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Appendectomy and Parkinson's Disease Risk: A Meta-Analysis

Khalid Alhazmi[1*], Salah Alghamdi[2]

[1]Department of Pathology, Faculty of Medicine, University of Tabuk, Kingdom of Saudi Arabia.
[2]Department of Surgery, Faculty of Medicine, University of Tabuk, Kingdom of Saudi Arabia.

ABSTRACT

The emergence of alternative methods of treating appendicitis and the fact that the gut lymphoid tissue is active (in terms of immune modulation and gut microbiota replenishment) increased the concern about the association of appendectomy with systemic diseases. The literature on the association between appendectomy and Parkinson's disease (PD) lacks the current meta-analysis aimed to assess the association between appendectomy and PD. We systematically searched PubMed, Cochrane Library, and Google Scholar for relevant articles published in the English language, the searching engine was limited to the period from January 2010 to January 2021. Studies on humans were eligible, while animal and experimental studies were excluded, the keywords used were Parkinson's disease, appendicitis, Parkinsonism, appendectomy, gut lymphoid tissue, and movement disorders with protean "AND" or "OR". Out of the 263 references found, 39 full texts were screened, and only five studies fulfilled the inclusion and exclusion criteria, the studies included 8210081 patients and showed that no association between appendectomy and PD, odd ratio, 1.16, 95% CI, 0.92-1.46, and P-value, 0.20. Significant heterogeneity was observed between the studies included (three from the United States of America and two from Europe) and no relationship was evident between appendectomy and PD, further studies controlling for the causes of appendectomy and temporal profile of both PD and appendectomy are recommended.

Keywords: *Appendectomy, Parkinson's disease, Gut lymphoid tissue, Disease risk*

Corresponding author: Khalid Alhazmi
e-mail ✉ kalhazmi@ut.edu.sa
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INTRODUCTION

The caecal appendix was previously thought of as a redundant organ of revolution, however, the rare malformation and being highly conserved suggested a role, the appendix is rich in lymphoid tissue and a primary source of immunoglobulin A. Studying the lymphoid system in the appendix is relevant due to the increasing population age, and the parallel substantial lymphoid changes with that. The light center of the appendix is lost in the elderly (in some a complete closure was noted) affecting lymphoid transformation and lymphocyte migration (Aminova, 2018; Girard-Madoux *et al*., 2018). Furthermore, due to its position and shape, it could be a primary niche for the gut microbiota (the intestinal flora). Indeed, the appendix is continuously shedding microbiota to replenish especially after a diarrheal episode. Thus, it is suggested to play a major role in systemic diseases (including Parkinson's disease) by controlling the immune system, the number and diversity of gut flora, and keeping the integrity of the intestinal barrier (Holzer & Farzi, 2014; Kooij *et al*., 2016).

There is an increasing awareness that Parkinson's disease is a systemic disease (Ahmad, *et al*., 2017; AlJohani & AlZahrani 2017; Jabbar *et al*., 2021). The observations of a reduced rate of PD after vagotomy and the high concentration of alpha-synuclein in the appendix relative to other parts in the gastrointestinal tract suggested a role in the pathology of PD (Holmqvist *et al*., 2014; Svensson *et al*., 2015; Borghammer & Hamani, 2017). The hypothesis is that: the synthesis of α-synuclein in the appendix is modulated by the gut microbiota and reaches the brain by retrograde axonal transport (Palacios *et al*., 2018).

The association between Parkinson's disease (PD) and the accumulation of misfolded α-synuclein is established. However, the association with gut α-synuclein has been discussed controversially. Importantly, α-synuclein was suggested as an interventional and diagnostic measure for PD (Bu *et al*., 2019). There is increasing evidence of treating uncomplicated appendicitis less invasively (antibiotic or conservative) (Rollins *et al.,* 2016). Investigating the association of gut lymphoid tissue removal with systemic diseases might support either approach. Thus, we conducted this review and meta-analysis to assess the relationship between appendectomy and Parkinson's disease.

MATERIALS AND METHODS

Eligibility criteria according to PICOS

We included retrospective, prospective cohorts, and case-control studies investigating the relationship between appendectomies and Parkinson's disease in adults and published in English. Case reports, case series, experimental, and animal studies were excluded, not including randomized trials is obvious due to the difficulty in conducting such methodologies.

