


RESEARCH ARTICLE

Impact of COVID-19 pandemic on patients with Parkinson's disease: A meta-analysis of 13,878 patients

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Abstract

Background: The clinical, neuropsychological, and socioeconomic factors affecting Parkinson's disease (PD) during COVID-19 pandemic across different populations have not been systematically studied. To address this, we conducted a meta-analysis of factors that impact the well-being of PD patients during the pandemic. **Methods:** Medline and Embase were searched for articles published between 2020 and 2022. We conducted random-effects pooling of estimates and meta-regression. **Results:** Twenty-seven studies involving 13,878 patients from America, Europe, Asia, and Africa were included. There is a high prevalence of decreased physical activity and exercise, and worsening motor and neuropsychiatric symptoms (17–56%). Patients in lower-income countries more frequently reported worsening anxiety (adjusted OR [aOR] 8.94, 95% confidence interval [CI] 1.62–49.28, $p = 0.012$), sleep (aOR 5.16, 95% CI 1.15–23.17, $p = 0.032$), and PD symptoms (aOR 3.57, 95% CI 0.96–13.34, $p = 0.058$). Lockdown was associated with decreased exercise levels (aOR 0.13, 95% CI 0.02–0.78, $p = 0.025$) and worsening mood (aOR 0.48, 95% CI 0.24–0.95, $p = 0.035$). Younger age correlated with decreased physical activity ($\beta -0.30$, 95% CI -0.53 to -0.07 , $p = 0.012$), exercise ($\beta -0.11$, 95% CI -0.15 to -0.07 , $p < 0.001$), worsening PD symptoms ($\beta -0.08$, 95% CI -0.15 to -0.01 , $p = 0.018$), and sleep ($\beta -0.14$, 95% CI -0.27 to 0 , $p = 0.044$). Female PD patients reported a greater decrease in physical activity ($\beta 11.94$, 95% CI 2.17–21.71, $p = 0.017$) and worse sleep ($\beta 10.76$, 95% CI 2.81–18.70, $p = 0.008$). **Conclusion:** This large meta-analysis of PD patients in diverse populations identified a high prevalence of physical and mental worsening during the COVID-19 pandemic, with patients in lower-income countries being exceptionally vulnerable.

Introduction

The coronavirus disease 2019 (COVID-19) has impacted the physical and mental well-being of patients with chronic disabilities across the world. Parkinson's disease (PD) is a prototype common age-related neurodegenerative disorder with motor and non-motor disabilities. The anxiety from fear of contracting COVID-19, physical and social limitations with decreased accessibility of care and lack of social support are major concerns among PD patients.¹ Moreover, isolation due to the COVID-19 pandemic has negatively affected the patients' mental health

as well.² All these factors have culminated in a greater sense of insecurity and emotional burden for the PD patients as well as their caregivers. Even among those without prior COVID-19 infection, the negative effects of the pandemic on their physical and mental well-being are considerable.³

PD is especially vulnerable to pandemic-related decline in health, and disease worsening frequently involves various motor, non-motor, and neuropsychiatric symptoms.^{4–8} Furthermore, the prevalence of depression and anxiety in these patients is already high,^{9,10} and they are likely to experience a substantial deterioration due to

pandemic-related factors. Socio-demographics are also key when assessing the likely impact of the pandemic on the patients. For example, patients from developing countries are more vulnerable for numerous reasons.¹¹ First, such countries may be less prepared to handle the pandemic owing to a lack of financial reserves. Next, access to care and medications may already be less when compared with developed countries. As such, sociodemographic factors often have a profound impact on the extent to which PD patients are adversely affected by the COVID-19 pandemic.¹²

There is a need to identify subgroups of PD patients that may require more attention and support.¹³ It is currently not clear if biological sex, race and ethnicity, nationality, and socioeconomic status influence patients' responses to the pandemic.³ These factors may also not be adequately captured by single studies or in specific populations. To our knowledge, there has been no systematic study to evaluate common and unique clinical, neuropsychological, and socioeconomic factors that are associated with COVID-19 pandemic across different populations. To address this knowledge gap, we conducted a systematic review and meta-analysis to assess the impact of the COVID-19 pandemic on PD patients without COVID-19 infection.

