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A Systemic Review and Meta-Analysis of the Risk of Venous Thromboembolic Events in Parkinson's Patients

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ABSTRACT

Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder affecting more than 10 million people worldwide. The actual prevalence and relative risk of venous thromboembolism (VTE) in PD have not been systematically examined, especially in various study designs and surgical settings. To address this gap in knowledge, we conducted a meta-analysis on the risk of VTE and in PD.

Methods: We searched PubMed, Embase, and Cochrane from inception to 22 June 2024 to identify cross-sectional, cohort, and case–control studies comparing the frequency of VTE, deep vein thrombosis (DVT) and pulmonary embolism (PE) events in PD and non-PD patients. We computed risk ratios (RR) with 95% confidence intervals (CIs) for each study and pooled results using a random-effects meta-analysis. Quality assessment was performed using Joanna Briggs Institute Critical Appraisal Tools.

Results: Out of 758 studies screened initially, 13 studies involving 775,144 patients were included. VTE risk was elevated (RR 1.73, 95% CI 1.47–2.04) when comparing PD patients to non-PD patients. In subgroup analysis comparing neurological and non-neurological surgeries, there was no significant ($p = 0.11$) difference in VTE risk. Cross-sectional studies had a higher elevated VTE risk (RR 5.43, 95% CI 3.40–8.67) when compared to case–control (RR 1.58, 95% CI 1.14–2.20) and cohort (RR 1.50, 95% CI 1.22–1.84) studies ($p < 0.01$).

Conclusion: Our meta-analysis showed an elevated risk of VTE events in PD patients. There was no significant difference between neurological and non-neurological surgeries in the incidence of VTE. Greater vigilance should be exercised to detect VTE events early in PD patients due to impaired mobility.

1 | Introduction

Venous thromboembolism (VTE) is the third leading cause of vascular death [1] and the single most common preventable cause of death in hospitalized patients. VTE events have been linked to early mortality, with recent studies demonstrating up to 20% mortality [2] within a year of occurrence, with pulmonary embolism specifically linked to a high 3-month mortality of 10%–20%.

Parkinson's disease (PD) is a chronic neurological condition, affecting more than 10 million individuals [3, 4] annually. However, as it is typically a neurodegenerative disorder, the life expectancy of patients is relatively unaffected, with survival ranging from 9.6 [5] to 23.3 years from various studies upon diagnosis.

PD may have an increased incidence of venous thromboembolism events like pulmonary embolism (PE) and deep vein

thrombosis (DVT) due to immobility, autonomic dysfunction, inflammatory processes, muscular changes, medication side effects, endothelial dysfunction, shared genetic predisposition, blood pressure variability, and impaired respiratory function in various pathophysiology studies. PD patients may be more prone to thromboembolism events such as DVT compared to other neurodegenerative disorders (5). However, PD is not included in the modified Wells' score [6], a common criterion utilized heavily in healthcare settings to estimate the likelihood of PE and DVT in patients to guide investigations and management of potential venous thromboembolism risk.

To our knowledge, there has not been a systemic review and meta-analysis on the relative incidence of venous thromboembolism events in PD patients, mainly DVT and PE, in various settings such as different surgical settings. It would be useful to quantify the relative susceptibility of PD patients to venous thromboembolism events and help decide the degree of measures taken to address them in different settings, especially when prophylactic interventions are readily available.

2 | Methods

This systematic review and meta-analysis adhered to the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [7].

2.1 | Information Source and Search Strategy

A systematic search was conducted in Pubmed, EMBASE, and Cochrane using Medical Subject Headings (MeSH) and keywords. Keywords and MeSH terms synonymous with "Parkinson Disease," "Parkinsonian Disorders," "Venous Thrombosis," and "Pulmonary Embolism" formed the basis of the search strategy. The search period included articles from inception to 22 June 2024. Additionally, we reviewed the reference lists of included articles and any prior systematic reviews to identify additional studies and attempted to contact authors for missing information, where appropriate. Only full-text articles published in the English language were included. The full search strategy and search terms are included in Table S1. References were imported into Covidence for the removal of duplicates.

2.2 | Study Selection

Two authors (WYC and CKMC) reviewed each reference in a blinded manner, and any disagreements were resolved through discussion or referred to a third independent author for the final decision (JDJW). The review was carried out in two stages: first, the titles and abstracts were reviewed, and second, the full texts of selected references were retrieved and reviewed.

Original studies, published in English, discussing venous thromboembolism in adults with PD were included. Accepted study designs included case–control, cross-sectional, cohort studies, and randomized controlled trials. Non-peer reviewed articles, review articles (including other systematic reviews and meta-analyses), editorials, letters to the editor, conference abstracts, and studies involving animal or non-human subjects were excluded. In addition, studies without control groups comparing PD patients to non-PD patients were excluded from the meta-analysis.

