2020

Gastrointestinal dysfunction in Parkinson's disease

Michal Lubomski
The University of Notre Dame Australia, michal.lubomski@nd.edu.au

Ryan L. Davis

Carolyn M. Sue

This article was originally published as:
Lubomski, M., Davis, R. L., & Sue, C. M. (2020). Gastrointestinal dysfunction in Parkinson's disease. *Journal of Neurology, Early View, Online First*.

Original article available here:
https://doi.org/10.1007/s00415-020-09723-5

Gastrointestinal dysfunction in Parkinson's disease

Michal Lubomski[1,2,3], Ryan L. Davis[2*], Carolyn M. Sue[1,2*]

[1] Department of Neurology, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW, Australia.

[2] Department of Neurogenetics, Kolling Institute, Faculty of Medicine and Health, University of Sydney and Northern Sydney Local Health District, St Leonards, NSW, Australia.

[3] The University of Notre Dame Australia, School of Medicine, Sydney, NSW, Australia.

* Co-last authors

Corresponding Author – Michal Lubomski
Email: mlub6241@uni.sydney.edu.au
(Phone) +612 9463 1733 (Fax) +612 9463 1071
Postal Address: Department of Neurology, Clinical Admin 3E, Level 3, ASB,
Royal North Shore Hospital, Reserve Rd, St Leonards NSW, 2065.

Word Counts:

Abstract: 254
Article: 3770
Figures: 4
Tables: 2
References: 45
Supplementary Files: 0

Not industry sponsored.

Supported by a Parkinson's New South Wales, Research Seed Grant.

Keywords:
1. Parkinson's disease
2. Gastrointestinal dysfunction
3. Constipation
4. Dysmotility
5. Gastroparesis

Author Contributions:
Michal Lubomski: Study design, reviewed patients, collected and analysed data, drafted and reviewed the manuscript
Ryan L. Davis: Study design, drafted and reviewed the manuscript
Carolyn M. Sue: Study design, drafted and reviewed the manuscript

Author Disclosures:
Michal Lubomski: reports no disclosures
Ryan L. Davis: reports no disclosures
Carolyn M. Sue: reports no disclosures

Abstract:

Background: Gastrointestinal (GI) dysfunction is prevalent in Parkinson's disease (PD). Symptoms are evident throughout the disease course, affect the length of the GI tract and impact on patient quality of life and management. We clarify real-life differences in the frequency and severity of GI symptoms in a cohort of PD and healthy control (HC) subjects.

Methods: 103 PD patients were compared to 81 HC subjects. Outcome measures collected from validated questionnaires included constipation severity, upper and lower GI symptoms and physical activity.

Results: PD patients were three-times more likely to experience constipation than HC subjects, (78.6% vs 28.4%), exhibited a fourfold increase in constipation severity and formed harder stools. PD patients also reported increased symptoms of indigestion, nausea, excessive fullness and bloating, compared to the HCs. A higher mean Leeds Dyspepsia Questionnaire score for PD patients (8.3 (standard deviation (SD) 7.7) vs 4.6 (SD 6.1), p=0.001)) indicated increased symptom severity. Chronic pain was more frequently reported and correlated with constipation and upper GI dysfunction, being more prevalent and severe in women. Physical activity was notably decreased in the PD cohort (1823.6 (± 1693.6) vs 2942.4 (± 2620.9) metabolic equivalent-minutes/week, p=0.001) and correlated with constipation severity. PD therapies were associated with increased fullness and bloating and harder stools.

Conclusions: PD patients report more prevalent and severe GI dysfunction, although our cohort comprised of many later-stage participants. Earlier recognition of GI dysfunction in PD provides the opportunity to direct treatment for chronic pain and constipation, promote physical activity and rationalise PD therapies for optimal patient care.

Introduction:

PD is an incurable multisystem disorder that contributes to significant morbidity and healthcare burden [1]. GI dysfunctions are the most prevalent non-motor symptoms (NMS) of PD, being present in approximately 65% of patients [2] and conferring a considerably negative impact on quality of life (QoL) [3, 4]. Common GI symptoms include constipation, bloating, drooling, dysphagia, nausea, vomiting and gastroparesis and can precede motor symptoms by up to 20 years [5-7]. Symptoms are evident throughout the disease course and involve the whole length of the GI tract [8].

Consistent with clinico-epidemiological observations, several neuropathological studies have found early accumulation of Lewy bodies (LB) in the Enteric Nervous System (ENS) and dorsal motor nucleus of the vagus. These findings correlate with motor and gastrointestinal symptom severity, [9, 10] and reflect impaired intestinal peristalsis / motility, vagal dysfunction, altered intestinal permeability, sensory impairments of the GI tract as well as medication effects, which together can influence GI dysfunction in PD [11, 12].

GI disorders, such as malnutrition, aspiration pneumonia, megacolon, intestinal obstruction and intestinal perforation, are a frequent cause of hospitalisation in PD [1, 5, 13]. In addition, approximately 40-50% of PD patients report suffering from chronic constipation, whereby the frequency is dependent on the type of questionnaire used [14]. Constipation is believed to result from delayed GI transit and paradoxical contraction of voluntary sphincters during defecation [15, 16]. Constipation severity has been suggested to predict a faster motor and cognitive disease progression, as well as severely impacting QoL [17].

The treatment of GI dysfunction in PD is often ineffective and frequently complicated by side-effects [12]. Gastroparesis and delayed intestinal absorption negatively impact on treatment, causing erratic levodopa uptake that may lead to motor fluctuations [18]. Emerging research also suggests that the bidirectional communication between the gut and the brain, termed the microbiota-gut-brain-axis, may further impact GI dysfunction, PD pathogenicity, [19, 20] and levodopa metabolism [21].

Given the evident and considerable association between GI dysfunction and PD, this study examined the patterns of GI dysfunction in an Australian PD cohort using self-reported symptoms of upper and lower GI dysfunction, QoL and clinical features relating to patient management.

Methods:

Study settings and subjects

Subjects were consecutively recruited from the movement disorder and neurology clinics at Royal North Shore Hospital, Sydney, Australia, between 2018 and 2019. Inclusion criteria were, 1) >18 years of age, 2) a clinical diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [22], and 3) being managed by a specialist neurologist. The HC inclusion criteria were, 1) >18 years of age, 2) exhibiting no clinical indication of PD, and 3) a spouse, sibling or child with similar dietary habits to their respective PD subject. Exclusion criteria included secondary Parkinsonism, tube feeding, medical or surgical disorders preventing completion of questionnaires and significant cognitive impairment demonstrated by incapacity to provide consent. Ethical approval was granted by the Northern Sydney Local Health District Human Research Ethics Committee and the North Shore Private Hospital ethics committee, HREC/18/HAWKE/109, NSPHEC 2018-LNR-009 respectively. Written informed consent was obtained from all patients at the time of recruitment.

Data collection

Patients completed self-administered questionnaires, as well as providing a stool and blood sample at the time of recruitment. Stool samples were assessed according to the Bristol Stool Scale (BSS) [23], whilst blood samples were assessed for liver function tests, glycaemic profiles, non-fasting lipid profiles, Erythrocyte Sedimentation Rate and C-Reactive Protein.

Information regarding socio-demographic factors, lifestyle and clinical management was collected from validated surveys. Patients completed the Leeds Dyspepsia Questionnaire (LDQ) [24] assessing upper gastrointestinal symptoms. Constipation severity and gut motility were evaluated by the Rome-IV criteria [25] and the Cleveland Constipation Score (CCS) [26]. QoL and NMS were assessed by the Non-Motor Symptoms Scale (NMSS) [27]. Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) [28]. Clinical motor assessments were performed by one neurologist during a patient's ‘on’ state, as an objective measure of the prevailing motor function, in accordance with the Movement Disorder Society – Unified Parkinson’s Disease

Rating Scale – Part III (MDS-UPDRS III) criteria [29]. Medications were compared following standard methods for calculating daily levodopa equivalent dose (LED) [30], whilst chronic pain severity was assessed by the Visual Analogue Scale [31].

Statistical analysis

Normal distribution of all data was confirmed using the Shapiro-Wilk test. Independent *t*-tests were used to analyse differences between groups for continuous variables. Chi-squared (χ^2) tests were used to compare differences between categorical variables. Logistic and linear regression models were constructed to evaluate differences in the prevalence of various GI symptoms between the PD and HC groups, as well as within the PD cohort, after controlling for demographic and clinical variables. Correlation of clinically relevant variables was evaluated using Pearson's correlation test. $p<0.05$ was considered significant. Data analysis was performed using SPSS, version 25 (SPSS Inc, Chicago, Illinois, USA).

Results:

Demographic characteristics

103 PD patients and 81 HC's were enrolled into the study (Table 1). 56.3% of the PD participants were male with a mean age of 67.1years (range 35-88, standard deviation (SD) 12.2), whilst two thirds of the HCs were female, with a mean age of 62.4 years (range 18-90, SD 15.6, p=0.001). For the combined cohort (PD and HC), 80% of the participants were married and identified as Caucasian. The mean Body Mass Index was 26.0 (SD 4.90) and 5.5% of subjects reported a history of diabetes, with no statistically significant differences observed between the groups for these measures. Biochemical analysis between the two groups showed that PD patients had lower total cholesterol levels (4.8; SD 0.9 vs 5.2; SD 1.1, p=0.014), lower high density lipoprotein (HDL) levels (1.4; SD 0.4 vs 1.6; SD 0.4, p=0.033), and lower albumin levels (38.7; SD 3.5 vs 39.8; SD 3.1, p=0.023), compared to the HC group, although still within normal physiological ranges. Approximately one third of all participants identified as being prior smokers and approximately 88% reported daily caffeine consumption, although PD participants did report a lower daily intake of 2.3 (SD 1.7) vs 3.1 (SD 1.8) cups (p=0.003). Additionally, PD patients reported a lower rate of alcohol consumption, (70% vs 87.7%, p=0.003) (Table 1).

