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

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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 5×10^{-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 3.3×10^{-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 = 3.3×10^{-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 3.3×10^{-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.

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

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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.

454 **Table 2.** Causal effect estimates using different Mendelian randomization (MR) methods and
455 heterogeneity analysis of causal effect estimates for Parkinson's disease (PD) by using various (a)
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460 **Supplementary Table 1a.** Details of follow-up genetic variants in the replication and pooled exposure
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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	5×10^{-8}	2401708	NA	4	0	3	48.9 (44.8-67.4)	1.05
2	Fasting glucose (FG)	Manning et al. 2012	58074	5×10^{-8}	2628879	505	22	0	22	41.8 (29.8-455.9)	4.80
3	Fasting insulin (FI)	Manning et al. 2012	51750	5×10^{-8}	2627848	34	4	0	4	35.6 (32.7-40.2)	1.20
4	Fasting proinsulin (FPI)	Strawbridge et al. 2011	10701	5×10^{-8}	2496073	407	8	0	8	53.7 (31.7-189)	1.92
5	Hemoglobin A1c (HbA1c)	Wheeler et al. 2017	123491	5×10^{-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	5×10^{-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	5×10^{-8}	2458073	0	NA	NA	NA	NA	NA
8	Modified stumvoll insulin sensitivity index (ISI)	Walford et al. 2016	16753	5×10^{-8}	2423410	0	NA	NA	NA	NA	NA
9	Type 2 Diabetes (T2D)	Mahajan et al. 2018	74123 cases/824006 controls	5×10^{-8}	23465132	19227	202	NA	202	47.6 (29.2-2018)	NA
Anthopoimetric traits											
1	Body mass index (BMI)	Pulit et al. 2019	694649	5×10^{-8}	27381302	85104	548	2	548	49.0 (28.4-2030.6)	5.77
2	Waist hip ratio (WHR)	Pulit et al. 2019	694649	5×10^{-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

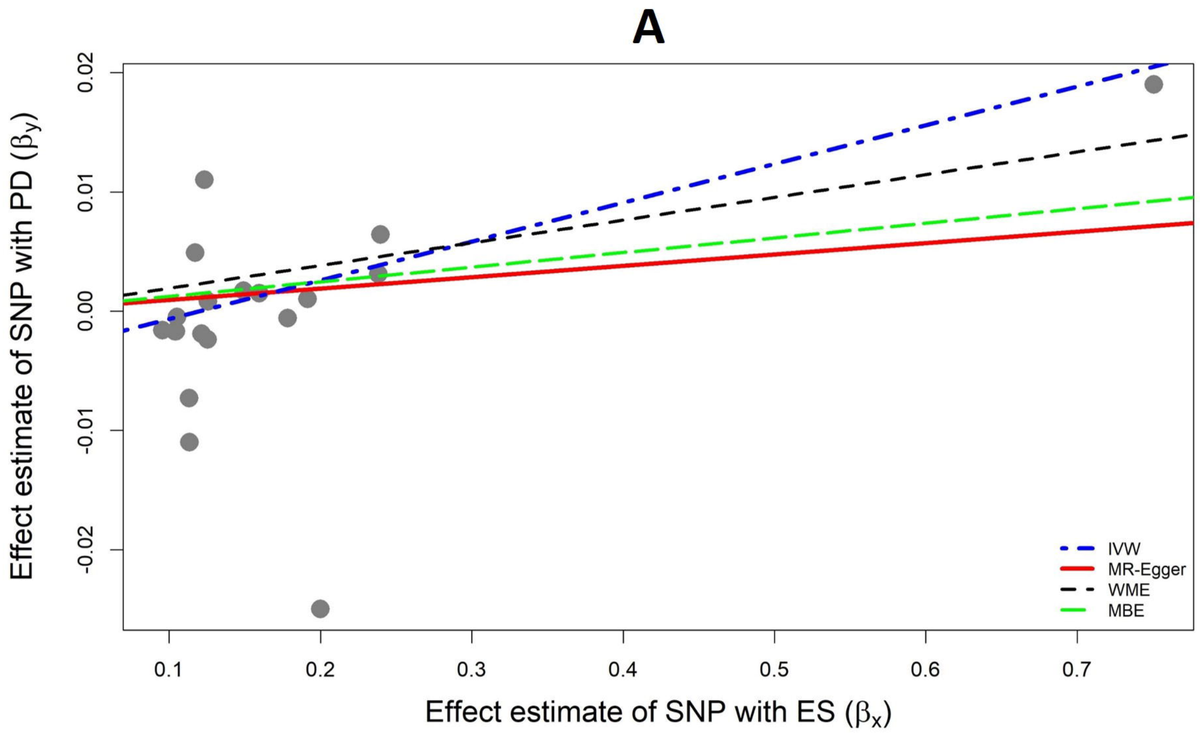
*Discovery cohort for 2 hour glucose (2hGlu) was not available.