Intervention and outcomes measures

Appendectomy conducted at any age and confirmed by records and the development of Parkinson's disease confirmed by a physician were considered, the self-reported diagnosis was not. No specification for the follow-up period.

The search strategy

The PubMed, Cochrane library, and Google Scholar databases were systematically searched for relevant articles; Two Authors (S. A. and K. A) Independently screened the titles and abstracts. Also, the references of the retrieved articles were screened for inclusion or exclusion and discrepancies were solved by agreement. The keywords used were Parkinson's disease, appendicitis, Parkinsonism, appendectomy, gut lymphoid tissue, and movement disorders with protean "AND" or "OR". Studies published from January 2010 up to January 2021 were eligible. Out of the 263 references found, 39 full texts were screened, and only five studies fulfilled the inclusion and exclusion criteria. We used the Ottawa Newcastle scale for non-randomized studies (Cook & Reed, 2015; Azzawi *et al*., 2021) **(Figure 1, Table 1)**.

Statistical analysis

The most recent RevMan version 5.4 was used for data analysis, the data were entered manually at 95% *CI* a P-value of <0.05 was considered significant. The fixed effect was used unless significant heterogeneity was observed (>50%). The funnel plot was used to test for sensitivity (lateralization).

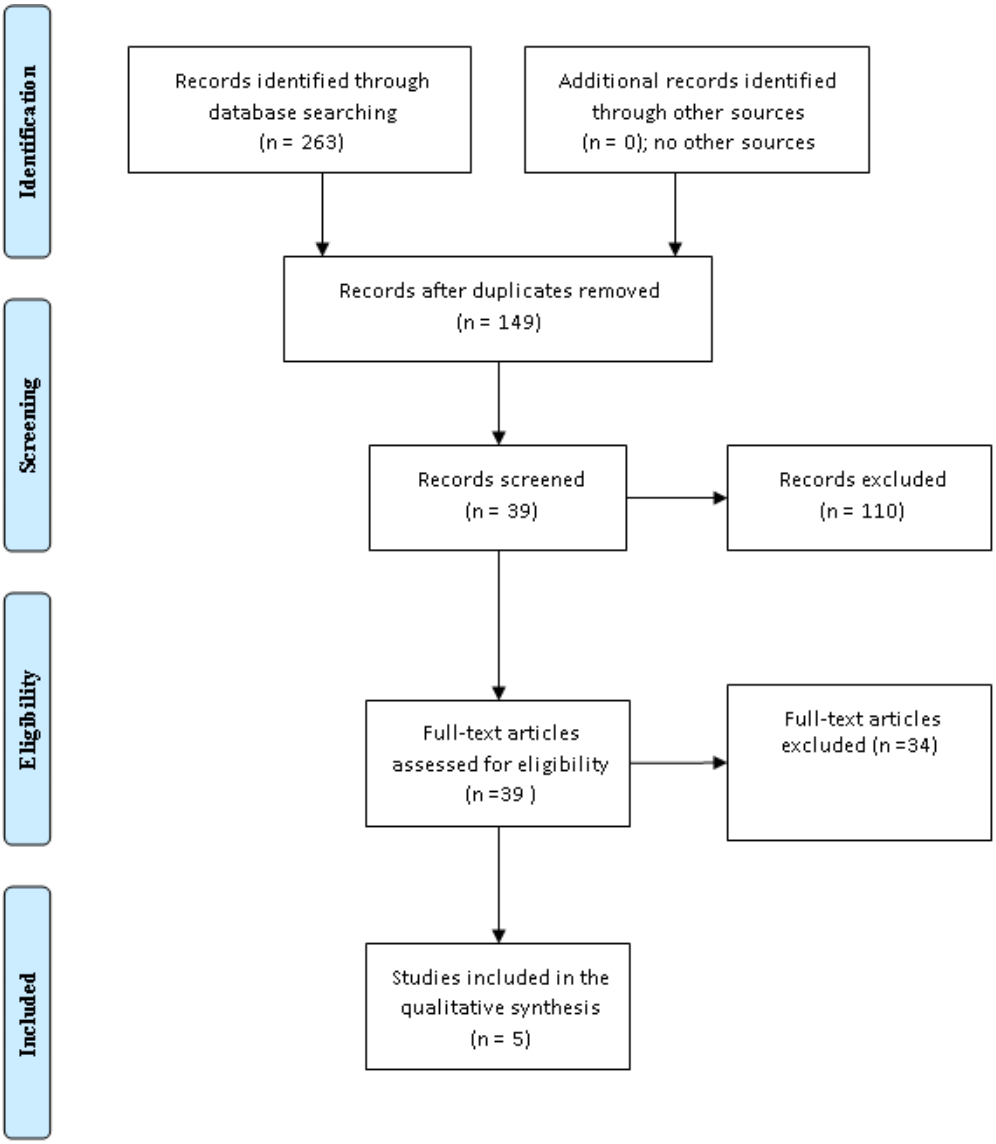

Figure 1. Trials included in the association between appendectomy and Parkinson's disease.

