

Serotonin, Lipids and Parkinson's disease Risk: A Retrospective Study and Mendelian Randomization Analysis

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Research Article

Keywords: Serotonin, Serum lipids, Parkinson's diseases, Mendelian Randomization

Posted Date: September 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10141870/v1>

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Additional Declarations: No competing interests reported.

Abstract

Objective: Study suggests that *Turicibacter* affects gut serotonin levels and lipid metabolism. Enrichment of the *Turicibacter* can be observed in Parkinson's disease (PD) patients, but its specific role is currently ambiguous. The purpose of this study is to evaluate the relationship of serotonin and serum lipids, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and lipoproteins, with the PD risk.

Methods: We first used 16S rRNA sequencing to detect alterations in the abundance of *Turicibacter* in PD patients. Then, a retrospective study was conducted to evaluate the serum lipid levels, and whether there were gender differences in lipid levels of PD patients, and further Mendelian randomization (MR) analysis was performed using public GWAS data on PD, serotonin, and lipids to explore the causality of serotonin, lipids with PD risk.

Results: In this study, an increase in *Turicibacter* abundance and a significant decrease in lipid levels, including TC, TG, LDL-C, and HDL-C, were observed in PD patients, which were more pronounced in male patients. A causal inverse association of serotonin (OR 0.119, 95% CI 0.017–0.847, $P=0.034$), TC (OR=0.602, 95% CI=0.377-0.961, $P=0.033$) and LDL-C (OR=0.495, 95% CI=0.323-0.757, $P=0.001$) with PD risk was further suggested by the MR analysis.

Conclusion: Our findings emphasize the causality that the higher levels of serotonin and lipids and the lower PD risk in the future, which provides theoretical foundation for further study on the potential roles of the *Turicibacter* and its related serotonin and lipids in PD.

Introduction

The neurodegenerative injuries of Parkinson's disease (PD) involve damage of dopaminergic and serotonergic neurons, followed by a decrease in dopamine and serotonin levels (Buddhala et al. 2015). Moreover, the dopaminergic and serotonergic systems in mammals are believed to be anatomically and functionally interconnected, which may result in the alterations in the serotonergic system further exacerbating the disruption of the dopaminergic circuit in the substantia nigra (SN) and striatum of PD (Pagan et al. 2017]. It is believed that the environmental factors, genetic susceptibility, and other possible factors are instrumental for the complexity of PD pathogenesis (Tysnes and Storstein 2017). According to large-scale genome-wide association studies (GWAS), although loci that can increase the risk of PD have been identified, researchers estimate that genetic factors may account for a relatively low proportion (Nalls et al. 2019). Importantly, as is well known, PD is largely sporadic. Therefore, we speculate that genome and environmental factors may interact to jointly affect the occurrence and development of PD.

As one of the important environmental factors, gut microbiota dysbiosis exists in PD. The changes in different gut microbiota components may affect the risk of PD through various mechanisms. For example, gut microbiota regulates brain function and behavior by influencing metabolic product levels.

Studies have found that the abnormalities in the serotonergic system in the brain of PD patients include decreased striatal levels of serotonin (5-hydroxytryptamine, 5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), decreased expression of tryptophan hydroxylase (TPH), and decreased availability of serotonin transporter (SERT) and 5-HT receptors in the striatum (Zárate et al. 2022). In fact, dysfunction of serotonergic neurotransmission can lead to resting tremors and levodopa-induced motor disorders, as well as the emergence of non-motor symptoms such as depression and cognitive impairment (Sgambato-Faure and Tremblay 2018). In addition, there was that the level of serotonin in peripheral blood of PD patients also decreases (Wang et al. 2023). In the periphery, over 90% of circulating serotonin is synthesized by enterochromaffin cell dispersed in the gastrointestinal tract (Erspamer 1954). About 50% of gut-derived serotonin is regulated by the gut microbiota, especially the *Turicibacter* (Yano et al. 2015; Hata et al. 2017). The CUW_0748 protein expressed by *Turicibacter* shares sequence and structural homology with mammalian SERT, which are both considered as a sodium-dependent neurotransmitter transporters, responsible for the reuptake and inactivation of serotonin in many organs, including the intestine (Fung et al. 2019). However, due to the inability of peripheral serotonin to pass through the blood-brain barrier (BBB), researchers think that the central and peripheral pools of serotonin are anatomically separate (Jones et al. 2020). Therefore, it is worth exploring whether peripheral serotonin can serve as a promising diagnostic biomarker and potential therapeutic target for PD.

