Original research

# Gastrointestinal syndromes preceding a diagnosis of Parkinson's disease: testing Braak's hypothesis using a nationwide database for comparison with Alzheimer's disease and cerebrovascular diseases

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## ABSTRACT

**Objective** Braak's hypothesis states that Parkinson's disease (PD) originates in the gastrointestinal (GI) tract, and similar associations have been established for Alzheimer's disease (AD) and cerebrovascular diseases (CVD). We aimed to determine the incidence of GI syndromes and interventions preceding PD compared with negative controls (NCs), AD and CVD.

**Design** We performed a combined case-control and cohort study using TriNetX, a US based nationwide medical record network. Firstly, we compared subjects with new onset idiopathic PD with matched NCs and patients with contemporary diagnoses of AD and CVD, to investigate preceding GI syndromes, appendectomy and vagotomy. Secondly, we compared cohorts with these exposures to matched NCs for the development of PD, AD and CVD within 5 years.

**Results** We identified 24 624 PD patients in the case-control analysis and matched 18 cohorts with each exposure to their NCs. Gastroparesis, dysphagia, irritable bowel syndrome (IBS) without diarrhoea and constipation showed specific associations with PD (vs NCs, AD and CVD) in both the case-control (odds ratios (ORs) vs NCs 4.64, 3.58, 3.53 and 3.32, respectively, all $p<0.0001$) and cohort analyses (relative risks (RRs) vs NCs 2.43, 2.27, 1.17 and 2.38, respectively, all $p<0.05$). While functional dyspepsia, IBS with diarrhoea, diarrhoea and faecal incontinence were not PD specific, IBS with constipation and intestinal pseudo-obstruction showed PD specificity in the case-control (OR 4.11) and cohort analysis (RR 1.84), respectively. Appendectomy decreased the risk of PD in the cohort analysis (RR 0.48). Neither inflammatory bowel disease nor vagotomy were associated with PD.

**Conclusion** Dysphagia, gastroparesis, IBS without diarrhoea and constipation might specifically predict Parkinson's disease.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Braak's hypothesis states that Parkinson's disease (PD) originates in the gut in a subset of patients, but no studies to date have systematically investigated a broad range of gastrointestinal (GI) symptoms and diagnoses before a diagnosis of PD.

### WHAT THIS STUDY ADDS

⇒ This is the first multicentre study to establish that dysphagia, gastroparesis, constipation and irritable bowel syndrome without diarrhoea specifically increase the risk of a subsequent new onset diagnosis of idiopathic Parkinson's disease, even compared with other neurological diseases, such as Alzheimer's disease and cerebrovascular diseases.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early detection of GI syndromes might contribute to the identification of patients at risk of PD during a phase were disease modifying therapies could prevent the progression of α-synuclein pathology.

## INTRODUCTION

Parkinsonism is a clinical syndrome characterised by bradykinesia, rest tremor, rigidity and postural instability.[1] Its most common cause is Parkinson's disease (PD), the pathological hallmark of which is thought to be cytoplasmatic eosinophilic Lewy body (LB) depositions. These depositions, mainly consisting of misfolded α-synuclein, have not only been found in the CNS but also in the vagus nerve and enteric nervous system (ENS) of patients with PD.[1]

These findings led Braak *et al* to state the neuroanatomical hypothesis that α-synuclein pathology progresses from peripheral sites such as the ENS to the CNS via vagal or olfactory pathways, thereby introducing the concept that the gastrointestinal (GI) tract might serve as a gateway for environmental factors that induce α-synuclein misfolding and lead to PD.[2] A large body of evidence has since then accumulated to support this claim. Even in early untreated stages of the disease, neuropathological studies have found that α-synuclein concentrations in the ENS of patients with PD were higher than those of otherwise healthy individuals, in a

characteristic rostrocaudal gradient following visceromotor projections of the vagus nerve.[3–5] Complementary studies have shown that various motility disorders[5–7] and inflammatory bowel disease (IBD)[8] can precede PD and therefore may be risk factors for its development. Moreover, since Gray and colleagues[9] first identified the vermiform appendix as a potential source of misfolded α-synuclein, conflicting observational studies have been published about the impact of an appendicectomy on the risk of idiopathic PD.[9–14] Finally, two recent registry based studies have strengthened the concept of retrograde vagal α-synuclein propagation by showing that a truncal vagotomy might be protective against the development of PD.[15 16] Apart from the bottom up link formulated by Braak, a top down aetiology in which GI symptoms are present in early phases when neurological manifestations are still unnoticed is also supported by experimental evidence.[1] Even if no causal link exists, GI syndromes might still represent a risk factor through other mechanisms, or both might be related to a yet unknown third factor.

Apart from PD, other neurological disorders have also been hypothesised to have GI precedents, either through similar neuroimmune pathways or translocation of microbiome derived neurotoxins into the CNS.[17] A strong pathological link between microbiome derived neurotoxins, including *Escherichia coli* derived Lipopolysaccharide, has been established with disrupted intestinal cell adhesion, impaired synaptic signalling in the Alzheimer's disease (AD) brain and exacerbation of inflammatory neuropathology.[18 19] Additionally, given the prominent role of reactive oxygen species induced inflammation in cerebrovascular diseases (CVD),[20] proinflammatory intestinal[21] and extraintestinal[22] diseases have been linked to a higher risk of CVD than that predicted by conventional risk factors.[20]

Previous studies on this topic have been limited by small sample sizes and inadequate controls. Therefore, we used a nationwide electronic health record (EHR) network to investigate the incidence of various GI syndromes and interventions, such as appendectomy and vagotomy, before the onset of PD. Because previous studies lacked specificity for exposures associated with PD, we used a case-control study design to compare patients with PD not only with negative controls (NCs), but also with patients diagnosed with AD and CVD. Additionally, we established a cohort study design for each exposure in the case-control design to validate these findings and establish relative risk (RR) estimates relevant in clinical practice.

## METHODS

### Study design and data source

To investigate the association between various GI syndromes and interventions with the subsequent development of new onset PD, we analysed electronic medical records from the TriNetX Analytics Research Network (Cambridge, Massachusetts, USA). At the moment of data collection, the network consisted of more than 80 million patients from 57 predominantly academic medical centres in the USA. Additional information can be found in the online supplemental methods.

### Study population and variables of interest

In the case control analysis, we examined the incidence of exposures retrospectively (ie, before an initial diagnosis of PD compared with matched controls). Patients with PD were captured using a previously validated method.[23] Patients were queried using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis of PD (G20), if documented between 1 January 2005 and 1 July 2021; the first ever diagnosis was used as the index event. Only those with at least two prescriptions of an antiparkinsonian drug and a documented ambulatory visit at least 2 years before the first diagnosis of PD were included; secondary causes of PD were excluded. To determine PD specific exposures, control subjects comprised three groups: NCs, and patients with a diagnosis of AD and CVD. NCs consisted of patients without a recorded ICD-10 diagnosis of PD, with at least two documented ambulatory visits between the ages of 50 and 90 years, at least 2 years apart, recorded between 1 January 2005 and 1 July 2021. A minimum of 2 years of retrospective follow-up was ensured by using the second of these visits as the index event. Similarly, 2 years of follow-up was ensured for the AD and CVD groups, and the first ever documented respective ICD-10 diagnosis in the medical records after 1 January 2005 was chosen as the index event. In a pairwise fashion, these groups where then matched to the PD group for age, sex, race and ethnicity using a propensity score matching algorithm.

To cover the entirety of the GI tract, 18 exposures were investigated: achalasia, dysphagia, gastro-oesophageal reflux disease (GORD), gastroparesis (GP), functional dyspepsia (FD), paralytic ileus (PI), diarrhoea, irritable bowel syndrome (IBS) with constipation (IBS-C), IBS with diarrhoea (IBS-D), IBS without diarrhoea, intestinal pseudo-obstruction (approximate synonym of K59.8: other specified functional GI disorders), faecal incontinence (FI), Crohn's disease (CD), ulcerative colitis (UC), microscopic colitis (MC), appendectomy and vagotomy. We conducted additional sensitivity analyses in the network, which included stratified analyses based on sex and age at the diagnosis of the index event. A detailed breakdown of the query, inclusion and exclusion criteria, stratified analyses and coding can be found in the online supplemental methods.

To validate the results from the case-control analyses, we set up a complementary cohort study design. Eighteen cohorts, each diagnosed with one of the investigated exposures in the case-control analysis, were queried and compared with a respective NC cohort (ie, without the exposure) for the prospective risk of developing PD, AD or CVD. Only those with at least 5 years of prospective follow-up were included, and were propensity score matched for age, sex, race and ethnicity, and additionally for a set of potential risk factors and risk modifiers for the development of PD, AD and CVD: arterial hypertension, diabetes mellitus, atrial fibrillation and flutter, and nicotine dependence.

### Statistical analysis

In the case-control analyses, patients were counted as positive for an exposure if the respective ICD-10 code was documented any time before the first diagnosis of PD or the control health event. To approximate the diagnostic interval between each exposure and the first PD diagnosis, a yearly cross sectional prevalence for each exposure was calculated for the PD and NC groups, up to 6 years before the index event. To detect and quantify potential surveillance bias in our case-control analyses, we collected an agnostic set of negative exposures (Charlson comorbidities). This allowed us to determine the OR that should be considered as indicative of no association. Additionally, we collected positive exposures based on a previous case-control study that identified prodromal motor and non-motor symptoms of PD.[24] This enabled us to assess the ability of our dataset to reproduce existing associations. The coding can be found in the online supplemental methods.

In the cohort analyses, patients diagnosed with the exposure of interest and their NCs were counted as positive for an outcome

**Table 1** Baseline characteristics for subjects with PD and controls in the case-control analyses after pairwise matching.

| Characteristic * | Patients (n (%)) | | | | | |
|---|---|---|---|---|---|---|
| | Parkinson's disease (n=24 624) | Negative controls (n=24 624) | Parkinson's disease (n=19 046) | Alzheimer's disease (n=19 046) | Parkinson's disease (n=23 942) | Cerebrovascular diseases (n=23 942) |
| Age | | | | | | |
| Age (years) (mean (SD)) | 70.8 (8.49) | 70.3 (8.68) | 72.7 (7.93) | 73.4 (7.99) | 70.8 (8.51) | 70.6 (8.68) |
| Sex | | | | | | |
| Men | 14 254 (57.89) | 14 254 (57.89) | 9948 (52.23) | 9979 (52.39) | 13 874 (57.95) | 13 874 (57.95) |
| Women | 10 103 (41.03) | 10 103 (41.03) | 8869 (46.57) | 8835 (46.39) | 9801 (40.94) | 9801 (40.94) |
| Unknown | 267 (1.08) | 267 (1.08) | 229 (1.2) | 232 (1.22) | 267 (1.12) | 267 (1.12) |
| Race | | | | | | |
| White | 20 476 (83.15) | 20 476 (83.15) | 15 458 (81.16) | 15 461 (81.18) | 19 906 (83.14) | 19 906 (83.14) |
| Black or African American | 1294 (5.26) | 1294 (5.26) | 1166 (6.12) | 1176 (6.17) | 1182 (4.94) | 1182 (4.94) |
| Other and unknown† | 2854 (11.59) | 2854 (11.59) | 2425 (12.73) | 2413 (12.67) | 2856 (11.93) | 2854 (11.92) |
| Ethnicity | | | | | | |
| Hispanic or Latino | 939 (3.81) | 939 (3.81) | 810 (4.25) | 806 (4.23) | 942 (3.93) | 942 (3.93) |
| Not Hispanic of Latino | 19 746 (80.19) | 19 746 (80.19) | 15 419 (80.96) | 15 411 (80.91) | 19 771 (82.58) | 19 771 (82.58) |
| Unknown | 3939 (16) | 3939(16) | 2817 (14.79) | 2829 (14.85) | 3229 (13.49) | 3229 (13.49) |

*Characteristics were identified using electronic medical health record data from the TriNetX Research Network. Baseline characteristics before matching can be found in online supplemental table 1, and p values and standardised mean differences between groups in online supplemental table 2.
†Includes Asian, American Indian, Alaska Native, Native Hawaiian or other Pacific islander, or unknown.

(PD, AD or CVD) if the respective new onset ICD-10 diagnosis occurred within a 5 year follow-up. Subjects who already had the outcome of interest before the index event were excluded after propensity score matching.

Exposures and outcomes were collected as absolute numbers; ORs and RRs were calculated with 95% CIs. Standardised mean differences (SMDs) were used to compare baseline characteristics; an SMD of <0.2 was considered well balanced. A Pearson $\chi^2$ test was calculated to compare outcomes, and a two sided P value of <0.05 was used to indicate statistical significance. Correction for false discovery rate (FDR) was performed using the step up procedure by Benjamini and Yekutieli, with the Stats package in R (V.4.3.0).[25]

## RESULTS

For the case control-study, 24 624 patients with PD met all of the criteria and were matched with 8 267 744 NCs, and 36 187 AD and 528 207 CVD patients, giving 24 624 patients in the comparison with NCs, 19 046 with AD and 23 942 with CVD. Baseline characteristics after pairwise matching are presented in table 1; minimal differences in age at index persisted. SMDs and p values before and after matching can be found in online supplemental tables 1,2.

The results of the case-control analyses are presented in figure 1 and online supplemental table 3. All GI syndromes were significantly increased in the PD group compared with NCs (OR >1; p<0.05). However, only dysphagia (OR 3.58), GP (OR 4.64), FD (OR 3.39), intestinal pseudo-obstruction (OR 3.01), diarrhoea (OR 2.85), constipation (OR 3.32), IBS-C (OR 4.11), IBS-D (OR 4.31), IBS without diarrhoea (OR 3.53) and FI (OR 3.76) gave ORs that were numerically greater than the upper limit of the negative exposures (OR range 1.20–2.79; online supplemental tables 4–6 and online supplemental figures 1–3). Furthermore, only dysphagia, GP, IBS-C, IBS without diarrhoea and constipation were specific for PD (OR >1; p<0.05) when compared with both the AD and CVD group. After correcting for FDR, GP and constipation did not remain significantly different (p>0.05) compared with the CVD and AD groups, respectively. Other exposures were not only significantly associated with PD, but also showed strong associations with the AD or CVD group. For example, FI appeared to be equally increased before AD, and diarrhoea was even more increased before the onset of both AD and CVD.

For FD, IBS-D and intestinal pseudo-obstruction, the risk of PD, AD and CVD did not differ significantly (p>0.05). The remaining exposures, including achalasia (OR 1.92), GORD (OR 2.18), PI (OR 2.63), CD (OR 1.99), UC (OR 1.87), MC (OR 2.19) and appendectomy (OR 2.40) showed positive associations with PD compared with NCs, but gave ORs below the upper limit of what is expected by surveillance bias (OR range 1.20–2.79). Only for GORD and appendectomy we observed significant differences compared with AD (OR 1.14, p<0.0001) and CVD (OR 0.57, p=0.03), respectively. The latter did not remain significant after correction for FDR (p=0.21). Prior vagotomy did not impact the risk of PD.

For GP, women were approximately twice as likely as men to develop PD (OR 7.3 for women, 3.05 for men, both p<0.0001 (online supplemental tables 7–9 and online supplemental figure 4), and the OR for GP was especially high for early onset PD (online supplemental tables 10–11). Exclusion of previous antidopaminergic drug use did not significantly alter any associations with PD compared with NCs (online supplemental table 12 and online supplemental figure 5). The ORs of all PD specific exposures were positioned well within the range of those of established motor and non-motor prodromes of PD (ie, positive exposures; OR PD vs NCs 2.04–7.41). An approximation of the diagnostic interval for each exposure can be found in online supplemental figure 6.

Figure 2 and online supplemental tables 13–14 show the results of the cohort analyses. A significantly increased RR of new onset PD (RR >1; p<0.05) was found after a diagnosis of dysphagia (RR 2.27), GORD (RR 1.13), GP (RR 2.43), FD (RR 1.15), intestinal pseudo-obstruction (RR 1.84), diarrhoea (RR 1.32), constipation (RR 2.38), IBS without diarrhoea (RR 1.17) and FI (RR 1.74); all except for FD (p=0.09) remained significant after correction for FDR. However, only for dysphagia, GP, intestinal pseudo-obstruction, IBS without diarrhoea and constipation was this RR numerically higher than the RR of developing AD and

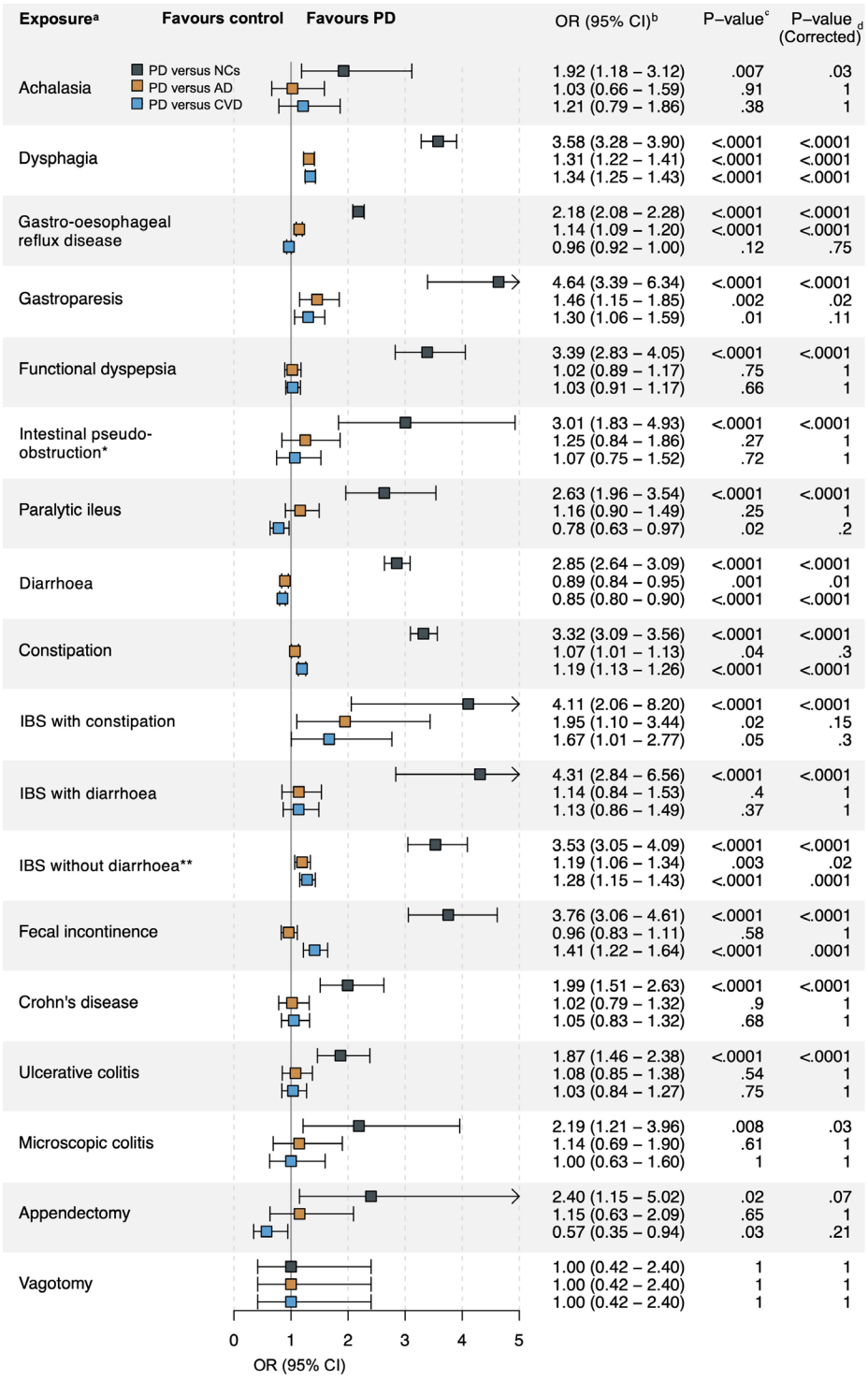


**Figure 1** Case-control analyses. Odds ratios (ORs) of previous exposures in patients with Parkinson's disease (PD) compared with matched negative controls (NCs), or patients with Alzheimer's disease (AD) and cerebrovascular diseases (CVD). [a]In the case-control analysis, the incidence of exposures was examined retrospectively (ie, before an initial diagnosis of PD compared with matched NCs, and AD and CVD patients). Patients were diagnosed with PD or the respective control health event between 1 January 2005 and 1 July 2021, and NCs were queried using two ambulatory visits during the same time window. Patients and exposures were identified with the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes, and Current Procedural Terminology (CPT) codes, using electronic medical health record data from the TriNetX research network (online supplemental methods). Exposures were included if they were documented any time before the diagnosis of PD or the control health event, in the available medical records. [b]ORs were calculated as follows: odds of documented exposure in the PD cohort/odds of documented exposure in the control cohort. Absolute rates can be found in online supplemental table 3. [c]P values were calculated using a Pearson $\chi^2$ test, after matching for baseline characteristics (ie, age, sex, race and ethnicity). [d]Correction for false discovery rate was performed using the step up procedure by Benjamini and Yekutieli, with the Stats package in R. *The term intestinal pseudo-obstruction was used as an approximate synonym for the ICD-10 code K59.8 other specified functional intestinal disorders.**The term IBS not otherwise specified is commonly used as an approximate synonym for the ICD-10 code K58.9 IBS without diarrhoea. IBS, irritable bowel syndrome.

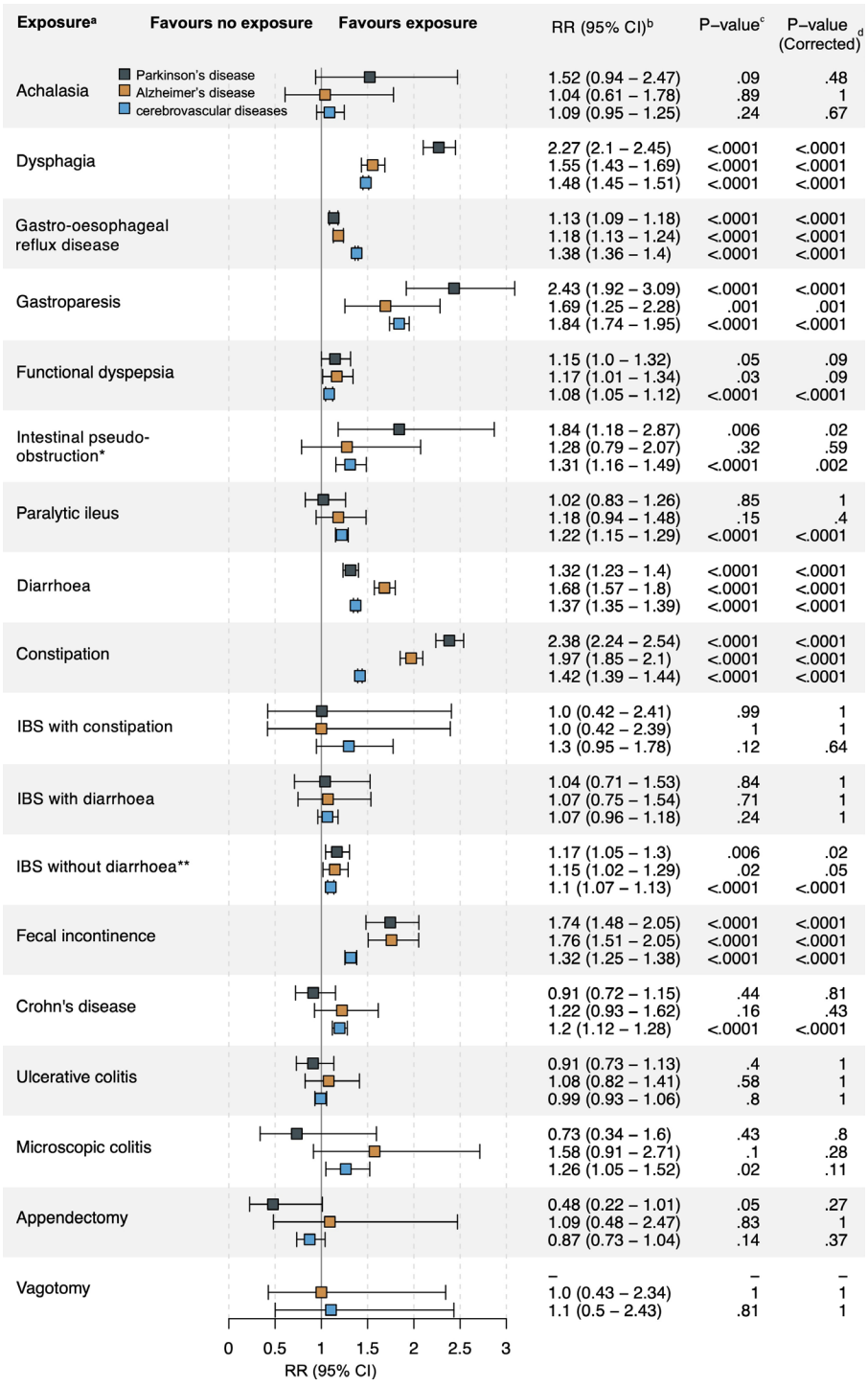


**Figure 2** Cohort analyses. Relative risks (RRs) of developing Parkinson's disease (PD), Alzheimer's disease (AD) or cerebrovascular diseases (CVD) within 5 years of the diagnosis of a given exposure, compared with negative control (NCs) without the respective exposure. [a]For each analysis, a cohort of patients identified by the diagnosis of a given exposure was compared with their respective NCs for the prospective risk of PD, AD and CVD within 5 years of the index event (ie, diagnosis of the given exposure, or a visit for NCs). After propensity score matching, patients that already had the investigated outcome (ie, PD, AD or CVD) documented before the index event were excluded from the analysis. Exposures and outcomes were identified using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10,) and Current Procedural Terminology (CPT) codes. Electronic medical health record data were collected from the TriNetX research network. Diagnostic coding can be found in the online supplemental methods. [b]RRs were calculated as follows: risk of outcome in the exposure cohort/risk of outcome in the control cohort. Absolute rates can be found in online supplemental table 13. [c]P values were calculated with a Pearson $\chi^2$ test, after matching for baseline characteristics and risk factors. Baseline characteristics included age, sex, race and ethnicity; risk factors included arterial hypertension, diabetes mellitus, atrial fibrillation and flutter, and nicotine dependence. [d]Correction for false discovery rate was performed with the step up procedure by Benjamini and Yekutieli, using the Stats package in R. *The term intestinal pseudo-obstruction was used as an approximate synonym for the ICD-10 code K59.8 other specified functional intestinal disorders. **The term IBS not otherwise specified is commonly used as an approximate synonym for the ICD-10 code K58.9 IBS without diarrhoea. IBS, Irritable bowel syndrome.

