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SYSTEMATIC REVIEW AND META-ANALYSIS

Safety and Efficacy of SSRIs in Improving Poststroke Recovery: A Systematic Review and Meta-Analysis

Heba M. Kalbouneh, PhD*; Ahmad A. Toubasi, MD*; Farah H. Albustanji, MD; Yazan Y. Obaid, MD; Layla M. Al-Harasis, MD

BACKGROUND: Several studies investigated the role of selective serotonin reuptake inhibitors (SSRIs) in improving poststroke recovery; thus, we have decided to conduct this systematic review and meta-analysis to investigate the efficacy and safety of SSRIs in poststroke recovery.

METHODS AND RESULTS: In this meta-analysis we searched the following databases: PubMed, Cochrane, Scopus, and Google Scholar. The studies were included if they were placebo-controlled trials in design and reported SSRIs' effects on poststroke depression, anxiety, disability, dependence, motor abilities, and cognitive functions. The quality of the included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials. The search yielded 44 articles that included 16 164 patients, and about half of the participants were treated with SSRIs. Our results showed that SSRIs had a significant effect on preventing depression (weighted mean difference [WMD], −7.05 [95% CI, −11.78 to −2.31]), treating depression according to the Hamilton Rating Scale for Depression score (WMD, −1.45 [95% CI, −2.77 to −0.14]), anxiety (relative risk, 0.23 [95% CI, 0.09–0.61]), dependence (WMD, 8.86 [95% CI, 1.23–16.48]), motor abilities according to National Institutes of Health Stroke Scale score (WMD, −0.79 [95% CI, −1.42 to −0.15]), and cognitive functions (WMD, 1.00 [95% CI, 0.12–1.89]). On the other hand, no significant effect of SSRIs on disability was observed. Additionally, we found that treating with SSRIs increased the risk of seizures (relative risk, 1.44 [95% CI, 1.13–1.83]), whereas there was no difference in the incidence of gastrointestinal symptoms or bleeding between SSRIs and a placebo.

CONCLUSIONS: Our study showed that SSRIs are effective in preventing and treating depression, and improving anxiety, motor function, cognitive function, and dependence in patients after stroke. These benefits were only reproducible with the citalopram subanalysis but not fluoxetine. Further well-conducted placebo-controlled trials are needed to investigate the safety and efficacy of citalopram among patients after stroke.

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Key Words: human ■ recovery ■ selective serotonin reuptake inhibitors ■ stroke

Every year, about 13.7 million individuals are affected by stroke globally,[1] and about half of the stroke survivors are suffering from disability.[2] Two meta-analyses estimated that the prevalence of poststroke depression among stroke survivors was 30%.[3,4] Moreover, these poststroke sequelae were associated with a higher risk for subsequent stroke mortality.[5] Despite the fact that considerable advances have been made in treating the acute form of stroke, there is a constant need to find new and improved methods of treatment. Specifically, those treatments revolve around the long-term recovery aspect of stroke regardless of eligibility for acute treatments.[6] Many interventions that involve monoaminergic drugs, including

Correspondence to: Ahmad A. Toubasi, MD, University of Jordan, Amman 11942, Jordan. Email: tubasi_ahmad@yahoo.com

*H. M. Kalbouneh and A. A. Toubasi contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- Our study is the first systematic review and meta-analysis to show that selective serotonin reuptake inhibitors are effective in improving poststroke recovery.
- Our study showed that selective serotonin reuptake inhibitors are effective in preventing and treating depression, and improving anxiety, motor function, cognitive function, and dependence in patients after stroke.
- Our positive findings on selective serotonin reuptake inhibitors were mainly driven by citalopram and not fluoxetine.

What Are the Clinical Implications?

- Further well-conducted placebo-controlled trials are needed to investigate the safety and efficacy of citalopram among patients after stroke.

Nonstandard Abbreviations and Acronyms

NIHSS	National Institutes of Health Stroke Scale
WMD	weighted mean difference

selective serotonin reuptake inhibitors (SSRIs), were shown to improve the neurological deficit and disability of patients with stroke.[7–9]

Several studies evaluated the role of SSRIs in several aspects of stroke recovery. However, the results of these studies were contradictory, with some studies concluding that SSRIs improved poststroke recovery, whereas others indicated that SSRIs did not provide any benefits for patients with stroke. Moreover, 2 Cochrane systematic reviews in 2012 and 2018 showed that SSRIs failed to improve poststroke recovery.[10,11] However, these reviews highlighted that the included studies had several limitations and heterogeneity. In response to this conclusion, an international collaboration developed a core protocol for 3 trials of fluoxetine for recovery after stroke.[12,13] The aforementioned Cochrane reviews, conducted before the development of this protocol, did not evaluate the role of SSRIs in treating mental disorders among patients with stroke and did not investigate the efficacy of each drug in the SSRIs family solely. Additionally, several trials were completed since the last Cochrane review in 2018. This necessitates a more updated systematic review and meta-analysis that accounts for the mentioned issues; hence, we decided to conduct this study to evaluate the role of SSRIs in poststroke recovery.

METHODS

Registration

The data that support the findings of this study are available from the corresponding author upon reasonable request. In this meta-analysis, we followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* guidelines. This study was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42021285766). The institutional review board at our institution approved the conductance of this research.

Search Strategy

The search was conducted on October 20, 2021 and November 20, 2021 by A.A.T. and F.H.A. independently, using the following databases; PubMed, Cochrane, Google Scholar, and Scopus. The following keywords, selective serotonin reuptake inhibitors AND stroke, and their related Medical Subject Headings terms were used. Afterward, the search results were cross-matched, and any discrepancies were resolved by discussion. The search results, after cross-matching, were imported to Rayyan (www.rayyan.ai), and duplicates were removed.

Selection Process

The inclusion criteria of selecting the studies were if they were placebo-controlled trials in design and reported SSRIs' effects on poststroke depression, anxiety, disability, dependence, motor abilities, and cognitive functions. Any studies that did not meet these criteria were excluded from our analysis. The exposure of interest was using SSRIs among stroke patients, and the outcomes of interest were poststroke depression, anxiety, disability, dependence, motor abilities, and cognitive functions as well as side effects of using SSRIs. Depression was measured using the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory, and Patient Health Questionnaire 9, whereas anxiety was measured using the Hamilton Anxiety Scale. Cognitive function was assessed by the Montreal Cognitive Assessment and the Mini-Mental State Examination (MMSE), whereas motor functions were measured using the National Institutes of Health Stroke Scale (NIHSS) and Fugl-Meyer Assessment of Motor Recovery. Additionally, dependence was measured using the Functional Independence Measure Score and Barthel Index, whereas disability was measured by modified Rankin Scale score. Any study that used tools different from the aforementioned scales were included in the systematic review but not in the meta-analysis to prevent large heterogeneity in the analysis. The following SSRIs side effects were assessed: gastrointestinal symptoms including abdominal pain, nausea, vomiting

and diarrhea, seizures, and bleeding. These side effects were chosen because seizures and bleeding can result in risks that outweigh any benefit from using SSRIs among stroke patients.[10] Also, the gastrointestinal side effects were selected because of their high frequency and their significant association with noncompliance.[14] Additionally, all the mentioned outcomes were assessed as binary variables and continuous variables. The study selection was done by A.A.T. and F.H.A. independently, and any discrepancies were resolved by discussion.

Data Extraction and Quality Assessment

The variables of interest were extracted by A.A.T. and F.H.A. independently, then checked by Y.Y.O. and L.M.A.-H., and any discrepancies were resolved by discussion. After the data were extracted, the quality of the included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials, which was also done by A.A.T. and F.H.A. independently, then checked by Y.Y.O. and L.M.A.-H, and any differences in the scoring were resolved by discussion.

Statistical Analysis

After the data were extracted, the relative risk (RR) and its corresponding 95% CI were calculated for binary outcomes using the Altman equation, and if any 0 had been encountered in the outcomes, 0.5 was added to all cells.[15] The RR and its 95% CI were used as the effect size for the binary outcomes. For continuous outcomes, the mean and standard deviation were used as the measure of effect in the data analysis. Whenever median and interquartile range were encountered in the extracted data, they were converted to mean and standard deviation using the method described by Hozo et al.[16] Finally, the mean and standard deviation for the continuous outcomes were used to measure the differences in the outcomes between the intervention groups using the weighted mean difference (WMD) and its related CI. The analysis was done by creating a model for each outcome by pooling the studies that assessed the same outcome using the same measurement tool. The studies were pooled using the random-effects model when I^2 was >50%, whereas they were pooled using the fixed-effects model when I^2 was ≤50%. We used the Cochran Q heterogeneity test and I^2 statistic to assess statistical heterogeneity. Meta XL version 5.3 (EpiGear International, Queensland, Australia) was used in the data analysis.

RESULTS

Search Results

Our search yielded 1629 articles, and of them 350 were duplicates. The remaining 1279 articles were screened using the title and abstract, of which 1047 articles were excluded for having a nonexperimental design, using a different intervention, or assessing a different population. The 232 remaining articles were tested against the inclusion criteria using the full-text form. Of them, 188 articles were excluded because they were non–placebo-controlled trials or no data about the outcomes of interest, including studies, investigated the effect of SSRIs on pathological crying, muscle strength measurements, visual improvements, and brain activity using imaging such as functional magnetic resonance imaging. Finally, 44 articles were included in the quantitative and qualitative data synthesis. The detailed study selection process is described in Figure 1.

General Characteristics

The total number of the included patients was 16 164 patients from 44 studies.[17–60] Of them, 50.5% were treated using SSRIs (8137/16 164), whereas 49.5% were treated using a placebo (8027/16 164). The majority of the studies were conducted in Asia and Europe. The most common comorbidities included in the studies were diabetes and hypertension; 50.0% and 43.2%, respectively, of the included articles included patients with these comorbidities. Furthermore, the most common outcome assessed by the included studies was the efficacy of SSRIs in treating depression; 47.7% of the included articles evaluated this outcome. This was followed by dependence and disability; 38.6% of the included studies evaluated each of these outcomes. Depression and anxiety were most commonly assessed using the HAM-D and Hamilton Anxiety Scale, respectively. In addition, the majority of the studies used the MMSE, NIHSS, and Barthel Index in assessing cognitive deficit, motor function, and dependence, respectively. Most of the studies assessed disability as a binary variable. Moreover, 58.8% of the included studies evaluated the efficacy of fluoxetine, whereas 38.6% of them evaluated citalopram. The summary of the characteristics of the included studies are described in the Table.

Quality Assessment of the Included Studies

The revised Cochrane risk-of-bias tool for randomized trials quality assessment of the included studies[17–60] showed that 59.1% of the included studies had low risk of bias. On the other hand, 38.6% and 2.3% of the included studies had moderate and high risk of bias, respectively (Figure S1). The detailed revised Cochrane risk-of-bias tool for randomized trials quality assessment of the included studies[17–60] is illustrated in Figure S2.

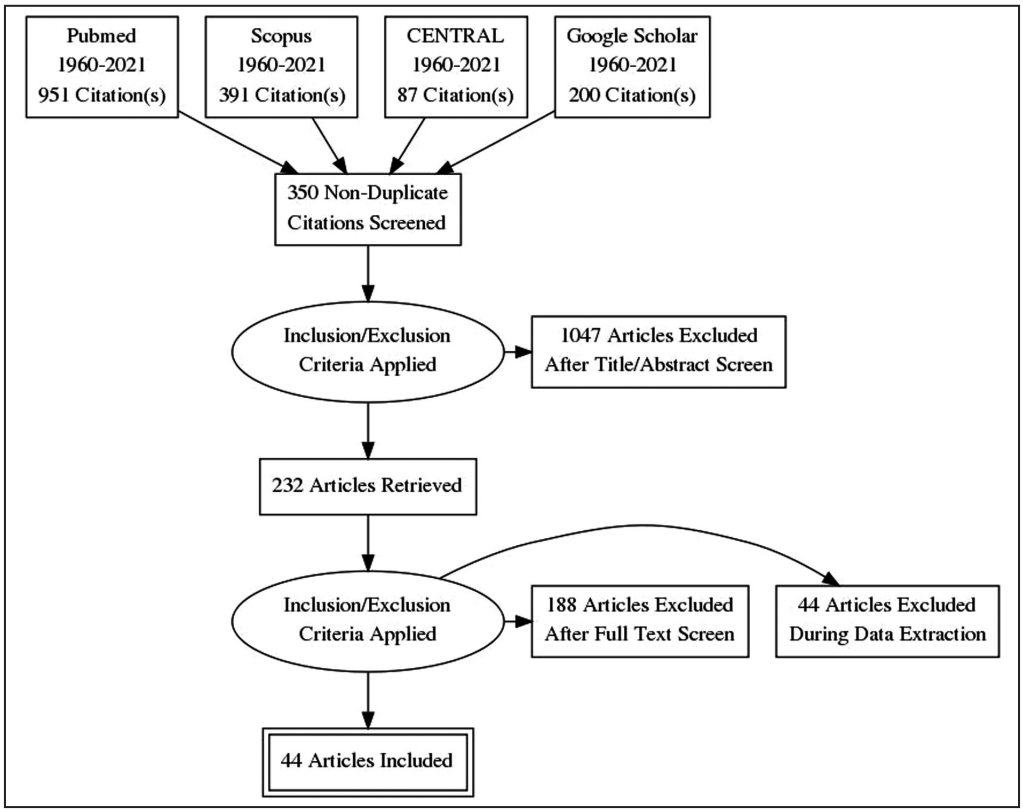

Figure 1. PRISMA flowchart.
PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses. CENTRAL, Cochrane.

Main Outcomes

Preventing Depression

The model that evaluated the effect of SSRIs in preventing poststroke depression according to HAM-D score included 2 articles.[26,30] This model showed no significant difference in depression HAM-D scores between the SSRI group and the placebo group at baseline. This model showed insignificant heterogeneity (Figure 2; P=0.95, I^2=0%). At the end of follow-up, the SSRI group had significantly lower HAM-D depression score compared with the placebo group (Figure 2; WMD, −7.05 [95% CI, −11.78 to −2.31]). This model showed significant heterogeneity (Figure 2; P=0.00, I^2=96%).