Turicibacter can also alter the expression of gene in the intestine, which is related to lipid and steroid metabolism (Fung et al. 2019). Numerous studies have demonstrated that lipid metabolism plays an important role in the development of PD. Given that cholesterol is the main component of neuronal cell membranes and myelin sheaths, so the brain is the organ with the highest cholesterol content in the vivo, which is crucial for maintaining synaptogenesis, dendritic formation, and axonal guidance (Mauch et al. 2001). It is worth noting that due to the BBB blocking the entry of peripheral cholesterol, almost all (> 95%) of cholesterol in the brain is synthesized from scratch (Dietschy 2009). Furthermore, the study found that serum cholesterol levels in PD patients decreased compared to the healthy controls (Fang et al. 2019). Reasonably suspect that peripheral cholesterol levels have a certain biological impact on the risk of PD.

In the present study, we first investigated the changes in *Turicibacter* abundance in PD patients through 16S rRNA sequencing. In addition, the Mendelian randomization (MR) approach could use genetic variation as instrumental variable to infer the causality between exposures (some biomarkers) and outcomes (various diseases). Therefore, we used Mendelian randomization analysis to evaluate the causality between serotonin and lipids, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C ratio, triglycerides (TG), and lipoprotein(a) (Lp[a]) and the risk of PD.

Methods

Clinical participants

The present study was approved by the institutional review boards and human subject committees at the participating institutions. First, 20 PD patients and 20 age and sex-matched healthy controls were included in this study to compare the gut microbiome changes. Second, an additional independent cohort of 80 patients with PD and 80 age and sex-matched healthy controls were enrolled to examine the lipid changes. All serum samples of the participants were obtained during the general health check in an outpatient visit or hospitalization period. This study that involved samples of human subjects was approved by the Ethics Board at the Fourth Affiliated Hospital of Zhejiang University School of Medicine (approval code: K2022178). All recruited participants signed written informed consent.

PD patients who conform to the International Parkinson Disease and Movement Disorder Society in 2015 clinical diagnostic criteria were included into this study (Postuma et al. 2015). The age and gender of the enrolled healthy controls with normal neurologicity matched with PD patients. The exclusion criteria that were suitable for all participants included with the atypical or secondary Parkinsonism; taking antibiotics or probiotic supplements within 3 months before fecal collection; a history of inflammatory bowel disease, irritable bowel syndrome, colitis, colon cancer. The motor symptoms were evaluated by the motor sub-scores of the Unified Parkinson's Disease Rating Scale (UPDRS part III) and Hoehn-Yahr staging, meanwhile, the Non-Motor Symptom assessment Scale (NMSS), Hamilton Depression Scale (HAMD); REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) were applied to assess the non-motor symptoms. Fecal samples collected at hospital were immediately frozen in liquid nitrogen and then stored at -80°C before analysis. As previously published (Yan et al. 2021), the gut microbial DNA was extracted using DNeasy PowerSoil Kit (Qiagen, Hilden, Germany) and then analysed by 16S ribosomal RNA sequencing.

Serum biochemical analysis

Serum was harvested from patients with PD and healthy controls, and the levels of TC (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), and TG (mmol/L) were measured by enzymatic techniques, Lp (a) (mg/dL) were measured by immunoturbidimetry.

Mendelian randomisation analysis

The single nucleotide polymorphisms (SNPs) from the publicly available GWASs were employed to the MR study, which can investigate the causal relationships among serotonin, TC, LDL-C and PD (Table S1). The whole design of our MR framework is presented in Figure S1.

In the present MR study, genetic instruments for serotonin and various lipids were obtained from the IEU Open GWAS project. There was no usable SNPs for serotonin when the threshold of genome-wide significance was set at 5×10^{-8} . Thus, we relaxed the criteria to 1×10^{-5} for instrumental variable selection. On the other hand, the SNPs for various lipids were selected as the instrumental variable (IV) when the threshold of genome-wide significance was set at 5×10^{-8} (Table S2). Genetic associations for

PD were summarized in the IEU Open GWAS project (Alfradique-Dunham et al. 2021). The dataset accession numbers ebi-a-GCST90000014 including 1,570 PD cases and 1,259 controls. We identified 19 SNPs for PD from the outcome datasets through excluding SNPs that were in linkage disequilibrium (r^2 threshold < 0.001 within a 10-Mb window) (Hemani et al. 2018). The unavailable SNPs in the outcome GWAS dataset were replaced by proxy SNPs in LD ($r^2 > 0.8$) (Pierce et al. 2011). Then, the R^2 and F statistic of each SNP were calculated. The SNPs with an F statistic > 10 were considered as the robust exposures and shown in Table S3 (Brion et al. 2013).

In our MR analysis, we applied the inverse-variance weighted (IVW), MR Egger, Weighted median, Simple mode, and Weighted model to assess the causal relationship between exposure and outcome. Since the IVW approach is considered as the primary method (Burgess et al. 2015), the IVW results with P value < 0.05 provided suggestive evidence for reported association. Furthermore, Cochran's Q statistic and leave-one-out analysis were performed to evaluate the degree of heterogeneity across each SNP. The MR-Egger intercept test, the MR-PRESSO global test, and visual inspection of the funnel plot were conducted to detect horizontal pleiotropy (Bowden et al. 2015; Verbanck et al. 2018).