CVD, and statistical significance (p<0.05) was achieved only for constipation and dysphagia (online supplemental table 15). In line with the case control analyses, FI equally increased the risk of PD and AD (PD: RR 1.74; AD: RR 1.76, both p<0.0001), and in the GORD cohort the RR of developing CVD was higher than that of PD (CVD: RR 1.38; PD: RR 1.13, both p<0.0001). FD and diarrhoea were associated with all three disorders (p≤0.05), and PI, CD and MC only increased the risk of CVD (RR 1.22, p<0.0001; RR 1.20, p<0.0001; RR 1.26, p=0.02, respectively). Although no specific association was found in the case-control analysis, appendectomy significantly reduced the risk of developing PD (RR 0.48, p=0.05), which did not remain significant after correction for FDR. For all other exposures (ie, achalasia, UC, IBS-C, IBS-D and vagotomy), no significant associations were found.

## DISCUSSION

We used a nationwide EHR network to comprehensively investigate disorders across the entire GI tract before a diagnosis of PD. We used two complementary study designs to establish that dysphagia, gastroparesis, constipation and IBS without diarrhoea specifically increase the risk of a subsequent new onset diagnosis of idiopathic PD, even compared with other neurological diseases, such as AD and CVD.

Surveillance bias is an inherent problem in observational studies. When not addressed appropriately, it can compromise the validity of causal inference and lead to irreproducible results.[26] A broader implementation of empirical approaches to evaluate and correct for the presence of systematic error in observational studies is needed.[27] Therefore, we set up an approach to understand the true extent of surveillance bias in our study and its potential contribution to implicating premorbid factors for PD. Hence we collected data on all diagnoses included in the Charlson comorbidity index. These premorbid conditions were considered as a comprehensive set of agnostic negative exposures. In our case-control study, we observed statistically significant increases in most of these exposures in PD cases compared with NCs, but not compared with AD and CVD (online supplemental figure 1). To establish whether these increases represented surveillance bias or true associations (although unlikely based on the current literature), we investigated the same exposures for other neurological disorders (AD and CVD) compared with their NCs (online supplemental figure 3). Since the same significant correlations emerged, surveillance bias was likely. Subsequently, we determined the range of ORs that should be expected if they are a result of surveillance bias alone. These ORs ranged between 1.20 and 2.79 in the analysis of PD with NCs. To determine whether existing associations with PD could be replicated with ORs greater than those of negative exposures, we also collected prodromal motor and non-motor symptoms of PD (ie, positive exposures). These resulted in ORs ranging between 2.04 and 7.41 (online supplemental figure 1).

Having established a measure of surveillance bias in the case-control study, we then determined ORs for the putative GI pre/comorbidities of PD. Relative to the upper limit of the negative exposures, GI exposures fell into two categories. First were those for which the ORs overlapped with the ORs expected for surveillance bias (OR 1.20–2.79). For these exposures, including achalasia, GORD, PI, IBD (ie, CD, UC, and MC), appendectomy and vagotomy, we cannot be confident that these were true associations, although within the constraints of our study we cannot categorically state that they were not. Second were those for which the ORs were clearly higher than the ORs expected for surveillance bias (OR >2.79). For these exposures, including dysphagia, GP, FD, intestinal pseudo-obstruction, diarrhoea, constipation, IBS-C, IBS-D, IBS without diarrhoea and FI, we can confidently state to have established significant associations with new onset PD. To determine the specificity of the identified significant exposures for PD in the case-control analyses, we subsequently compared subjects with PD with subjects with AD and CVD. Only dysphagia, GP, constipation, IBS without diarrhoea and IBS-C remained specific for PD compared with both neurological diseases (table 2). Importantly, we cannot exclude the possibility that these factors might still be associated with these diseases, although at a smaller scale. Similarly, while other exposures were not specific for PD (ie, FD, intestinal pseudo-obstruction, diarrhoea, IBS-D and FI), we cannot strictly exclude the possibility that these conditions might still be risk factors for PD.

Finally, to validate these findings both in terms of their significance and specificity and establish one RR estimate of developing PD after the diagnosis of each exposure, we set up a complementary cohort study. Here, five exposures (ie, dysphagia, GP, IBS without diarrhoea, intestinal pseudo-obstruction and constipation) significantly increased the risk of PD and resulted in RRs that were numerically greater than those of AD and CVD

**Table 2** Summary of Parkinson's disease specific exposures in the case-control and cohort studies

| Outcome summary | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Case-control study** | | | | **Cohort study** | | | |
| **Exposures associated with a significantly increased OR of developing PD, compared with NCs, AD and CVD*** | **OR of developing PD compared with:** | | | **Exposures associated with a significantly increased RR of developing PD†, higher than that of AD and CVD‡** | **RR of developing:** | | |
| | **NCs** | **AD** | **CVD** | | **PD** | **AD** | **CVD** |
| Dysphagia | 3.58 (3.28–3.90) | 1.31 (1.22–1.41) | 1.34 (1.25–1.43) | Dysphagia§ | 2.27 (2.10–2.45) | 1.55 (1.43–1.69) | 1.48 (1.45–1.51) |
| Gastroparesis | 4.64 (3.39–6.34) | 1.46 (1.15–1.85) | 1.30 (1.06–1.59) | Gastroparesis | 2.43 (1.92–3.09) | 1.69 (1.25–2.28) | 1.84 (1.74–1.95) |
| Constipation | 3.32 (3.09–3.56) | 1.07 (1.01–1.13) | 1.19 (1.13–1.26) | Constipation§ | 2.38 (2.24–2.54) | 1.97 (1.85–2.10) | 1.42 (1.39–1.44) |
| IBS without diarrhoea¶ | 3.53 (3.05–4.09) | 1.19 (1.06–1.34) | 1.28 (1.15–1.43) | IBS without diarrhoea | 1.17 (1.05–1.30) | 1.15 (1.02–1.29) | 1.10 (1.07–1.13) |
| IBS with constipation | 4.11 (2.06–8.20) | 1.95 (1.10–3.44) | 1.67 (1.01–2.77) | Intestinal pseudo-obstruction** | 1.84 (1.18–2.87) | 1.28 (0.79–2.07) | 1.31 (1.16–1.49) |

*OR PD versus NCs and PD versus AD and PD versus CVD >1; p<0.05.
†RR PD >1; p<0.05.
‡RR PD>RRAD and RR PD>RR CVD.
§The RR of PD was significantly greater that the RR of AD and CVD (p<0.05).
¶The term IBS not otherwise specified is commonly used as an approximate synonym for the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code K58.9 IBS without diarrhoea.
**'The term intestinal pseudo-obstruction was used as an approximate synonym for the ICD-10 code K59.8 other specified functional intestinal disorders.
AD, Alzheimer's disease; CVD, cerebrovascular diseases; IBS, irritable bowel syndrome; NC, negative control; OR, odds ratio; PD, Parkinson's disease; RR, relative risk.

(table 2). Four of these provide internal validation for PD specific exposures identified in the case-control analysis. These exposures are thus very unlikely to be a result of selection or surveillance bias and can therefore be considered the most significant findings from our study. Minor discrepancies can be explained by intrinsic differences in the study designs.

The consistent correlation between constipation and PD (RR 2.38, 95% CI 2.24 to 2.54) confirms an abundance of existing literature. Previous reports have stated that constipation can even precede PD by up to 20 years.[28] More surprising is the strong association for dysphagia (RR 2.27, 95% CI 2.10 to 2.45), which has so far mainly been reported after its diagnosis.[1] The prevalence of oesophageal dysmotility in PD has been shown to be as high as 80% when using objective measures,[29] but a delay in oropharyngeal transit has also been found in drug naïve and subjectively asymptomatic phases of the disease.[30 31] While evidence supports that oropharyngeal function might be affected through brainstem and cortical areas,[6 29] post mortem studies by Mu *et al* showed that pharyngeal muscles, sensory neurons and motor neurons are also often affected by LB pathology in PD.[32 33] Interestingly, the highest RR was observed for GP (RR 2.43, 95% 1.92 to 3.09), a disorder characterised by delayed gastric emptying (GE) in the presence of symptoms such as nausea, vomiting, early satiety, postprandial fullness, belching and bloating, and the absence of mechanical obstruction.[34] As Braak *et al* hypothesised,[35] the multitude of gastric vagal connections makes GP an especially promising candidate as a biomarker of PD.[6]

Furthermore, despite considerable overlap in symptoms and pathology,[36] the lack of PD specificity for FD suggests that an established delay in GE in the presence of symptoms is more strongly associated with PD than symptoms alone, assuming that ICD codes are taken at face value. This indicates that objective changes in enteric physiology may provide a more reliable measure for evaluating enteric involvement in PD. Although the prevalence of delayed GE in PD has been reported to range from 70% to 100%,[37] reports of GP preceding PD remain anecdotal.[37] Because of its relatively low prevalence, it should not be a surprise that our study is the first to provide observational evidence that GP and dysphagia might precede PD.[5 6] More established is the association of IBS with the subsequent development of PD.[38–40] IBS-C and IBS without diarrhoea were both specifically increased in the case-control analysis, but only the latter was replicated in the cohort analysis (RR 1.17, 95% CI 1.05 to 1.3). Importantly, a Swedish study revealed that although the positive predictive value of ICD-10 codes for IBS is generally high (80–95%), their accuracy in indicating specific subtypes was considerably lower (55–67%).[41] Nevertheless, increased intestinal permeability constitutes a core pathophysiological mechanism in a major subset of IBS patients,[42] and has also been found in PD.[38] Routine colonoscopies for clinically suspect IBS could become important to determine the presence of LB pathology in patients at risk for PD, only if intestinal LB pathology becomes an established biomarker, which until now it has not.[39]

Although anorectal symptoms are among the most frequent GI symptoms in PD, our data suggest that the presence of FI might not distinguish between the development of PD and other neurodegenerative diseases.[43] Even if not prodromal to AD, our findings support the fact that the progression of cognitive decline in AD is frequently unmasked by FI.[44] While diarrhoea and FD increased the risk of all three diseases, intestinal pseudo-obstruction showed specificity for PD in the cohort analyses (RR 1.84, 95% CI 1.18 to 2.87). This disorder, characterised by impaired peristalsis and presumably caused by a neuropathy or myopathy, has been described in various neurological disorders, including PD.[45]

Finally, some exposures in the case-control analyses gave ORs in the range of those expected from surveillance bias. These exposures included achalasia, GORD, PI, IBD (ie, CD, UC, and MC), appendectomy and vagotomy. Other than for GORD, the cohort analyses also did not show any significant associations with PD for these exposures. While IBD has been linked to PD in various observational[46 47] and genetic studies,[48] neither of our study designs supported this link. However, we cannot strictly dismiss the possibility of an association based on this empirical surveillance bias cut-off and a relatively limited follow-up. In addition, we were unable to assess the impact of anti-tumour necrosis factor (anti-TNF) therapy exposure, which has been hypothesised to decrease the risk of PD.[49] Prospective studies are necessary to investigate this association and to establish whether anti-TNF therapy can effectively protect against PD. Notably, concordant with an earlier study that linked reflux oesophagitis to an increased risk of stroke and transient ischaemic attack in patients with atrial fibrillation,[21] the risk of CVD in our study was significantly greater after a diagnosis of GORD, CD and MC. These findings suggest that a better understanding of the link between GI inflammation and cerebrovascular events may lead to improved risk stratification and identification of new preventive strategies.[21]

After Grey *et al* first discovered that α-synuclein was most abundant in the appendiceal mucosa,[9] conflicting evidence has emerged about the impact of an appendectomy on PD risk. While three studies did not find any association,[11 14 50] one abstract reported an increased risk of PD[13] and two large observational studies supported a protective effect.[10 12] Despite our limited follow-up and sample size compared with the aforementioned studies, we observed a relative risk reduction of 52% in our cohort analysis, while the case-control analysis was likely underpowered to detect any consistent association for appendectomy. Multiple studies suggest that the appendix constitutes a prominent source of seeding competent pathologically folded α-synuclein,[10] and houses bacteria capable of releasing inflammatory mediators.[10] The subsequent migration of α-synuclein to the CNS has been substantiated by studies showing a protective effect of a truncal vagotomy on PD development.[15 16] Compared with these reports, our study was underpowered to detect any consistent associations for vagotomy.[15 16]

Finally, we attempted to assess the proximity of each diagnosis to the diagnosis of PD in the case-control study (online supplemental figure 5). We found that the OR for dysphagia and constipation decreased considerably as the distance from the diagnosis of PD increased, while the OR for GP and IBS without diarrhoea remained relatively constant. This suggests that differences in lead time exist, but future longitudinal population based studies will be crucial to determine whether these PD specific GI syndromes are part of the early manifestation of PD or truly precede the disease. Importantly, the combination of two complementary study designs reduced the potential for selection bias. The case-control analysis consisted of patients with PD, AD or CVD without the requirement of any previous exposure, while the cohort analyses consisted of patients with newly diagnosed GI exposures without the requirement of a subsequent PD, AD or CVD diagnosis. This study is subject to intrinsic limitations of EHR data, including unknown completeness of records and absent validation of diagnoses. The multicentre character and inclusion of racially and ethnically diverse subjects ensured that these results are generalisable to patients at academic medical centres across the USA.

## CONCLUSION

This study is the first to establish substantial observational evidence that the clinical diagnosis of not only constipation, but also dysphagia, GP and IBS without diarrhoea might specifically predict the development of PD, whereas other exposures were less specific. An appendectomy appeared protective, leading to further speculation about its role in PD pathophysiology. These findings warrant alertness for GI syndromes in patients at higher risk for PD and highlight the need for further investigation of GI precedents in AD and CVD. To establish a stronger body of clinicopathological evidence, we advocate for future studies to assess the sensitivity and specificity of these disorders and their clinicopathological correlates for the early detection of neuropathology.

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**Contributors** BK: conceptualisation, methodology, formal analysis, data curation, validation, visualisation, writing-original draft, and writing-review and editing. LV: conceptualisation, resources, and investigation. JV: conceptualisation, methodology, and visualisation. GB: conceptualisation, resources, and investigation. RB: conceptualisation, resources, and investigation. MM: conceptualisation. KH: conceptualisation, methodology, and validation. GY: methodology and formal analysis. JT: writing-review and editing. PJP: guarantor, supervision, conceptualisation, methodology, validation, and writing-review and editing.

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**Data availability statement** Data are available upon reasonable request. Data exported from TriNetX were saved in Excel files and archived. Every co-author affiliated to Johns Hopkins University was granted access to the TriNetX Research network by the Institute of Clinical and Translational Research (ICTR). The online supplemental materials contain an extensive list of tables representing the original data; researchers will be granted access to the original aggregated data upon reasonable request, with agreement of the corresponding author (PJP).



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**Online supplemental material**

# "Gastrointestinal syndromes preceding the diagnosis of Parkinson's disease: testing Braak's hypothesis using a nationwide database for comparison with Alzheimer's and cerebrovascular disease"

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**Supplemental Figure 5:** ORs of prior exposures in patients with PD compared to NCs, after exclusion of patients with prescriptions of antidopaminergic drugs

**Supplemental Figure 6:** Heatmap of the cross-sectional prevalence of each exposure every year prior to the index event



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**Supplemental methods**

### 1. Queries case-control study

**Query Parkinson's disease (PD):** The PD group consisted of those who had a first diagnosis of Parkinson's disease (G20) between the age of 50 and 90, and an ambulatory visit preceding this diagnosis by at least 2 years, occurring between Jan 1, 2005 and July 1, 2021. For each patient, two or more prescriptions of any antiparkinsonian drug (levodopa, carbidopa, pramipexole, ropinirole, rotigotine, apomorphine, selegiline, rasagiline, safinamide, zonisamide, entacapone, opicapone, tolcapone, anticholinergics, amantadine, istradefylline or clozapine [1]) on or after Jan 1, 2005 were required. Secondary causes of PD were excluded: secondary Parkinsonism (G21), 'Other drug induced secondary Parkinsonism' (G21.1), 'Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders' (F20-F29), Dementia (F01-F03) and young onset Parkinson's disease (G20 under the age of 50) [1]. To investigate prodromal events (GI disorders, vagotomy and appendectomy), the first diagnosis of PD was used as the index event.

**Query Alzheimer's disease (AD)**: The AD group consisted of those who had a first diagnosis of Alzheimer's disease (G30) between the age of 50 and 90, and an ambulatory visit preceding this diagnosis by at least 2 years, occurring between Jan 1, 2005 and July 1, 2021. Patients with a diagnosis of dementia prior to their first AD diagnosis were excluded. The first diagnosis of AD was used as the index event, to investigate prior exposures.

**Query cerebrovascular diseases (CVD)**: The CVD group consisted of those who had a first diagnosis of cerebrovascular disease (I60-I69) between the age of 50 and 90, and an ambulatory visit preceding this diagnosis by at least 2 years, occurring between Jan 1, 2005 and July 1, 2021. Patients with a diagnosis of dementia prior to their first CVD diagnosis were excluded. The first diagnosis of CVD was used as the index event, to investigate prior exposures.

**Query negative controls (NCs)**: A negative control group was queried by selecting all patients with 2 subsequent ambulatory visits between the age of 50 and 90 years old at least two years apart, occurring between Jan 1, 2005 and July 1, 2021. For the comparison between PD and NCs, patients with a diagnosis of PD were excluded from the negative control population. For the comparison between AD and CVD with their NCs, patients with the diagnosis of AD and CVD were excluded from the negative control population, respectively. Patients and NCs were propensity score matched for age (at the index event), sex, race and ethnicity.

### 2. Queries cohort study

**Query exposure cohort**: For each of the exposures included in the case-control study design (achalasia, dysphagia, gastro-esophageal reflux disease (GERD), gastroparesis (GP), functional dyspepsia (FD), intestinal pseudo-obstruction (other specified functional intestinal disorders), paralytic ileus (PI), diarrhoea, irritable bowel syndrome with constipation (IBS), irritable bowel syndrome with diarrhoea (IBS), IBS without diarrhoea, fecal incontinence (FI), Crohn's disease (CD), ulcerative colitis (UC), microscopic colitis (MC), appendectomy, and vagotomy), a cohort was created using the following generic design: patients with a diagnosis of exposure x on or after the age of 18 were selected using the appropriate diagnostic/procedural code. The diagnosis of the exposure was used as the index event. For each patient, an ambulatory visit at least 5 years after the diagnosis of exposure x was required, thereby ensuring 5 years of prospective follow-up after the index event to investigate the development of PD, AD and CVD.

**Query Negative control cohort**: Negative controls for each exposure were queried by selecting all patients with 2 subsequent ambulatory visits at least 5 years apart on or after the age of 18, without the diagnosis of the respective exposure. Patients and NCs were propensity score matched for age (at the index event), sex, race and ethnicity, and 4 risk factors or risk modifiers: diabetes mellitus (E8-E13), arterial hypertension (I10), atrial fibrillation and flutter (I48), and nicotine dependence (F17).

### 3. Supplementary Methods

**Data source:** TriNetX Analytics provides real-time access to aggregated longitudinal data, anonymized at a patient and organizational level. Captured information includes demographics,



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diagnoses, procedures, medications, and visits from patients independent of insurance status. Structured data in the medical records is mapped to standard and controlled clinical terms in the database and is formatted in the most updated version of the of International Classification of Disease (ICD-10), Current Procedural Terminology (CPT 2021 version), Health Common Procedure Coding System (HCPCS 2021 version), Systematized Nomenclature of Medicine (SNOMED-CT 2021 version), the RxNorm coding language and native TriNetX (TNX) codes, allowing for reliable comparison of data between participating medical centers. ICD-9 codes are mapped to corresponding ICD-10 codes. These codes can be used as in- and exclusion criteria to define and query patient cohorts, after which they can be matched for confounding factors using a built-in propensity score matching (PSM) algorithm. An index event is chosen for each cohort to determine starting point for the collection of outcomes over a predefined retrospective or prospective follow-up. The Institute of Clinical and Translational Research (ICTR) manages the TriNetX platform at our institution and provides access to the end-users. The use of aggregated, de-identified data did not require institutional board (IRB) review. Results were reported according to the STROBE guidelines. For the case-control study design, all analyses were conducted between 08.09.2021 and 08.15.2021. For the cohort study design, all analyses were conducted between 12.20.2021 and 12.26.2021.

**Propensity score matching**: Cohorts were matched using a built-in propensity score matching tool in TriNetX. A propensity score for each covariate in each patient was calculated by logistic regression performed using the scikit-learn package in Python (version 3.7). Greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations of the aggregated propensity scores was used to create 1:1 matched subsets of patients. A randomization of the order of records was performed before performing nearest neighbor matching to reduce bias caused by order of rows in each covariate matrix after to centralization of pooled covariate matrices from each participating HCO.

**Exposures (or outcomes) of interest**: Achalasia, dysphagia, gastro-esophageal reflux disease (GERD), gastroparesis (GP), functional dyspepsia (FD), intestinal pseudo-obstruction (other specified functional intestinal disorders), paralytic ileus (PI), diarrhoea, irritable bowel syndrome with constipation (IBS), irritable bowel syndrome with diarrhoea (IBS), IBS without diarrhoea, fecal incontinence (FI), Crohn's disease (CD), ulcerative colitis (UC), microscopic colitis (MC), appendectomy, vagotomy. To increase the sensitivity of detecting early signs of constipation, laxatives were included as well: bulk-forming laxatives, hyperosmotic laxatives, lubricant laxatives, stimulant laxatives, and stool softeners. Other GI drugs with antidopaminergic properties were collected, including: domperidone, prochlorperazine, promethazine, metoclopramide. Coding can be found in the table below.

**Stratified analyses (case-control study design)**: For every analysis (PD vs NCs; PD vs AD; PD vs CVD), stratified results for sex were collected. For the analysis comparing PD with NCs, stratified analyses were also created based on the age at the index event (i.e., diagnosis of PD for cases; second ambulatory visit for NCs). Additionally, for each exposure, the cross-sectional period-prevalence was collected for each respective year before the diagnosis of PD. Follow-up for the time window under consideration was ensured for both the PD and NC cohort by only including the subset of patients that had an ambulatory visit at the beginning of the time window under consideration. Because of limited data-availability more than 6 years prior to the index event, this cross-sectional analysis was only conducted up to 6 years before the index event. Important to note is that for all supplementary analyses, the disease groups were re-queried from the network with an additional criterium (sex or age) and were subsequently re-matched to NCs. The sum of the absolute numbers in the sensitivity analyses therefore might differ ever so slightly from those reported in the primary analyses. These secondary analyses were pulled from the network during the same day as the primary analyses, as to minimize any differences based on the time of data collection. Furthermore, to investigate the impact of antidopaminergic drug use on outcomes, a sensitivity analyses was conducted where the use of several antidopaminergic drugs (i.e. domperidone, prochlorperazine, promethazine, metoclopramide) was formally excluded in the analysis between PD vs NCs.

**Positive exposures**: To detect potential surveillance bias, the following motor- and non-motor symptoms were collected: fatigue, dizziness, depression, shoulder pain or stiffness, anxiety, neck pain or stiffness, urinary dysfunction, erectile dysfunction, insomnia, balance impairments, hypotension and memory problems. Comorbidities in the Charlson Comorbidity index were used as an agnostic set of **negative exposures**.

