Scientific Research Publishing

Advances in Parkinson's Disease, 2024, 13, 27-56
https://www.scirp.org/journal/apd
ISSN Online: 2169-9720
ISSN Print: 2169-9712

# Monoamine Oxidase-B Inhibitor Rasagiline Effects on Motor and Non-Motor Symptoms in Individuals with Parkinson's Disease: A Systematic Review and Meta-Analysis

**Paula Abola, Mitchell Wolden**

Department of Clinical Research, University of Jamestown, Jamestown, United States of America
Email: paula.abola@uj.edu

**How to cite this paper:** Abola, P. and Wolden, M. (2024) Monoamine Oxidase-B Inhibitor Rasagiline Effects on Motor and Non-Motor Symptoms in Individuals with Parkinson's Disease: A Systematic Review and Meta-Analysis. *Advances in Parkinson's Disease*, **13**, 27-56.
https://doi.org/10.4236/apd.2024.133003

**Received:** May 8, 2024
**Accepted:** June 8, 2024
**Published:** June 11, 2024



## Abstract

**Objective**: In the manuscript titled "Monoamine Oxidase-B Inhibitor Rasagiline Effects on Motor and Non-Motor Symptoms in Individuals with Parkinson's Disease: A Systematic Review and Meta-Analysis", the objective was to conduct a systematic review with meta-analysis to investigate the effects that Rasagiline has on motor and non-motor symptoms in individuals with PD. **Introduction**: Rasagiline is a second-generation monoamine oxidase-B (MAO-B) inhibitor used both as monotherapy and adjunctive therapy for Parkinson's Disease (PD). **Methods**: A systematic literature search and meta-analysis were performed with randomized control trials that investigated the effects of Rasagiline on motor and non-motor symptoms in individuals with PD. The systematic search was conducted in PubMed, Cochrane, and EBSCO databases. Methodological quality was assessed using the Cochrane Grading Recommendations Assessment, Development and Evaluation approach. **Results**: Fourteen studies were included in our review. There were trivial to small and statistically significant improvements in motor symptoms for individuals with PD treated with Rasagiline compared to placebo. Non-motor symptoms showed no significant improvement with Rasagiline compared to placebo in five of six meta-analyses. Results were based on very low to moderate certainty of evidence. **Conclusion**: 1 mg/day Rasagiline significantly improved Parkinsonian motor symptoms in individuals with PD compared with placebo. For all outcomes, the 1 mg/day Rasagiline group was favored over the placebo group.

## Keywords

Parkinson's Disease, Monoamine Oxidase-B Inhibitor, Rasagiline, Non-Motor Symptoms, Motor Symptoms, UPDRS, PDQ-39, OFF Time

## 1. Introduction

Parkinson's Disease (PD) is a chronic degenerative disease of the central nervous system [1] and is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) region of the brain [2]. The loss of these neurons results in dopamine deficiency and neurotransmission in the nigrostriatal pathway, leading to Parkinsonian motor symptoms including bradykinesia, tremor, and loss of balance [2]. Beyond motor symptoms, individuals with PD also exhibit non-motor symptoms including depression, anxiety, sleep problems, fatigue, pain, and cognitive impairments, all of which reduce the quality of life in individuals with the disease [3]. Treatment of PD that focuses on slowing the progression of symptoms (neuroprotection) is different among individuals, chosen according to age, disease stage, most troubling symptoms, and the balance between efficacy and risk of adverse events [1].

Rasagiline is a second-generation monoamine oxidase-B (MAO-B) inhibitor used both as monotherapy and adjunctive therapy for PD [4]. MAO-B inhibitors act by blocking monoamine oxidase. Monoamine oxidase is responsible for breaking down dopamine and its inhibition leads to an increasing amount of dopamine in the striatum [5]. Preliminary evidence shows improved motor and non-motor symptoms in individuals with PD treated with 1 mg/day Rasagiline. Other doses, such as 0.5, 2, or 4 mg/day, have also been investigated but have not shown significantly better results. Therefore, 1 mg/day remains the optimal dose [6]. In clinical trials, Rasagiline has been effective, safe, and well-tolerated. In clinical trials, Rasagiline, as an adjunct to Levodopa, has significantly decreased OFF time; the time when Parkinsonian symptoms return between medication doses [7]. Delayed-start clinical trials on Rasagiline have shown the potential for enhancing neuroprotection: slowing down or even reversing the disease [7].

Despite the preliminary evidence of improved motor and non-motor symptoms, a systematic review with meta-analysis has not been performed to investigate the efficacy of 1 mg/day Rasagiline as monotherapy or adjunctive therapy compared to placebo. Our purpose was to conduct a systematic review with meta-analysis to investigate the effects 1 mg/day Rasagiline has on motor and non-motor symptoms in individuals with PD.

## 2. Materials and Methods

### 2.1. Source Data and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [8]. The review protocol was registered on PROSPERO: CRD42024518717 and vetted by a professional research librarian. An extensive literature search on the MAO-B inhibitor Rasagiline was performed using PubMed, Cochrane, and EBSCO electronic databases and manual searches. They were searched from in-

ception to March 21st, 2024. Searches were restricted to articles in the English language and randomized controlled trials (RCTs). **Appendix 1** provides a detailed list of search terms utilized.

## 2.2. Outcome Measures

The Unified Parkinson's Disease Rating Scale (UPDRS) is a frequently used outcome measure to quantify the severity and progression of PD. The UPDRS includes four sections that assess: (1) mentation, behavior, and mood (UPDRS I), (2) activities of daily living (UPDRS II), (3) motor symptoms (UPDRS III), and (4) complications of therapy in patients with PD (UPDRS IV). Clinicians and researchers use the sectional and total scores to assess the status of PD symptoms and monitor the disease progress [9]. The 39-item Parkinson's Disease Questionnaire (PDQ-39) is a patient-reported outcome measure that assesses the quality of life for individuals with PD and includes eight domains: (1) mobility, (2) activities of daily living, (3) emotional well-being, (4) stigma, (5) social support, (6) cognitions, (7) communications, and (8) bodily discomfort [10]. OFF time is a frequently used outcome measure to quantify the time when the motor and non-motor symptoms of individuals with PD return between medication doses. OFF time can occur in the morning before the first dose of medication or it can occur during the day between scheduled doses of medication [11]. UPDRS total, UPDRS Part II, and UPDRS Part III scores, PDQ-39 total, PDQ-39 mobility, PDQ-39 activities of daily living, and PDQ-39 bodily discomfort scores, and OFF time were used to assess the progression of motor symptoms in individuals with PD. UPDRS Part I scores, PDQ-39 emotional well-being, PDQ-39 stigma, PDQ-39 social support, PDQ-39 cognition, and PDQ-39 communication scores were used to assess the progression of non-motor symptoms in individuals with PD.

## 2.3. Inclusion and Exclusion Criteria

Studies were included with the following criteria: female and male individuals aged 30 or over with a clinical diagnosis of PD consistent with the UK Brain Bank criteria [12] who have a Hoehn and Yahr (H&Y) Stage 5 or less. The intervention studied is the MAO-B inhibitor Rasagiline and the outcomes assessed are UPDRS total, UPDRS Part I, UPDRS Part II, and UPDRS Part III scores, PDQ-39 total and subdomain scores, and/or OFF time. The study design search was limited to Randomized Controlled Trials (RCTs) published in English (**Table 1**).

Studies were excluded with the following criteria: individuals with a mini-mental state examination score of 24 or less. Studies were also excluded if the outcomes assessed were not UPDRS total, UPDRS Part I, UPDRS Part II, or UPDRS Part III scores, PDQ-39 total or subdomain scores, or OFF time, or if the study design was expert opinion, editorial, case report, abstracts without full results, and preprints.

Table 1. PICOS criteria for inclusion and exclusion criteria of studies.

| Parameter | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Female and male individuals over the age of 30 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria who have a Hoehn and Yahr Stage 5 or less during OFF state | Individuals with a mini-mental state examination score of 24 or less |
| **Intervention** | MAO-B inhibitor Rasagiline | Other types of PD medication |
| **Comparator** | Placebo | No comparator |
| **Outcome** | UPDRS Part I, UPDRS Part II, UPDRS Part III, UPDRS Part IV and UPDRS total scores, PDQ-39 subdomain and total scores, and/or OFF time as efficacy endpoints | UPDRS Part I, UPDRS Part II, UPDRS Part III, UPDRS Part IV and UPDRS total scores, PDQ-39 subdomain and total scores, and/or OFF time not included as efficacy endpoints |
| **Study design** | Randomized Controlled Trials published in English | Expert opinions, editorials, case reports, abstracts without full reports, and preprints. Published in any other language than English |

### 2.4. Study Selection

Two reviewers (PA, MW) independently screened all titles and abstracts of the identified studies. Full texts were obtained for the studies deemed eligible from the initial screening. Two reviewers (PA, MW) independently reviewed full texts. Any discrepancies were discussed and resolved through discussion between reviewers (PA, MW).

### 2.5. Data Extraction

Data were extracted into a standardized form that included lead author, publication date, country, study design, intervention type, sample size, age, and results for UPDRS total, UPDRS Part I, UPDRS Part II, and UPDRS Part III scores, PDQ-39 total and subdomain scores, and OFF time outcome measures by one independent reviewer (PA). A second reviewer (MW) conducted a reliability check. No discrepancies in data extraction were identified between the reviewers. If there was missing data, the authors were contacted for additional information.

### 2.6. Risk of Bias

Methodological quality was examined using the Cochrane Risk of Bias 2 (RoB 2) tool [13]. The RoB 2 is structured into five domains of bias: (1) randomization process, (2) deviations from the intended interventions (effect of assignment and adhering to intervention), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. From the results in each domain, an overall risk of bias was determined. Overall risk of bias was judged as high risk of bias, some concerns, or low risk of bias. Two reviewers (PA, MW)

independently conducted the risk of bias analysis. Any discrepancies were discussed and resolved through discussion between reviewers (PA, MW).

### 2.7. Data Analysis

We performed a random-effects meta-analysis using the Hedges' g method to calculate the standardized mean difference (SMD) and 95% confidence interval (CI) of 1 mg/day Rasagiline compared to placebo on UPDRS total, UPDRS Part I, UPDRS Part II, and UPDRS Part III scores, PDQ-39 total and subdomain scores, and OFF time. The SMD and 95% CI were estimated when at least two or more studies included the same outcome measure. An SMD value of less than 0.20 was considered trivial, 0.20 to 0.49 was considered a small effect, 0.50 to 0.79 was considered a medium effect, and 0.80 and above was considered a large effect [14].

We assessed heterogeneity using Q, p, and $I^2$ values and the 95% prediction interval (PI). The $I^2$ value of 0% - 40% was interpreted as small heterogeneity, 30% - 60% as moderate heterogeneity, 50% - 90% as substantial heterogeneity, and 75% - 100% as considerable heterogeneity [15]. The 95% PI was estimated when the meta-analysis included more than two studies. Publication bias was assessed in meta-analyses with at least ten studies [16]. Publication bias was assessed by inspection of the standard error funnel plots, trim-and-fill analysis, Egger's regression test, and Begg and Mezumdar's rank correlation test. If a meta-analysis did not include at least ten studies, the standard error funnel plot was still generated for qualitative review. All statistical analyses were conducted using STATA 18 (StataCorp. Stata statistical software: release 18. College Station, TX: StataCorp LP. 2023).

### 2.8. Certainty

Two reviewers (PA, MW) independently assessed the certainty of evidence using the GRADE approach for each meta-analysis (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from gradepro.org) [17]. Each meta-analysis was classified as very low, low, moderate, or high-quality certainty of evidence.