Statistical analysis

All statistical analyses were carried out using R software (version 4.3.2). Experimental results are displayed as mean $\pm$ SD. The student's t-test and Wilcoxon rank-sum test were applied to analyze global differences between PD patients and controls. Correlations between PD clinical parameters and serum lipid levels were calculated using Spearman's rank-correlation analysis for 80 PD patients. A P value < 0.05 was considered statistically significant.

Results

Alterations in *Turicibacter* relative abundance between PD patients and healthy controls

The clinical data of PD and healthy controls were shown in Table S4. We observed that at genus level, relative abundance of *Turicibacter* increased in PD patients by 16SrRNA sequence analysis, though the alteration was not significant (Figure S2).

Alterations in serum lipid and lipoprotein levels between PD patients and healthy controls

The lipid levels of the study participants are shown in Table 1. Consistently, the serum levels of TC, TG and LDL-C were increased in the PD patients than healthy controls, which means that increasing levels of TC, TG and LDL-C were all associated with a decreasing risk of PD. Similarly, these differences between men and women are also present (all P values < 0.01 with the exception of TG). Among the women, the

lipid levels (including TC, TG, LDL-C, and HDL-C) increased than men. We next investigated the correlations between lipid levels and motor severity of PD, and found that there were obviously negative correlations between the serum levels of TC and LDL-C and UPDRS part III scores (Figure S3).

Table 1
Clinical characteristics of the study participants

	Control (n = 80)	PD (n = 80)	P Value	PD		P Value
				Men (n = 40)	Women (n = 40)	
Age (years)	66.91 ± 8.28	67.93 ± 7.59	P = 0.104	67.33 ± 7.45	68.53 ± 7.78	P = 0.483
Disease duration (years)	N.A.	6.04 ± 3.77		5.63 ± 3.43	6.45 ± 4.07	P = 0.513
UPDRS part III	N.A.	42.53 ± 17.87		45.91 ± 19.32	39.15 ± 15.81	P = 0.138
TC (mmol/L)	5.01 ± 0.54	3.77 ± 0.74	P < 0.001	3.47 ± 0.62	4.07 ± 0.72	P < 0.001
TG (mmol/L)	1.35 ± 0.50	1.01 ± 0.43	P < 0.001	0.99 ± 0.51	1.03 ± 0.34	P = 0.214
LDL-C (mmol/L)	3.10 ± 0.53	2.04 ± 0.62	P < 0.001	1.84 ± 0.58	2.25 ± 0.61	P = 0.003
HDL-C (mmol/L)	1.28 ± 0.31	1.24 ± 0.30	P = 0.527	1.12 ± 0.23	1.37 ± 0.32	P < 0.001
LDL-C/HDL-C ratio	2.57 ± 0.80	1.72 ± 0.62	P < 0.001	1.72 ± 0.67	1.72 ± 0.58	P = 0.989
Lp (a) (mg/dL)	21.76 ± 21.23	20.30 ± 20.51	P = 0.510	16.67 ± 16.21	23.84 ± 23.65	P = 0.197
PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale; N.A., not available. Numbers are expressed as mean ± standard deviation.						

The causality between serotonin and PD

Under the IVW model, we viewed the suggestive evidence that the increase in serotonin was associated with a lower risk PD (OR 0.119, 95% CI 0.017–0.847, P = 0.034) (Table S5). In the sensitivity analysis, the heterogeneity (Q-value = 11.655, PQ = 0.556), or horizontal pleiotropy (intercept = − 0.0126, Pintercept = 0.785; PMR-PRESSO = 0.575) was not discovered via Cochran's Q test, MR-Egger intercept test and MR-PRESSO global test (Table S6). Furthermore, Steiger filtering tests failed to reveal reverse causality.

Finally, we conducted a leave-one-out analysis and generated forest plot, scatter plot, funnel plot which were used to visually display the relationships between serotonin and PD risk (Figure. 1).

The causality between lipids and PD

The IVW model indicated that a higher level of TC was associated with a lower risk of PD (OR = 0.602, 95% CI = 0.377–0.961, P = 0.033) (Table S5). Similar results were noted for LDL-C (OR = 0.495, 95% CI = 0.323–0.757, P = 0.001) (Table S5). Moreover, MR-Egger intercept test and MR-PRESSO global test provided consistent results that there was no horizontal pleiotropy (Table S6). Meanwhile, Cochran's Q test supported the evidence of non-heterogeneity. The leave-one-out analysis for TC and LDL-C was applied to identify the SNPs that substantially influenced the IVW model (Figure. 2A and 2B). Subsequently, the scatter plot, forest plot and funnel plot for TC and LDL-C were all drawn and shown in Figures. 3 and 4, respectively.