**4. Codes used to identify diagnoses and exposures of interest:**

| Code language | Code | Term |
|---|---|---|
| **Ambulatory visit (*)** | | |
| **TNX** | visit: ambulatory | |
| **CPT** | 99202 | Office or other outpatient visit for the evaluation and management of a new patient. which requires a medically appropriate history and/or examination and straightforward medical decision making. When using time for code selection. 15-29 minutes of total time is spent on the date of the encounter). |
| | 99203 | Office or other outpatient visit for the evaluation and management of a new patient. which requires a medically appropriate history and/or examination and low level of medical decision making. When using time for code selection. 30-44 minutes of total time is spent on the date of the encounter. |
| | 99204 | Office or other outpatient visit for the evaluation and management of a new patient. which requires a medically appropriate history and/or examination and moderate level of medical decision making. When using time for code selection. 45-59 minutes of total time is spent on the date of the encounter. |
| | 99205 | Office or other outpatient visit for the evaluation and management of a new patient. which requires a medically appropriate history and/or examination and high level of medical decision making. When using time for code selection. 60-74 minutes of total time is spent on the date of the encounter. |
| | 99211 | Office or other outpatient visit for the evaluation and management of an established patient. that may not require the presence of a physician or other qualified health care professional. Usually. the presenting problem(s) are minimal. |
| | 99212 | Office or other outpatient visit for the evaluation and management of an established patient. which requires a medically appropriate history and/or examination and straightforward medical decision making. When using time for code selection. 10-19 minutes of total time is spent on the date of the encounter. |
| | 99213 | Office or other outpatient visit for the evaluation and management of an established patient. which requires a medically appropriate history and/or examination and low level of medical decision making. When using time for code selection. 20-29 minutes of total time is spent on the date of the encounter. |
| | 99214 | Office or other outpatient visit for the evaluation and management of an established patient. which requires a medically appropriate history and/or examination and moderate level of medical decision making. When using time for code selection. 30-39 minutes of total time is spent on the date of the encounter. |
| | 99215 | Office or other outpatient visit for the evaluation and management of an established patient. which requires a medically appropriate history and/or examination and high level of medical decision making. When using time for code selection. 40-54 minutes of total time is spent on the date of the encounter. (For services 55 minutes or longer. see Prolonged Services 99XXX) |
| **Antiparkinsonian drugs** | | |

| | | |
|---|---|---|
| **TNX** | 6375 | levodopa |
| | 2019 | carbidopa |
| | 746741 | pramipexole |
| | 72302 | ropinirole |
| | 616739 | rotigotine |
| | 1043 | apomorphine |
| | 9639 | selegiline |
| | 134748 | rasagiline |
| | 1922448 | safinamide |
| | 39998 | zonisamide |
| | 60307 | entacapone |
| | 2362167 | opicapone |
| | 72937 | tolcapone |
| | AU350 | parasympatholytics |
| | 620 | amantadine |
| | 2199015 | istradefylline |
| | 2626 | clozapine |
| **Dementia** | | |
| **ICD-10** | F02 | Dementia in other diseases classified elsewhere |
| | F03 | Unspecified dementia |
| | F01 | Vascular dementia |
| **Matching covariates (cohort-analysis)** | | |
| **ICD-10** | E08-E13 | Diabetes Mellitus |
| | I10 | Arterial (essential) hypertension |
| | I48 | Atrial fibrillation and flutter |
| | F17 | Nicotine dependence |
| **Exposures** | | |
| **ICD-10** | K22.0 | Achalasia |
| | R13.1 | Dysphagia |
| | K21 | GERD |
| | K31.84 | Gastroparesis |
| | K30 | Functional dyspepsia |
| | K59.8 | Other specified functional intestinal disorders* |
| | K56.0 | Paralytic ileus |
| | R19.7 | Diarrhoea |
| | K59.0 | Constipation |
| | K58.1 | IBS with constipation |
| | K58.0 | IBS with diarrhoea |

| | | |
|---|---|---|
| | K58.9 | IBS without diarrhoea |
| | R15 | Fecal incontinence |
| | K50 | Crohns disease |
| | K51 | Ulcerative colitis |
| | K52.83 | Microscopic colitis |
| | 008Q | Vagotomy |
| **TNX** | 1014622 | Appendectomy |
| | GA202 | Hyperosmotic laxatives |
| | GA204 | Stimulant laxatives |
| | GA201 | Bulk-forming laxatives |
| | GA205 | Stool softener |
| | 3626 | Domperidone |
| | 8704 | Prochlorperazine |
| | 8745 | Promethazine |
| | 6915 | Metoclopramide |
| **Positive exposures: prodromal motor- and non-motor symptoms** | | |
| **ICD-10** | R53.8 | Fatigue (other fatigue and malaise) |
| | R42 | Dizziness (Dizziness and giddiness) |
| | F32 | Depression (major depressive disorder, single episode) |
| | F33 | Depression (major depressive disorder, recurrent) |
| | M25.51 | Shoulder pain |
| | M25.61 | Shoulder stiffness |
| | F41 | Anxiety (other anxiety disorders) |
| | M54.2 | Neck pain (cervicalgia) |
| | M25.60 | Neck stiffness (stiffness of unspecified joint) |
| | N30-N39 | Urinary dysfunction (other diseases of the urinary system) |
| | N52 | Erectile dysfunction (male erectile dysfunction) |
| | G47.0 | Insomnia (insomnia) |
| | R26 | Balance impairments (abnormalities of gait and mobility) |
| | I95 | Hypotension (hypotension) |
| | R41.3 | Memory problems (other amnesia) |
| **Negative exposures: charleson comorbidities** | | |
| **ICD-10** | I50 | Heart failure |
| | I21 | Acute myocardial infarction |
| | I73.9 | Peripheral vascular disease, unspecified |
| | K76.6 | Portal hypertension |
| | K74 | Fibrosis and cirrhosis of liver |
| | N18 | Chronic kidney disease (CKD) |

| | | |
|---|---|---|
| | N17 | Acute kidney failure |
| | N18.6 | End stage renal disease |
| | G82 | Paraplegia (paraparesis) and quadriplegia (quadriparesis) |
| | B20 | Human immunodeficiency virus [HIV] disease |
| | M06.09 | Rheumatoid arthritis, unspecified |
| | K27 | Peptic ulcer, site unspecified |
| | J44 | Chronic obstructive pulmonary disease, unspecified |
| | E10.9 | DM I without complications |
| | E11 | DM II |
| | C80.1 | Malignant (primary) neoplasm, unspecified |
| | C79.9 | Secondary malignant neoplasm of unspecified site |

* 'Intestinal pseudo-obstruction (acute/chronic)' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.



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**Supplemental tables**

**Supplemental Table 1. Baseline characteristics for subjects with PD and controls in the case-control analyses, before matching.**

| | Patients, No. (%) | | | | P-value[b] | | | SMD[c] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic[a]** | **PD (n = 24 624)** | **NC (n = 8 267 744)** | **AD (n = 36 187)** | **CVD (n = 528 207)** | **PD vs NC** | **PD vs AD** | **PD vs CVD** | **PD vs NC** | **PD vs AD** | **PD vs CVD** |
| **Age** | | | | | | | | | | |
| Age; mean (SD); y | 70.8 ± 8.49 | 63.7 ± 8.99 | 76.4 ± 7.56 | 68.5 ± 9.43 | <0.0001 | <0.0001 | <0.0001 | 0.7899 | -0.7044 | 0.2449 |
| **Sex** | | | | | | | | | | |
| Male | 14,254 (57.89) | 3,586,633 (43.38) | 13,397 (37.02) | 250,346 (47.4) | <.0001 | <.0001 | <.0001 | 0.3223 | 0.4683 | 0.2329 |
| Female | 10,103 (41.03) | 4,635,580 (56.07) | 22,418 (61.95) | 269,617 (51.04) | <.0001 | <.0001 | <.0001 | -0.3345 | -0.4687 | -0.2229 |
| Unknown sex | 267 (1.08) | 45,531 (.55) | 372 (1.03) | 8,244 (1.56) | <.0001 | <.0001 | <.0001 | 0.3765 | 0.0264 | -0.2054 |
| **Race** | | | | | | | | | | |
| White | 20,476 (83.15) | 6,157,753 (74.48) | 27,354 (75.59) | 398,126 (75.37) | <.0001 | <.0001 | <.0001 | 0.2898 | 0.2571 | 0.2635 |
| Black | 1,294 (5.26) | 923,250 (11.17) | 4,256 (11.76) | 74,454 (14.1) | <.0001 | <.0001 | <.0001 | -0.4511 | -0.4834 | -0.5976 |
| Other or unknown race | 2,854 (11.59) | 1,186,741 (14.35) | 4,577 (12.65) | 55,627 (10.53) | <.0001 | <.0001 | <.0001 | -0.1347 | -0.0544 | -0.0923 |
| **Ethnicity** | | | | | | | | | | |
| Hispanic or Latino | 939 (3.81) | 412,592 (4.99) | 1,838 (5.08) | 29,623 (5.61) | <.0001 | <.0001 | <.0001 | -0.1551 | -0.1653 | -0.2237 |
| Not Hispanic or Latino | 19,746 (80.19) | 5,953,446 (72.01) | 28,308 (78.23) | 429,725 (81.36) | <.0001 | <.0001 | 0.05 | 0.2499 | 0.0658 | -0.0414 |
| Unknown ethnicity | 3,939 (16.) | 1,901,706 (23.) | 6,041 (16.69) | 68,859 (13.04) | <.0001 | <.0001 | <.0001 | -0.2482 | -0.0281 | 0.1319 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; SMD, Standardized mean difference

[a] Characteristics were identified using electronic medical health record data from the TriNetX Research Network.

[b] P-value of the PD group compared to the respective control group. P-values were calculated using a Pearson Chi-Squared test for categorical variables and an unpaired t-test for continuous variables.

[c] Standardized mean difference compared to PD.

**Supplemental Table 2. Baseline characteristics for subjects with PD and controls in the case-control analyses, after matching.**

| | Patients, No (%) | | | | Patients, No (%) | | | | Patients, No (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic[a]** | **PD (n = 24,624)** | **NC (n = 24,624)** | **P-value[b]** | **SMD[c]** | **PD (n = 19,046)** | **AD (n = 19,046)** | **P-value** | **SMD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **P-value** | **SMD** |
| **Age** | | | | | | | | | | | | |
| Age; mean (SD); y | 70.8 (8.49) | 70.3 (8.68) | <0.0001 | 0.0582 | 72.7 (7.93) | 73.4 (7.99) | <0.0001 | -0.0879 | 70.8 (8.51) | 70.6 (8.68) | 0.01 | 0.0233 |
| **Sex** | | | | | | | | | | | | |
| Male | 14,254 (57.89) | 14,254 (57.89) | 1 | 0 | 9,948 (52.23) | 9,979 (52.39) | 0.83 | -0.0036 | 13,874 (57.95) | 13,874 (57.95) | 1 | 0 |
| Female | 10,103 (41.03) | 10,103 (41.03) | 1 | 0 | 8,869 (46.57) | 8,835 (46.39) | 0.8 | 0.004 | 9,801 (40.94) | 9,801 (40.94) | 1 | 0 |
| Unknown sex | 267 (1.08) | 267 (1.08) | 1 | 0 | 229 (1.2) | 232 (1.22) | 0.89 | -0.0028 | 267 (1.12) | 267 (1.12) | 1 | 0 |
| **Race** | | | | | | | | | | | | |
| White | 20,476 (83.15) | 20,476 (83.15) | 1 | 0 | 15,458 (81.16) | 15,461 (81.18) | 0.99 | -0.0006 | 19,906 (83.14) | 19,906 (83.14) | 1 | 0 |
| Black | 1,294 (5.26) | 1,294 (5.26) | 1 | 0 | 1,166 (6.12) | 1,176 (6.17) | 0.84 | -0.005 | 1,182 (4.94) | 1,182 (4.94) | 1 | 0 |
| Other or unknown race | 2,854 (11.59) | 2,854 (11.59) | 1 | 0 | 2,425 (12.73) | 2,413 (12.67) | 0.86 | 0.003 | 2,856 (11.93) | 2,854 (11.92) | 0.98 | 0 |
| **Ethnicity** | | | | | | | | | | | | |
| Hispanic or Latino | 939 (3.81) | 939 (3.81) | 1 | 0 | 810 (4.25) | 806 (4.23) | 0.92 | 0.0029 | 942 (3.93) | 942 (3.93) | 1 | 0 |
| Not Hispanic or Latino | 19,746 (80.19) | 19,746 (80.19) | 1 | 0 | 15,419 (80.96) | 15,411 (80.91) | 0.96 | 0.0015 | 19,771 (82.58) | 19,771 (82.58) | 1 | 0 |
| Unknown ethnicity | 3,939 (16.) | 3,939 (16.) | 1 | 0 | 2,817 (14.79) | 2,829 (14.85) | 0.87 | -0.0028 | 3,229 (13.49) | 3,229 (13.49) | 1 | 0 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; SMD, Standardized mean difference

[a] Characteristics were identified using electronic medical health record data from the TriNetX Research Network.

[b] P-value of the PD group compared to the respective control group. P-values were calculated using a Pearson Chi-Squared test for categorical variables and an unpaired t-test for continuous variables.

[c] Standardized mean difference compared to PD.

**Supplemental Table 3. ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, AD or CVD patients**

| | OR (95% CI) [b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure [a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NC (n = 24,624)** | **Uncorrected [c]** | **Corrected [d]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **Uncorrected** | **Corrected** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **Uncorrected** | **Corrected** |
| **Esophagus** | | | | | | | | | | | | | | | |
| Achalasia | 1.92 (1.18 - 3.12) | 48 (.19) | 25 (.1) | 0.007 | 0.03 | 1.03 (0.66 - 1.59) | 41 (.22) | 40 (.21) | 0.91 | 1 | 1.21 (0.79 - 1.86) | 46 (.19) | 38 (.16) | 0.38 | 1 |
| Dysphagia | 3.58 (3.28 - 3.90) | 2,321 (9.43) | 696 (2.83) | <.0001 | <.0001 | 1.31 (1.22 - 1.41) | 1,830 (9.61) | 1,427 (7.49) | <.0001 | <.0001 | 1.34 (1.25 - 1.43) | 2,246 (9.38) | 1,721 (7.19) | <.0001 | <.0001 |
| GERD | 2.18 (2.08 - 2.28) | 6,375 (25.89) | 3,401 (13.81) | <.0001 | <.0001 | 1.14 (1.09 - 1.20) | 5,098 (26.77) | 4,613 (24.22) | <.0001 | <.0001 | 0.96 (0.92 - 1.00) | 6,193 (25.87) | 6,367 (26.59) | 0.12 | 0.75 |
| **Stomach** | | | | | | | | | | | | | | | |
| Gastroparesis | 4.64 (3.39 - 6.34) | 221 (.9) | 48 (.19) | <.0001 | <.0001 | 1.46 (1.15 - 1.85) | 170 (.89) | 117 (.61) | 0.002 | 0.02 | 1.30 (1.06 - 1.59) | 218 (.91) | 168 (.7) | 0.01 | 0.11 |
| Functional dyspepsia | 3.39 (2.83 - 4.05) | 517 (2.1) | 155 (.63) | <.0001 | <.0001 | 1.02 (0.89 - 1.17) | 413 (2.17) | 404 (2.12) | 0.75 | 1 | 1.03 (0.91 - 1.17) | 510 (2.13) | 496 (2.07) | 0.66 | 1 |
| **Intestine** | | | | | | | | | | | | | | | |
| Paralytic ileus | 2.63 (1.96 - 3.54) | 160 (.65) | 61 (.25) | <.0001 | <.0001 | 1.16 (0.90 - 1.49) | 131 (.69) | 113 (.59) | 0.25 | 1 | 0.78 (0.63 - 0.97) | 156 (.65) | 199 (.83) | 0.02 | 0.2 |
| Diarrhoea | 2.85 (2.64 - 3.09) | 2,395 (9.73) | 896 (3.64) | <.0001 | <.0001 | 0.89 (0.84 - 0.95) | 1,893 (9.94) | 2,095 (11.) | 0.001 | 0.01 | 0.85 (0.80 - 0.90) | 2,298 (9.6) | 2,660 (11.11) | <.0001 | <.0001 |
| Constipation | 3.32 (3.09 - 3.56) | 3,298 (13.39) | 1,096 (4.45) | <.0001 | <.0001 | 1.07 (1.01 - 1.13) | 2,677 (14.06) | 2,530 (13.28) | 0.04 | 0.3 | 1.19 (1.13 - 1.26) | 3,173 (13.25) | 2,721 (11.36) | <.0001 | <.0001 |
| IBS-C | 4.11 (2.06 - 8.20) | 41 (.17) | 10 (.04) | <.0001 | <.0001 | 1.95 (1.10 - 3.44) | 35 (.18) | 18 (.09) | 0.02 | 0.15 | 1.67 (1.01 - 2.77) | 40 (.17) | 24 (.1) | 0.05 | 0.3 |
| IBS-D | 4.31 (2.84 - 6.56) | 116 (.47) | 27 (.11) | <.0001 | <.0001 | 1.14 (0.84 - 1.53) | 92 (.48) | 81 (.43) | 0.4 | 1 | 1.13 (0.86 - 1.49) | 111 (.46) | 98 (.41) | 0.37 | 1 |

**Supplemental Table 3 (continued). ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, AD or CVD patients**

| | OR (95% CI) [b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure [a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NC (n = 24,624)** | **Uncorrected [c]** | **Corrected [d]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **Uncorrected** | **Corrected** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **Uncorrected** | **Corrected** |
| IBS without Diarrhoea | 3.53 (3.05 - 4.09) | 800 (3.25) | 232 (.94) | <.0001 | <.0001 | 1.19 (1.06 - 1.34) | 659 (3.46) | 555 (2.91) | 0.003 | 0.02 | 1.28 (1.15 - 1.43) | 789 (3.3) | 620 (2.59) | <.0001 | 0.0001 |
| Intestinal pseudo-obstruction* | 3.01 (1.83 - 4.93) | 63 (.26) | 21 (.09) | <.0001 | <.0001 | 1.25 (0.84 - 1.86) | 55 (.29) | 44 (.23) | 0.27 | 1 | 1.07 (0.75 - 1.52) | 63 (.26) | 59 (.25) | 0.72 | 1 |
| **Pelvic floor** | | | | | | | | | | | | | | | |
| Fecal incontinence | 3.76 (3.06 - 4.61) | 430 (1.75) | 116 (.47) | <.0001 | <.0001 | 0.96 (0.83 - 1.11) | 358 (1.88) | 373 (1.96) | 0.58 | 1 | 1.41 (1.22 - 1.64) | 419 (1.75) | 298 (1.24) | <.0001 | 0.0001 |
| **Inflammatory bowel disease** | | | | | | | | | | | | | | | |
| Crohn's disease | 1.99 (1.51 - 2.63) | 151 (.61) | 76 (.31) | <.0001 | <.0001 | 1.02 (0.79 - 1.32) | 116 (.61) | 114 (.6) | 0.9 | 1 | 1.05 (0.83 - 1.32) | 147 (.61) | 140 (.58) | 0.68 | 1 |
| Ulcerative colitis | 1.87 (1.46 - 2.38) | 186 (.76) | 100 (.41) | <.0001 | <.0001 | 1.08 (0.85 - 1.38) | 137 (.72) | 127 (.67) | 0.54 | 1 | 1.03 (0.84 - 1.27) | 182 (.76) | 176 (.74) | 0.75 | 1 |
| Microscopic colitis | 2.19 (1.21 - 3.96) | 35 (.14) | 16 (.06) | 0.008 | 0.03 | 1.14 (0.69 - 1.90) | 32 (.17) | 28 (.15) | 0.61 | 1 | 1.00 (0.63 - 1.60) | 35 (.15) | 35 (.15) | 1 | 1 |
| **Interventions** | | | | | | | | | | | | | | | |
| Appendectomy | 2.40 (1.15 - 5.02) | 24 (.1) | 10 (.04) | 0.02 | 0.07 | 1.15 (0.63 - 2.09) | 23 (.12) | 20 (.11) | 0.65 | 1 | 0.57 (0.35 - 0.94) | 24 (.1) | 42 (.18) | 0.03 | 0.21 |
| Vagotomy | 1.00 (0.42 - 2.40) | 10 (.04) | 10 (.04) | 1 | 1 | 1.00 (0.42 - 2.40) | 10 (.05) | 10 (.05) | 1 | 1 | 1.00 (0.42 - 2.40) | 10 (.04) | 10 (.04) | 1 | 1 |

**Supplemental Table 3 (continued). ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, AD or CVD patients**

| | OR (95% CI) [b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure [a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NC (n = 24,624)** | **Uncorrected [c]** | **Corrected [d]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **Uncorrected** | **Corrected** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **Uncorrected** | **Corrected** |
| **Laxative prescriptions** | | | | | | | | | | | | | | | |
| Hyperosmotic laxatives | 2.67 (2.56 - 2.79) | 7,899 (32.08) | 3,698 (15.02) | <.0001 | <.0001 | 1.26 (1.21 - 1.32) | 6,362 (33.4) | 5,410 (28.4) | <.0001 | <.0001 | 1.07 (1.03 - 1.11) | 7,737 (32.32) | 7,396 (30.89) | 0.006 | 0.07 |
| Stimulant laxatives | 2.48 (2.36 - 2.60) | 6,043 (24.54) | 2,856 (11.6) | <.0001 | <.0001 | 1.25 (1.19 - 1.31) | 4,867 (25.55) | 4,101 (21.53) | <.0001 | <.0001 | 0.98 (0.94 - 1.02) | 5,901 (24.65) | 6,012 (25.11) | 0.31 | 1 |
| Bulk-forming laxatives | 3.26 (2.87 - 3.70) | 1,020 (4.14) | 322 (1.31) | <.0001 | <.0001 | 1.24 (1.12 - 1.38) | 851 (4.47) | 691 (3.63) | <.0001 | 0.0005 | 1.53 (1.39 - 1.69) | 1,017 (4.25) | 675 (2.82) | <.0001 | <.0001 |
| Stool softeners | 2.75 (2.62 - 2.88) | 6,428 (26.1) | 2,806 (11.4) | <.0001 | <.0001 | 1.31 (1.25 - 1.38) | 5,249 (27.56) | 4,280 (22.47) | <.0001 | <.0001 | 1.09 (1.05 - 1.14) | 6,350 (26.52) | 5,954 (24.87) | 0.0004 | 0.005 |
| **Antidopaminergic prescriptions** | | | | | | | | | | | | | | | |
| Domperidone | 2.30 (1.10 - 4.84) | 23 (.09) | 10 (.04) | 0.02 | 0.09 | 1.80 (0.83 - 3.90) | 18 (.09) | 10 (.05) | 0.13 | 0.87 | 2.30 (1.10 - 4.84) | 23 (.1) | 10 (.04) | 0.02 | 0.2 |
| Prochlorperazine | 2.32 (2.09 - 2.57) | 1,237 (5.02) | 549 (2.23) | <.0001 | <.0001 | 1.49 (1.35 - 1.64) | 987 (5.18) | 675 (3.54) | <.0001 | <.0001 | 0.90 (0.83 - 0.97) | 1,224 (5.11) | 1,356 (5.66) | 0.009 | 0.1 |
| Promethazine | 2.21 (2.08 - 2.35) | 3,509 (14.25) | 1,724 (7.) | <.0001 | <.0001 | 1.24 (1.17 - 1.32) | 2,697 (14.16) | 2,231 (11.71) | <.0001 | <.0001 | 0.94 (0.89 - 0.99) | 3,361 (14.04) | 3,541 (14.79) | 0.03 | 0.22 |
| Metoclopramide | 2.23 (2.06 - 2.41) | 2,034 (8.26) | 957 (3.89) | <.0001 | <.0001 | 1.39 (1.29 - 1.50) | 1,661 (8.72) | 1,224 (6.43) | <.0001 | <.0001 | 0.99 (0.93 - 1.05) | 2,013 (8.41) | 2,036 (8.5) | 0.72 | 1 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea); GERD, Gastro-esophageal reflux disease; GI, gastrointestinal

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes (**online supplemental methods)**. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event in the available medical records.

[b] ORs were calculated as follows: odds of the documented exposure in the PD cohort/ odds of the documented exposure in respective control cohort.

[c] P-values of the comparison between the PD group and the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (**Methods**).

***** 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 4. Positive and negative exposures in patients with PD compared to matched NCs and patients with AD and CVD.**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure[a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NCs (n = 24,624)** | **P-value[c]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **P-value** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **P-value** |
| **Prodromal motor- and non-motor symptoms** | | | | | | | | | | | | |
| Fatigue | 3.21 (3.04 - 3.38) | 6,040 (24.53) | 2,266 (9.2) | <.0001 | 1.04 (0.99 - 1.09) | 4,800 (25.2) | 4,666 (24.5) | 0.17 | 1.06 (1.02 - 1.11) | 5,834 (24.37) | 5,569 (23.26) | 0.01 |
| Dizziness | 3.26 (3.06 - 3.47) | 4,160 (16.89) | 1,447 (5.88) | <.0001 | 0.97 (0.92 - 1.02) | 3,356 (17.62) | 3,439 (18.06) | 0.31 | 0.91 (0.87 - 0.95) | 4,014 (16.77) | 4,346 (18.15) | 0.0003 |
| Depression, single episode | 2.95 (2.79 - 3.13) | 4,639 (18.84) | 1,796 (7.29) | <.0001 | 0.76 (0.73 - 0.80) | 3,567 (18.73) | 4,413 (23.17) | <.0001 | 1.17 (1.12 - 1.23) | 4,502 (18.8) | 3,948 (16.49) | <.0001 |
| Depression, recurrent | 3.60 (3.17 - 4.10) | 1,061 (4.31) | 304 (1.23) | <.0001 | 0.81 (0.73 - 0.89) | 786 (4.13) | 962 (5.05) | <.0001 | 1.31 (1.19 - 1.44) | 1,008 (4.21) | 780 (3.26) | <.0001 |
| Shoulder pain | 2.91 (2.73 - 3.11) | 3,563 (14.47) | 1,352 (5.49) | <.0001 | 1.09 (1.03 - 1.15) | 2,757 (14.48) | 2,565 (13.47) | 0.008 | 1.05 (1.00 - 1.10) | 3,440 (14.37) | 3,301 (13.79) | 0.09 |
| Shoulder stiffness | 4.70 (3.40 - 6.49) | 210 (.85) | 45 (.18) | <.0001 | 1.59 (1.24 - 2.03) | 166 (.87) | 105 (.55) | 0.0002 | 1.77 (1.41 - 2.23) | 205 (.86) | 116 (.48) | <.0001 |
| Anxiety | 2.71 (2.56 - 2.88) | 4,174 (16.95) | 1,723 (7.) | <.0001 | 0.91 (0.86 - 0.96) | 3,205 (16.83) | 3,470 (18.22) | 0.001 | 1.19 (1.13 - 1.25) | 4,026 (16.82) | 3,471 (14.5) | <.0001 |
| Neck pain | 2.04 (1.91 - 2.18) | 2,959 (12.02) | 1,544 (6.27) | <.0001 | 1.12 (1.06 - 1.20) | 2,314 (12.15) | 2,087 (10.96) | 0.0006 | 1.00 (0.95 - 1.06) | 2,870 (11.99) | 2,861 (11.95) | 0.91 |
| Neck stiffness | 5.53 (3.93 - 7.78) | 214 (.87) | 39 (.16) | <.0001 | 0.61 (0.47 - 0.78) | 103 (.54) | 169 (.89) | <.0001 | 1.57 (1.26 - 1.95) | 211 (.88) | 135 (.56) | <.0001 |
| Urinary dysfunction | 2.70 (2.56 - 2.85) | 5,287 (21.47) | 2,261 (9.18) | <.0001 | 0.95 (0.90 - 0.99) | 4,366 (22.92) | 4,549 (23.88) | 0.05 | 1.07 (1.03 - 1.12) | 5,085 (21.24) | 4,812 (20.1) | 0.006 |