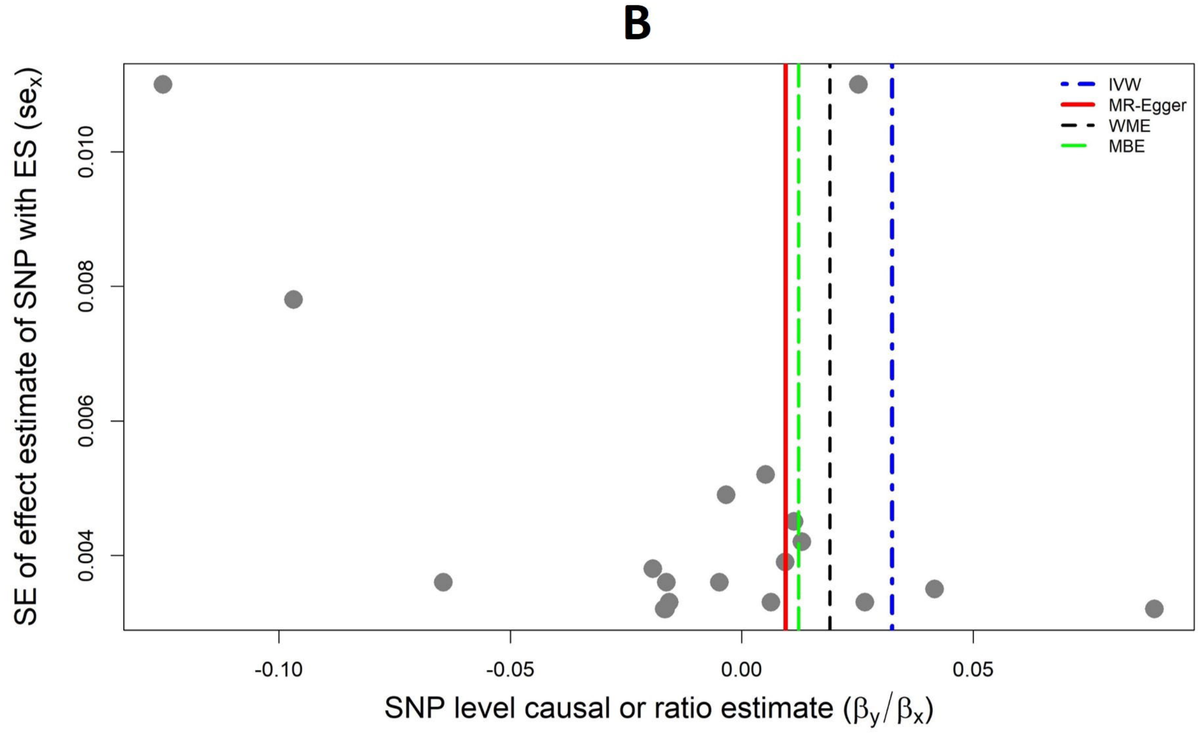
**OR is for T2D; β is for other outcome variables

