

Research Article

Constipation preceding Parkinson's disease – a systematic review and meta-analysis

Kerala L. Adams-Carr¹, Jonathan P Bestwick², Samuel Shribman³, Andrew Lees⁴, Anette Schrag⁴, Alastair J Noyce^{4*}

Affiliations:

1. Charing Cross Hospital, London, UK
2. Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, London, UK
3. National Hospital for Neurology and Neurosurgery, London, UK
4. Institute of Neurology, University College London, London, UK

***Corresponding Author**

Dr Alastair Noyce. Department of Molecular Neuroscience and Reta Lila Weston Institute, UCL Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK Tel: +44-20 7679 4246, Fax: +44-20 7278 4993, Email: a.noyce@ucl.ac.uk

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ABSTRACT

Objective: To systematically review published literature to estimate the magnitude of association between premorbid constipation and later diagnosis of Parkinson's disease.

Background: Constipation is a recognised non-motor feature of Parkinson's and has been reported to predate diagnosis in a number of observational studies.

Methods: A systematic review and meta-analysis was carried out following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria. A literature search was undertaken in December 2014 using PubMed and the search terms 'Parkinson's disease' and 'constipation'. Articles were screened for suitability and reviewed against inclusion and exclusion criteria. Studies were included if they assessed constipation by means of a structured questionnaire or if constipation/drugs used to treat constipation were coded in patient medical records. Data were extracted using a standardised template and effect size estimates combined using a fixed-effects model. Heterogeneity was explored with the I^2 statistic.

Results: 9 studies were included in the meta-analysis, with a combined sample size of 741 593 participants. Those with constipation had a pooled OR of 2.27 (95% CI 2.09 to 2.46) for developing subsequent Parkinson's disease compared to those without constipation. Weak evidence for heterogeneity was found ($I^2=18.9\%$, $p=0.282$). Restricting analysis to studies assessing constipation more than 10 years prior to Parkinson's disease gave a pooled OR of 2.13 (95% CI 1.78 to 2.56; $I^2=0.0\%$).

Conclusion: This systematic review and meta-analysis demonstrates that people with constipation are at a higher risk of developing Parkinson's disease compared to those without and that constipation can predate Parkinson's diagnosis by over a decade.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder with a prevalence of approximately 0.4% - a figure which is expected to double by 2040.[1] PD is diagnosed when motor features such as tremor, bradykinesia and rigidity become overt, by which time approximately 50% of neurons within the substantia nigra remain.[2] Over the past two decades, a variety of prodromes have been recognised and may comprise a number of early non-motor symptoms including those attributable to autonomic dysfunction, mood and cognitive disturbance, sleep disorders and sensory disruption.[3] Greater understanding of these early features may help the identification of individuals at higher risk of being diagnosed with PD, some of whom may be candidates for neuroprotective drug trials.

Constipation, a consequence of autonomic dysfunction, is one of the most studied of the prodromal symptoms of PD. A recent study of the prevalence of selected non-motor symptoms before and after diagnosis of PD found that constipation was the second most common non-motor symptom of PD after anosmia, with a prevalence of 50% in established PD, and occurring prior to diagnosis in approximately 20% of patients overall.[4] To date only one meta-analysis has examined the magnitude of risk associated with constipation and the later development of PD, as part of a wider investigation of risk and protective factors for PD.[5] In this, data were pooled from two studies giving an effect size (ES) estimate of 2.34 for the development of PD in people with constipation as compared to those without. However the confidence intervals (CI) were relatively wide, with the true population estimate potentially between 1.6 and 3.5 times higher. Since this initial meta-analysis published in 2012, several large cohort and case-control studies have been

published,[6–10] contributing a further 10,697 PD cases, where there were previously only 545. We have refined the ES estimate of the risk of future PD in those that are constipated, as well as undertaking analysis restricted to studies providing risk estimates for constipation with onset ≥ 10 years prior to PD diagnosis.