**Supplemental Table 4 (continued). Positive and negative exposures in patients with PD compared to matched NCs and patients with AD and CVD.**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure[a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NCs (n = 24,624)** | **P-value[c]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **P-value** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **P-value** |
| Erectile dysfunction | 2.21 (2.03 - 2.41) | 1,727 (7.01) | 813 (3.3) | <.0001 | 1.05 (0.96 - 1.14) | 1,192 (6.26) | 1,141 (5.99) | 0.29 | 1.10 (1.03 - 1.18) | 1,657 (6.92) | 1,513 (6.32) | 0.01 |
| Insomnia | 2.58 (2.38 - 2.80) | 2,179 (8.85) | 892 (3.62) | <.0001 | 0.92 (0.86 - 0.99) | 1,656 (8.69) | 1,779 (9.34) | 0.04 | 1.00 (0.94 - 1.07) | 2,093 (8.74) | 2,093 (8.74) | 1 |
| Balance impairments | 7.41 (6.83 - 8.04) | 4,488 (18.23) | 719 (2.92) | <.0001 | 1.77 (1.67 - 1.87) | 3,654 (19.19) | 2,254 (11.83) | <.0001 | 2.48 (2.35 - 2.63) | 4,317 (18.03) | 1,948 (8.14) | <.0001 |
| Hypotension | 3.18 (2.91 - 3.48) | 2,019 (8.2) | 672 (2.73) | <.0001 | 1.03 (0.96 - 1.10) | 1,640 (8.61) | 1,601 (8.41) | 0.49 | 0.95 (0.89 - 1.01) | 1,956 (8.17) | 2,052 (8.57) | 0.13 |
| Memory problems | 3.84 (3.45 - 4.27) | 1,625 (6.6) | 445 (1.81) | <.0001 | 0.11 (0.10 - 0.12) | 1,267 (6.65) | 7,499 (39.37) | <.0001 | 1.31 (1.21 - 1.41) | 1,559 (6.51) | 1,212 (5.06) | <.0001 |
| **Charleson comorbidities** | | | | | | | | | | | | |
| Heart failure | 1.70 (1.59 - 1.82) | 2,330 (9.46) | 1,424 (5.78) | <.0001 | 1.01 (0.94 - 1.08) | 1,994 (10.47) | 1,978 (10.39) | 0.8 | 0.64 (0.60 - 0.68) | 2,265 (9.46) | 3,361 (14.04) | <.0001 |
| Acute myocardial infarction | 1.77 (1.60 - 1.97) | 984 (4.) | 565 (2.29) | <.0001 | 0.89 (0.80 - 0.98) | 809 (4.25) | 908 (4.77) | 0.02 | 0.59 (0.55 - 0.64) | 960 (4.01) | 1,574 (6.57) | <.0001 |
| Peripheral vascular disease | 2.05 (1.87 - 2.23) | 1,539 (6.25) | 777 (3.16) | <.0001 | 0.89 (0.82 - 0.96) | 1,242 (6.52) | 1,383 (7.26) | 0.006 | 0.58 (0.54 - 0.62) | 1,459 (6.09) | 2,425 (10.13) | <.0001 |
| Portal hypertension | 1.77 (1.33 - 2.36) | 129 (.52) | 73 (.3) | <.0001 | 1.19 (0.88 - 1.61) | 93 (.49) | 78 (.41) | 0.25 | 0.56 (0.45 - 0.70) | 123 (.51) | 218 (.91) | <.0001 |
| Fibrosis and cirrhosis of liver | 1.53 (1.30 - 1.82) | 345 (1.4) | 226 (.92) | <.0001 | 0.95 (0.79 - 1.13) | 246 (1.29) | 260 (1.37) | 0.53 | 0.63 (0.55 - 0.72) | 330 (1.38) | 521 (2.18) | <.0001 |

**Supplemental Table 4 (continued). Positive and negative exposures in patients with PD compared to matched NCs and patients with AD and CVD.**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure[a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NCs (n = 24,624)** | **P-value[c]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **P-value** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **P-value** |
| Chronic kidney disease (CKD) | 1.83 (1.71 - 1.95) | 2,685 (10.9) | 1,544 (6.27) | <.0001 | 0.87 (0.82 - 0.93) | 2,192 (11.51) | 2,469 (12.96) | <.0001 | 0.70 (0.66 - 0.74) | 2,535 (10.59) | 3,476 (14.52) | <.0001 |
| Acute kidney failure | 2.05 (1.89 - 2.23) | 1,718 (6.98) | 869 (3.53) | <.0001 | 0.89 (0.82 - 0.96) | 1,242 (6.52) | 1,383 (7.26) | 0.006 | 0.70 (0.66 - 0.75) | 1,653 (6.9) | 2,285 (9.54) | <.0001 |
| End stage renal disease | 1.87 (1.55 - 2.25) | 325 (1.32) | 175 (.71) | <.0001 | 0.97 (0.81 - 1.15) | 251 (1.32) | 259 (1.36) | 0.72 | 0.54 (0.47 - 0.62) | 318 (1.33) | 586 (2.45) | <.0001 |
| Paraplegia and quadriplegia | 2.64 (1.82 - 3.83) | 100 (.41) | 38 (.15) | <.0001 | 1.56 (1.07 - 2.27) | 70 (.37) | 45 (.24) | 0.02 | 1.05 (0.79 - 1.40) | 97 (.41) | 92 (.38) | 0.72 |
| Human immunodeficiency virus disease | 1.54 (1.04 - 2.28) | 63 (.26) | 41 (.17) | 0.03 | 1.11 (0.71 - 1.76) | 39 (.2) | 35 (.18) | 0.64 | 0.77 (0.56 - 1.08) | 62 (.26) | 80 (.33) | 0.13 |
| Rheumatoid arthritis | 1.20 (0.60 - 2.38) | 18 (.07) | 15 (.06) | 0.6 | 1.44 (0.76 - 2.72) | 23 (.12) | 16 (.08) | 0.26 | 0.89 (0.46 - 1.72) | 17 (.07) | 19 (.08) | 0.74 |
| Peptic ulcer | 2.79 (2.22 - 3.50) | 282 (1.15) | 102 (.41) | <.0001 | 0.92 (0.76 - 1.11) | 215 (1.13) | 234 (1.23) | 0.37 | 0.92 (0.78 - 1.08) | 269 (1.12) | 293 (1.22) | 0.31 |
| Chronic obstructive pulmonary disease | 1.54 (1.44 - 1.65) | 2,109 (8.56) | 1,410 (5.73) | <.0001 | 0.87 (0.82 - 0.94) | 1,695 (8.9) | 1,914 (10.05) | 0.0003 | 0.63 (0.59 - 0.67) | 2,042 (8.53) | 3,086 (12.89) | <.0001 |
| Diabetes mellitus I without complications | 1.99 (1.66 - 2.38) | 361 (1.47) | 183 (.74) | <.0001 | 0.77 (0.66 - 0.91) | 283 (1.49) | 364 (1.91) | 0.001 | 0.74 (0.64 - 0.85) | 348 (1.45) | 470 (1.96) | <.0001 |
| Diabetes mellitus II | 1.48 (1.42 - 1.55) | 5,425 (22.03) | 3,943 (16.01) | <.0001 | 0.87 (0.83 - 0.91) | 4,255 (22.34) | 4,726 (24.81) | <.0001 | 0.68 (0.65 - 0.70) | 5,195 (21.7) | 6,959 (29.07) | <.0001 |

**Supplemental Table 4 (continued). Positive and negative exposures in patients with PD compared to matched NCs and patients with AD and CVD.**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | | OR (95% CI) | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure[a]** | **Odds PD / odds NC** | **PD (n = 24,624)** | **NCs (n = 24,624)** | **P-value[c]** | **Odds PD / odds AD** | **PD (n = 19,046)** | **AD (n = 19,046)** | **P-value** | **Odds PD / odds CVD** | **PD (n = 23,942)** | **CVD (n = 23,942)** | **P-value** |
| Malignant (primary) neoplasm | 1.74 (1.47 - 2.07) | 358 (1.45) | 207 (.84) | <.0001 | 1.12 (0.95 - 1.33) | 288 (1.51) | 257 (1.35) | 0.18 | 0.65 (0.57 - 0.75) | 342 (1.43) | 522 (2.18) | <.0001 |
| Secondary malignant neoplasm of unspecified site | 2.16 (1.42 - 3.29) | 69 (.28) | 32 (.13) | 0.0002 | 1.66 (1.09 - 2.53) | 58 (.3) | 35 (.18) | 0.02 | 0.51 (0.38 - 0.69) | 68 (.28) | 132 (.55) | <.0001 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

**Supplemental Table 5. Positive and negative exposures in patients with PD compared to matched NCs, after exclusion of antidopaminergic drug prescriptions [d].**

| | OR (95% CI) [b] | Patients, No (%) | | |
|---|---|---|---|---|
| **Exposure [a]** | **Odds PD / odds NC** | **Parkinson's disease (n = 26,805)** | **Negative controls (n = 26,805)** | **P-value [c]** |
| **Prodromal motor- and non-motor symptoms** | | | | |
| Fatigue | 3.11 (2.95 - 3.28) | 5,931 (22.13) | 2,244 (8.37) | <.0001 |
| Dizziness | 3.20 (3.02 - 3.40) | 4,417 (16.48) | 1,555 (5.8) | <.0001 |
| Depression, single episode | 2.92 (2.76 - 3.10) | 4,474 (16.69) | 1,720 (6.42) | <.0001 |
| Depression, recurrent | 3.34 (2.94 - 3.80) | 1,005 (3.75) | 309 (1.15) | <.0001 |
| Shoulder pain | 2.98 (2.79 - 3.19) | 3,437 (12.82) | 1,260 (4.7) | <.0001 |
| Shoulder stiffness | 4.13 (2.99 - 5.70) | 189 (.71) | 46 (.17) | <.0001 |
| Anxiety | 2.60 (2.45 - 2.75) | 4,319 (16.11) | 1,846 (6.89) | <.0001 |
| Neck pain | 3.10 (2.87 - 3.34) | 2,803 (10.46) | 974 (3.63) | <.0001 |
| Neck stiffness | 3.94 (3.00 - 5.16) | 258 (.96) | 66 (.25) | <.0001 |
| Urinary dysfunction | 2.69 (2.55 - 2.84) | 5,134 (19.15) | 2,171 (8.1) | <.0001 |
| Erectile dysfunction | 2.43 (2.23 - 2.65) | 1,780 (6.64) | 763 (2.85) | <.0001 |
| Insomnia | 2.68 (2.47 - 2.91) | 2,088 (7.79) | 819 (3.06) | <.0001 |
| Balance impairments | 7.31 (6.76 - 7.91) | 4,739 (17.68) | 765 (2.85) | <.0001 |
| Hypotension | 3.31 (3.02 - 3.62) | 2,037 (7.6) | 650 (2.42) | <.0001 |
| Memory problems | 3.63 (3.28 - 4.01) | 1,785 (6.66) | 517 (1.93) | <.0001 |

**Supplemental Table 5 (continued). Positive and negative exposures in patients with PD compared to matched NCs, after exclusion of antidopaminergic drug prescriptions [d].**

| | OR (95% CI) [b] | Patients, No (%) | | |
|---|---|---|---|---|
| **Exposure [a]** | **Odds PD / odds NC** | **Parkinson's disease (n = 26,805)** | **Negative controls (n = 26,805)** | **P-value [c]** |
| **Charleson comorbidities** | | | | |
| Heart failure | 1.61 (1.50 - 1.72) | 2,320 (8.66) | 1,493 (5.57) | <.0001 |
| Acute myocardial infarction | 1.66 (1.50 - 1.84) | 1,011 (3.77) | 618 (2.31) | <.0001 |
| Peripheral vascular disease | 1.88 (1.73 - 2.04) | 1,597 (5.96) | 875 (3.26) | <.0001 |
| Portal hypertension | 1.36 (1.02 - 1.82) | 109 (.41) | 80 (.3) | 0.03 |
| Fibrosis and cirrhosis of liver | 1.45 (1.22 - 1.73) | 311 (1.16) | 215 (.8) | <.0001 |
| Chronic kidney disease (CKD) | 1.78 (1.67 - 1.90) | 2,766 (10.32) | 1,629 (6.08) | <.0001 |
| Acute kidney failure | 2.05 (1.87 - 2.23) | 1,560 (5.82) | 786 (2.93) | <.0001 |
| End stage renal disease | 2.23 (1.88 - 2.65) | 427 (1.59) | 193 (.72) | <.0001 |
| Paraplegia and quadriplegia | 2.66 (1.80 - 3.93) | 93 (.35) | 35 (.13) | <.0001 |
| Human immunodeficiency virus disease | 2.00 (1.46 - 2.76) | 114 (.43) | 57 (.21) | <.0001 |
| Rheumatoid arthritis | 2.35 (1.33 - 4.15) | 40 (.15) | 17 (.06) | 0.002 |
| Peptic ulcer | 2.02 (1.61 - 2.52) | 231 (.86) | 115 (.43) | <.0001 |
| Chronic obstructive pulmonary disease | 1.48 (1.38 - 1.59) | 1,951 (7.28) | 1,351 (5.04) | <.0001 |
| Diabetes mellitus I without complications | 2.01 (1.66 - 2.44) | 316 (1.18) | 158 (.59) | <.0001 |
| Diabetes mellitus II | 1.50 (1.43 - 1.57) | 5,031 (18.77) | 3,572 (13.33) | <.0001 |
| Malignant (primary) neoplasm | 2.22 (1.90 - 2.59) | 521 (1.94) | 237 (.88) | <.0001 |
| Secondary malignant neoplasm of unspecified site | 1.91 (1.33 - 2.75) | 84 (.31) | 44 (.16) | 0.0004 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Antidopaminergic drugs include: metoclopramide, domperidone, promethazine, prochlorperazine. Only patients with any of these prescriptions within 2 years before the index event were excluded from further analysis.

**Supplemental Table 6. Positive and negative exposures in patients with AD and CVD, compared to their respective matched NCs**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI)[a] | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|
| **Exposure [a]** | **Odds CVD / odds NC** | **Cerebrovascular diseases (n = 841,567)** | **Negative controls (n = 841,567)** | **P-value[c]** | **Odds AD / odds NC** | **Alzheimer's disease (n = 47,982)** | **Negative controls (n = 47,982)** | **P-value** |
| **Prodromal motor- and non-motor symptoms** | | | | | | | | |
| Fatigue | 3.80 (3.76 - 3.83) | 214,887 (25.53) | 69,736 (8.29) | <.0001 | 3.34 (3.22 - 3.46) | 12,301 (25.64) | 4,494 (9.37) | <.0001 |
| Dizziness | 4.74 (4.69 - 4.79) | 178,954 (21.26) | 45,366 (5.39) | <.0001 | 3.21 (3.09 - 3.35) | 9,811 (20.45) | 3,553 (7.4) | <.0001 |
| Depression, single episode | 3.11 (3.07 - 3.14) | 161,370 (19.17) | 59,724 (7.1) | <.0001 | 3.95 (3.79 - 4.12) | 10,889 (22.69) | 3,316 (6.91) | <.0001 |
| Depression, recurrent | 2.99 (2.93 - 3.06) | 34,506 (4.1) | 11,849 (1.41) | <.0001 | 4.72 (4.31 - 5.18) | 2,553 (5.32) | 564 (1.18) | <.0001 |
| Shoulder pain | 3.17 (3.14 - 3.21) | 130,142 (15.46) | 45,882 (5.45) | <.0001 | 3.12 (2.97 - 3.27) | 6,858 (14.29) | 2,438 (5.08) | <.0001 |
| Shoulder stiffness | 3.23 (3.06 - 3.40) | 5,706 (.68) | 1,776 (.21) | <.0001 | 3.76 (2.95 - 4.78) | 314 (.65) | 84 (.18) | <.0001 |
| Anxiety | 2.77 (2.75 - 2.80) | 157,112 (18.67) | 64,330 (7.64) | <.0001 | 2.95 (2.83 - 3.07) | 9,444 (19.68) | 3,681 (7.67) | <.0001 |
| Neck pain | 3.60 (3.56 - 3.64) | 119,300 (14.18) | 36,912 (4.39) | <.0001 | 3.17 (3.00 - 3.34) | 5,746 (11.98) | 1,977 (4.12) | <.0001 |
| Neck stiffness | 5.30 (5.05 - 5.56) | 10,201 (1.21) | 1,944 (.23) | <.0001 | 3.76 (3.05 - 4.63) | 418 (.87) | 112 (.23) | <.0001 |
| Urinary dysfunction | 2.81 (2.78 - 2.83) | 180,061 (21.4) | 74,433 (8.84) | <.0001 | 2.76 (2.67 - 2.85) | 13,136 (27.38) | 5,770 (12.03) | <.0001 |
| Erectile dysfunction | 2.06 (2.03 - 2.10) | 47,902 (5.69) | 23,903 (2.84) | <.0001 | 2.62 (2.41 - 2.85) | 2,020 (4.21) | 791 (1.65) | <.0001 |
| Insomnia | 3.09 (3.05 - 3.13) | 83,704 (9.95) | 29,027 (3.45) | <.0001 | 3.08 (2.91 - 3.27) | 4,705 (9.81) | 1,635 (3.41) | <.0001 |
| Balance impairments | 4.10 (4.04 - 4.16) | 83,407 (9.91) | 21,986 (2.61) | <.0001 | 3.55 (3.37 - 3.73) | 6,776 (14.12) | 2,126 (4.43) | <.0001 |
| Hypotension | 4.18 (4.12 - 4.25) | 72,213 (8.58) | 18,467 (2.19) | <.0001 | 2.72 (2.57 - 2.89) | 4,193 (8.74) | 1,631 (3.4) | <.0001 |
| Memory problems | 3.41 (3.35 - 3.48) | 42,944 (5.1) | 13,048 (1.55) | <.0001 | 27.26 (25.58 - 29.06) | 18,245 (38.02) | 1,056 (2.2) | <.0001 |

**Supplemental Table 6 (continued). Positive and negative exposures in patients with AD and CVD, compared to their respective matched NCs**

| | OR (95% CI) [b] | Patients, No (%) | | | OR (95% CI)[a] | Patients, No (%) | | |
|---|---|---|---|---|---|---|---|---|
| **Exposure [a]** | **Odds CVD / odds NC** | **Cerebrovascular diseases (n = 841,567)** | **Negative controls (n = 841,567)** | **P-value[c]** | **Odds AD / odds NC** | **Alzheimer's disease (n = 47,982)** | **Negative controls (n = 47,982)** | **P-value** |
| **Charleson comorbidities** | | | | | | | | |
| Heart failure | 3.49 (3.45 - 3.53) | 120,225 (14.29) | 38,351 (4.56) | <.0001 | 1.67 (1.60 - 1.75) | 5,770 (12.03) | 3,622 (7.55) | <.0001 |
| Acute myocardial infarction | 4.04 (3.97 - 4.11) | 57,346 (6.81) | 14,967 (1.78) | <.0001 | 1.96 (1.83 - 2.11) | 2,385 (4.97) | 1,245 (2.59) | <.0001 |
| Peripheral vascular disease | 5.10 (5.02 - 5.19) | 84,229 (10.01) | 17,952 (2.13) | <.0001 | 2.19 (2.07 - 2.31) | 4,109 (8.56) | 1,970 (4.11) | <.0001 |
| Portal hypertension | 3.32 (3.18 - 3.47) | 8,876 (1.05) | 2,692 (.32) | <.0001 | 1.85 (1.44 - 2.37) | 175 (.36) | 95 (.2) | <.0001 |
| Fibrosis and cirrhosis of liver | 2.80 (2.73 - 2.88) | 21,542 (2.56) | 7,812 (.93) | <.0001 | 1.90 (1.66 - 2.17) | 621 (1.29) | 329 (.69) | <.0001 |
| Chronic kidney disease (CKD) | 3.49 (3.46 - 3.53) | 141,662 (16.83) | 46,090 (5.48) | <.0001 | 1.96 (1.88 - 2.04) | 7,420 (15.46) | 4,098 (8.54) | <.0001 |
| Acute kidney failure | 3.99 (3.93 - 4.05) | 86,503 (10.28) | 23,476 (2.79) | <.0001 | 2.25 (2.13 - 2.38) | 4,233 (8.82) | 1,976 (4.12) | <.0001 |
| End stage renal disease | 5.86 (5.72 - 6.01) | 40,929 (4.86) | 7,273 (.86) | <.0001 | 2.08 (1.86 - 2.32) | 950 (1.98) | 462 (.96) | <.0001 |
| Paraplegia and quadriplegia | 2.64 (2.48 - 2.80) | 3,774 (.45) | 1,434 (.17) | <.0001 | 1.78 (1.30 - 2.43) | 110 (.23) | 62 (.13) | 0.0003 |
| Human immunodeficiency virus disease | 3.11 (2.98 - 3.24) | 9,127 (1.08) | 2,958 (.35) | <.0001 | 3.06 (2.36 - 3.97) | 232 (.48) | 76 (.16) | <.0001 |
| Rheumatoid arthritis | 2.62 (2.36 - 2.90) | 1,322 (.16) | 505 (.06) | <.0001 | 2.36 (1.55 - 3.59) | 73 (.15) | 31 (.06) | <.0001 |
| Peptic ulcer | 3.30 (3.17 - 3.42) | 11,356 (1.35) | 3,478 (.41) | <.0001 | 2.38 (2.06 - 2.76) | 610 (1.27) | 258 (.54) | <.0001 |
| Chronic obstructive pulmonary disease | 3.07 (3.04 - 3.11) | 105,546 (12.54) | 37,529 (4.46) | <.0001 | 1.74 (1.66 - 1.82) | 4,946 (10.31) | 2,975 (6.2) | <.0001 |
| Diabetes mellitus I without complications | 4.09 (3.96 - 4.23) | 18,108 (2.15) | 4,501 (.53) | <.0001 | 3.38 (2.93 - 3.89) | 834 (1.74) | 250 (.52) | <.0001 |
| Diabetes mellitus II | 2.71 (2.69 - 2.73) | 236,175 (28.06) | 105,900 (12.58) | <.0001 | 1.82 (1.76 - 1.88) | 11,523 (24.02) | 7,115 (14.83) | <.0001 |
| Malignant (primary) neoplasm | 3.74 (3.65 - 3.83) | 30,295 (3.6) | 8,315 (.99) | <.0001 | 1.80 (1.63 - 1.99) | 1,097 (2.29) | 616 (1.28) | <.0001 |
| Secondary malignant neoplasm of unspecified site | 4.06 (3.86 - 4.27) | 7,625 (.91) | 1,893 (.22) | <.0001 | 1.41 (1.13 - 1.76) | 192 (.4) | 136 (.28) | 0.002 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.



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**Supplemental Table 7. ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, stratified for sex.**

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI)[b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
| Exposure[a] | Odds PD / odds NC | PD (n = 14,249) | NC (n = 14,249) | Uncorrected[c] | Corrected[d] | Odds PD / odds NC | PD (n = 10,095) | NC (n = 10,095) | Uncorrected | Corrected |
| **Esophagus** | | | | | | | | | | |
| Achalasia | 1.90 (0.88 - 4.09) | 19 (.13) | 10 (.07) | 0.09 | 0.41 | 2.91 (1.42 - 5.96) | 29 (.29) | 10 (.1) | 0.002 | 0.01 |
| Dysphagia | 3.24 (2.89 - 3.63) | 1,256 (8.81) | 413 (2.9) | <.0001 | <.0001 | 3.47 (3.05 - 3.95) | 1,022 (10.12) | 317 (3.14) | <.0001 | <.0001 |
| GERD | 2.15 (2.02 - 2.29) | 3,352 (23.52) | 1,782 (12.51) | <.0001 | <.0001 | 2.28 (2.13 - 2.44) | 2,935 (29.07) | 1,539 (15.25) | <.0001 | <.0001 |
| **Stomach** | | | | | | | | | | |
| Gastroparesis | 3.05 (1.94 - 4.80) | 76 (.53) | 25 (.18) | <.0001 | <.0001 | 7.30 (4.51 - 11.80) | 137 (1.36) | 19 (.19) | <.0001 | <.0001 |
| Functional dyspepsia | 2.89 (2.27 - 3.68) | 260 (1.82) | 91 (.64) | <.0001 | <.0001 | 3.71 (2.83 - 4.86) | 244 (2.42) | 67 (.66) | <.0001 | <.0001 |
| **Intestine** | | | | | | | | | | |
| Paralytic ileus | 1.76 (1.27 - 2.44) | 100 (.7) | 57 (.4) | 0.0006 | 0.004 | 2.81 (1.69 - 4.69) | 56 (.55) | 20 (.2) | <.0001 | 0.0002 |
| Diarrhoea | 2.87 (2.55 - 3.21) | 1,133 (7.95) | 417 (2.93) | <.0001 | <.0001 | 2.79 (2.50 - 3.11) | 1,223 (12.11) | 476 (4.72) | <.0001 | <.0001 |
| Constipation | 3.45 (3.13 - 3.82) | 1,706 (11.97) | 540 (3.79) | <.0001 | <.0001 | 3.27 (2.95 - 3.63) | 1,522 (15.08) | 520 (5.15) | <.0001 | <.0001 |
| IBS-C | 1.30 (0.57 - 2.97) | 13 (.09) | 10 (.07) | 0.53 | 1 | 2.50 (1.20 - 5.22) | 25 (.25) | 10 (.1) | 0.01 | 0.05 |
| IBS-D | 2.82 (1.42 - 5.62) | 31 (.22) | 11 (.08) | 0.002 | 0.01 | 3.09 (1.99 - 4.82) | 80 (.79) | 26 (.26) | <.0001 | <.0001 |
| IBS without Diarrhoea | 3.16 (2.46 - 4.07) | 253 (1.78) | 81 (.57) | <.0001 | <.0001 | 2.90 (2.45 - 3.44) | 527 (5.22) | 188 (1.86) | <.0001 | <.0001 |
| Intestinal pseudo-obstruction* | 2.46 (1.29 - 4.70) | 32 (.22) | 13 (.09) | 0.005 | 0.02 | 2.70 (1.31 - 5.59) | 27 (.27) | 10 (.1) | 0.005 | 0.02 |
| **Pelvic floor** | | | | | | | | | | |
| Fecal incontinence | 4.31 (3.06 - 6.09) | 171 (1.2) | 40 (.28) | <.0001 | <.0001 | 4.01 (3.04 - 5.30) | 248 (2.46) | 63 (.62) | <.0001 | <.0001 |

**Supplemental Table 7 (continued). ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, stratified for sex.**

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI)[b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
| Exposure[a] | Odds PD / odds NC | PD (n = 14,249) | NC (n = 14,249) | Uncorrected[c] | Corrected[d] | Odds PD / odds NC | PD (n = 10,095) | NC (n = 10,095) | Uncorrected | Corrected |
| **Laxative prescriptions** | | | | | | | | | | |
| Hyperosmotic laxatives | 2.40 (2.27 - 2.54) | 4,476 (31.41) | 2,281 (16.01) | <.0001 | <.0001 | 2.94 (2.74 - 3.15) | 3,295 (32.64) | 1,430 (14.17) | <.0001 | <.0001 |
| Stimulant laxatives | 2.27 (2.13 - 2.42) | 3,435 (24.11) | 1,749 (12.27) | <.0001 | <.0001 | 2.78 (2.57 - 3.00) | 2,492 (24.69) | 1,065 (10.55) | <.0001 | <.0001 |
| Bulk-forming laxatives | 3.52 (2.95 - 4.19) | 564 (3.96) | 165 (1.16) | <.0001 | <.0001 | 3.93 (3.20 - 4.83) | 441 (4.37) | 116 (1.15) | <.0001 | <.0001 |
| Stool softeners | 2.49 (2.33 - 2.65) | 3,662 (25.7) | 1,741 (12.22) | <.0001 | <.0001 | 3.00 (2.78 - 3.25) | 2,649 (26.24) | 1,069 (10.59) | <.0001 | <.0001 |
| **Antidopaminergic prescriptions** | | | | | | | | | | |
| Domperidone | - | 10 (.07) | 0 (0) | 0.002 | 0.008 | 1.50 (0.67 - 3.34) | 15 (.15) | 10 (.1) | 0.32 | 1 |
| Prochlorperazine | 2.06 (1.79 - 2.37) | 617 (4.33) | 306 (2.15) | <.0001 | <.0001 | 2.55 (2.19 - 2.96) | 616 (6.1) | 251 (2.49) | <.0001 | <.0001 |
| Promethazine | 1.91 (1.76 - 2.07) | 1,767 (12.4) | 985 (6.91) | <.0001 | <.0001 | 2.38 (2.17 - 2.60) | 1,706 (16.9) | 796 (7.89) | <.0001 | <.0001 |
| Metoclopramide | 1.99 (1.79 - 2.22) | 1,028 (7.21) | 535 (3.75) | <.0001 | <.0001 | 2.72 (2.40 - 3.07) | 963 (9.54) | 377 (3.73) | <.0001 | <.0001 |
| **IBD** | | | | | | | | | | |
| Crohn's disease | 1.72 (1.22 - 2.45) | 86 (.6) | 50 (.35) | 0.002 | 0.01 | 1.77 (1.16 - 2.70) | 60 (.59) | 34 (.34) | 0.007 | 0.03 |
| Ulcerative colitis | 2.06 (1.50 - 2.84) | 115 (.81) | 56 (.39) | <.0001 | <.0001 | 2.23 (1.46 - 3.42) | 69 (.68) | 31 (.31) | 0.0001 | 0.0008 |
| Microscopic colitis | 1.00 (0.42 - 2.40) | 10 (.07) | 10 (.07) | 1 | 1 | 1.45 (0.79 - 2.64) | 26 (.26) | 18 (.18) | 0.23 | 0.95 |
| **Interventions** | | | | | | | | | | |
| Appendectomy | 1.10 (0.47 - 2.59) | 11 (.08) | 10 (.07) | 0.83 | 1 | 1.20 (0.52 - 2.78) | 12 (.12) | 10 (.1) | 0.67 | 1 |
| Vagotomy | - | 0 (0) | 10 (.07) | 0.002 | 0.008 | - | 10 (.1) | 0 (0) | 0.002 | 0.008 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease; IBD, Inflammatory bowel disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: Methods).