Within the PD cohort, the mean age of diagnosis was 58.8 years (SD 13.6) and mean duration of disease was 9.2 years (SD 6.5), with 49.5% of patients reporting a late onset diagnosis (>60 years)

and 10.7% being diagnosed as young onset (<40 years) (Table 2). Approximately one third of PD patients had either a tremor dominant or akinetic rigid phenotype. More than half identified troublesome motor fluctuations, particularly dyskinesias, with more than 80% reporting medications 'wearing off' prior to their next dose. Of the NMS, three quarters reported hyposmia, half reported Rapid Eye Movement Sleep Behaviour Disorder and 60.2% recognised suffering from constipation. Approximately 5% of the PD cohort was treatment naïve, 90% utilised oral levodopa, 35% dopamine agonists (DA), 18% monoamine oxidase-B inhibitors (MAO-B), 13% anticholinergics, 23% catechol-O-methyltransferase (COMT) inhibitors and 13% amantadine. Of those receiving device-assisted therapies, 9% utilised levodopa-carbidopa intestinal gel (LCIG) infusions, 11% Deep Brain Stimulation (DBS) and 7% subcutaneous apomorphine infusions.

Clinical characteristics of the cohort

Gastrointestinal symptoms

Subjects with PD reported increased lower and upper gastrointestinal symptoms compared to the HC group. Definitive functional constipation diagnosed by the Rome-IV criteria (score ≥ 2, range 0-15) confirmed 78.6% of PD participants vs 28.4% of HC suffered from constipation (χ^2=46.6, df=1, p<0.001, Table 1). The higher mean constipation score of 4.4 (SD 3.5) vs 1.1 (SD 1.4) (p<0.001), gave an odds ratio of 9.3 (95% confidence interval 4.7-18.2) for PD patients to suffer from constipation (Figure 1A). Furthermore, the CCS (range 0-30) confirmed increased constipation severity in PD patients; 7.2 (SD 4.7) vs 3.1 (SD 2.9) in HCs (p<0.001) (Figure 1B). Examination of the BSS (scale of 1-7) reflected lower scores (firmer and lumpier stools) in PD subjects (mean score = 2.8; SD 1.5) as compared with HCs (mean score = 3.9; SD 1.3) (p<0.001) (Figure 1C). Weak negative correlations were apparent between BSS and Rome-IV constipation scores (r=-0.171, p=0.020) for the combined cohort, confirming individuals with increased constipation severity tended to have firmer stools (Figure 2A). Upper GI dysfunction assessed by the LDQ (range 0-40) also reflected increased symptom burden in the PD cohort, with subjects reporting increased indigestion (18.4% vs 8.6%), nausea (15.6% vs 7.4%), as well as excess fullness and bloating (20.4% vs 14.8%) (χ^2=15.2, df=7, p=0.034). Moreover, the mean LDQ score was higher in the PD (8.3; SD 7.7) compared to the HC group (4.6; SD 6.1) (p=0.001), reflecting a higher severity of symptoms (Figure 1D).

Chronic pain, physical activity and lifestyle influences

Various physical and functional measures that influence GI function impacted the PD cohort more substantially. Chronic pain (>3 months) was more frequently reported in the PD group (72.8% vs 39.5%, $p<0.001$), in addition to PD patients reporting a higher mean pain score (4.9; SD 2.5 vs 3.9; SD 1.7, $p=0.046$), as assessed by the Visual Analogue Scale. No differences in analgesia use, including opioids, were noted between the groups. In the combined population, linear regression modelling showed that those with chronic pain and with higher pain severity scores were more likely to report increased constipation severity (CCS; $\beta=-0.349$, $r^2=0.195$, $p<0.001$ and Rome-IV score; $\beta=-0.334$, $r^2=0.116$, $p<0.001$) and increased upper GI dysfunction (LDQ score; $\beta=-0.264$, $r^2=0.145$, $p<0.001$) after controlling for patient age and sex.

Physical activity assessed by the IPAQ identified that patients with PD reported a lower physical activity score (1823.6 (metabolic-equivalent) MET-minutes/week; SD 1693.6) compared to the HC group (2942.4 MET-minutes/week; SD 2620.9, $p=0.001$). Likewise, a higher proportion of PD patients had lower IPAQ categorical scores (35.2% vs 19.8%, $p=0.029$), inferring a lower score category (<600 MET-minutes/week). Similarly, PD patients reported an increased mean daily sitting time of 6.5 (SD 3.5) hours per day, compared to the HC group 4.8 (SD 2.3) ($p<0.001$, Table 1). Additionally, significant correlations were also identified in the whole cohort between the IPAQ score and the CCS ($r=-0.271$, $p<0.001$) and the IPAQ Score and the Rome-IV score ($r=-0.256$, $p<0.001$), indicating that those patients with reduced physical activity had increased constipation severity (Figure 2B). Caffeine intake and smoking status did not appear to impact on either upper or lower GI symptoms or NMS in the combined or PD cohorts. However, within the combined and PD cohorts, those who consumed any alcohol were noted to report decreased constipation severity, as assessed by the Rome-IV criteria ($\beta=0.194$, $r^2=0.063$, $p=0.008$) and CCS ($\beta=0.174$, $r^2=0.060$, $p=0.018$), whilst also reporting increased IPAQ scores ($\beta=-0.188$, $r^2=0.035$, $p=0.011$), when controlling for age and sex.

Logistic regression models, evaluating differences between the PD and HC groups for specific GI complaints, showed that statistical significance persisted for differences in the CCS score (Wald $\chi^2=22.1$, $df=5$, $p<0.001$), Rome-IV criteria (Wald $\chi^2=25.8$, $df=5$, $p<0.001$), BSS (Wald $\chi^2=12.3$, $df=5$, $p<0.001$), LDQ score (Wald $\chi^2=9.4$, $df=5$, $p=0.002$), most troublesome upper GI symptom assessed by the LDQ (Wald $\chi^2=3.7$, $df=5$, $p=0.047$), chronic pain (Wald $\chi^2=6.5$, $df=5$, $p=0.011$) and the IPAQ score (Wald $\chi^2=6.0$, $df=4$, $p=0.015$) after controlling for age, sex, alcohol and caffeine consumption and the IPAQ score.

Parkinson's disease cohort: clinical characteristics and influences of therapies

The PD cohort's mean daily LED was 824.8 mg (SD 527.3), with a mean 'on' MDS-UPDRS III score of 32.9 (SD 17.7), (range 0-132) (Table 2). Within the PD cohort, linear regression models were used to assess the effect of PD duration on various GI symptoms. After controlling for age, sex and daily LED, advancing PD duration reflected increased constipation severity (CCS; β=0.239, r^2=0.129, p=0.039 and the Rome-IV criteria; β=0.129, r^2=0.326, p=0.048) (Figures 3, A and B). Similarly, advancing PD duration was associated with increased upper GI symptoms, as assessed by the LDQ, after controlling for patient age, sex and daily LED (β=0.120, r^2=0.124, p=0.048).

No correlations between PD phenotype or daily LED and upper and lower GI symptoms were identified, including the BSS. However, motor fluctuations, hallmarked by dyskinesias, were more frequently observed in patients with increased constipation severity, when controlling for patient age, sex and daily LED (CCS; β=-0.146, r^2=0.106, p=0.043 and Rome-IV criteria; β=-0.163, r^2=0.143, p=0.047). Motor fluctuations were also significantly more prevalent in PD patients with increased LDQ scores, (β=-0.252, r^2=0.165, p=0.018), controlling for patient age, sex and daily LED. Furthermore, clinically significant differences were noted between sexes, with PD females reporting worse constipation severity (CCS; β=0.153, r^2=0.139, p=0.044 and Rome-IV criteria; β=0.142, r^2=0.125, p=0.048), as well as upper GI dysfunction, particularly nausea and indigestion (LDQ; β=0.242, r^2=0.167, p=0.013), controlling for patient age, PD duration and daily LED. Analysis of NMS in the PD cohort identified an MDS NMSS Total Score of 62.7 (range 0-243, SD 42.9), with a subgroup domain 6 (gastrointestinal symptoms) score of 6.1 (range 0-26, SD 6.3), indicating a significant negative impact to patient QoL.

When evaluating PD therapies, no significant differences reflecting either upper or lower GI dysfunction were identified in patients who were taking levodopa, MAO-B inhibitors, anticholinergics, COMT inhibitors or amantadine. However, patients receiving LCIG reported increased upper GI dysfunction with higher LDQ scores, particularly excess fullness and bloating, (β =-0.163, r^2=0.061, p=0.046), after controlling for patient age, sex and PD duration. PD patients using a DA showed markedly reduced BSS after controlling for age, sex and PD duration (β=0.248, r^2=0.209, p=0.008), with corresponding increases in CCS and Rome-IV constipation scores that did not quite reach statistical significance (p=0.052).

Discussion:

We identified clinically significant GI related differences across a number of demographic and clinical characteristics in patients with PD (Figure 4). Both upper and lower GI dysfunction was prevalent in PD patients, reflecting a negative impact to their clinical management and QoL. Constipation was prevalent in the PD group, at comparable frequencies to other studies [5, 12]. However, constipation was notably underrecognised by many PD participants, with only 60% of patients self-recognising their issue, compared to 79% meeting the diagnostic criteria, according to Rome-IV criteria (Table 1). Increased constipation prevalence and severity in the PD cohort was supported by two internationally validated constipation scales, the CCS and the Rome-IV criteria, both unanimously suggesting that lower GI dysfunction, hallmarked by constipation, was more prevalent and severe in PD patients.

