Original Article

Parkinson's disease and the risk of gastrointestinal cancers: a two-sample Mendelian randomization study

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Background: The association between Parkinson's disease (PD) and gastrointestinal (GI) cancers remains unknown. This study aims to assess the causal effect of PD on colon cancer (CC), gastric cancer (GC), esophageal cancer (EC), and rectal cancer (RC) using the two-sample Mendelian randomization (MR) method.

Methods: Five pairs of summary datasets of genome-wide association studies (GWAS) from publicly available studies [Integrative Epidemiology Unit (IEU) OpenGWAS project, FinnGen, and GWAS Catalog database] were enrolled. The inverse variance weighted (IVW) method was used as the primary outcome for MR analysis. Cochran Q-derived, MR-Egger intercept test, MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods, and leave-one-out analysis were used to test heterogeneity and directional pleiotropy.

Results: For the European population, no significant causal effect of PD on the risk of CC was found [odds ratio (OR) =0.9; 95%, confidence interval (CI): 1.00–1.11; P=0.42]. The same applied to the East Asian population (OR =1.05; 95% CI: 0.66–1.66; P=0.63). As for GC, no causal effect was found (OR =0.94, 95% CI: 0.89–0.99; P=0.22). Moreover, the genetic liability for PD was not associated with EC (OR =1.00; 95% CI: 0.99–1.00; P=0.32). Finally, no evidence was found for any causal effect of genetic liability for PD on an increased risk of RC (OR =1.00; 95% CI: 0.99–1.00; P=0.71).

Conclusions: There is no causal effect of genetic liability for PD on an increased risk of GI cancer.

Keywords: Parkinson's disease (PD); gastrointestinal cancer (GI cancer); Mendelian randomization (MR)

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and nonmotor symptoms. Motor symptoms include bradykinesia, tremor, muscle rigidity, postural instability, and gait difficulties. Non-motor dysfunctions include numerous gastrointestinal (GI) symptoms, for example, oropharyngeal dysphagia, constipation, early satiety, postprandial pain, and nausea (1,2). The overall GI dysfunction rate is reported to be as high as 77–81% among all PD patients, leading to higher medical cost and worse quality of life (3,4).

The incidence rate of colon cancer (CC), rectal cancer (RC), gastric cancer (GC), and esophageal cancer (EC) ranks 5th, 9th, 6th, and 10th among different cancers in the world (5), respectively, imposing a heavy burden on the healthcare system. Previous research reported that PD might lead to a series of GI disorders, which could further lead to GI cancers. Maeda *et al.* reported that the incidence

of gastroesophageal reflux disease (GERD) was as high as 26.5% in PD patients (6). About 2.3% to 8.3% of GERD patients will develop Barrett esophagus, which is a definite risk factor for esophageal adenocarcinoma (7). Besides, Dardiotis and colleagues' meta-analysis claimed that the prevalence of *H. pylori* infection was higher in PD patients than in healthy controls {odds ratio (OR) [95% confidence interval (CI)]: 1.47 (1.27, 1.70); P<0.00001} (8). In many regions of the world, such as Asia, the high prevalence of *H. pylori* mirrors the high prevalence of GC (9). Last but not least, the constipation caused by PD could increase the risk of CC, especially in black women (10). Besides, the incidence of GI cancers increases with age, especially CC, as 58% of CC patients are over 65 years old in the US (11). Similarly, the prevalence of PD is 1% in patients over 60 years old and 3% in patients aged over 80 years old. Therefore, it is important to figure out whether PD increases the risk of GI cancers to confirm the necessity of making a progressive endoscopy screening strategy for PD patients.

Olsen *et al.* first conducted a large sample retrospective cohort study on the correlation between CC and PD. They enrolled 8,090 European patients and reported a similar rate of CC among PD patients and healthy controls (12) (OR =1.29; P>0.05). Then, Lin *et al.* enrolled 62,023 East Asian PD patients and reported a higher rate of CC compared to normal people [hazard ratio (HR) =1.47; P<0.05] (13). On the contrary, two meta-analyses proved a significantly decreased rate of CC in PD patients with risk ratios of 0.85 and 0.79 (14,15). In terms of PD and EC, the results of different studies were also paradoxical. Lin *et al.* reported a higher risk of EC than normal controls with a HR of 1.81 and a P value of less than 0.01, but the meta-analysis conducted by Leong *et al.* showed no significant relationship (13,15).

Recently, Mendelian randomization (MR) analysis has been widely used to assess the potential causal associations between two diseases. By using genetic variants from the summary datasets of genome-wide association studies (GWAS) as instrumental variables for the tested exposure, it has a similar causal inference ability as randomized controlled trial (RCT). Therefore, this study aimed to conduct a MR analysis to explore the causal association between PD and the risk of GI cancers. We present this article in accordance with the STROBE-MR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-106/rc).

Highlight box

Key findings

- The large Mendelian randomization (MR) analysis indicated that the genetic liability toward Parkinson's disease (PD) was not associated with gastrointestinal (GI) cancers.

What is known and what is new?

- PD usually causes constipation, gastroesophageal reflux, and other GI symptoms which are high-risk factors for GI cancers. However, the association between PD and GI cancers remains unknown.
- Five pairs of genome-wide association studies summary datasets from global publicly available studies (Integrative Epidemiology Unit, FinnGen, and GWAS Catalog) were analyzed using the Two-sample MR method and the result indicated genetic liability toward PD was not associated with GI cancers.