Treating Depression

The model that investigated the effect of SSRIs in treating poststroke depression according to HAM-D score included 8 articles.[32,38,39,46,49,50,52,53] The results showed that there was no significant difference between the SSRI group and placebo group at baseline. The heterogeneity of this model was significant (Figure 3; P=0.00, I^2=97%). On the other hand, at the end of treatment, the SSRI group had a significantly lower HAM-D score compared with a placebo (Figure 3; WMD, −1.45 [95% CI, −2.77 to −0.14]). This model showed significant heterogeneity (Figure 3; P=0.00, I^2=69%). In addition, Andersen et al showed that using SSRIs in treating poststroke depression was significantly effective in reducing depression provided by HAM-D scores. Furthermore, 2 studies[38,49] evaluated the effect of SSRIs in treating poststroke depression according to Beck Depression Inventory scores. The results of these studies conducted by Acler et al[49] and Fruehwald et al[38] showed that there was no significant difference in Beck Depression Inventory scores between the SSRI group and placebo group at baseline or at the end of treatment. In addition, 2 studies[38,60] evaluated the efficacy of SSRIs in treating poststroke depression according to Patient Health Questionnaire 9 scores. The study by Almeida et al[60] showed that there was significant improvement in Patient Health Questionnaire 9 scores after treatment, whereas the study by Fruehwald et al[38] showed insignificant difference after the treatment.

Treating Anxiety

Two studies assessed the efficacy of SSRIs in treating poststroke anxiety as a binary variable.[18,36]

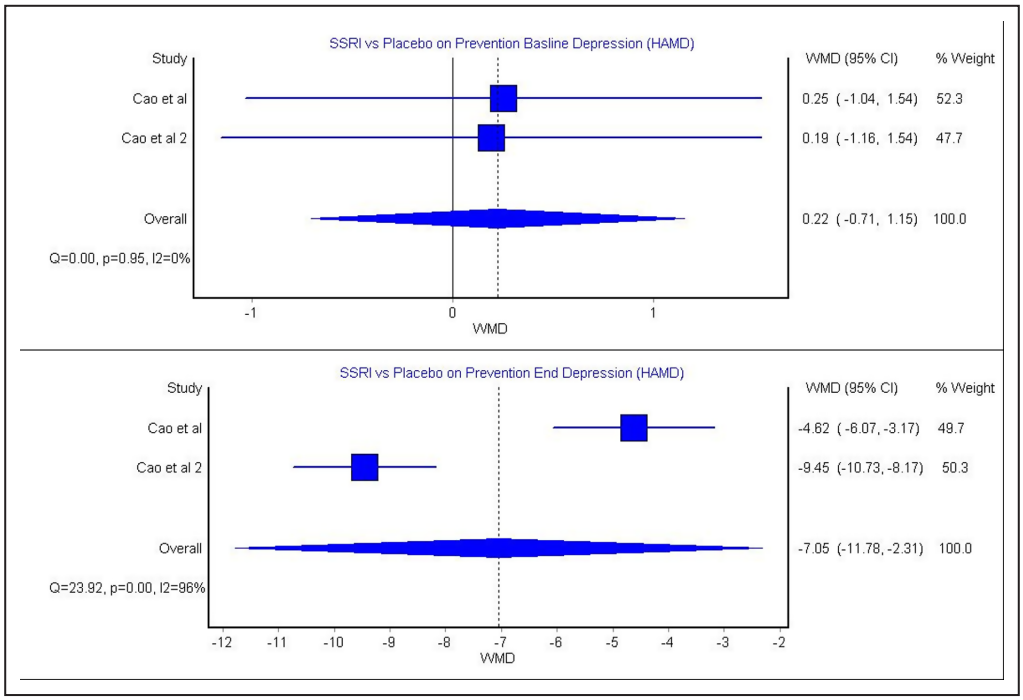

Figure 2. SSRIs for preventing poststroke depression provided by HAM-D.[26,30]
HAMD indicates Hamilton Rating Scale for Depression; SSRIs, selective serotonin reuptake inhibitors; and WMD, weighted mean difference.

The model that pooled those studies showed significantly lower anxiety among the SSRI group compared with the placebo group (Figure 4; RR, 0.23 [95% CI, 0.09–0.61]). This model showed insignificant heterogeneity (Figure 4; P=0.98, I^2=0%).

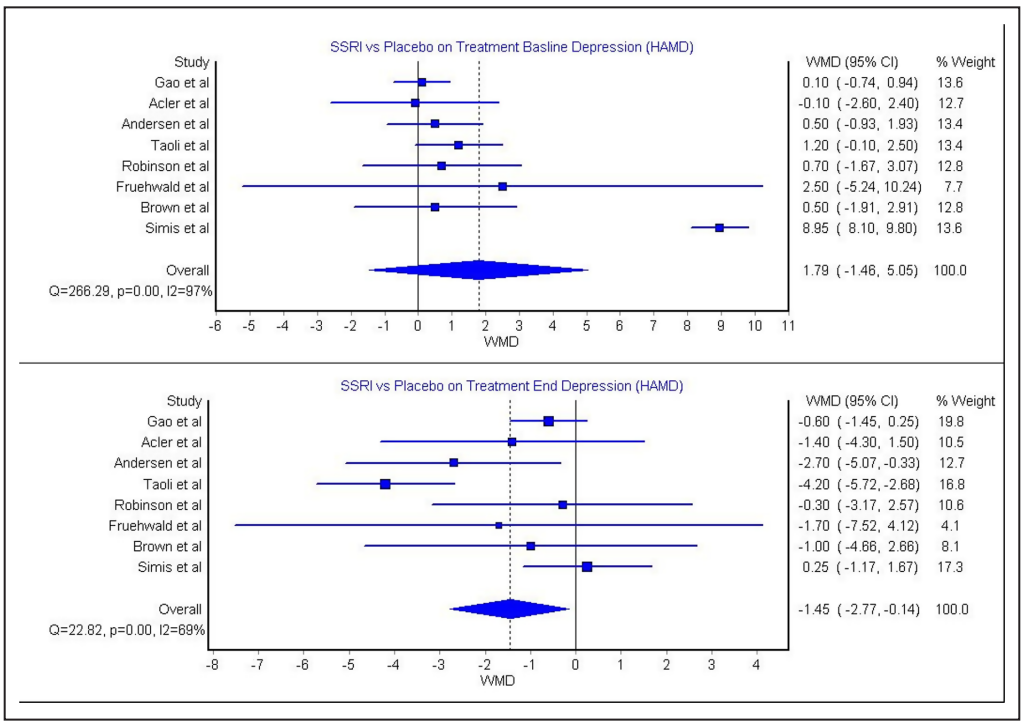

Figure 3. SSRIs for treating poststroke depression provided by HAM-D.[32,38,39,46,49,50,52,53]
HAMD indicates Hamilton Rating Scale for Depression; SSRIs, selective serotonin reuptake inhibitors; and WMD, weighted mean difference.

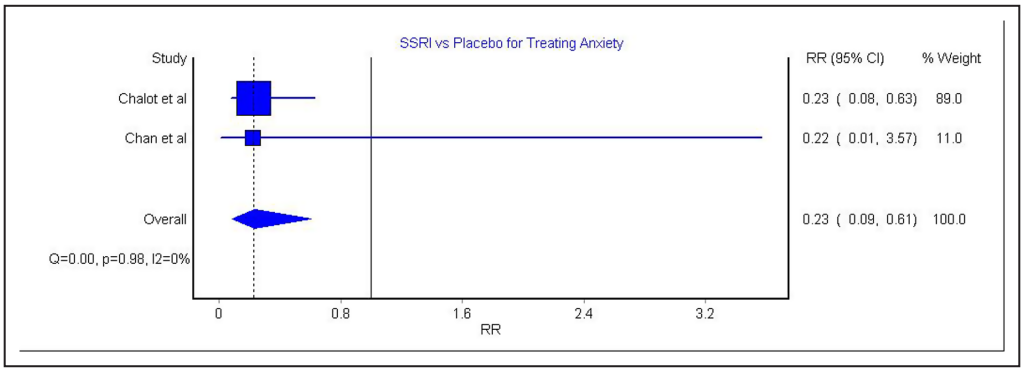

Figure 4. SSRIs for treating poststroke anxiety.[18,36]
RR indicates relative risk; and SSRIs, selective serotonin reuptake inhibitors.

Dependence

The model that studied the effect of SSRIs on poststroke dependence provided by Barthel Index scores included 10 articles.[1] This model showed insignificant difference between the SSRI group and placebo group at baseline. This model showed significant heterogeneity (Figure 5; P=0.00, I^2=62%). At the end of the treatment, the analysis revealed that the SSRI group had significantly lower dependence (higher Beck Depression Inventory scores) compared with the placebo group (Figure 5; WMD, 8.86 [95% CI, 1.23–16.48]). This model showed significant heterogeneity (Figure 5; P=0.00, I^2=99%).

Disability

Two studies conducted by Kim et al[33] and Kraglund et al[24] assessed the efficacy of SSRIs in reducing poststroke disability as a continuous variable

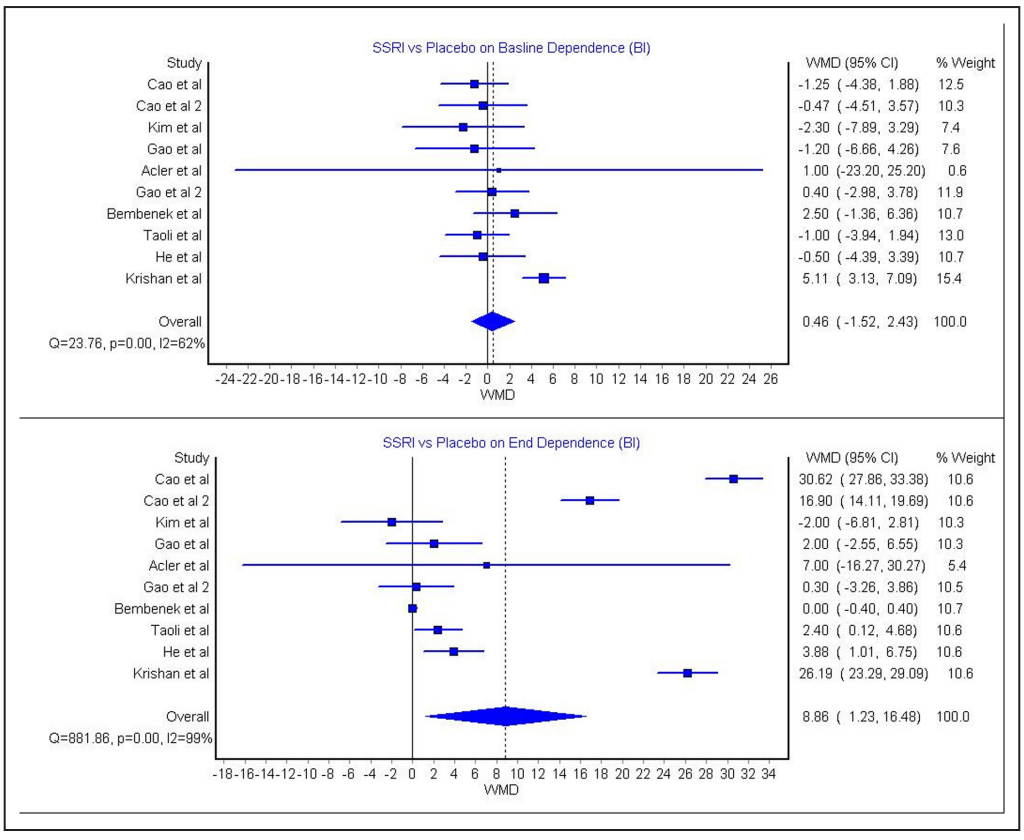

Figure 5. SSRIs for poststroke dependence provided by BI.
[22,26,30,32–34,46,49,59,61]

BI indicates Barthel Index; SSRIs, selective serotonin reuptake inhibitors; and WMD, weighted mean difference.

*References 22, 26, 30, 32–34, 46, 49, 59, 61.

Table. Characteristics of the Included Studies

Study	Country	No. of participants	No. of placebo patients	No. of treatment patients	Age, mean±SD/median (range)	Comorbidities	Funding status	Outcomes (tools)
Nct[18]	France	102	55	57	Fluoxetine: 66.4±11.7, placebo: 62.9±13.4	Diabetes, hypertension, hyperlipidemia, smoker, cardiac disease, and stroke	Not funded	Disability (mRS) and depression (HAM-D) and motor function (NIHSS and FMMS)
Gong et al[19]	China	126	62	64	Fluoxetine: 56.68±17.59, placebo: 57.79±17.54	Hypertension and diabetes	Not funded	Motor disability (NIHSS and FMMS) and disability (mRS)
Savadi Oskouie et al[20]	Iran	144	72	72	Citalopram: 65±10.90, placebo: 66.20±11.37	Diabetes, hypertension, hyperlipidemia, smoker, coronary artery disease, and stroke	Not funded	Disability (binary)
Effects trial[21]	Sweden	1500	750	750	Fluoxetine: 70.6±11.3, placebo: 71.0±10.5	Coronary artery diseases, stroke, diabetes, and depression	Not funded	Motor functions (NIHSS) and disability (mRS)
Bembenek et al[22]	Poland	61	30	31	Fluoxetine: 66.60±12.60, placebo: 66.35±12.46	Depression, diabetes, coronary artery diseases, hypertension, smoking, alcohol, obesity, hyperlipidemia, stroke, and intracerebral hemorrhage	Not funded	Motor deficit (MRC and NIHSS), disability (mRS), and dependence (BI)
Marquez-Romero et al[23]	Mexico	30	14	16	Fluoxetine: 54±10, placebo: 60.5±18	Diabetes, hyperlipidemia, smoker, and hypertension	Funded	Disability (mRS) and motor function (FMMS and NIHSS)
Kraglund et al[24]	Denmark	641	323	319	Citalopram: 68 (24–97), placebo: 68 (19–99)	Peripheral arterial disease, hypertension, smoker, coronary artery disease, and diabetes	Not funded	Disability (mRS)
Bonin Pinto et al[25]	USA	18	10	8	Fluoxetine: 50.5±16.57, placebo: 57.38	N/A	Not funded	Motor function (JHFT)

(*Continued*)

Table. (Continued)