2.3 | Data Extraction

Two investigators (WYC and JDJW) independently extracted information from the included studies. The data collected included authors, year of publication, type of study, total number of participants, age and sex of study participants, sample size, presence and type of intervention utilized in the study, incidence of DVT and PE. Regarding discrepancies, a third author (CKMC) was consulted to make the final decision regarding the data extraction process.

2.4 | Quality Assessment

The Joanna Briggs Institute Critical Appraisal Tools [8] was used for the quality assessment of included articles. Two investigators (CKMC and JDJW) independently reviewed all included studies and in case of disagreements, a third independent author (WYC) was consulted, and a consensus was reached through discussion. The maximum score attainable (signifying high quality) is 8 points for analytical cross-sectional studies, 10 points for case–control studies, and 11 points for cohort studies.

2.5 | Data Analysis

All analyses were undertaken using RStudio version 4.3.3. Prevalence estimates of DVT and PE were calculated by pooling the study-specific estimates using random-effects models. Pooled risk ratios (RRs) were meta-analyzed using the Mantel–Haenszel method. The level of significance is defined as $p \leq 0.05$. The choice between the fixed-effect and random-effects models was made depending on the I^2 index and Cochran Q test p-value. An I^2 of less than 25% is indicative of low heterogeneity, 25%–75% of moderate heterogeneity, and more than 75% of high heterogeneity. In cases with minimal heterogeneity, a fixed-effect model was used. Otherwise, a random-effects model was used. All results were presented as their effect sizes with the accompanying 95% CIs, along with the p values where applicable. In addition, we conducted subgroup analysis according to the type of study (cohort vs. cross-sectional vs. case–control) and type of intervention (neurological vs. non-neurological surgeries). Neurological and non-neurological studies were compared for their incidence of venous thromboembolism events. Neurological surgeries were defined as deep brain stimulation (DBS) and spinal surgeries. Funnel plots were not included due to the relatively small number of studies [9].

3 | Results

A total of 758 studies were found after searching Pubmed, EMBASE, and Cochrane. After removing 152 duplicates 606 studies remained for title and abstract screening. Of these, 511 studies were excluded, leaving 94 studies for full-text assessment. Following the full-text review, 81 studies were excluded. The study selection process and reasons for excluding these 81 studies are illustrated in the PRISMA-P flow diagram (Figure 1). Finally, 13 studies involving 775,144 patients (PD and non-PD) were included in the final analysis.

3.1 | Characteristics of Included Studies

Among the 13 studies included, 7 were cohort studies [10–16], 2 were cross-sectional studies [17, 18], and 4 were case–control studies [14, 19–22]. These studies were conducted across various countries, including the United States [10, 11, 13–15, 17, 20, 21], Germany [16, 22], Taiwan [19], and Japan [12, 18]. A mix of data sources was used, with some studies drawing from national or state databases, while others were based on single-center data.

Several studies involved the use of various interventions, specifically surgeries. In terms of surgery types, several studies focused on the use of deep brain stimulation (DBS) [11, 15, 16], spinal surgeries [10, 12, 14, 17, 21, 22], and non-neurological studies [19] such as total knee arthroplasty [13, 20]. Among the included studies, the majority focused on the prevalence of VTE events in PD patients such as DVT and PE. A summary of the quality of studies using the Joanna Briggs Institute (JBI) Critical Appraisal Tools can be found in Table 1.

3.2 | VTE Events When Comparing PD and Non-PD Patients

In an analysis of 13 studies comprising 34,781 PD participants (Figure 2), the pooled risk ratio (RR) for VTE in PD patients compared to controls was 1.97 (95% CI 1.33–2.91). The analysis exhibited moderate heterogeneity, with an I^2 of 67%, and the Cochran Q test was significant ($p < 0.01$). When examining specific VTE outcomes, the pooled RR for DVT events from 12 studies was 2.20 (95% CI 1.26–3.85) with moderate heterogeneity ($I^2 = 73\%$, $p < 0.01$). Similarly, the pooled RR