The BSS rating correlated well with a patient's constipation severity, showing PD patients to have lower BSS overall (harder and lumpier stools), which is likely resultant of slowed colonic transit times [32]. In addition, upper GI dysfunction was more prevalent and severe in PD patients, particularly the symptoms of indigestion, nausea and excess fullness and bloating. These symptoms likely result from delayed gastric emptying and gastroparesis, which may be seen in approximately 70% of PD patients [12]. However, a recent meta-analysis suggests this number may be an overestimation and is dependent on the type of assessment utilised, either by gastric scintigraphy or breath test studies [33]. The increased rates of motor fluctuations and dyskinesias that were seen in patients with higher LDQ scores, imply ineffective levodopa absorption in the small intestine, manifesting as a delayed or complete loss of benefit [12].

Chronic pain is endemic in PD, with other studies reporting a prevalence of between 40-83% [34]. Our PD cohort supports these findings, reflecting that nearly three quarters of patients, compared to 40% of HC's, live with chronic pain. Pain is often related with a significant negative impact to a patient's QoL and GI function, with this study demonstrating that the presence of chronic pain was significantly associated with both upper and lower GI dysfunction. Following on from this, chronic pain often poses significant management difficulties due to the reinforcement of a vicious positive feedback loop; constipation perpetuates abdominal discomfort that induces pain and provokes worsening constipation severity. Interestingly, the criteria proposed by Ford *et al.*, which categorises PD related pain originating from either musculoskeletal pain, dystonia-associated pain,

radicular or peripheral pain, central pain, or akathisia [35], may fail to recognise the significant associations between chronic pain and GI related causes, as suggested by our findings.

Physical activity also has significant influences on PD-related GI function. We identified that patients with PD had lower daily physical activity scores and increased daily sitting times overall. Importantly, we showed that a reduced level of physical activity correlated with the severity of constipation in the combined cohort and PD group. This highlights that exercise should be considered as an important modifiable risk factor for constipation in PD and could be considered as a useful treatment strategy [5]. Other lifestyle factors, including caffeine intake and smoking status, previously suggested as potential risk modifiers for PD development [36], did not appear to have any significant effect on GI function in our study. Interestingly, alcohol consumption and increased physical activity were consistent with a lower severity of constipation. These findings suggest that individuals with more troublesome constipation were less likely to exercise or drink alcohol.

Blood biochemical analysis within our cohort showed subtle, yet interesting insights into potentially important nutritional differences between PD and HC patients. Although relatively minor and still within normal physiological range, lower total cholesterol, HDL and albumin levels in PD may reflect an emerging pattern suggestive of malnourishment [37].

Within our PD cohort we showed that increased PD duration was significantly implicated in the severity of constipation, with older PD patients reporting increased constipation. With increasing PD duration patients were more likely to report increased upper and lower GI dysfunction severity, possibly consistent with spreading α–Synuclein pathology through the ENS [38], although this is controversial [39]. No associations between PD phenotypes and any GI symptoms were identified. However, patients with motor fluctuations, particularly dyskinesias, were more likely to report increased constipation and upper GI dysfunction severity. These findings suggest that motor fluctuations may arise due to worsening gastroparesis and gastric emptying, impairing the absorption of antiparkinsonian drugs [12, 19].

Sex differences in PD are also becoming increasingly recognised and constitute significant implications to a patient's QoL and their clinical management [40]. Here, PD females reported worse constipation and upper GI dysfunction severity, particularly reflecting increased nausea and indigestion, compared to men with PD. The mechanisms behind these findings are poorly understood but may reflect women's moderately increased PD duration (11 vs 7 years), although younger age (55 vs 61 years), respectively. Other possibilities include potentially increased

sensitivity from PD medications, such as levodopa, in addition to poorly understood oestrogenic effects in the gut and central nervous system, [40] or reporting bias.

PD treatment appears to reflect significant implications to both upper and lower GI function, as well as patient QoL. LCIG use was associated with an increased severity of excess fullness and bloating compared to other therapies. Perhaps not surprisingly, a percutaneous infusion of levodopa-carbidopa through a gastrojejunostomy tube to the upper GI tract may account for some of the mechanical and pharmacological implications responsible for increased bloating and excess fullness [41]. Furthermore, patients utilising a DA showed a lower BSS, suggesting an increased risk for constipation. No significant differences between upper or lower GI dysfunction were found in patients taking levodopa, MAO-B inhibitors, COMT inhibitors, amantadine and anticholinergics. Although greater constipation severity was noted in patients using anticholinergics, despite not reaching statistical significance, likely due to the smaller population size. The treatment related effects identified from patients utilising LCIG suggested increased rates of upper GI dysfunction. However, it is unclear whether such therapy effects are genuine or indicative of increased PD severity, rather than PD duration, as was discounted by our analysis.

Whilst our data does not address certain potential confounding factors, including other comorbidities and medication effects, several important GI related differences in PD were identified. Medication use for GI dysfunction (e.g., laxatives, anti-diarrhoea medication and reflux medication), as well as GI tract medical diagnosis (e.g., Inflammatory Bowel Disease, Inflammatory Bowel Syndrome and Coeliac Disease), are important modulators in the GI measures, but were not available and were not considered in the analysis. A relatively small sample size for both cohorts, in addition to non-optimally matched PD and HC groups for age and sex, due to spousal recruitment, may have resulted in a potential under-representation of GI dysfunctions from within the HC group. It is known that constipation increases with age [42] and this may further explain why the on average 4.7 year age difference for the PD cohort reported increased constipation severity compared to the HC group. Our PD cohort comprised of many later-stage patients, with a mean disease duration of 9.2 years (SD 6.5). Consequently, the reported prevalence of GI NMS in our study may not represent the general PD population. Interestingly, our HC group reported a constipation frequency of 28.4%, which is slightly higher than other worldwide estimates that vary between 12-19% [42]. However, this frequency of constipation was comparable to other studies from Sydney, Australia, [43] and may reflect differences in cultural backgrounds and dietary patterns, particularly fibre content. [44] Furthermore, the definition of constipation in Parkinson's disease is inconsistent and highly dependent on the questionnaire used, with more than 10 different

definitions of constipation throughout the Parkinson's disease literature. [14] Although our definition of constipation was derived from the Rome-IV criteria, the resulting constipation prevalence of 78% in the PD cohort would be unlikely to be supported by the CSS criteria, with our mean PD cohort value of 7.2, as some studies have employed a cut-off score as high as 15 to define constipation. [26] Accordingly, the type of questionnaire utilised to define constipation is defining.

The findings of this study should be interpreted in light of its limitations, including the self-reporting nature of the data and potential selection bias of the study population being drawn from specialist PD clinics. The greater GI dysfunction burden demonstrated by PD patients in this study may be a reflection of recruitment bias inherent in this cross-sectional survey design, whereby PD patients with greater GI symptomology may have been over-represented among the clinic attendees. Furthermore, our sample only reflected the experience of patients from a single metropolitan area, whereas previous studies from Australia have shown PD patients from regional areas to be comparably older with an older age of diagnosis [45].

Conclusion:

We highlight novel clinical associations and unravel their influences on GI dysfunction in PD, a NMS that is hallmarked by prevalent constipation and upper GI dysfunction in patients with PD. Increasing PD duration, motor fluctuations, chronic pain, decreased physical activity, female gender, as well as certain PD therapies, appear to predispose PD patients and negatively impact GI dysfunction. In light of our findings, we recommend optimising and proactively treating constipation and upper GI symptoms, encouraging physical exercise, treating chronic pain as well as rationalising PD therapies. These practical measures aim to modify risk factors and may help to reduce the considerable burden of GI dysfunction in PD.

Author Contributions:

Michal Lubomski: Study design, collected data and performed analyses, drafted and reviewed the manuscript.

Ryan L. Davis: Study design, drafted and reviewed the manuscript.

Carolyn M. Sue: Study design, drafted and reviewed the manuscript.

Conflict of Interest:

Not industry sponsored. All authors report no relevant disclosures.

Acknowledgements

We thank Parkinson's New South Wales for a Research Seed Grant. We would also like to thank all our participants. RLD is a New South Wales Health Early-Mid Career Research Fellow. CMS is the recipient of a NHMRC Practitioner Fellowship (APP1136800).

Figures:

Figure 1: Plots Identifying Gastrointestinal Dysfunction in Parkinson's Disease and Healthy Control Subjects.

A) Rome IV Criteria Constipation Score comparison suggested increased constipation severity in the Parkinson's disease cohort; 4.4 (SD 3.5) compared to the healthy control group; 1.1 (SD 1.4) ($p<0.001$).

B) Cleveland Constipation Score comparison suggested increased constipation severity in Parkinson's disease patients compared to healthy controls; 7.2 (SD 4.7) vs 3.1 (SD 2.9) ($p<0.001$).

C) Bristol Stool Scale comparison identified lower scores in Parkinson's disease subjects (firmer and lumpier stools); 2.8 (SD 1.5) compared to the healthy control group; 3.9 (SD 1.3) ($p<0.001$).

D) Leeds Dyspepsia Questionnaire score comparison showed higher scores in the Parkinson's disease cohort; 8.3 (SD 7.7) compared to the healthy control group; 4.6 (SD 6.1) ($p=0.001$), suggesting increased upper gastrointestinal symptom severity.

Figure 2: Correlations Identifying Gastrointestinal Dysfunction in Parkinson's Disease.

A) Weak negative correlations between the Bristol Stool Scale and Rome-IV Criteria Constipation score were identified for the combined cohort, ($r=-0.171$, $p=0.020$), confirming individuals with increased constipation severity tended to have firmer stools.