Study	Country	No. of participants	No. of placebo patients	No. of treatment patients	Age, mean±SD/median (range)	Comorbidities	Funding status	Outcomes (tools)
Cao et al[26]	China	100	47	53	N/A	N/A	Not funded	Depression (HAM-D), dependence (BI), cognitive functions (MMSE), and motor functions (NIHSS)
Dennis et al[27]	UK	3106	1553	1553	Fluoxetine: 71.24±12.35, placebo: 71.48±12.06	Coronary artery disease, stroke, diabetes, hyponatremia, intracerebral hemorrhage, fractures, depression, and gastrointestinal bleeding	Not funded	Motor function (NIHSS) and disability (mRS)
Rampello et al[28]	Italy	68	34	34	Citalopram: 73.13±4.00, placebo: 74.71±4.66	Hypertension, diabetes, and hyperlipidemia	Not funded	Depression (HAM-D and BDI)
Asadollahi et al[29]	Iran	90	30	60	Fluoxetine: 60.2±8.52, citalopram: 58.7±8.56, placebo: 61.7±9.6	Hypertension, hyperlipidemia, smoking, and coronary artery disease	Not funded	Motor function (FMMS)
Cao et al[30]	China	97	48	49	Citalopram: 62±10.9, placebo: 63±9.7	N/A	Not funded	Motor functions (NIHSS), cognitive function (MMSE), dependence (BI), and depression (HAM-D)
Choi-Kwon et al[31]	South Korea	83	43	40	Fluoxetine: 57.28±8.3, placebo: 56.48±8.4	Hypertension, diabetes, coronary artery disease, smoking, and hyperlipidemia	Not funded	Depression (binary)
Li et al[32]	China	90	30	60	Fluoxetine: 69.2±3.50, placebo: 67.8±3.90	N/A	Not funded	Depression (HAM-D), dependence (BI)
Kim et al[33]	South Korea	405	195	210	Citalopram: 63.6±12.6, placebo: 63.5±12.0	Hypertension, diabetes, hyperlipidemia, coronary artery disease, smoking, and alcohol	Funded	Depression (HAM-D), disability (mRS), cognitive function (MOCA), and motor functions (NIHSS)
He et al[34]	China	374	187	187	Fluoxetine: 60.46±10.35, placebo: 62.66±11.69	Hypertension, diabetes, and smoking	Not funded	Motor (binary)

(*Continued*)

Table. (Continued)

Study	Country	No. of participants	No. of placebo patients	No. of treatment patients	Age, mean±SD/median (range)	Comorbidities	Funding status	Outcomes (tools)
Mikami et al[35]	USA	98	47	51	Citalopram: 60.8±14.0, placebo: 62.7±13.3	Hypertension, hyperlipidemia, diabetes, coronary artery disease, and heart failure	Not funded	Cognitive functions (RBANS) and dependence (FIMS)
Chan et al[36]	USA	19	13	6	N/A	Mental disorders and alcohol	Not funded	Anxiety (HAMA) and depression (HAM-D)
Choi-Kwon et al[37]	Korea	125	64	61	Fluoxetine: 58.41±8.92, placebo: 58.18±8.85	Hypertension, diabetes, coronary artery disease, smoker, and hyperlipidemia	Not funded	Depression (binary)
Robinson et al[56]	USA and Argentina	33	17	16	Fluoxetine: 65±14, placebo: 73±8	None	Not funded	Dependence (FIMS), cognitive function (MMSE), anxiety (HAMA), and depression (HAM-D)
Andersen et al[17]	Denmark	16	16	16	N/A	None	Funded	Depression (HAM-D)
Fruehwald et al[38]	Switzerland	50	24	26	Fluoxetine: 64.8±13.8, placebo: 64.0±14.3	None	Not funded	Depression (HAM-D and BDI)
Robinson et al[39]	USA	117	58	59	Citalopram: 61.3±13.7, placebo: 63.9±13.3	Mental disorders, hypertension, hyperlipidemia, diabetes, coronary artery disease, heart failure, and chronic obstructive lung disease	Not funded	Depression (binary)
Hankey et al[40]	Australia, New Zealand, and Vietnam	1221	615	606	N/A	N/A	Funded	Depression (PHQ9)
Choi-Kwon et al[41]	Korea	152	76	76	Fluoxetine: 58.41±8.92, placebo: 58.18±8.85	N/A	Not funded	Depression (binary)
Jorge et al[42]	USA	88	45	43	Citalopram: 60.8±14.4, placebo: 64.2±13.9	N/A	Not funded	Cognitive function (RABNS)
Mikami et al[43]	USA	61	29	32	Fluoxetine: 65.7±12.4, placebo: 72.5±9.4	N/A	Funded	Disability (mRS)
Wiart et al[44]	France	31	15	16	Fluoxetine: 66.3±7.1, placebo: 68.9±11.6	N/A	Funded	Depression (HAM-D), dependence (FIMS), and cognitive function (MMSE)

(*Continued*)

Table. (Continued)

Study	Country	No. of participants	No. of placebo patients	No. of treatment patients	Age, mean±SD/median (range)	Comorbidities	Funding status	Outcomes (tools)
Gou et al[45]	China	182	92	90	Fluoxetine: 59.52±10.52, placebo: 60.51±11.69	Smoking, hypertension, and diabetes	Not funded	Motor function (NIHSS)
Gao et al[46]	China	182	91	91	Citalopram: 46±50.5, placebo: 48±52.7	Coronary artery disease, hypertension, diabetes, smoker, and alcohol	Not funded	Dependence (BI and FIMS) and depression (HAM-D)
Mikami et al[47]	USA	96	49	47	Citalopram: 61.5±13.7, placebo: 64.8±13.5	Hypertension, coronary artery disease, diabetes, congestive heart failure, and atrial fibrillation	Not funded	Anxiety and depression (binary)
Acler et al[49]	Italy	20	10	10	N/A	N/A	Not funded	Depression (HAM-D and BDI), dependence (BI), motor function (NIHSS)
Brown et al[50]	UK	19	10	9	N/A	N/A	Not funded	Depression (HAM-D)
Narushima et al[51]	USA	33	16	17	N/A	N/A	Not funded	Depression (HAM-D)
Simis et al[52]	Brazil	93	57	36	N/A	N/A	Funded	Depression (HAM-D)
Andersen et al[53]	Denmark	66	33	33	Citalopram: 68.2±4.2, placebo: 65.8±9.0	N/A	Funded	Depression (HAM-D and MMSE)
Rasmussen et al[54]	Denmark	137	67	70	Sertraline: 72.0±9.0, placebo: 68.0±11.0	N/A	Funded	Depression (binary)
Andersen et al[55]	Denmark	16	8	8	N/A	N/A	Funded	Depression (HAM-D)
Lundstorm et al[57]	Sweden	1500	750	750	Fluoxetine: 70.6±11.3, placebo: 71.0±10.5	Coronary artery disease, stroke, diabetes, intracranial bleeding, gastrointestinal bleeding, fractures, and depression	Not funded	Cognitive function (MOCA), motor function (NIHSS)
Focus Collaboration[58]	UK	3127	1563	1564	Fluoxetine: 71.5±12.1, placebo: 71.5±12.1	Coronary artery disease, stroke, diabetes, hyponatremia, intracranial bleeding, gastrointestinal bleeding, fractures, and depression	Not funded	Mental health (MHI) and disability (mRS)

(*Continued*)

Table. (Continued)

Study	Country	No. of participants	No. of placebo patients	No. of treatment patients	Age, mean±SD/median (range)	Comorbidities	Funding status	Outcomes (tools)
Krishnan et al[59]	India	168	84	84	N/A	Diabetes, hypertension, and coronary artery disease	Funded	Dependence (BI)
He et al[34]	China	30	15	15	Fluoxetine: 59.07±15.17, placebo: 60.54±14.02	Diabetes, hyperlipidemia, and hypertension	Not funded	Depression (PHQ9)
Almeida et al[60]	Australia and New Zealand	1280	638	642	N/A	N/A	Not funded	Depression (PHQ9)

BDI indicates Beck Depression Inventory; BI, Barthel Index; FIMS, Functional Independence Measure Score; FMMS, Fugl-Meyer Assessment of Motor Recovery; HAMA, Hamilton Anxiety Scale; HAM-D, Hamilton Rating Scale for Depression; JHFT, Jebsen Hand Function Test; MHI, mental health inventory; MMSE, Mini-Mental State Exam; MOCA, Montreal Cognitive Assessment; MRC, medical research council; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; PHQ9, Patient Health Questionnaire 9; and RABNS, repeatable battery for the assessment of neuropsychological status.

provided by modified Rankin Scale scores. Both studies showed that SSRIs were not significantly associated with improvement in modified Rankin Scale disability scores. Moreover, the model that assessed disability as a binary variable included 10 articles.[2] This model showed an insignificant difference between the SSRI group and the placebo group in disability (Figure S3; RR, 0.95 [95% CI, 0.88–1.04;). This model showed significant heterogeneity (Figure S3; P=0.00, I^2=79%). Furthermore, Bembenek et al[22] showed that SSRIs did not significantly reduce poststroke disability provided by the Medical Research Council and Brunstorm tools. On the other hand, Mikami et al[43] showed that SSRIs significantly improved poststroke disability.

Cognitive Function

Four studies evaluated the efficacy of SSRIs in treating poststroke cognitive deficit.[26,30,39,44] The model that included those articles showed insignificant difference at baseline between the SSRI group and the placebo group. This model showed insignificant heterogeneity (Figure S4; P=0.98, I^2=0%). At the end of treatment, the analysis showed significantly higher cognitive functions among the SSRI group compared with the placebo group (Figure S4; WMD, 1.00 [95% CI, 0.12–1.89]). This model showed insignificant heterogeneity (Figure S4; P=0.12, I^2=48%). Furthermore, Jorge et al[42] showed that patients who were treated with fluoxetine had significantly higher cognitive function provided by the Repeatable Battery for the Assessment of Neuropsychological Status scores.

Motor Function

The model that evaluated the efficacy of SSRIs in improving motor function according to the NIHSS score included 11 articles.[3] This model showed insignificant difference in NIHSS scores between the SSRI group and the placebo group at baseline; this model had insignificant heterogeneity (Figure S5; P=0.87, I^2=0%). At the end of treatment, the model showed significantly higher motor functions among the SSRI group (lower NIHSS score) compared with the placebo group (Figure S5; WMD, −0.79 [95% CI, −1.42 to −0.15]). This model had significant heterogeneity (Figure S5; P=0.00, I^2=97%). Moreover, the model that assessed the efficacy of SSRIs in improving motor functions according to the Fugl-Meyer Assessment of Motor Recovery score included 5 studies.[18,19,28,29] This model showed insignificant difference between the SSRI group and the placebo group at baseline. This model

†References 18, 19, 21, 22, 24, 27, 28, 40, 57, 58.

‡References 18, 21, 22, 26, 28, 30, 33, 34, 49, 53, 57.

showed insignificant heterogeneity (Figure S6; P=0.72, I^2=0%). However, at the end of the treatment, the model showed significantly higher motor functions (higher Fugl-Meyer Assessment of Motor Recovery scores) among the SSRI group compared with the placebo group (Figure S6; WMD, 14.67 [95% CI, 3.64–25.69]). This model showed significant heterogeneity (Figure S6; P=0.00, I^2=81%). In addition, the model that assessed the efficacy of SSRIs in improving motor function as a binary variable showed insignificant difference between the SSRI group and the placebo group[20,22,27] (Figure S7; RR, 1.00 [95% CI, 0.97–1.03]). This model showed significant heterogeneity (Figure S7; P=0.01, I^2=77%). Furthermore, Pinto et al showed that fluoxetine was significantly associated with better motor functions provided by the Jebsen Hand Function Test tool.

Side Effects

Gastrointestinal Side Effects

The occurrence of gastrointestinal symptoms as side effects of SSRIs were assessed by 20 studies.[4] The model that pooled those studies showed that patients on SSRIs were not significantly different in the incidence of gastrointestinal symptoms compared with patients on a placebo (Figure S8; RR, 1.29 [95% CI, 1.00–1.67]). This model showed significant heterogeneity (Figure S8; P=0.00, I^2=80%).

Bleeding

The model that evaluated the risk of bleeding from SSRIs included 10 studies.[5] This model revealed that SSRIs were not significantly associated with higher risk of bleeding compared with a placebo (Figure S8; RR, 0.92 [95% CI, 0.76–1.12]). This model had insignificant heterogeneity (Figure S8; P=0.45, I^2=0%).

Seizures

The model that evaluated SSRIs for the risk of seizures included 8 studies.[18,21,27,34,40,45,53,58] This model showed that SSRIs were significantly associated with higher risk of seizures compared with a placebo (Figure S8; RR, 1.44 [95% CI, 1.13–1.83]). This model had insignificant heterogeneity (Figure S8; P=0.82, I^2=0%).

Sensitivity Analysis

Fluoxetine

Our models showed that fluoxetine was significantly effective in treating poststroke depression[18,31,32,36,37,40,41] (Figure S9; RR, 0.62 [95% CI, 0.43–0.90]). This model had significant heterogeneity (Figure S9; P=0.01, I^2=67%). On the other hand, the analysis revealed that fluoxetine was not significantly associated with prevention of poststroke depression or treating it provided by HAM-D score[6] (Figures S10 and S11). In addition, fluoxetine use was not significantly associated with preventing poststroke depression or improvement of poststroke dependence, disability, or motor function[#] (Figures S12 through S14). Furthermore, 2 studies[39,44] evaluated the efficacy of fluoxetine in improving poststroke cognitive functions provided by the MMSE. Both studies showed that fluoxetine was insignificantly associated with improvement in MMSE scores.

Citalopram

Similar to the primary analysis, our models showed that citalopram was significantly associated with poststroke depression prevention[26,30] (Figure S15; at end: WMD, –7.05 [95% CI, –11.78 to –2.31], P=0.00, I^2=96%) and treatment[46,49,53] (Figure S16; at end: WMD, –0.88 [95% CI, –1.65 to –0.11], P=0.25, I^2=29%) provided by HAM-D score. Also, treatment with citalopram was significantly associated with treating poststroke depression as a binary variable[18,43] (Figure S17; RR, 0.23 [95% CI, 0.10–0.54], P=not available, I^2=0%). However, citalopram did not significantly reduce poststroke depression as a binary variable[26,33,56] (Figure S18). Also, it was not significantly effective in improving disability provided by the modified Rankin Scale score[24,33] (Figure S19) or as a binary variable[20,24] (Figure S20). In addition, treatment with citalopram was not significantly associated with improvement of dependence provided by Barthel Index scores[30,33,46,49] (Figure S21). Moreover, consistent with the primary analysis, citalopram significantly improved poststroke cognitive deficit as shown in the MMSE scores[26,30] (Figure S22; at end: WMD, 1.50 [95% CI, 0.52–2.48], P=0.56, I^2=0%) and motor functions as shown in the NIHSS scores[19,20,33,49] (Figure S23; at end: WMD, –1.37 [95% CI, –2.44 to –0.29], P=0.00, I^2=96%).

DISCUSSION

In this systematic review and meta-analysis, we included 44 randomized controlled trials that investigated the effect of SSRIs on poststroke recovery (depression, anxiety, disability, dependence, motor abilities, and cognitive functions). Our results showed that SSRIs were significantly effective in preventing and treating poststroke depression. Moreover, the results also showed significant improvement of poststroke anxiety, dependence, motor abilities, and cognitive functions among patients

[§]References 18, 20, 23–26, 29–34, 42–45, 54, 56, 59.

[‖]References 20, 21, 24, 27, 34, 39, 40, 45, 53, 58.

[¶]References 18, 21, 32, 38, 39, 50–52, 57, 58, 60.