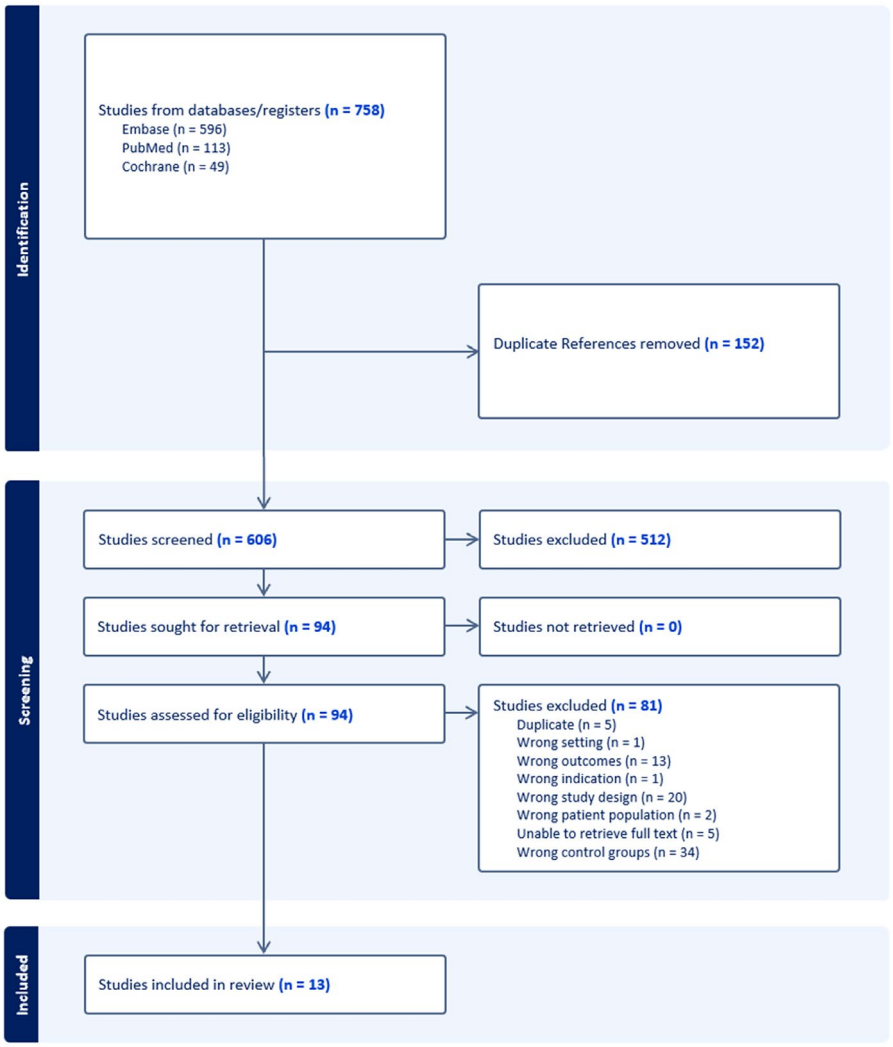

FIGURE 1 | PRISMA flow diagram for studies included in the current analysis.

TABLE 1 | Summary characteristics of studies utilized in current meta-analysis with risk of bias assessment (JBI scale) shown.

		Parkinson's disease participants/patients			Control participants/patients			
Study (year)	**Study design**	**Participants (*n*)**	**Gender male, %**	**Mean age (SD)**	**Participants (*n*)**	**Gender male, %**	**Mean age (SD)**	**JBI score**
Berreta (2023)	Cohort study	725	47.17	58.07	26,259	35.20	68.5	9/11
Cheppalli (2022)	Case–control study	3082	49.74	71.44 (7.88)	555,289	38.43	66.59 (9.51)	10/10
Hitti (2020)	Cohort study	320	NA	61.1 (9.4)	80	NA	NA	8/11
Huang (2016)	Case–control study	6455	48.30	73.0 (5.1)	12,910	48.30	72.8 (5.1)	9/10
Katsumi (2019)	Cohort study	26	11.54	76.0 (8.0)	296	22.30	75.0 (10.8)	9/11
Marchand (2022)	Cohort Study	18,082	43.51	NA	54,244	43.51	NA	11/11
Martini (2020)	Cross-sectional study	535	71.03	NA	75,335	54.28	NA	8/8
McClelland (2017)	Cohort study	4301	57.99	69.7	15,000	NA	NA	9/11
Shah (2019)	Case–control study	288	48.96	69.7	288	42.36	70.2	10/10
Takeda (2024)	Cross-sectional study	61	55.74	77.3 (5.7)	168	54.76	69.6 (10.0)	8/8
Umemura (2003)	Cohort study	81	66.67	60	28	57.14	50.4	8/11
Voges (2007)	Cohort study	789	53.87	NA	394	46.70	NA	6/11
Westermann (2017)	Case–control study	36	55.56	72.5 (6.4)	72	55.56	72.6 (6.4)	10/10