Discussion

This study systematically evaluated the causal relationship between serotonin and serum lipids that were influenced by gut microbiota and the risk of PD. First, we found that PD patients have dysbiosis of gut microbiota, such as the enrichment of *Turicibacter* in PD. Moreover, compared with the healthy controls, the levels of TC, TG, LDL-C, and HDL-C in PD patients remained consistently lower. Second, in Mendelian randomization analysis, our findings further support the view that the decrease in serotonin and serum lipids (including TC and LDL-C) is associated with an increased PD risk.

The communication of gut-microbiota-brain axis has been shown to play a crucial role in PD. It has been found that the abundance of *Turicibacter* typically increases in PD (Jin et al. 2019), which is consistent with our research findings. However, research on the impact of the *Turicibacter* genus on PD is currently unclear. Significantly, *Turicibacter* belongs to a type of opportunistic pathogen and is considered to have pro-inflammatory properties (Zackular et al. 2013). On the one hand, *Turicibacter* expresses CUW_0748 protein to decrease the serotonin in the intestine (Fung et al. 2019). On the other hand, *Turicibacter* promotes inflammation by causing abnormal lipid metabolism in the body (Fung et al. 2019). In addition, the increased availability of serotonin in the intestine can interact with *Turicibacter* in the intestine via CUW_0748 protein, then leading to increased *Turicibacter* colonization, changes in host bacterial community structure, as well subsequent alterations in steroid and lipid metabolism (Fung et al. 2019). Therefore, *Turicibacter* is considered a potential mediator of gut-brain axis in PD, due to its ability to consume serotonin and regulate lipid metabolism.

We found that serotonin is a protective factor for PD. In the peripheral system, serotonin is regarded as a critical factor in the pathogenesis of chronic constipation, as it is an important cholinergic neurotransmitter that can improve intestinal permeability, increase intestinal osmotic pressure and water secretion, as well promote intestinal peristalsis (Cheng et al. 2020). In the central nervous system (CNS), serotonin can regulate neuronal differentiation and migration, axonal growth, myelin sheath and synaptic

formation. For example, Fanibunda et al. reported that serotonin regulates SIRT1-PGC-1 α through the 5-HT_{2A} receptor to promote neuronal mitochondrial biogenesis (Fanibunda et al. 2019). The typical pathological feature of PD is the degeneration of dopaminergic neurons in the SN and striatum, leading to defects in dopaminergic neurotransmitters (Buddhala et al. 2015). The significantly serotonergic innervation in the striatum can compensate for the loss of dopaminergic neuron function (Pagano et al. 2017). Once the dopaminergic neurons in the SN and striatum decrease to a certain level, the serotonergic fibers in the striatum will play a major role in dopamine neurotransmission. In addition, peripheral serotonin can connect the intestine with the CNS. Although peripheral serotonin cannot enter the CNS through the BBB, platelets can absorb and store serotonin from the intestine (Rust et al. 2023). Subsequently, platelets can recognize the main gangliosides near the BBB to enter the brain (Dukhinova et al. 2018; Kopeikina et al. 2020). Research has shown that platelet serotonin levels are applied to evaluate and study various neurological and psychological disorders. For example, a clinical experiment that divides PD patients into tremor dominant (TD) subtypes and non-tremor dominant (NTD) subtypes found a decrease in platelet serotonin levels in TD patients, and a negative correlation between platelet serotonin levels and the severity of resting tremors, which supports the involvement of peripheral serotonin dysfunction in resting tremors in PD (Wang et al. 2023). Moreover, in PD, multiple studies have shown that selective serotonin reuptake inhibitors (SSRIs) acting on SERT can alleviate movement disorders in PD patients, which possibly dependent on SSRIs blocking the uptake of serotonin by CUW_0748 protein and inhibiting the colonization of *Turicibacter* in the intestine (Zárate et al. 2022). However, the complex changes in serotonin, serotonin transporter proteins, and serotonin receptors behind the onset and development of PD require further clarification. Therefore, the potential role of serotonin in PD is worth further exploration.

Multiple studies have shown that serum lipids are a core factor in PD. We found a decrease in various serum lipid levels in clinical PD patients, including TG, TC, LDL-C, and HDL-C. In the subgroup analysis of PD, the serum TC, LDL-C, and HDL-C levels of female patients were significantly higher than those of male patients, consistent with previous PACOS study (Luca et al. 2022). In Mendelian randomization studies, we found that the higher the levels of TC and LDL-C, the lower the risk of PD. Consistent with our findings, multiple case-control studies, prospective cohort studies, and PD animal models have reported a negative correlation between TC and LDL-C and PD risk (Lim et al. 2012; Rozani et al. 2018). Cholesterol has a wide range of effects in the CNS. As an essential component of cell membranes, lipid rafts, and myelin sheaths, it is crucial for axonal growth, dendritic spine maintenance, and synaptic function. Neurons cannot produce enough cholesterol to support the massive formation of synapses, thus relying on cholesterol from other sources (Pfriege 2003). However, compared with the healthy controls, PD patients had lower average cholesterol biosynthesis and higher cholesterol consumption (Musanti et al. 1993). For example, research found that PD patients generally experience weight loss, which may be mainly due to a decrease in fat content rather than muscle mass (Yong et al. 2020). In PD, lipid signaling involves oxidative stress response, endosomal-lysosomal functioning, endoplasmic reticulum stress response, and immune response, which are the main mechanisms leading to dopaminergic neuron death. For example, dopaminergic neurons express oxygen-carrying hemoglobin,

