Gastrointestinal Surgery and Risk of Parkinson’s Disease: A Meta-Analysis

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ABSTRACT
Several studies have explored gastrointestinal surgery and the risk of Parkinson’s disease (PD), but the results of these studies are still controversial. This meta-analysis aimed to evaluate undergoing gastrointestinal surgery and the risk of PD in patients. PubMed, EMBase, the Cochrane Library, CNKI, and WanFang Data databases were electronically searched to collect studies from inception to 1 March 2023. Stata15.1 software was used to perform meta-analysis of the data. Of 260 references screened, 8 studies involving 9,596,121 people were included eventually. Gastrointestinal surgery had no significant effect on the risk of PD (OR = 1.059, 95% CI: 0.915-1.224, I² = 90.4%, p = 0.443). Several subgroup analyses showed that the patients with different regions, different surgical locations and different sample sizes after gastrointestinal surgery were not associated with the risk of PD. Furthermore, sensitivity analysis confirmed that the patients after gastrointestinal surgery were not associated with the risk of PD. There was no significant effect of gastrointestinal surgery on the risk of PD, but more studies should be included to confirm this observation.

Key Words: Gastrointestinal surgery, Risk factor, Parkinson’s disease, Meta-analysis.


INTRODUCTION
Parkinson’s disease (PD), the second most common neurodegenerative disease after Alzheimer’s disease, is more common in middle-aged and elderly people.¹ The estimated incidence of PD worldwide is 102 new cases per 100,000 people per year.² Recently, it was recognised that pathological changes in PD can involve multiple systems of the body. Although clinically diagnosed on the basis of bradykinesia and other major motor features, PD manifests many non-motor symptoms that increase overall disability, particularly in the digestive system. Misfolded α-synuclein (termed Lewy bodies) accumulates within neurons and causes neuroinflammation, leading to degenerative changes in dopaminergic neurons in the substantia nigra that are pathological features of PD.³ The neuropathological evidence suggested that misfolded α-synuclein leading to PD may originate from the enteric nervous system,⁴,⁵ so it can be assumed that the altered gut microenvironment is a potential trigger for the PD process.

There are more than 1,000 species of bacteria and over 100 trillion microbes in the human gut. The gut microbiota (GM) influences neurodevelopment, modulate behaviour, and contribute to neurological disorders.

In patients with gastrointestinal surgery, the gastrointestinal microenvironment will change after the surgical treatment on the basis of their own disease.⁶ GM disorders are associated with a variety of diseases, and GM has been reported to be related to some neurological disorders as a mediator between gastrointestinal pathology and neuropsychiatric disorders, such as anxiety, depression, and autism.⁷ Several studies have explored whether patients with a history of gastrointestinal surgery have a low risk of PD or otherwise,⁸,⁹ but the results of these studies are still controversial. For this reason, the aim of this meta-analysis was to evaluate the relationship between gastrointestinal surgery and PD in the available published literature, in order to provide a basis for the aetiology and prevention of PD.

METHODOLOGY
PubMed, EMBase, the Cochrane Library, CNKI, and WanFang Data databases were electronically searched to collect studies from inception to 1 March 2023. The search term employed was Parkinson’s disease or Parkinsonian disorders or Parkinson or Parkinson’s disease or idiopathic Parkinson’s disease or idiopathic Parkinson’s disease or paralysis agitans or Parkinsonism and appendectomy or appendicectomy or append* or gastrectomy or gastrectomies or colectomy or colectomies or colorectal surgery or large bowel resection or large bowel resections or haemicolectomy or haemicolectomies or proctectomy or proctectomies or rectum excision or rectum excisions or rectum resection or rectum resections. The searches were conducted using a combination of subject words and free words, adjusted to the characteristics of each database.

The studies were eligible for inclusion if the applicable data could be extracted from studies for the evaluation of patients with or without...
gastrointestinal surgery; if the patients met the diagnostic criteria for PD; and there were data on standardised incidence ratios capable of calculating odds ratios (OR) or 95% confidence intervals (CI). Studies were excluded if the number of patients with PD could not be extracted from the studies; or articles had incomplete or unusable data; or it was a repeat publication.

Two researchers independently performed study selection, data extraction and assessment of risk of bias. If there were a discrepancy, it was discussed with the third person to determine whether or not to include it. To select the literature, the title and abstract of the article was first read to exclude the irrelevant literature, then, the full text was read for rescreening and to determine the final inclusion according to the inclusion and exclusion criteria. The content of the data extraction included the first author, time of publication, nationality, baseline characteristics of the study subjects, outcomes of interest, and outcome measures, etc.