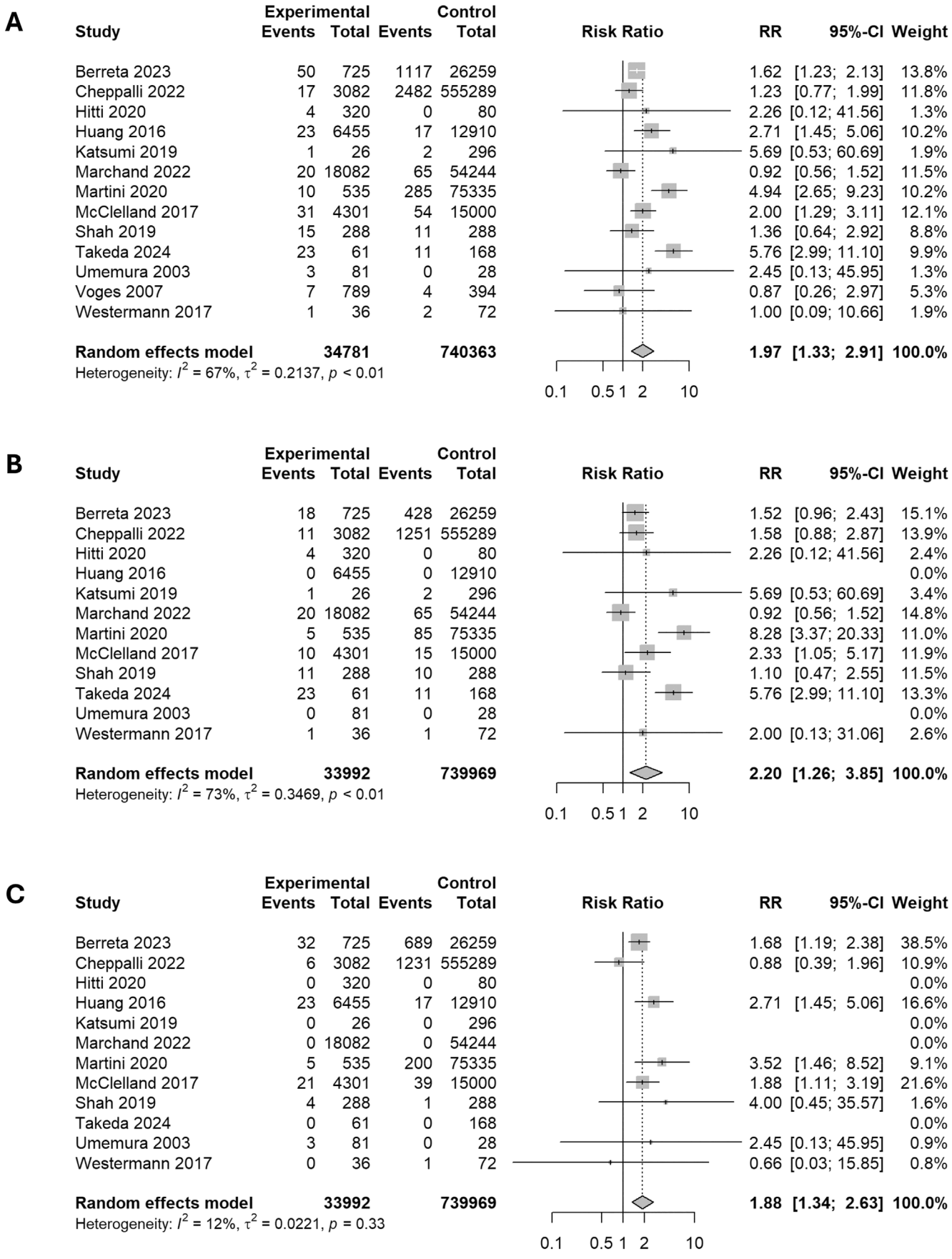

FIGURE 2 | Forest plot of risk ratios of venous thromboembolism events when comparing PD to non-PD patients. A is combined venous thromboembolism events, B is deep vein thrombosis events, and C is pulmonary embolism events. PD, Parkinson's disease.

for PE from 12 studies was 1.88 (95% CI 1.34–2.63), though statistical significance was not established ($p = 0.33$) for the Cochran Q test.

3.3 | Subgroup Analysis of VTE Events in Different Study Designs

A subgroup analysis was conducted to compare the risk of VTE, DVT, and PE incidence in PD to non-PD patients based on different study designs: cohort, case–control, and cross-sectional studies (Figure 3). For VTE, the analysis revealed significant differences across study designs ($p < 0.01$), with cross-sectional studies showing the highest risk (RR 5.31, 95% CI 2.01–14.04), while cohort (RR 1.51, 95% CI 1.07–2.12) and case–control studies (RR 1.59, 95% CI 0.83–3.06) demonstrated lower risks.