which is oxidized to release cytotoxic heme, and then converted into ferrous iron in dopaminergic neurons to increase oxidative stress (Klemann et al. 2017). Cholesterol can bind to ferrous ion, which are then stored in lysosomes through autophagy to prevent ferrous iron induced oxidative stress and neurodegeneration (Klemann et al. 2017). Consistent with the view that higher serum cholesterol and LDL-C levels are associated with lower PD risk, the usage of statins may lead to a higher risk of PD by reducing serum cholesterol levels (Jeong et al. 2012). Nevertheless, the role of cholesterol metabolism disorders in PD is still controversial. Contrary to the above studies, some researchers thought that higher lipid levels can diminish the incidence of PD, and then the usage of statins is associated with a decreased risk of PD (Nguyen et al. 2023). Therefore, further laboratory research is needed in the future to elucidate the effects of lipid levels and statin drug usage in PD, as well as their specific potential mechanisms.

This study has both advantages and limitations. One strength is that clinical case-control studies combined with Mendelian randomization analysis have elucidated the causality between gut microbiota and its related metabolites serotonin and serum lipid levels and PD. However, the sample size for lipid level analysis in this study is small and lack of long-term follow-up data. Second, previous research demonstrated that chronic depletion of cholesterol can reduce the binding affinity between serotonin and 5-HTR. However, this study lacks an introduction to the correlation between serotonin and cholesterol. Finally, the GWAS summary statistical data selected in the Mendelian randomization analysis of this study came from European ancestry, while the PD patients selected in the case-control study of serum lipid levels were from China. Therefore, racial inconsistency may cause some bias in the research results.

Conclusion

Our study combines clinical case-control study and Mendelian randomization analysis based on GWAS summary statistical data for serotonin and different lipids in PD, providing new evidence for the important role of *Turicibacter* genus and their related serotonin and lipids in PD.

Declarations

Funding

The present study was supported by the Youth Project of Zhejiang Provincial Natural Science Fund [grant number LQN25H090011], the Key Projects of Zhejiang Provincial Natural Science Fund [grant number LZ23H090004] and the Major Health Science and Technology Program of Zhejiang Province [grant number WKJ-ZJ-2208] and A Project Supported by Scientific Research Fund of Zhejiang University [grant number XY2025079].

Acknowledgments

We thank the all participants who provided fecal and serum samples. We would also like to acknowledge the participants used for the GWAS summary statistics.

Conflict of interest

The authors report no competing interests.

Data Availability

The data used or analyzed during this study are available from the corresponding author on reason able request.

Authors' Roles

Zhenzhen Yan: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing—original draft; Jiaxin Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology; Yuhang Zhao and Qinger Mo: Data curation, Investigation, Visualization; Guohua Zhao: Conceptualization, Funding acquisition, Supervision, Writing—review & editing.