RESULTS AND DISCUSSION

Out of the 263 references found, 39 full texts were screened, and only five studies (three from the United States of America and two from Europe) fulfilled the inclusion and exclusion criteria. Two studies (Svensson *et al*., 2016; Yilmaz *et al*., 2017) showed the association of appendectomy and Parkinson's disease, another two studies were on the side that

appendectomy might be protective (Palacios *et al*., 2018; Liu *et al*., 2020), while one study was neutral (Killinger *et al*., 2018). The studies included 8210081 patients (1339594 cases and 6870487 controls) without appendectomy. The random effect was applied due to the significant heterogeneity observed (I^2=92%, P-value<0.001). The diamond showed no protective effect of appendectomy against Parkinson's disease, odd ratio, 1.16, 95% CI, 0.92-1.46, and P-value, 0.20 **(Figure 2, Table 2)**.

Table 1. Ottawa Newcastle assessment for the included studies

Author	Selection	Compatibility	Outcome	Score
Killinger *et al.* (2018)	3	2	4	9
Liu *et al*. (2020)	3	2	4	9
Palacios *et al*. (2018)	3	2	4	9
Svensson *et al*. (2016)	3	2	4	9
Yilmaz *et al*. (2017)	3	2	4	9

Table 2. The relationship between gut lymphoid tissue removal and Parkinson's disease.

Author	Year	Country	Type of study	No of patients	result
Killinger *et al.*	2018	USA	Case-control	644/551,647 vs. 1608/1146353	Lower risk
Liu *et al.*	2020	Sweden	Case-control, nested	1908/78,650 vs. 78120/3,146,000	Risk reduction
Palacios *et al.*	2018	USA	Prospective	177/ 442700 vs. 406/ 1249191	No relationship
Svensson *et al.*	2016	USA	A case-control	19/265,758 vs. 15/1,328,790	Small increase
Yilmaz *et al.*	2017	Germany	Retrospective	69/839 vs. 12/153	No relationship