METHODS

Search Strategy

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for systematic review and meta-analysis of observational studies in epidemiology were adhered to throughout this study. Two researchers (KLA-C & AJN) independently undertook a literature search on the 7 December 2014 using PubMed and the search terms “constipation” and “Parkinson’s disease”. The search was restricted to English articles, and titles and abstracts were screened for their suitability. Articles whose abstracts did not report on constipation and PD, or solely reported prevalence or management of constipation in established PD were excluded. Full articles were then obtained and reviewed to determine suitability for inclusion or exclusion. Differences of opinion were resolved through discussion. The reference lists of all full articles included, as well as the references from reviews and meta-analyses identified in the original search, were hand-searched for additional relevant titles which were then subjected to the same filtering process described above.

Inclusion criteria

Published studies that met the following criteria were included: (1) observational studies with a cohort or case-control design; (2) cases were patients diagnosed with PD according to standard clinical criteria, such as Queen Square Brain Bank Criteria; [11] (3) controls were healthy or had no history of neurological disease; (4) controls were drawn from the same population as cases; (5) constipation in controls was assessed over the same time period as for patients; (6) constipation was assessed by means of a structured questionnaire, or coded in patient medical records as constipation or medication used to treat constipation and (7) original data were reported.

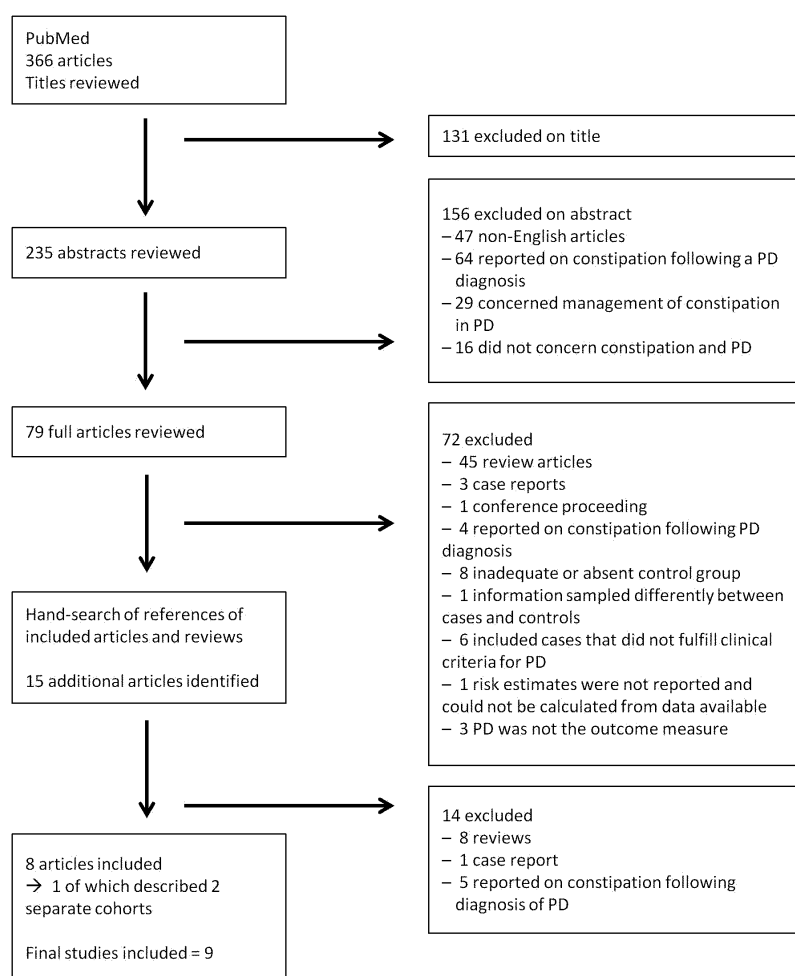


Figure 1 - Flowchart depicting literature search. (PD = Parkinson's disease).

Exclusion criteria

Abstracts, editorials, review articles, conference proceedings, case reports and letters that did not report new data were excluded. We also excluded studies that (1) reported on constipation only after the diagnosis of PD; (2) reported on bowel function other than constipation; (3) reported on the management of constipation in PD; (4) did not provide adequate details of the control group, or used inappropriate controls (chronically ill or neurological disease); (5) did not report sufficient data to calculate risk estimates; (6) recorded information differently for cases and controls; or (7) studied outcomes other than PD.