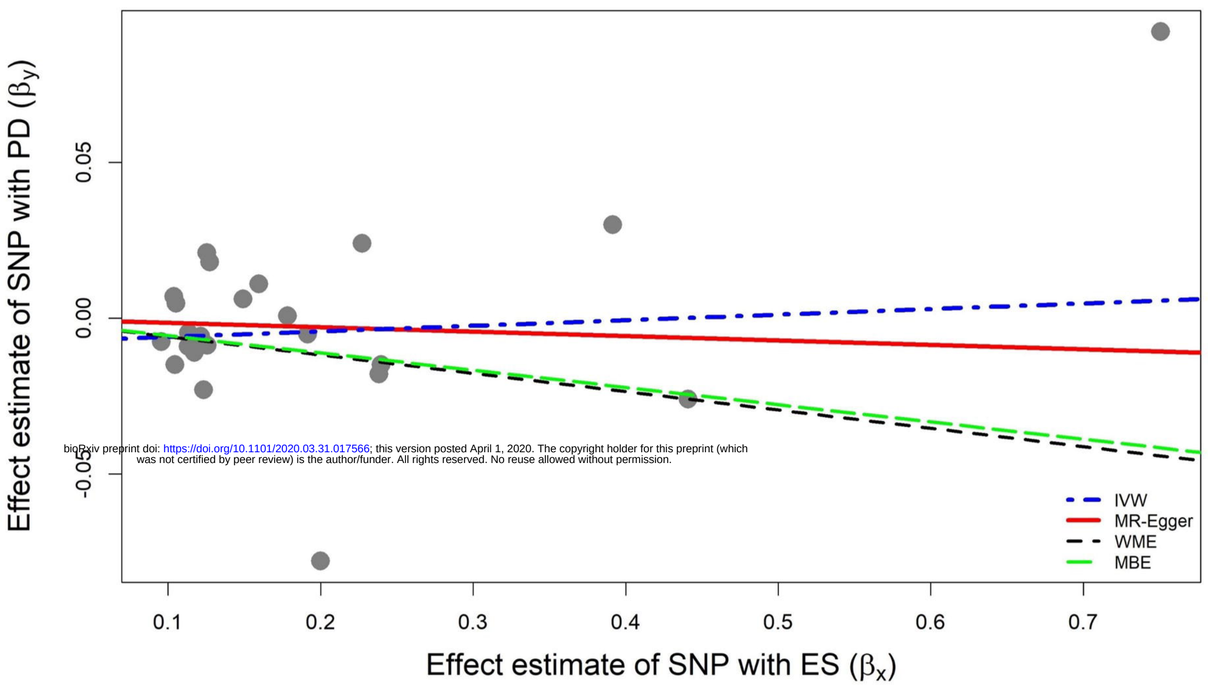
Table 3b. Causal effect estimates using different Mendelian randomization methods and heterogeneity analysis of causal effect estimates for various modifiable anthropometric traits using Parkinson's disease as an exposure.