[#]References 18, 19, 21, 22, 27–29, 32, 34, 57–59.

who were treated with SSRIs. There was no significant improvement in disability after treatment with SSRIs. Furthermore, our study demonstrated that treatment with SSRIs was significantly associated with higher risk of seizures compared with a placebo, whereas there was no significant difference in the incidence of gastrointestinal symptoms or bleeding between the SSRI and placebo groups. On the other hand, the Cochrane review showed that SSRIs were significantly effective in treating poststroke depression but not in preventing it.[10] Also, in contrast with our results, the Cochrane review showed that there was no significant improvement in dependence, motor abilities, and cognitive functions among patients who were treated with SSRIs.[10] Additionally, the Cochrane review showed that SSRIs significantly increased the incidence of gastrointestinal symptoms but not seizures compared with a placebo. The deviation in our study findings compared with the Cochrane study results published in 2019 is a consequence of the large heterogeneity in the Cochrane study, because it was conducted before the implementation of the core protocol developed by international collaboration in 2019.[12,13] On the other hand, our review included several studies after the implementation of this protocol, which reduces the heterogeneity in our study compared with the Cochrane review. Furthermore, although the Cochrane collaboration updated their review in 2021, and their results contradict our findings,[62] the latest Cochrane review searched the databases up to December 2020,[62] whereas we searched the databases up to November 2021, and we identified 5 trials that were published during 2021 that were not included in the latest Cochrane review. However, the Cochrane review included more studies with wider ethnic variation, because they included studies with different languages and settings, whereas we only included studies that were published in English. In addition, previous studies showed that several genetic polymorphisms affect the efficacy and safety of SSRIs, which might explain the differences between our study and the previously mentioned Cochrane review.[63,64] Also, it is important to mention that the investigators of the latest Cochrane review were involved in several trials that assessed SSRIs efficacy and safety in improving poststroke depression outcomes, which might affect the results of their review.

On the safety of SSRIs among patients after stroke, our study demonstrated that SSRIs were significantly associated with higher risk of seizures compared with a placebo. However, this finding can be confounded by many variables including the low sodium and serotonin levels, which were both described in patients after stroke[61,65] and can induce seizures.[61,66] It is important to mention that none of the included studies accounted for the serotonin or sodium level among their patients before starting the intervention. Furthermore, several observational studies and open-label trials showed that SSRIs were not associated with seizures, and in contrast, they were associated with reduction in seizure frequency and duration among patients with epilepsy.[67]

We conducted a subanalysis to investigate the effect of different SSRI agents on poststroke recovery. Similar to the primary analysis, the subanalysis results showed that citalopram was significantly associated with improving the poststroke recovery of depression, cognitive function, and motor function. However, fluoxetine was only effective in treating poststroke depression. This indicates that the beneficial effects of SSRIs on poststroke recovery that we found in the primary analysis were driven by citalopram not fluoxetine. Similar to our findings, several studies showed that citalopram had higher efficacy and tolerability compared with fluoxetine in treating depression among adults.[68] These differences in the efficacy between fluoxetine and citalopram can be explained by the fact that fluoxetine has an extremely long half-life compared with citalopram; hence, a much longer duration is required with fluoxetine to reach a steady state concentration and exert its action.[69] Also, it was shown that fluoxetine has active metabolites resulting in prolongation of the SSRIs' side effects compared with citalopram.[69]

This is the most updated systematic review and meta-analysis after the implementations of the international collaboration core guidelines in conducting trials for the effect of SSRIs on poststroke recovery. In addition, this is the first review to show that citalopram could improve poststroke recovery. Also, this study was conducted based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* and Cochrane Collaboration guidelines. However, this study had several limitations. First of all, we only included studies that were published in the English language, which might limit the generalizability of our results. Second, a large proportion of the included studies were low-moderate-quality studies. Third, different scales were used by the included trials to measure the same outcome, which reduced the number of the trials in several models. This necessitates well-conducted placebo-controlled clinical trials that use standardized tools for assessing poststroke recovery outcomes to assess the safety and the efficacy of SSRIs in promoting poststroke recovery. Fourth, there was high heterogeneity across several outcomes, which might be attributed to different times of starting SSRIs after the stroke, different SSRI doses used by the trials, and different characteristics of patients included in the trials.

CONCLUSIONS

Our study showed that SSRIs are effective in preventing and treating depression, and improving anxiety, motor function, cognitive function, and dependence in patients after stroke. These benefits were only

reproducible with the citalopram subanalysis but not fluoxetine, suggesting that citalopram but not fluoxetine improved the recovery outcomes of patients after stroke. Further well-conducted placebo-controlled trials are needed to investigate the safety and efficacy of citalopram among patients after stroke.

ARTICLE INFORMATION

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Affiliations

Department of Anatomy, Faculty of Medicine (H.M.K.), and Faculty of Medicine (A.A.T., F.H.A., Y.Y.O.), University of Jordan, Amman, Jordan; and Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan (L.M.A.-H.).

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Supplemental Material

Figures S1–S23

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SUPPLEMENTAL MATERIAL

Figure S1: Summary of Cochrane Risk of Bias Assessment of the Included Studies 17-60.

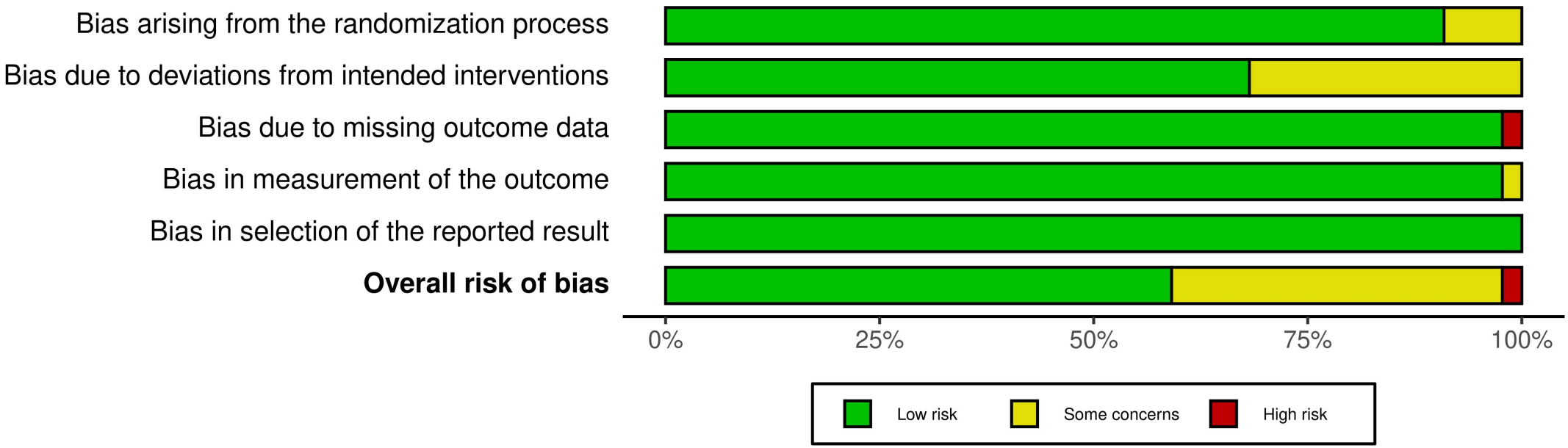


Figure S2: The Detailed Risk of Bias Assessment of the Included Studies 17-60.

Figure S3: SSRIs for Improving Post-stroke Disability Provided by mRS as Binary Variable 18,19,21,22,24,27,28, 40,57,58.

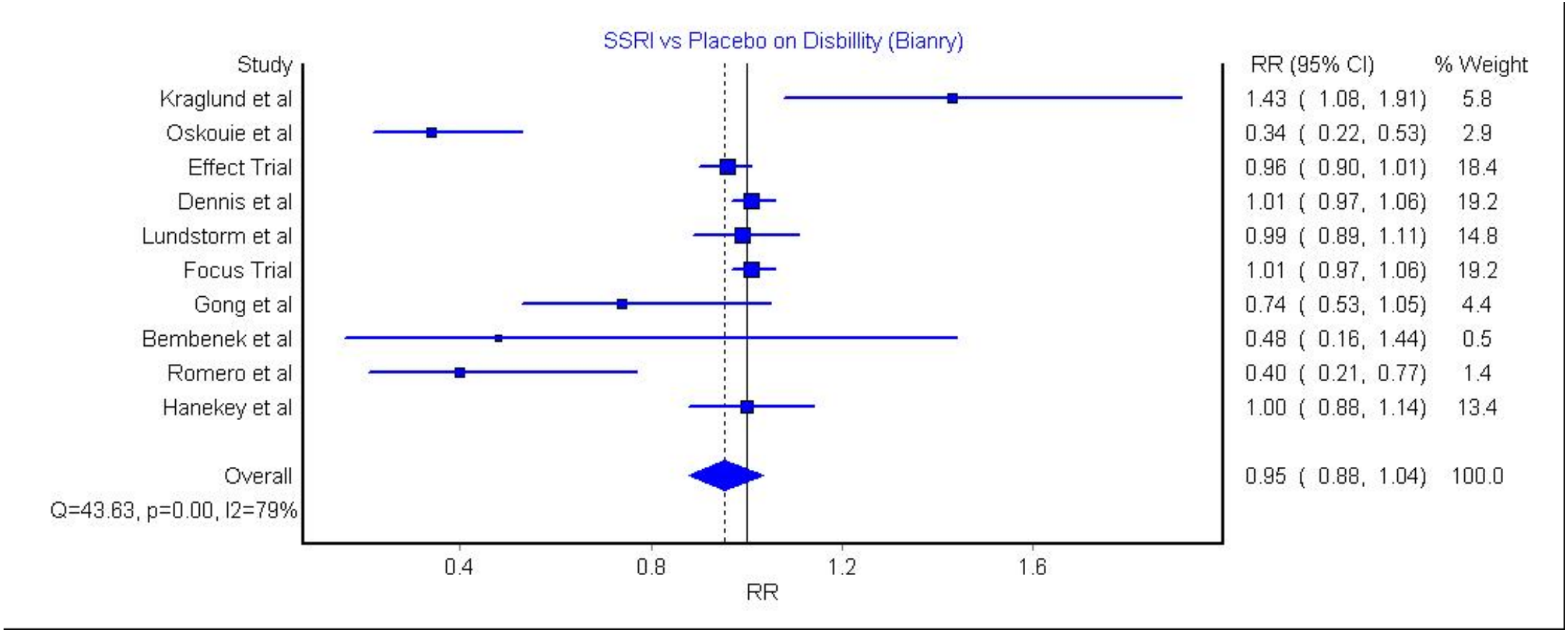
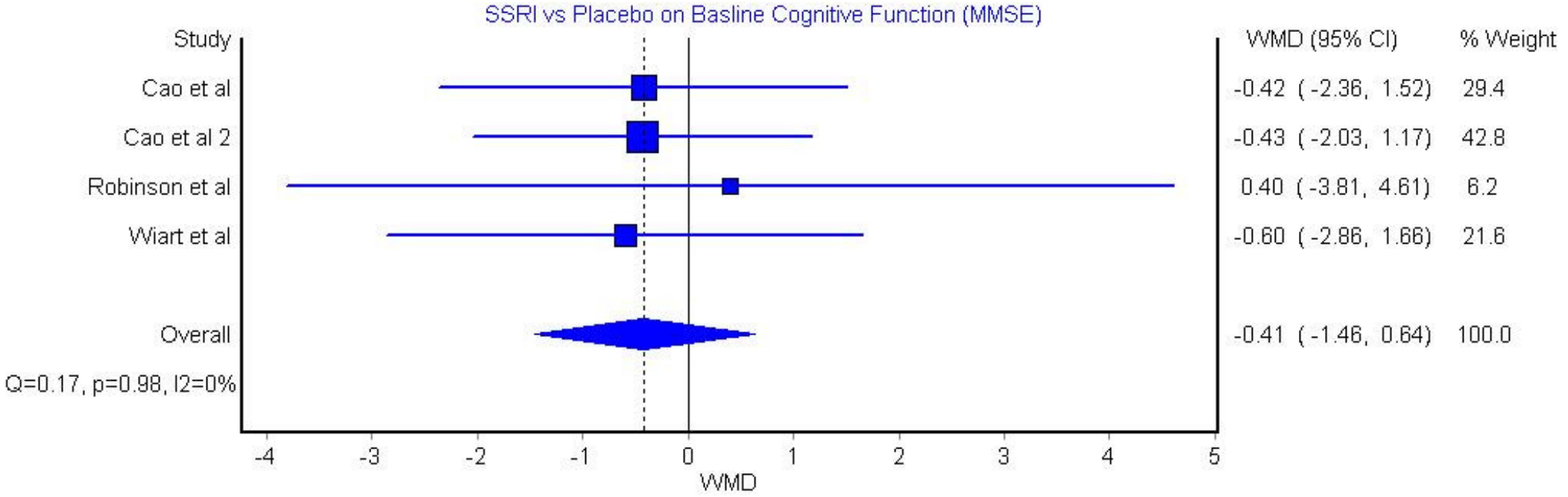


Figure S4: SSRIs for Improving Post-stroke Cognitive Function Provided by MMSE 26,30,39,43,44.