What is the implication, and what should change now?

- No evidence supports the need for progressive endoscopy screen for PD patients.

Methods

Study design

A two-sample MR approach was adopted to investigate the potential causality of PD on CC, RC, GC, and EC. MR design was based on three assumptions: (I) genetic variants were robustly associated with the exposure of interest (PD in this study); (II) genetic variants were not associated with potential confounders; and (III) genetic variants affected the outcome (CC, RC, GC, and EC in this study) only through the exposure of interest. To avoid selection bias and eliminate the influence of different ethnic groups, GWAS summary datasets were collected from publicly available studies. The Medical Research Council (MRC) Integrative Epidemiology Unit (IEU) Open GWAS data infrastructure (IEU; https://gwas.mrcieu.ac.uk/) (16,17), the FinnGen study (FinnGen; https://risteys.finregistry.fi/) (18), and National Human Genome Research Institute-European Bioinformatics Institute (NHGRI-EBI) GWAS Catalog (GWAS Catalog; https://www.ebi.ac.uk/gwas/) (19) were separately enrolled. An overview of the study design is presented in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Selection of instrumental variables

The instrumental single nucleotide polymorphisms (SNPs) in the MR analysis were selected according to predefined criteria. The SNPs with a correlation P value $<5\times10^{-8}$ were first selected. In the traits that had no SNP surviving the P

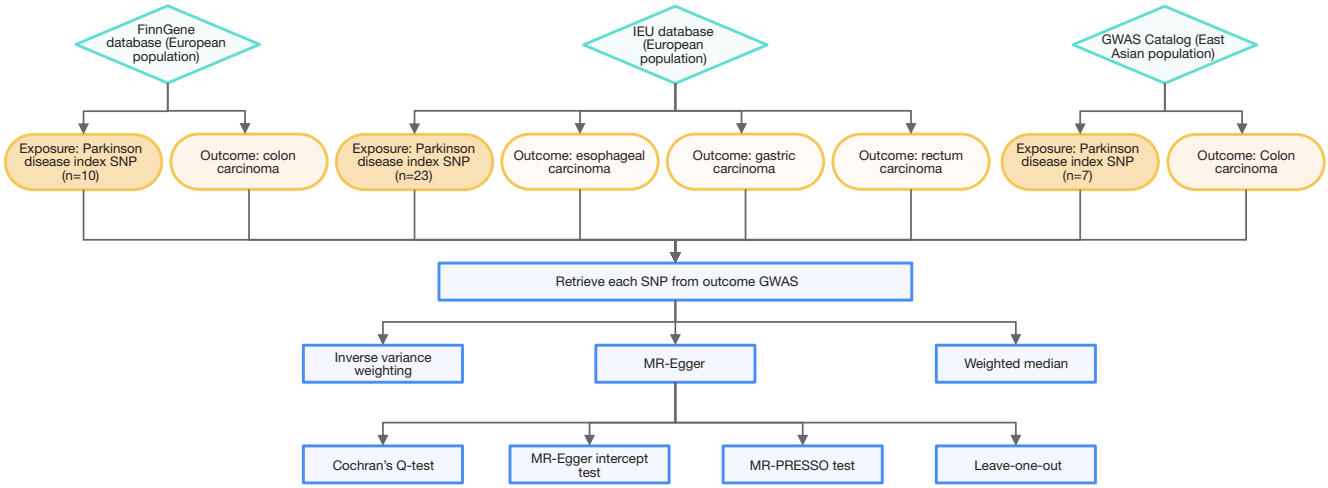

Figure 1 Study flowchart. IEU, Integrative Epidemiology Unit; GWAS, genome-wide association studies; SNP, single nucleotide polymorphism; MR, Mendelian randomization; MR-PRESSO, MR-Pleiotropy Residual Sum and Outlier.

value limit, a P value of $<1\times10^{-5}$ was selected according to previous MR studies. Then, the data was clumped with an r^2 threshold of 0.001 and a distance window of 10,000 kB to minimize the bias caused by linkage disequilibrium. Different super-populations such as European or East Asian populations, which had slightly different sets of markers were clumped separately. Thirdly, the exposure data and the outcome data were harmonized by removing SNPs for incompatible alleles or SNPs for being palindromic with intermediate allele frequencies, and a dataset containing data for both exposure traits.

Moreover, the F statistics for the SNPs were calculated by the following equation: $F = R^2 \times (N - 2)/(1 - R^2)$. R^2 was the proportion of variance, and N represented the sample size. R^2 was calculated by $R^2 = 2 \times MAF \times (1 - MAF) \times beta^2$ (MAF was an abbreviation of minor allele frequency). Week instruments were identified by the F statistics of less than 10 (F<10) and it was excluded from the analysis.

Statistical analyses

After harmonization of the effect alleles across the GWAS of PD and GI cancers, we used inverse variance weighted (IVW), weighted median, and MR-Egger method to estimate the causality between PD and GI cancers. IVW method, which assumes that instruments can affect the outcome only through the exposure of interest and not through any alternative pathway, was used as the primary outcome. Because MR-Egger and weighted median methods were more robust and less efficient, they were used as secondary outcomes. If the estimates of these approaches in our study were inconsistent, a tightened instrument P value threshold was set. Cochran Q-test was used to test the heterogeneity. The intercept obtained from the MR-Egger regression and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods was used to test directional pleiotropy. Leave-one-out analysis was also performed to evaluate whether the MR estimate was driven or biased by a single SNP. Analyses were implemented by the package Two SampleMR (version 0.4.25) and MR-PRESSO (version 1.0) in R (version 4.3.1).