Methods

Search strategy

This systematic review and meta-analysis was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴ and is registered with PROSPERO at CRD42022314871. We screened the bibliographies of related articles in Medline and Embase between 2020 and 2022. The search utilized a combination of keywords and controlled vocabulary synonymous with "COVID-19", "Parkinson's disease", "physical health", and "mental health". A copy of the search strategy for Medline can be found in Table S1. The search results were exported to Zotero for duplicate removal prior to screening, as well as for reference management.

Study selection

Two authors independently reviewed the titles and abstracts of each reference, and any discrepancies were resolved through discussion. Following this, the full texts of the included references were retrieved for further review. We included any study that discussed the impact of the COVID-19 pandemic on the physical or mental health of PD patients, mainly assessed through the

self-reported new-onset or worsening symptoms. Any study that recruited PD patients with an active COVID-19 infection was excluded unless a subgroup analysis restricted to non-COVID-19-infected PD patients was presented. Conference abstracts, commentaries, and editorials were also excluded.

Data extraction

We were interested in the perceived worsening of symptoms, or those of new onset, in the following areas: (1) physical activity, (2) exercise (either aerobic or resistance training), (3) PD-related symptoms, (4) balance, (5) mood, (6) depression, (7) anxiety, (8) cognition, and (8) sleep. Data were extracted and checked by two independent authors, with disagreements resolved through reaching a consensus before the analysis was undertaken. We extracted the following domains: (1) study-related information—the geographical region of the study, income level of the study country according to *The World Bank* classification for the fiscal year of 2021–2022, whether the study required the patients to reflect on the effects of lockdown specifically, and the sample size; (2) patient demographics—age, sex, and disease duration; (3) outcome-related data—number of individuals reporting the onset or worsening of the aforementioned symptoms. If continuous data were presented using measures alternative to means and standard deviations (SD), we converted these data to means and SD using the formulas derived by Wan et al.¹⁵

Statistical analysis

RStudio (version 4.1.1) was used to conduct all statistical analyses in this study. We employed the functions of the *meta* (for the pooling of effect sizes and bivariate meta-regression) and *metafor* packages (for multivariate meta-regression). We analyzed the outcomes as logit-transformed proportions using a generalized linear mixed model. We employed the random-effects model, with the maximum likelihood estimator for τ^2 , in view of the high heterogeneity as quantified by the I^2 index and the p -value for the Cochran's Q test. $I^2 < 25\%$ is indicative of low heterogeneity, 25–75% of moderate heterogeneity, and $>75\%$ of high heterogeneity; a $p < 0.05$ for the Cochran's Q test suggests significant heterogeneity. The results were presented as proportions (in %) with their 95% confidence intervals (CI). To assess publication bias, we inspected the funnel plots for asymmetry and conducted Egger's regression test to confirm our assessment.

To further explore heterogeneity, as well as the effects of study characteristics and patient demographics on the study outcomes, we conducted subgroup analyses and

meta-regressions. We utilized a mixed-effects model with the maximum likelihood estimator for τ^2 for meta-regression, and the statistical significance of the regression weights was evaluated through a Wald-type test. The impact of study characteristics was examined through subgroup analyses, following which a multivariate meta-regression was conducted. We also assessed the relationship between patient demographics and the study outcomes using both bivariate and multivariate meta-regressions. For continuous variables, the β -coefficients and their 95% CI were reported; for binary variables (i.e. subgroups), the β -coefficients with their 95% CI were exponentiated with the natural base to obtain adjusted OR (aOR) for the multivariate meta-regression.

Quality assessment

We used the *Joanna Briggs Institute Critical Appraisal Tools (Checklist for Analytical Cross-Sectional Studies)* for the quality assessment of included articles. The tool assesses the study quality across eight domains: (1) reporting of inclusion criteria, (2) reporting of study subjects and setting, (3) objective measurement of exposure, (4) objective measurement of condition, (5) identification of confounding factors, (6) strategies to minimize confounding, (7) valid measurement of outcomes, (8) appropriate statistical analysis. Two blinded reviewers conducted the assessment, and any conflicts were resolved through discussion.