***** 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 8**. **ORs and absolute rates of prior exposures in patients with PD compared to matched AD, stratified for sex.**

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI)[b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
| Exposure[a] | Odds PD / odds AD | PD (n = 9,966) | AD (n = 9,966) | Uncorrected[c] | Corrected [d] | Odds PD / odds AD | PD (n = 8,817) | AD (n = 8,817) | Uncorrected | Corrected |
| **Esophagus** | | | | | | | | | | |
| Achalasia | 0.83 (0.42 - 1.65) | 15 (.15) | 18 (.18) | 0.6 | 1 | 1.45 (0.79 - 2.64) | 26 (.29) | 18 (.2) | 0.23 | 1 |
| Dysphagia | 1.31 (1.18 - 1.45) | 917 (9.2) | 718 (7.2) | <.0001 | <.0001 | 1.38 (1.24 - 1.53) | 898 (10.18) | 670 (7.6) | <.0001 | <.0001 |
| GERD | 1.12 (1.05 - 1.19) | 2,434 (24.42) | 2,235 (22.43) | 0.004 | 0.04 | 1.18 (1.11 - 1.26) | 2,594 (29.42) | 2,297 (26.05) | <.0001 | 0.0003 |
| **Stomach** | | | | | | | | | | |
| Gastroparesis | 1.00 (0.66 - 1.52) | 44 (.44) | 44 (.44) | 1 | 1 | 1.66 (1.23 - 2.24) | 114 (1.29) | 69 (.78) | 0.0009 | 0.01 |
| Functional dyspepsia | 1.15 (0.94 - 1.42) | 198 (1.99) | 172 (1.73) | 0.18 | 1 | 0.86 (0.71 - 1.03) | 211 (2.39) | 245 (2.78) | 0.11 | 0.86 |
| **Intestine** | | | | | | | | | | |
| Paralytic ileus | 1.23 (0.89 - 1.69) | 82 (.82) | 67 (.67) | 0.22 | 1 | 1.04 (0.70 - 1.56) | 49 (.56) | 47 (.53) | 0.84 | 1 |
| Diarrhoea | 0.85 (0.77 - 0.94) | 800 (8.03) | 924 (9.27) | 0.003 | 0.03 | 0.94 (0.86 - 1.03) | 1,053 (11.94) | 1,111 (12.6) | 0.21 | 1 |
| Constipation | 1.10 (1.01 - 1.19) | 1,295 (12.99) | 1,193 (11.97) | 0.04 | 0.37 | 1.06 (0.97 - 1.15) | 1,329 (15.07) | 1,265 (14.35) | 0.21 | 1 |
| IBS-C | 1.00 (0.42 - 2.40) | 10 (.1) | 10 (.1) | 1 | 1 | 1.92 (0.95 - 3.86) | 23 (.26) | 12 (.14) | 0.06 | 0.53 |
| IBS-D | 0.91 (0.50 - 1.67) | 20 (.2) | 22 (.22) | 0.76 | 1 | 1.24 (0.88 - 1.74) | 74 (.84) | 60 (.68) | 0.23 | 1 |
| IBS without Diarrhoea | 1.05 (0.85 - 1.30) | 170 (1.71) | 162 (1.63) | 0.66 | 1 | 1.27 (1.10 - 1.46) | 466 (5.29) | 372 (4.22) | 0.001 | 0.01 |
| Intestinal pseudo-obstruction* | 1.13 (0.64 - 1.98) | 26 (.26) | 23 (.23) | 0.67 | 1 | 1.32 (0.72 - 2.39) | 25 (.28) | 19 (.22) | 0.37 | 1 |
| **Pelvic floor** | | | | | | | | | | |
| Fecal incontinence | 0.87 (0.69 - 1.09) | 137 (1.37) | 158 (1.59) | 0.22 | 1 | 1.10 (0.91 - 1.34) | 220 (2.5) | 200 (2.27) | 0.33 | 1 |

**Supplemental table 8 (continued)**. **ORs and absolute rates of prior exposures in patients with PD compared to matched AD, stratified for sex.**

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI)[b] | Patients, No. (%) | | P-value | | OR (95% CI) | Patients, No. (%) | | P-value | |
| **Exposure[a]** | **Odds PD / odds AD** | **PD (n = 9,966)** | **AD (n = 9,966)** | **Uncorrected[c]** | **Corrected [d]** | **Odds PD / odds AD** | **PD (n = 8,817)** | **AD (n = 8,817)** | **Uncorrected** | **Corrected** |
| **Laxative prescriptions** | | | | | | | | | | |
| Hyperosmotic laxatives | 1.27 (1.19 - 1.34) | 3,298 (33.09) | 2,800 (28.1) | <.0001 | <.0001 | 1.35 (1.27 - 1.44) | 2,955 (33.51) | 2,394 (27.15) | <.0001 | <.0001 |
| Stimulant laxatives | 1.24 (1.17 - 1.33) | 2,559 (25.68) | 2,165 (21.72) | <.0001 | <.0001 | 1.35 (1.26 - 1.45) | 2,238 (25.38) | 1,770 (20.07) | <.0001 | <.0001 |
| Bulk-forming laxatives | 1.41 (1.22 - 1.63) | 445 (4.47) | 320 (3.21) | <.0001 | <.0001 | 1.20 (1.04 - 1.40) | 400 (4.54) | 335 (3.8) | 0.02 | 0.15 |
| Stool softeners | 1.27 (1.19 - 1.35) | 2,776 (27.85) | 2,323 (23.31) | <.0001 | <.0001 | 1.46 (1.36 - 1.56) | 2,398 (27.2) | 1,800 (20.42) | <.0001 | <.0001 |
| **Antidopaminergic prescriptions** | | | | | | | | | | |
| Domperidone | - | 0 (0) | 0 (0) | - | - | 1.30 (0.57 - 2.97) | 13 (.15) | 10 (.11) | 0.53 | 1 |
| Prochlorperazine | 1.00 (0.42 - 2.40) | 10 (.1) | 10 (.1) | 1 | 1 | 1.59 (1.39 - 1.83) | 531 (6.02) | 341 (3.87) | <.0001 | <.0001 |
| Promethazine | 1.49 (1.28 - 1.73) | 440 (4.42) | 300 (3.01) | <.0001 | <.0001 | 1.36 (1.25 - 1.48) | 1,445 (16.39) | 1,112 (12.61) | <.0001 | <.0001 |
| Metoclopramide | 1.34 (1.19 - 1.50) | 735 (7.38) | 560 (5.62) | <.0001 | <.0001 | 1.46 (1.31 - 1.63) | 863 (9.79) | 610 (6.92) | <.0001 | <.0001 |
| **IBD** | | | | | | | | | | |
| Crohn's disease | 1.11 (0.75 - 1.64) | 52 (.52) | 47 (.47) | 0.62 | 1 | 0.91 (0.62 - 1.33) | 50 (.57) | 55 (.62) | 0.63 | 1 |
| Ulcerative colitis | 1.03 (0.74 - 1.43) | 72 (.72) | 70 (.7) | 0.87 | 1 | 1.32 (0.90 - 1.93) | 62 (.7) | 47 (.53) | 0.15 | 1 |
| Microscopic colitis | 1.00 (0.42 - 2.40) | 10 (.1) | 10 (.1) | 1 | 1 | 1.24 (0.70 - 2.20) | 26 (.29) | 21 (.24) | 0.47 | 1 |
| **Interventions** | | | | | | | | | | |
| Appendectomy | 1.00 (0.42 - 2.40) | 10 (.1) | 10 (.1) | 1 | 1 | 1.20 (0.52 - 2.78) | 12 (.14) | 10 (.11) | 0.67 | 1 |
| Vagotomy | - | 0 (0) | 0 (0) | - | - | 1.00 (0.42 - 2.40) | 10 (.11) | 10 (.11) | 1 | 1 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease; IBD, Inflammatory bowel disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

* 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 9. ORs and absolute rates of prior exposures in patients with PD compared to matched CVD, stratified for sex**.

| | **Male** | | | | | **Female** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)[b]** | **Patients, No. (%)** | | **P-value[b]** | | **OR (95% CI)** | **Patients, No. (%)** | | **P-value** | |
| **Exposure[a]** | Odds PD / odds CVD | PD (n = 13,874) | CVD (n = 13,874) | Uncorrected[c] | Corrected [d] | Odds PD / odds CVD | PD (n = 9,801) | CVD (n = 9,801) | Uncorrected | Corrected |
| **Esophagus** | | | | | | | | | | |
| Achalasia | 0.70 (0.39 - 1.27) | 19 (.14) | 27 (.19) | 0.24 | 1 | 1.13 (0.65 - 1.95) | 27 (.28) | 24 (.24) | 0.67 | 1 |
| Dysphagia | 1.24 (1.13 - 1.35) | 1,223 (8.82) | 1,005 (7.24) | <.0001 | 0.0001 | 1.26 (1.14 - 1.39) | 981 (10.01) | 797 (8.13) | <.0001 | 0.0006 |
| GERD | 0.94 (0.89 - 1.00) | 3,273 (23.59) | 3,419 (24.64) | 0.07 | 0.62 | 0.89 (0.83 - 0.94) | 2,838 (28.96) | 3,089 (31.52) | 0.001 | 0.02 |
| **Stomach** | | | | | | | | | | |
| Gastroparesis | 1.00 (0.73 - 1.38) | 76 (.55) | 76 (.55) | 1 | 1 | 1.14 (0.89 - 1.46) | 134 (1.37) | 118 (1.2) | 0.31 | 1 |
| Functional dyspepsia | 0.89 (0.74 - 1.06) | 230 (1.66) | 258 (1.86) | 0.2 | 1 | 0.96 (0.80 - 1.15) | 240 (2.45) | 249 (2.54) | 0.68 | 1 |
| **Intestine** | | | | | | | | | | |
| Paralytic ileus | 0.91 (0.69 - 1.19) | 100 (.72) | 110 (.79) | 0.49 | 1 | 1.00 (0.69 - 1.46) | 54 (.55) | 54 (.55) | 1 | 1 |
| Diarrhoea | 0.90 (0.82 - 0.98) | 1,095 (7.89) | 1,208 (8.71) | 0.02 | 0.26 | 0.88 (0.81 - 0.95) | 1,168 (11.92) | 1,309 (13.36) | 0.005 | 0.06 |
| Constipation | 1.26 (1.17 - 1.36) | 1,647 (11.87) | 1,342 (9.67) | <.0001 | <.0001 | 1.11 (1.03 - 1.20) | 1,464 (14.94) | 1,338 (13.65) | 0.02 | 0.19 |
| IBS-C | 1.30 (0.57 - 2.97) | 13 (.09) | 10 (.07) | 0.53 | 1 | 1.33 (0.72 - 2.46) | 24 (.24) | 18 (.18) | 0.35 | 1 |
| IBS-D | 1.58 (0.89 - 2.81) | 30 (.22) | 19 (.14) | 0.12 | 0.89 | 1.40 (0.99 - 1.97) | 78 (.8) | 56 (.57) | 0.06 | 0.57 |
| IBS without Diarrhoea | 1.52 (1.25 - 1.86) | 248 (1.79) | 164 (1.18) | <.0001 | 0.0009 | 1.27 (1.11 - 1.44) | 523 (5.34) | 418 (4.26) | 0.0006 | 0.02 |
| Intestinal pseudo-obstruction* | 0.84 (0.53 - 1.35) | 32 (.23) | 38 (.27) | 0.47 | 1 | 1.35 (0.76 - 2.41) | 27 (.28) | 20 (.2) | 0.31 | 1 |
| **Pelvic floor** | | | | | | | | | | |
| Fecal incontinence | 1.35 (1.07 - 1.70) | 172 (1.24) | 128 (.92) | 0.01 | 0.18 | 1.16 (0.96 - 1.40) | 237 (2.42) | 205 (2.09) | 0.13 | 1 |

**Supplemental Table 9 (continued). ORs and absolute rates of prior exposures in patients with PD compared to matched CVD, stratified for sex**

| | **Male** | | | | | **Female** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)[b]** | **Patients, No. (%)** | | **P-value[b]** | | **OR (95% CI)** | **Patients, No. (%)** | | **P-value** | |
| **Exposure[a]** | Odds PD / odds CVD | PD (n = 13,874) | CVD (n = 13,874) | Uncorrected[c] | Corrected [d] | Odds PD / odds CVD | PD (n = 9,801) | CVD (n = 9,801) | Uncorrected | Corrected |
| **Laxative prescriptions** | | | | | | | | | | |
| Hyperosmotic laxatives | 1.01 (0.96 - 1.07) | 4,388 (31.63) | 4,345 (31.32) | 0.65 | 1 | 1.11 (1.05 - 1.18) | 3,229 (32.95) | 3,005 (30.66) | 0.005 | 0.06 |
| Stimulant laxatives | 0.94 (0.89 - 0.99) | 3,363 (24.24) | 3,522 (25.39) | 0.06 | 0.5 | 1.03 (0.96 - 1.10) | 2,430 (24.79) | 2,377 (24.25) | 0.44 | 1 |
| Bulk-forming laxatives | 1.41 (1.24 - 1.60) | 564 (4.07) | 405 (2.92) | <.0001 | <.0001 | 1.44 (1.24 - 1.67) | 440 (4.49) | 310 (3.16) | <.0001 | 0.0002 |
| Stool softeners | 1.04 (0.99 - 1.10) | 3,629 (26.16) | 3,525 (25.41) | 0.22 | 1 | 1.17 (1.10 - 1.25) | 2,613 (26.66) | 2,324 (23.71) | <.0001 | 0.001 |
| **Antidopaminergic prescriptions** | | | | | | | | | | |
| Domperidone | 1.00 (0.42 - 2.40) | 10 (.07) | 10 (.07) | 1 | 1 | 1.50 (0.67 - 3.34) | 15 (.15) | 10 (.1) | 0.32 | 1 |
| Prochlorperazine | 0.87 (0.78 - 0.98) | 617 (4.45) | 701 (5.05) | 0.02 | 0.26 | 0.95 (0.84 - 1.06) | 607 (6.19) | 639 (6.52) | 0.36 | 1 |
| Promethazine | 0.93 (0.86 - 1.00) | 1,709 (12.32) | 1,825 (13.15) | 0.05 | 0.5 | 0.98 (0.90 - 1.05) | 1,622 (16.55) | 1,656 (16.9) | 0.55 | 1 |
| Metoclopramide | 0.96 (0.88 - 1.05) | 1,020 (7.35) | 1,062 (7.65) | 0.36 | 1 | 1.17 (1.06 - 1.29) | 952 (9.71) | 823 (8.4) | 0.002 | 0.04 |
| **IBD** | | | | | | | | | | |
| Crohn's disease | 1.26 (0.91 - 1.74) | 83 (.6) | 66 (.48) | 0.16 | 1 | 0.92 (0.65 - 1.31) | 60 (.61) | 65 (.66) | 0.65 | 1 |
| Ulcerative colitis | 1.22 (0.92 - 1.61) | 112 (.81) | 92 (.66) | 0.16 | 1 | 1.10 (0.78 - 1.55) | 68 (.69) | 62 (.63) | 0.6 | 1 |
| Microscopic colitis | 0.67 (0.30 - 1.48) | 10 (.07) | 15 (.11) | 0.32 | 1 | 1.00 (0.58 - 1.72) | 26 (.27) | 26 (.27) | 1 | 1 |
| **Interventions** | | | | | | | | | | |
| Appendectomy | 0.46 (0.22 - 0.94) | 11 (.08) | 24 (.17) | 0.03 | 0.31 | 0.67 (0.32 - 1.38) | 12 (.12) | 18 (.18) | 0.27 | 1 |
| Vagotomy | - | 0 (0) | 10 (.07) | 0.002 | 0.03 | 1.00 (0.42 - 2.40) | 10 (.1) | 10 (.1) | 1 | 1 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease; IBD, Inflammatory bowel disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

***** 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 10. ORs of prior exposures in patients with PD compared to matched NCs, stratified for age at the diagnosis of PD.**

| | 50-60 | | | 60-70 | | | 70-80 | | | 80-90 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) [b] | P-value | | OR (95% CI) | P-value | | OR (95% CI) | P-value | | OR (95% CI) | P-value | |
| **Exposure[a]** | **Odds PD / odds NC** | **Uncorrected[c]** | **Corrected [d]** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** |
| **Esophagus** | | | | | | | | | | | | |
| Achalasia | 1.00 (0.42 - 2.41) | 1 | 1 | 1.00 (0.45 - 2.23) | 1 | 1 | 1.47 (0.79 - 2.73) | 0.22 | 0.99 | 1.00 (0.42 - 2.41) | 1 | 1 |
| Dysphagia | 3.27 (2.58 - 4.14) | <.0001 | <.0001 | 2.83 (2.45 - 3.26) | <.0001 | <.0001 | 2.42 (2.16 - 2.71) | <.0001 | <.0001 | 1.77 (1.51 - 2.08) | <.0001 | <.0001 |
| GERD | 1.69 (1.49 - 1.92) | <.0001 | <.0001 | 1.55 (1.44 - 1.67) | <.0001 | <.0001 | 1.53 (1.44 - 1.63) | <.0001 | <.0001 | 1.38 (1.24 - 1.52) | <.0001 | <.0001 |
| **Stomach** | | | | | | | | | | | | |
| Gastroparesis | 4.13 (2.13 - 8.01) | <.0001 | <.0001 | 4.12 (2.58 - 6.58) | <.0001 | <.0001 | 2.64 (1.75 - 3.97) | <.0001 | <.0001 | 2.11 (0.99 - 4.48) | 0.05 | 0.29 |
| Functional dyspepsia | 1.87 (1.24 - 2.84) | 0.003 | 0.02 | 1.69 (1.32 - 2.17) | <.0001 | 0.0003 | 2.02 (1.63 - 2.51) | <.0001 | <.0001 | 1.40 (0.98 - 1.99) | 0.06 | 0.36 |
| **Intestine** | | | | | | | | | | | | |
| Paralytic ileus | 2.11 (0.99 - 4.48) | 0.05 | 0.24 | 1.61 (1.00 - 2.58) | 0.05 | 0.25 | 2.08 (1.42 - 3.06) | 0.0001 | 0.0007 | 1.31 (0.76 - 2.25) | 0.34 | 1 |
| Diarrhoea | 2.35 (1.92 - 2.87) | <.0001 | <.0001 | 1.89 (1.67 - 2.13) | <.0001 | <.0001 | 1.72 (1.55 - 1.90) | <.0001 | <.0001 | 1.33 (1.14 - 1.55) | 0.0005 | 0.004 |
| Constipation | 2.62 (2.14 - 3.19) | <.0001 | <.0001 | 2.54 (2.26 - 2.86) | <.0001 | <.0001 | 2.42 (2.20 - 2.65) | <.0001 | <.0001 | 1.83 (1.60 - 2.09) | <.0001 | <.0001 |
| IBS-C | 1.00 (0.42 - 2.41) | 1 | 1 | 1.40 (0.62 - 3.16) | 0.41 | 1 | 1.90 (0.88 - 4.09) | 0.09 | 0.47 | 1.00 (0.42 - 2.41) | 1 | 1 |
| IBS-D | 1.50 (0.67 - 3.35) | 0.32 | 1 | 1.89 (1.05 - 3.40) | 0.03 | 0.18 | 1.31 (0.86 - 1.99) | 0.21 | 0.98 | 2.91 (1.42 - 5.99) | 0.002 | 0.02 |
| IBS without Diarrhoea | 2.09 (1.52 - 2.88) | <.0001 | <.0001 | 1.94 (1.58 - 2.37) | <.0001 | <.0001 | 1.86 (1.56 - 2.22) | <.0001 | <.0001 | 1.74 (1.30 - 2.32) | 0.0002 | 0.002 |
| Intestinal pseudo-obstruction* | 1.00 (0.42 - 2.41) | 1 | 1 | 1.70 (0.78 - 3.72) | 0.18 | 0.85 | 3.61 (1.79 - 7.27) | 0.0001 | 0.0007 | 1.20 (0.52 - 2.78) | 0.67 | 1 |
| **Pelvic floor** | | | | | | | | | | | | |
| Fecal incontinence | 3.78 (2.13 - 6.70) | <.0001 | <.0001 | 3.10 (2.19 - 4.40) | <.0001 | <.0001 | 2.24 (1.75 - 2.88) | <.0001 | <.0001 | 1.84 (1.30 - 2.60) | 0.0006 | 0.005 |

**Supplemental Table 10 (continued). ORs of prior exposures in patients with PD compared to matched NCs, stratified for age at the diagnosis of PD.**

| | 50-60 | | | 60-70 | | | 70-80 | | | 80-90 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) [b] | P-value | | OR (95% CI) | P-value | | OR (95% CI) | P-value | | OR (95% CI) | P-value | |
| **Exposure[a]** | **Odds PD / odds NC** | **Uncorrected[c]** | **Corrected [d]** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** | **Odds PD / odds NC** | **Uncorrected** | **Corrected** |
| **Laxative prescriptions** | | | | | | | | | | | | |
| Hyperosmotic laxatives | 2.16 (1.91 - 2.45) | <.0001 | <.0001 | 1.68 (1.56 - 1.80) | <.0001 | <.0001 | 1.95 (1.83 - 2.07) | <.0001 | <.0001 | 1.69 (1.54 - 1.86) | <.0001 | <.0001 |
| Stimulant laxatives | 2.31 (2.01 - 2.67) | <.0001 | <.0001 | 1.80 (1.67 - 1.95) | <.0001 | <.0001 | 1.87 (1.75 - 2.00) | <.0001 | <.0001 | 1.62 (1.47 - 1.79) | <.0001 | <.0001 |
| Bulk-forming laxatives | 3.16 (2.13 - 4.69) | <.0001 | <.0001 | 1.96 (1.60 - 2.41) | <.0001 | <.0001 | 2.16 (1.85 - 2.52) | <.0001 | <.0001 | 2.15 (1.71 - 2.70) | <.0001 | <.0001 |
| Stool softeners | 2.48 (2.16 - 2.86) | <.0001 | <.0001 | 1.98 (1.83 - 2.14) | <.0001 | <.0001 | 2.02 (1.89 - 2.15) | <.0001 | <.0001 | 2.11 (1.68 - 2.64) | <.0001 | <.0001 |
| **Antidopaminergic prescriptions** | | | | | | | | | | | | |
| Domperidone | - | 0.002 | 0.009 | 1.00 (0.42 - 2.40) | 1 | 1 | 1.00 (0.42 - 2.40) | 1 | 1 | 10.02 (1.28 - 78.33) | 0.007 | 0.05 |
| Prochlorperazine | 2.48 (1.90 - 3.25) | <.0001 | <.0001 | 1.66 (1.43 - 1.94) | <.0001 | <.0001 | 1.77 (1.54 - 2.04) | <.0001 | <.0001 | 1.29 (1.02 - 1.63) | 0.04 | 0.26 |
| Promethazine | 2.06 (1.77 - 2.41) | <.0001 | <.0001 | 1.61 (1.47 - 1.77) | <.0001 | <.0001 | 1.53 (1.41 - 1.66) | <.0001 | <.0001 | 1.23 (1.07 - 1.41) | 0.006 | 0.04 |
| Metoclopramide | 2.07 (1.68 - 2.55) | <.0001 | <.0001 | 1.75 (1.55 - 1.98) | <.0001 | <.0001 | 1.63 (1.47 - 1.82) | <.0001 | <.0001 | 1.46 (1.23 - 1.75) | <.0001 | 0.0005 |
| **IBD** | | | | | | | | | | | | |
| Crohn's disease | 2.41 (1.15 - 5.05) | 0.02 | 0.09 | 1.34 (0.92 - 1.96) | 0.13 | 0.64 | 1.18 (0.81 - 1.73) | 0.38 | 1 | 1.34 (0.68 - 2.61) | 0.4 | 1 |
| Ulcerative colitis | 1.40 (0.72 - 2.73) | 0.32 | 1 | 2.15 (1.45 - 3.20) | 0.0001 | 0.0007 | 1.35 (0.97 - 1.88) | 0.08 | 0.42 | 1.04 (0.59 - 1.83) | 0.89 | 1 |
| Microscopic colitis | - | 0.002 | 0.009 | 1.00 (0.42 - 2.40) | 1 | 1 | 0.86 (0.47 - 1.60) | 0.64 | 1 | 1.00 (0.42 - 2.41) | 1 | 1 |
| **Interventions** | | | | | | | | | | | | |
| Appendectomy | 1.00 (0.42 - 2.41) | 1 | 1 | 1.00 (0.42 - 2.40) | 1 | 1 | 1.20 (0.60 - 2.38) | 0.6 | 1 | 1.00 (0.42 - 2.41) | 1 | 1 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vagotomy | - | 0.002 | 0.009 | - | 0.002 | 0.009 | - | 0.002 | 0.009 | - | - | - |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease; IBD, Inflammatory bowel disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