Results

Datasets

The GWAS summary data for PD from FinnGen R9 enrolled 3,824 patients. The endpoint definition was strictly confined to PD. The control group excluded PD patients. The parent code in the International Classification of Diseases, 10th revision (ICD-10) was G20–G26. Among them, 2,353 patients were males and the mean age at the first event was 68.73 years old. The unadjusted prevalence was 1.01 for PD patients. The GWAS summary data for PD from IEU was IEU-b-7, which included 33,674 PD patients and 449,056 controls. The population was European and the dataset was built in 2019 by the International Parkinson's Disease Genomics Consortium with the SNPs of 17,891,936. The PD GWAS dataset from the GWAS

Catalog was GCST90018674. Three hundred and forty East Asian ancestry cases and 175,788 East Asian ancestry controls were enrolled, and the platform was Illumina [13429429]. The related article was published in Nature Genetics on 2021-9-30 (20).

The GWAS summary data for CC from FinnGen R9 enrolled 6,509 patients including 3,850 males and 2,659 females. The endpoint definition was C3_COLORECTAL_EXALLC. The unadjusted prevalence was 1.73 and the mean age at first event was 66.67 years old. The control group excluded C3 cancer. The CC dataset from the GWAS Catalog was GCST90246023. The reported trait was ICD10-C18: malignant neoplasm of the colon. It enrolled 434 Chinese ancestry cases and 75,513 Chinese ancestry control (21). The GC, EC, and RC datasets from the IEU database were ebi-a-GCST90018849, ieu-b-4960, and ukb-b-19425. They contained 1,029 European GC patients, 740 EC, and 1085 RC patients with 475,087, 372,016, and 461,925 patients as controls respectively. They were built in 2021 by Sakaue with 24,188,668 (20), by UK Biobank with 8,970,465 SNPs, and by UK Biobank with 9,851,867 SNPs.

The causal effect of PD on CC

For the European population, the data from FinnGen showed no potential causal effect of PD on the risk of CC. By using the 8 PD-related SNPs from FinnGen, the IVW test showed no statistical significance (OR =0.9; 95% CI: 1.00–1.11; P=0.42) (*Table 1*). Meanwhile, similar risk estimates were gained using the MR-Egger regression (OR =1.09; 95% CI: 0.90–1.31; P=0.99) and weighted median approaches (OR =0.99; 95% CI: 0.87–1.14; P=0.91) (*Figures 2,3A*). For the East Asian population, with 10 SNPs as instrumental variables, the data from GWAS Catalog showed no causal effect of PD on CC (IVW: OR =1.05; 95% CI: 0.66–1.66; P=0.63; MR-Egger regression: OR =1.04; 95% CI: 0.88–1.23; P=0.63; weighted median: OR =0.97; 95% CI: 0.79–1.19; P=0.79) (*Table 1*, *Figures 2,3B*). All the instrumental SNPs had an F value over 10, which meant that they were closely related to PD.

To remove the potential influence of possible heterogeneity and pleiotropy effect, a series of measures had been adopted. MR-Egger intercept test showed no evidence for a significant intercept in three pairs of datasets, indicating that no directional pleiotropy was observed (FinnGen: P=0.34; GWAS Catalog: P=0.98). This result was further confirmed by the MR-PRESSO test (FinnGen: P=0.36; GWAS Catalog: P=0.63). Furthermore, the Cochran Q-test derived P values were 0.33 and 0.32 in FinnGen, while they were 0.24 and 0.35 in the GWAS Catalog, respectively, proving no obvious heterogeneity (*Table 2*). Leave-one-out sensitivity analysis showed that no single SNP strongly violated the overall effect of PD on CC (all values ≥0), which confirmed no significant heterogeneity (*Figure 3C,3D*).

The causal effect of PD on GC

With 23 SNPs as instrumental variables, although MR-

Table 1 SNP used for MR analysis

Type of cancer	Number	Instrument SNPs	Exposure								Outcome			
			Effect allele	Other allele	Beta	SE	EAF	P	R^2	F	Beta	SE	EAF	P
FinnGen														
CC	1	rs34311866	C	T	0.14	0.03	0.21	3.14E−07	0.01	25.02	−0.02	0.02	0.21	0.28
	2	rs35603727	A	G	0.35	0.05	0.04	1.05E−11	0.01	36.30	0	0.05	0.04	0.92
	3	rs356182	A	G	−0.12	0.02	0.65	5.93E−07	0.01	25.21	−0.01	0.02	0.65	0.53
	4	rs3934591	G	A	0.11	0.02	0.51	5.67E−07	0.01	23.25	−0.03	0.02	0.51	0.10
	5	rs45480197	A	G	0.44	0.09	0.01	2.84E−07	0.00	14.71	−0.04	0.08	0.01	0.66
	6	rs62073178	T	C	−0.26	0.04	0.08	1.40E−09	0.01	38.41	−0.06	0.03	0.08	0.07
	7	rs6982337	G	T	0.11	0.02	0.49	3.72E−07	0.01	23.25	−0.01	0.02	0.49	0.52
	8	rs77628790	G	T	0.23	0.05	0.05	8.17E−07	0.01	19.30	0.04	0.04	0.05	0.31