Results

Summary of included articles

A total of 365 references, with 79 duplicates, were exported to Zotero. Following duplicate removal, we screened the remaining 286 studies for eligibility. We sought to retrieve the full texts of 52 references but were unable to locate the full texts of 15 references. These 15 references were either conference abstracts (for which we sought to find the published paper but failed), or had full texts published in languages other than English, or for which the full-text links cannot be found. We further reviewed the full texts of the remaining 37 studies, and 27 studies involving 13,878 PD patients were included in the final analysis (Fig. 1).^{4-8,16-37} Of these, three studies were conducted in North America, 10 in Europe, 10 in Asia, two in Africa, and two in South America. A total of 16 studies were conducted in high-income countries, five in upper-middle-income countries, and six in lower-middle-income countries. In addition, 14 studies required the participants to reflect specifically on the effects of lockdown or home confinement on their health. Most of the

included studies were of high quality, scoring the maximum 8 points; five studies scored 6 points as they did not identify potential confounders and minimize their impact on the findings reported. Further details on the included studies can be found in Table 1.

Prevalence of new-onset or worsening symptoms

Decreased levels of physical activity were assessed across 10 studies of 3080 patients, and the pooled prevalence was 56.65% (95% CI 48.20–64.74).^{6,8,16,17,21,24,27,33,35,36} Seven studies with 7120 patients reported self-reported changes in exercise levels, and 51.75% (95% CI 37.11–66.09) of patients perceived a decrease.^{4,7,16,21,27,29,34} Worsening PD symptoms were pooled across 13 studies with a sample size of 1824 patients, and the prevalence was 51.86% (95% CI 36.38–67.00).^{5,7,8,16,18,22,23,27,29,32,34,35,37} New problems with or worsening balance were reported by 17.10% (95% CI 9.78–28.18), as reported across 10 studies of 10,045 PD patients.^{4,16,17,20,22,27,28,31,33,35}

Twelve studies involving 8922 individuals examined worsening mood due to the COVID-19 pandemic, and the pooled estimate for prevalence was 31.14% (95% CI 21.77–42.35).^{4,17,18,21,22,26,27,29,31,33,35,37} Worsening or new-onset depression was assessed in 15 studies of 9233 patients, and we found the prevalence to be 26.42% (95% CI 18.37–36.43).^{4,6,7,17,19,21,23–28,30,34,36} Worsening or new anxiety was studied in 18 papers involving a total of 12,496 patients, and the prevalence was 36.15% (95% CI 24.59–49.57).^{4-8,17-21,23-25,27,28,30,34,35} Perceived deterioration in cognition was investigated in seven studies of 7177 patients, and the prevalence was 20.20% (95% CI 14.32–27.71).^{4,16,17,27,28,35,36} Worse or reduced sleep was examined in 15 studies of 12,381 patients, and we found the prevalence to be 27.97% (95% CI 18.34–40.17).^{4,7,16-18,20-23,26,28,31,34-36} We observed substantial heterogeneity in the pooled estimates described here (I^2 94–99%, Cochran's Q test $p < 0.001$). Further details are presented in Table 2.

Subgroup analysis

We conducted subgroup analyses according to geographical region (Table S2), income level (Table S3), and lockdown status (Table S4). We found no significant differences when comparing North America/Europe with other regions in all outcomes except for cognition ($p < 0.001$). North America and Europe reported a significantly lower prevalence of perceived worsening cognition (16.70%, 95% CI 11.13–24.29) in comparison with other regions (32.55%, 95% CI 29.68–35.55). In addition, we