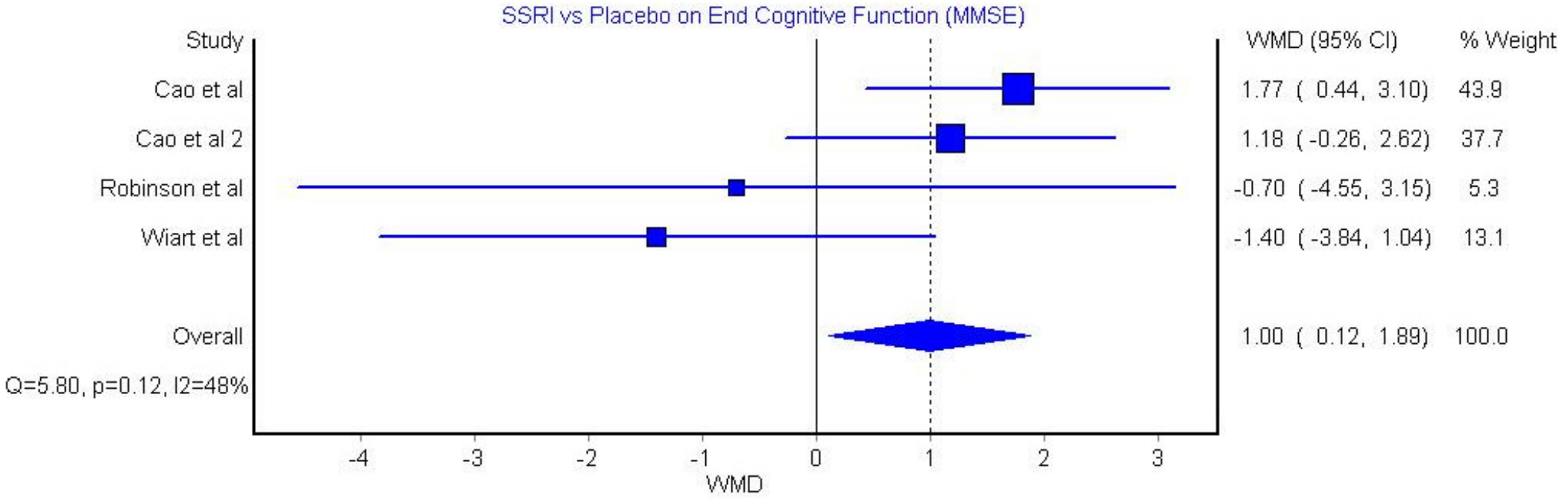
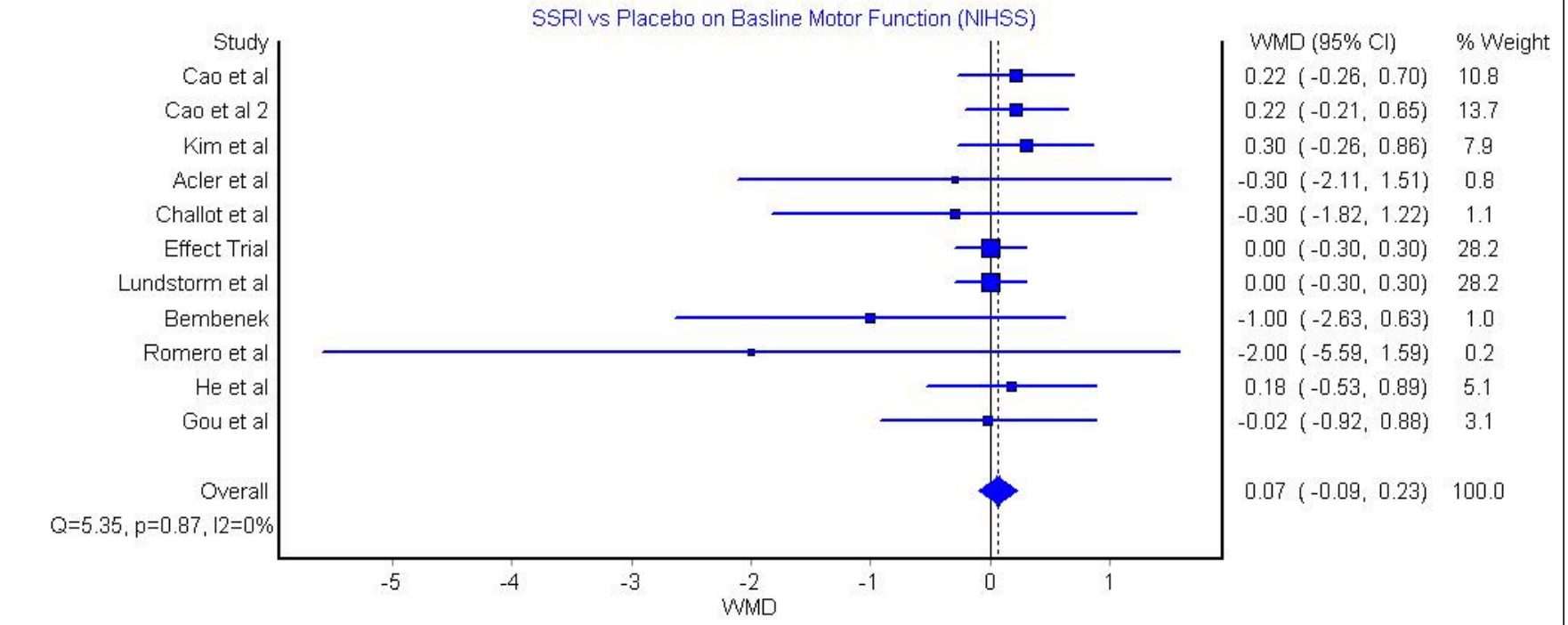


Figure S5: SSRIs for Improving Post-stroke Motor Function Provided by NIHSS 18,21,22,26,28,30,33,34,49,53, 57.



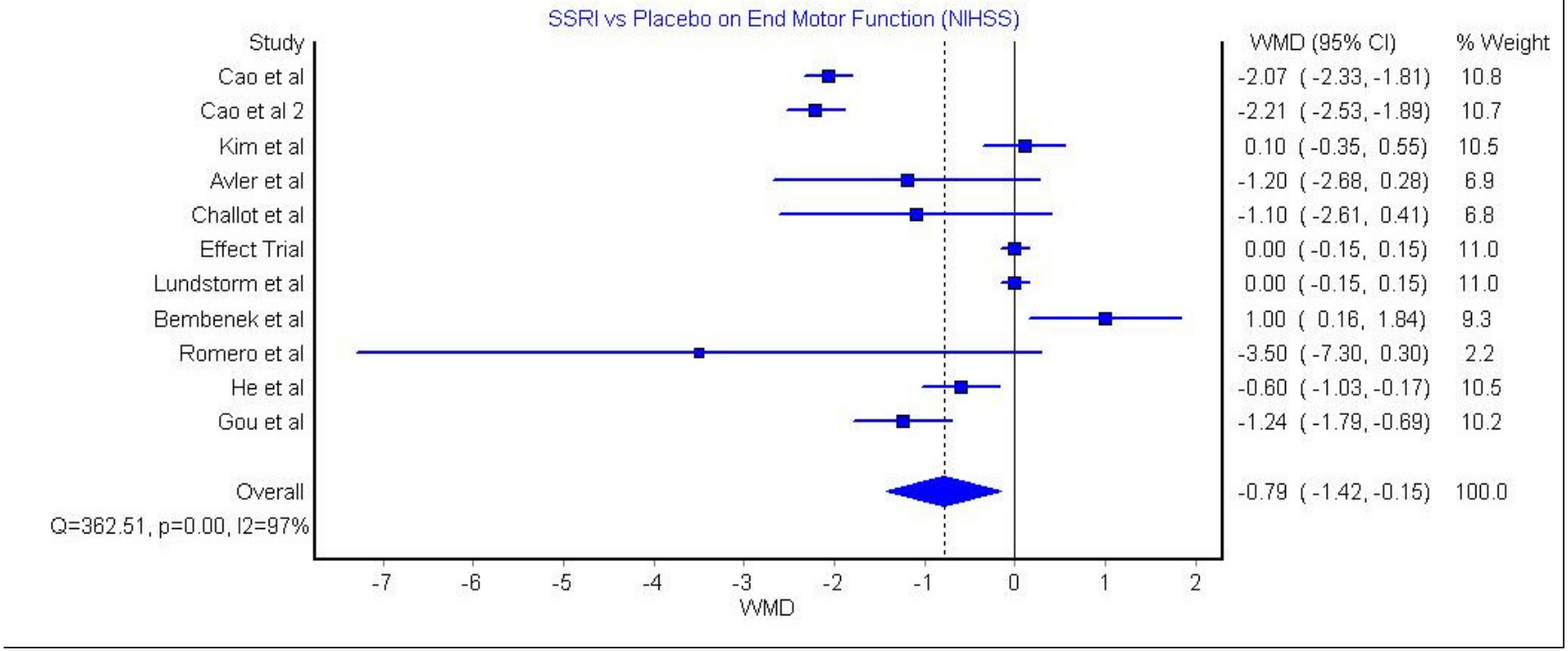
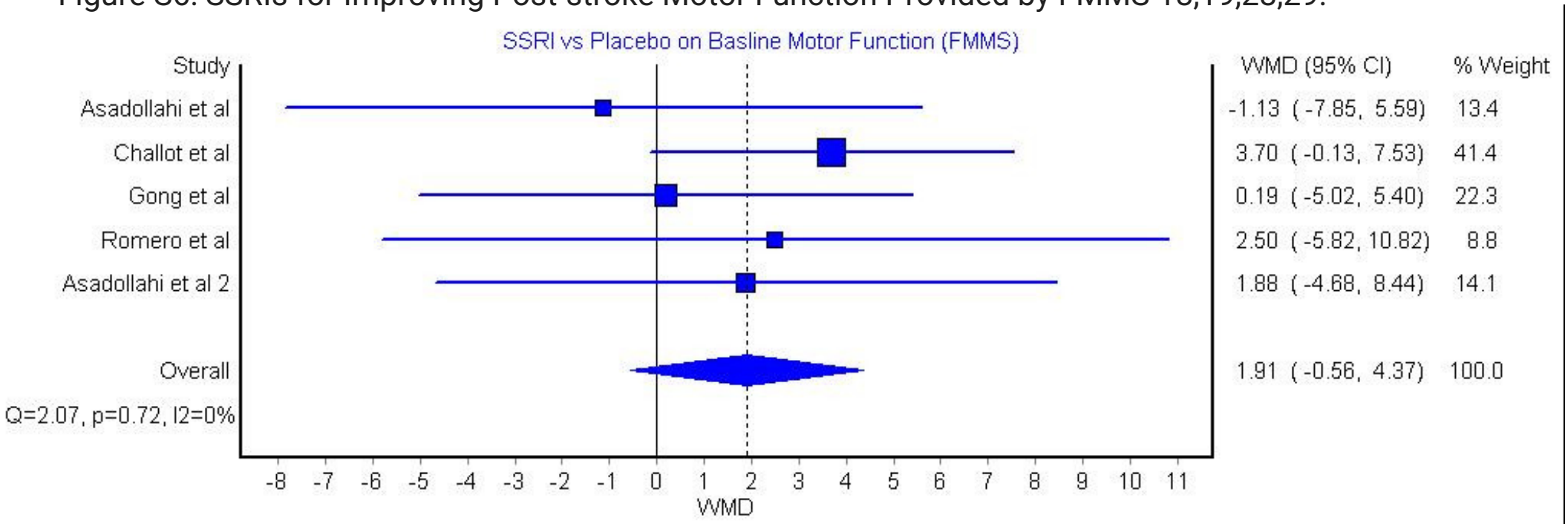


Figure S6: SSRIs for Improving Post-stroke Motor Function Provided by FMMS 18,19,28,29.



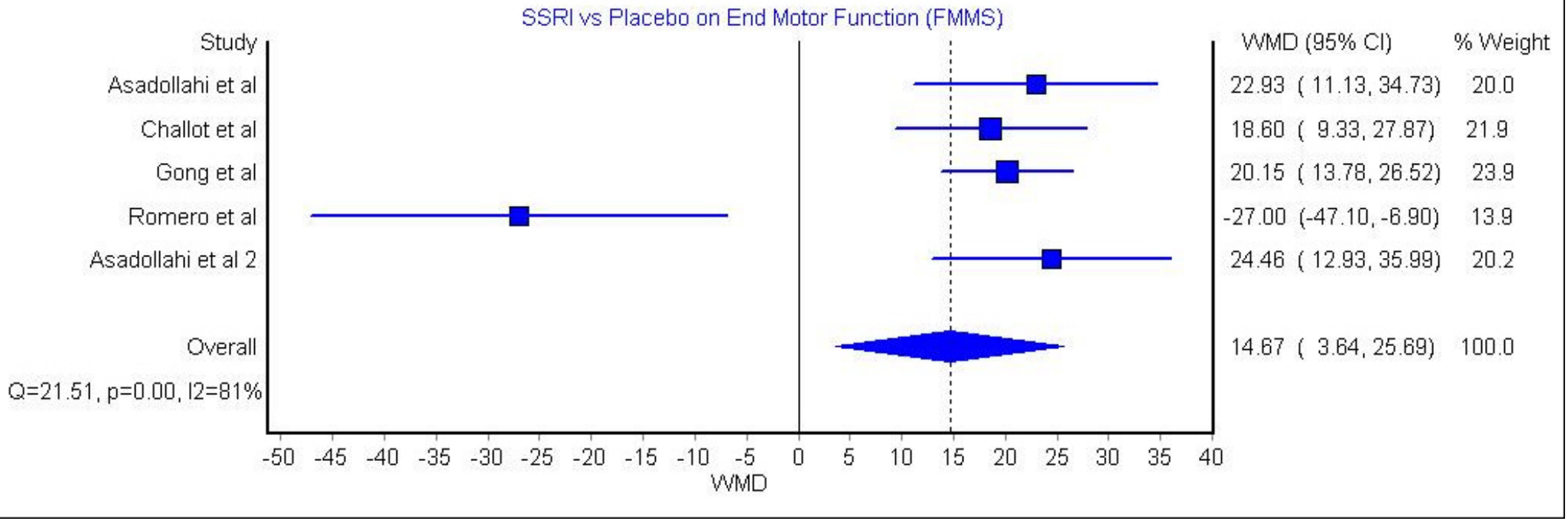


Figure S7: SSRIs for Improving Post-stroke Motor Function as a Binary Variable 20,22,27.