## 3. Results

### 3.1. Study Selection

The electronic search of databases yielded 528 articles. One-hundred-forty-seven articles were found to be duplicates, leaving a total of 381 articles. Three-hundred-thirty-seven articles were excluded after reviewing titles and abstracts. The remaining 44 articles were retrieved and assessed for eligibility. Thirty articles were excluded because they did not meet the inclusion criteria. Fourteen remaining articles were found eligible and included in the review [18]-[31] (**Figure 1**). Eleven of the included articles were utilized to perform meta-analyses. Three articles [20] [23] [31] could not be included in the meta-analysis due to missing data.

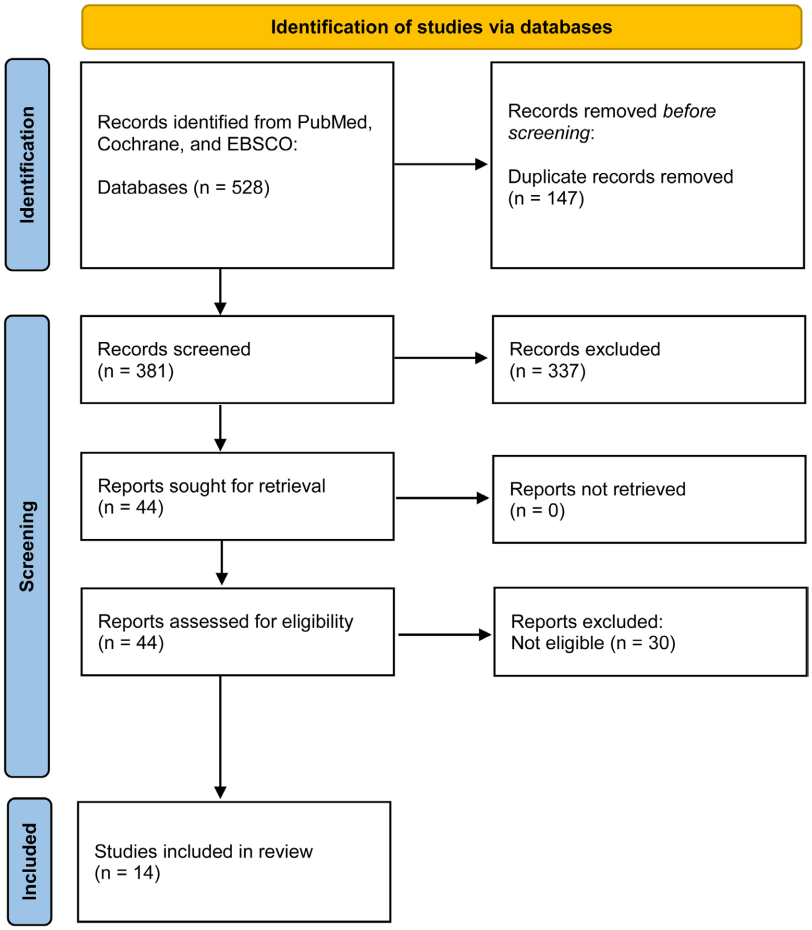



**Figure 1.** PRISMA flow diagram for searches.

### 3.2. Characteristics of Selected Studies

As summarized in **Table 2**, 4621 participants were assessed in studies across Europe [21], Denmark [20], Italy [27], Hungary [18], Israel [18] [20] [21] [22], Turkey [24], China [25], Japan [29] [30] [31], Argentina [21], Canada [23], and the United States [19] [23] [26] [28]. The duration of the studies ranged between 10 to 72 weeks. Three studies included a 0.5 mg/day Rasagiline group [18] [20] [29], all studies included a 1 mg/day Rasagiline group [18]-[31], four studies included a 2 mg/day Rasagiline group [18] [19] [22] [23], and one study included a 4 mg/day Rasagiline group [19]. All studies included a placebo as the control.

### 3.3. Characteristics of Participants

The mean age of individuals ranged from 57.4 to 67.4 years in the Rasagiline groups and from 57 to 67.9 in the placebo groups. The H&Y Stage of individuals was 5 or less. The mean range of H&Y scores for the Rasagiline groups was 1 - 1.9 in three studies [19] [22] [23], 2 - 2.9 in five studies [20] [24] [28] [30] [31], and 3 - 4 in one study [29]. The mean range of H&Y scores for the placebo group was 1 - 1.9 in four studies [19] [22] [23] [29], 2 - 2.9 in four studies [20] [28] [30] [31], and 3 - 4 in one study [29]. One study reported one individual in

the 1 - 1.5 H&Y score range, nine individuals in the 2 - 2.5 range, 16 individuals in the 3 - 4 range for the Rasagiline groups, and three individuals in the 2 - 2.5 range, and three individuals in the 3 - 4 range for the placebo group [18]. One study reported 21 individuals in the 1 - 1.5 H&Y range, 34 individuals in the 2 - 2.5 range, three individuals in the 3-4 range for the Rasagiline group, and 20 individuals in the 1 - 1.5 range, 40 individuals in the 2 - 2.5 range, and five individuals in the 3 - 4 range for the placebo group [27]. The mean percentage of female individuals ranged from 21 to 61.1%.

### 3.4. Study Quality

The overall risk of bias was low for three included studies [19] [21] [25], some concerns for nine included studies [20] [22] [23] [24] [26] [27] [28] [29] [30], and high risk for two included studies [18] [31] (**Figure 2**). In nine studies [18] [20] [23] [24] [26] [27] [28] [29] [30], the cause of some concern in the first domain was the lack of information regarding intervention allocation techniques. In two studies [20] [22], the cause of some concern in the second domain was the lack of statistical analyses to account for participants who dropped out. In one study [18], the cause of high concern in the second domain was inconsistent data with participant drop-out. In one study [31], the cause of high concern in the first domain was the lack of randomization due to the study being open-label.

**Table 2.** Summary of the studies on the MAO-B inhibitor Rasagiline retrieved from the literature.

| Authors | Number of participants at baseline | Gender allocation | Mean age of participants in the Rasagiline group | Group allocation | Intervention duration |
|---|---|---|---|---|---|
| **Rabey *et al.*, 2000** | 70 | 55.7% male, 44.3% female | 57.4 ± 4.9 in the 0.5 mg/day Rasagiline group, 56.7 ± 6.4 in the 1 mg/day Rasagiline group, 56.6 ± 7.5 in the 2 mg/day Rasagiline group | 21 participants received 0.5 mg/day Rasagiline, 18 participants received 1 mg/day Rasagiline, 18 participants received 2 mg/day Rasagiline, and 13 participants received the placebo | 12 weeks |
| **Stern *et al.*, 2004** | 56 | 67.9% male, 32.1% female | 59.3 ± 8.6 in the 1 mg/day Rasagiline group, 60.3 ± 7.2 in the 2 mg/day Rasagiline group, 62.0 ± 9.7 mg/day in the 4 mg/day Rasagiline group | 15 participants received 1 mg/day Rasagiline, 14 participants received 2 mg/day Rasagiline, 14 participants received 4 mg/day Rasagiline, 13 participants received the placebo | 10 weeks |
| **Parkinson Study Group, 2005** | 472 | 64.6% male, 35.4% female | 62.6 ± 9.5 in the 0.5 mg/day Rasagiline group, 62.9 ± 8.9 in the 1 mg/day Rasagiline group | 164 participants received 0.5 mg/day Rasagiline, 149 participants received 1 mg/day Rasagiline, 159 participants received the placebo | 26 weeks |

**Continued**

| | | | | | |
|---|---|---|---|---|---|
| **Rascol *et al.*, 2005** | 687 | 61.9% male, 38.1% female | 63.9 ± 9.0 | 231 participants received 1 mg/day Rasagiline, 227 participants received entacapone, 229 participants received the placebo | 18 weeks |
| **Olanow *et al.*, 2009** | 1176 | 61.1% male, 38.9% female | 62.4 ± 9.7 in the early-start 1 mg/day Rasagiline group, 62.3 ± 9.6 in the early-start 2 mg/day Rasagiline group | 288 participants received 1 mg/day Rasagiline for 72 weeks and 300 participants received placebo for 36 weeks followed by 1 mg/day Rasagiline for the remaining 36 weeks. 293 participants received 2 mg/day Rasagiline for 72 weeks and 295 participants received placebo for 36 weeks followed by 2 mg/day Rasagiline for the remaining 36 weeks. | 72 weeks |
| **Hauser *et al.*, 2009** | 404 | 63.6% male, 36.4% female | 61.0 ± 10.8 in the early-start Rasagiline group | 266 participants received 1 mg/day or 2 mg/day Rasagiline for 12 months. 138 participants received placebo for 6 months followed by 2 mg/day Rasagiline for the remaining 6 months. | 12 months |
| **Hasmet *et al.*, 2011** | 48 | 68.7% male, 31.3% female | 65.17 ± 9.5 | 23 participants received 1 mg/day Rasagiline, 25 participants received the placebo | 12 weeks |
| **Zhang *et al.*, 2013** | 244 | 53.7% male, 46.3% female | 61.64 ± 8.53 | 119 participants received 1 mg/day Rasagiline, 125 participants received the placebo | 12 weeks |
| **Hauser *et al.*, 2014** | 321 | 68.2% male, 31.8% female | 62.3 ± 9.3 | 159 participants received 1 mg/day Rasagiline, 162 participants received the placebo | 18 weeks |
| **Barone *et al.*, 2015** | 123 | 52.8% male, 47.2% female | 66.0 ± 8.74 | 58 participants received 1 mg/day Rasagiline, 65 participants received the placebo | 12 weeks |
| **Weintraub *et al.*, 2016** | 162 | 79% male, 21% female | 67.4 ± 7.19 | 82 participants received 1 mg/day Rasagiline, 80 participants received the placebo | 24 weeks |

Continued

| | | | | | |
|---|---|---|---|---|---|
| **Hattori *et al.*, 2018 (Phase 2/3)** | 404 | 38.9% male, 61.1% female | 66.1 ± 8.74 in the 0.5 mg/day Rasagiline group, 65.8 ± 8.48 in the 1 mg/day Rasagiline group | 134 participants received 0.5 mg/day Rasagiline, 129 participants received 1 mg/day Rasagiline, 141 participants received the placebo | 26 weeks |
| **Hattori *et al.*, 2018 (Phase 3)** | 243 | 43.9% male, 56.1% female | 67.4 ± 8.81 | 117 participants received 1 mg/day Rasagiline, 126 participants received the placebo | 26 weeks |
| **Hattori *et al.*, 2018 (open-label, Phase 3, participant overlap with above study)** | 210 | 44.2% male, 55.8% female in the first 26 weeks, 53% male, 64% female in the remaining 26 weeks | 65.4 ± 9.13 in the first 26 weeks, 67.4 ± 8.99 in the remaining 26 weeks | 117 participants received 1 mg/day Rasagiline, 126 participants received the placebo, 198 participants entered the extension study, receiving 1 mg/day Rasagiline for the remaining 26 weeks | 52 weeks |