For DVT events, a similar pattern was observed. Cross-sectional studies reported a much higher risk of DVT (RR 6.54, 95% CI 0.72–59.00), contributing to a significant subgroup difference across study designs ($p < 0.01$). In contrast, cohort (RR 1.45, 95% CI 0.81–2.60) and case–control studies (RR 1.42, 95% CI 0.82–2.45) showed lower but more consistent risks.

For PE events, there was no difference in case–control (RR 1.74, CI 1.45–2.10) and cross-sectional studies (RR 1.71, CI 1.45–2.10) as the test for subgroup differences was not statistically significant ($p = 0.33$).

3.4 | Subgroup Analysis of VTE Events in Different Surgical Settings

VTE (RR 1.74, 95% CI 1.23–2.46), DVT (RR 1.86, 95% CI 1.07–3.24), and PE (RR 1.88, 95% CI 1.34–2.63) risks were elevated in surgical settings.

A subgroup analysis based on surgery subtypes was conducted (Figure 4). For VTE, neurological surgeries (which include deep brain stimulation and spinal surgeries) showed an increased risk of VTE among PD patients (RR 1.99, 95% CI 1.32–3.00) while non-neurological surgeries also had a lower risk (RR 1.42, 95% CI 0.37–5.48). For DVT, neurological surgeries showed an increased risk (RR 2.34, 95% CI 1.15–4.76) while non-neurological surgeries showed a lower risk among PD patients (RR 1.18, 95% CI 0.04–36.02). For PE, neurological surgeries showed an increased risk of DVT among PD patients (RR 1.87, 95% CI 1.41–2.50) while non-neurological surgeries also showed increased VTE among PD patients (RR 1.88, 95% CI 1.34–2.63).

However, the differences between these surgery types did not reach statistical significance for either of the VTEs (VTE, $p = 0.35$; DVT, $p = 0.08$; PE, $p = 0.77$).

4 | Discussion

4.1 | Higher Risk of Thromboembolism in PD Patients and Pathophysiology Links

In our meta-analysis, PD is associated with a higher incidence of thromboembolism events (VTE, DVT and PE events). This could be due to various reasons, including immobility, autonomic dysfunction, inflammatory changes, endothelial dysfunction, medication side effects, genetic predisposition, dehydration, and impaired respiratory function.

PD patients are likely to have reduced mobility as patients experience relative impairments [23] in posture, balance, and gait, leading to a greater risk of falls. Gait in PD patients is slower (40 m/min compared to 90 m/min), with smaller steps and is generally more narrowed based with asymmetrical arm swing. With reduced mobility, PD patients are likely to have greater venous stasis, one of the key components of Virchow's triad and therefore leading to greater thromboembolic events such as PE and DVT.

PD patients are also more likely to experience autonomic dysfunction such as orthostatic hypotension. where the prevalence is estimated to range from 30% to 40% [24], This is mediated by α-synuclein accumulation and neuronal destruction in both the parasympathetic and sympathetic nervous system leading to a reduced baroreflex response during positional changes. This is due to a lower sensitivity as there is noradrenergic denervation, affecting the response of the sympathetic nervous system. Parasympathetic dysfunction is also associated with orthostatic hypotension [25], through the mechanism is less clear. Orthostatic hypotension leads to increased venous thromboembolism events as it could lead to periods of reduced blood flow and venous pooling, leading to greater stasis, a key component of Virchow's triad.

Dehydration and potentially impaired respiratory function in PD, together with dysphagia, could lead to reduced fluid intake and dehydration [26], increasing blood viscosity and thereby promoting clot formation. Dysphagia also often leads to respiratory impairment [27] due to rigidity and decreased diaphragmatic movement. This would lead to reduced venous return from the lower extremities, promoting venous stasis and therefore more venous thromboembolism events. Furthermore, anticholinergics, which are commonly prescribed in PD, could contribute to dehydration.

Inflammation also promotes a procoagulant state [28] and neuroinflammatory responses in PD have been well documented [27, 28]. An increased clotting state has a significantly increased risk of thromboembolism specifically associated with DVT and PE.