Table 1 *(continued)*

Table 1 *(continued)*

Type of cancer	Number	Instrument SNPs	Exposure								Outcome			
			Effect allele	Other allele	Beta	SE	EAF	P	R^2	F	Beta	SE	EAF	P
GWAS Catalog														
CC	1	rs115742571	A	T	0.51	0.12	0.14	9.11E−06	0.06	11,768.20	0.02	0.17	0.05	0.92
	2	rs11807932	C	G	1.5	0.32	0.02	1.79E−06	0.09	17,036.97	0.21	0.18	0.04	0.26
	3	rs140206515	A	G	1.24	0.27	0.03	3.60E−06	0.09	17,310.29	−0.24	0.22	0.03	0.27
	4	rs142447717	T	C	1.06	0.24	0.03	8.42E−06	0.07	12,323.37	0.33	0.27	0.02	0.22
	5	rs1433992	A	C	0.91	0.18	0.06	6.64E−07	0.09	18,146.98	0.41	0.24	0.03	0.09
	6	rs278948	A	G	−0.37	0.08	0.58	5.64E−06	0.07	12,586.70	−0.09	0.08	0.62	0.28
	7	rs4725002	G	C	0.37	0.08	0.57	3.22E−06	0.07	12,669.78	0.02	0.07	0.67	0.76
	8	rs541615	G	A	−0.36	0.08	0.44	3.72E−06	0.06	12,016.05	0.02	0.07	0.42	0.79
	9	rs646526	C	T	−0.46	0.09	0.77	7.94E−07	0.07	14,269.93	0.04	0.09	0.79	0.64
	10	rs9375320	A	G	0.42	0.1	0.21	9.85E−06	0.06	10,949.44	0.01	0.08	0.24	0.95
IEU														
GC	1	rs10451230	T	A	−0.1	0.02	0.57	4.42E−08	0.00	2,377.99	0	0.02	0.53	0.88
	2	rs10513789	G	T	−0.16	0.02	0.18	3.18E−13	0.01	3,675.81	−0.02	0.02	0.31	0.24
	3	rs10847864	T	G	0.13	0.02	0.36	9.81E−13	0.01	3,788.76	−0.04	0.02	0.4	0.03
	4	rs12934900	T	A	0.12	0.02	0.66	4.33E−11	0.01	3,140.03	−0.06	0.05	0.64	0.19
	5	rs144814361	T	C	0.44	0.07	0.02	9.07E−11	0.01	3,691.50	−0.1	0.19	0.01	0.61
	6	rs329647	C	G	−0.11	0.02	0.67	1.94E−10	0.01	2,596.79	−0.01	0.02	0.75	0.57
	7	rs34311866	C	T	0.23	0.02	0.2	7.97E−23	0.02	8,312.33	−0.04	0.02	0.18	0.09
	8	rs35265698	G	C	−0.2	0.03	0.15	3.93E−11	0.01	4,974.57	0.02	0.02	0.2	0.24
	9	rs356203	T	C	−0.24	0.02	0.62	3.01E−41	0.03	13,467.30	0.02	0.02	0.58	0.22
	10	rs35749011	A	G	0.75	0.07	0.02	5.02E−30	0.02	10,884.15	0.08	0.23	0.01	0.74
	11	rs4488803	A	G	−0.11	0.02	0.37	1.08E−08	0.01	2,738.53	0.02	0.02	0.44	0.22
	12	rs4588066	A	G	0.1	0.02	0.33	4.45E−09	0.00	2,144.10	0	0.02	0.34	0.78
	13	rs4613239	G	C	0.18	0.02	0.13	6.21E−13	0.01	3,563.98	−0.01	0.02	0.15	0.65
	14	rs4698412	A	G	0.13	0.02	0.55	7.05E−14	0.01	4,072.33	−0.02	0.02	0.5	0.14
	15	rs4774417	A	G	0.11	0.02	0.74	4.63E−08	0.00	2,258.13	0.01	0.02	0.73	0.53
	16	rs58879558	C	T	−0.24	0.03	0.22	1.36E−21	0.02	9,735.17	0.02	0.02	0.28	0.21
	17	rs620490	G	T	−0.12	0.02	0.28	6.46E−10	0.01	2,819.13	0.02	0.02	0.32	0.36
	18	rs6741007	G	T	−0.12	0.02	0.45	2.09E−12	0.01	3,465.59	−0.03	0.03	0.51	0.31
	19	rs75505347	T	C	0.39	0.07	0.02	6.12E−09	0.01	2,895.44	0	0.13	0.01	0.99
	20	rs75646569	G	T	0.19	0.03	0.11	5.62E−13	0.01	3,436.39	0.03	0.03	0.08	0.32
	21	rs7695720	C	A	−0.13	0.02	0.21	1.53E−09	0.01	2,722.12	−0.02	0.04	0.17	0.5
	22	rs823106	C	G	−0.15	0.02	0.85	4.10E−10	0.01	2,785.63	0	0.02	0.79	0.81
	23	rs858295	G	A	−0.1	0.02	0.39	3.83E−09	0.00	2,307.80	0	0.02	0.36	0.9