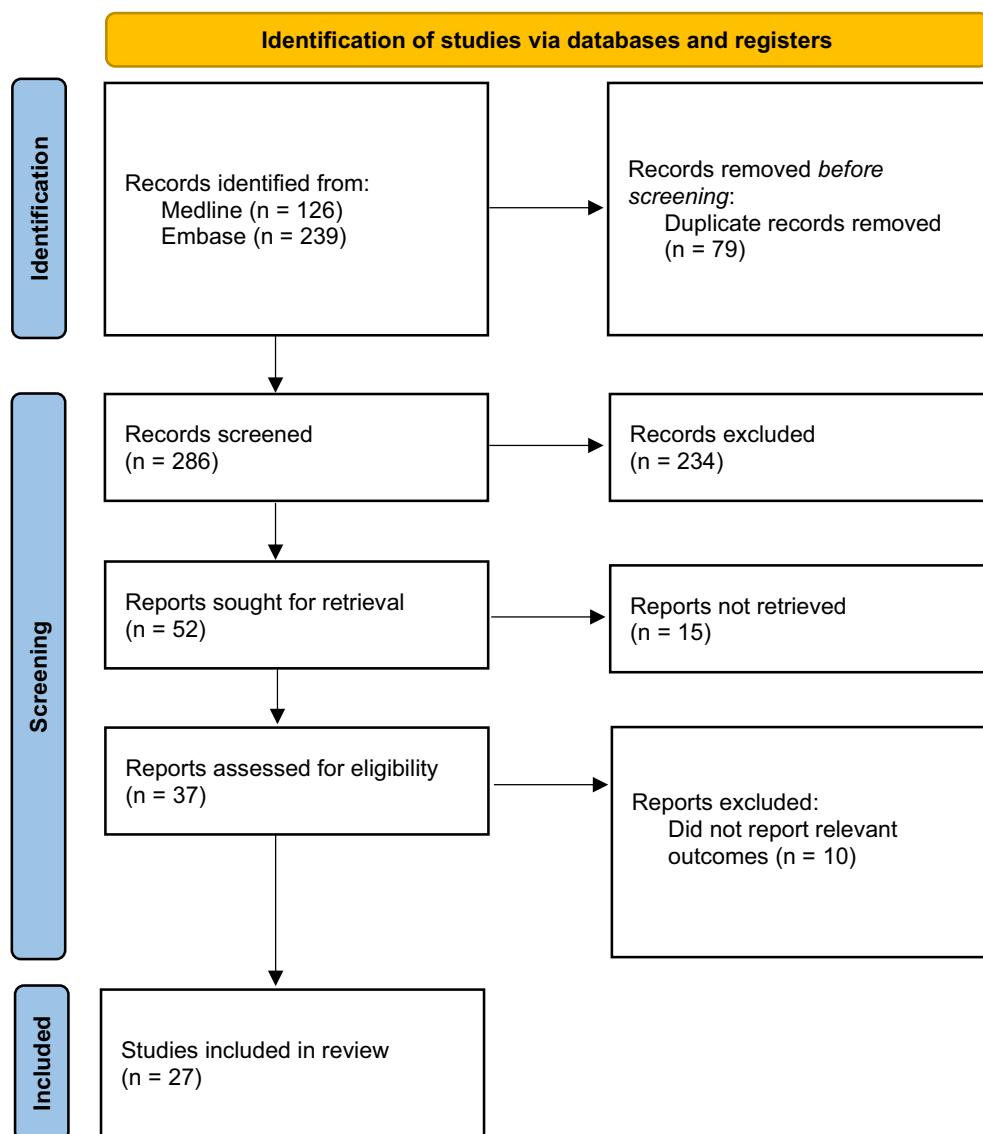


Figure 1. PRISMA flow diagram.

found significant differences when comparing lockdown status ($p = 0.045$). Studies on lockdown or home confinement reported a lower prevalence of worse mood (22.70%, 95% CI 16.62–30.20) than those not on lockdown (38.85%, 95% CI 24.99–54.79). No significant differences were found when comparing high-income to lower-income countries (comprising upper-middle- and lower-middle-income countries).

Meta-regression

Upon conducting multivariate meta-regression with the subgroups defined above, we found patients in lower-income countries to have significantly higher odds of

worsening anxiety (aOR 8.94, 95% CI 1.62–49.28, $p = 0.012$) and reduced sleep (aOR 5.16, 95% CI 1.15–23.17, $p = 0.032$), as well as deterioration in PD symptoms with borderline significance (aOR 3.57, 95% CI 0.96–13.34, $p = 0.058$). Interestingly, being in lockdown or home confinement is associated with decrease in exercise levels (aOR 0.13, 95% CI 0.02–0.78, $p = 0.025$), as well as worsening mood (aOR 0.48, 95% CI 0.24–0.95, $p = 0.035$), anxiety (aOR 0.38, 95% CI 0.14–0.94, $p = 0.038$), cognition (aOR 0.46, 95% CI 0.25–0.85, $p = 0.013$), and sleep (aOR 0.28, 95% CI 0.11–0.68, $p = 0.005$). The remaining results are shown in Table 3.

In the bivariate meta-regression with patient demographics as predictors, we found older age to correlate

Table 1. Summary of studies.