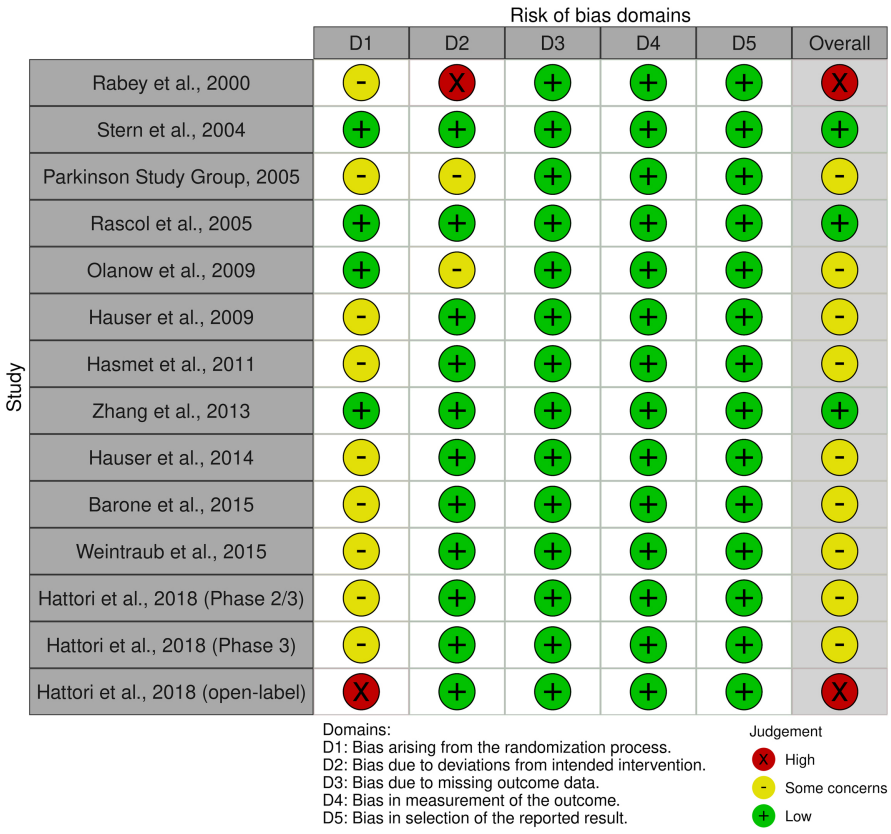



**Figure 2.** Traffic-light plot of RoB 2.

## 3.5. Study Outcomes

All included studies assessed outcomes immediately following the intervention.

In four studies [18] [19] [22] [26], UPDRS total scores were an efficacy endpoint. In two studies [29] [30], UPDRS Part I scores were an efficacy endpoint. In six studies [21] [24] [26] [28] [29] [30], UPDRS Part II and UPDRS Part III scores were efficacy endpoints. In three studies [27] [29] [30], PDQ-39 total, PDQ-39 mobility, PDQ-39 activities of daily living, PDQ-39 emotional well-being, PDQ-39 stigma, PDQ-39 social support, PDQ-39 cognition, PDQ-39 communication, and PDQ-39 bodily discomfort scores were efficacy endpoints. In three studies [21] [25] [29], OFF time was an efficacy endpoint.

## 3.6. Meta-Analysis: Motor Symptoms

### 3.6.1. UPDRS Total

Four studies [16] [18] [19] [22] (n = 1264) investigated the effect of 1 mg/day Rasagiline compared to placebo on UPDRS total scores. There was a small and statistically significant overall effect on UPDRS total scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.31; 95% CI −0.53, −0.08). There was a moderate and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 6.01, p = 0.11, $I^2$ = 52.56%; 95% PI −1.14, 0.53) (**Figure 3**). Asymmetry was observed in the funnel plot (**Appendix 2**).

### 3.6.2. UPDRS Part II

Six studies [21] [24] [26] [28] [29] [30] (n = 1484) investigated the effect of 1 mg/day Rasagiline compared to placebo on UPDRS Part II scores. There was a small and statistically significant overall effect on UPDRS Part II scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.37; 95% CI −0.52, −0.21). There was a moderate and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 9.73, p = 0.08, $I^2$ = 49.86%; 95% PI −0.79, 0.06) (**Figure 4**). Asymmetry was not observed in the funnel plot (**Appendix 3**).

### 3.6.3. UPDRS Part III

Six studies [21] [24] [26] [28] [29] [30] (n = 1484) investigated the effect of 1 mg/day Rasagiline compared to placebo on UPDRS Part III scores. There was a small and statistically significant overall effect on UPDRS Part III scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.37; 95% CI −0.47, −0.27). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 3.82, p = 0.58, $I^2$ = 0.00%; 95% PI −0.52, −0.23) (**Figure 5**). Asymmetry was not observed in the funnel plot (**Appendix 4**).

### 3.6.4. PDQ-39 Total

Three studies [27] [29] [30] (n = 624) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 total scores. There was a small and statistically significant overall effect on PDQ-39 total scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.30; 95% CI −0.46, −0.14). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.18, p = 0.56, $I^2$ = 0.00%; 95% PI −1.32, 0.72) (**Figure 6**). Asymmetry was not observed in the funnel plot (**Appendix 5**).

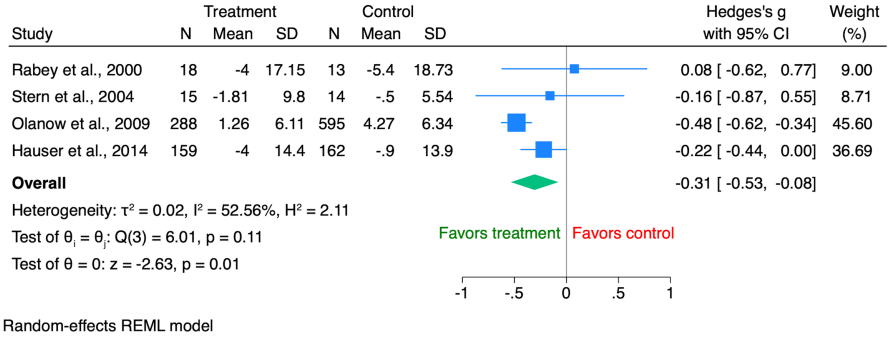



**Figure 3.** Forest plot UPDRS total scores.

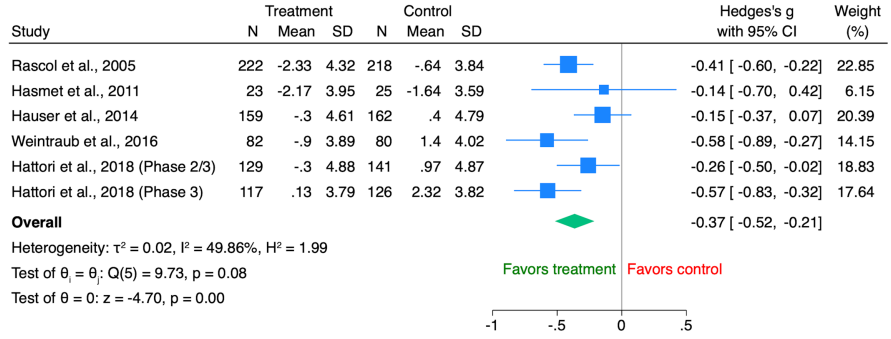



**Figure 4.** Forest plot UPDRS Part II scores.

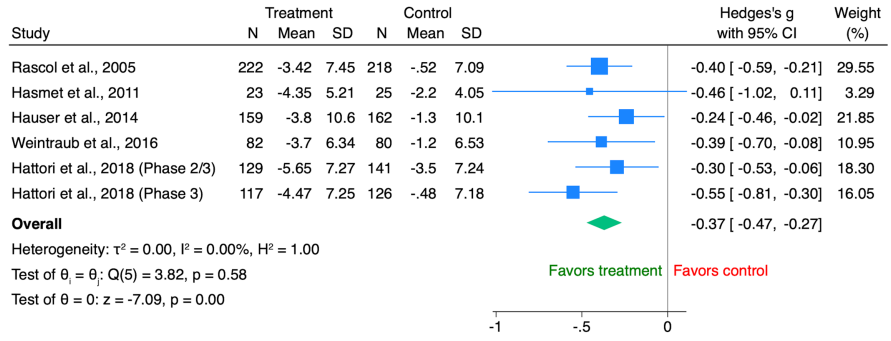



**Figure 5.** Forest plot UPDRS Part III scores.

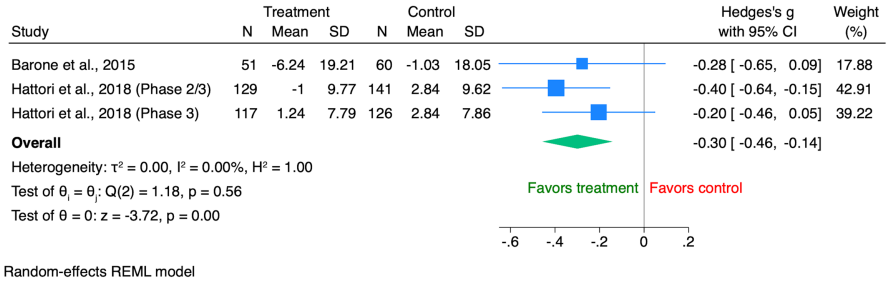



**Figure 6.** Forest plot PDQ-39 total scores.

### 3.6.5. PDQ-39 Mobility

Three studies [27] [29] [30] (n = 624) investigated the effect of 1 mg/day Rasa-

giline compared to placebo on PDQ-39 mobility scores. There was a small and statistically significant overall effect on PDQ-39 mobility scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.30; 95% CI −0.46, −0.15). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.95, p = 0.38, $I^2$ = 0.00%; 95% PI −1.33, 0.72) (**Figure 7**). Asymmetry was not observed in the funnel plot (**Appendix 6**).

#### 3.6.6. PDQ-39 Activities of Daily Living

Three studies [27] [29] [30] (n = 625) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 activities of daily living scores. There was a small and statistically significant overall effect on PDQ-39 activities of daily living scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.41; 95% CI −0.56, −0.25). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.22, p = 0.54, $I^2$ = 0.00%; 95% PI −1.43, 0.62) (**Figure 8**). Asymmetry was not observed in the funnel plot (**Appendix 7**).

#### 3.6.7. PDQ-39 Bodily Discomfort

Three studies [27] [29] [30] (n = 625) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 bodily discomfort scores. There was a trivial and statistically non-significant overall effect on PDQ-39 bodily discomfort scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.13; 95% CI −0.30, 0.04). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 2.01, p = 0.37, $I^2$ = 13.72%; 95% PI −1.45, 1.19) (**Figure 9**). Asymmetry was not observed in the funnel plot (**Appendix 8**).

#### 3.6.8. OFF Time

Three studies [21] [25] [29] (n = 954) investigated the effect of 1 mg/day Rasagiline compared to placebo on OFF time. There was a small and statistically significant overall effect on OFF time of 1 mg/day Rasagiline compared to placebo (SMD = −0.47; 95% CI −0.65, −0.28). There was a moderate and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 4.08, p = 0.13, $I^2$ = 51.08%; 95% PI −2.40, 1.47) (**Figure 10**). Asymmetry was not observed in the funnel plot (**Appendix 9**).

### 3.7. Meta-Analysis: Non-Motor Symptoms

#### 3.7.1. UPDRS Part I

Two studies [29] [30] (n = 513) investigated the effect of 1 mg/day Rasagiline compared to placebo on UPDRS Part I scores. There was a trivial and statistically non-significant overall effect on UPDRS Part I scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.15; 95% CI −0.41, 0.12). There was a moderate and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 2.31, p = 0.13, $I^2$ = 56.62%) (**Figure 11**). Due to only two studies included in the meta-analysis, the 95% prediction interval was not estimated. Asymmetry was not observed in the funnel plot (**Appendix 10**).