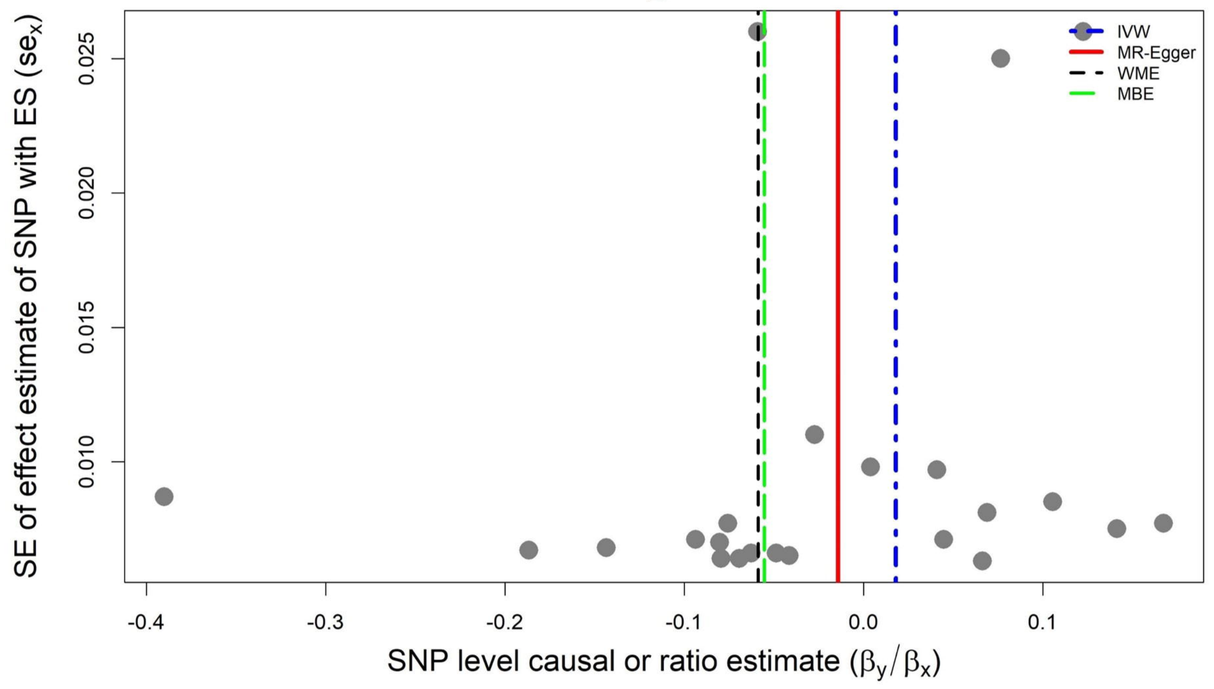
Trait*	MR methodology	Number of SNPs	Reverse causal effect estimate			Tests of heterogeneity	
			β	95% CI	p		
Body mass index (BMI)	Inverse variance weighted (2nd order weights)	23	-0.005434556	-0.0242-0.0133	0.5538	MR-Egger intecept (p-value)	0.4102
	MR Egger		0.0129	-0.0362-0.0620	0.5910	I square (IVW)	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

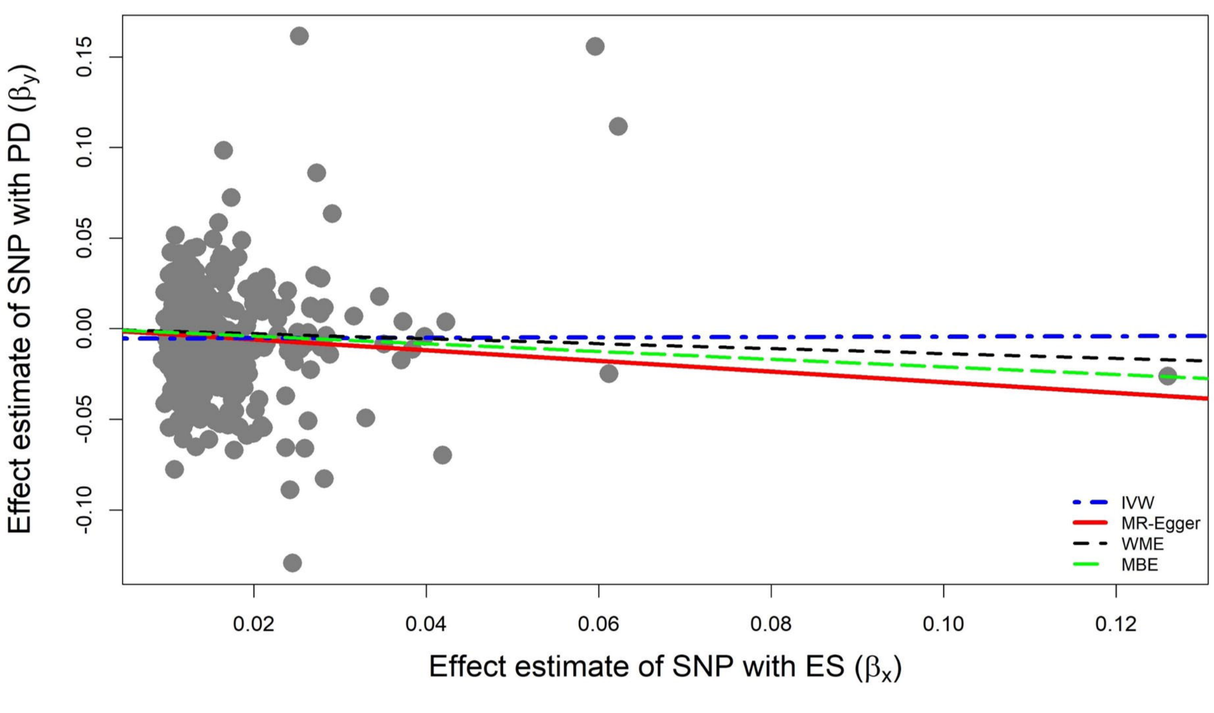
Hip circumference (HC)	Inverse variance weighted (2nd order weights)	19	0.0005	-0.0216-0.0227	0.9609	MR-Egger intecept (p-value)	0.343
	MR Egger		0.0246	-0.0320-0.0812	0.3724	I square (IVW)	39.1%
	Weighted median method		0.0090	-0.0019-0.0201	0.4195	Cochrane Q-test (IVW) (p-value)	0.0419
	Weighted mode 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