B) Correlations within the combined cohort between the International Physical Activity Questionnaire score and the Cleveland Constipation Score ($r=-0.271$, $p<0.001$), and the International Physical Activity Questionnaire score and the Rome-IV Criteria Constipation score ($r=-0.256$, $p<0.001$), indicated that patients with reduced physical activity experienced increased constipation severity.

Figure 3: Correlations Between Parkinson's Disease Duration and Constipation Severity Scores.

A) Correlation showing that increasing Parkinson's disease duration reflected increased constipation severity, according to the Cleveland Constipation Score.

B) Correlation showing that increasing Parkinson's disease duration reflected increased constipation severity, according to the Rome IV Criteria Constipation scores.

Figure 4: Factors Leading to Gastrointestinal Dysfunction in Parkinson's Disease.

Tables:

Table 1: Cohort Demographic and Clinical Characteristics.

Table 2: Parkinson's Disease Clinical Characteristics.

References:

1. Lubomski M, Rushworth RL, Tisch S. Hospitalisation and comorbidities in Parkinson's disease: a large Australian retrospective study. J Neurol Neurosurg Psychiatry. 2015;86(3):324-30.
2. Makaroff L, Gunn A, Gervasoni C, Richy F. Gastrointestinal disorders in Parkinson's disease: prevalence and health outcomes in a US claims database. Journal of Parkinson's disease. 2011;1(1):65-74.
3. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. The Lancet Neurology. 2003;2(2):107-16.
4. Yu QJ, Yu SY, Zuo LJ, Lian TH, Hu Y, Wang RD, et al. Parkinson disease with constipation: clinical features and relevant factors. Scientific reports. 2018;8(1):567.
5. Poirier AA, Aube B, Cote M, Morin N, Di Paolo T, Soulet D. Gastrointestinal Dysfunctions in Parkinson's Disease: Symptoms and Treatments. Parkinsons Dis. 2016;2016:6762528.
6. Abbott RD, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology. 2001;57(3):456-62.

7. Savica R, Carlin JM, Grossardt BR, Bower JH, Ahlskog JE, Maraganore DM, et al. Medical records documentation of constipation preceding Parkinson disease: A case-control study. Neurology. 2009;73(21):1752-8.
8. Klingelhoefer L, Reichmann H. The Gut and Nonmotor Symptoms in Parkinson's Disease. Int Rev Neurobiol. 2017;134:787-809.
9. Cersosimo MG, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. Neurobiology of disease. 2012;46(3):559-64.
10. Lebouvier T, Neunlist M, Bruley des Varannes S, Coron E, Drouard A, N'Guyen JM, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. PloS one. 2010;5(9):e12728.
11. Park A, Stacy M. Non-motor symptoms in Parkinson's disease. J Neurol. 2009;256 Suppl 3:293-8.
12. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. The Lancet Neurology. 2015;14(6):625-39.
13. Guneysel O, Onultan O, Onur O. Parkinson's disease and the frequent reasons for emergency admission. Neuropsychiatr Dis Treat. 2008;4(4):711-4.
14. Knudsen K, Krogh K, Ostergaard K, Borghammer P. Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives. Movement disorders. 2017;32(1):94-105.
15. Edwards LL, Quigley EM, Harned RK, Hofman R, Pfeiffer RF. Characterization of swallowing and defecation in Parkinson's disease. Am J Gastroenterol. 1994;89(1):15-25.
16. Ashraf W, Pfeiffer RF, Quigley EM. Anorectal manometry in the assessment of anorectal function in Parkinson's disease: a comparison with chronic idiopathic constipation. Movement disorders. 1994;9(6):655-63.
17. Camacho M, Evans J, Breen D, Cummins G, Wijeyekoon R, Scott K, et al. Early gastrointestinal dysfunction is predictive of faster progression in Parkinson's disease. Movement Disorders. 2018;33 (Supplement 2):S729.
18. Djaldetti R, Baron J, Ziv I, Melamed E. Gastric emptying in Parkinson's disease: patients with and without response fluctuations. Neurology. 1996;46(4):1051-4.
19. Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease. Current Treatment Options in Neurology. 2018;20 (12) (no pagination)(54).
20. Lubomski M, Tan AH, Lim SY, Holmes AJ, Davis RL, Sue CM. Parkinson's disease and the gastrointestinal microbiome. J Neurol. 2019.
21. Lubomski M, Davis RL, Sue CM. The gut microbiota: A novel therapeutic target in Parkinson's disease? Parkinsonism & related disorders. 2019.

22. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992;55(3):181-4.
23. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4.
24. Moayyedi P, Duffett S, Braunholtz D, Mason S, Richards ID, Dowell AC, et al. The Leeds Dyspepsia Questionnaire: a valid tool for measuring the presence and severity of dyspepsia. Alimentary pharmacology & therapeutics. 1998;12(12):1257-62.
25. Sood R, Ford AC. Diagnosis: Rome IV criteria for FGIDs - an improvement or more of the same? Nature reviews Gastroenterology & hepatology. 2016;13(9):501-2.
26. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. Diseases of the colon and rectum. 1996;39(6):681-5.
27. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Movement disorders. 2007;22(13):1901-11.
28. Hagstromer M, Oja P, Sjostrom M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public health nutrition. 2006;9(6):755-62.
29. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement disorders. 2008;23(15):2129-70.
30. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649-53.
31. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18(4):1007-19.
32. Saad RJ, Rao SS, Koch KL, Kuo B, Parkman HP, McCallum RW, et al. Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. Am J Gastroenterol. 2010;105(2):403-11.
33. Knudsen K, Szwebs M, Hansen AK, Borghammer P. Gastric emptying in Parkinson's disease - A mini-review. Parkinsonism & related disorders. 2018;55:18-25.

34. Mylius V, Ciampi de Andrade D, Cury RG, Teepker M, Ehrt U, Eggert KM, et al. Pain in Parkinson's Disease: Current Concepts and a New Diagnostic Algorithm. Mov Disord Clin Pract. 2015;2(4):357-64.
35. Ford B. Pain in Parkinson's disease. Mov Disord. 2010;25 Suppl 1:S98-103.
36. Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT, Jr., Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. Am J Epidemiol. 2002;155(8):732-8.
37. Budrewicz S, Zmarzly A, Raczka D, Szczepanska A, Koziorowska-Gawron E, Slotwinski K, et al. Clinical and nutritional correlations in Parkinson's disease: Preliminary report. Adv Clin Exp Med. 2019;28(2):193-8.
38. Recasens A, Dehay B. Alpha-synuclein spreading in Parkinson's disease. Front Neuroanat. 2014;8:159.
39. Lee HJ, Jung KW, Chung SJ, Hong SM, Kim J, Lee JH, et al. Relation of Enteric alpha-Synuclein to Gastrointestinal Dysfunction in Patients With Parkinson's Disease and in Neurologically Intact Subjects. J Neurogastroenterol Motil. 2018;24(3):469-78.
40. Lubomski M, Louise Rushworth R, Lee W, Bertram KL, Williams DR. Sex differences in Parkinson's disease. J Clin Neurosci. 2014;21(9):1503-6.
41. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014;13(2):141-9.
42. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99(4):750-9.
43. Fragakis A, Zhou J, Mannan H, Ho V. Association between Drug Usage and Constipation in the Elderly Population of Greater Western Sydney Australia. Int J Environ Res Public Health. 2018;15(2).
44. Yang J, Wang HP, Zhou L, Xu CF. Effect of dietary fiber on constipation: a meta analysis. World journal of gastroenterology. 2012;18(48):7378-83.
45. Lubomski M, Rushworth RL, Lee W, Bertram K, Williams DR. A cross-sectional study of clinical management, and provision of health services and their utilisation, by patients with Parkinson's disease in urban and regional Victoria. J Clin Neurosci. 2013;20(1):102-6.

Tables:

Table 1: Cohort Demographic and Clinical Characteristics

	Parkinson's Disease	Healthy Control	Test Statistic	p value
Number of Patients (n=)	103	81		
Age, (years) [SD, Range]	67.1 [12.2, 33-88]	62.4 [15.6, 18-90]	t=2.3 (182)$^{\wedge}$	**0.023**
Gender, (%)			χ^2=10.7 (1)$^{\infty}$	**0.001**
Male	56.3	32.1		
Female	43.7	67.9		
Marital Status, (%)			χ^2=4.2 (3)$^{\infty}$	0.244
Married / de facto	76.7	85.1		
Single	9.7	9.9		
Widowed	5.8	1.2		
Other	7.7	3.7		
Ethnicity, (%)			χ^2=2.3 (3)$^{\infty}$	0.506
Caucasian	78.6	79.0		
Asian	3.9	6.2		
Middle Eastern	6.8	2.5		
Other	10.7	12.3		
Body Mass Index, [SD]	25.7 [5.2]	26.2 [4.6]	t=-0.7 (182)$^{\wedge}$	0.485
Smoking History, (%)				
Current Smoker	1.9	3.7	χ^2=0.6 (1)$^{\infty}$	0.457
Prior Smoker	36.9	33.7	χ^2=0.2 (1)$^{\infty}$	0.659
Pack Year History, [SD]	13.3 [13.8]	14.4 [14.6]	t=-0.3 (63)$^{\wedge}$	0.758
Alcohol Consumption, (%)	70.0	87.7	χ^2=8.7 (1)$^{\infty}$	**0.003**
< Weekly	23.5	27.2	χ^2=0.3 (1)$^{\infty}$	0.574
Several Times Weekly	31.1	33.3	χ^2=0.8 (1)$^{\infty}$	0.778
Daily	16.7	28.4	χ^2=3.6 (1)$^{\infty}$	0.057
Caffeine Consumption (Coffee/Tea), (%)	85.4	91.4	χ^2=1.5 (1)$^{\infty}$	0.219
Number of Daily Cups, [SD]	2.3 [1.7]	3.1 [1.8]	t=3.0 (182)$^{\wedge}$	**0.003**
History of Diabetes, (%)	4.9	6.2	χ^2=0.2 (1)$^{\infty}$	0.695
Gastrointestinal Symptoms				
Cleveland Constipation Score, [SD]	7.2 [4.7]	3.1 [2.9]	t=6.9 (182)$^{\wedge}$	**<0.001**
Constipation Score as per Rome IV Criteria, [SD]	4.4 [3.5]	1.1 [1.4]	t=7.9 (182)$^{\wedge}$	**<0.001**
Functional Constipation as per Rome IV Criteria, (%)	78.6	28.4	χ^2=46.6 (1)$^{\infty}$	**<0.001**
Bristol Stool Score, [SD]	2.8 [1.5]	3.9 [1.3]	t=4.0 (182)$^{\wedge}$	**<0.001**
Leeds Dyspepsia Questionnaire (LDQ) Score, [SD]	8.3 [7.7]	4.6 [6.1]	t=3.5 (182)$^{\wedge}$	**0.001**
Most Troublesome Symptom, (%)			χ^2=15.2 (7)$^{\wedge}$	**0.034**
Indigestion	18.4	8.6		
Heartburn	7.8	9.9		
Regurgitation	6.8	7.4		
Belching	7.8	6.2		
Nausea	15.6	7.4		