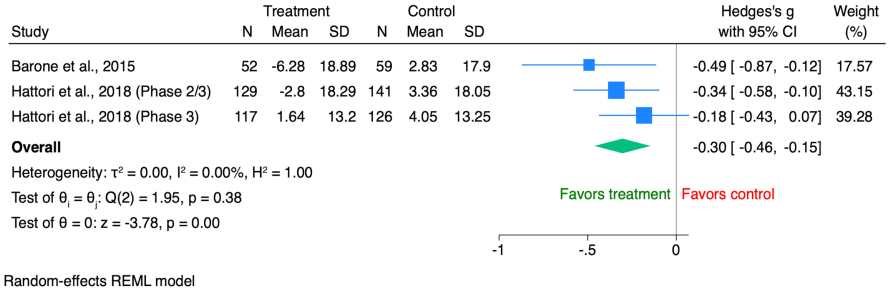



**Figure 7.** Forest plot PDQ-39 mobility scores.

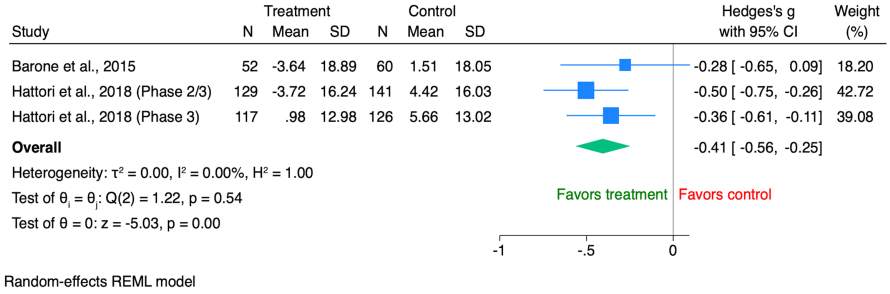



**Figure 8.** Forest plot PDQ-39 activities of daily living scores.

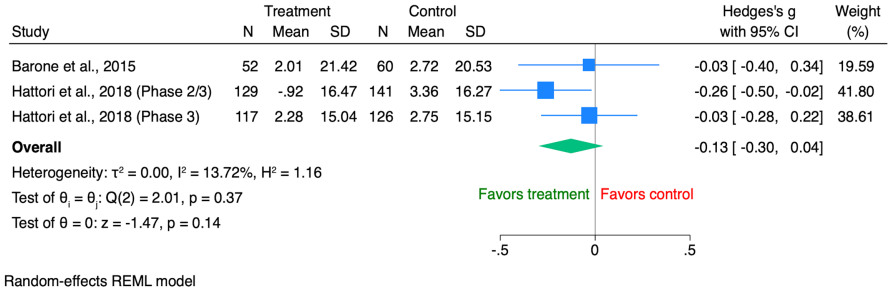



**Figure 9.** Forest plot PDQ-39 bodily discomfort scores.

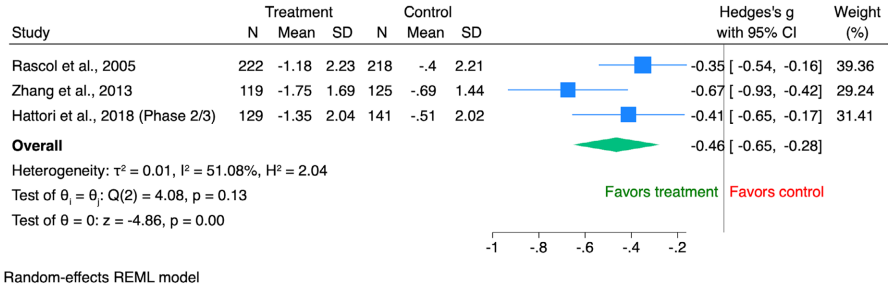



**Figure 10.** Forest plot OFF time.

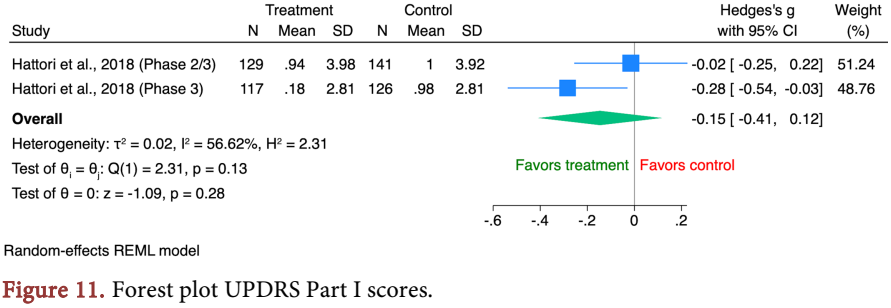



**Figure 11.** Forest plot UPDRS Part I scores.

### 3.7.2. PDQ-39 Emotional Well-Being

Three studies [27] [29] [30] (n = 625) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 emotional well-being scores. There was a small and statistically significant overall effect on PDQ-39 emotional well-being scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.27; 95% CI −0.43, −0.11). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.33, p = 0.85, $I^2$ = 0.00%; 95% PI −1.29, 0.75) (**Figure 12**). Asymmetry was not observed in the funnel plot (**Appendix 11**).

### 3.7.3. Stigma

Three studies [27] [29] [30] (n = 622) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 stigma scores. There was a trivial and statistically non-significant overall effect on PDQ-39 stigma scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.13; 95% CI −0.29, 0.02). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.23, p = 0.89, $I^2$ = 0.00%; 95% PI −1.15, 0.88) (**Figure 13**). Asymmetry was not observed in the funnel plot (**Appendix 12**).

### 3.7.4. Social Support

Three studies [27] [29] [30] (n = 623) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 social support scores. There was a trivial and statistically non-significant overall effect on PDQ-39 social support scores of 1 mg/day Rasagiline compared to placebo (SMD = -0.10; 95% CI −0.26, 0.06). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.03, p = 0.98, $I^2$ = 0.00%; 95% PI −1.12, 0.92) (**Figure 14**). Asymmetry was not observed in the funnel plot (**Appendix 13**).

### 3.7.5. Cognition

Three studies [27] [29] [30] (n = 624) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 cognition scores. There was a trivial and statistically non-significant overall effect on PDQ-39 cognition scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.11; 95% CI −0.27, 0.05). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 2.80, p = 0.25, $I^2$ = 0.00%; 95% PI −1.13, 0.91) (**Figure 15**). Asymmetry was observed in the funnel plot (**Appendix 14**).

### 3.7.6. Communication

Three studies [27] [29] [30] (n = 623) investigated the effect of 1 mg/day Rasagiline compared to placebo on PDQ-39 communication scores. There was a trivial and statistically non-significant overall effect on PDQ-39 communication scores of 1 mg/day Rasagiline compared to placebo (SMD = −0.14; 95% CI −0.29, 0.02). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.76, p = 0.68, $I^2$ = 0.00%; 95% PI −1.15, 0.88) (**Figure 16**). Asymmetry was observed in the funnel plot (**Appendix**

15).

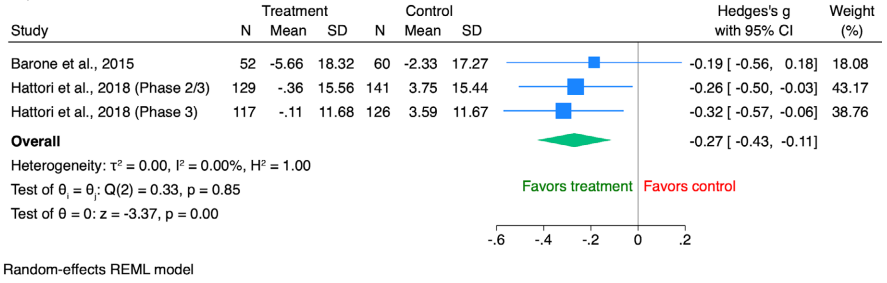



**Figure 12.** Forest plot PDQ-39 emotional well-being scores.

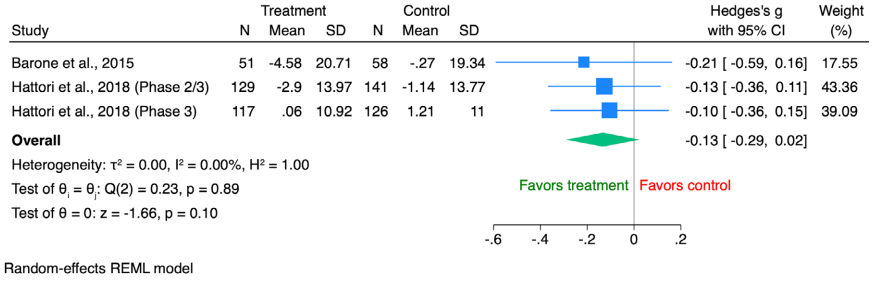



**Figure 13.** Forest plot PDQ-39 stigma scores.

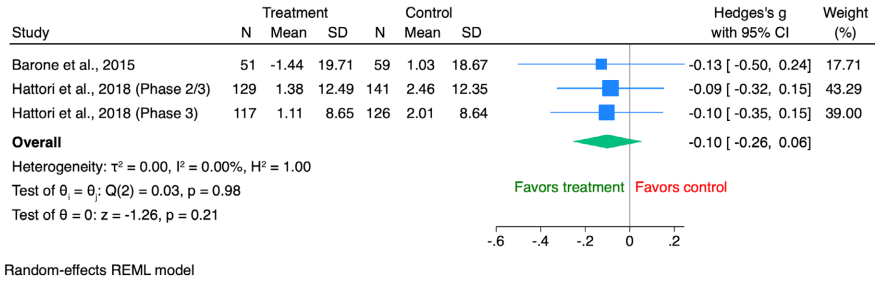



**Figure 14.** Forest plot PDQ-39 social support scores.

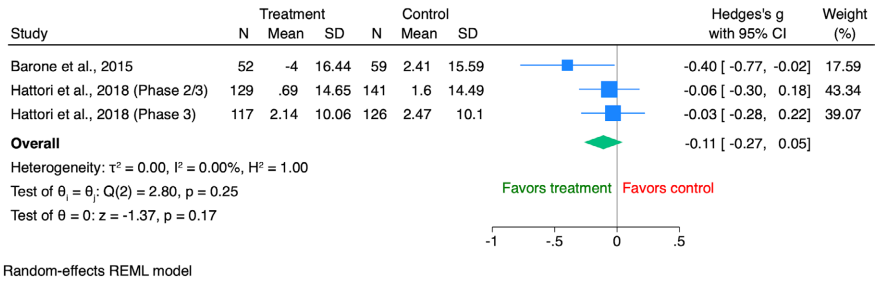



**Figure 15.** Forest plot PDQ-39 cognition scores.

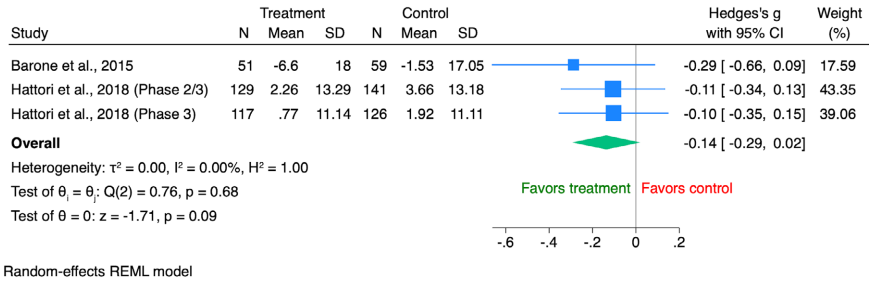


Figure 16. Forestplot PDQ-39 communication scores.

### 3.8. Overall Quality of Evidence

Using the Cochrane GRADE approach, the level of evidence was downgraded by 1 level for all meta-analyses as the overall effect size of 95% CI was deemed trivial or small (imprecision, −1). The overall quality was deemed very low to moderate for all meta-analyses (Appendix 16).