Data handling

Study characteristics and risk estimates were extracted from all studies eligible for inclusion and tabulated in standard template tables. Where risk estimates (relative risk (RR) / hazard ratio (HR) / odds ratio (OR)) were not available, data were reviewed and an OR calculated where possible (odds in the exposed divided by odds in the unexposed). Where risk estimates for constipation were provided at multiple time points less than 10 years prior to PD diagnosis, the median time point was chosen. A second risk estimates table was compiled to tabulate data from those studies that had an average time between constipation onset and PD diagnosis ≥ 10 years. Where risk estimates were separated into multiple time points ≥ 10 years pre-PD diagnosis (i.e. 7-12, 13-18, and 19-24 years [6]) and pooling of these data was not possible, these estimates were excluded.

We used a definition of constipation of < 3 bowel movements (BMs) per week, a criterion within the Rome III definition for Functional Constipation.[12] Where this definition of

constipation was not used by studies, risk estimates corresponding to the closest available definition were extracted. For the one study where constipation was defined by laxative-use as a proxy for severity, the category likely to give the most conservative risk estimate ('mild' laxative use) was chosen. Where constipation was coded in medical records as a binary term, it was not possible to ascertain the diagnostic criteria used but data were still included within the meta-analysis.

Where figures were available that excluded patients enrolled less than 2 years prior to PD diagnosis, these figures were preferred in order to avoid confounding by prevalent disease. Where figures adjusted for laxative use, the unadjusted figures were selected.

Where the above conditions were met and there still remained a choice between risk estimates, the risk estimates matched or adjusted for age and gender, that reflected the full range of participants and did not have data missing, were used. Finally, studies were assessed for quality using the Newcastle Ottawa Scale (NOS).[13]

Statistical Analysis

Measures of effect were combined using standard meta-analysis methods. ORs were used as an estimate of RRs / HRs where necessary (given rare disease assumption) along with 95% CIs. A pooled ES estimate was calculated using a fixed-effects model in the absence of clear heterogeneity. Statistical heterogeneity was explored using the I^2 statistic based on a χ^2 test of observed ES in each study against the (expected) pooled estimate. The pre-specified significance level for heterogeneity was set at 5%. Publication bias was assessed using the Egger test and a funnel plot.[14] Statistical analysis was undertaken in Stata V.13.

RESULTS

The literature search yielded 366 results (see figure 1). Of these, 47 were excluded as they were not written in English, and a further 240 were excluded on the basis of their title and abstract. Review of the remaining 79 full articles led to 72 exclusions based on criteria described above. Hand searching of references of included studies and all reviews led to the inclusion of one additional study, which brought the total number of included studies to eight. One of the included studies[6] described two separate cohorts - one male (Health Professionals Follow-up Study) and one female (Nurses' Health Study), and these were included as two distinct studies for the purposes of analysis, bringing the total number of studies included in the analysis to nine. Of these, four were prospective cohort studies, [6,8,15] and the remaining five had a case-control design.[7,9,10,16,17] Four of the five case-control studies utilised information from formal patient medical records. The combined sample size of the nine studies was 741 593.

Summary characteristics and risk estimates for all included studies are provided in tables 1-3 and online supplementary table S1. Studies were assessed for quality using the NOS and the results of this can be viewed in online supplementary table S2. With NOS quality criteria, all studies scored $\geq 6/9$ and four of the included studies scored 8/9.

Meta-analysis to pool data from all nine studies revealed a positive association between constipation and subsequent diagnosis of PD (figure 2). The ES estimate for those with constipation and the association with PD was 2.27 (95% CI 2.09 to 2.46) compared to those without constipation. Weak evidence for heterogeneity was found ($I^2=18.1\%$, $p=0.282$) and there was no evidence for publication bias ($p\text{-value}=0.757$; see online supplementary figure S4).