Lastly, genes implicated in PD, such as the glucocerebrosidase (GBA) gene [29] are known to lead to pro-coagulation states. Other more common PD genes such as LRRK2 [30] are

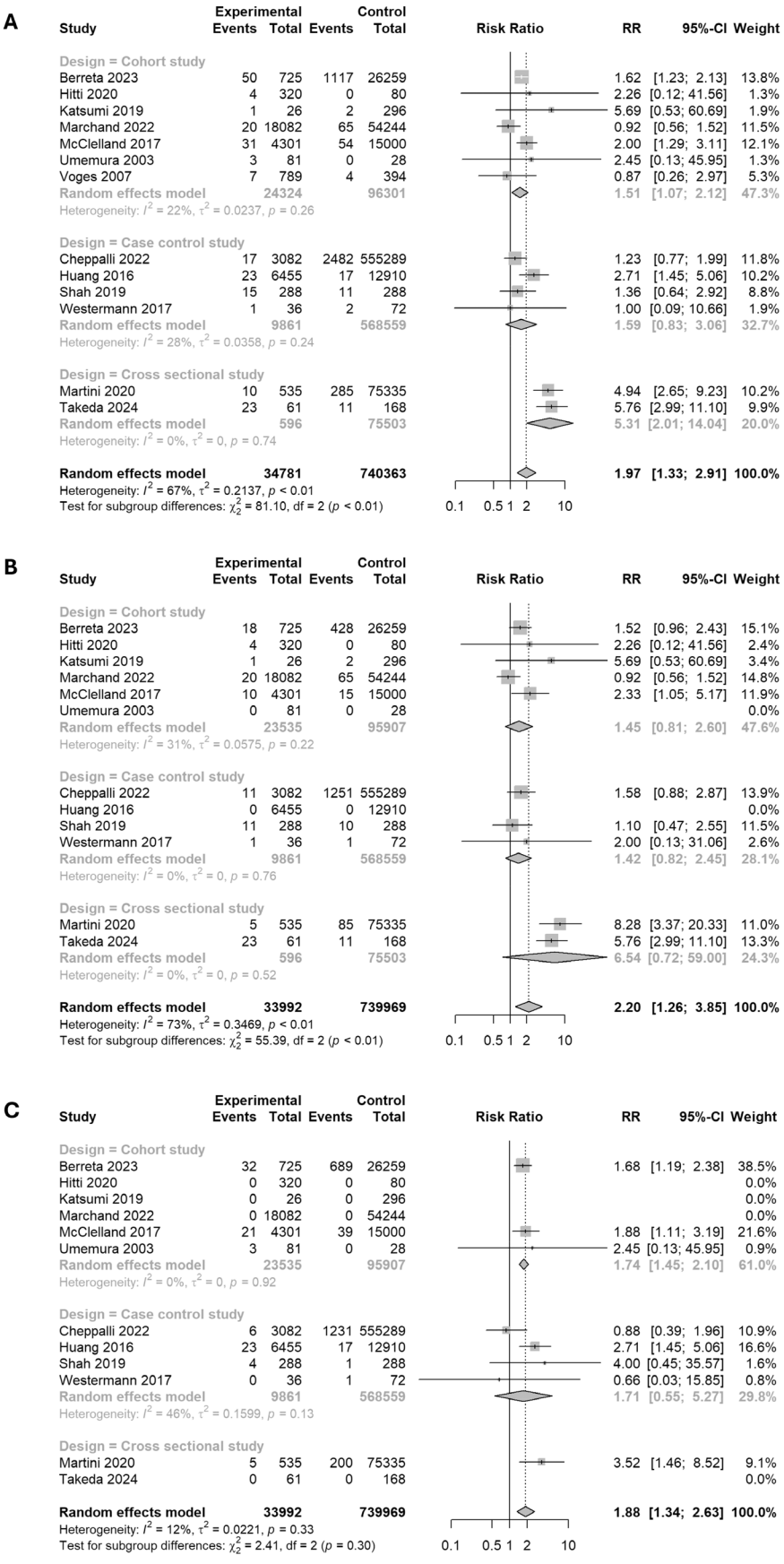

FIGURE 3 | Forest plot of risk ratios of venous thromboembolism events when comparing PD to non-PD patients between different study designs of cohort study, case–control, and cross-sectional studies. A is combined venous thromboembolism events, B is deep vein thrombosis events, and C is pulmonary embolism events. PD, Parkinson's disease.