## 4. Discussion

Neuroprotection aims to slow or stop the progression of PD. Propargylamines have been shown to stop cell death associated with neurodegenerative changes in *in vitro* and *in vivo* animal studies [32] [33]. Since Rasagiline is a propargylamine, it has been suggested that it is a candidate for providing neuroprotection in PD [34]. Delayed-start study designs have provided preliminary evidence for a disease-modifying effect of Rasagiline on motor and non-motor symptoms in individuals with PD [22] [23]. To our knowledge, this is the first systematic review with meta-analysis to compare the effects of Rasagiline to placebo on motor and non-motor symptoms in individuals with PD. Our study revealed there is very low to moderate certainty of evidence that trivial to small and statistically significant improvements in motor symptoms occur in individuals with PD treated with 1 mg/day MAO-B inhibitor Rasagiline compared to placebo.

### 4.1. Motor Symptoms

Motor symptoms of PD result from changes to the neural anatomy responsible for action selection, motor sequencing, and coordination and execution of movement. These motor symptoms include tremors, rigidity, bradykinesia, gait disturbance, changes in handwriting, and others [35]. Motor symptoms become increasingly severe in individuals as PD progresses and are associated with reduced quality of life and the progression of disability in individuals with PD. The increased severity of motor symptoms is a leading reason why individuals with PD get detained in a wheelchair or a bed [36]. Although medication can control motor symptoms, individuals with the disease can develop motor fluctuations known as OFF time between their medication doses. The severity and unpredictability of OFF time are reasons for reduced quality of life in individuals with PD [37].

Consistent with our findings, Rasagiline is known to improve Parkinsonian motor symptoms in individuals with PD compared to placebo [38]. Using Rasagiline to improve motor symptoms can combat individuals' functional decline and allow for greater independence and quality of life. The effects of Rasagiline have been investigated both as monotherapy and adjunctive therapy compared to placebo, and Rasagiline has been shown to have beneficial effects in both types of therapy [7] [39].

As adjunctive therapy, Rasagiline is most often administered with oral Levo-

dopa. Although oral Levodopa monotherapy has been the gold standard medication for managing Parkinsonian motor symptoms, its short half-life is associated with increased peaks and valleys in the medication concentration in the blood. Over time, oral Levodopa treatment is associated with the development of additional motor symptoms [40], such as motor fluctuations and dyskinesia [41]. The short half-life of oral forms of Levodopa is believed to be the reason behind the pathogenesis of motor fluctuations and dyskinesia [42]. Consistent with others [21], our findings provide low to moderate certainty of evidence that the administration of Rasagiline as adjunctive therapy to oral Levodopa improves motor symptoms and may decrease motor fluctuations and dyskinesia.

### 4.2. Non-Motor Symptoms

Non-motor symptoms of PD result from the loss of neurons in the dopaminergic and non-dopaminergic pathways in the brain. These non-motor symptoms include depression, anxiety, fatigue, pain, insomnia, speech and swallowing issues, hallucinations, constipation, and hyposmia, and may have a greater effect on quality of life than motor symptoms. Non-motor symptoms are common and can precede Parkinsonian motor symptoms by up to a decade [43] [44]. Considering the range and complexity of non-motor symptoms that can present, it was not surprising that we identified mixed results for the effects of Rasagiline.

Motor symptoms of PD are directly linked to the non-motor symptoms of the disease. Both motor and non-motor symptoms result in severe negative social consequences such as stigma, dehumanization, and loneliness. This, in turn, leads to reduced quality of life in individuals with PD [45]. Consistent with others [18]-[31], our findings suggest Rasagiline can improve both motor and non-motor symptoms in individuals with PD, potentially increasing the ability of these individuals to engage in social activities and improve their quality of life.

Improving both motor and non-motor symptoms is important to improving the quality of life in individuals with PD. Non-motor symptoms become increasingly common and obvious as PD progresses. They also reduce quality of life and contribute to the development of overall disability caused by motor symptoms in individuals with PD [46] [47]. Future research is needed to investigate further the effects of Rasagiline on non-motor symptoms.

### 4.3. Rasagiline and Other Treatments

Rasagiline is often administered as adjunctive therapy to oral Levodopa to reduce the motor fluctuations caused by oral Levodopa by reducing the OFF time between oral Levodopa doses. [7] However, Rasagiline is not the only MAO-B inhibitor used in the treatment of PD. Other MAO-B inhibitors are Selegiline and Safinamide [48]. Selegiline is a first-generation irreversible MAO-B inhibitor that is associated with higher rates of adverse events due to its chemical structure that contains an amphetamine backbone. When Selegiline undergoes

first-pass metabolism in the liver, it is transformed into L-amphetamine and L-methamphetamine which can cause cardiovascular and central nervous system adverse events [49]. Rasagiline is a second-generation irreversible MAO-B inhibitor that does not have an amphetamine backbone and is associated with fewer adverse events [50]. Safinamide is an alpha-aminoamide derivative introduced into the market as a reversible MAO-B inhibitor. Safinamide has a higher MAO-B selectivity than Selegiline or Rasagiline and is linked to fewer adverse events than both Selegiline and Rasagiline [51].

### 4.4. Study Limitations

This study had several limitations. First, due to the limited number of studies included in each meta-analysis, we did not investigate the long-term effects of Rasagiline on motor and non-motor symptoms. Second, our review only included published randomized controlled trials and did not include "gray literature." Third, due to the limited number of studies, we were unable to adequately assess the potential for publication bias.

## 5. Conclusion

Based on very low to moderate certainty of evidence, 1 mg/day of Rasagiline significantly improved Parkinsonian motor symptoms. For all outcomes, the 1 mg/day Rasagiline group was favored over the placebo group. Both motor and non-motor symptoms of PD result in reduced quality of life in individuals with the disease. Our findings suggest that Rasagiline improves motor symptoms, and can potentially improve non-motor symptoms, including engagement in social activities and quality of life in individuals with PD. As adjunctive therapy in individuals treated with optimized oral Levodopa, Rasagiline may also reduce the motor fluctuations caused by oral Levodopa. Higher quality studies to investigate the effects of Rasagiline on both motor and non-motor symptoms are needed to better understand the role of neuroprotection that the medication can provide in individuals with PD.

## Ethics Approval and Consent to Participate

This is not applicable to this manuscript because this is a systematic review and meta-analysis of previously published literature and there were no interactions with human patients.

## Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

## Authors Contributions

Two researchers (PA, MW) worked independently to perform two (independent) searches using three electronic databases: PubMed, Cochrane, and EBSCO.

Both authors were involved in the writing and editing of the manuscript (PA, MW).

## Conflicts of Interest

The authors declare that they have no competing interests.

## References

[1] Ferreira, J.J., Katzenschlager, R., Bloem, B.R., *et al.* (2012) Summary of the Recommendations of the EFNS/MDS-ES Review on Therapeutic Management of Parkinson's Disease. *European Journal of Neurology*, **20**, 5-15. https://doi.org/10.1111/j.1468-1331.2012.03866.x

[2] Kalia, L.V. and Lang, A.E. (2015) Parkinson's Disease. *The Lancet*, **386**, 896-912. https://doi.org/10.1016/S0140-6736(14)61393-3

[3] Tsuboi, T., Satake, Y., Hiraga, K., *et al.* (2022) Effects of MAO-B Inhibitors on Non-Motor Symptoms and Quality of Life in Parkinson's Disease: A Systematic Review. *NPJ Parkinson's Disease*, **8**, Article No. 75. https://doi.org/10.1038/s41531-022-00339-2

[4] Chen, J., Swope, D. and Dashtipour, K. (2007) Comprehensive Review of Rasagiline, A Second-Generation Monoamine Oxidase Inhibitor, for the Treatment of Parkinson's Disease. *Clinical Therapeutics*, **29**, 1825-1849. https://doi.org/10.1016/j.clinthera.2007.09.021

[5] Riederer, P. and Laux, G. (2011) MAO-Inhibitors in Parkinson's Disease. *Experimental Neurobiology*, **20**, 1-17. https://doi.org/10.5607/en.2011.20.1.1

[6] Chang, H.Y., Li, Y.Y., Hong, C.T. and Kuan, Y.C. (2022) Efficacy of Rasagiline Monotherapy for Early Parkinson Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Psychopharmacology*, **36**, 704-714. https://doi.org/10.1177/02698811221093795

[7] Stocchi, F. and Rabey, J.M. (2011) Effect of Rasagiline as Adjunct Therapy to Levodopa on Severity of off in Parkinson's Disease. *European Journal of Neurology*, **18**, 1373-1378. https://doi.org/10.1111/j.1468-1331.2011.03512.x

[8] Page, M.J., McKenzie, J.E., Bossuyt, P.M., *et al.* (2021) The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *British Medical Journal*, **372**, n71.

[9] Scanlon, B.K., Katzen, H.L., Levin, B.E., Singer, C. and Papapetropoulos, S. (2008) A Formula for the Conversion of UPDRS-III Scores to Hoehn and Yahr Stage. *Parkinsonism & Related Disorders*, **14**, 379-380. https://doi.org/10.1016/j.parkreldis.2007.09.010

[10] University of Oxford: Parkinson's Disease Questionnaire. Oxford University Innovation. https://innovation.ox.ac.uk/outcome-measures/parkinsons-disease-questionnaire-pdq-39-pdq-8/

[11] Nayak, L. and Henchcliffe, C. (2008) Rasagiline in Treatment of Parkinson's Disease. *Neuropsychiatric Disease and Treatment*, **4**, 23-32. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515917/#:~:text=Rasagiline%20prevents%20dopamine%20metabolism%20irreversibly

[12] Clarke, C.E., Smitaa, P., Ives, N., *et al.* (2016) UK Parkinson's Disease Society Brain Bank Diagnostic Criteria.

https://www.ncbi.nlm.nih.gov/books/NBK379754/

[13] Sterne, J.A.C., Savović, J., Page, M.J., *et al.* (2019) RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials. *BMJ*, **366**, L4898. https://doi.org/10.1136/bmj.l4898

[14] Cohen, J. (1992) A Power Primer. *Psychological Bulletin*, **112**, 155-159. https://doi.org/10.1037/0033-2909.112.1.155

[15] (2019) Cochrane. 9.5.2 Identifying and Measuring Heterogeneity. https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm

[16] (2019) Cochrane. 10.4.3.1 Recommendations on Testing for Funnel Plot Asymmetry. https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm

[17] Zeng, L., Brignardello-Petersen, R., Hultcrantz, M., *et al.* (2021) GRADE Guidelines 32: GRADE Offers Guidance on Choosing Targets of GRADE Certainty of Evidence Ratings. *Journal of Clinical Epidemiology*, **137**, 163-175. https://doi.org/10.1016/j.jclinepi.2021.03.026

[18] Rabey, J.M., Sagi, I., Huberman, M., *et al.* (2000) Rasagiline Mesylate, a New Mao-B Inhibitor for the Treatment of Parkinson's Disease: A Double-Blind Study as Adjunctive Therapy to Levodopa. *Clinical Neuropharmacology*, **23**, 324-330. https://doi.org/10.1097/00002826-200011000-00005

[19] Stern, M.B., Marek, K.L., Friedman, J., *et al.* (2004) Double-Blind, Randomized, Controlled Trial of Rasagiline as Monotherapy in Early Parkinson's Disease Patients. *Movement Disorders*, **19**, 916-923. https://doi.org/10.1002/mds.20145