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Figures

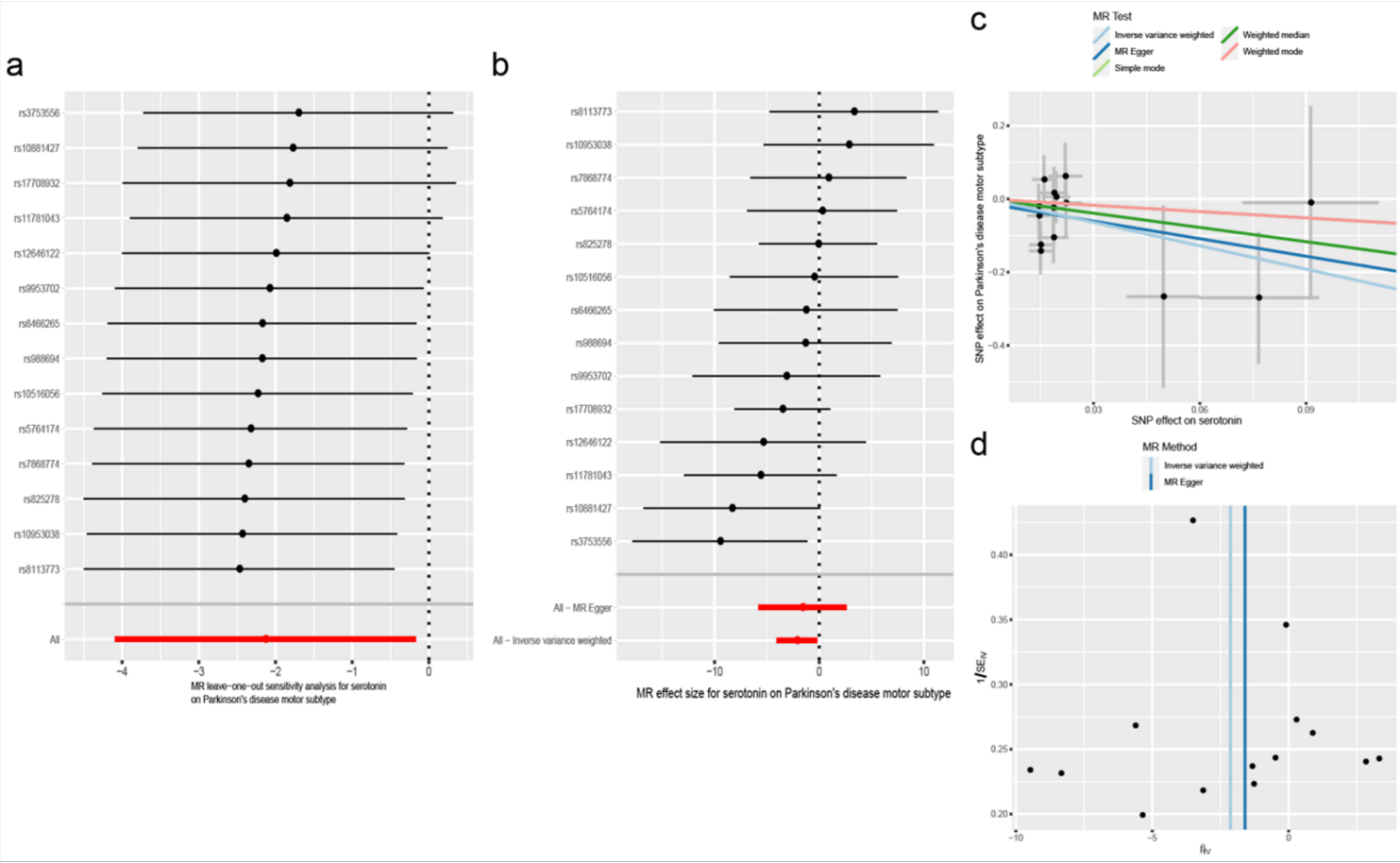


Figure 1

Leave-one-out sensitivity analysis (a) and generated forest plot (b), scatter plot (c), funnel plot (d) of the causal effect of serotonin on PD risk. PD, Parkinson's Disease.