Table 1 *(continued)*

Table 1 *(continued)*

Type of cancer	Number	Instrument SNPs	Exposure								Outcome			
			Effect allele	Other allele	Beta	SE	EAF	P	R^2	F	Beta	SE	EAF	P
EC	1	rs10451230	T	A	−0.10	0.02	0.57	4.42E−08	0.00	2,190.71	0	0	0.56	0.74
	2	rs10513789	G	T	−0.16	0.02	0.18	3.18E−13	0.01	3,698.70	0	0	0.19	0.00
	3	rs10847864	T	G	0.13	0.02	0.36	9.81E−13	0.01	3,648.63	0	0	0.35	0.28
	4	rs12934900	T	A	0.12	0.02	0.66	4.33E−11	0.01	3,219.55	0	0	0.63	0.42
	5	rs144814361	T	C	0.44	0.07	0.02	9.07E−11	0.01	3,233.19	0	0	0.02	0.13
	6	rs329647	C	G	−0.11	0.02	0.67	1.94E−10	0.01	2,755.84	0	0	0.68	0.12
	7	rs34311866	C	T	0.23	0.02	0.20	7.97E−23	0.02	7,977.08	0	0	0.18	0.28
	8	rs35265698	G	C	−0.20	0.03	0.15	3.93E−11	0.01	5,103.42	0	0	0.19	0.12
	9	rs356203	T	C	−0.24	0.02	0.62	3.01E−41	0.03	13,444.24	0	0	0.63	0.81
	10	rs4488803	A	G	−0.11	0.02	0.37	1.08E−08	0.01	2,936.63	0	0	0.38	0.47
	11	rs4588066	A	G	0.10	0.02	0.33	4.45E−09	0.00	2,332.20	0	0	0.31	0.84
	12	rs4613239	G	C	0.18	0.02	0.13	6.21E−13	0.01	3,560.22	0	0	0.12	0.04
	13	rs4698412	A	G	0.13	0.02	0.55	7.05E−14	0.01	3,811.40	0	0	0.55	0.20
	14	rs4774417	A	G	0.11	0.02	0.74	4.63E−08	0.00	2,064.54	0	0	0.73	0.12
	15	rs58879558	C	T	−0.24	0.03	0.22	1.36E−21	0.02	9,687.16	0	0	0.23	0.96
	16	rs620490	G	T	−0.12	0.02	0.28	6.46E−10	0.01	2,674.92	0	0	0.29	0.16
	17	rs6741007	G	T	−0.12	0.02	0.45	2.09E−12	0.01	3,661.32	0	0	0.38	0.94
	18	rs75505347	T	C	0.39	0.07	0.02	6.12E−09	0.01	2,848.90	0	0	0.02	0.71
	19	rs75646569	G	T	0.19	0.03	0.11	5.62E−13	0.01	3,542.52	0	0	0.09	0.18
	20	rs7695720	C	A	−0.13	0.02	0.21	1.53E−09	0.01	2,527.92	0	0	0.22	0.63
	21	rs823106	C	G	−0.15	0.02	0.85	4.10E−10	0.01	2,755.83	0	0	0.88	0.06
	22	rs858295	G	A	−0.10	0.02	0.39	3.83E−09	0.01	2,502.92	0	0	0.39	0.42
RC	1	rs858295	G	A	−0.10	0.02	0.39	3.83E−09	0.01	2,400.69	0	0	0.39	0.18
	2	rs10847864	T	G	0.13	0.02	0.36	9.81E−13	0.01	3,499.59	0	0	0.35	0.70
	3	rs4698412	A	G	0.13	0.02	0.55	7.05E−14	0.01	3,655.72	0	0	0.55	0.06
	4	rs4488803	A	G	−0.11	0.02	0.37	1.08E−08	0.01	2,816.67	0	0	0.38	0.47
	5	rs12934900	T	A	0.12	0.02	0.66	4.33E−11	0.01	3,088.04	0	0	0.63	0.48
	6	rs10451230	T	A	−0.10	0.02	0.57	4.42E−08	0.00	2,101.23	0	0	0.56	0.36
	7	rs356203	T	C	−0.24	0.02	0.62	3.01E−41	0.03	12,895.08	0	0	0.63	0.26
	8	rs6741007	G	T	−0.12	0.02	0.45	2.09E−12	0.01	3,511.76	0	0	0.38	0.98
	9	rs329647	C	G	−0.11	0.02	0.67	1.94E−10	0.01	2,643.27	0	0	0.65	0.64

SNP, single nucleotide polymorphism; MR, Mendelian randomization; SE, standard error; EAF, effect allele frequency; CC, colon cancer; GWAS, genome-wide association studies; IEU, Integrative Epidemiology Unit; GC, gastric cancer; EC, esophageal cancer; RC, rectal cancer.