[20] Parkinson Study Group (2005) A Randomized Placebo-Controlled Trial of Rasagiline in Levodopa-Treated Patients with Parkinson Disease and Motor Fluctuations. *Archives of Neurology*, **62**, 241-248. https://doi.org/10.1001/archneur.62.2.241

[21] Rascol, O., Brooks, D., Melamed, E., *et al.* (2005) Rasagiline as an Adjunct to Levodopa in Patients with Parkinson's Disease and Motor Fluctuations (LARGO, Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily, Study): A Randomised, Double-Blind, Parallel-Group Trial. *The Lancet*, **365**, 947-954. https://doi.org/10.1016/S0140-6736(05)71083-7

[22] Olanow, C.W., Rascol, O., Hauser, R., *et al.* (2009) A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. *New England Journal of Medicine*, **361**, 1268-1278. https://doi.org/10.1056/NEJMoa0809335

[23] Hauser, R.A., Lew, M.F., Hurtig, H.I., Ondo, W.G., Wojcieszek, J. and Fitzer-Attas, C.J. (2009) Long-Term Outcome of Early versus Delayed Rasagiline Treatment in Early Parkinson's Disease. *Movement Disorders*, **24**, 564-573. https://doi.org/10.1002/mds.22402

[24] Hanagasi, H.A., Gurvit, H., Unsalan, P., *et al.* (2011) The Effects of Rasagiline on Cognitive Deficits in Parkinson's Disease Patients without Dementia: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *Movement Disorders: Official Journal of the Movement Disorder Society*, **26**, 1851-1858. https://doi.org/10.1002/mds.23738

[25] Zhang, L., Zhang, Z., Chen, Y., *et al.* (2013) Efficacy and Safety of Rasagiline as an Adjunct to Levodopa Treatment in Chinese Patients with Parkinson's Disease: A Randomized, Double-Blind, Parallel-Controlled, Multi-Centre Trial. *International Journal of Neuropsychopharmacology*, **16**, 1529-1537.

https://doi.org/10.1017/S1461145713000175

[26] Hauser, R.A., Silver, D., Choudhry, A., Eyal, E. and Isaacson, S. (2014) Randomized, Controlled Trial of Rasagiline as an Add-On to Dopamine Agonists in Parkinson's Disease. *Movement Disorders*, **29**, 1028-1034. https://doi.org/10.1002/mds.25877

[27] Barone, P., Santangelo, G., Morgante, L., *et al.* (2015) A Randomized Clinical Trial to Evaluate the Effects of Rasagiline on Depressive Symptoms in Non-Demented Parkinson's Disease Patients. *European Journal of Neurology*, **22**, 1184-1191. https://doi.org/10.1111/ene.12724

[28] Weintraub, D., Hauser, R.A., Elm, J.J., *et al.* (2016) Rasagiline for Mild Cognitive Impairment in Parkinson's Disease: A Placebo-Controlled Trial. *Movement Disorders: Official Journal of the Movement Disorder Society*, **31**, 709-714. https://doi.org/10.1002/mds.26617

[29] Hattori, N., Takeda, A., Takeda, S., *et al.* (2018) Efficacy and Safety of Adjunctive Rasagiline in Japanese Parkinson's Disease Patients with Wearing-Off Phenomena: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *Parkinsonism & Related Disorders*, **53**, 21-27. https://doi.org/10.1016/j.parkreldis.2018.04.025

[30] Hattori, N., Takeda, A., Takeda, S., *et al.* (2019) Rasagiline Monotherapy in Early Parkinson's Disease: A Phase 3, Randomized Study in Japan. *Parkinsonism & Related Disorders*, **60**, 146-152. https://doi.org/10.1016/j.parkreldis.2018.08.024

[31] Hattori, N., Takeda, A., Takeda, S., *et al.* (2019) Long-Term, Open-Label, Phase 3 Study of Rasagiline in Japanese Patients with Early Parkinson's Disease. *Journal of Neural Transmission*, **126**, 299-308. https://doi.org/10.1007/s00702-018-1964-3

[32] Yi, H., Maruyama, W., Akao, Y., *et al.* (2006) N-Propargylamine Protects SH-SY5Y Cells from Apoptosis Induced by an Endogenous Neurotoxin, N-Methyl(R)Salsolinol, through Stabilization of Mitochondrial Membrane and Induction of Anti-Apoptotic Bcl-2. *Journal of Neural Transmission*, **113**, 21-32. https://doi.org/10.1007/s00702-005-0299-z

[33] Olanow, C.W. (2006) Rationale for Considering That Propargylamines Might Be Neuroprotective in Parkinson's Disease. *Neurology*, **66**, S69-S79. https://doi.org/10.1212/WNL.66.10_suppl_4.S69

[34] Weinreb, O., Amit, T., Bar-Am, O., Chillag-Talmor, O. and Youdim, M.B.H. (2005) Novel Neuroprotective Mechanism of Action of Rasagiline Is Associated with Its Propargyl Moiety: Interaction of Bcl-2 Family Members with PKC Pathway. *Annals of the New York Academy of Sciences*, **1053**, 348-355. https://doi.org/10.1111/j.1749-6632.2005.tb00043.x

[35] Moustafa, A.A., Chakravarthy, S., Phillips, J.R., *et al.* (2016) Motor Symptoms in Parkinson's Disease: A Unified Framework. *Neuroscience & Biobehavioral Reviews*, **68**, 727-740. https://doi.org/10.1016/j.neubiorev.2016.07.010

[36] Bock, M.A., Brown, E.G., Zhang, L. and Tanner, C. (2022) Association of Motor and Nonmotor Symptoms with Health-Related Quality of Life in a Large Online Cohort of People with Parkinson Disease. *Neurology*, **98**, e2194-e2203. https://doi.org/10.1212/WNL.0000000000200113

[37] Mantri, S., Lepore, M., Edison, B., *et al.* (2021) The Experience of OFF Periods in Parkinson's Disease: Descriptions, Triggers, and Alleviating Factors. *Journal of Patient-Centered Research and Reviews*, **8**, 232-238. https://doi.org/10.17294/2330-0698.1836

[38] Pistacchi, M., Martinello, F., Gioulis, M. and Zambito Marsala, S. (2013) Rasagiline and Rapid Symptomatic Motor Effect in Parkinson's Disease: Review of Literature.

*Neurology and Therapy*, **3**, 41-66. https://doi.org/10.1007/s40120-013-0014-1

[39] Siddiqui, M.A.A. and Plosker, G.L. (2005) Rasagiline. *Drugs & Aging*, **22**, 83-91. https://doi.org/10.2165/00002512-200522010-00006

[40] Poewe, W., Antonini, A., Zijlmans, J.C., Burkhard, P.R. and Vingerhoets, F. (2010) Levodopa in the Treatment of Parkinson's Disease: An Old Drug Still Going Strong. *Clinical Interventions in Aging*, **5**, 229-238. https://doi.org/10.2147/CIA.S6456

[41] Freitas, M.E., Hess, C.W. and Fox, S.H. (2017) Motor Complications of Dopaminergic Medications in Parkinson's Disease. *Seminars in Neurology*, **37**, 147-157. https://doi.org/10.1055/s-0037-1602423

[42] Olanow, C.W., Agid, Y., Mizuno, Y., *et al.* (2004) Levodopa in the Treatment of Parkinson's Disease: Current Controversies. *Movement Disorders*, **19**, 997-1005. https://doi.org/10.1002/mds.20243

[43] Todorova, A., Jenner, P. and Ray Chaudhuri, K. (2014) Non-Motor Parkinson's: Integral to Motor Parkinson's, yet often Neglected. *Practical Neurology*, **14**, 310-322. https://doi.org/10.1136/practneurol-2013-000741

[44] Parkinson, J. (2002) An Essay on the Shaking Palsy. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **14**, 223-236. https://doi.org/10.1176/jnp.14.2.223

[45] Prenger, M.T.M., Madray, R., Van Hedger, K., Anello, M. and MacDonald, P.A. (2020) Social Symptoms of Parkinson's Disease. *Parkinson's Disease*, **2020**, Article ID: 8846544. https://doi.org/10.1155/2020/8846544

[46] Reichmann, H., Klasser, M., Apfel, R. and Fendji, D. (2015) Efficacy and Tolerability of Rasagiline in Daily Clinical Use—A Post Marketing Observational Study in Patients with Parkinson's Disease Focusing on Non-Motor Symptoms and QoL. *Basal Ganglia*, **5**, 101-106. https://doi.org/10.1016/j.baga.2015.09.003

[47] Poewe, W. (2008) Non-Motor Symptoms in Parkinson's Disease. *European Journal of Neurology*, **15**, 14-20. https://doi.org/10.1111/j.1468-1331.2008.02056.x

[48] Asano, H., Tian, Y.S., Hatabu, A., Takagi, T., Ueda, M. and Ikeda, K. (2023) Safety Comparisons among Monoamine Oxidase Inhibitors against Parkinson's Disease Using FDA Adverse Event Reporting System. *Scientific Reports*, **13**, Article No. 19272. https://doi.org/10.1038/s41598-023-44142-2

[49] Tábi, T., Vécsei, L., Youdim, M.B., Riederer, P. and Szökő, É. (2019) Selegiline: A Molecule with Innovative Potential. *Journal of Neural Transmission*, **127**, 831-842. https://doi.org/10.1007/s00702-019-02082-0

[50] Müller, T., Hoffmann, J.A., Dimpfel, W. and Oehlwein, C. (2012) Switch from Selegiline to Rasagiline Is Beneficial in Patients with Parkinson's Disease. *Journal of Neural Transmission*, **120**, 761-765. https://doi.org/10.1007/s00702-012-0927-3

[51] Kulisevsky, J. (2015) Emerging Role of Safinamide in Parkinson's Disease Therapy. *European Neurological Review*, **9**, 108-112. https://doi.org/10.17925/ENR.2014.09.02.108

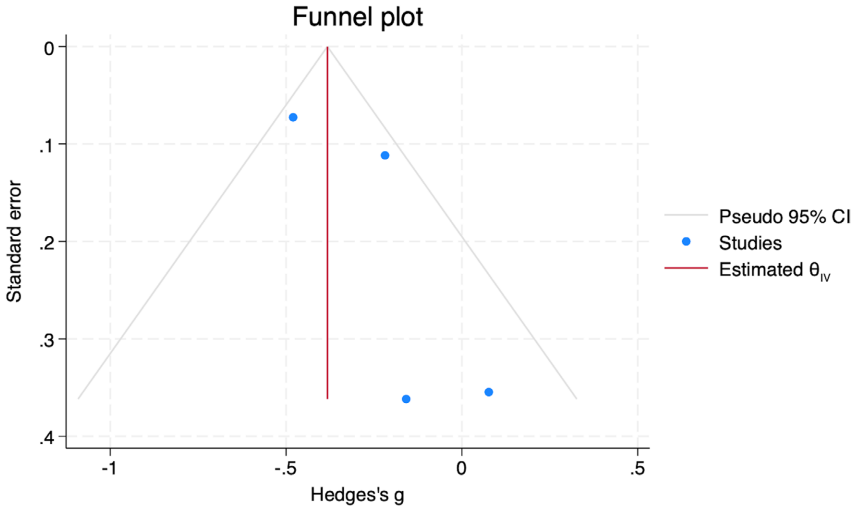
## Appendix 1: Search Terms

The search terms for the PubMed database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Rasagiline") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "balance" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "cognitive impairment" OR "cognitive problems" OR "cognitive changes" OR "depression" OR "anxiety" OR "UPDRS" OR "PDQ-39" OR "OFF time"). Filters: English, Exclude preprints.