Case-control and cohort studies were analysed separately to examine heterogeneity between estimates. The summary ES of case-control studies was 2.24 (95% CI 2.05 to 2.46), while that of cohort studies was 2.36 (95% CI 2.00 to 2.80). There was no evidence for heterogeneity between these sub-groups ($p=0.592$).

The average time between exposure assessment and diagnosis of PD varied greatly amongst these studies, ranging from <2 years to >20 years. When analysis was restricted to those risk estimates corresponding to constipation with an onset ≥ 10 years prior to PD diagnosis (figure 3), a similarly strong positive association was again found, with an ES of 2.13 (95% CI 1.78 to 2.56; $I^2=0.0\%$, $p=0.758$).

Table 1 - Study Characteristics*

Ref	Year	Author	Study design	Population	Follow up (years)	Exposure to outcome (years)	Cohort size	PD cases	Control	Definition of PD	Definition of Constipation	Exposure Assessment
16	1997	Gonera	Case-Control	63 general practices	10	NK	NA	60	58	Neurologist diagnosed, Queen Square Brain Bank Criteria	ICPC defined	General Practice record review
15	2001	Abbott	Cohort	Honolulu Heart Program	24	12	6790	96	6694	Hospital Records / Death certificates / Neurologist diagnosed	<1 BM per day (≤ 3 per week) compared to daily	Structured questionnaire
17	2009	Savica	Case-Control	Rochester Epidemiology Project, Olmsted County, Minnesota	38	>20	NA	196	196	Medical record review (2/4 cardinal features exc other causes). Validated.	Diagnosis of constipation or use of laxatives	Medical record review
6	2011	Gao	Cohort	Health Professionals Follow up Study	6	NK	33 901	156	33 745	Neurologist diagnosed or 2/3 of cardinal features exc other causes	BM every 3 days or less (<3 per week) compared to daily	Structured questionnaire
6	2011	Gao	Cohort	Nurses' Health Study	24	NK	93 767	37	93 730	Neurologist diagnosed or 2/3 of cardinal features exc other causes	BM every 3 days or less (<3 per week) compared to daily	Structured questionnaire
7	2014	Plouvier	Case-Control	CMR database; University of Nijmegen	2	NK	12000	86	78	GP or neurologist diagnosed - coded within CMR database	Diagnosis in the CMR database	CMR record review
8	2014	Lin	Cohort	National Health Insurance Database	5.5	NK	551324	2336	548 988	Hospital discharge diagnosis or Neurologist diagnosed	Diagnosis in database and use of laxatives	Database review
9	2014	Schrag	Case-Control	Health Improvement Network UK Primary care database	14	> 10	NA	8166	46 755	Read code in database and ≥ 2 PD medications	Read code in database or laxative prescription	Database review
10	2014	Pont-Sunyer	Case-Control	11 outpatient clinics	>10	>10	NA	109	107	Queen Square Brain Bank Criteria	3 months of < 3 BMs per week or straining	NMS questionnaire

*Abridged table – see supplementary table S1 for complete table. BM, bowel movement; PD, Parkinson's Disease; NK, not known; NA, not available; NMS, non motor symptom; CMR, continuous morbidity registration; ICPC, International classification of primary care; GP, general practitioner.

Table 2 - Risk estimates across all studies included in primary analysis

Ref	Year	Author	Study Design	p value	RR	HR	OR	CI lower	CI upper
16	1997	Gonera	Case-control	0.209	-	-	0.45	0.13	1.57
15	2001	Abbott	Cohort	0.013	2.30	-	-	1.2	4.5
17	2009	Savica	Case-control	0.0005	-	-	2.48	1.49	4.11
6	2011	Gao – HPFS	Cohort	<0.0001	4.35	-	-	1.80	10.5
6	2011	Gao – NHS	Cohort	0.03	2.98	-	-	1.09	8.14
7	2014	Plouvier	Case-control	0.039	-	-	3.32	1.1	10.4
8	2014	Lin	Cohort	<0.0001	-	2.29	-	1.91	2.74
9	2014	Schrag	Case-control	-	2.24	-	-	2.04	2.46
10	2014	Pont-Sunyer	Case-control	<0.05	-	-	2.7	1.4	5.2