The Newcastle-Ottawa Scale (NOS) was used for literature quality assessment. NOS consisted of 3 dimensions and 8 items, with a maximum score of 9. A score of 6–9 was considered to be a high quality study.

The statistical analysis for this study was performed using Stata15.1 software. The odds ratio (OR) was used for the effect analysis for the count data. Heterogeneity between included studies was judged by $I^2$ quantification. If there was statistical heterogeneity between the study results, the source of heterogeneity was further analysed after the effects of significant clinical heterogeneity were ruled out, and meta-analysis was performed using a random-effects model. Conversely, a fixed-effect model was used. Any value equal to or greater than 50% indicated significant differences between the studies. Forest plots were used to assess whether there was publication bias. Funnel plots were presented in order of weight for each study. Stata15.1 software was used to draw a funnel plot and assess publication bias in conjunction with the Egger’s test.

**RESULTS**

A total of 260 relevant literature was obtained in the preliminary search. Following the removal of duplicates, the eligibility of 196 abstracts was assessed. Then, 163 studies were excluded because of the irrelevance of titles and abstracts. Of the remaining 33 articles, 25 were excluded due to lack of clinical data. Finally, 8 studies were included in the review, including 6 prospective cohort studies,8,10,12,14,15 and 2 case-control studies,9,11 reporting a total of 9,596,121 patients. The selection process is demonstrated in Figure 1.

The eight studies, first published in 2016 and as late as 2021, involved 9,596,121 people from six countries: Sweden, Canada, the United States, Denmark, Germany, and South Korea. Sample sizes varied widely between the studies: six of the studies analysed national or province-wide data, with samples ranging from 85,998 to 3,224,650, while two studies involved samples of 1,625 and 5,621 people. The basic characteristics of the included studies are presented in Table I.

A total of 8 studies involving 9,596,121 people were included to assess the potential relationship between gastrointestinal surgery and the risk of PD. The results showed that previous gastrointestinal surgery had no significant effect on the risk of PD (OR = 1.059, 95% CI: 0.915-1.224, $I^2$ = 90.4%, $p = 0.443$, Figure 2a). Funnel plots suggested no publication bias for the gastrointestinal surgery and the risk of PD (Figure 2b), the p-values of Egger’s test ($p = 0.458$) also suggested no publication bias.

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**Tables**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, et al. (2020)</td>
<td>0.98 (0.93, 1.02)</td>
<td>16.51</td>
</tr>
<tr>
<td>Marras, et al. (2016)</td>
<td>1.39 (1.06, 1.81)</td>
<td>10.72</td>
</tr>
<tr>
<td>Palacios, et al. (2018)</td>
<td>1.13 (0.99, 1.29)</td>
<td>14.70</td>
</tr>
<tr>
<td>Kellinge, et al. (2018)</td>
<td>0.83 (0.76, 0.91)</td>
<td>15.74</td>
</tr>
<tr>
<td>Svensson, et al. (2016)</td>
<td>1.36 (1.23, 1.50)</td>
<td>15.54</td>
</tr>
<tr>
<td>Yilmaz, et al. (2017)</td>
<td>0.99 (0.70, 1.42)</td>
<td>8.42</td>
</tr>
<tr>
<td>Chok, et al. (2021)</td>
<td>0.82 (0.72, 0.94)</td>
<td>14.73</td>
</tr>
<tr>
<td>Kim, et al. (2019)</td>
<td>1.65 (0.84, 3.24)</td>
<td>3.64</td>
</tr>
<tr>
<td>Overall, DL ($I^2$ = 90.4%, $p = 0.000$)</td>
<td>1.06 (0.92, 1.22)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 1:** Flow chart of research data screening.

**Figure 2:** Meta-analysis of gastrointestinal surgery and the risk of PD; (a) Forest plots; (b) Funnel plots.
Gastrointestinal surgery and risk of Parkinson’s disease

In order to explore whether certain factors (regions, surgical locations, sample sizes) may affect the potential relationship between gastrointestinal surgery and the risk of PD, a subgroup analysis was performed according to the different surgical locations, sample sizes and regions. The patients with surgical locations (Figure 3a), sample sizes (Figure 3b), and different regions (Figure 3c) were not found to be associated with the risk of PD.