***** 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 11. Absolute rates of prior exposures in patients with PD compared to matched NCs, stratified for age at the diagnosis of PD.**

| | 50-60 | | | | 60-70 | | | | 70-80 | | | | 80-90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value[b] | | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value | |
| **Exposure** | **PD (n = 3,232)** | **NC (n = 3,232)** | **Uncorrected[b]** | **Corrected[c]** | **PD (n = 8,571)** | **NC (n = 8,571)** | **Un-corrected** | **Corrected[c]** | **PD (n = 11,124)** | **NC (n = 11,124)** | **Un-corrected** | **Corrected** | **PD (n = 3,992)** | **NC (n = 3,992)** | **Un-corrected** | **Corrected** |
| **Esophagus** | | | | | | | | | | | | | | | | |
| Achalasia | 10 (.31) | 10 (.31) | 1 | 1 | 12 (.14) | 12 (.14) | 1 | 1 | 25 (.22) | 17 (.15) | 0.22 | 0.99 | 10 (.25) | 10 (.25) | 1 | 1 |
| Dysphagia | 291 (9.) | 95 (2.94) | <.0001 | <.0001 | 742 (8.66) | 278 (3.24) | <.0001 | <.0001 | 1,058 (9.51) | 463 (4.16) | <.0001 | <.0001 | 442 (11.07) | 262 (6.56) | <.0001 | <.0001 |
| GERD | 724 (22.4) | 472 (14.6) | <.0001 | <.0001 | 2,078 (24.24) | 1,468 (17.13) | <.0001 | <.0001 | 3,029 (27.23) | 2,187 (19.66) | <.0001 | <.0001 | 1,139 (28.53) | 897 (22.47) | <.0001 | <.0001 |
| **Stomach** | | | | | | | | | | | | | | | | |
| Gastroparesis | 45 (1.39) | 11 (.34) | <.0001 | <.0001 | 90 (1.05) | 22 (.26) | <.0001 | <.0001 | 84 (.76) | 32 (.29) | <.0001 | <.0001 | 21 (.53) | 10 (.25) | 0.05 | 0.29 |
| Functional dyspepsia | 65 (2.01) | 35 (1.08) | 0.003 | 0.02 | 166 (1.94) | 99 (1.16) | <.0001 | 0.0003 | 256 (2.3) | 128 (1.15) | <.0001 | <.0001 | 75 (1.88) | 54 (1.35) | 0.06 | 0.36 |
| **Intestine** | | | | | | | | | | | | | | | | |
| Paralytic ileus | 21 (.65) | 10 (.31) | 0.05 | 0.24 | 45 (.53) | 28 (.33) | 0.05 | 0.25 | 81 (.73) | 39 (.35) | 0.0001 | 0.0007 | 30 (.75) | 23 (.58) | 0.34 | 1 |
| Diarrhoea | 321 (9.93) | 145 (4.49) | <.0001 | <.0001 | 795 (9.28) | 440 (5.13) | <.0001 | <.0001 | 1,075 (9.66) | 652 (5.86) | <.0001 | <.0001 | 416 (10.42) | 321 (8.04) | 0.0005 | 0.004 |
| Constipation | 356 (11.01) | 146 (4.52) | <.0001 | <.0001 | 989 (11.54) | 418 (4.88) | <.0001 | <.0001 | 1,575 (14.16) | 710 (6.38) | <.0001 | <.0001 | 672 (16.83) | 398 (9.97) | <.0001 | <.0001 |
| IBS-C | 10 (.31) | 10 (.31) | 1 | 1 | 14 (.16) | 10 (.12) | 0.41 | 1 | 19 (.17) | 10 (.09) | 0.09 | 0.47 | 10 (.25) | 10 (.25) | 1 | 1 |
| IBS-D | 15 (.46) | 10 (.31) | 0.32 | 1 | 32 (.37) | 17 (.2) | 0.03 | 0.18 | 51 (.46) | 39 (.35) | 0.21 | 0.98 | 29 (.73) | 10 (.25) | 0.002 | 0.02 |
| IBS without Diarrhoea | 117 (3.62) | 57 (1.76) | <.0001 | <.0001 | 280 (3.27) | 147 (1.72) | <.0001 | <.0001 | 360 (3.24) | 196 (1.76) | <.0001 | <.0001 | 125 (3.13) | 73 (1.83) | 0.0002 | 0.002 |

**Supplemental Table 11 (continued). Absolute rates of prior exposures in patients with PD compared to matched NCs, stratified for age at the diagnosis of PD.**

| | 50-60 | | | | 60-70 | | | | 70-80 | | | | 80-90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value[b] | | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value | |
| **Exposure** | **PD (n = 3,232)** | **NC (n = 3,232)** | **Uncorrected[b]** | **Corrected[c]** | **PD (n = 8,571)** | **NC (n = 8,571)** | **Un-corrected** | **Corrected[c]** | **PD (n = 11,124)** | **NC (n = 11,124)** | **Un-corrected** | **Corrected** | **PD (n = 3,992)** | **NC (n = 3,992)** | **Un-corrected** | **Corrected** |
| Intestinal pseudo-obstruction* | 10 (.31) | 10 (.31) | 1 | 1 | 17 (.2) | 10 (.12) | 0.18 | 0.85 | 36 (.32) | 10 (.09) | 0.0001 | 0.0007 | 12 (.3) | 10 (.25) | 0.67 | 1 |
| **Pelvic floor** | | | | | | | | | | | | | | | | |
| Fecal incontinence | 56 (1.73) | 15 (.46) | <.0001 | <.0001 | 129 (1.51) | 42 (.49) | <.0001 | <.0001 | 200 (1.8) | 90 (.81) | <.0001 | <.0001 | 91 (2.28) | 50 (1.25) | 0.0006 | 0.005 |
| **Laxative prescriptions** | | | | | | | | | | | | | | | | |
| Hyperosmotic laxatives | 896 (27.72) | 487 (15.07) | <.0001 | <.0001 | 2,492 (29.07) | 1,682 (19.62) | <.0001 | <.0001 | 3,684 (33.12) | 2,255 (20.27) | <.0001 | <.0001 | 1,492 (37.37) | 1,042 (26.1) | <.0001 | <.0001 |
| Stimulant laxatives | 659 (20.39) | 322 (9.96) | <.0001 | <.0001 | 1,957 (22.83) | 1,208 (14.09) | <.0001 | <.0001 | 2,802 (25.19) | 1,696 (15.25) | <.0001 | <.0001 | 1,297 (32.49) | 915 (22.92) | <.0001 | <.0001 |
| Bulk-forming laxatives | 102 (3.16) | 33 (1.02) | <.0001 | <.0001 | 274 (3.2) | 142 (1.66) | <.0001 | <.0001 | 507 (4.56) | 241 (2.17) | <.0001 | <.0001 | 237 (5.94) | 114 (2.86) | <.0001 | <.0001 |
| Stool softeners | 708 (21.91) | 328 (10.15) | <.0001 | <.0001 | 2,040 (23.8) | 1,170 (13.65) | <.0001 | <.0001 | 2,975 (26.74) | 1,706 (15.34) | <.0001 | <.0001 | 239 (5.99) | 117 (2.93) | <.0001 | <.0001 |
| **Antidopaminergic prescriptions** | | | | | | | | | | | | | | | | |
| Domperidone | 10 (.31) | 0 (0) | 0.002 | 0.009 | 10 (.12) | 10 (.12) | 1 | 1 | 10 (.09) | 10 (.09) | 1 | 1 | 10 (.25) | 1 (.03) | 0.007 | 0.05 |
| Prochlorperazine | 187 (5.79) | 78 (2.41) | <.0001 | <.0001 | 443 (5.17) | 272 (3.17) | <.0001 | <.0001 | 548 (4.93) | 316 (2.84) | <.0001 | <.0001 | 163 (4.08) | 128 (3.21) | 0.04 | 0.26 |

**Supplemental Table 11 (continued). Absolute rates of prior exposures in patients with PD compared to matched NCs, stratified for age at the diagnosis of PD.**

| | 50-60 | | | | 60-70 | | | | 70-80 | | | | 80-90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value[b] | | Patients, No. (%) | | P-value | | Patients, No. (%) | | P-value | |
| **Exposure** | **PD (n = 3,232)** | **NC (n = 3,232)** | **Uncorrected[b]** | **Corrected [c]** | **PD (n = 8,571)** | **NC (n = 8,571)** | **Un-corrected** | **Corrected[c]** | **PD (n = 11,124)** | **NC (n = 11,124)** | **Un-corrected** | **Corrected** | **PD (n = 3,992)** | **NC (n = 3,992)** | **Un-corrected** | **Corrected** |
| Promethazine | 517 (16.) | 273 (8.45) | <.0001 | <.0001 | 1,262 (14.72) | 828 (9.66) | <.0001 | <.0001 | 1,545 (13.89) | 1,061 (9.54) | <.0001 | <.0001 | 504 (12.63) | 420 (10.52) | 0.006 | 0.04 |
| Metoclopramide | 273 (8.45) | 138 (4.27) | <.0001 | <.0001 | 713 (8.32) | 422 (4.92) | <.0001 | <.0001 | 909 (8.17) | 575 (5.17) | <.0001 | <.0001 | 317 (7.94) | 222 (5.56) | <.0001 | 0.0005 |
| **Inflammatory bowel disease** | | | | | | | | | | | | | | | | |
| Crohn's disease | 24 (.74) | 10 (.31) | 0.02 | 0.09 | 63 (.74) | 47 (.55) | 0.13 | 0.64 | 58 (.52) | 49 (.44) | 0.38 | 1 | 20 (.5) | 15 (.38) | 0.4 | 1 |
| Ulcerative colitis | 21 (.65) | 15 (.46) | 0.32 | 1 | 77 (.9) | 36 (.42) | 0.0001 | 0.0007 | 82 (.74) | 61 (.55) | 0.08 | 0.42 | 25 (.63) | 24 (.6) | 0.89 | 1 |
| Microscopic colitis | 10 (.31) | 0 (0) | 0.002 | 0.009 | 10 (.12) | 10 (.12) | 1 | 1 | 19 (.17) | 22 (.2) | 0.64 | 1 | 10 (.25) | 10 (.25) | 1 | 1 |
| **Interventions** | | | | | | | | | | | | | | | | |
| Appendectomy | 10 (.31) | 10 (.31) | 1 | 1 | 10 (.12) | 10 (.12) | 1 | 1 | 18 (.16) | 15 (.13) | 0.6 | 1 | 10 (.25) | 10 (.25) | 1 | 1 |
| Vagotomy | 0 (0) | 10 (.31) | 0.002 | 0.009 | 10 (.12) | 0 (0) | 0.002 | 0.009 | 10 (.09) | 0 (0) | 0.002 | 0.009 | 0 (0) | 0 (0) | - | - |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

[b] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[c] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

* 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 12. ORs and absolute rates of prior exposures in patients with PD compared to matched NCs, after exclusion of antidopaminergic drug prescriptions [e].**

| | OR (95% CI)[b] | Patients, No. (%) | | P-value | |
|---|---|---|---|---|---|
| **Exposure[a]** | **Odds PD / odds NC** | **PD (n = 26,805)** | **NC (n = 26,805)** | **Uncorrected[c]** | **Corrected [d]** |
| **Esophagus** | | | | | |
| Achalasia | 2.19 (1.31 - 3.67) | 46 (.17) | 21 (.08) | 0.002 | 0.009 |
| Dysphagia | 3.77 (3.46 - 4.12) | 2,360 (8.8) | 669 (2.5) | <.0001 | <.0001 |
| GERD | 2.03 (1.94 - 2.13) | 6,263 (23.37) | 3,494 (13.03) | <.0001 | <.0001 |
| **Stomach** | | | | | |
| Gastroparesis | 3.57 (2.55 - 5.01) | 153 (.57) | 43 (.16) | <.0001 | <.0001 |
| Functional dyspepsia | 3.07 (2.55 - 3.69) | 455 (1.7) | 150 (.56) | <.0001 | <.0001 |
| **Intestine** | | | | | |
| Paralytic ileus | 1.67 (1.26 - 2.21) | 130 (.48) | 78 (.29) | 0.0003 | 0.001 |
| Diarrhoea | 2.93 (2.71 - 3.17) | 2,508 (9.36) | 912 (3.4) | <.0001 | <.0001 |
| Constipation | 3.52 (3.28 - 3.78) | 3,361 (12.54) | 1,049 (3.91) | <.0001 | <.0001 |
| IBS-C | 4.76 (2.55 - 8.87) | 57 (.21) | 12 (.04) | <.0001 | <.0001 |
| IBS-D | 2.96 (2.04 - 4.27) | 112 (.42) | 38 (.14) | <.0001 | <.0001 |
| IBS without Diarrhoea | 3.25 (2.83 - 3.74) | 836 (3.12) | 263 (.98) | <.0001 | <.0001 |
| Intestinal pseudo-obstruction* | 2.53 (1.52 - 4.19) | 53 (.2) | 21 (.08) | 0.0002 | 0.0009 |
| **Pelvic floor** | | | | | |
| Fecal incontinence | 4.87 (3.85 - 6.16) | 404 (1.51) | 84 (.31) | <.0001 | <.0001 |
| **Laxative prescriptions** | | | | | |
| Hyperosmotic laxatives | 2.81 (2.69 - 2.94) | 7,629 (28.46) | 3,324 (12.4) | <.0001 | <.0001 |
| Stimulant laxatives | 2.63 (2.50 - 2.76) | 5,689 (21.22) | 2,495 (9.31) | <.0001 | <.0001 |
| Bulk-forming laxatives | 3.57 (3.11 - 4.11) | 910 (3.39) | 261 (.97) | <.0001 | <.0001 |
| Stool softeners | 2.82 (2.68 - 2.97) | 5,758 (21.48) | 2,371 (8.85) | <.0001 | <.0001 |
| **Inflammatory bowel disease** | | | | | |
| Crohn's disease | 2.37 (1.70 - 3.29) | 118 (.44) | 50 (.19) | <.0001 | <.0001 |
| Ulcerative colitis | 1.82 (1.37 - 2.41) | 136 (.51) | 75 (.28) | <.0001 | 0.0001 |
| Microscopic colitis | 3.08 (1.65 - 5.76) | 40 (.15) | 13 (.05) | 0.0002 | 0.0009 |
| **Interventions** | | | | | |
| Appendectomy | 2.18 (1.07 - 4.46) | 24 (.09) | 11 (.04) | 0.03 | 0.1 |
| Vagotomy | - | 0 (0) | 10 (.04) | 0.002 | 0.006 |

Abbreviations: PD, Parkinson's Disease; NC, Negative control; AD, Alzheimer's Disease; CVD, cerebrovascular diseases; OR, Odds Ratio; IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea), GERD, Gastro-esophageal reflux disease

[a] Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in the **online supplemental methods**.

[b] ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

[e] Antidopaminergic drugs include: metoclopramide, domperidone, promethazine, prochlorperazine. Only patients with any of these prescriptions within 2 years before the index event were excluded from further analysis.

* 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 13. The absolute rates of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome[a]** | **Rate exposure cohort** | **Rate control cohort** | **P-value[c]** | **Corrected P-value[d]** | **Rate exposure cohort** | **Rate control cohort** | **P-value** | **Corrected P-value** |
| **Achalasia versus negative control** | **Outcome / total (%)** | | | | **Outcome / total (%)** | | | |
| Parkinson's disease | 46/5,798 (.79) | 37/5,822 (.64) | 0.31 | 0.86 | 41/5,629 (.73) | 27/5,646 (.48) | 0.09 | 0.48 |
| Alzheimer's disease | 30/5,824 (.52) | 25/5,835 (.43) | 0.5 | 0.91 | 27/5,653 (.48) | 26/5,661 (.46) | 0.89 | 1 |
| Cerebrovascular disease | 439/5,445 (8.06) | 333/5,759 (5.78) | <.0001 | <.0001 | 391/5,309 (7.36) | 372/5,495 (6.77) | 0.24 | 0.67 |
| **Dysphagia versus negative control** | | | | | | | | |
| Parkinson's disease | 2,162/242,596 (.89) | 976/245,234 (.40) | <.0001 | <.0001 | 2,108/242,117 (.87) | 939/244,719 (.38) | <.0001 | <.0001 |
| Alzheimer's disease | 1,534/245,045 (.63) | 851/245,524 (.35) | <.0001 | <.0001 | 1,473/244,587 (.60) | 949/244,959 (.39) | <.0001 | <.0001 |
| Cerebrovascular disease | 19,868/220,241 (9.02) | 11,229/242,871 (4.62) | <.0001 | <.0001 | 19,193/220,184 (8.72) | 13,931/236,579 (5.89) | <.0001 | <.0001 |
| **GERD versus negative control** | | | | | | | | |
| Parkinson's disease | 6,496/1,268,876 (.51) | 5,601/1,271,126 (.44) | <.0001 | <.0001 | 4,847/1,060,916 (.46) | 4,287/1,062,527 (.40) | <.0001 | <.0001 |
| Alzheimer's disease | 5,629/1,271,995 (.44) | 4,313/1,273,062 (.34) | <.0001 | <.0001 | 3,912/1,063,507 (.37) | 3,309/1,064,068 (.31) | <.0001 | <.0001 |
| Cerebrovascular disease | 85,129/1,216,094 (7.00) | 51,026/1,259,873 (4.05) | <.0001 | <.0001 | 60,610/1,027,958 (5.90) | 44,546/1,043,329 (4.27) | <.0001 | <.0001 |
| **Gastroparesis versus negative control** | | | | | | | | |
| Parkinson's disease | 235/29,250 (.80) | 95/29,420 (.32) | <.0001 | <.0001 | 230/29,261 (.79) | 95/29,426 (.32) | <.0001 | <.0001 |
| Alzheimer's disease | 126/29,412 (.43) | 81/29,446 (.28) | 0.002 | 0.003 | 115/29,420 (.39) | 68/29,442 (.23) | 0.0005 | 0.0009 |
| Cerebrovascular disease | 3,067/26,995 (11.36) | 1,219/29,185 (4.18) | <.0001 | <.0001 | 2,944/27,024 (10.89) | 1,672/28,245 (5.92) | <.0001 | <.0001 |

**Supplemental Table 13 (continued). The absolute rates of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome[a]** | **Rate exposure cohort** | **Rate control cohort** | **P-value[c]** | **Corrected P-value[d]** | **Rate exposure cohort** | **Rate control cohort** | **P-value** | **Corrected P-value** |
| **Functional dyspepsia versus negative control** | | | | | | | | |
| Parkinson's disease | 460/111,734 (.41) | 389/111,902 (.35) | 0.01 | 0.03 | 439/108,333 (.41) | 383/108,450 (.35) | 0.05 | 0.09 |
| Alzheimer's disease | 444/111,920 (.40) | 339/112,028 (.30) | 0.0002 | 0.0005 | 422/108,517 (.39) | 362/108,591 (.33) | 0.03 | 0.09 |
| Cerebrovascular disease | 6,351/106,348 (5.97) | 4,579/110,935 (4.13) | <.0001 | <.0001 | 5,977/103,108 (5.80) | 5,613/104,918 (5.35) | <.0001 | <.0001 |
| **Intestinal pseudo-obstruction* versus negative control** | | | | | | | | |
| Parkinson's disease | 56/6,997 (.80) | 40/7,024 (.57) | 0.1 | 0.27 | 55/6,793 (.81) | 30/6,822 (.44) | 0.006 | 0.02 |
| Alzheimer's disease | 41/7,032 (.58) | 30/7,037 (.43) | 0.19 | 0.35 | 37/6,827 (.54) | 29/6,830 (.42) | 0.32 | 0.59 |
| Cerebrovascular disease | 569/6,362 (8.94) | 335/6,946 (4.82) | <.0001 | <.0001 | 511/6,200 (8.24) | 412/6,553 (6.29) | <.0001 | 0.0002 |
| **Paralytic ileus versus negative control** | | | | | | | | |
| Parkinson's disease | 173/30,516 (.57) | 199/30,610 (.65) | 0.19 | 0.34 | 172/30,352 (.57) | 169/30,447 (.56) | 0.85 | 1 |
| Alzheimer's disease | 167/30,619 (.55) | 133/30,673 (.43) | 0.05 | 0.13 | 163/30,453 (.54) | 138/30,496 (.45) | 0.15 | 0.4 |
| Cerebrovascular disease | 2,479/27,661 (8.96) | 1,661/30,285 (5.48) | <.0001 | <.0001 | 2,387/27,542 (8.67) | 2,064/29,047 (7.11) | <.0001 | <.0001 |
| **Diarrhoea versus negative control** | | | | | | | | |
| Parkinson's disease | 2,339/498,847 (.47) | 1,806/499,577 (.36) | <.0001 | <.0001 | 2,191/483,636 (.45) | 1,668/484,243 (.34) | <.0001 | <.0001 |
| Alzheimer's disease | 2,465/499,477 (.49) | 1,412/500,169 (.28) | <.0001 | <.0001 | 2,283/484,235 (.47) | 1,359/484,788 (.28) | <.0001 | <.0001 |
| Cerebrovascular disease | 32,194/473,459 (6.80) | 18,172/495,659 (3.67) | <.0001 | <.0001 | 29,300/460,758 (6.36) | 21,813/469,900 (4.64) | <.0001 | <.0001 |

**Supplemental Table 13 (continued). The absolute rates of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome[a]** | **Rate exposure cohort** | **Rate control cohort** | **P-value[c]** | **Corrected P-value[d]** | **Rate exposure cohort** | **Rate control cohort** | **P-value** | **Corrected P-value** |
| **Constipation versus negative control** | | | | | | | | |
| Parkinson's disease | 3,432/455,315 (.75) | 1,516/458,982 (.33) | <.0001 | <.0001 | 3,239/439,684 (.74) | 1,370/443,194 (.31) | <.0001 | <.0001 |
| Alzheimer's disease | 3,196/458,479 (.70) | 1,550/459,375 (.34) | <.0001 | <.0001 | 2,945/442,818 (.67) | 1,497/443,522 (.34) | <.0001 | <.0001 |
| Cerebrovascular disease | 32,589/427,119 (7.63) | 18,623/454,863 (4.09) | <.0001 | <.0001 | 29,422/414,522 (7.10) | 21,518/429,507 (5.01) | <.0001 | <.0001 |
| **IBS-C versus negative control** | | | | | | | | |
| Parkinson's disease | 10/1,102 (.91) | 10/1,106 (.90) | 0.99 | 1 | 10/1,241 (.81) | 10/1,247 (.80) | 0.99 | 1 |
| Alzheimer's disease | 10/1,106 (.90) | 10/1,108 (.90) | 1 | 1 | 10/1,246 (.80) | 10/1,246 (.80) | 1 | 1 |
| Cerebrovascular disease | 70/1,057 (6.62) | 45/1,096 (4.11) | 0.01 | 0.06 | 83/1,191 (6.97) | 65/1,209 (5.38) | 0.12 | 0.64 |
| **IBS-D versus negative control** | | | | | | | | |
| Parkinson's disease | 47/10,666 (.44) | 43/10,668 (.40) | 0.67 | 1 | 53/11,113 (.48) | 51/11,125 (.46) | 0.84 | 1 |
| Alzheimer's disease | 61/10,675 (.57) | 54/10,691 (.51) | 0.51 | 1 | 61/11,125 (.55) | 57/11,136 (.51) | 0.71 | 1 |
| Cerebrovascular disease | 692/10,048 (6.89) | 513/10,584 (4.85) | <.0001 | <.0001 | 702/10,468 (6.71) | 675/10,724 (6.29) | 0.24 | 1 |
| **IBS-without-D versus negative control** | | | | | | | | |
| Parkinson's disease | 699/165,298 (.42) | 581/165,528 (.35) | 0.0009 | 0.002 | 681/164,520 (.41) | 584/164,750 (.35) | 0.006 | 0.02 |
| Alzheimer's disease | 608/165,600 (.37) | 469/165,729 (.28) | <.0001 | <.0001 | 586/164,821 (.36) | 512/164,914 (.31) | 0.02 | 0.05 |
| Cerebrovascular disease | 8,809/159,647 (5.52) | 6,557/164,197 (3.99) | <.0001 | <.0001 | 8,301/159,003 (5.22) | 7,630/160,898 (4.74) | <.0001 | <.0001 |