Vomiting	1	0		
Excess Fullness / Bloating	20.4	14.8		
None	22.3	45.7		
Chronic Pain Over Last 3 Months, (%)	72.8	39.5	χ^2=20.7 (1)$^{\infty}$	**<0.001**
Pain Score (Visual Analogue Scale), [SD]	4.9 [2.5]	3.9 [1.7]	*t*=2.0 (105)$^{\wedge}$	**0.046**
International Physical Activity Questionnaire (IPAQ) Score (MET-minutes/week), [SD]	1823.6 [1693.6]	2942.4 [2620.9]	*t*=-3.5 (182)$^{\wedge}$	**0.001**
IPAQ Categorical Score, (%)			χ^2=7.1 (2)$^{\infty}$	**0.029**
Low	35.2	19.8		
Moderate	37.9	39.6		
High	26.2	40.7		
Sitting Hours / Day, [SD]	6.5 [3.5]	4.8 [2.3]	*t*=3.7 (182)$^{\wedge}$	**<0.001**
Able to Walk 1km, (%)	73.8	97.5	χ^2=19.3 (1)$^{\infty}$	**<0.001**
Able to Climb 1 Flight of Stairs, (%)	86.4	100	χ^2=11.9 (1)$^{\infty}$	**0.001**
Biochemical Characteristics, [SD]				
Erythrocyte Sedimentation Rate	9.5 [13.4]	9.5 [10.4]	t=-0.1 (181)$^{\wedge}$	0.991
C-Reactive Protein	3.9 [10.8]	2.2 [2.5]	t=1.4 (182)$^{\wedge}$	0.177
Total Cholesterol	4.8 [0.9]	5.2 [1.1]	t=-2.5 (182)$^{\wedge}$	**0.014**
Low Density Lipoprotein	2.7 [0.7]	2.9 [0.9]	t=-1.5 (178)$^{\wedge}$	0.132
High Density Lipoprotein	1.4 [0.4]	1.6 [0.4]	t=-2.2 (181)$^{\wedge}$	**0.033**
Triglycerides	1.3 [1.0]	1.5 [0.9]	t=-1.2 (182)$^{\wedge}$	0.239
Random Glucose	5.8 [0.6]	5.9 [0.9]	t=-0.8 (182)$^{\wedge}$	0.438
HbA1c%	5.3 [0.4]	6.0 [5.2]	t=-1.2 (182)$^{\wedge}$	0.217
Albumin	38.7 [3.5]	39.8 [3.1]	t=-2.3 (182)$^{\wedge}$	**0.023**

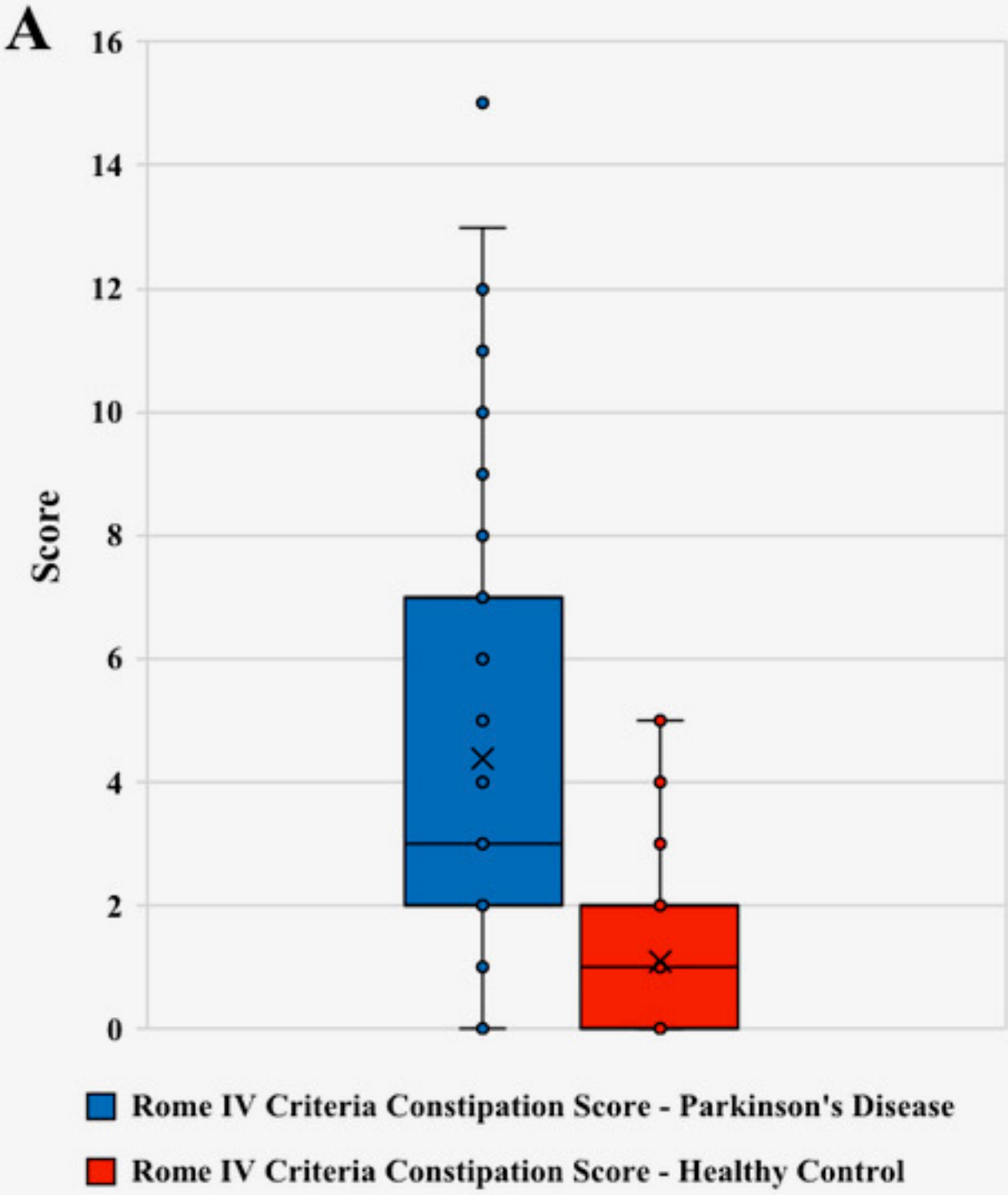
^(Independent Sample *t*-Test); $^{\infty}$(Pearson's chi-squared test); df (degrees of freedom), SD [Standard Deviation]