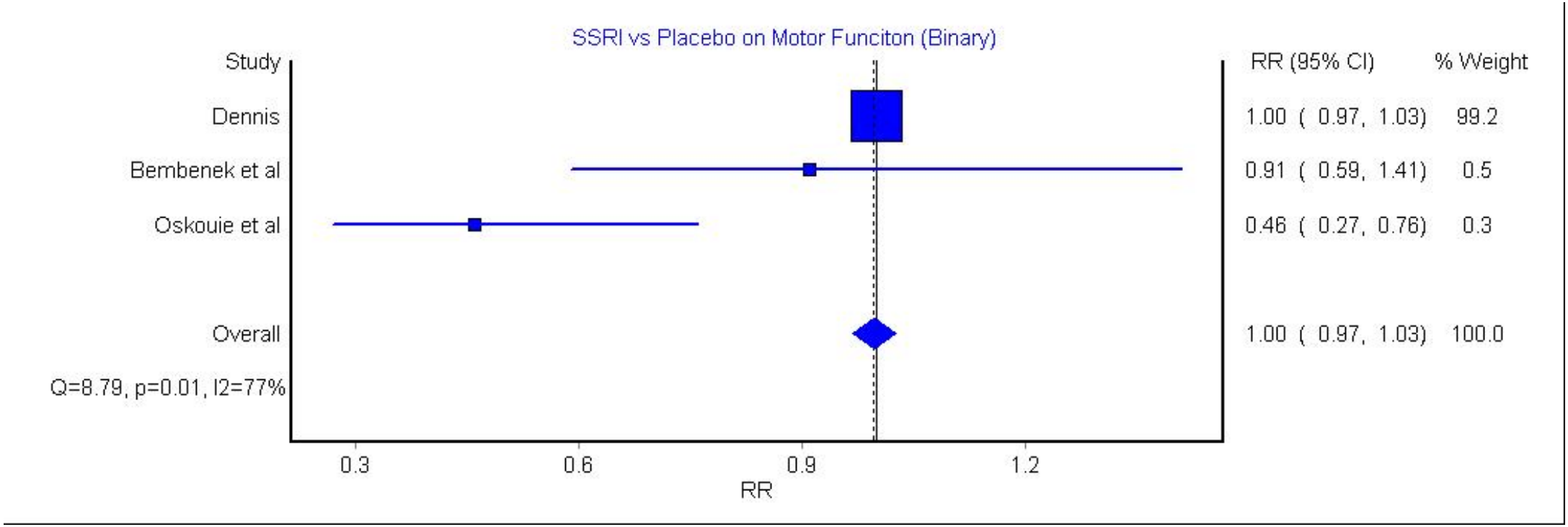
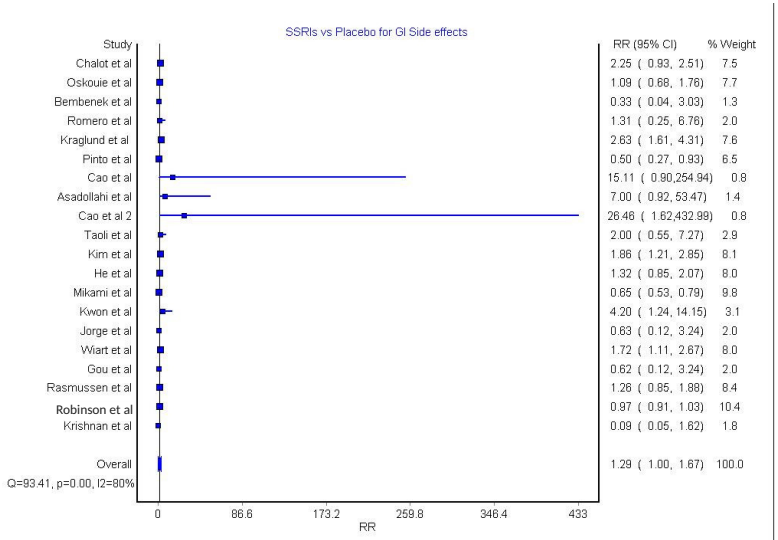
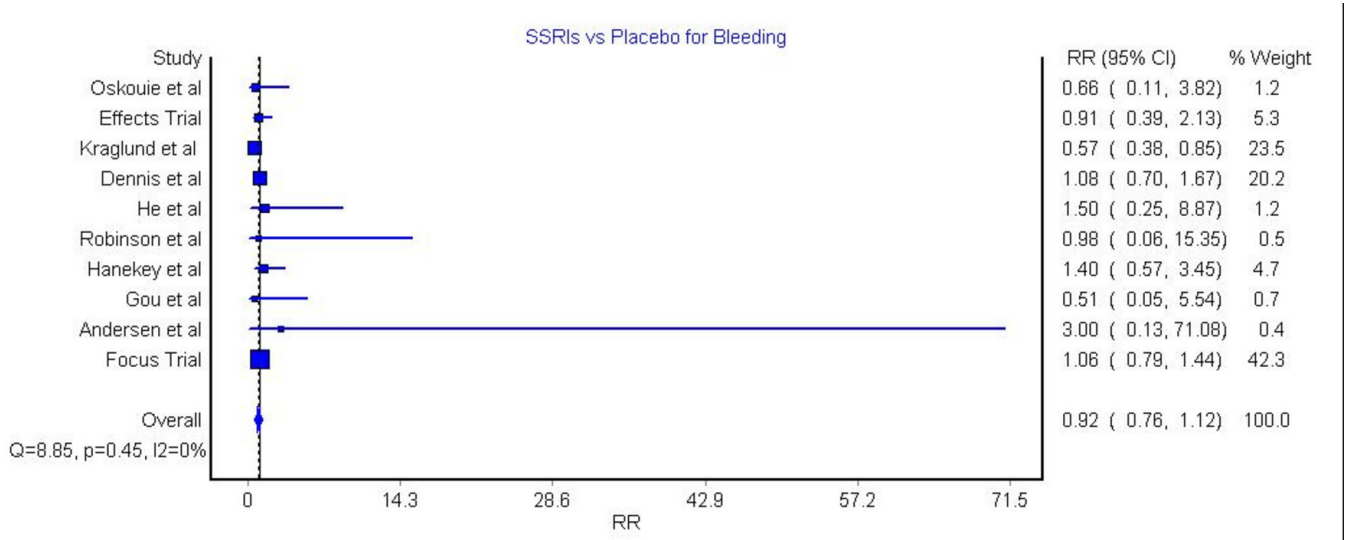


Figure S8: Side Effects of SSRIs 18,20,21,23-27,29-34,39,40,42-45,53,54,56,58,59.





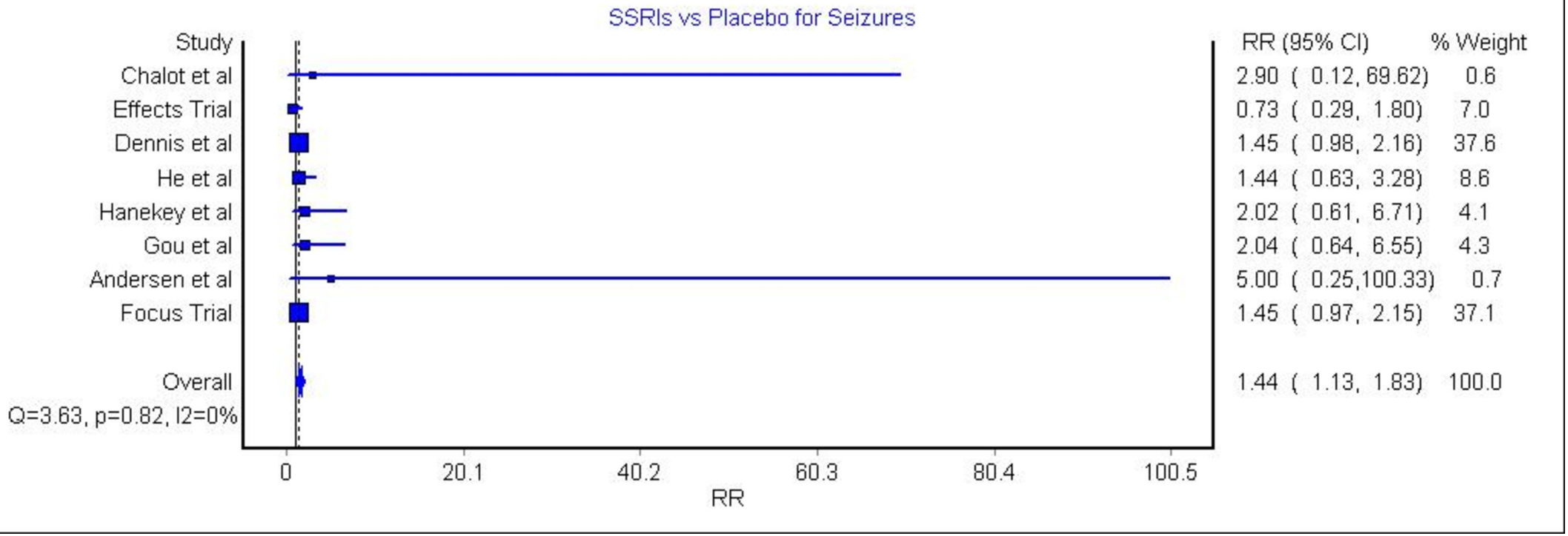


Figure S9: Fluoxetine for Treating Post-stroke Depression as a Binary Variable 18,31,32,36,37,40,41.

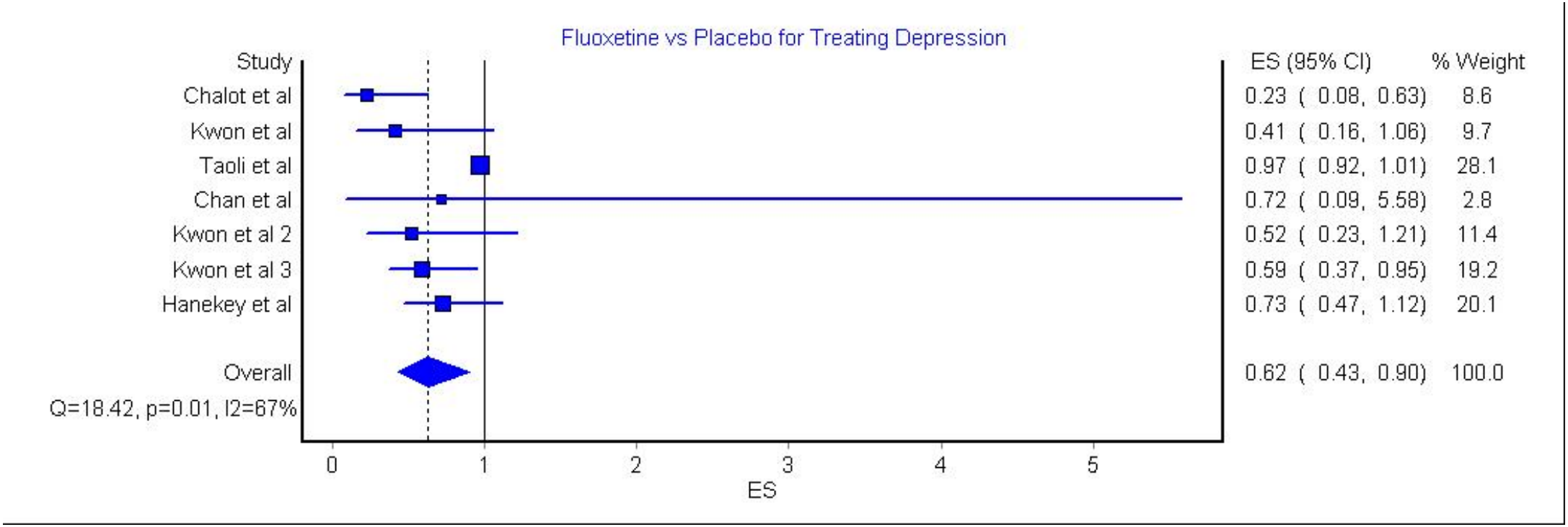
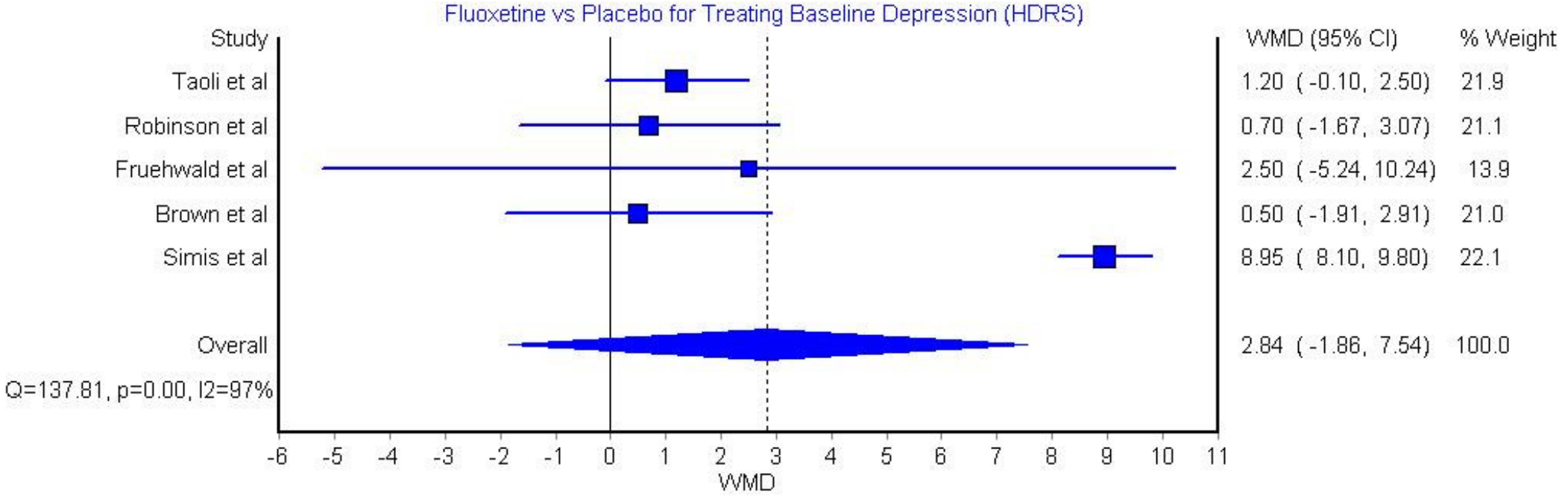


Figure S10: Fluoxetine for Treating Post-stroke Depression Provided by HAMD 32,38,39,50,52.



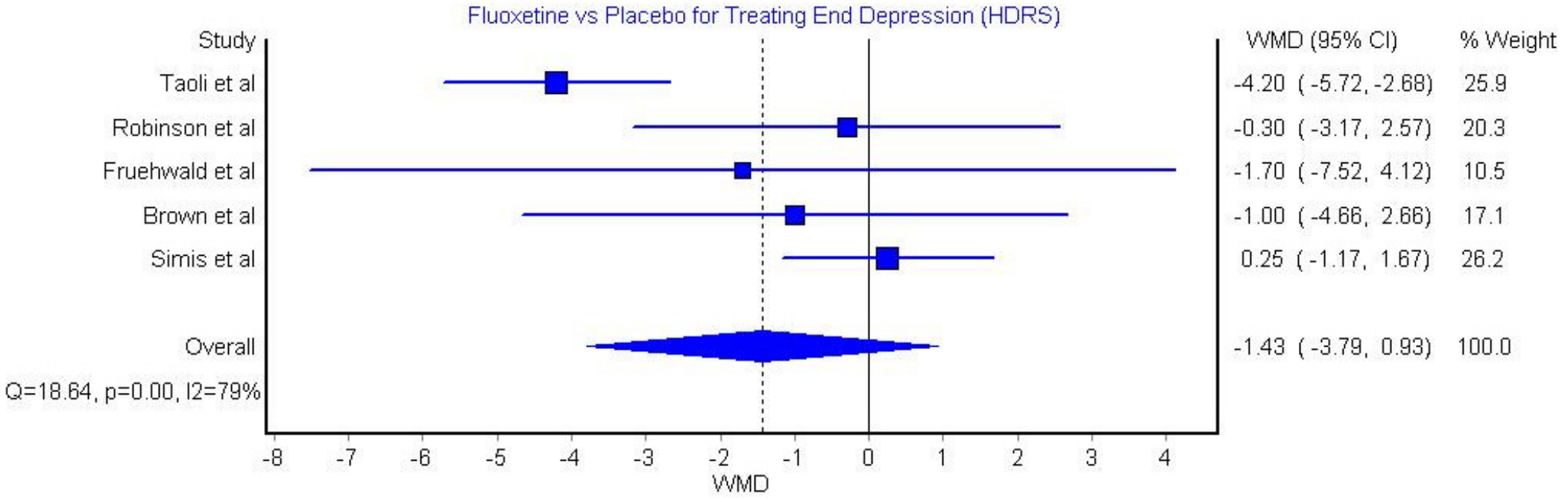


Figure S11: Fluoxetine for Preventing Post-stroke Depression as a Binary Variable 18,21,27,51,57,58,60.