RR, relative risk; HR, hazard ratio; OR, odds ratio; CI, confidence interval

Table 3 - Risk estimates corresponding to constipation ≥ 10 years pre-PD

Ref	Year	Author	Study Design	Exposure to outcome (years)	p value	RR	HR	OR	CI lower	CI upper
15	2001	Abbott	Cohort	12	0.013	2.30	-	-	1.2	4.5
17	2009	Savica	Case-control	> 20	0.0005	-	-	2.48	1.49	4.11
9	2014	Schrag	Case-control	> 10	-	2.01	-	-	1.62	2.49
10	2014	Pont-Sunyer	Case-control	> 10	<0.05	-	-	2.7	1.4	5.2

RR, relative risk; HR, hazard ratio; OR, odds ratio; CI, confidence interval, PD, Parkinson's disease

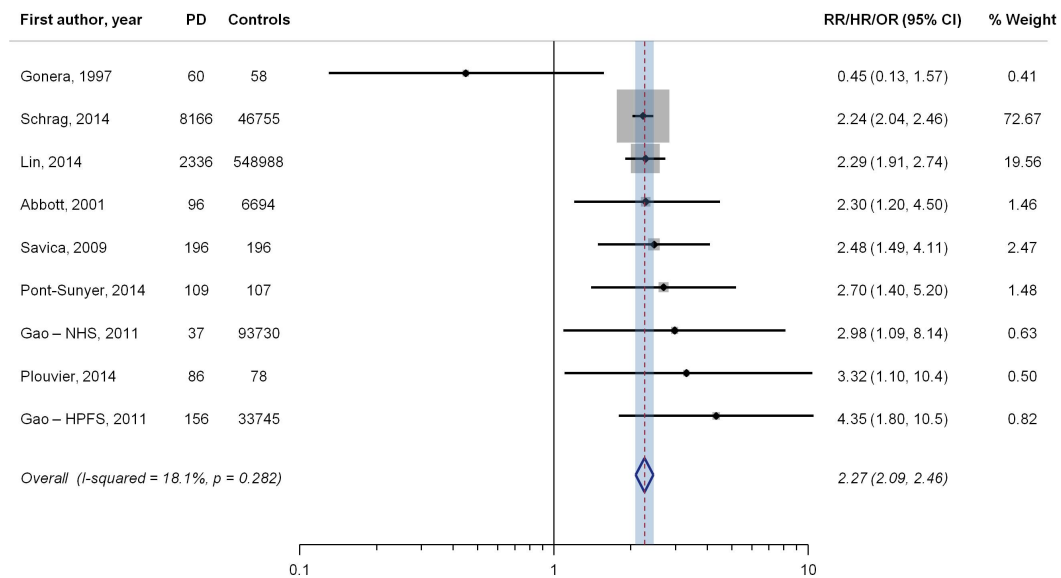


Figure 2 - Forest plot demonstrating increased PD risk in those with pre-morbid constipation as compared to those without. (PD, Parkinson’s disease; RR, relative risk; HR, hazard ratio; OR, odds ratio; CI, confidence interval).