**Supplemental Table 13 (continued). The absolute rates of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome[a]** | **Rate exposure cohort** | **Rate control cohort** | **P-value[c]** | **Corrected P-value[d]** | **Rate exposure cohort** | **Rate control cohort** | **P-value** | **Corrected P-value** |
| **Fecal incontinence versus negative control** | | | | | | | | |
| Parkinson's disease | 409/38,037 (1.08) | 232/38,293 (.61) | <.0001 | <.0001 | 392/38,127 (1.03) | 226/38,347 (.59) | <.0001 | <.0001 |
| Alzheimer's disease | 434/38,178 (1.14) | 205/38,333 (.53) | <.0001 | <.0001 | 438/38,272 (1.14) | 250/38,403 (.65) | <.0001 | <.0001 |
| Cerebrovascular disease | 3,437/34,407 (9.99) | 2,297/37,839 (6.07) | <.0001 | <.0001 | 3,334/34,531 (9.66) | 2,689/36,673 (7.33) | <.0001 | <.0001 |
| **Crohn's disease versus negative control** | | | | | | | | |
| Parkinson's disease | 139/47,658 (.29) | 151/47,695 (.32) | 0.49 | 0.89 | 133/47,411 (.28) | 146/47,442 (.31) | 0.44 | 0.81 |
| Alzheimer's disease | 122/47,718 (.26) | 86/47,740 (.18) | 0.01 | 0.03 | 110/47,471 (.23) | 90/47,490 (.19) | 0.16 | 0.43 |
| Cerebrovascular disease | 1,881/46,642 (4.03) | 1,654/47,333 (3.49) | <.0001 | 0.0001 | 1,770/46,440 (3.81) | 1,502/47,158 (3.19) | <.0001 | <.0001 |
| **Ulcerative colitis versus negative control** | | | | | | | | |
| Parkinson's disease | 162/43,010 (.38) | 152/43,040 (.35) | 0.57 | 1 | 150/42,871 (.35) | 165/42,898 (.38) | 0.4 | 1 |
| Alzheimer's disease | 115/43,081 (.27) | 111/43,100 (.26) | 0.79 | 1 | 110/42,947 (.26) | 102/42,954 (.24) | 0.58 | 1 |
| Cerebrovascular disease | 1,906/41,823 (4.56) | 1,693/42,688 (3.97) | <.0001 | 0.0002 | 1,777/41,728 (4.26) | 1,807/42,066 (4.30) | 0.8 | 1 |
| **Microscopic colitis versus negative control** | | | | | | | | |
| Parkinson's disease | 10/2,016 (.50) | 20/2,019 (.99) | 0.07 | 0.13 | 11/2,157 (.51) | 15/2,160 (.69) | 0.43 | 0.8 |
| Alzheimer's disease | 32/2,017 (1.59) | 13/2,021 (.64) | 0.005 | 0.01 | 33/2,159 (1.53) | 21/2,164 (.97) | 0.1 | 0.28 |
| Cerebrovascular disease | 207/1,870 (11.07) | 139/1,991 (6.98) | <.0001 | 0.0001 | 221/2,002 (11.04) | 181/2,072 (8.74) | 0.02 | 0.11 |

**Supplemental Table 13 (continued). The absolute rates of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome[a]** | **Rate exposure cohort** | **Rate control cohort** | **P-value[c]** | **Corrected P-value[d]** | **Rate exposure cohort** | **Rate control cohort** | **P-value** | **Corrected P-value** |
| **Appendectomy versus negative control** | | | | | | | | |
| Parkinson's disease | 10/6,972 (.14) | 27/6,978 (.39) | 0.005 | 0.03 | 10/7,065 (.14) | 21/7,068 (.30) | 0.05 | 0.27 |
| Alzheimer's disease | 14/6,980 (.20) | 10/6,985 (.14) | 0.41 | 0.76 | 12/7,073 (.17) | 11/7,076 (.16) | 0.83 | 1 |
| Cerebrovascular disease | 257/6,759 (3.80) | 209/6,934 (3.01) | 0.01 | 0.03 | 227/6,858 (3.31) | 261/6,888 (3.79) | 0.14 | 0.37 |
| **Vagotomy versus negative control** | | | | | | | | |
| Parkinson's disease | 00/163 (.00) | 00/164 (.00) | - | - | 00/180 (.00) | 10/179 (5.59) | - | - |
| Alzheimer's disease | 10/164 (6.10) | 10/164 (6.10) | 1 | 1 | 10/180 (5.56) | 10/180 (5.56) | 1 | 1 |
| Cerebrovascular disease | 14/158 (8.86) | 10/163 (6.13) | 0.37 | 1 | 12/171 (7.02) | 11/173 (6.36) | 0.81 | 1 |

Abbreviations: IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea); GERD, Gastro-esophageal reflux disease; NC, Negative control; AD; Alzheimer's disease; CVD, cerebrovascular diseases; PD, Parkinson's disease.

[a] Each analysis compares a cohort of patients identified by the diagnosis of a given exposure with their respective negative controls for the prospective development of PD, AD and CVD (i.e. outcome) within 5 years of the index event (i.e. diagnosis of the exposure or visit for NCs). After propensity score matching, subjects that already had the investigated outcome (i.e. PD, AD or CVD) documented prior to the index event were excluded from further analysis. Exposures and outcomes were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Diagnostic coding can be found in **the online supplemental methods**.

[b] Baseline characteristics include: age, sex, race and ethnicity; Risk factors include arterial hypertension (AHT), Diabetes Mellitus (DM), Atrial fibrillation (Afib) and flutter and nicotine dependence.

[c] P-value of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (see: methods).

* 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 14. The Relative Risk (RR) of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| Outcome[a] | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Achalasia versus negative control** | **RR** | **OR** | **P-value[c]** | **Corrected P-value [d]** | **RR** | **OR** | **P-value** | **Corrected P-value** |
| Parkinson's disease | 1.25 (0.81 - 1.92) | 1.25 (0.81 - 1.93) | 0.31 | 0.86 | 1.52 (0.94 - 2.47) | 1.53 (0.94 - 2.49) | 0.09 | 0.48 |
| Alzheimer's disease | 1.2 (0.71 - 2.04) | 1.2 (0.71 - 2.05) | 0.5 | 0.91 | 1.04 (0.61 - 1.78) | 1.04 (0.61 - 1.78) | 0.89 | 1 |
| Cerebrovascular disease | 1.39 (1.22 - 1.6) | 1.43 (1.23 - 1.66) | <.0001 | <.0001 | 1.09 (0.95 - 1.25) | 1.09 (0.94 - 1.27) | 0.24 | 0.67 |
| **Dysphagia versus negative control** | | | | | | | | |
| Parkinson's disease | 2.24 (2.08 - 2.41) | 2.25 (2.09 - 2.43) | <.0001 | <.0001 | 2.27 (2.1 - 2.45) | 2.28 (2.11 - 2.46) | <.0001 | <.0001 |
| Alzheimer's disease | 1.81 (1.66 - 1.96) | 1.81 (1.67 - 1.97) | <.0001 | <.0001 | 1.55 (1.43 - 1.69) | 1.56 (1.44 - 1.69) | <.0001 | <.0001 |
| Cerebrovascular disease | 1.95 (1.91 - 2.0) | 2.05 (2.0 - 2.09) | <.0001 | <.0001 | 1.48 (1.45 - 1.51) | 1.53 (1.49 - 1.56) | <.0001 | <.0001 |
| **GERD versus negative control** | | | | | | | | |
| Parkinson's disease | 1.16 (1.12 - 1.2) | 1.16 (1.12 - 1.21) | <.0001 | <.0001 | 1.13 (1.09 - 1.18) | 1.13 (1.09 - 1.18) | <.0001 | <.0001 |
| Alzheimer's disease | 1.31 (1.26 - 1.36) | 1.31 (1.26 - 1.36) | <.0001 | <.0001 | 1.18 (1.13 - 1.24) | 1.18 (1.13 - 1.24) | <.0001 | <.0001 |
| Cerebrovascular disease | 1.73 (1.71 - 1.75) | 1.78 (1.76 - 1.8) | <.0001 | <.0001 | 1.38 (1.36 - 1.4) | 1.4 (1.39 - 1.42) | <.0001 | <.0001 |
| **Gastroparesis versus negative control** | | | | | | | | |
| Parkinson's disease | 2.49 (1.96 - 3.16) | 2.5 (1.97 - 3.17) | <.0001 | <.0001 | 2.43 (1.92 - 3.09) | 2.45 (1.92 - 3.11) | <.0001 | <.0001 |
| Alzheimer's disease | 1.56 (1.18 - 2.06) | 1.56 (1.18 - 2.06) | 0.002 | 0.003 | 1.69 (1.25 - 2.28) | 1.7 (1.26 - 2.29) | 0.0005 | 0.0009 |
| Cerebrovascular disease | 2.72 (2.55 - 2.9) | 2.94 (2.75 - 3.15) | <.0001 | <.0001 | 1.84 (1.74 - 1.95) | 1.94 (1.83 - 2.07) | <.0001 | <.0001 |
| **Functional dyspepsia versus negative control** | | | | | | | | |
| Parkinson's disease | 1.18 (1.03 - 1.36) | 1.19 (1.04 - 1.36) | 0.01 | 0.03 | 1.15 (1.0 - 1.32) | 1.15 (1.0 - 1.32) | 0.05 | 0.09 |
| Alzheimer's disease | 1.31 (1.14 - 1.51) | 1.31 (1.14 - 1.51) | 0.0002 | 0.0005 | 1.17 (1.01 - 1.34) | 1.17 (1.01 - 1.34) | 0.03 | 0.09 |
| Cerebrovascular disease | 1.45 (1.39 - 1.5) | 1.48 (1.42 - 1.53) | <.0001 | <.0001 | 1.08 (1.05 - 1.12) | 1.09 (1.05 - 1.13) | <.0001 | <.0001 |

**Supplemental Table 14 (continued). The Relative Risk (RR) of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| Outcome[a] | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Achalasia versus negative control** | **RR** | **OR** | **P-value[c]** | **Corrected P-value [d]** | **RR** | **OR** | **P-value** | **Corrected P-value** |
| **Intestinal pseudo-obstruction* versus negative control** | | | | | | | | |
| Parkinson's disease | 1.41 (0.94 - 2.11) | 1.41 (0.94 - 2.12) | 0.1 | 0.27 | 1.84 (1.18 - 2.87) | 1.85 (1.18 - 2.89) | 0.006 | 0.02 |
| Alzheimer's disease | 1.37 (0.85 - 2.19) | 1.37 (0.85 - 2.2) | 0.19 | 0.35 | 1.28 (0.79 - 2.07) | 1.28 (0.79 - 2.08) | 0.32 | 0.59 |
| Cerebrovascular disease | 1.85 (1.63 - 2.11) | 1.94 (1.69 - 2.23) | <.0001 | <.0001 | 1.31 (1.16 - 1.49) | 1.34 (1.17 - 1.53) | <.0001 | 0.0002 |
| **Paralytic ileus versus negative control** | | | | | | | | |
| Parkinson's disease | 0.87 (0.71 - 1.07) | 0.87 (0.71 - 1.07) | 0.19 | 0.34 | 1.02 (0.83 - 1.26) | 1.02 (0.83 - 1.26) | 0.85 | 1 |
| Alzheimer's disease | 1.26 (1.0 - 1.58) | 1.26 (1.0 - 1.58) | 0.05 | 0.13 | 1.18 (0.94 - 1.48) | 1.18 (0.94 - 1.49) | 0.15 | 0.4 |
| Cerebrovascular disease | 1.63 (1.54 - 1.74) | 1.7 (1.59 - 1.81) | <.0001 | <.0001 | 1.22 (1.15 - 1.29) | 1.24 (1.17 - 1.32) | <.0001 | <.0001 |
| **Diarrhoea versus negative control** | | | | | | | | |
| Parkinson's disease | 1.3 (1.22 - 1.38) | 1.3 (1.22 - 1.38) | <.0001 | <.0001 | 1.32 (1.23 - 1.4) | 1.32 (1.24 - 1.4) | <.0001 | <.0001 |
| Alzheimer's disease | 1.75 (1.64 - 1.87) | 1.75 (1.64 - 1.87) | <.0001 | <.0001 | 1.68 (1.57 - 1.8) | 1.69 (1.58 - 1.8) | <.0001 | <.0001 |
| Cerebrovascular disease | 1.85 (1.82 - 1.89) | 1.92 (1.88 - 1.95) | <.0001 | <.0001 | 1.37 (1.35 - 1.39) | 1.4 (1.37 - 1.42) | <.0001 | <.0001 |
| **Constipation versus negative control** | | | | | | | | |
| Parkinson's disease | 2.28 (2.15 - 2.42) | 2.29 (2.16 - 2.43) | <.0001 | <.0001 | 2.38 (2.24 - 2.54) | 2.39 (2.25 - 2.55) | <.0001 | <.0001 |
| Alzheimer's disease | 2.07 (1.94 - 2.19) | 2.07 (1.95 - 2.2) | <.0001 | <.0001 | 1.97 (1.85 - 2.1) | 1.98 (1.86 - 2.1) | <.0001 | <.0001 |
| Cerebrovascular disease | 1.86 (1.83 - 1.9) | 1.93 (1.9 - 1.97) | <.0001 | <.0001 | 1.42 (1.39 - 1.44) | 1.45 (1.42 - 1.48) | <.0001 | <.0001 |
| **IBS-C versus negative control** | | | | | | | | |
| Parkinson's disease | 1.0 (0.42 - 2.4) | 1.0 (0.42 - 2.42) | 0.99 | 1 | 1.0 (0.42 - 2.41) | 1.0 (0.42 - 2.42) | 0.99 | 1 |
| Alzheimer's disease | 1.0 (0.42 - 2.4) | 1.0 (0.42 - 2.42) | 1 | 1 | 1.0 (0.42 - 2.39) | 1.0 (0.41 - 2.41) | 1 | 1 |
| Cerebrovascular disease | 1.61 (1.12 - 2.32) | 1.66 (1.13 - 2.43) | 0.01 | 0.06 | 1.3 (0.95 - 1.78) | 1.32 (0.94 - 1.84) | 0.12 | 0.64 |

**Supplemental Table 14 (continued). The Relative Risk (RR) of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| Outcome[a] | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Achalasia versus negative control** | **RR** | **OR** | **P-value[c]** | **Corrected P-value[d]** | **RR** | **OR** | **P-value** | **Corrected P-value** |
| **IBS-D versus negative control** | | | | | | | | |
| Parkinson's disease | 1.09 (0.72 - 1.65) | 1.09 (0.72 - 1.66) | 0.67 | 1 | 1.04 (0.71 - 1.53) | 1.04 (0.71 - 1.53) | 0.84 | 1 |
| Alzheimer's disease | 1.13 (0.79 - 1.63) | 1.13 (0.78 - 1.63) | 0.51 | 1 | 1.07 (0.75 - 1.54) | 1.07 (0.75 - 1.54) | 0.71 | 1 |
| Cerebrovascular disease | 1.42 (1.27 - 1.59) | 1.45 (1.29 - 1.63) | <.0001 | <.0001 | 1.07 (0.96 - 1.18) | 1.07 (0.96 - 1.19) | 0.24 | 1 |
| **IBS-without-D versus negative control** | | | | | | | | |
| Parkinson's disease | 1.2 (1.08 - 1.34) | 1.21 (1.08 - 1.35) | 0.0009 | 0.002 | 1.17 (1.05 - 1.3) | 1.17 (1.05 - 1.31) | 0.006 | 0.02 |
| Alzheimer's disease | 1.3 (1.15 - 1.46) | 1.3 (1.15 - 1.46) | <.0001 | <.0001 | 1.15 (1.02 - 1.29) | 1.15 (1.02 - 1.29) | 0.02 | 0.05 |
| Cerebrovascular disease | 1.38 (1.34 - 1.43) | 1.4 (1.36 - 1.45) | <.0001 | <.0001 | 1.1 (1.07 - 1.13) | 1.11 (1.07 - 1.14) | <.0001 | <.0001 |
| **Fecal incontinence versus negative control** | | | | | | | | |
| Parkinson's disease | 1.77 (1.51 - 2.08) | 1.78 (1.52 - 2.1) | <.0001 | <.0001 | 1.74 (1.48 - 2.05) | 1.75 (1.49 - 2.07) | <.0001 | <.0001 |
| Alzheimer's disease | 2.13 (1.8 - 2.51) | 2.14 (1.81 - 2.53) | <.0001 | <.0001 | 1.76 (1.51 - 2.05) | 1.77 (1.51 - 2.07) | <.0001 | <.0001 |
| Cerebrovascular disease | 1.65 (1.56 - 1.73) | 1.72 (1.63 - 1.81) | <.0001 | <.0001 | 1.32 (1.25 - 1.38) | 1.35 (1.28 - 1.42) | <.0001 | <.0001 |
| **Crohn's disease versus negative control** | | | | | | | | |
| Parkinson's disease | 0.92 (0.73 - 1.16) | 0.92 (0.73 - 1.16) | 0.49 | 0.89 | 0.91 (0.72 - 1.15) | 0.91 (0.72 - 1.15) | 0.44 | 0.81 |
| Alzheimer's disease | 1.42 (1.08 - 1.87) | 1.42 (1.08 - 1.87) | 0.01 | 0.03 | 1.22 (0.93 - 1.62) | 1.22 (0.93 - 1.62) | 0.16 | 0.43 |
| Cerebrovascular disease | 1.15 (1.08 - 1.23) | 1.16 (1.08 - 1.24) | <.0001 | 0.0001 | 1.2 (1.12 - 1.28) | 1.2 (1.12 - 1.29) | <.0001 | <.0001 |
| **Ulcerative colitis versus negative control** | | | | | | | | |
| Parkinson's disease | 1.07 (0.86 - 1.33) | 1.07 (0.85 - 1.33) | 0.57 | 1 | 0.91 (0.73 - 1.13) | 0.91 (0.73 - 1.13) | 0.4 | 1 |
| Alzheimer's disease | 1.04 (0.8 - 1.34) | 1.04 (0.8 - 1.35) | 0.79 | 1 | 1.08 (0.82 - 1.41) | 1.08 (0.82 - 1.41) | 0.58 | 1 |
| Cerebrovascular disease | 1.15 (1.08 - 1.23) | 1.16 (1.08 - 1.24) | <.0001 | 0.0002 | 0.99 (0.93 - 1.06) | 0.99 (0.93 - 1.06) | 0.8 | 1 |

**Supplemental Table 14 (continued). The Relative Risk (RR) of developing PD, AD or CVD within 5 years of the diagnosis of a given exposure, compared to NCs without the respective exposure.**

| Outcome[a] | Matched for baseline demographics | | | | Matched for baseline demographics and risk factors[b] | | | |
|---|---|---|---|---|---|---|---|---|
| **Achalasia versus negative control** | **RR** | **OR** | **P-value[c]** | **Corrected P-value [d]** | **RR** | **OR** | **P-value** | **Corrected P-value** |
| **Microscopic colitis versus negative control** | | | | | | | | |
| Parkinson's disease | 0.5 (0.23 - 1.07) | 0.5 (0.23 - 1.07) | 0.07 | 0.13 | 0.73 (0.34 - 1.6) | 0.73 (0.34 - 1.6) | 0.43 | 0.8 |
| Alzheimer's disease | 2.47 (1.3 - 4.69) | 2.49 (1.3 - 4.76) | 0.005 | 0.01 | 1.58 (0.91 - 2.71) | 1.58 (0.91 - 2.75) | 0.1 | 0.28 |
| Cerebrovascular disease | 1.59 (1.29 - 1.95) | 1.66 (1.32 - 2.08) | <.0001 | 0.0001 | 1.26 (1.05 - 1.52) | 1.3 (1.05 - 1.59) | 0.02 | 0.11 |
| **Appendectomy versus negative control** | | | | | | | | |
| Parkinson's disease | 0.37 (0.18 - 0.77) | 0.37 (0.18 - 0.76) | 0.005 | 0.03 | 0.48 (0.22 - 1.01) | 0.48 (0.22 - 1.01) | 0.05 | 0.27 |
| Alzheimer's disease | 1.4 (0.62 - 3.15) | 1.4 (0.62 - 3.16) | 0.41 | 0.76 | 1.09 (0.48 - 2.47) | 1.09 (0.48 - 2.48) | 0.83 | 1 |
| Cerebrovascular disease | 1.26 (1.05 - 1.51) | 1.27 (1.06 - 1.53) | 0.01 | 0.03 | 0.87 (0.73 - 1.04) | 0.87 (0.73 - 1.04) | 0.14 | 0.37 |
| **Vagotomy versus negative control** | | | | | | | | |
| Parkinson's disease | - | - | - | - | - | - | - | - |
| Alzheimer's disease | 1.0 (0.43 - 2.34) | 1.0 (0.4 - 2.47) | 1 | 1 | 1.0 (0.43 - 2.34) | 1.0 (0.41 - 2.46) | 1 | 1 |
| Cerebrovascular disease | 1.44 (0.66 - 3.16) | 1.49 (0.64 - 3.46) | 0.37 | 1 | 1.1 (0.5 - 2.43) | 1.11 (0.48 - 2.59) | 0.81 | 1 |

Abbreviations: IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea); GERD, Gastro-esophageal reflux disease; RR, relative risk

[a] Each analysis compares a cohort of patients identified by the diagnosis of a given exposure with their respective NCs for the prospective development of PD, AD and CVD (i.e. outcomes) within 5 years of the index event (i.e. diagnosis of the exposure or ambulatory visit for NCs). After propensity score matching, subjects that already had the investigated outcome (i.e. PD, AD or CVD) documented prior to the index event were excluded from further analyses. RRs were calculated as follows: risk of the outcome in cohort with the exposure/ risk of the outcome in the negative control cohort. Exposures and outcomes were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes (**online supplemental methods)**. Electronic medical health record data was collected from the TriNetX Research Network.

[b] Baseline characteristics include: age, sex, race and ethnicity; Risk factors include arterial hypertension (AHT), Diabetes Mellitus (DM), Atrial fibrillation (Afib) and flutter and nicotine dependence.

[c] P-values of the PD group compared to the respective control group were calculated using a Pearson Chi-Squared test.

[d] Correction for false discovery rate (FDR) was performed using the step-up procedure by Benjamini and Yekutieli, using the stats package in R (**Methods**).

* 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

**Supplemental Table 15: P-values for differences between ORs, after matching for both demographics and risk factors.**

| | **Matched for baseline demographics and risk factors** | | | |
|---|---|---|---|---|
| **Achalasia versus negative control** | OR | PD vs AD | PD vs CVD | AD vs CVD |
| Parkinson's disease | 1.53 (0.94 - 2.49) | 0.3 | 0.2 | 0.86 |
| Alzheimer's disease | 1.04 (0.61 - 1.78) | | | |
| Cerebrovascular disease | 1.09 (0.94 - 1.27) | | | |
| **Dysphagia versus negative control** | | | | |
| Parkinson's disease | 2.28 (2.11 - 2.46) | <.0001 | <.0001 | 0.63 |
| Alzheimer's disease | 1.56 (1.44 - 1.69) | | | |
| Cerebrovascular disease | 1.53 (1.49 - 1.56) | | | |
| **GERD versus negative control** | | | | |
| Parkinson's disease | 1.13 (1.09 - 1.18) | 0.17 | <.0001 | <.0001 |
| Alzheimer's disease | 1.18 (1.13 - 1.24) | | | |
| Cerebrovascular disease | 1.4 (1.39 - 1.42) | | | |
| **Gastroparesis versus negative control** | | | | |
| Parkinson's disease | 2.45 (1.92 - 3.11) | 0.06 | 0.07 | 0.38 |
| Alzheimer's disease | 1.7 (1.26 - 2.29) | | | |
| Cerebrovascular disease | 1.94 (1.83 - 2.07) | | | |
| **Functional dyspepsia versus negative control** | | | | |
| Parkinson's disease | 1.15 (1.0 - 1.32) | 0.87 | 0.46 | 0.35 |
| Alzheimer's disease | 1.17 (1.01 - 1.34) | | | |
| Cerebrovascular disease | 1.09 (1.05 - 1.13) | | | |
| **Intestinal pseudo-obstruction* versus negative control** | | | | |
| Parkinson's disease | 1.85 (1.18 - 2.89) | 0.27 | 0.18 | 0.86 |
| Alzheimer's disease | 1.28 (0.79 - 2.08) | | | |
| Cerebrovascular disease | 1.34 (1.17 - 1.53) | | | |
| **Paralytic ileus versus negative control** | | | | |
| Parkinson's disease | 1.02 (0.83 - 1.26) | 0.35 | 0.08 | 0.7 |
| Alzheimer's disease | 1.18 (0.94 - 1.49) | | | |
| Cerebrovascular disease | 1.24 (1.17 - 1.32) | | | |
| **Diarrhoea versus negative control** | | | | |
| Parkinson's disease | 1.32 (1.24 - 1.4) | <.0001 | 0.09 | <.0001 |
| Alzheimer's disease | 1.69 (1.58 - 1.8) | | | |
| Cerebrovascular disease | 1.4 (1.37 - 1.42) | | | |

**Supplemental Table 15 (continued): P-values for differences between ORs, after matching for both demographics and risk factors.**

| | **Matched for baseline demographics and risk factors** | | | |
|---|---|---|---|---|
| **Achalasia versus negative control** | OR | PD vs AD | PD vs CVD | AD vs CVD |
| **Constipation versus negative control** | | | | |
| Parkinson's disease | 2.39 (2.25 - 2.55) | <.0001 | <.0001 | <.0001 |
| Alzheimer's disease | 1.98 (1.86 - 2.1) | | | |
| Cerebrovascular disease | 1.45 (1.42 - 1.48) | | | |
| **IBS-C versus negative control** | | | | |
| Parkinson's disease | 1.0 (0.42 - 2.42) | 0.99 | 0.57 | 0.56 |
| Alzheimer's disease | 1.0 (0.41 - 2.41) | | | |
| Cerebrovascular disease | 1.32 (0.94 - 1.84) | | | |
| **IBS-D versus negative control** | | | | |
| Parkinson's disease | 1.04 (0.71 - 1.53) | 0.91 | 0.89 | 0.99 |
| Alzheimer's disease | 1.07 (0.75 - 1.54) | | | |
| Cerebrovascular disease | 1.07 (0.96 - 1.19) | | | |
| **IBS-without-D versus negative control** | | | | |
| Parkinson's disease | 1.17 (1.05 - 1.31) | 0.81 | 0.35 | 0.58 |
| Alzheimer's disease | 1.15 (1.02 - 1.29) | | | |
| Cerebrovascular disease | 1.11 (1.07 - 1.14) | | | |
| **Fecal incontinence versus negative control** | | | | |
| Parkinson's disease | 1.75 (1.49 - 2.07) | 0.94 | 0.003 | 0.001 |
| Alzheimer's disease | 1.77 (1.51 - 2.07) | | | |
| Cerebrovascular disease | 1.35 (1.28 - 1.42) | | | |
| **Crohn's disease versus negative control** | | | | |
| Parkinson's disease | 0.91 (0.72 - 1.15) | 0.11 | 0.03 | 0.92 |
| Alzheimer's disease | 1.22 (0.93 - 1.62) | | | |
| Cerebrovascular disease | 1.2 (1.12 - 1.29) | | | |
| **Ulcerative colitis versus negative control** | | | | |
| Parkinson's disease | 0.91 (0.73 - 1.13) | 0.34 | 0.47 | 0.55 |
| Alzheimer's disease | 1.08 (0.82 - 1.41) | | | |
| Cerebrovascular disease | 0.99 (0.93 - 1.06) | | | |
| **Microscopic colitis versus negative control** | | | | |
| Parkinson's disease | 0.73 (0.34 - 1.6) | 0.11 | 0.17 | 0.5 |
| Alzheimer's disease | 1.58 (0.91 - 2.75) | | | |
| Cerebrovascular disease | 1.3 (1.05 - 1.59) | | | |

**Supplemental Table 15: P-values for differences between ORs, after matching for both demographics and risk factors.**

| | **Matched for baseline demographics and risk factors** | | | |
|---|---|---|---|---|
| **Achalasia versus negative control** | OR | PD vs AD | PD vs CVD | AD vs CVD |
| **Appendectomy versus negative control** | | | | |
| Parkinson's disease | 0.48 (0.22 - 1.01) | 0.14 | 0.13 | 0.59 |
| Alzheimer's disease | 1.09 (0.48 - 2.48) | | | |
| Cerebrovascular disease | 0.87 (0.73 - 1.04) | | | |
| **Vagotomy versus negative control** | | | | |
| Parkinson's disease | - | - | - | 0.87 |
| Alzheimer's disease | 1.0 (0.41 - 2.46) | | | |
| Cerebrovascular disease | 1.11 (0.48 - 2.59) | | | |

Abbreviations: IBS, Irritable bowel syndrome (-C, constipation; -D, Diarrhoea); GERD, Gastro-esophageal reflux disease; NC, Negative control; AD; Alzheimer's disease; CVD, cerebrovascular diseases; PD, Parkinson's disease.