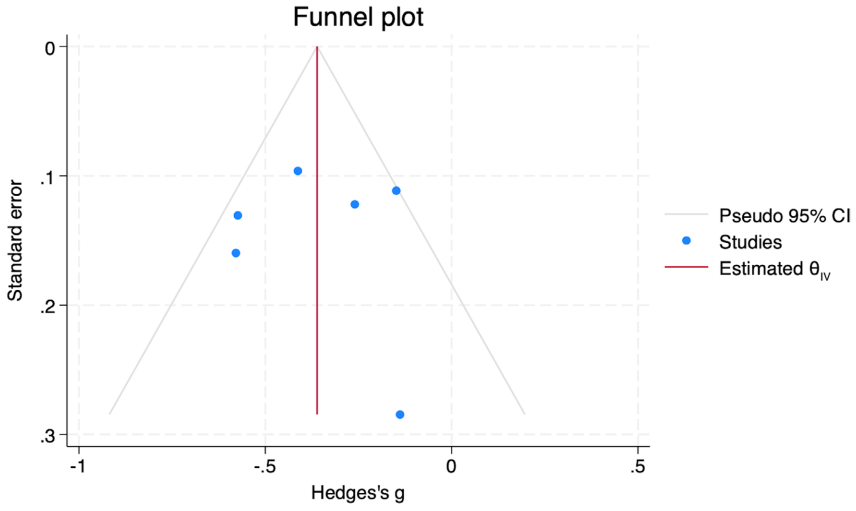
The search terms for the Cochrane database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Rasagiline") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "balance" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "cognitive impairment" OR "cognitive problems" OR "cognitive changes" OR "depression" OR "anxiety" OR "UPDRS" OR "PDQ-39" OR "OFF time"). Filters: English.

The search terms for the EBSCO database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Rasagiline") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "balance" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "cognitive impairment" OR "cognitive problems" OR "cognitive changes" OR "depression" OR "anxiety" OR "UPDRS" OR "PDQ-39" OR "OFF time"). Filters: Search mode "find any of my search terms", English.

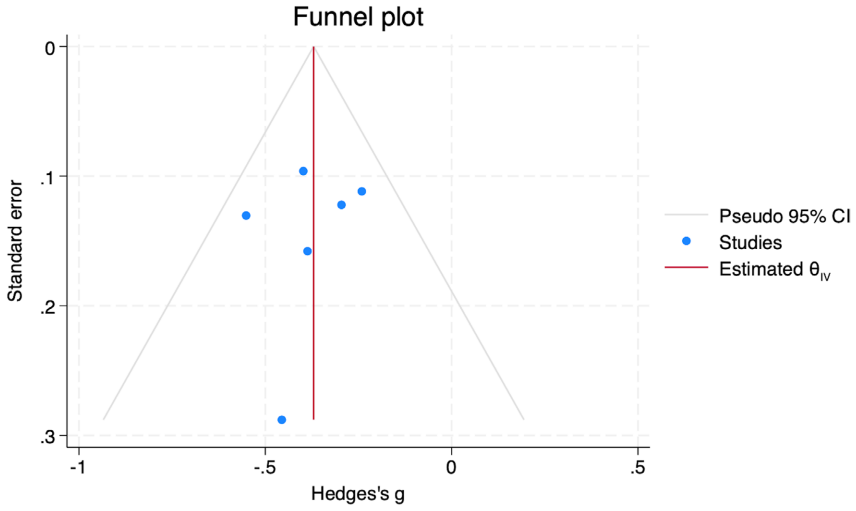
## Appendix 2: Funnel Plot UPDRS Total Scores



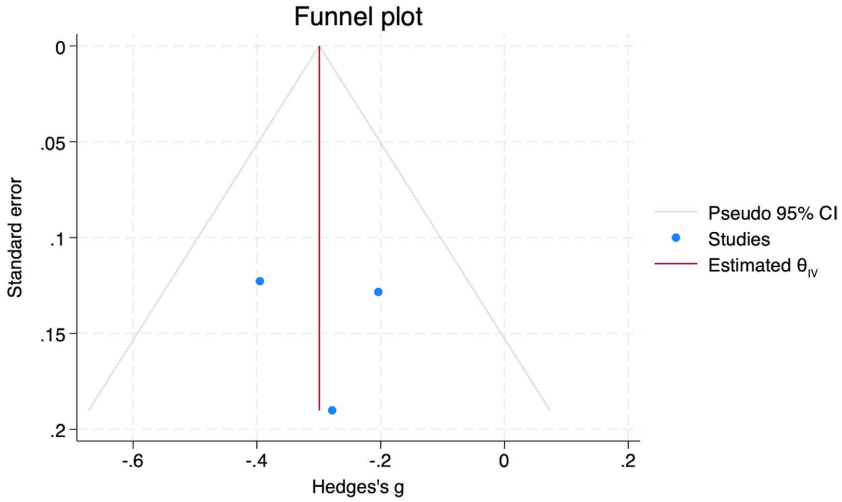

## Appendix 3: Funnel Plot UPDRS Part II Scores



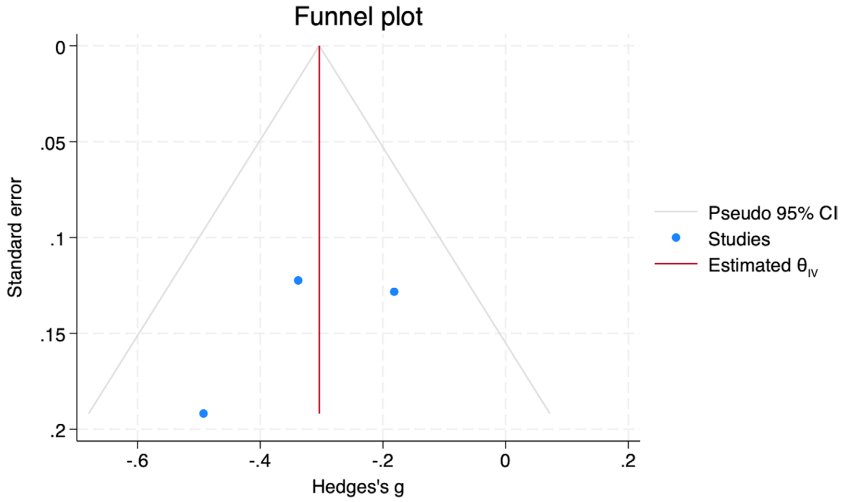

## Appendix 4: Funnel Plot UPDRS Part III Scores



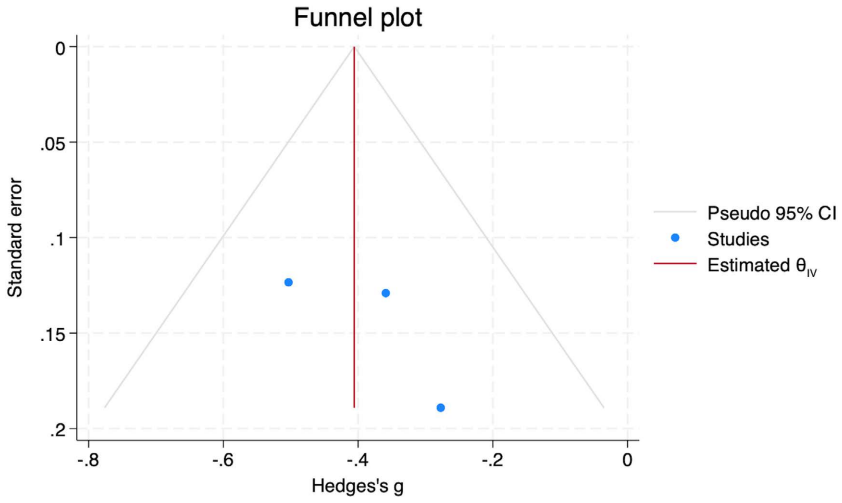
## Appendix 5: Funnel Plot PDQ-39 Total Scores



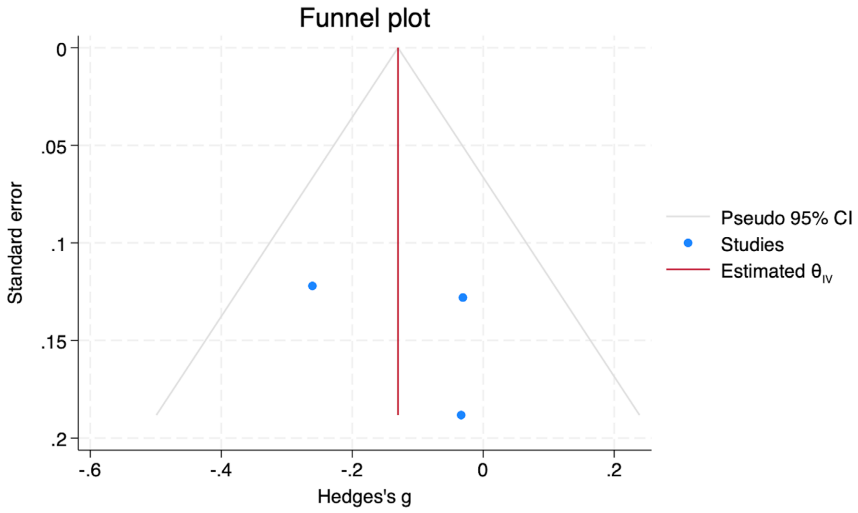

## Appendix 6: Funnel Plot PDQ-39 Mobility Scores



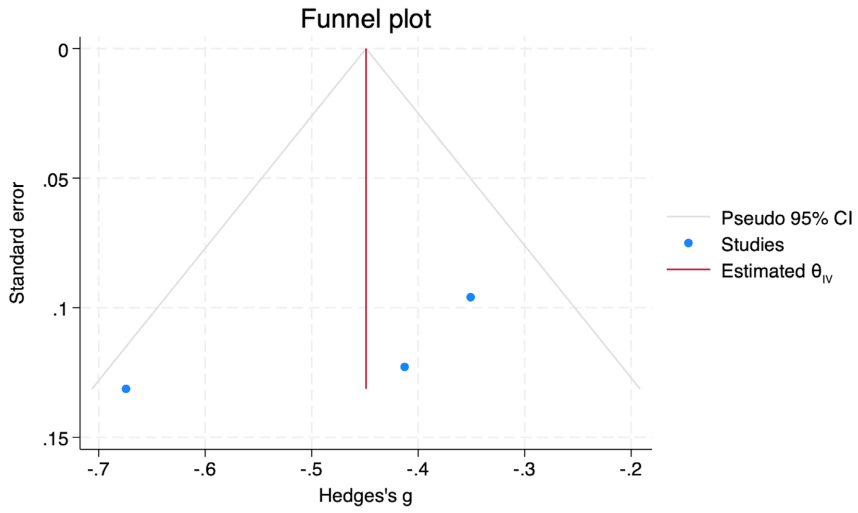

## Appendix 7: Funnel Plot PDQ-39 Activities of Daily Living scores



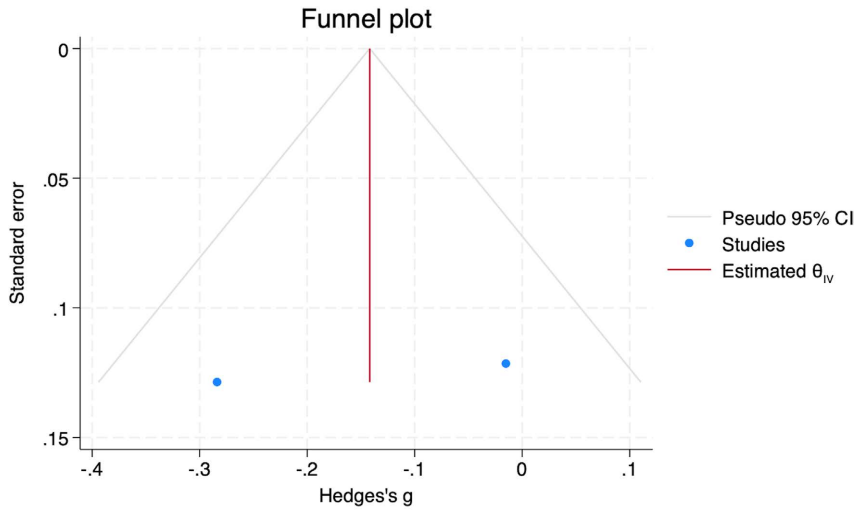
## Appendix 8: Funnel Plot PDQ-39 Bodily Discomfort Scores