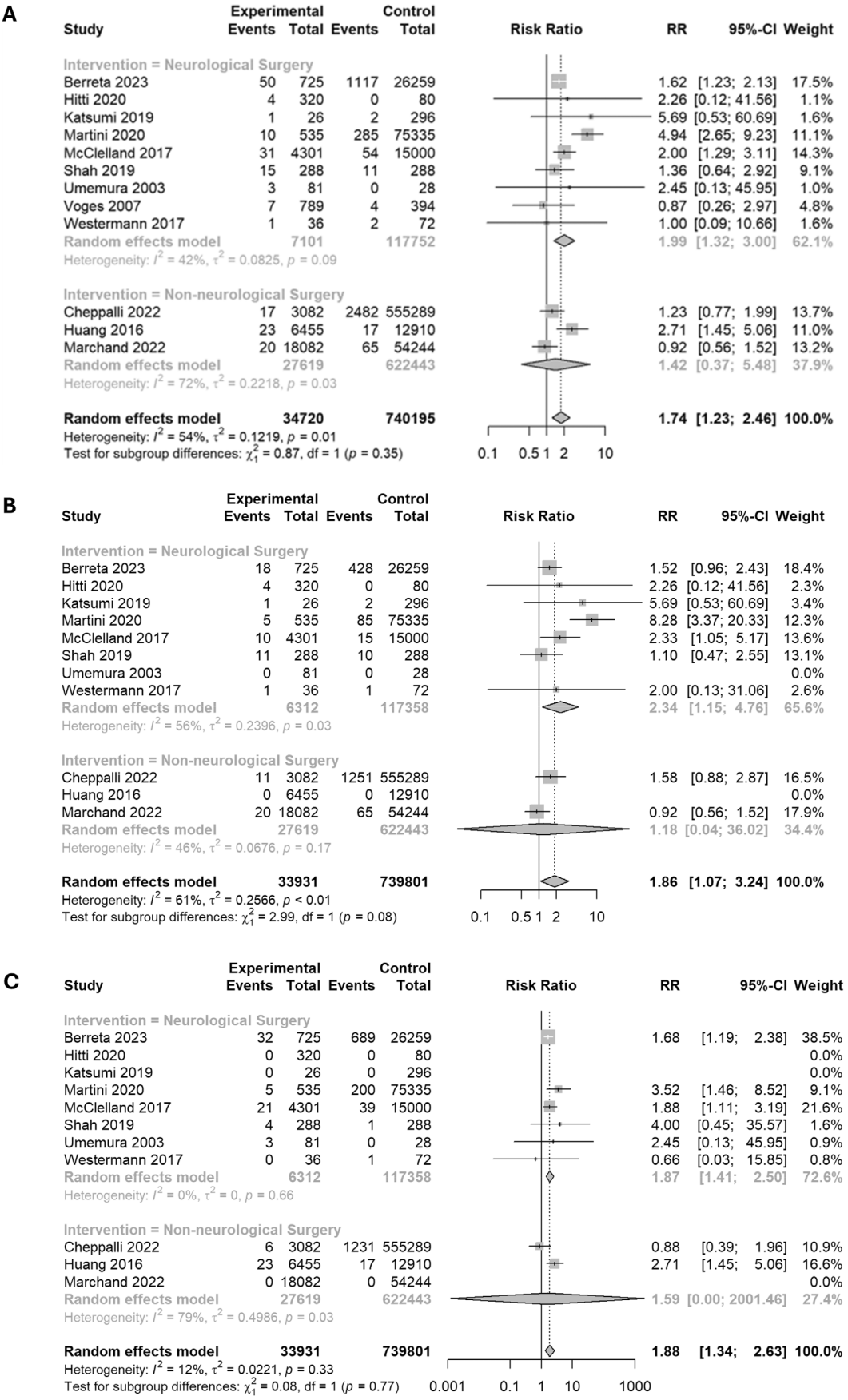

FIGURE 4 | Forest plot of risk ratios of venous thromboembolism events when comparing PD to non-PD patients between different surgery types (neurological vs. non-neurological). A is combined venous thromboembolism events, B is deep vein thrombosis events, and C is pulmonary embolism events. PD, Parkinson's disease.

hypothesized to be involved in endothelial dysfunction and therefore could lead to an increased risk of thromboembolic events, although this link is yet to be established.

This finding is further supported by additional studies that have identified positive correlations between the development of DVT and higher modified Medical Research Council (mMRS) dyspnea scores in patients with more advanced Hoehn and Yahr staging [31].

4.2 | The Risk of Thromboembolic Events Is Elevated in Surgical Patients, but no Difference Exists Between Surgical Types

The findings from the subgroup analysis highlight the elevated risk of thromboembolic events, specifically total VTE and DVT events, among PD patients following surgery. These results underscore the heightened vulnerability of PD patients to thromboembolic complications after surgical procedures, likely due to a combination of factors co-shared between PD and surgery, such as reduced mobility and autonomic dysfunction [32].

The subgroup analysis comparing different types of surgical intervention did not find a significant difference between neurological and non-neurological surgeries in VTE, DVT, and PE events ($p = 0.35$, 0.08, 0.77 respectively) although neurological surgeries had a consistently higher RR compared to non-neurological surgeries. This implies that while there is an elevated risk associated with surgery in PD patients, the specific type of surgery may not be the key determinant of this risk, with other factors potentially playing a more significant role.