Table 2: Parkinson's Disease Clinical Characteristics

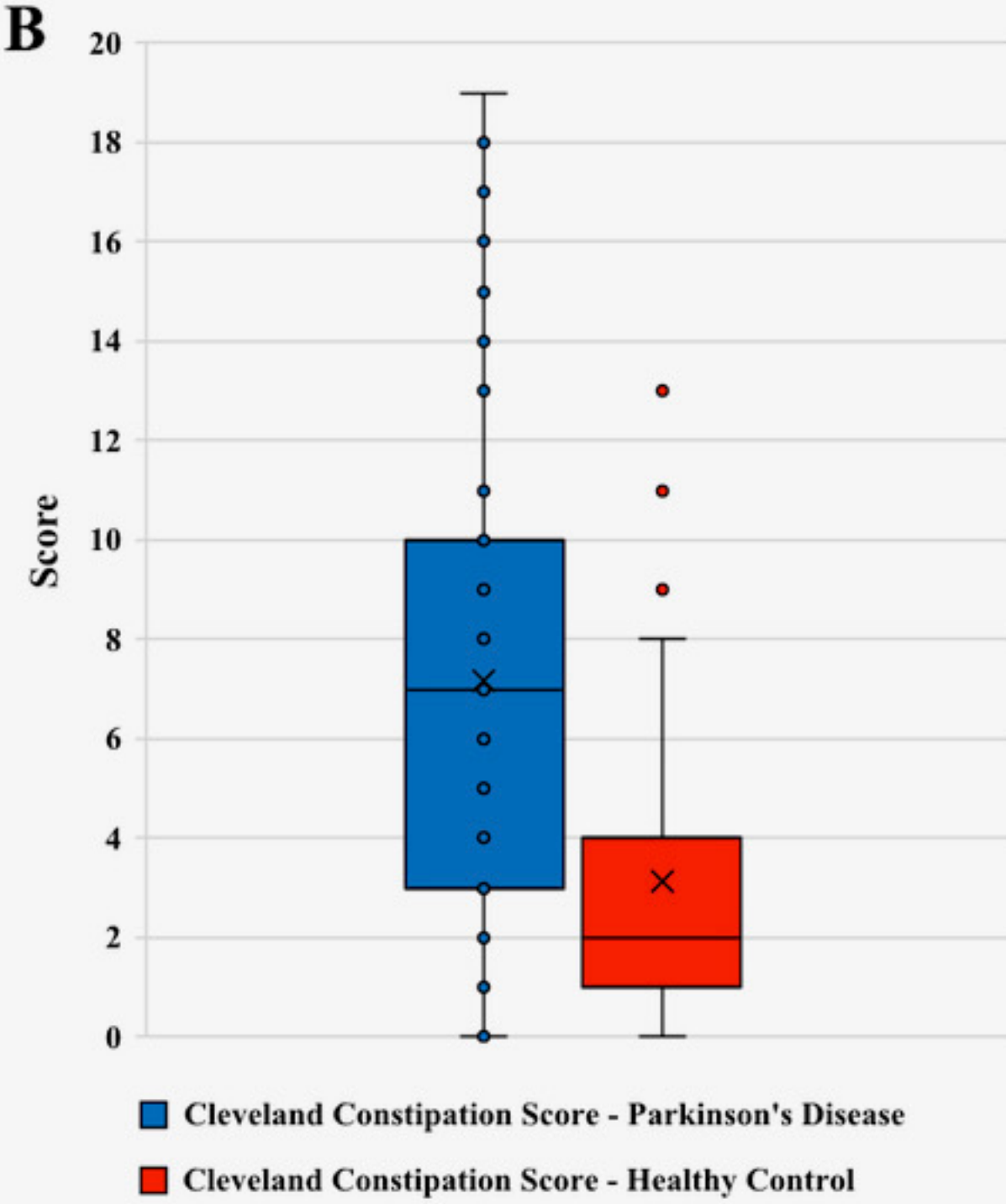
Age at Diagnosis, (years) [SD, Range]	58.8 [13.6, 24-88]
Parkinson's Disease Duration, (years) [SD, Range]	9.2 [6.5, 1-30]
Parkinson's Disease Phenotype, (%)	
Tremor Dominant	30.1
Postural Instability and Gait Impairment	20.4
Akinetic Rigid	38.9
Young Onset (<40 years)	10.7
Late Onset (>60 years)	49.5
Genetic Diagnosis, (%)	1.9
Disease Complications, (%)	
Motor Fluctuations	58.3
Dyskinesia	58.3
Wearing off	81.6
Impulse Control Disorder	19.4
Non-motor Symptoms, (%)	
Hyposmia	73.8
REM Sleep Behaviour Disorder	48.5
Constipation	60.2
MDS Total Non-Motor Symptoms Score (NMSS), [SD]	62.7 [42.9]
NMSS – Domain 6 (Gastrointestinal Symptoms), [SD]	6.1 [6.3]
Levodopa Equivalent Daily Dose (mg), [SD, Range]	834.8 [527.3, 0-2186]
MDS Unified Parkinson's Disease Rating Scale-III ('on' state), [SD, Range]	32.9 [17.7, 5-91]
Parkinson's Disease Therapy, (%)	
Treatment Naïve	(n=5) 4.9
Oral Levodopa	(n=92) 89.3
Dopamine Agonist	(n=36) 35.0
Monoamine Oxidase B Inhibitor	(n=19) 18.4
Anticholinergic	(n=13) 12.6
Catechol-O-methyl Transferase Inhibitor	(n=24) 23.3
Amantadine	(n=13) 12.6
Levodopa-Carbidopa Intestinal Gel (LCIG)	(n=9) 8.7
Deep Brain Stimulation	(n=11) 10.7
Apomorphine (Subcutaneous Infusion)	(n=7) 6.8

SD [Standard Deviation]

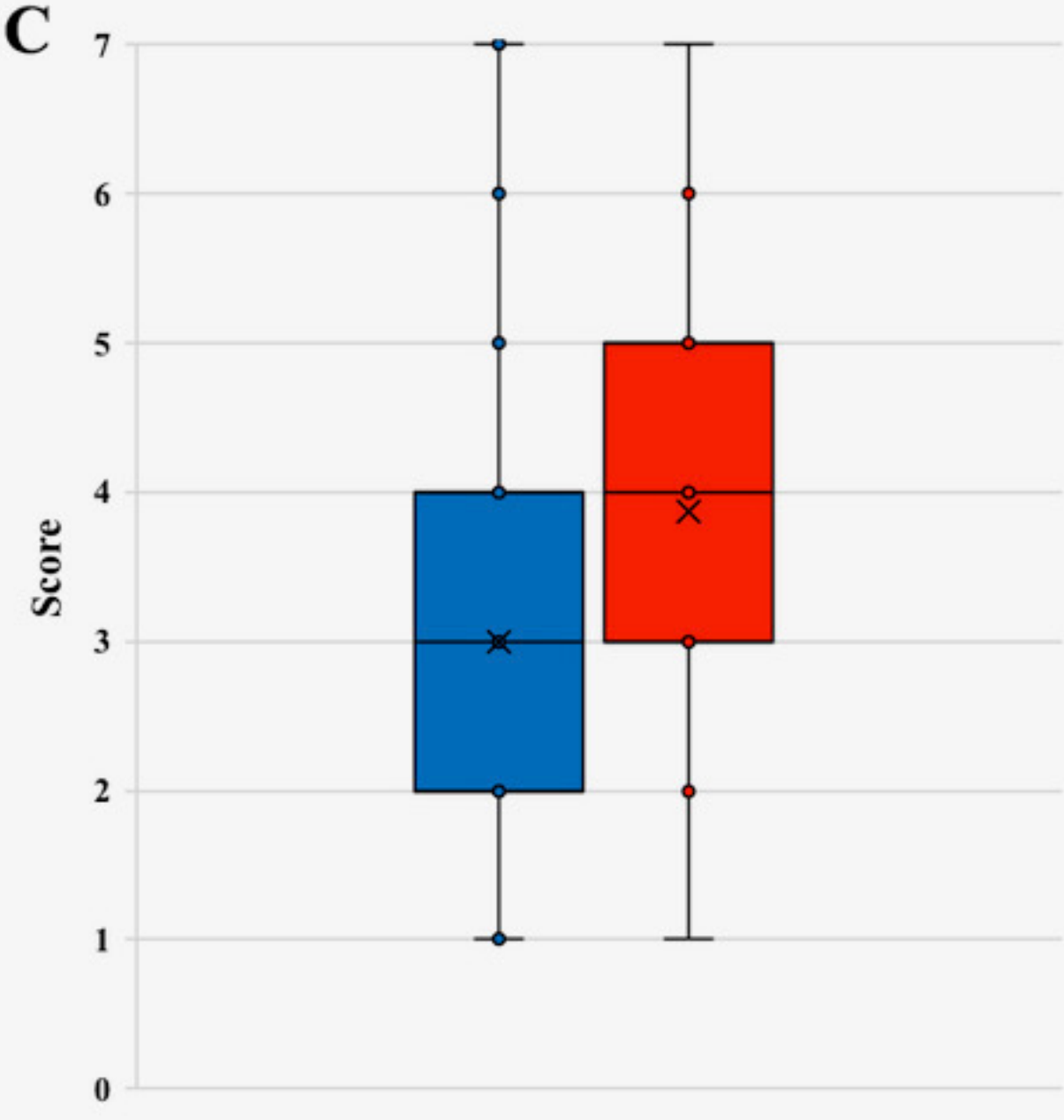
A


Score
16
14
12
10
8
6
4
2
0
Rome IV Criteria Constipation Score - Parkinson's Disease
Rome IV Criteria Constipation Score - Healthy Control