Study	Country	Lockdown ¹	Income level ²	sample size	Age	Female	Disease duration	Quality ³
Balci et al (2021)	Turkey	Yes	Upper middle	45	66.8 ± 10.3	15 (33.3)	7.7 ± 3.8	8
Brown et al (2020)	United States	No	High	5378	66.0 ± 8.4	2598 (48.3)	–	8
de Rus Jacquet et al (2021) ⁴	Canada (Quebec)	Yes	High	240	68.5 ± 9.5	87 (36.3)	8.6 ± 6.4	8
	Canada (Alberta)			177	67.9 ± 9.5	73 (41.2)	7.8 ± 4.9	
Del Prete et al (2021)	Italy	Yes	High	733	–	–	–	8
El Otmami et al (2021)	Morocco	Yes	Lower middle	50	60.4 ± 10.4	26 (52.0)	–	6
Fabbri et al (2021)	France	Yes	High	2653	–	1194 (45.0)	–	8
Feeney et al (2021)	United States	No	High	1342	70.9 ± 8.3	679 (50.6)	7.0 ± 6.1	8
Goel et al (2022)	India	No	Lower middle	31	58.3 ± 13.6	11 (35.5)	6.1 ± 2.5	8
Guo et al (2020)	China	Yes	Upper MIDDLE	108	69.5 ± 7.8	47 (43.5)	6.1 ± 0.8	6
Haas et al (2022)	Brazil	Yes	Upper middle	156	64.0 ± 11.0	78 (50.0)	–	8
Hero et al (2022)	Croatia	No	High	87	71.8 ± 8.1	51 (58.6)	9.5 ± 7.1	8
Janiri et al (2020)	Italy	Yes	High	101	73.0 ± 6.0	43 (42.6)	–	8
Krzysztoń et al (2022)	Poland	No	High	47	72.1 ± 8.9	17 (36.2)	–	8
Kumar et al (2021)	India	Yes	Lower middle	832	–	257 (30.9)	–	8
Leavy et al (2021)	Sweden	No	High	89	71.0 ± 4.4	41 (46.1)	6.0 ± 3.2	8
Montanaro et al (2022)	Italy	Yes	High	100	62.4 ± 9.0	40 (40.0)	13.4 ± 4.6	6
Salari et al (2020)	Iran	No	Lower middle	137	55.0 ± 10.7	90 (65.7)	–	6
Saluja et al (2021)	India	Yes	Lower middle	64	63.3 ± 11.0	25 (39.1)	4.5 ± 3.4	8
Schirinzi et al (2020)	Italy	Yes	High	74	61.3 ± 9.3	37 (50.0)	6.5 ± 4.5	8
Shalash et al (2020)	Egypt	Yes	Lower middle	38	55.6 ± 10.0	9 (23.7)	4.7 ± 3.2	8
Silva-Batista et al (2021)	Brazil	No	Upper middle	478	67.3 ± 9.5	167 (34.9)	8.5 ± 6.3	8
Song et al (2020)	Korea	No	High	100	69.4 ± 10.3	46 (46.0)	6.7 ± 4.5	6
Suzuki et al (2021)	Japan	No	High	100	72.1 ± 9.1	55 (55.0)	5.8 ± 4.4	8
van der Heide et al (2020)	Netherlands	No	High	358	62.8 ± 9.0	138 (38.5)	3.9 ± 1.8	8
Xia et al (2020)	China	No	Upper middle	119	61.2 ± 8.8	58 (48.7)	6.8 ± 4.6	8
Yogev-Seligmann et al (2021)	Israel	Yes	High	142	70.6 ± 7.6	58 (40.8)	10.6 ± 8.3	8
Zipprich et al (2020)	Germany	No	High	99	72.0 ± 8.9	35 (35.4)	7.7 ± 3.8	8

Continuous outcomes are reported as mean ± SD, while binary outcomes are reported as *N* (%). –, data unavailable.

¹This is evaluated according to whether the study has required the patient to reflect on the effects of COVID-19-related lockdowns or home confinements.

²This is evaluated according to *The World Bank* classification of economies in the fiscal year of 2021–2022.

³Quality assessment is conducted using the *Joanna Briggs Institute Critical Appraisal Tools (Checklist for Analytical Cross-Sectional Studies)* and the total score is presented here.

⁴There are two separate cohorts evaluated in this study (Quebec and Alberta), and the outcomes are presented separately for each cohort.

with worse balance (β 0.16, 95% CI 0–0.32, $p = 0.046$), and female sex to correlate with less PD deterioration (β –6.32, 95% CI –12.36 to –0.28, $p = 0.040$). Longer disease duration is associated with decreased physical activity levels (β 0.15, 95% CI 0–0.29, $p = 0.048$), while a shorter disease duration is associated with decreased exercise (β –1.15, 95% CI –1.99 to –0.31, $p = 0.008$) and worsening cognition (β –0.31, 95% CI –0.43 to –0.18, $p < 0.001$). Further details can be found in Table S5.