This is in contrast to literature that suggests that neurological surgeries may have elevated VTE due to longer durations and delayed ambulation post-surgery [33]. However, the lack of statistically significant differences between these surgical subtypes in this meta-analysis suggests that, while certain procedures may inherently carry greater risks, other factors such as patient characteristics like gender and age, preoperative management measures such as rehabilitation, and the severity of PD, such as use of PD medications and staging on the Hoehn and Yahr scale [19], may have a more substantial impact on thromboembolic outcomes.

These findings have important clinical implications. They suggest that while neurological surgeries may warrant closer monitoring and more aggressive prophylaxis, solely looking at the surgery type to stratify thromboembolic risk may be inadequate. Instead, a more nuanced risk assessment that includes patient-specific factors such as PD severity and the overall surgical context is crucial for optimizing thromboembolic prevention in PD patients undergoing surgery. Future studies should aim to identify these key factors and develop more targeted intervention strategies to mitigate the heightened risk observed in this vulnerable population.

4.3 | The Risk of Thromboembolic Events Is Higher in Cross-Sectional Studies

The subgroup analysis by study design reveals important insights into how different methodologies may influence the observed risk of VTE, DVT, and PE in PD patients. Notably, cross-sectional studies consistently reported much higher risk estimates for VTE, DVT, and PE, with greater variability compared to cohort and case–control studies. The significantly elevated risk reported in cross-sectional studies suggests that they may have overestimated the risk due to their inherent limitations, such as the inability to establish temporal causality and the potential for selection bias [34].

In contrast, the risk estimates from cohort and case–control studies, which were more consistent with one another, likely provide a more reliable assessment of the true thromboembolic risk in PD patients. The lack of a significant difference between these two study designs suggests that either design may be effectively used to estimate thromboembolic risk in PD.

Moreover, the differences in the prevalence of DVT and VTE events may also be influenced by the diagnostic methods employed to detect their presence, such as routine ultrasound screening or reliance on symptom reporting by patients. This was exemplified by Takeda et al. [18], who demonstrated that the majority of DVT cases were asymptomatic, highlighting the potential for underdiagnosis in the absence of routine screening.

4.4 | Strengths and Limitations of the Study

We provide a comprehensive review of the relative risk of thromboembolism events in PD patients in various situations such as in specific surgeries like neurological surgery situations. This would serve as an important guide for clinicians when assessing the risk of thromboembolism in PD patients and enable them to better tailor treatment strategies and management plans for them. This understanding would also complement the modified Wells' score, which is commonly utilized in healthcare settings, enabling more precise care to be delivered to patients with PD.

There is a lack of clear treatment strategies in these studies for different subgroups of patients to reduce their VTE risk. This is largely because of the heterogeneity of treatment modalities utilized in the studies.

4.5 | Future Directions

Future research should focus on identifying the key factors that contribute to thromboembolic risk in PD patients amidst the many postulated and validated pathophysiological mechanisms to optimize VTE prophylactic measures. Developing and validating tailored strategies for prevention and management of VTE in

both surgical and nonsurgical settings would be useful. It would also be useful to evaluate the long-term effects of VTE events in PD patients and potential effects on cognition and other neuropsychiatric complications in longitudinal studies [35, 36].

5 | Conclusion

This systematic review and meta-analysis provide compelling evidence that PD patients are at a significantly increased risk of VTE. Therefore, incorporating PD as a potential risk factor in clinical tools like the modified Well's score could potentially improve identification of at-risk patients and guide the implementation of targeted prophylactic measures, especially in current clinical practice where it is not considered. Moreover, clinicians should have heightened vigilance for VTE events while treating PD patients.

There is no significant difference between neurological and nonneurological surgeries for VTE events in PD patients, and therefore factors beyond the type of surgery, such as patient-specific characteristics, should be considered in conjunction.

We also show that cross-sectional studies reported an elevated risk of VTE compared to cohort and case–control studies, and these differences need to be further examined. There should be a greater vigilance to detect VTE events early in PD patients due to impaired mobility.

Author Contributions

Jia Dong James Wang: conceptualization, investigation, writing – original draft, visualization, validation, software, project administration, formal analysis, methodology, writing – review and editing. **Claire Kar Min Chan:** data curation, writing – review and editing. **Wei Yu Chua:** data curation, writing – review and editing. **Yinxia Chao:** supervision, methodology, visualization. **Ling-Ling Chan:** supervision, methodology, visualization. **Eng-King Tan:** supervision, project administration, methodology, conceptualization, investigation.

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Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are not publicly available and may be made available by the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.