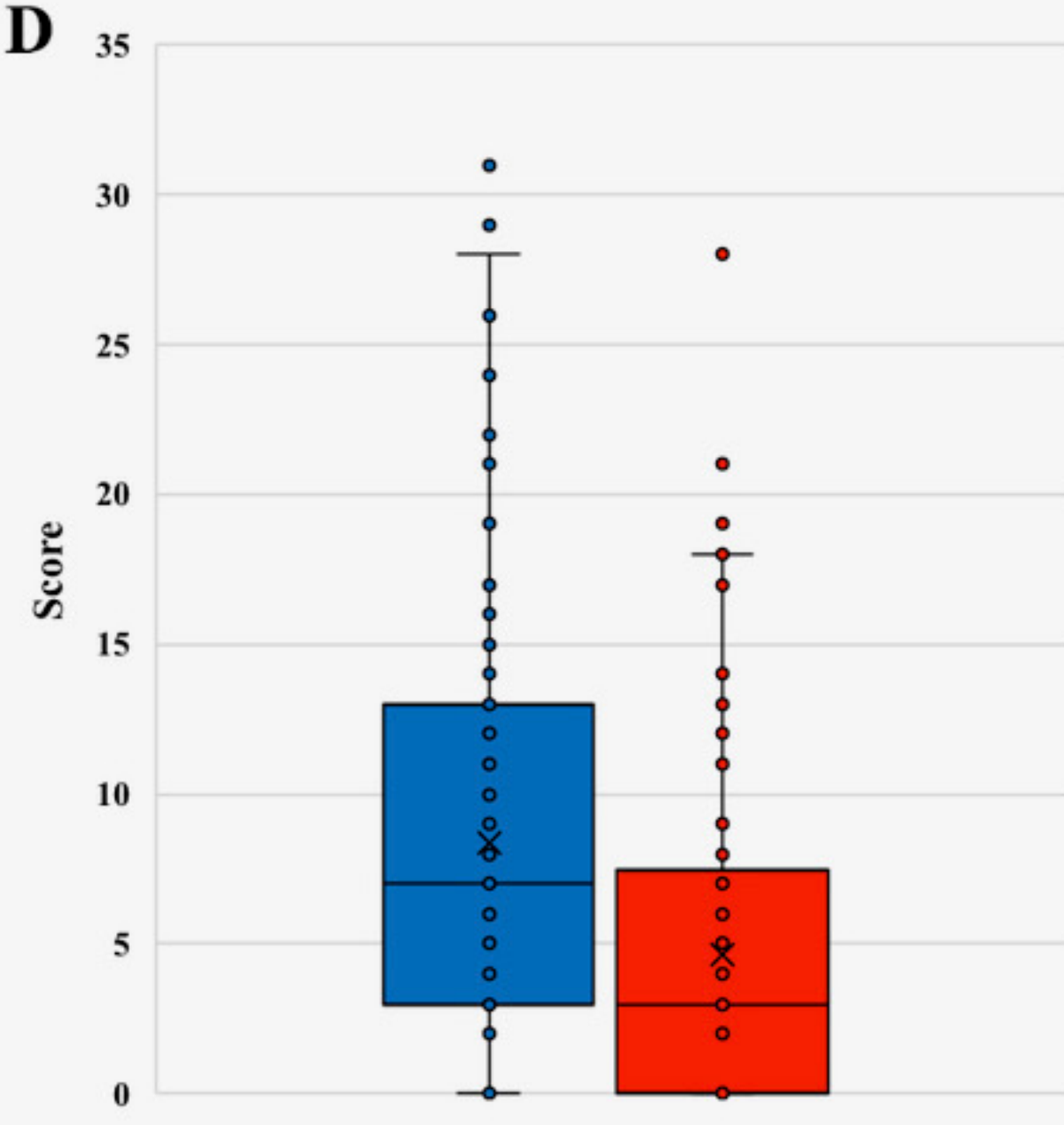
B


Score
20
18
16
14
12
10
8
6
4
2
0
Cleveland Constipation Score - Parkinson's Disease
Cleveland Constipation Score - Healthy Control

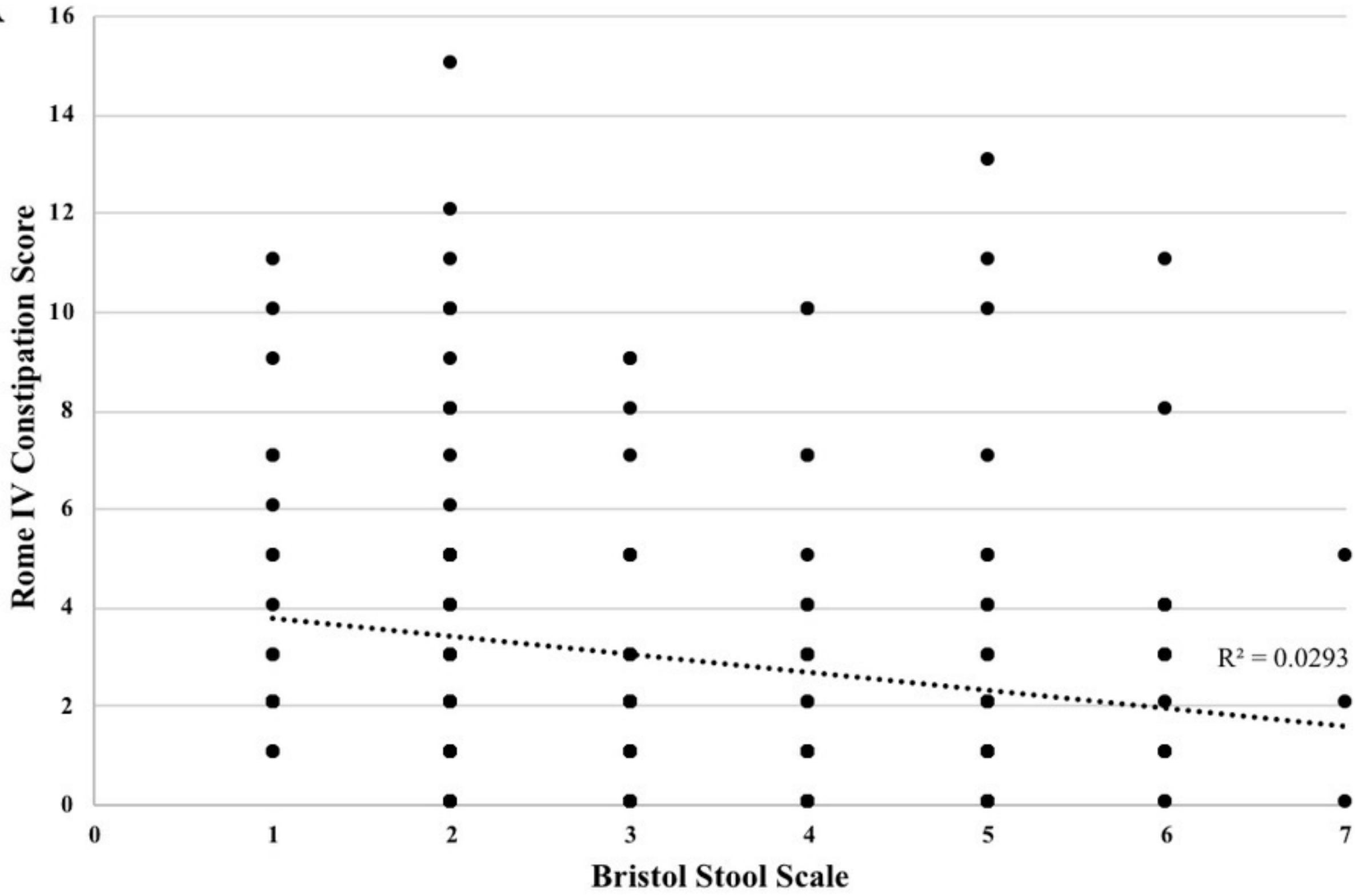
C


Score
7
6
5
4
3
2
1
0
Bristol Stool Scale - Parkinson's Disease
Bristol Stool Scale - Healthy Control

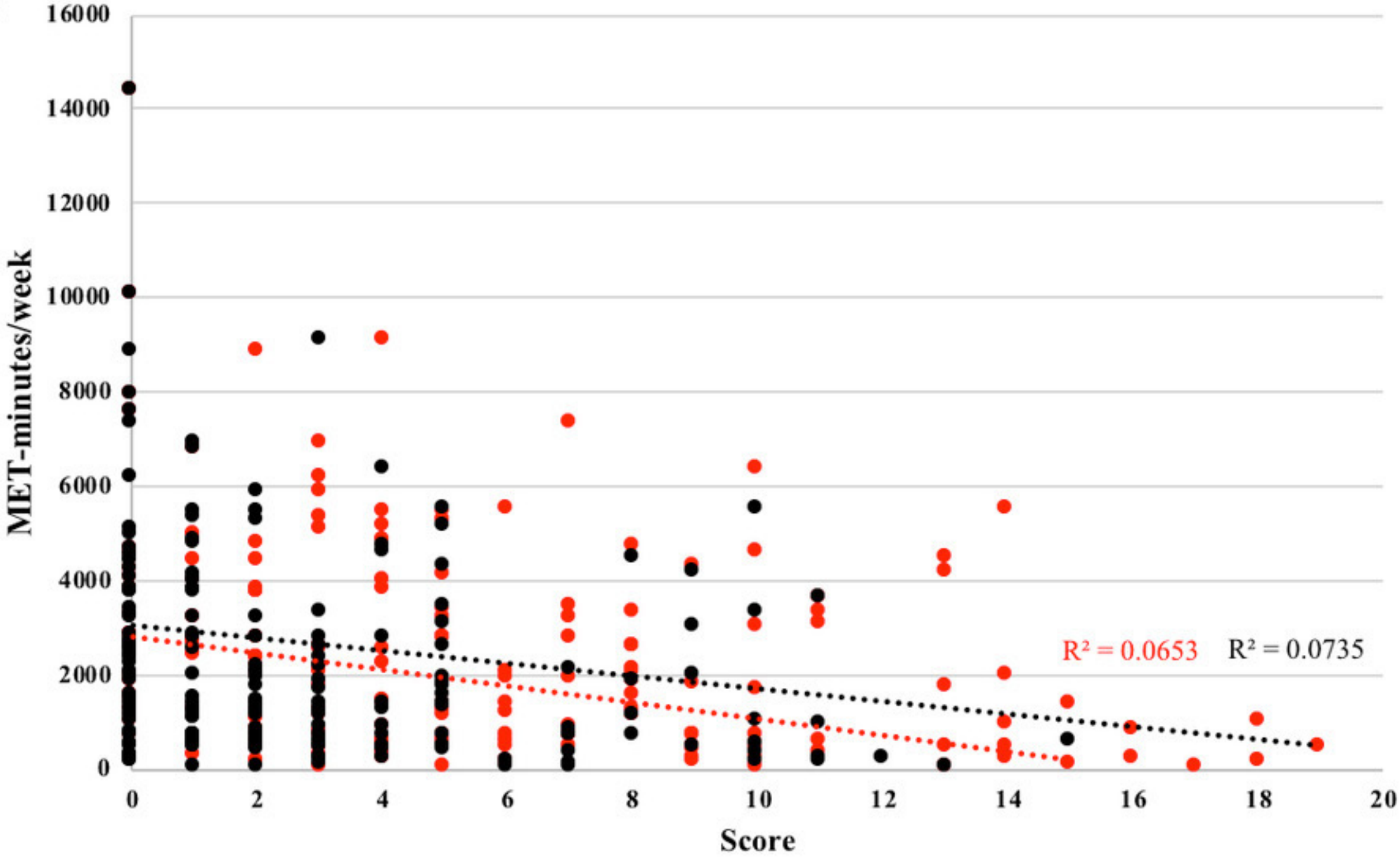
D


Score
35
30
25
20
15
10
5
0
Leeds Dyspepsia Questionnaire - Parkinson's Disease
Leeds Dyspepsia Questionnaire - Healthy Control