In the multivariate meta-regression, we found younger age to correlate with decreased physical activity (β –0.30, 95% CI –0.53 to –0.07, $p = 0.012$) and exercise (β –0.11, 95% CI –0.15 to –0.07, $p < 0.001$), as well as worsening in PD symptoms (β –0.08, 95% CI –0.15 to –0.01, $p = 0.018$) and sleep (β –0.14, 95% CI –0.27 to 0, $p = 0.044$). Female sex was associated with decrease in physical activity (β 11.94, 95% CI 2.17–21.71, $p = 0.017$) and worse sleep (β 10.76, 95% CI 2.81–18.70, $p = 0.008$), but with less PD deterioration (β –10.13, 95% CI –15.66

Table 2. Pooled estimates for prevalence of self-reported symptoms using the random-effects model.

Self-reported outcome	Number of studies	Total sample size	Prevalence (95% CI)	I^2	p -value for Cochran's Q
Decreased physical activity	11	3080	56.65% (48.20–64.74)	94%	<0.001
Decreased exercise	7	7120	51.75% (37.11–66.09)	98%	<0.001
Worsening PD symptoms	12	1091	51.86% (36.38–67.00)	94%	<0.001
Worsening balance	11	10,045	17.10% (9.78–28.18)	99%	<0.001
Worsening mood	12	8189	31.14% (21.77–42.35)	98%	<0.001
Worsening depression	16	9233	26.42% (18.37–36.43)	98%	<0.001
Worsening anxiety	18	11,763	36.15% (24.59–49.57)	99%	<0.001
Worsening cognition	8	7177	20.20% (14.32–27.71)	95%	<0.001
Reduced sleep	15	11,648	27.97% (18.34–40.17)	99%	<0.001

CI, confidence intervals; PD, Parkinson's disease.

to -4.61 , $p < 0.001$). A longer disease duration was associated with decreased physical activity (β 0.57, 95% CI 0.23–0.91, $p = 0.001$), while a shorter disease duration is associated with decreased exercise (β -1.17 , 95% CI -1.58 to -0.77 , $p < 0.001$), worsening PD symptoms (β -0.31 , 95% CI -0.53 to -0.08 , $p = 0.007$), cognition (β -0.43 , 95% CI -0.85 to -0.01 , $p = 0.047$). The remaining results are presented in Table 4.

Discussion

This study which involved 13,878 PD patients from different geographical locations, identified a high prevalence of symptomatic worsening across various domains in physical function, mental well-being, as well as sleep and cognition. Subgroup analysis found worsening cognition to differ in prevalence across geographical regions, with a lower frequency in North America and Europe compared with other regions. Interestingly, the subgroup of studies on lockdown or home confinement reported less worsening of mood. Our meta-regression analysis, when adjusted for geographical region and lockdown status, further found PD patients in lower-income countries to be at greater risk of worsening anxiety, sleep, and deterioration in PD symptoms. We also demonstrated that biological factors such as age, sex, and disease duration influenced the pandemic-related deterioration in symptoms.

The diminished physical activity (physical limitations or from fear of contracting COVID-19) during the pandemic, could have contributed to the perceived deterioration of symptoms. Higher levels of physical activity and exercise have been shown to benefit PD patients, and also have the potential to improve both motor and non-motor symptoms.³⁸ In addition to better motor function, balance and gait were also improved following exercise.^{39,40} Cognitive impairment and sleep dysfunction are also key contributors to disease burden but have limited treatment options; exercise, too, has been identified as a promising intervention.^{41,42} All exercise modalities appear

to be helpful, including aerobic exercise, resistance training, and even dance.³⁸

However, with the restrictions placed on PD patients by the COVID-19 pandemic, the motivation and access to such activities become limited. Our study highlights the high prevalence of decreased activity levels and exercise, and this could explain the worsening of PD symptoms reported by over half of the respondents. Studies have shown that participants who remain physically active reported better well-being and less disease worsening.^{32,34} In addition, the maintenance of physical activity could benefit the mental health of PD patients, as lower activity levels are associated with suicidal thoughts.²⁴ As such, physicians may encourage their PD patients to exercise and advise that they remain active. However, physical activity is only one of the many factors that may influence PD symptoms. Compliance to medications, healthy lifestyle (including keeping active and eating healthy), easy access to care, and adequate social support are important components of the holistic management.