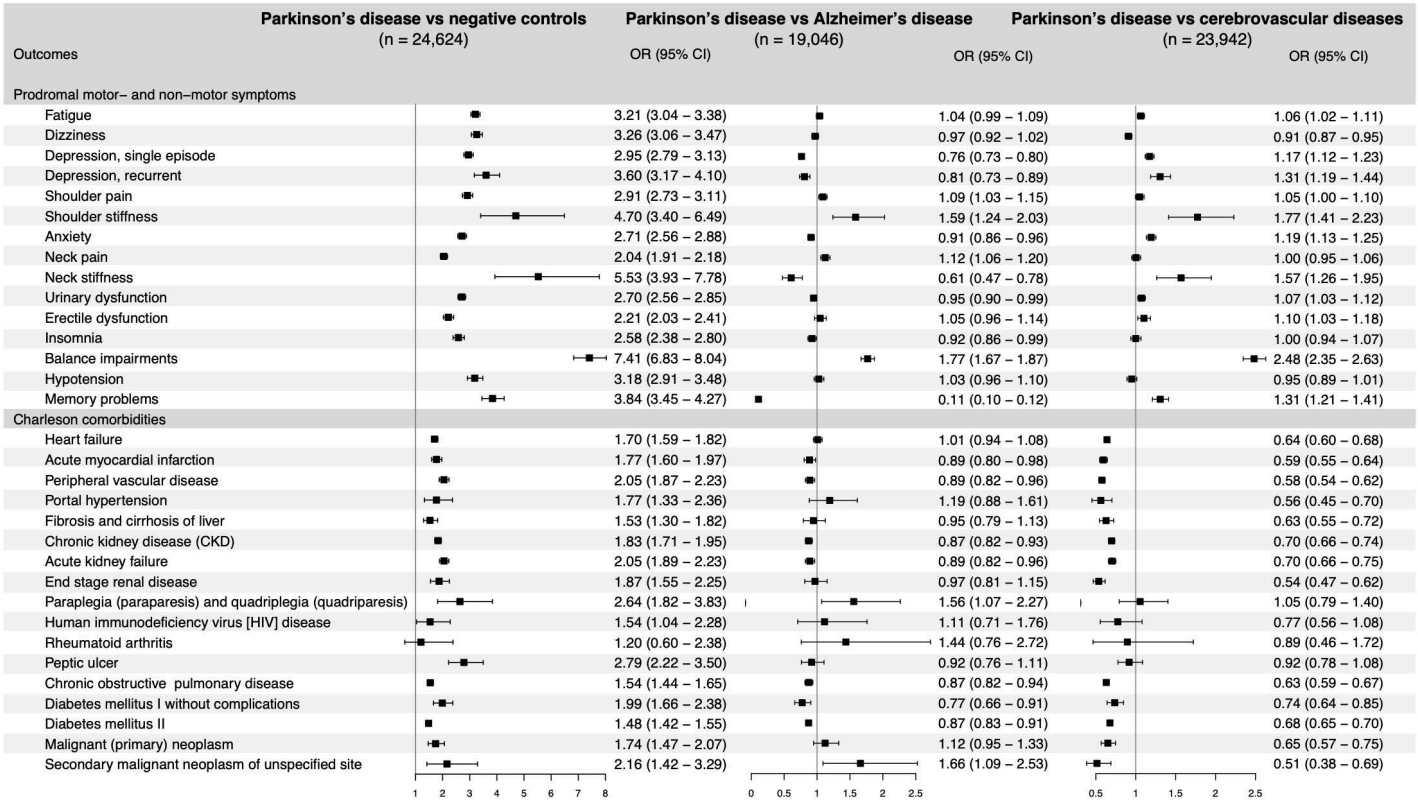
[a] Each analysis compares a cohort of patients identified by the diagnosis of a given exposure with their respective negative controls for the prospective development of PD, AD and CVD (i.e. outcome) within 5 years of the index event (i.e. diagnosis of the exposure or visit for NCs). After propensity score matching, subjects that already had the investigated outcome (i.e. PD, AD or CVD) documented prior to the index event were excluded from further analysis. RRs were calculated as follows: risk of the outcome in cohort with the exposure/ risk of the outcome in the negative control cohort. ORs were calculated as follows: odds of the outcome in cohort with the exposure/ odds of the outcome in the negative control cohort. Exposures and outcomes were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Diagnostic coding can be found in **the online supplemental methods**.

[b] Baseline characteristics include: age, sex, race and ethnicity; Risk factors include arterial hypertension (AHT), Diabetes Mellitus (DM), Atrial fibrillation (Afib) and flutter and nicotine dependence.

***** 'Intestinal pseudo-obstruction' was used as an approximate synonym for the ICD-10 code K59.8 'Other specified functional intestinal disorders'.

## Supplemental Figures

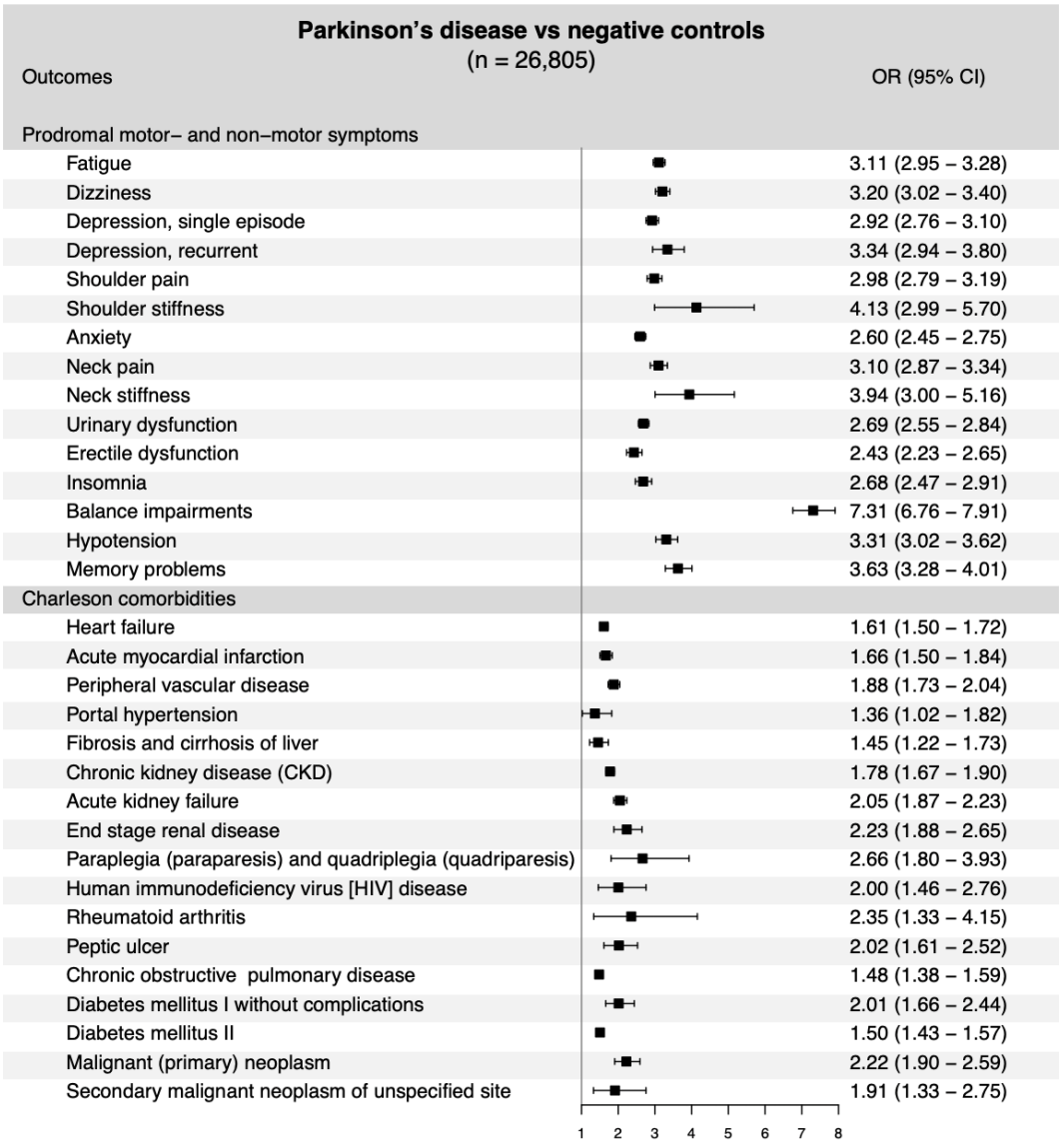
**Supplemental Figure 1: Forestplot of positive and negative exposures in patients with PD compared to matched NCs and patients with AD and CVD.**




Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

**Supplemental Figure 2: Forestplot of positive and negative exposures in patients with PD compared to NCs, after excluding patients with prescriptions of dopaminergic drugs.**

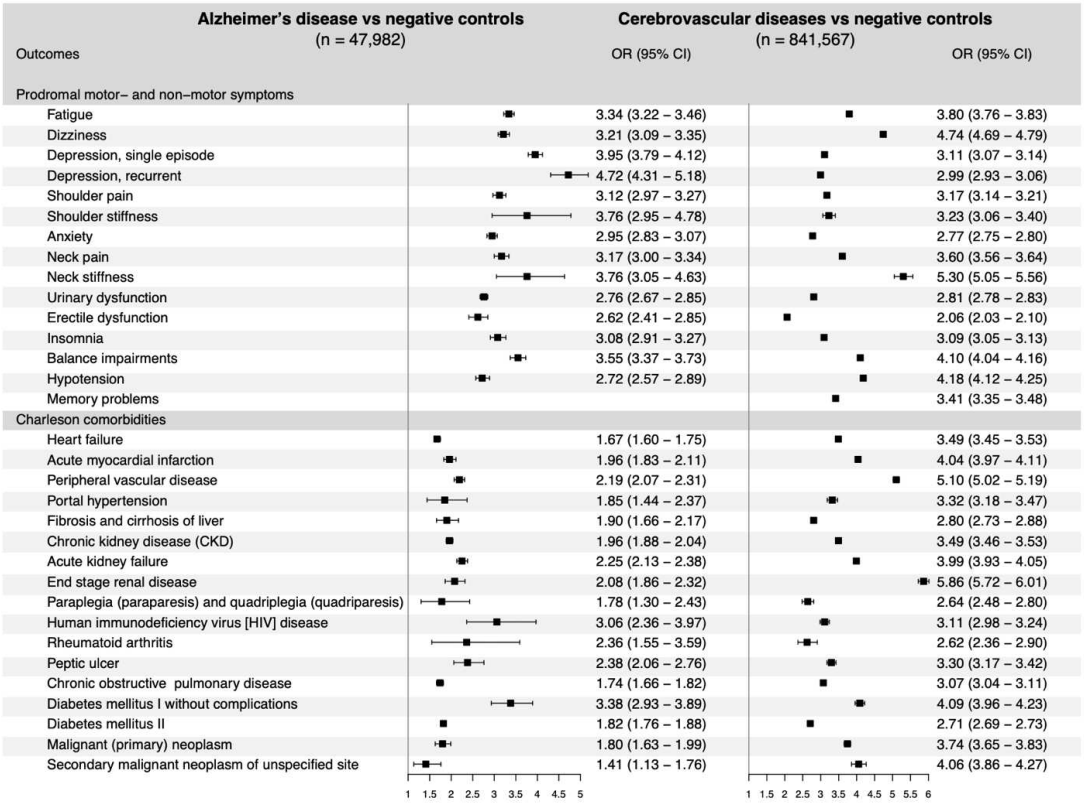



Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

Antidopaminergic drugs include: metoclopramide, domperidone, promethazine, prochlorperazine. Only patients with any of these prescriptions within 2 years before the index event were excluded from further analysis.

**Supplemental Figure 3: Forestplot of positive and negative exposures in patients with AD and CVD compared to their respective matched NCs**.

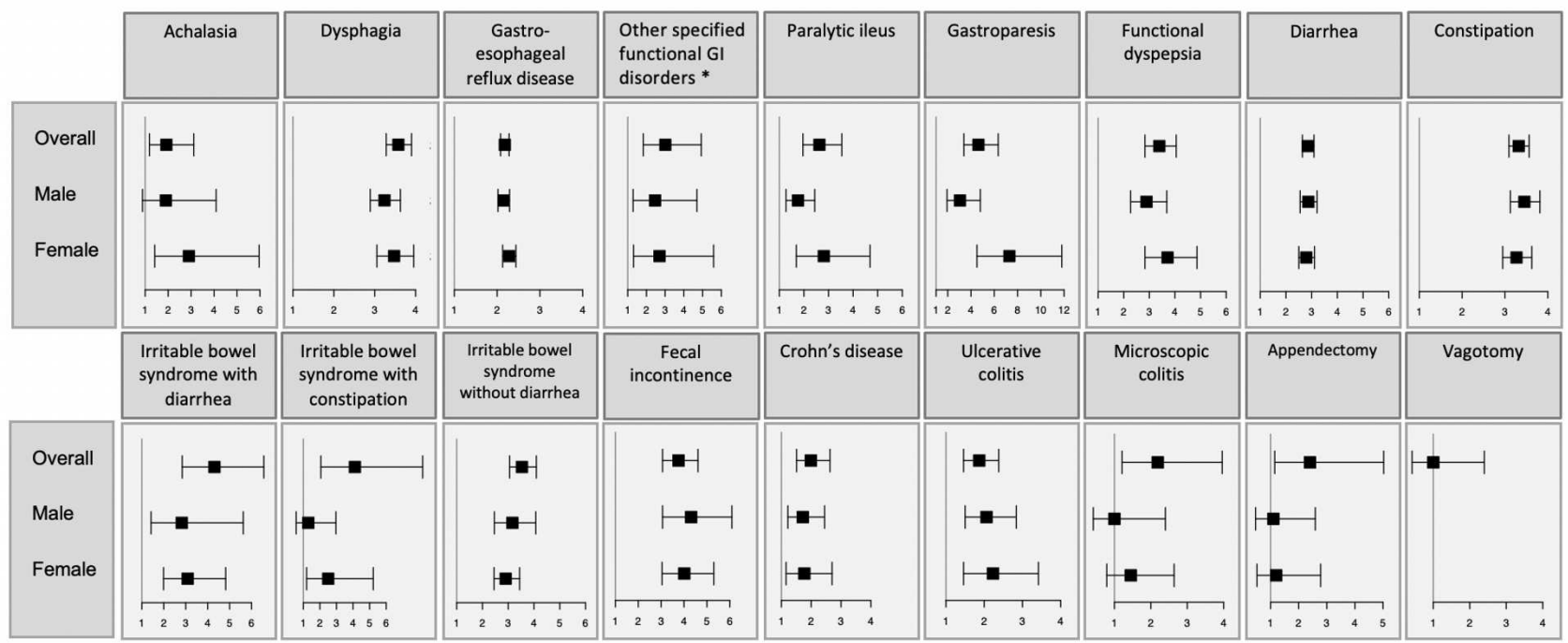



*****The positive exposure 'memory problems' in the analysis of AD and NCs was excluded from the forestplot because its OR (27.26 (25.58 - 29.06)) reached outside of the range of the x-axis.

Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

ORs were calculated as follows: odds of documented exposure in the AD or CVD cohort/ odds of documented exposure in control cohort.

**Supplemental Figure 4. Forestplot: ORs of prior exposures in patients with PD compared to matched NCs, stratified for sex.**

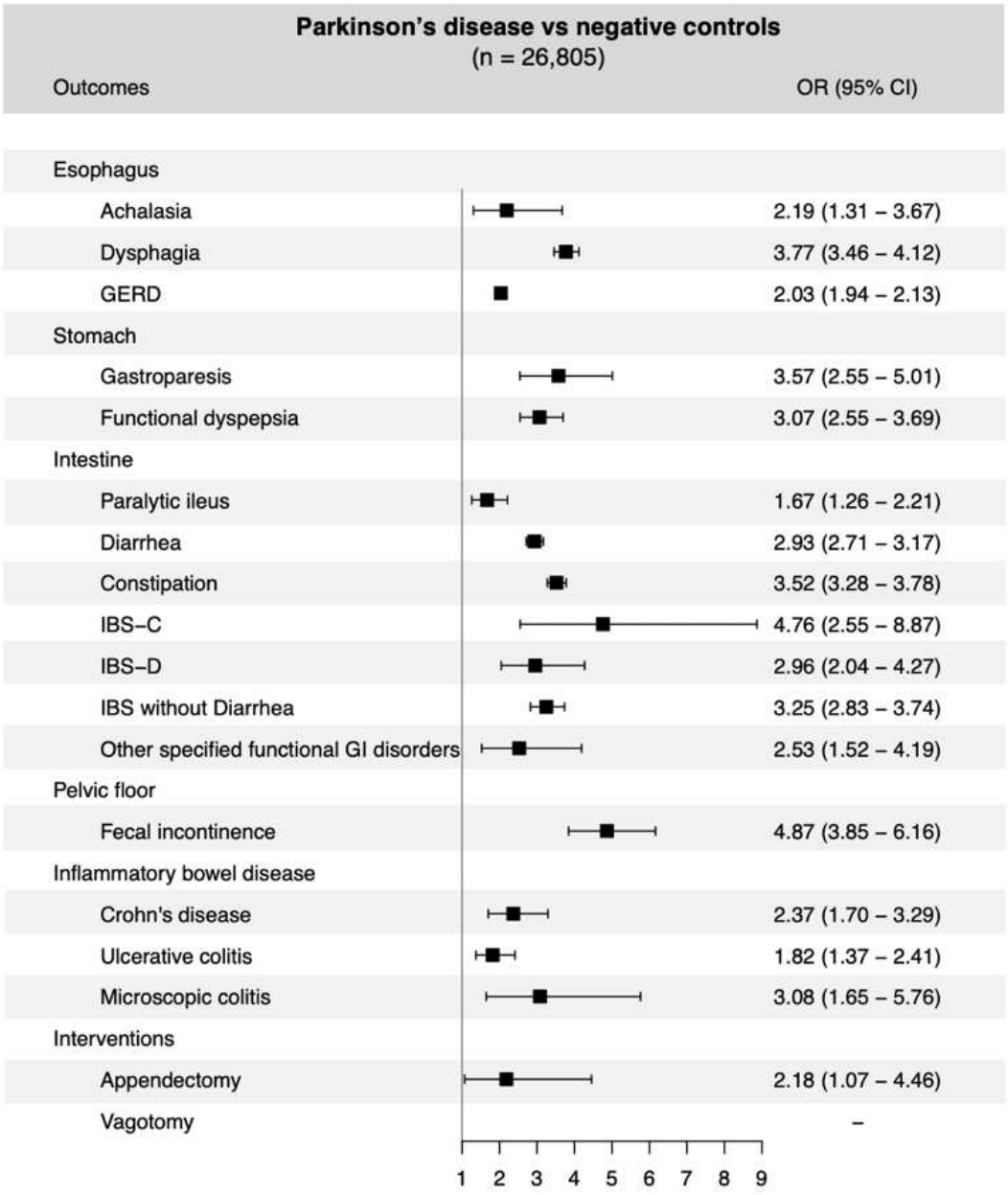



Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

*Approximate synonyms of the ICD-10 code K59.8 'Other specified functional intestinal disorders' includes Intestinal Pseudo-obstruction (acute/chronic).

**Supplemental Figure 5: ORs of prior exposures in patients with PD compared to NCs, after exclusion of patients with prescriptions of antidopaminergic drugs**

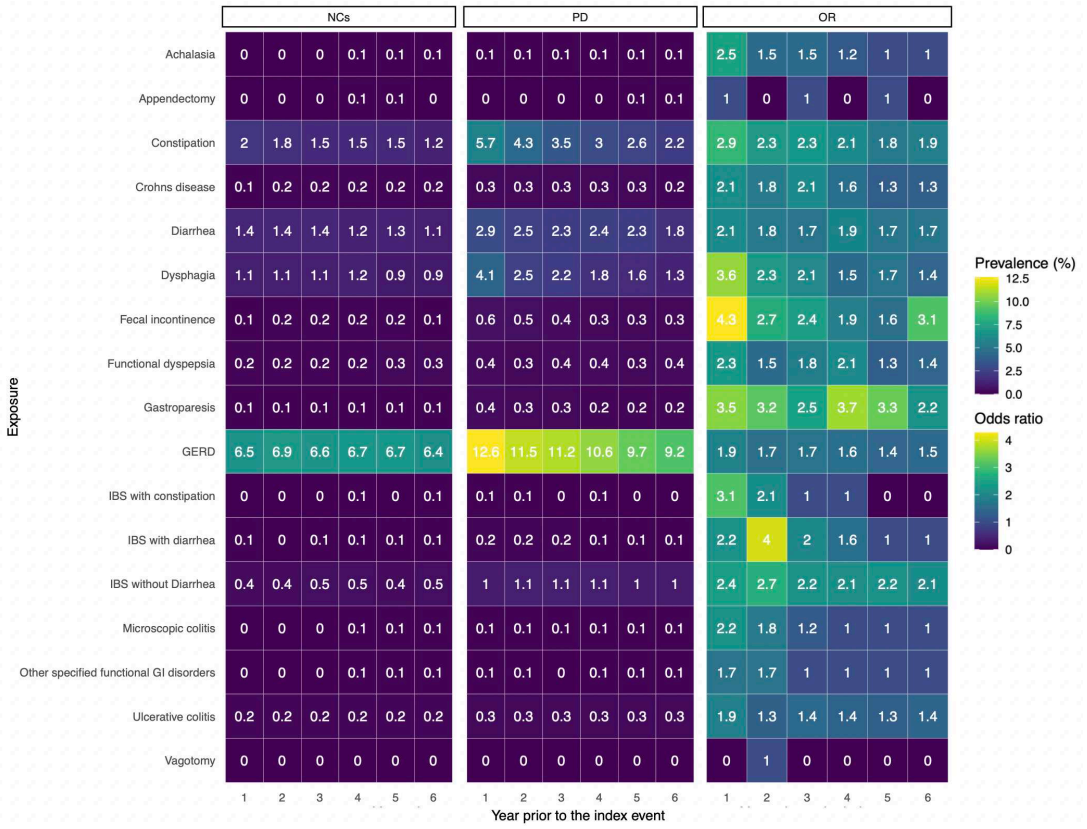



Exposures were identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) and *Current Procedural Terminology (CPT)* codes. Electronic medical health record data was collected from the TriNetX Research Network. Outcomes were included if they were documented any time prior to the diagnosis of PD or the control health event, in the available medical records. Diagnostic coding can be found in **the online supplemental methods**.

ORs were calculated as follows: odds of documented exposure in the PD cohort/ odds of documented exposure in control cohort.

*Antidopaminergic drugs include: metoclopramide, promethazine, prochlorperazine and domperidone. Only patients with any of the prescriptions above within 2 years before the index event were excluded from further analyses.

**Supplemental Figure 6: Heatmap of the cross-sectional prevalence of each exposure every year prior to the index event**




The cross-sectional prevalence (%) of each of the exposures for every year prior to the first diagnosis of the index event (PD in the Parkinsons disease cohort; ambulatory visit in the negative Controls). For each exposure, an OR of developing PD was calculated for every year prior to the index event. The x-axis represents the number of years prior to the index event, the y-axis holds the exposures of interest.

*Approximate synonyms of the ICD-10 code K59.8 'Other specified functional intestinal disorders' includes Intestinal Pseudo-obstruction (acute/chronic).

**References:**

1. Alonso, A., et al., *Gout and risk of Parkinson disease: a prospective study.* Neurology, 2007. **69**(17): p. 1696-700.