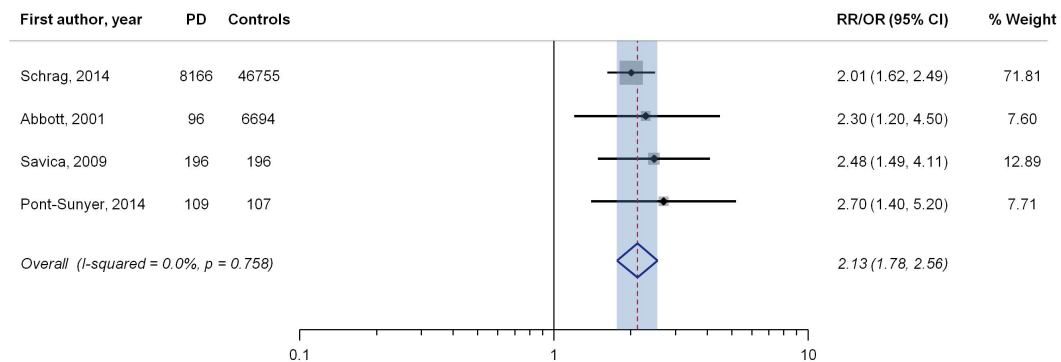


Figure 3 - Forest plot demonstrating increased risk of developing PD in those with constipation of duration ≥10 years as compared to those without constipation. (PD, Parkinson’s disease; RR, relative risk; OR, odds ratio; CI, confidence interval).

DISCUSSION

This systematic review and meta-analysis offers confirmation for the previously reported association between premorbid constipation and subsequent diagnosis of PD. The consistency of the association argues against the possibility that this could be a chance finding and its plausibility is high given similar findings in different study designs; both prospective and retrospective, with different biases, inherent assumptions and methods of exposure ascertainment. The CI for the ES is tight suggesting the true population risk estimate is in the range of 2.0-2.5-fold. The observation holds for pooled analysis of studies assessing the period more than 10 years before diagnosis.

Quantifying the magnitude of association between early non-motor features and subsequent PD may underpin efforts to identify higher risk participants for entry to interventional studies with neuroprotective aims.[18] Although the size of elevated risk conveyed by constipation might be modest overall, this is likely a consequence of constipation being a common symptom encountered in older age, and that many who suffer will not go on to be diagnosed with PD. However, the strength of association is similar more than a decade before diagnosis with PD, suggesting a long window of opportunity for intervention, were certainty of future PD to be improved through combination with other markers (clinical, imaging, laboratory) of the prodrome. Of note, one of the included case-control studies found significant associations with constipation predating PD diagnosis by 20 years, but the CIs for the association were wide.[17]

Three main possible underlying reasons for the association of constipation with PD are: (1) constipation is a manifestation of early PD within the bowel and therefore part of the

disease itself, (2) constipation is a risk factor for PD and it has a causal association with subsequent disease, or (3) constipation and PD are both outcomes of a common exposure.

Immunohistochemical studies have demonstrated the existence of abnormal deposits of α -synuclein within the submucosal and myenteric plexuses of the enteric nervous system.[19,20] Whilst the pathophysiological basis for colonic dysmotility and pelvic floor dysfunction that causes constipation in PD remains unclear, [21] the presence of these deposits raises the possibility of making a tissue diagnosis of PD during life. Several studies have reported positive findings from biopsies taken during routine colonoscopy in patients with PD compared with controls.[22,23] The investigation of gut biopsy in archival tissue obtained prior to PD diagnosis in small numbers of participants was prompted by the observation that constipation was an early non-motor feature of PD.[24] Subsequently, α -synuclein accumulation has been detected in colonic biopsies taken up to 7 years before the onset of motor symptoms.[25]

Endoscopic gastrointestinal biopsy remains an active area of PD biomarker research, but there is now also growing interest in the gut microbiome. In a recent pilot study, the abundance of Prevotellaceae in faeces was significantly lower in PD patients compared to controls and positive associations were found between abundance of Enterobacteriaceae and motor symptoms of PD.[26] Whether changes in gut flora are replicable must now be elucidated through further study, and if so, the matter of whether they are a cause or consequence of disease must be determined since both could confound the association between constipation and PD. Additional challenges lie in understanding the impact of laxative use and dietary habits, and these must be met before the microbiome could be considered a potential biomarker of disease state.

Laxative use is an important covariate in the association between constipation and PD, and requires some consideration. If constipation was associated with PD by way of being a manifestation of PD, then adjusting for laxative use in the analysis may underestimate the strength of this association. If, on the other hand, constipation were a risk factor for PD, then stratified analysis by laxative use would determine the strength of association in those that did and did not use laxatives, allowing an adjusted ES estimate to be calculated.