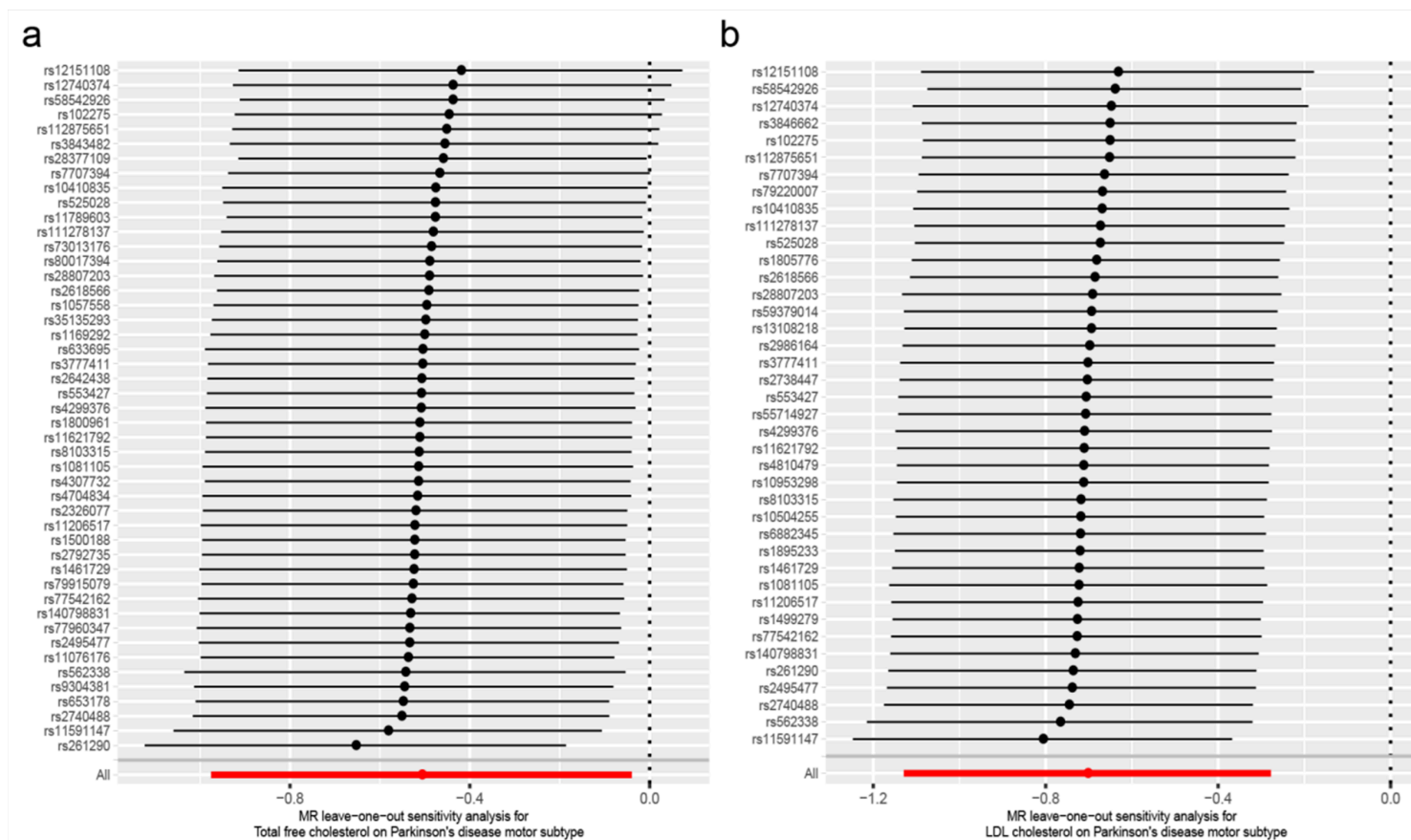


Figure 2

Leave-one-out sensitivity analysis for TC (a) and LDL-C (b) on PD. PD, Parkinson's Disease.