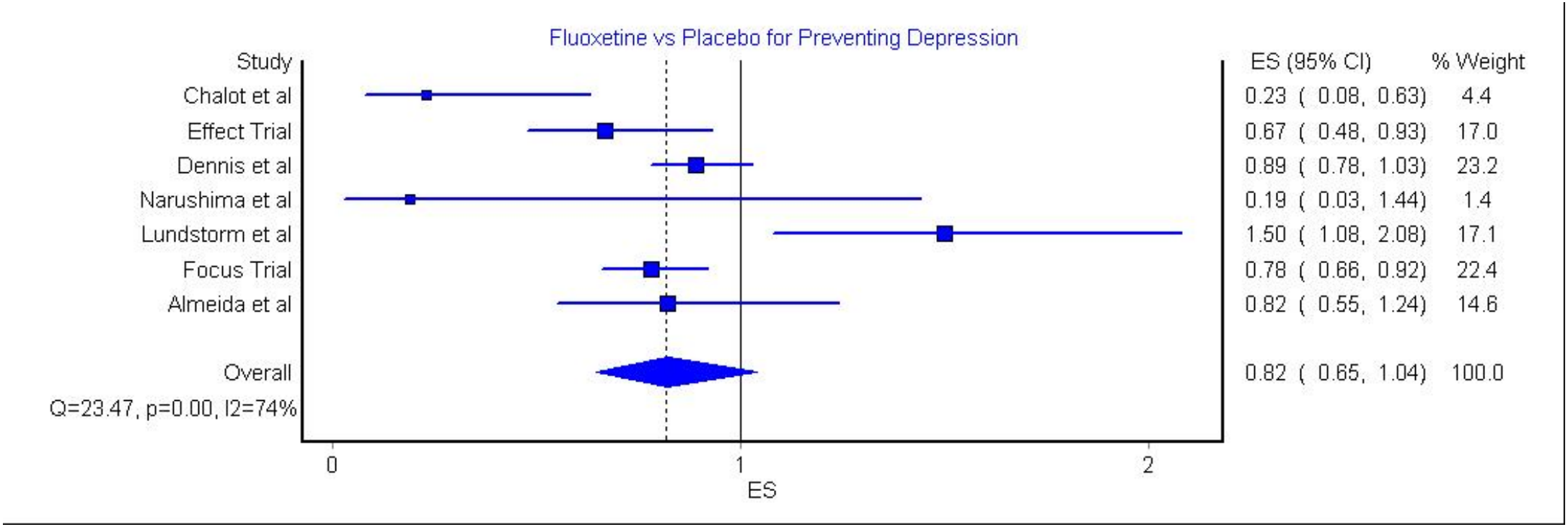
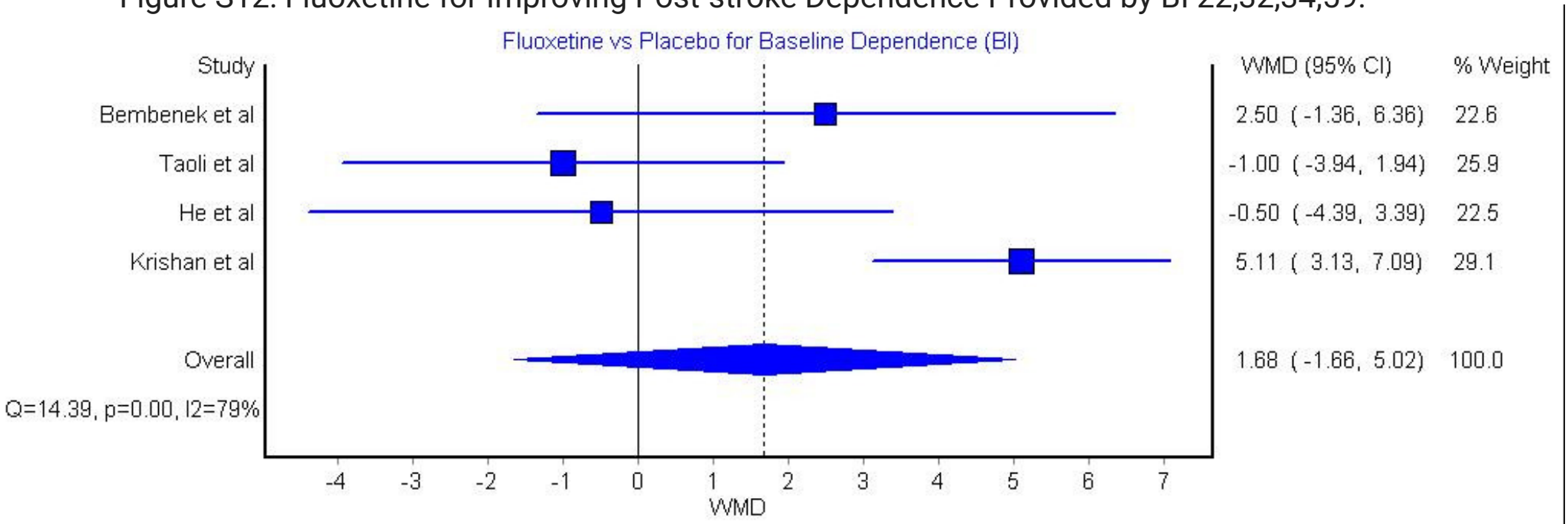


Figure S12: Fluoxetine for Improving Post-stroke Dependence Provided by BI 22,32,34,59.



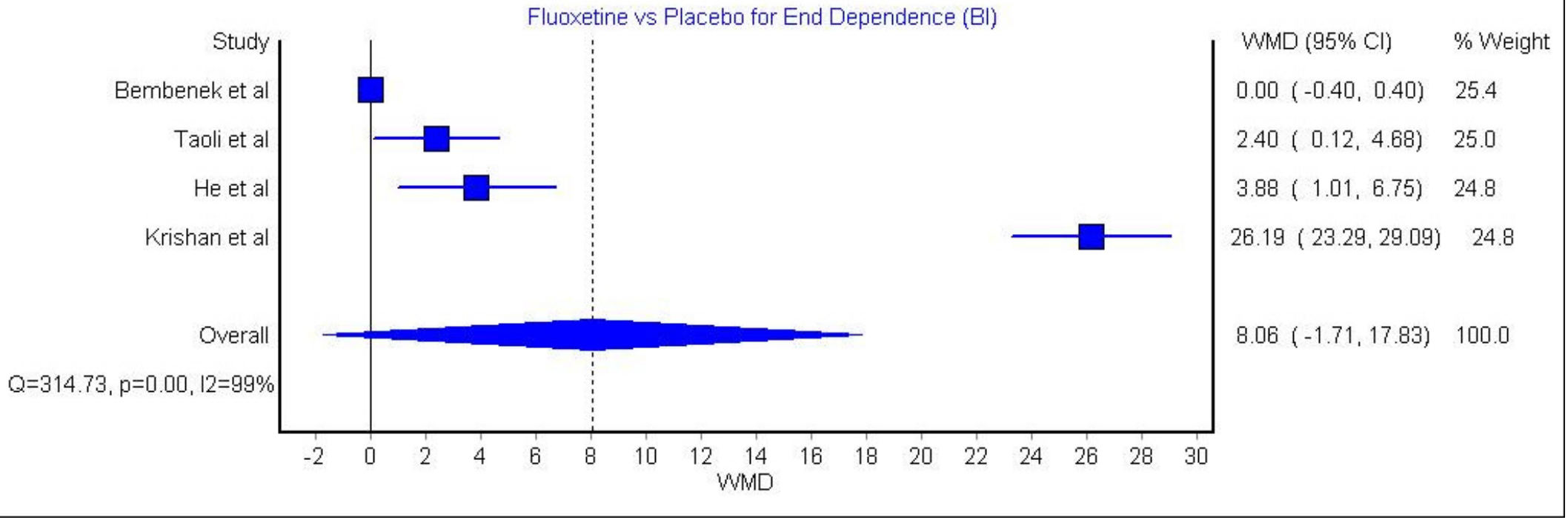


Figure S13: Fluoxetine for Improving Post-stroke Disability as a Binary Variable 19,21,23,27,40,57,58,.

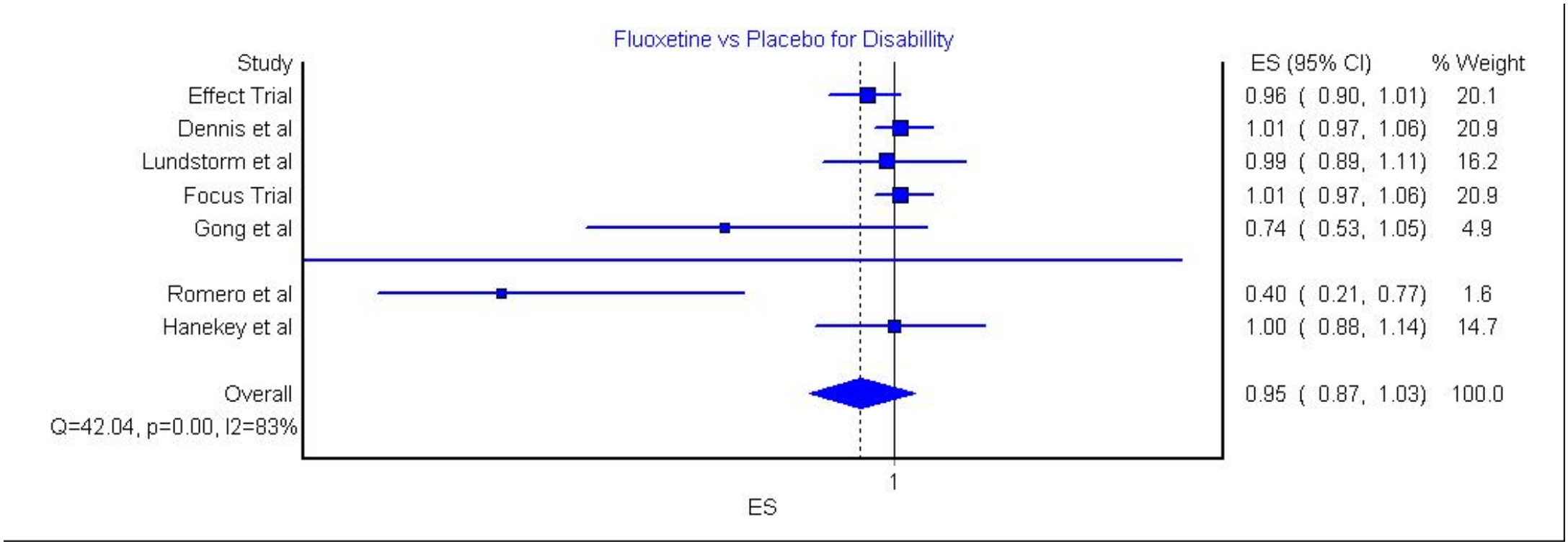
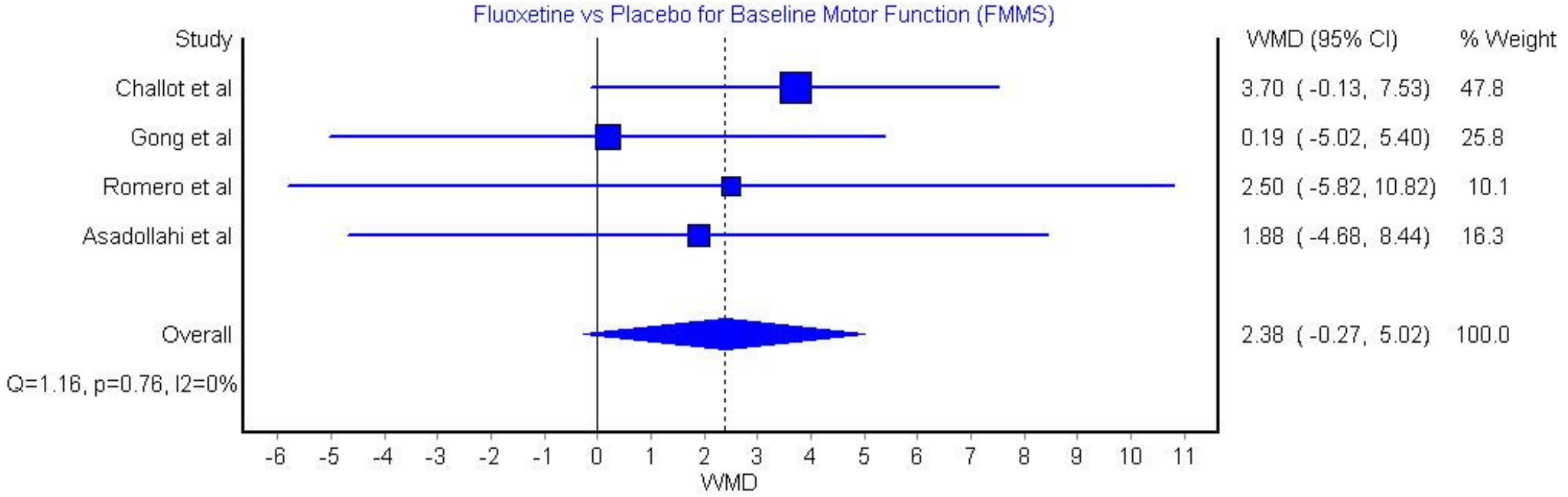


Figure S14: Fluoxetine for Improving Post-stroke Motor Function Provided by FMMS 18,19,23,29.