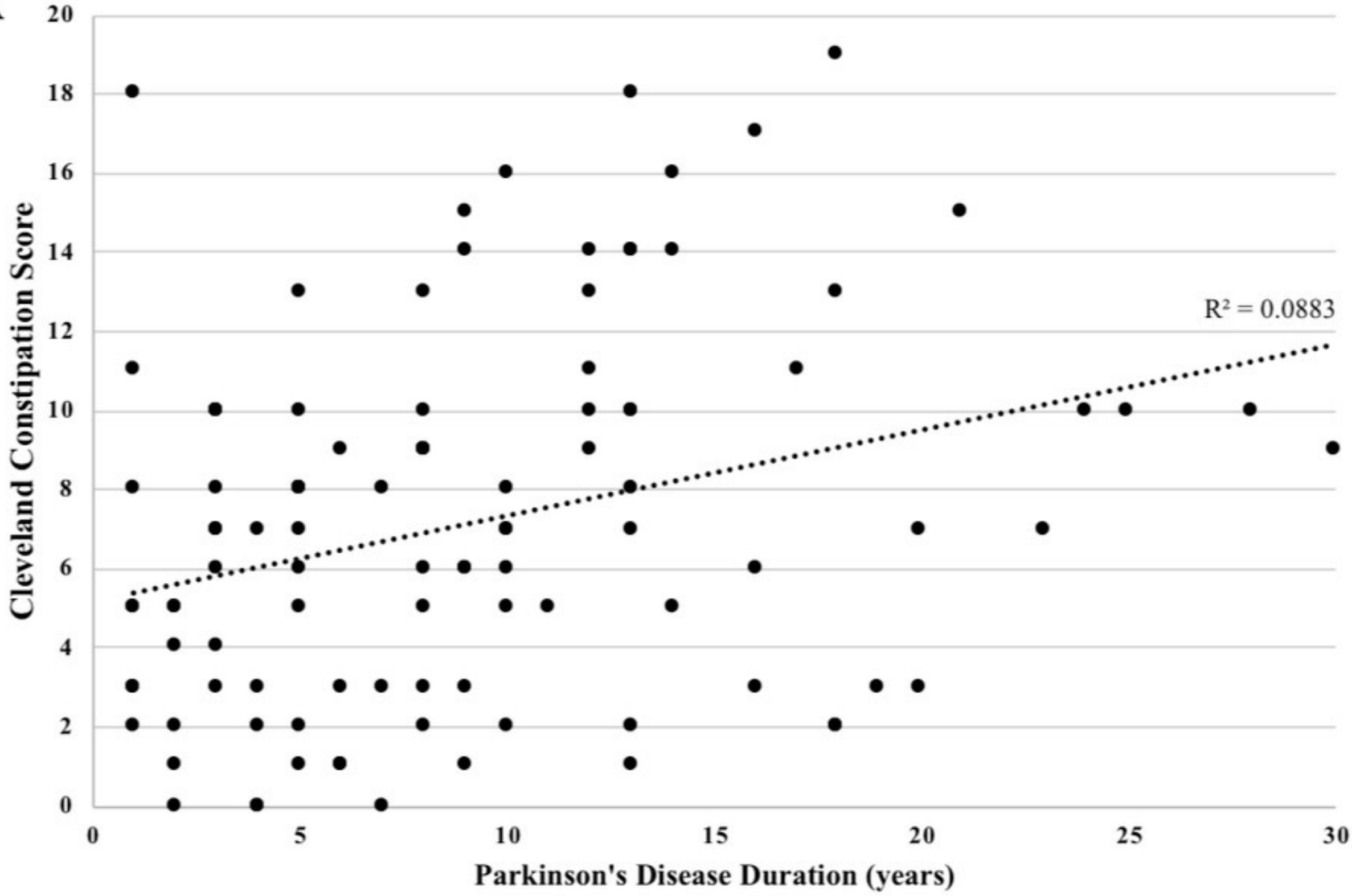
A


16
14
12
10
8
6
4
2
0
Rome IV Constipation Score
0
1
2
3
4
5
6
7
Bristol Stool Scale
R² = 0.0293

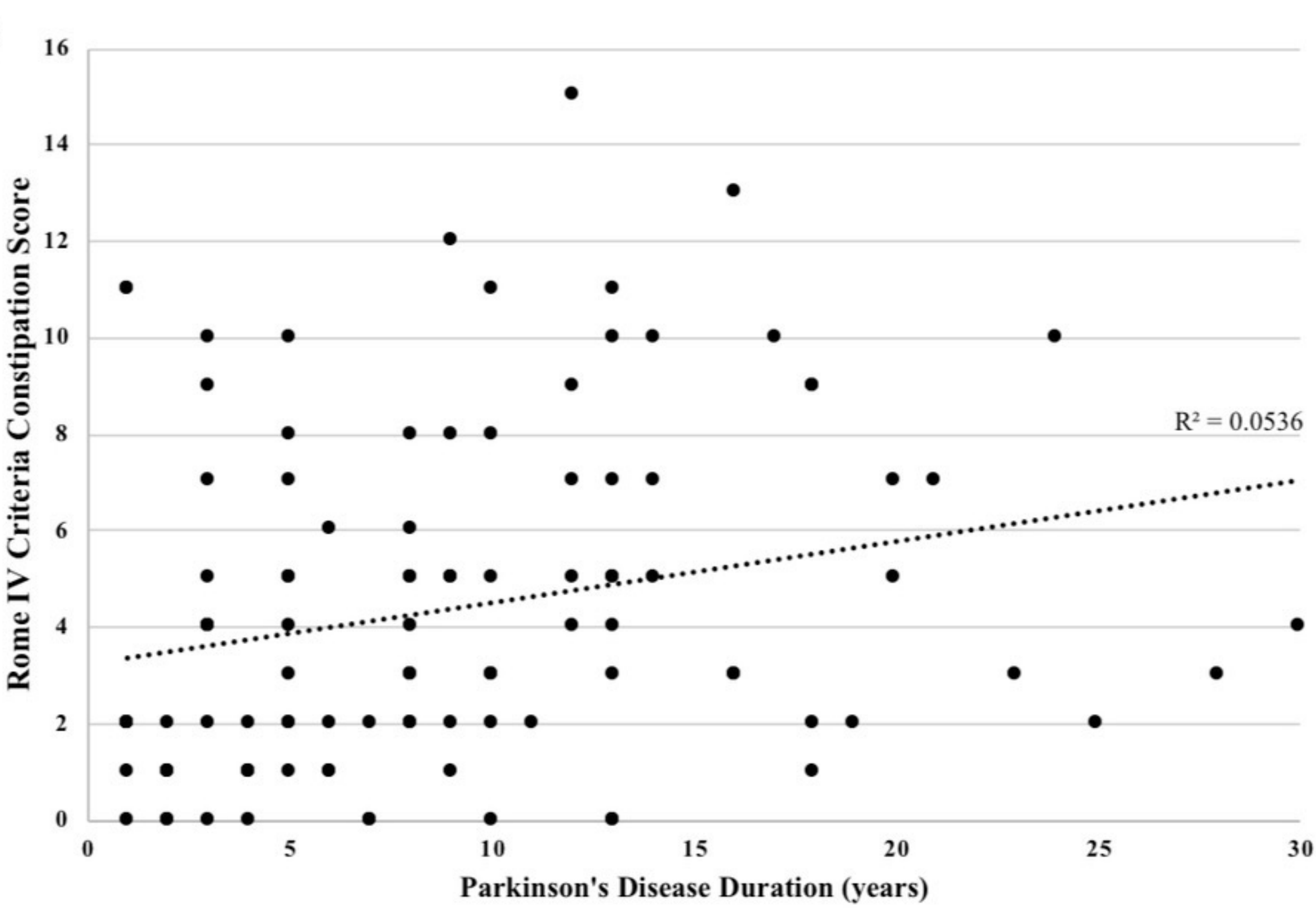
B


16000
14000
12000
10000
8000
6000
4000
2000
0
MET-minutes/week
0
2
4
6
8
10
12
14
16
18
20
Score
R² = 0.0653
R² = 0.0735
Cleveland Constipation Score
Rome IV Criteria Constipation Score

A


Cleveland Constipation Score
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
Parkinson's Disease Duration (years)
R² = 0.0883

B


Rome IV Criteria Constipation Score
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
Parkinson's Disease Duration (years)
R² = 0.0536

Constipation

- Prevalence of 79%
- Threefold ↑ compared to controls
- Significantly underrecognised by patients
- Fourfold ↑ in severity compared to controls
- ↑ with increasing disease duration
- Women more affected than men

Upper Gastrointestinal Dysfunction

- Indigestion, nausea, excess fullness and bloating - most troublesome symptoms
- ↑ with increasing disease duration
- Women more affected than men

Other Negative Influences

- ↑ Chronic pain and pain severity
- ↓ Physical activity
- ↓ Alcohol consumption
- Therapies: LCIG and Dopamine Agonists associated with increased gastrointestinal dysfunction