However, this may be inappropriate since it is feasible, albeit unlikely, that laxatives in fact lie on the causal pathway between constipation and PD. These issues may similarly apply to the role of diet, which is known to be difficult to measure and quantify.

Lack of concordance between studies in their approach to laxatives was a potential limitation of this study. Several of the case-control studies used included laxative use recorded in medical records as a proxy for constipation, while others excluded laxative users from the definition of constipation or adjusted for laxatives in secondary analyses. Given the ambiguity around the role that laxatives might play in the association between constipation and PD, where relevant, figures excluding laxative users were used in preference to figures adjusted for laxative use. This is in line with our conservative approach elsewhere during the data handling process (using mild constipation in preference to moderate or severe), and if it has any impact on the risk estimate it would be to underestimate it. Of note, one study provided risk estimates for later PD diagnosis for both the group with constipation as a whole, and for the subset of this group that required laxative treatment.[17] These risk estimates closely approximated each other, suggesting that laxative use may have little additional effect on later PD diagnosis when compared to constipation alone. However the numbers included within each group were small.

Other limitations of this study include the limits of the literature search: restricted to PubMed, to articles written in English, and to the search terms 'constipation' and 'Parkinson's disease', which may conceivably have led to some missing studies. However, the references of all full articles picked up in the initial search were hand searched for additional relevant studies, and only one additional paper was identified via this strategy. A broad range of study designs was included, with a variety of methods employed to determine and define 'constipation'. We limited variability where possible by selecting the definitions most in keeping with one another, and a definition in line with the Rome III criteria for functional constipation.[12] Where constipation or laxative use was coded in medical records, the exact definition of constipation in each case could not be determined. However, despite the impact this could have had on variability between study results, our analysis showed little evidence for heterogeneity between studies, and between case-control and cohort sub-groups as a whole, suggesting that the effect that different definitions of constipation and study designs had on risk estimates did not differ greatly.

Recall bias is a concern when including results from some case-control studies, however only one of the nine included studies adopted a retrospective design, whereby participants were asked to recall the date of onset of a number of non-motor symptoms. The introduction of recall bias in this particular study was minimised by recruiting patients only recently diagnosed with PD, with a median time between PD diagnosis and study evaluation of 1 month.[10]

The quality of the studies was assessed via means of the NOS.[13] All studies included in the main analysis had scores $\geq 6/9$, and all studies in the secondary analysis (studies that examined constipation over a decade before PD diagnosis) had a score of 8/9 (see online

supplementary table S2). Therefore, the risk estimate that resulted from this analysis may also be viewed as a fairly 'stringent' estimate, a result of the pooling of data from only highest quality studies. A further benefit of the secondary analysis is that any subjects with undiagnosed prevalent PD would likely not have been included, and so it avoids potential bias that would arise in this scenario.

It should be noted that the risk estimates provided here are more likely to underestimate the true magnitude of association between constipation and later development of PD than overestimate it. This is because more conservative definitions of constipation were selected where a choice was available. In future studies, we recommend: (1) that a universal definition of constipation is used where possible, such as < 3 BMs per week in the presence of other features (e.g. straining or hard stools), in line with Rome III criteria; and (2) that measures of effect are determined for both constipation and laxative use and unadjusted and stratum-specific measures of effect are reported to better determine the association with each.

In conclusion, we pool data from 741 593 people across nine studies to provide a consolidated risk estimate relating premorbid constipation to a later diagnosis of PD. Our risk estimate suggests that, compared with someone without, an individual with constipation is at a 2.27-fold increased risk of developing PD, and this increase in risk persists over a decade prior to diagnosis. This updates previous risk estimates (with associated wide CIs) and provides information that will help ascertain those at increased risk of PD and perhaps better understand the early stages of disease.

CONTRIBUTORS: KLA-C collected data, performed statistical analysis and drafted the manuscript. JPB conceived the project, performed statistical analysis and provided critical revision of the manuscript. SS provided critical revision of the manuscript. AL and AS conceived the project and provided critical revision of the manuscript. AJN conceived the study, collected data, performed statistical analysis and drafted the manuscript.

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