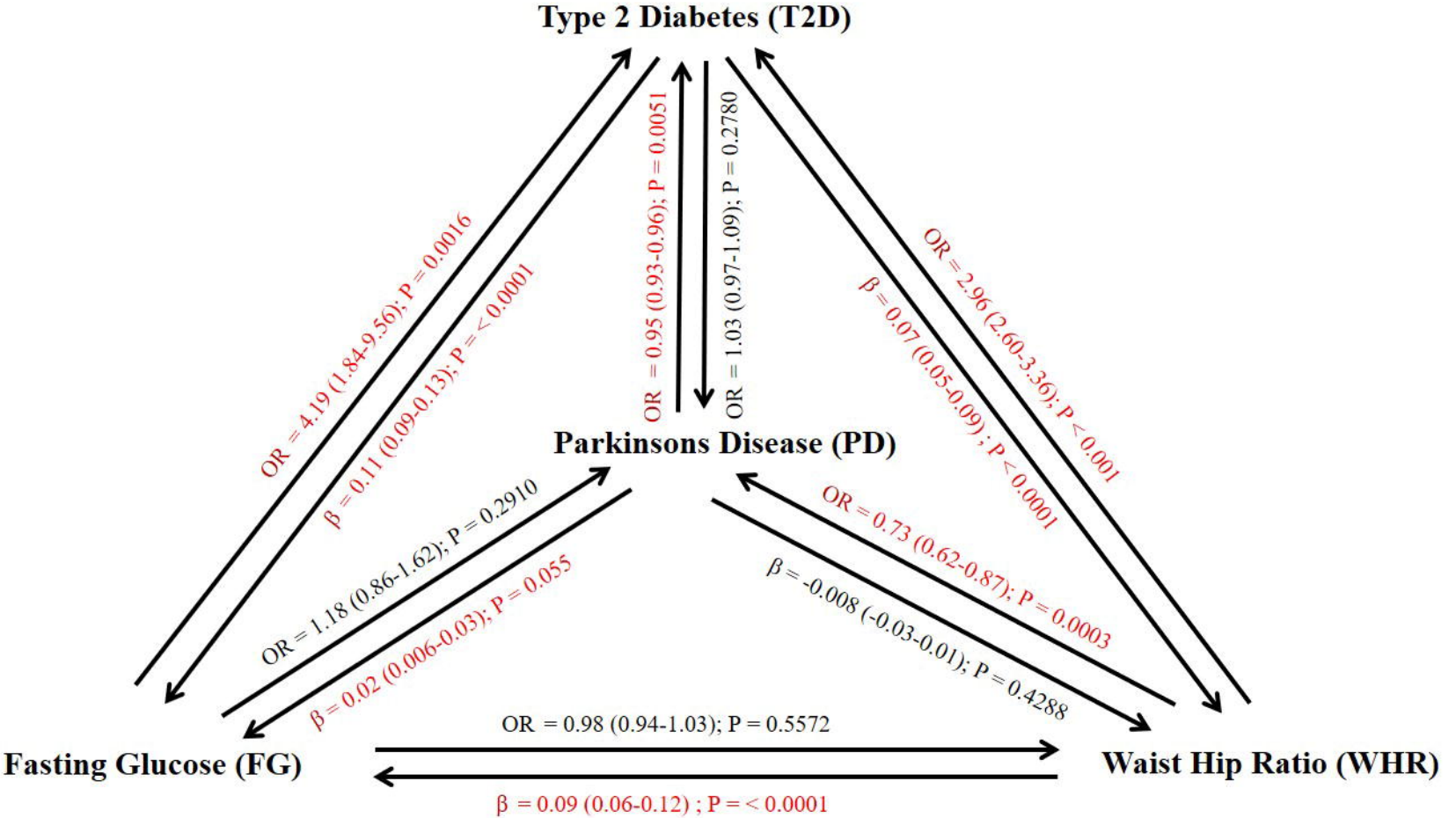
**OR is for T2D; β is for other outcome variables

**Table 3b.** Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for various modifiable anthropometric traits using Parkinson's disease as an exposure.