Sensitivity analysis was performed by removing one study at a time to elucidate causes of heterogeneity between studies, and the result confirmed that the patients after gastrointestinal surgery were not associated with the risk of PD (Figure 4).
DISCUSSION

As the pathological marker of PD, α-synuclein had been reported to originate from the gastrointestinal tract. Patients undergoing gastrointestinal surgery in later life may have accumulated enough α-synuclein from the gastrointestinal tract to cause PD to occur. Even after gastrointestinal surgery, this tract continues to drive disease progression. Based on the hypothesis of the previous studies, Lewy bodies may have originated in the gut and later migrated to the brain via the vagus nerve. Intriguingly, as early as more than 20 years before the onset of PD, the accumulation of α-synuclein can be observed in the gastrointestinal tract. However, till now, the incidence of PD after gastrointestinal surgery is still controversial. In this research, the meta-analysis of included studies and subgroup analyses showed no significant effect of gastrointestinal surgery on the risk of PD.

In the gastrointestinal tract, there is a huge ecosystem. It is made up of trillions of bacteria, viruses, protozoa, and fungi. They co-interact with the host and are involved in maintaining homeostasis, immune maturation, nutrient absorption, and metabolism of the intestinal barrier. Studies have shown that the GM communicates with the brain and is implicated in several neurodegenerative diseases, including PD. Small intestinal bacterial overgrowth is a common manifestation in patients with PD, which is associated with worsening of motor function and complications of PD. If the intestinal anatomy or motility changes, it can cause small intestinal bacterial overgrowth. Studies provided evidence on the association between small intestinal bacterial overgrowth and PD motor fluctuations, including poor motor function, prolonged delay, and delayed latency. The composition and habitat of the microbiome are affected by changes in the gastrointestinal environment resulting from gastrointestinal surgery. Therefore, it was speculated that alterations of the microbiome resulting from gastrointestinal surgery might be associated with the risk of PD. Although the pathogenic mechanism is not fully understood, the recent studies through vagotomy have shown its protective effect against PD based on the hypothesis that the causative substance is transmitted from the peripheral nervous system along the vagus nerve. Likewise, it was reasonable to assume that gastrointestinal surgery will reduce the risk of PD by preventing the causative agent from spreading to the central nervous system. However, the results differed from what was expected from the hypothesis that gastrointestinal surgery might reduce the risk of PD.

The relationship between gastrointestinal surgery and risk of PD had been reported in many studies. Some studies reported an association between gastrointestinal surgery and the risk of PD, however, studies of Marras et al. and Svensson et al. concluded that patients with a history of gastrointestinal surgery have a higher risk of PD than those without history of gastrointestinal surgery. In contrast, studies of Killinger et al. and Choi et al. strongly supported the higher risk of PD in patients without gastrointestinal surgery than those with gastrointestinal surgery. These results were conflicting. The different conditions for confirming PD cases between the studies, different control groups, monitoring bias, and insufficient follow-up time to explore the potential long-term protective effect of gastrointestinal surgery on PD are all potential explanations. This meta-analysis included 9,596,121 people to analyse the risk of PD in people with a history of gastrointestinal surgery and found that the gastrointestinal surgery had no significant effect on the risk of PD.

The study also had some limitations. Firstly, the databases of the included studies were based on European countries, predominantly North America and South Korea. Data from Latin American and African countries did not exist. Second, although the sources of heterogeneity were analysed, there was considerable heterogeneity among studies that could not be ignored. Furthermore, the relationship between gastrointestinal surgery and various symptoms of PD was not analysed, therefore, more studies are needed to be included for a further analysis.

CONCLUSION

Eight studies including 9,596,121 people were involved to analyse the risk of PD in patients with a history of gastrointestinal surgery. The results showed that gastrointestinal surgery had no significant effect on the risk of PD, and more studies should be included to confirm this conclusion.

PATIENTS’ CONSENT:
Informed consents were obtained from all participants included in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS’ CONTRIBUTION:
PW: Did the literature search, screening and data extraction, and drafted the manuscript.
MZ: Did the literature search, assisted in interpreting the results.
YW, ZJ: Assessed the data quality, assisted in the writing of paper.
TZ: Performed critical appraisal of all included studies.
GZ: Provided the research idea, study design, supervision and mentorship.
All authors read and approved the final manuscript.

REFERENCES