Due to the heterogeneous reporting in included studies, we were unable to evaluate the overall impact on access to consultations and medications. Some studies have shown that access to consultations—especially physical face-to-face ones—were most frequently compromised,^{7,22,23,35} while problems with the procurement of medications were much less common.^{6,7,35} The use of telemedicine in the monitoring and follow-up of PD patients will be particularly useful, with most patients indicating a supportive attitude towards the use of teleconsults.^{6,18,21}

One key finding from our study is the identification of increased vulnerability experienced by PD patients in lower-income countries. Lower income levels appear to correlate with greater odds of having uncontrollable anxiety and depression, as well as more frequent symptomatic worsening.^{4,21} Inadequate access to care in lower-income countries, which was reported by nearly 90% of the

Table 3. Multivariate meta-regression of outcomes according to study characteristics.

Study characteristics	aOR (95% CI) and p-value								
	Decreased physical activity	Decreased exercise	Worsening PD symptoms	Worsening balance	Worsening mood	Worsening depression	Worsening anxiety	Worsening cognition	Reduced sleep
NA/EU countries	1.55 (0.48–4.97) p = 0.463	1.37 (0.36–5.13) p = 0.643	1.77 (0.48–6.55) p = 0.389	0.23 (0.05–1.15) p = 0.074	0.53 (0.21–1.37) p = 0.192	4.16 (0.62–27.72) p = 0.141	4.35 (0.89–21.25) p = 0.070	0.56 (0.26–1.20) p = 0.136	3.83 (0.91–16.13) p = 0.067
Lower-income countries	1.51 (0.41–5.50) p = 0.533	3.32 (0.62–17.80) p = 0.161	3.57 (0.96–13.34) p = 0.058	0.54 (0.11–2.70) p = 0.451	1.09 (0.35–3.38) p = 0.876	6.09 (0.78–47.35) p = 0.084	8.94 (1.62–49.28) p = 0.012	1.64 (0.59–4.61) p = 0.345	5.16 (1.15–23.17) p = 0.032
Lockdown	1.31 (0.64–2.68) p = 0.457	0.13 (0.02–0.78) p = 0.025	1.36 (0.49–3.80) p = 0.560	0.79 (0.31–2.00) p = 0.612	0.48 (0.24–0.95) p = 0.035	0.92 (0.35–2.38) p = 0.860	0.36 (0.14–0.94) p = 0.038	0.46 (0.25–0.85) p = 0.013	0.28 (0.11–0.68) p = 0.005

Bolded outcomes indicate statistically significant results ($p < 0.05$). aOR, adjusted odds ratio; CI, confidence interval; EU, Europe; NA, North America; PD, Parkinson's disease.

Table 4. Multivariate meta-regression of outcomes according to patient demographics.

Baseline patient characteristics	β -coefficient (95% CI) and p-value								
	Decreased physical activity	Decreased exercise	Worsening PD symptoms	Worsening balance	Worsening mood	Worsening depression	Worsening anxiety	Worsening cognition	Reduced sleep
Age (years)	-0.30 (-0.53 to -0.07) p = 0.012	-0.11 (-0.15 to -0.07) p < 0.001	-0.08 (-0.15 to -0.01) p = 0.018	0.13 (-0.19 to 0.46) p = 0.418	-0.08 (-0.36 to 0.20) p = 0.578	-0.10 (-0.27 to 0.07) p = 0.244	0.01 (-0.20 to 0.22) p = 0.936	0.11 (-0.21 to 0.42) p = 0.502	-0.14 (-0.27 to 0) p = 0.044
Female sex	11.94 (2.17–21.71) p = 0.017	3.51 (-0.17 to 7.19) p = 0.062	-10.13 (-15.66 to -4.61) p < 0.001	3.13 (-15.46 to 21.72) p = 0.741	5.64 (-11.60 to 22.89) p = 0.521	4.59 (-5.01 to 14.19) p = 0.349	0.96 (-10.31 to 12.24) p = 0.867	-0.65 (-13.39 to 12.08) p = 0.920	10.76 (2.81–18.70) p = 0.008
Disease duration (years)	0.57 (0.23–0.91) p = 0.001	-1.17 (-1.58 to -0.77) p < 0.001	-0.31 (-0.53 to -0.08) p = 0.007	0.40 (-0.47 to 1.27) p = 0.369	0.30 (-0.22 to 0.82) p = 0.253	-0.06 (-0.29 to 0.18) p = 0.645	-0.02 (-0.33 to 0.28) p = 0.882	-0.43 (-0.85 to -0.01) p = 0.047	0.27 (-0.09 to 0.63) p = 0.137