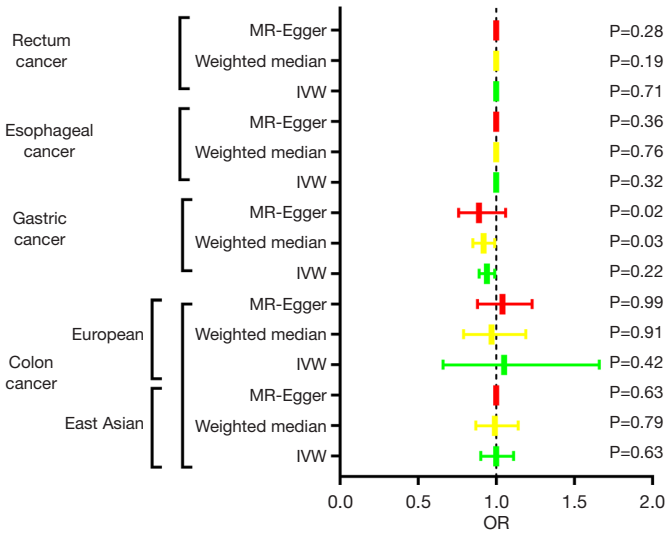

Figure 2 Estimation of the causal effect of PD on GI cancers. MR, Mendelian randomization; IVW, inverse variance weighted; OR, odds ratio; PD, Parkinson's disease; GI, gastrointestinal.

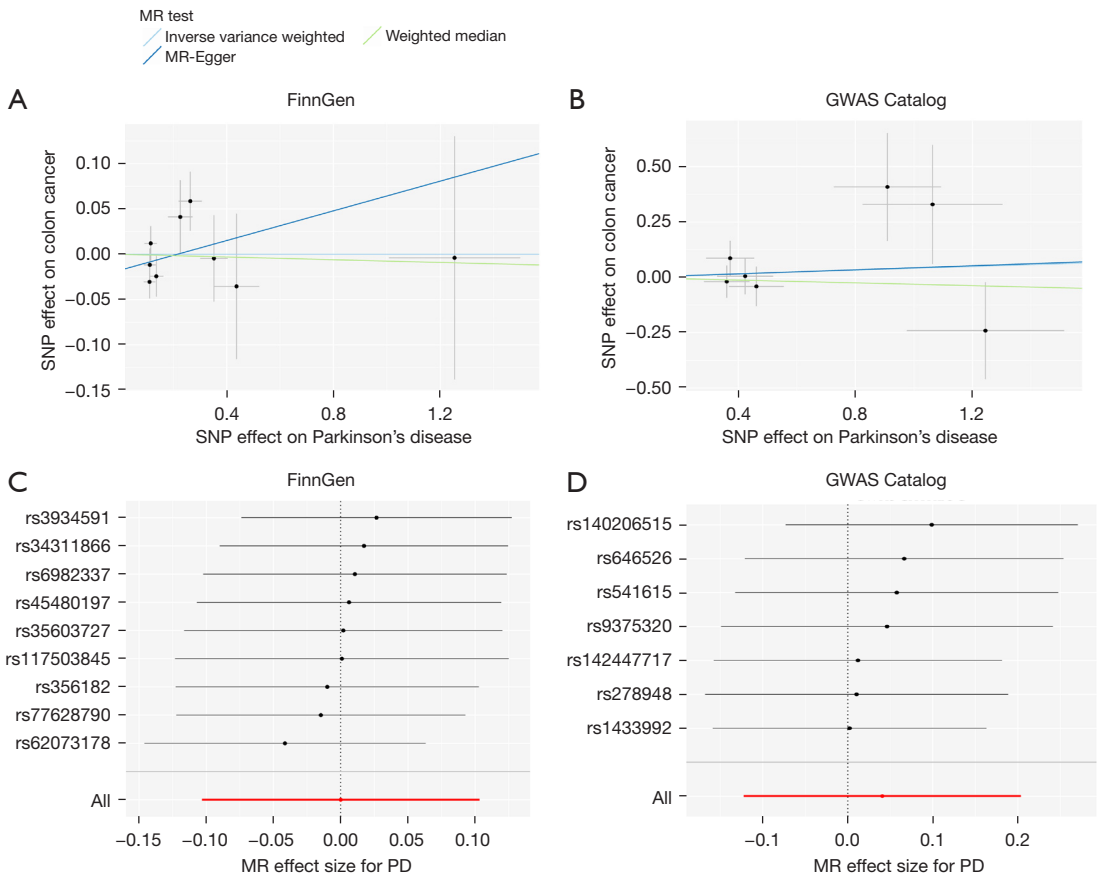

Figure 3 Correlation of PD on CCs and their leave-one-out analysis results. (A) Correlation of PD on CC in FinnGen. (B) Correlation of PD on CC in GWAS Catalog. (C) Leave-one-out analysis of PD on CC in FinnGen. (D) Leave-one-out analysis of PD on CC in GWAS Catalog. MR, Mendelian randomization; SNP, single nucleotide polymorphism; PD, Parkinson's disease; GWAS, genome-wide association studies; CC, colon cancer.

Table 2 Heterogeneity and directional pleiotropy analysis

Test	FinnGen	GWAS Catalog	IEU		
	CC	CC	GC	EC	RC
MR-PRESSO test	0.36	0.63	0.72	0.27	0.34
MR-Egger intercept test	0.34	0.98	0.58	0.53	0.31
Cochran Q-test					
MR-Egger	0.24	0.33	0.59	0.02	0.37
IVW	0.35	0.32	0.63	0.02	0.34

GWAS, genome-wide association studies; IEU, Integrative Epidemiology Unit; CC, colon cancer; GC, gastric cancer; EC, esophageal cancer; RC, rectal cancer; MR-PRESSO, Mendelian Randomization-Pleiotropy Residual Sum and Outlier; IVW, inverse variance weighted.