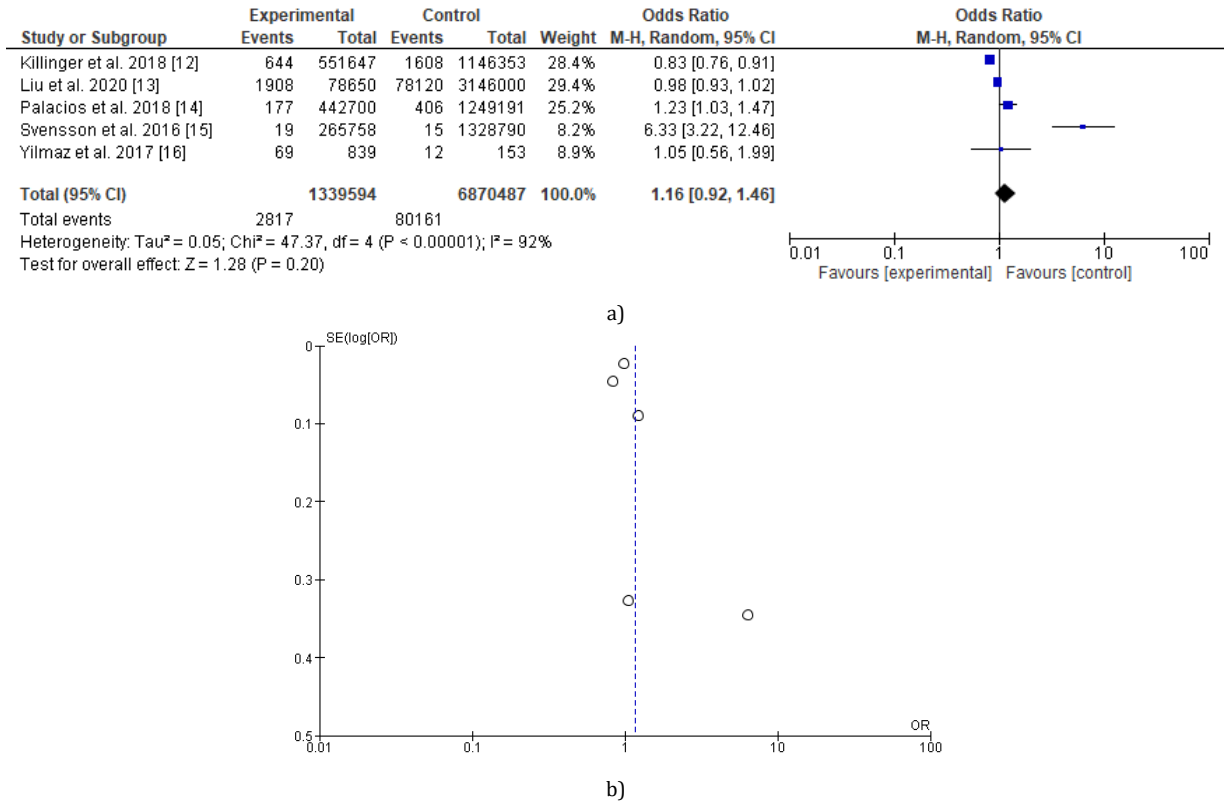

Figure 2. The relationship between gut lymphoid tissue removal and Parkinson's disease.

The pathogenesis of Parkinson's disease (the commonest neurodegenerative movement disorder) is the accumulation of misfolded α-synuclein, in Lewy bodies with a loss of dopaminergic neurons in the substantia nigra. Currently, no available treatment that modifies the course of this disabling disease (Balestrino & Schapira, 2020). The high concentration

of alpha-synuclein in the appendix relative to other parts of the gastrointestinal tract may be targeted as a therapeutic intervention. The present data showed a higher rate of PD (no amounting to statistical significance) among those without appendectomy compared to their counterparts' odd ratio, 1.16, 95% CI, 0.92-1.46, and P-value, 0.20. The present findings were similar to a previous study (Lu *et al*., 2019). However, the results were limited with significant heterogeneity (RR 1.02, 95% CI 0.87-1.20, I^2 = 83.1%, P = 0.789). The discrepancy observed between different studies might be explained by the temporal profile, Mendes *et al*. (2015) found a protective effect of appendectomy in middle age and late-onset PD and an effect that was not observed among the young age group. While Marras and colleagues (2016) who assessed PD incidence among adults (who underwent an appendectomy in late and middle) found a higher rate of the disease during the first five years following appendectomy but no thereafter. The underlying cause of appendectomy including secondary appendicitis, appendicitis within a hernia, and intraluminal foreign bodies are further confounders (Hines *et al*., 2016). Besides, alteration of the gut lymphoid expression is a great player on chronic inflammation and cancer development (Yuksel *et al.,* 2019; Dashti & Mirzakhani, 2021).

The gut lymphoid tissue and PD pathology

PD is a multisystem disorder with both motor and nonmotor components. Both central and peripheral neurons are affected. The pathology is the accumulation of misfolded α-Synuclein in enteric neurons and Lewy bodies of substantia nigra. The gut accumulation and nonmotor symptoms in the gastrointestinal tract precede the brain pathology by more than 20 years and during the prodromal phase of the disease (Stokholm *et al*., 2016; Killinger *et al*., 2018).

The high α-synuclein concentration in the appendix, the mucosa rich in immune cells, and the lack of a blood-tissue barrier suggested a role in PD development. In addition to its role in detecting and destroying pathogenic organisms. Besides, experimental studies found that α-synuclein migrates from cell to cell in a prion-like fashion and might ascend the vagus nerve to reach the brain. Furthermore, vagotomy was shown to reduce PD risk in some epidemiological studies (Volpicelli-Daley *et al.*, 2011; Tysnes *et al*., 2015; Liu *et al*., 2017).

The study was limited by the significant heterogeneity observed between the included studies and the fact that studies were published only in the United States and Europe. The literature in other parts of the World and the searched databases was not found.

CONCLUSION

No relationship was found between appendectomy and PD, the marked heterogeneity observed might affect the current results. Nevertheless, the association between the two common diseases was not documented. Further studies controlling for the causes of appendectomy and temporal profile of both PD and appendectomy are recommended.

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