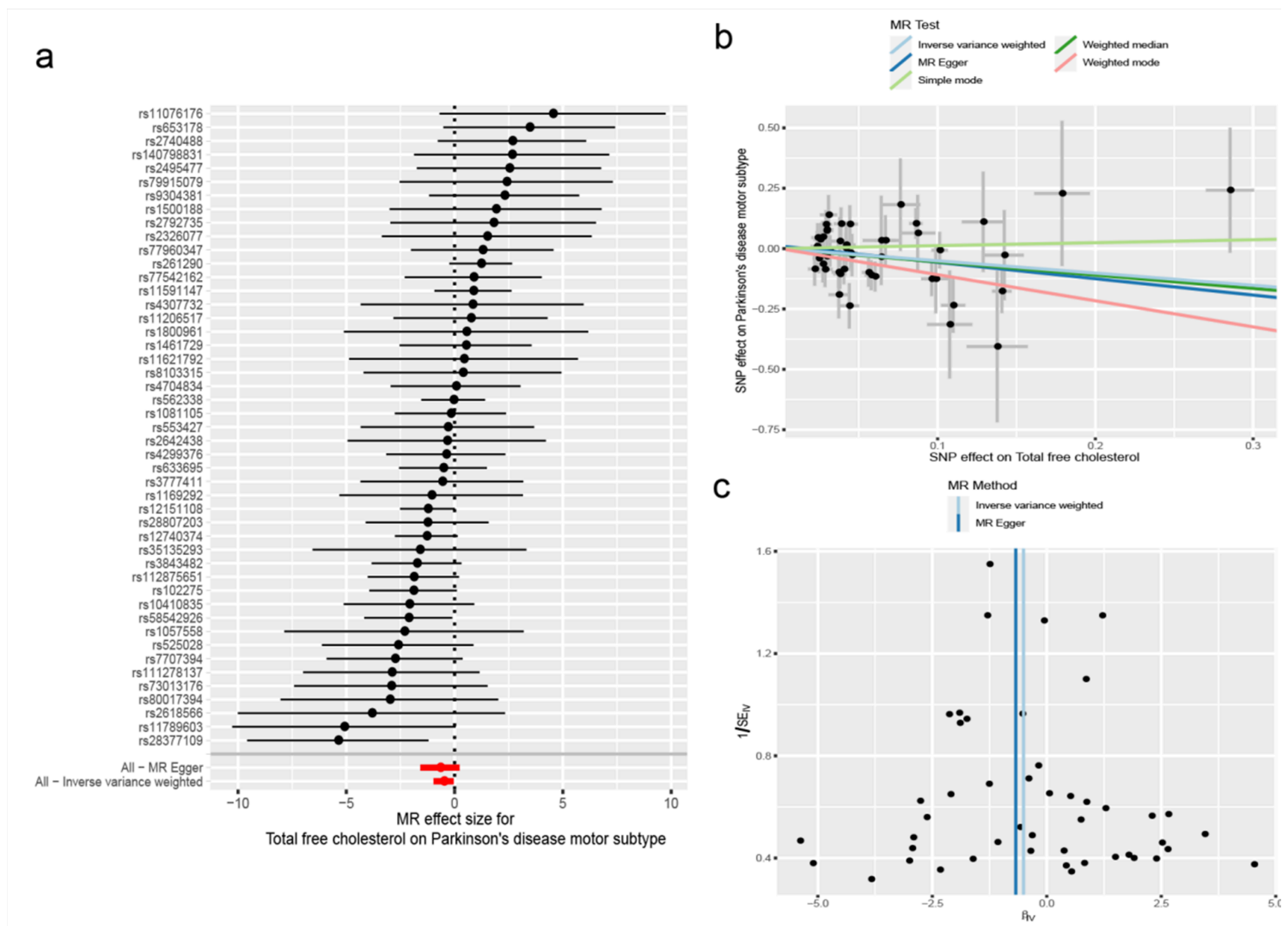


Figure 3

Forest plot (a), Scatter plot (b) and funnel plot (c) of the causal effect of TC on PD risk. PD, Parkinson's Disease.

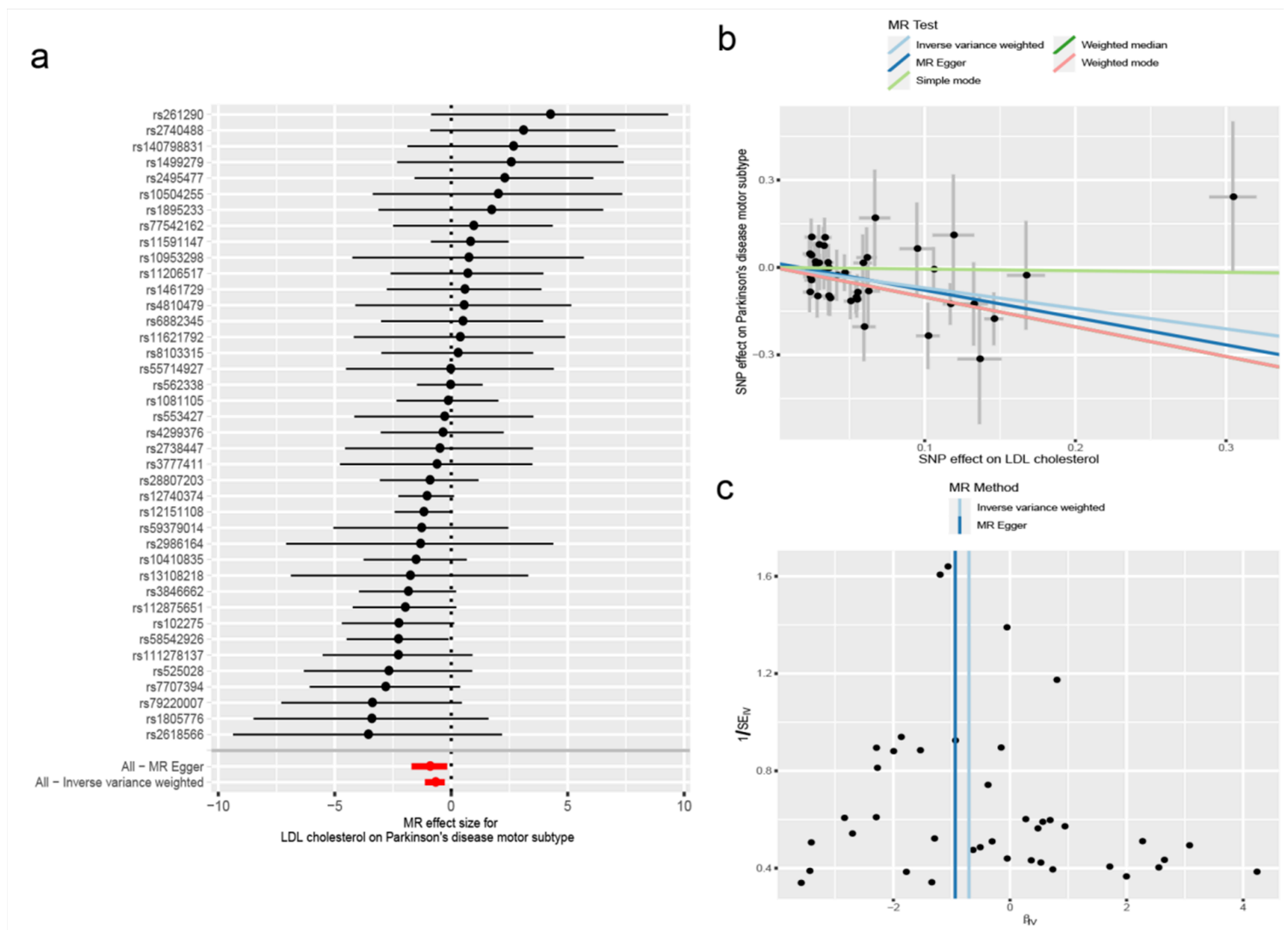


Figure 4

Forest plot (a), scatter plot (b) and funnel plot (c) of the causal effect of LDL-C on PD risk. PD, Parkinson's Disease.

Supplementary Files

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- [SupplementaryTable.xlsx](#)