| Trait* | MR methodology | Number of SNPs | Reverse causal effect estimate | | | Tests of heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | β | 95% CI | p | | |
| Body mass index (BMI) | Inverse variance weighted (2nd order weights) | 23 | -0.005434556 | -0.0242-0.0133 | 0.5538 | MR-Egger intecept (p-value) | 0.4102 |
| | MR Egger | | 0.0129 | -0.0362-0.0620 | 0.5910 | I square (IVW) | 84.6% |
| | Weighted median method | | -0.0102 | -0.0157--0.0046 | 0.0786 | Cochrane Q-test (IVW) (p-value) | <0.0001 |
| | Weighted mode method (NOME assumptions) | | -0.0144 | -0.0269--0.0019 | 0.0344 | Rucker's Q-test (p-value) | <0.0001 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 1.0006 |
| Waist hip ratio (WHR) | Inverse variance weighted (2nd order weights) | 23 | -0.0077 | -0.0277-0.0122 | 0.4288 | MR-Egger intecept (p-value) | 0.8462 |
| | MR Egger | | -0.0031 | -0.0562-0.0500 | 0.9035 | I square (IVW) | 84.1% |
| | Weighted median method | | -0.0019 | -0.0073-0.0034 | 0.7276 | Cochrane Q-test (IVW) (p-value) | <0.0001 |
| | Weighted mode method (NOME assumptions) | | -0.0056 | -0.0246-0.0133 | 0.5644 | Rucker's Q-test (p-value) | <0.0001 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 1.0170 |
| Waist circumference (WC) | Inverse variance weighted (2nd order weights) | 19 | -0.0034 | -0.0277-0.0208 | 0.7691 | MR-Egger intecept (p-value) | 0.6691 |
| | MR Egger | | 0.0084 | -0.0543-0.0712 | 0.7801 | I square (IVW) | 51.0% |
| | Weighted median method | | -0.0100 | -0.0214-0.0012 | 0.3863 | Cochrane Q-test (IVW) (p-value) | 0.0057 |
| | Weighted mode method (NOME assumptions) | | -0.0128 | -0.0391-0.0135 | 0.3528 | Rucker's Q-test (p-value) | 0.0038 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9960 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hip circumference (HC) | Inverse variance weighted (2nd order weights) | 19 | 0.0005 | -0.0216-0.0227 | 0.9609 | MR-Egger intecept (p-value) | 0.343 |
| | MR Egger | | 0.0246 | -0.0320-0.0812 | 0.3724 | I square (IVW) | 39.1% |
| | Weighted median method | | 0.0090 | -0.0019-0.0201 | 0.4195 | Cochrane Q-test (IVW) (p-value) | 0.0419 |
| | Weighted mode method (NOME assumptions) | | 0.0162 | -0.0118-0.0442 | 0.2715 | Rucker's Q-test (p-value) | 0.0408 |
| | | | | | | Rucker's test statistic/ Cochrane Q-statistic | 0.9598 |


A
Effect estimate of SNP with PD ($\beta_y$)
Effect estimate of SNP with ES ($\beta_x$)
IVW
MR-Egger
WME
MBE
B
SE of effect estimate of SNP with ES ($se_x$)
SNP level causal or ratio estimate ($\beta_y/\beta_x$)
C
D
E
F


Type 2 Diabetes (T2D)
Parkinsons Disease (PD)
Fasting Glucose (FG)
Waist Hip Ratio (WHR)
OR = 4.19 (1.84-9.56); P = 0.0016
β = 0.11 (0.09-0.13); P = < 0.0001
OR = 0.95 (0.93-0.96); P = 0.0051
OR = 1.03 (0.97-1.09); P = 0.2780
OR = 2.96 (2.60-3.36); P < 0.001
β = 0.07 (0.05-0.09) ; P < 0.0001
OR = 1.18 (0.86-1.62); P = 0.2910
β = 0.02 (0.006-0.03); P = 0.055
OR = 0.73 (0.62-0.87); P = 0.0003
β = -0.008 (-0.03-0.01); P = 0.4288
OR = 0.98 (0.94-1.03); P = 0.5572
β = 0.09 (0.06-0.12) ; P = < 0.0001