Bolded outcomes indicate statistically significant results ($p < 0.05$). CI, confidence interval; PD, Parkinson's disease.

respondents as compared with 22.8% in high-income countries, is another potential contributory factor.¹¹ Moreover, telemedicine utilization is lower in individuals with lower incomes, and this can further exacerbate the vulnerability to PD worsening in this group.²¹ Healthcare policies with greater public subsidies, priority access to facilities, and other supportive care programmes will be helpful for this more vulnerable group of patients.

Biological sex is known to influence PD phenotype and disease progression. Women tend to present at an older age with milder severity and more often develop a tremor-dominant PD phenotype with a slower rate of disease progression.^{43,44} Our study found women to be less prone to worsening PD symptoms, but they more frequently report decreased physical activity and poorer sleep, suggesting gender differences in the pandemic-related effects on PD. Future research should ensure adequate gender representation so that potential differences are not unintentionally masked, and specific measures can be instituted early for at-risk women with PD.^{45,46}

Our study interestingly found patients of younger age and shorter disease duration to be associated with decreased exercise and worsening symptoms, as well as deterioration in cognition and sleep. Since younger PD patients and those with shorter disease duration are likely to be more active,^{47,48} the COVID-19 pandemic may have a greater impact on these patients. As such, this greater decrease in activity levels may have resulted in a greater extent of disease worsening. Despite having less severe disease, attention must be paid to this patient subgroup as well; emotional support, as well as advice and encouragement to remain active, must be provided to these patients.

Conventional logic suggests that lockdown and home confinement are more likely to adversely impact PD symptom severity, as well as the quality of life.⁴⁹ Hence, it is intriguing that results of our meta-analysis suggested otherwise, with inconsistent results across different populations. Individual studies have reported discrepant findings with some finding no worsening of symptoms during lockdown,^{18,19} while others found an improvement in the quality of life and sleep after home confinement.⁵⁰ There may be many factors that can potentially confound the overall analysis, including the definition and duration of lockdown, the support and community services available, the use of telemedicine, the access to emergency services, geopolitical, and cultural differences. These factors should be further investigated in the future. Whatever the differences, central to the analysis is that accessibility of care needs to be maintained, even in the midst of lockdowns and confinement. Emotional and social support for PD patients should also be a priority.

Limitations

Our study has some inherent limitations. First, our study involved populations from different geographical locations and not a pooled analysis from a specific population with similar cultures or practices. We have tried to address this heterogeneity by conducting subgroup analysis and meta-regressions. However, combining findings from different populations is also a strength as the very large sample size (13,787 subjects) increases the power of analysis for the identification of common and rare factors. Second, as published studies were conducted using a cross-sectional methodology, we were unable to quantify the extent of symptomatic worsening over time. Further research employing semi-quantitative and quantitative evaluation to address this gap will be helpful. Last, COVID-19 pandemic represents an exceptionally challenging time for all individuals. The difference in the prevalence of worse physical health and mood between PD patients and other disease groups needs to be further evaluated.

Conclusions

This meta-analysis of 13,878 subjects across 27 studies identified a high prevalence of symptomatic worsening of physical and mental issues among PD patients during the COVID-19 pandemic. Meta-regression analysis (adjusted for geographical region and lockdown status) identified PD patients in lower-income countries to be at greater risk of worsening anxiety and sleep. Biological factors (age, sex, and disease duration) had a significant impact on PD symptoms during the pandemic. The findings from our study will help guide planning and optimize policy guidelines for pandemic preparedness. Specific measures to address at-risk subsets of PD (especially those from low-income locations) will ameliorate the physical and mental burden associated with current and future pandemics.

Conflict of Interest

The authors do not have any competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

A. S. Mai, J. H. Yong, B. J.-W. Tan, B. Xiao, and Professor E.-K. Tan contributed to (1) the conception and design of this project; (2) acquisition, analysis, and interpretation of data; (3) drafting and revising it critically for important intellectual content. All authors gave their final

approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy for Medline.

Table S2. Subgroup analysis according to geographical region.

Table S3. Subgroup analysis according to income level of countries.

Table S4. Subgroup analysis according to lockdown status.

Table S5. Bivariate meta-regression of outcomes according to patient demographics.