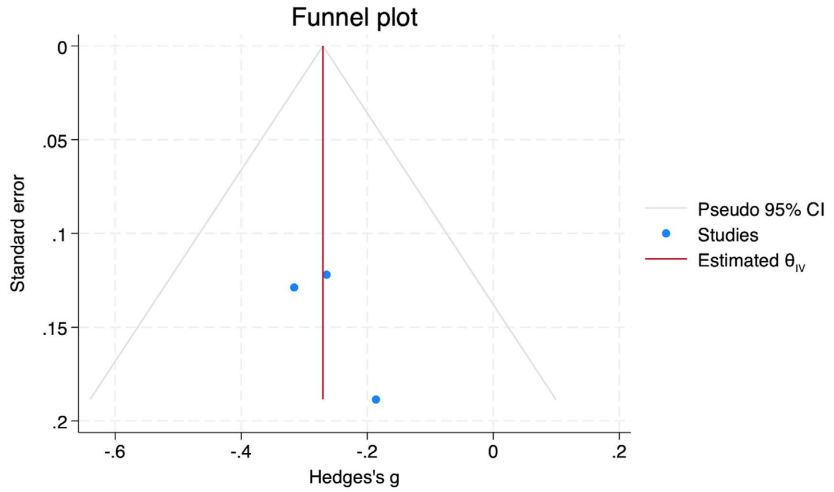

## Appendix 9: Funnel Plot OFF Time



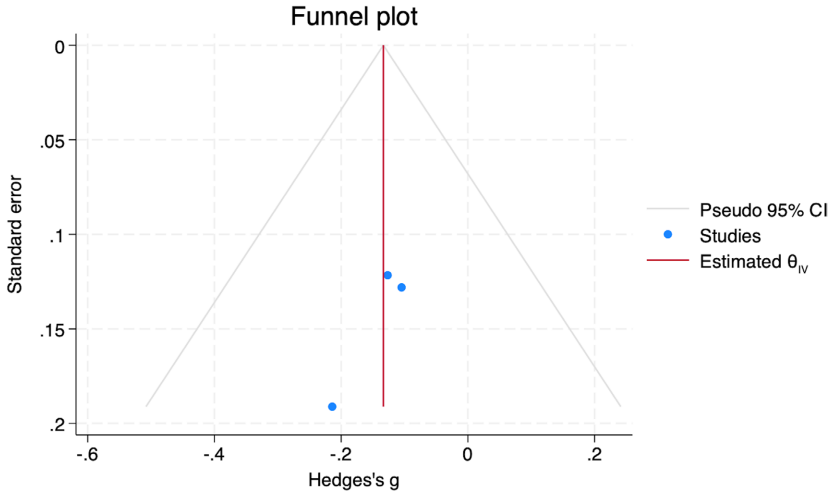

## Appendix 10: Funnel Plot UPDRS Part I Scores



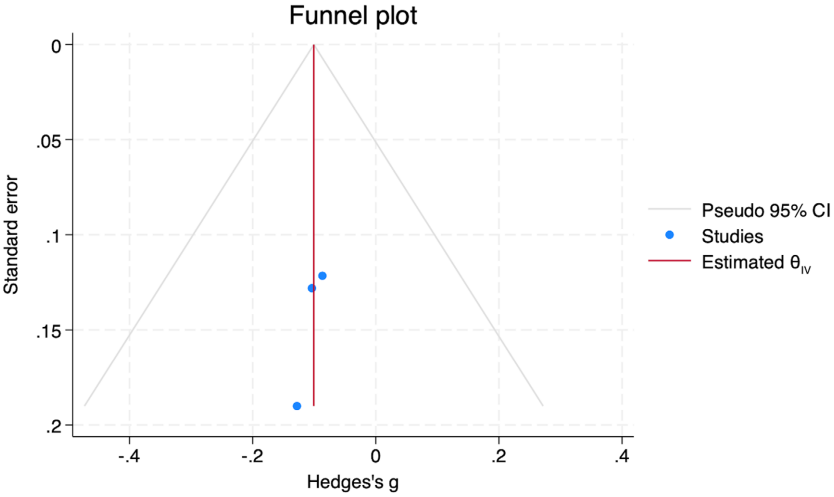
## Appendix 11: Funnel Plot PDQ-39 Emotional Well-Being Scores



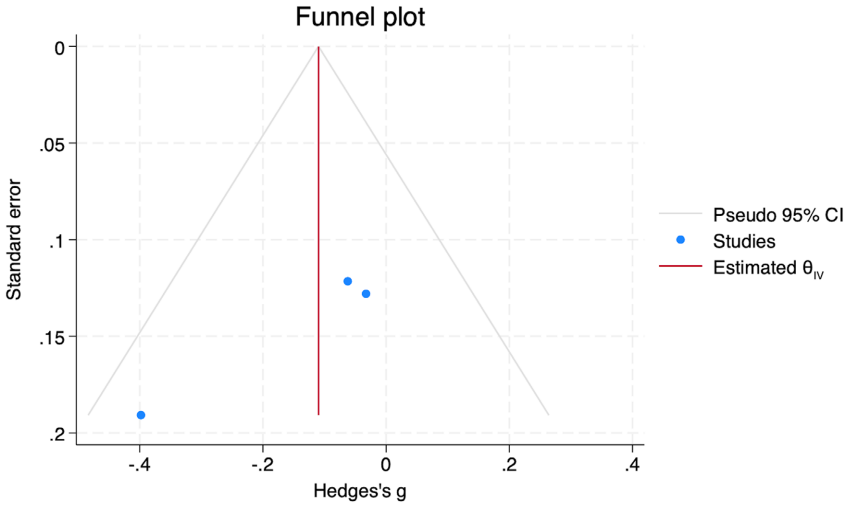

## Appendix 12: Funnel Plot PDQ-39 Stigma Scores



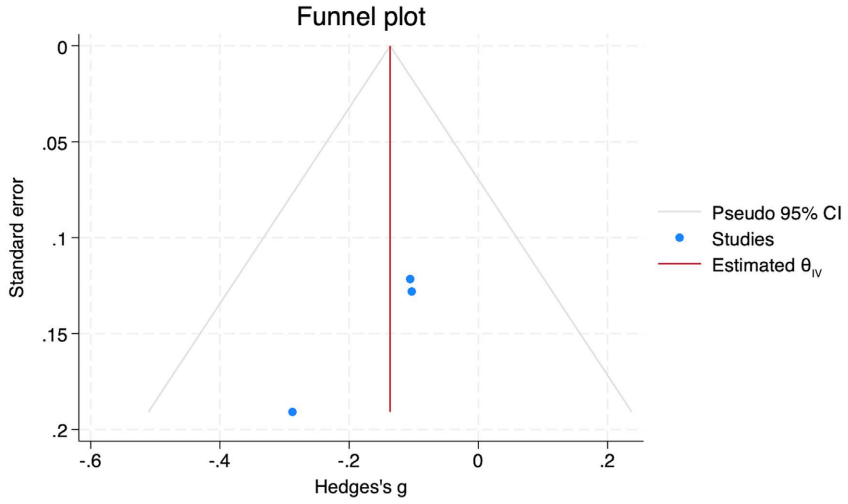

## Appendix 13: Funnel Plot PDQ-39 Social Support Scores



## Appendix 14: Funnel Plot PDQ-39 Cognition Scores




## Appendix 15: Funnel Plot PDQ-39 Communication Scores



## Appendix 16: GRADE Approach for Motor and Non-Motor Symptom Outcomes

**Question:** Rasagiline compared to placebo for Parkinson's Disease

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rasagiline | placebo | Relative (95% CI) | Absolute (95% CI) | |
| UPDRS Total (assessed with: SMD) | | | | | | | | | | | |
| 4 | randomised trials | serious | not serious | not serious | serious | publication bias strongly suspected | 480 | 784 | - | SMD 0.306 SD lower (0.534 lower to 0.078 lower) | ⊕◯◯◯ Very low |
| UPDRS Part I (assessed with: SMD) | | | | | | | | | | | |
| 2 | randomised trials | very serious | not serious | very serious | very serious | none | 246 | 267 | - | SMD 0.146 SD lower (0.409 lower to 0.117 higher) | ⊕◯◯◯ Very low |
| UPDRS Part II (assessed with: SMD) | | | | | | | | | | | |
| 6 | randomised trials | serious | not serious | not serious | not serious | none | 732 | 752 | - | SMD 0.365 SD lower (0.517 lower to 0.213 lower) | ⊕⊕⊕◯ Moderate |
| UPDRS Part III (assessed with: SMD) | | | | | | | | | | | |
| 6 | randomised trials | serious | not serious | not serious | not serious | none | 732 | 752 | - | SMD 0.37 SD lower (0.515 lower to 0.225 lower) | ⊕⊕⊕◯ Moderate |
| PDQ-39 Total (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | not serious | none | 297 | 327 | - | SMD 0.299 SD lower (0.457 lower to 0.142 lower) | ⊕⊕◯◯ Low |
| PDQ-39 Mobility (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | not serious | none | 298 | 326 | - | SMD 0.304 SD lower (0.461 lower to 0.146 lower) | ⊕⊕◯◯ Low |
| PDQ-39 Activities of Daily Living (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | not serious | none | 298 | 327 | - | SMD 0.406 SD lower (0.564 lower to 0.248 lower) | ⊕⊕◯◯ Low |
| PDQ-39 Emotional Well-Being (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | not serious | none | 298 | 327 | - | SMD 0.27 SD lower (0.427 lower to 0.113 lower) | ⊕⊕◯◯ Low |
| PDQ-39 Stigma (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | serious | none | 297 | 325 | - | SMD 0.133 SD lower (0.29 lower to 0.024 higher) | ⊕◯◯◯ Very low |
| PDQ-39 Social Support (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | serious | none | 297 | 326 | - | SMD 0.101 SD lower (0.257 lower to 0.056 higher) | ⊕◯◯◯ Very low |
| PDQ-39 Cognition (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | serious | publication bias strongly suspected | 298 | 326 | - | SMD 0.11 SD lower (0.267 lower to 0.047 higher) | ⊕◯◯◯ Very low |
| PDQ-39 Communication (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | not serious | serious | serious | publication bias strongly suspected | 297 | 326 | - | SMD 0.137 SD lower (0.293 lower to 0.02 higher) | ⊕◯◯◯ Very low |

**Continued**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PDQ-39 Bodily Discomfort (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | serious | serious | serious | serious | none | 298 | 327 | - | SMD 0.128 SD lower (0.298 lower to 0.043 higher) | ⊕◯◯◯ Very low |
| OFF Time (assessed with: SMD) | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | serious | none | 470 | 484 | - | SMD 0.465 SD lower (0.652 lower to 0.277 lower) | ⊕⊕⊕◯ Moderate |

**CI:** Confidence interval; **SMD:** Standardised mean difference.