Egger regression (OR =0.89; 95% CI: 0.76–1.06; P=0.03) and weighted median test (OR =0.92; 95% CI: 0.85–0.99; P=0.02) showed a negative causal effect, IVW test showed no causal effect of PD on GC (IVW: OR =0.94; 95% CI: 0.89–0.99; P=0.22) (*Figure 4A*). No instrument SNPs were excluded due to an F value under 10. MR-Egger intercept and MR-PRESSO test showed no directional pleiotropy (P=0.58 and 0.72, respectively). The Cochran Q-test (P=0.59 for MR-Egger and 0.63 for IVW, respectively) and leave-one-out sensitivity analysis showed no significant heterogeneity (*Table 2*, *Figure 4B*).

The causal effect of PD on EC

With 22 SNPs as instrumental variables, the data from IEU showed no causal effect of PD on EC. (IVW: OR =1.00; 95% CI: 0.99–1.00; P=0.32; MR-Egger regression: OR =1.00; 95% CI: 0.99–1.00; P=0.36; weighted median: OR =1.00; 95% CI: 0.99–1.00; P=0.76) (*Table 1*, *Figure 4C*). No instrumental SNPs were excluded due to the F value under 10. MR-Egger intercept and MR-PRESSO test showed no directional pleiotropy (P=0.53 and 0.27, respectively). The Cochran Q-test and leave-one-out sensitivity analysis indicated the existence of heterogeneity (P=0.02) (*Table 2*, *Figure 4D*). As a result, the random model was used, and the modified P value of IVW was still 0.32 with an OR of 1.00 (95% CI: 0.99–1.00).

The causal effect of PD on RC

With 9 SNPs as instrumental variables, MR-Egger regression (OR =0.99; 95% CI: 0.99–1.00; P=0.28), weighted median test (OR =0.99; 95% CI: 0.99–1.00; P=0.19) and IVW test showed no causal effect of PD on RC (IVW: OR =1.00; 95% CI: 0.99–1.00; P=0.71) (*Figure 4E*). MR-Egger intercept and MR-PRESSO test showed no directional pleiotropy (P=0.31 and 0.34, respectively). The Cochran Q-test (P=0.37 for MR-Egger and 0.34 for IVW, respectively) and leave-one-out sensitivity analysis showed no significant heterogeneity (*Table 2*, *Figure 4F*).

Discussion

This two-sample MR study aimed to find the correlation between PD and GI cancers. The datasets from five publicly available GWAS databases (FinnGen, IEU, and GWAS Catalog) were enrolled to avoid possible ethical differences and selection bias. MR analysis showed no correlation between PD and four GI cancers, which was quite different from previous clinical studies.

A lot of clinical studies also focused on the causal effect of PD on GI cancers. Møller, Oslen, Fois, and Wirdefeldt *et al.* adopted a cross-sectional design, but they did not exclude the patients that already had cancers before PD and they did not follow up (12,22-25). Lin, Peretz, and Ong *et al.* adopted a retrospective cohort design (13,26,27). They used the medical system to "follow up" the patients with PD, however, the retrospective design was less accurate in data collection than the prospective cohort design. Unlike observational studies, MR analysis can largely reduce potential bias from confounding and reverse causation. It is noteworthy that apart from Lin *et al.*'s research, most of the studies enrolled the European population and they found a negative causal effect of PD on GI cancers. On the contrary, Lin *et al.*'s research found that PD patients had significantly higher rates of EC. As a result, the GWAS dataset that enrolled the European and East Asian populations was separately analyzed to rule out ethnic differences.