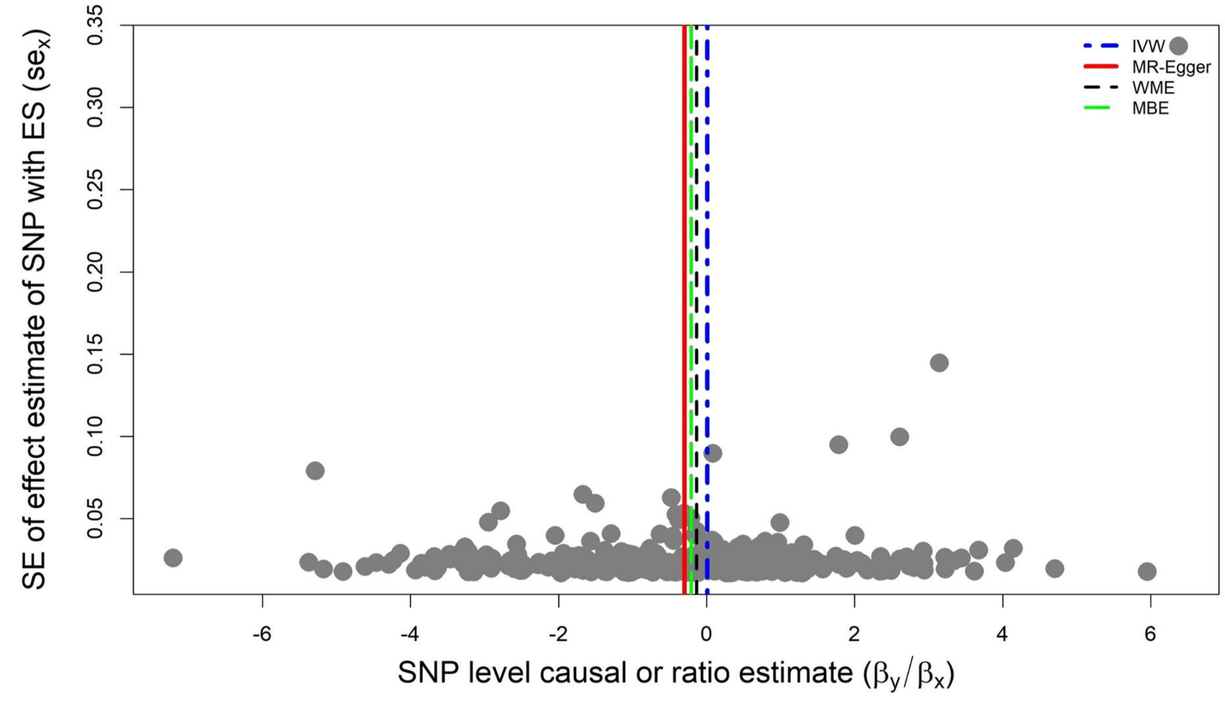


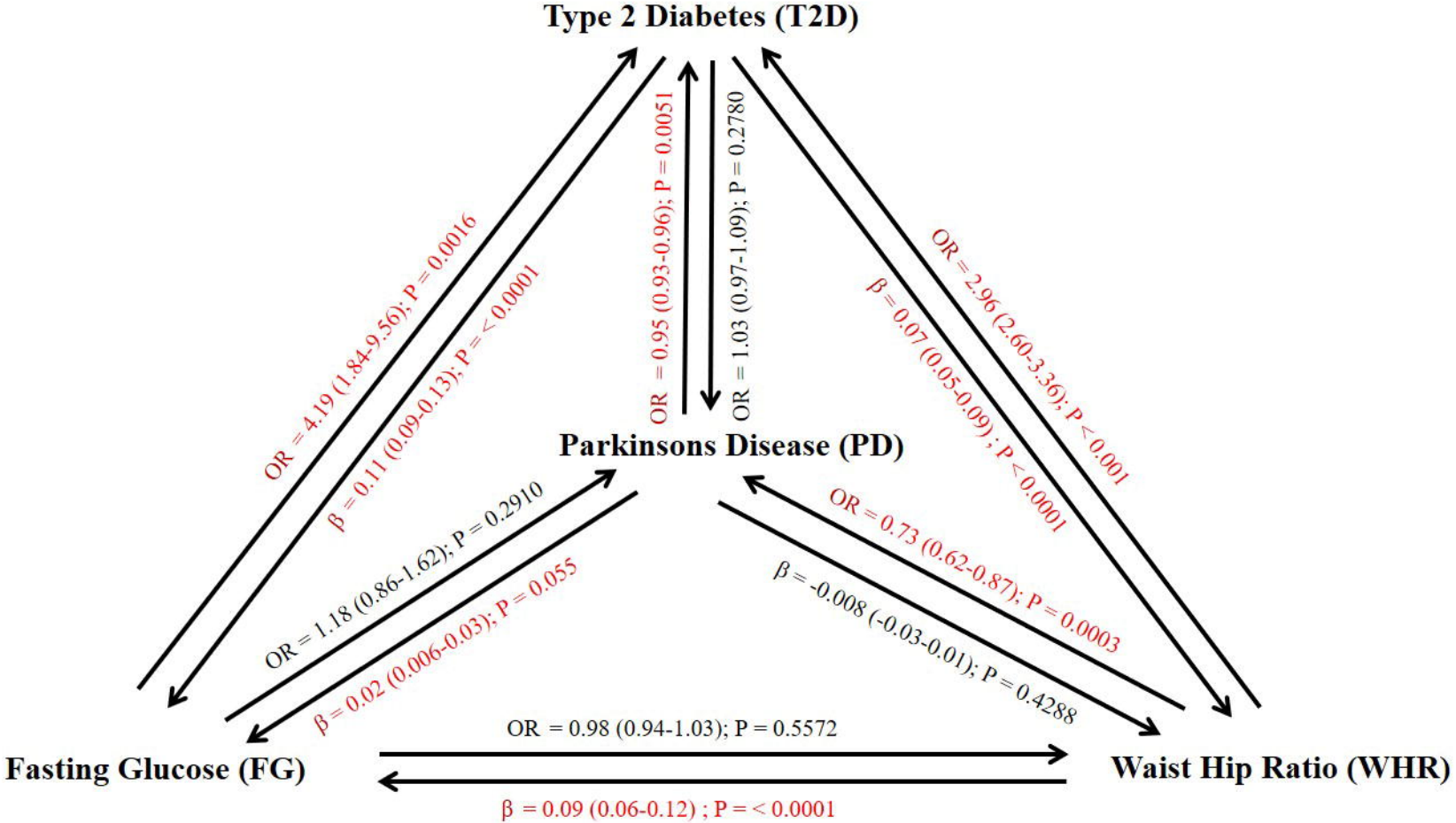











Type 2 Diabetes (T2D)
Parkinsons Disease (PD)
Fasting Glucose (FG)
Waist Hip Ratio (WHR)
OR = 4.19 (1.84-9.56); P = 0.0016
β = 0.11 (0.09-0.13); P = < 0.0001
OR = 0.95 (0.93-0.96); P = 0.0051
OR = 1.03 (0.97-1.09); P = 0.2780
OR = 2.96 (2.60-3.36); P < 0.001
β = 0.07 (0.05-0.09) ; P < 0.0001
OR = 1.18 (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