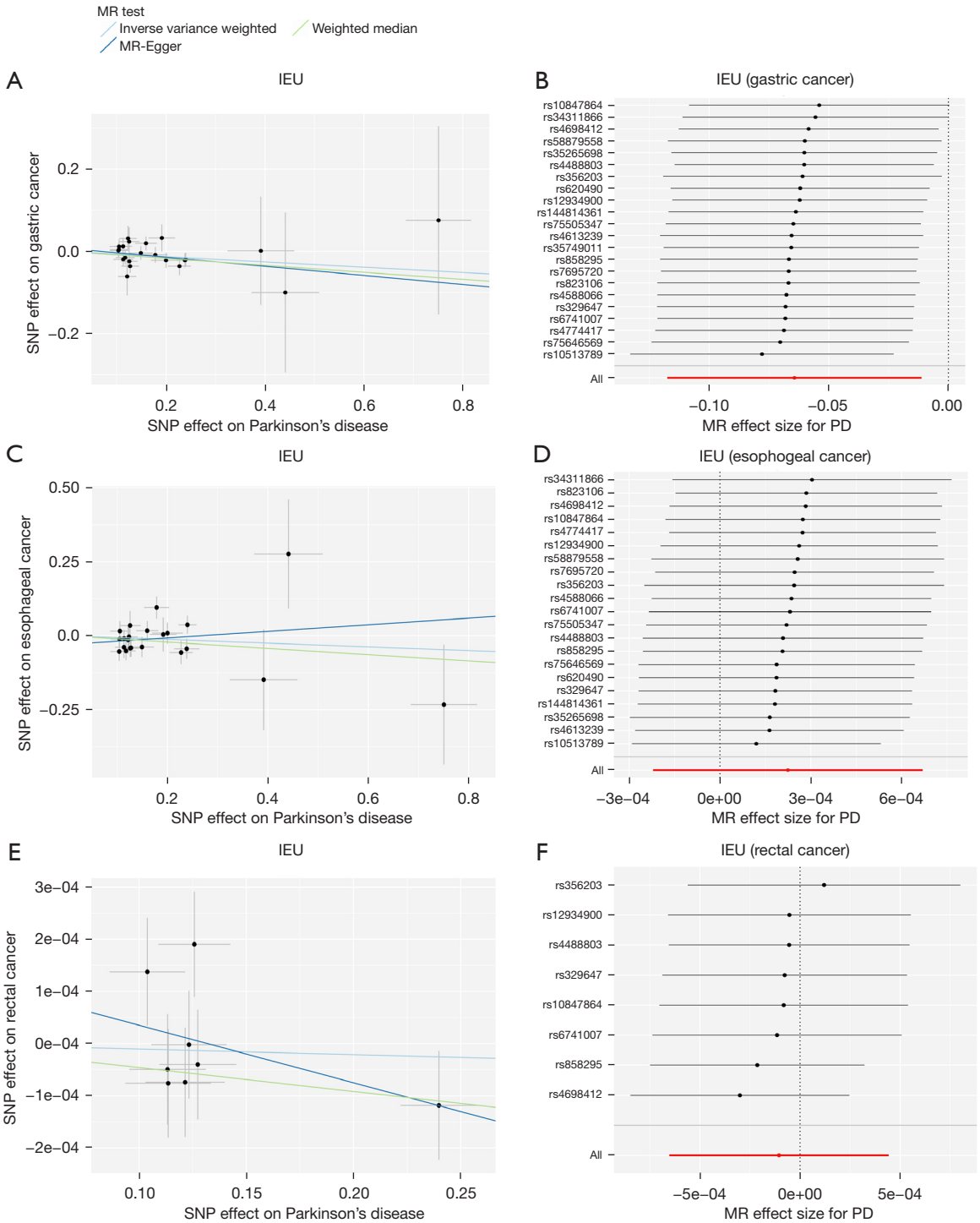

Figure 4 Correlation of PD on GC/EC/RC and its leave-one-out analysis results. (A) Correlation of PD on GC. (B) Leave-one-out analysis of PD on GC. (C) Correlation of PD on EC. (D) Leave-one-out analysis of PD on EC. (E) Correlation of PD on RC. (F) Leave-one-out analysis of PD on RC. MR, Mendelian randomization; IEU, Integrative Epidemiology Unit; SNP, single nucleotide polymorphism; PD, Parkinson's disease; GC, gastric cancer; EC, esophageal cancer; RC, rectal cancer.

In the present MR analysis, rs34311866 was the instrumental SNP in the causal effect of PD on GC, CC, and EC. Previous research reported that it was a common variant in the *TMEM175* gene, which was closely associated with an increased risk of developing PD by regulating lysosomal K^+ channel currents (28). Over the past few years, a considerable amount of evidence has been accumulating on the role of lysosomes and lysosomal ion channels in cancer cell migration and metastasis. Although the Ca^{2+}-activated big-conductance K^+ channels, another lysosomal channel, was proved to be associated with multiple cancers including CC, the function of *TMEM175* in regulating GI cancers is not clear. Further research might be needed to understand this pathway (29). Another important SNP was rs4698412, which modulated lingual gyrus functional alterations and was related to gait and balance dysfunction in PD (30). Since gait difficulty belongs to motor dysfunction and GI disorders in PD belong to non-motor dysfunction., this could explain why rs4698412 did not increase or decrease the GI cancer rate. Another interesting fact was that rs10513789, which is a variant in the lysosome-associated membrane protein 3 (LAMP3) loci, could reduce the risk of PD (31). However, *in vitro* experiments proved that in EC cells, LAMP3 could promote cancer progression (32). Since oncogenesis is so complicated, it is not surprising to see a different result between clinical research and basic research.

Apart from that, the dopamine (DA) signal pathway is closely related to GI cancers. It is well known that DA and its associated receptors are implicated in various tissues including vascular beds, heart, GI tract, eye, kidney, and pancreas (33). Former research proved that DA in combination with anticancer drugs, significantly inhibited CC cell proliferation and migration through the suppression of vascular endothelial growth factor (VEGF) receptor-2, mitogen-activated protein kinase, focal adhesion kinase phosphorylation, and Kruppel-like factor 2 (34,35). On the contrary, antipsychotic DA antagonist use may confer a small but significant risk of breast cancer (36). Moreover, DA receptor D2 mutations in PD are significantly associated with increased CC risk and adenoma recurrence (37,38).

There are several limitations in the present study. First, while we used the datasets from FinnGen and GWAS Catalog to explore the causal effect of PD on CC, limited SNPs were found to reach genome-wide significance, which can lead to weak genetic instruments. To address this, we loosened the statistical threshold ($P<1\times10^{-5}$) to include additional SNPs. Secondly, the biological actions of the selected SNPs are still unknown, making it difficult to fully rule out pleiotropy. Thirdly, when we explored the causal effect of PD on GC, the result of IVW, MR-Egger regression, and the weighted median test turned out to be different. As the IVW method was the primary method of MR analysis, we considered the result of IVW as the major result of this analysis.

Conclusions

In conclusion, we did not find a causal effect of PD on GI cancers. No evidence supports the need for progressive endoscopy screen for PD patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-106/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-106/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-106/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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