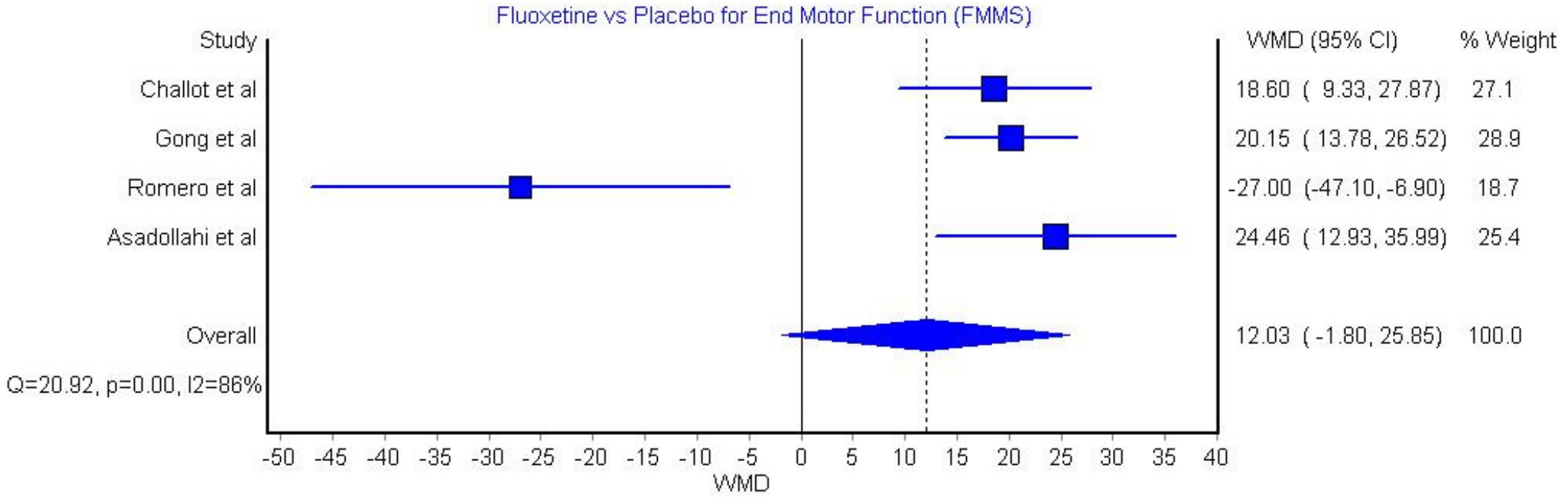
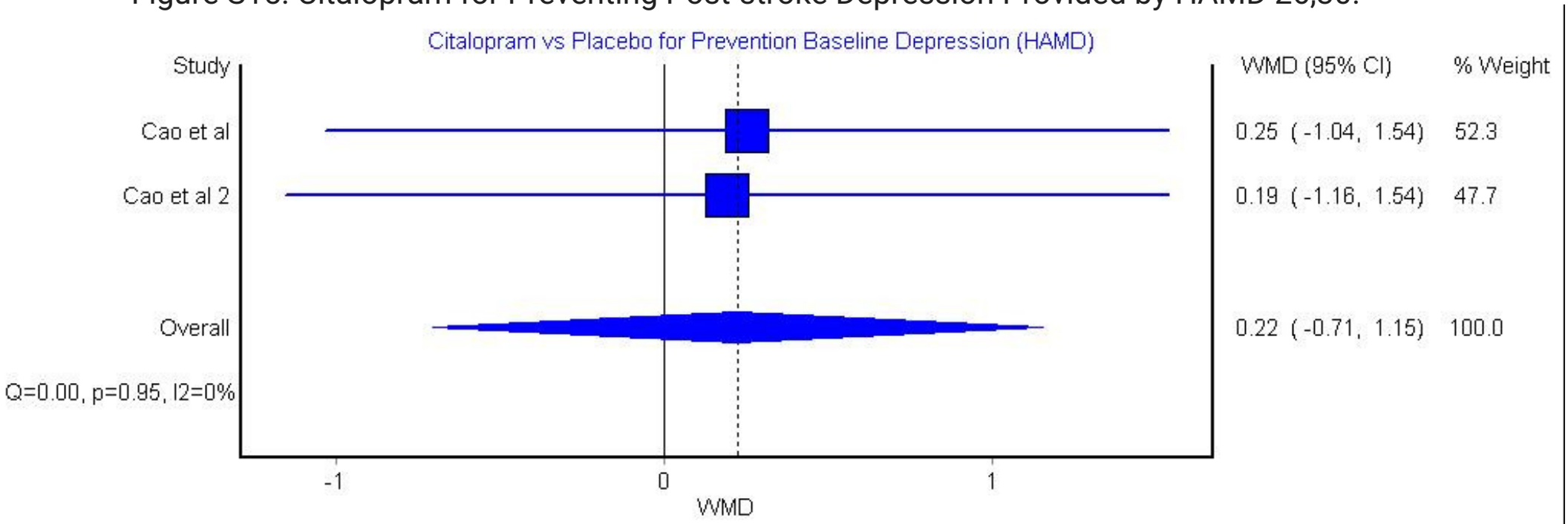


Figure S15: Citalopram for Preventing Post-stroke Depression Provided by HAMD 26,30.



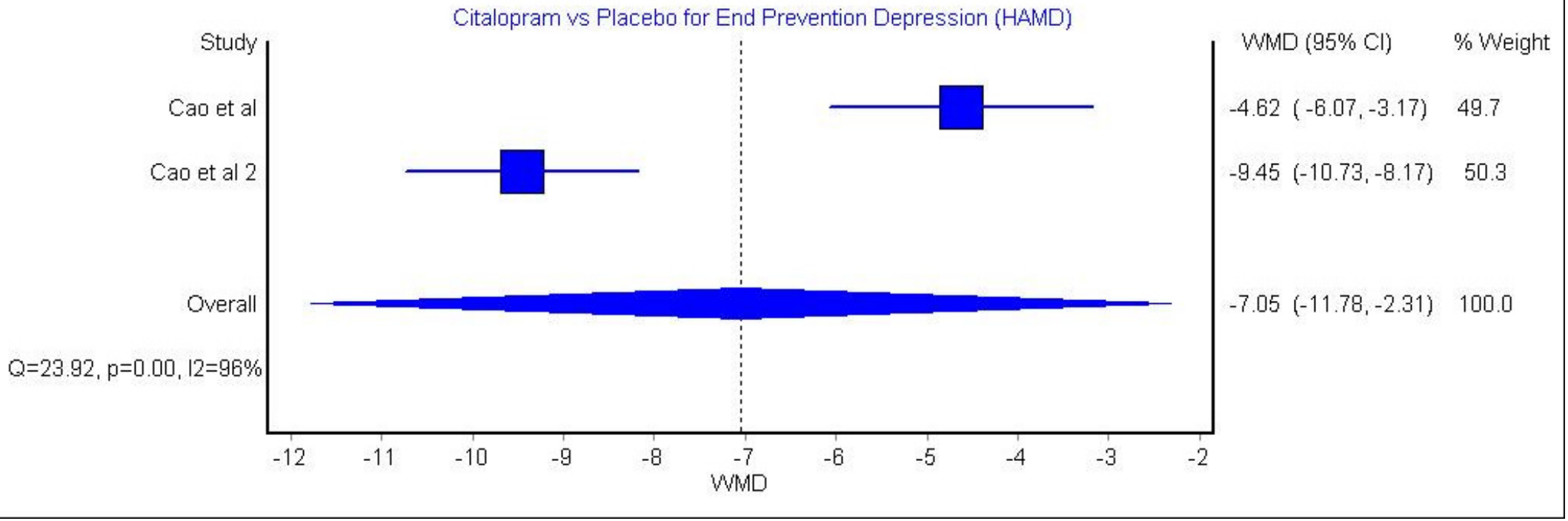
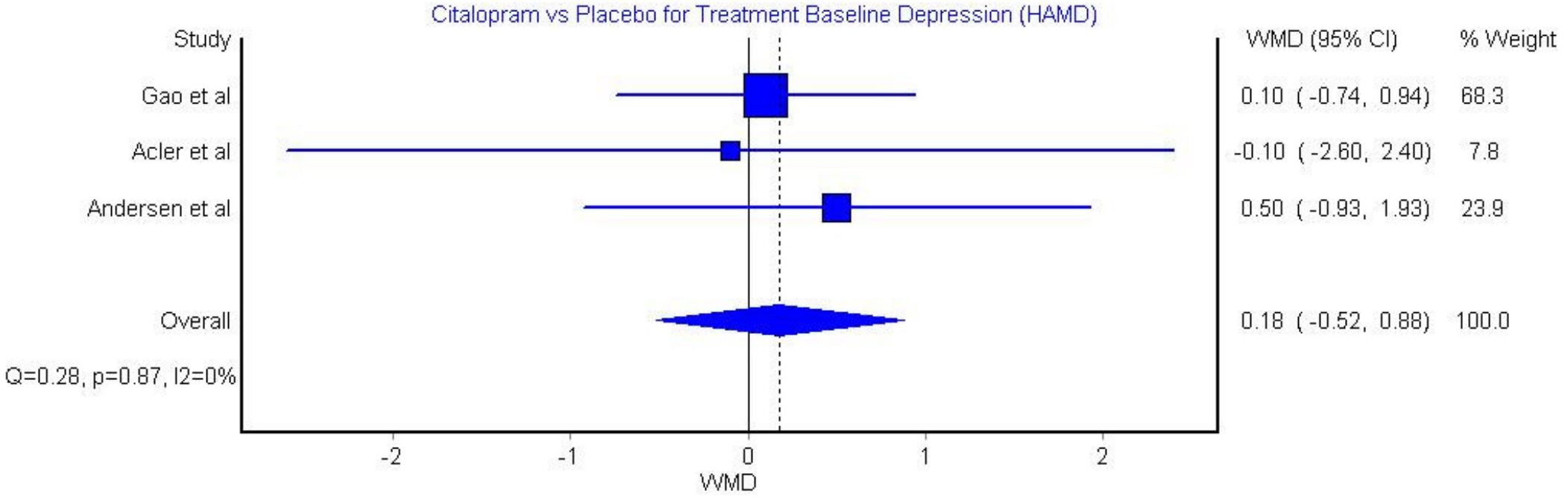


Figure S16: Citalopram for Treating Post-stroke Depression Provided by HAMD 46,49,53.



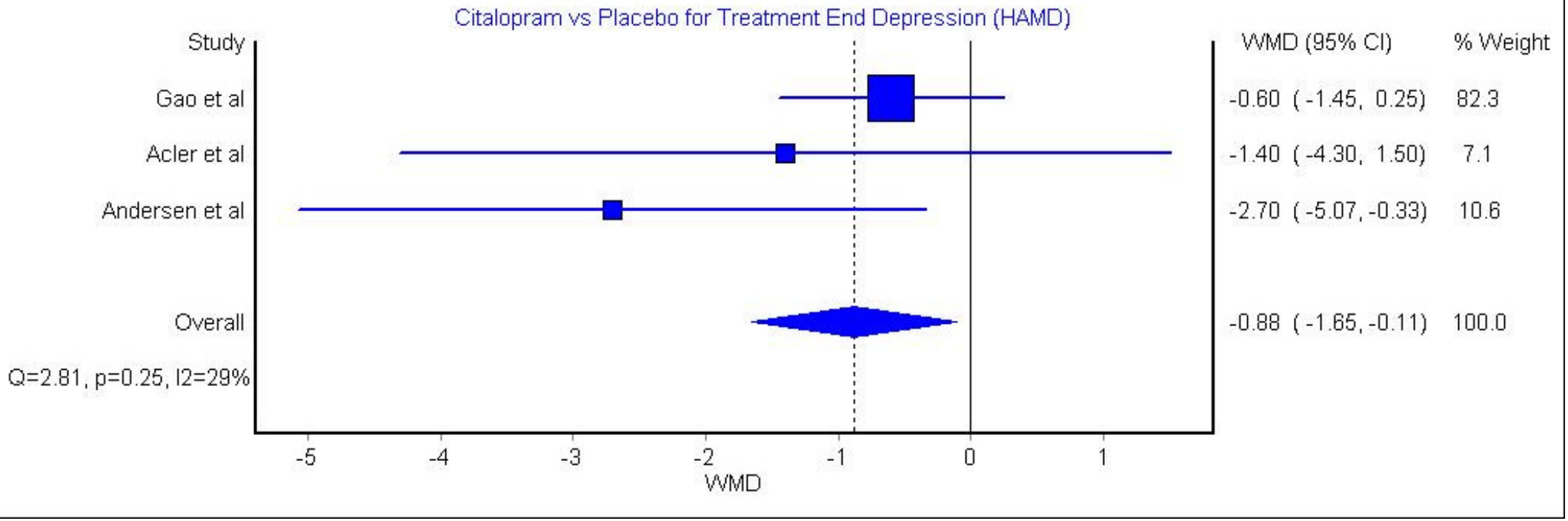


Figure S17: Citalopram for Treating Post-stroke Depression as a Binary Variable 18,43.

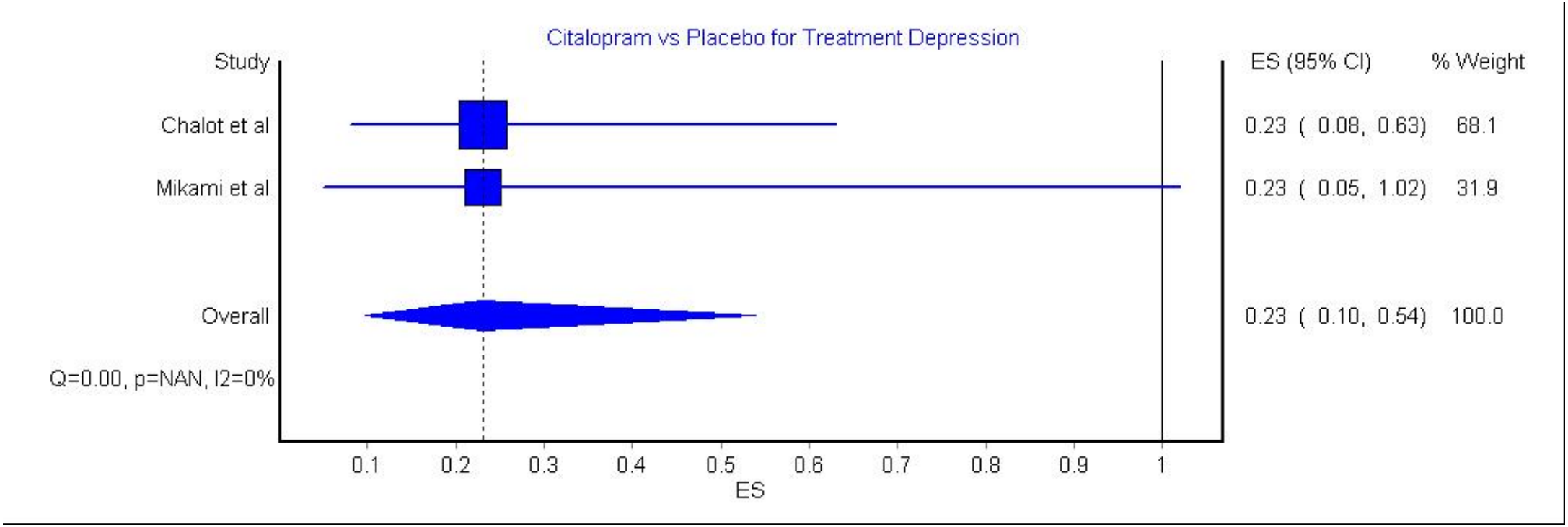


Figure S18: Citalopram for Preventing Post-stroke Depression as a Binary Variable 26,33,56.

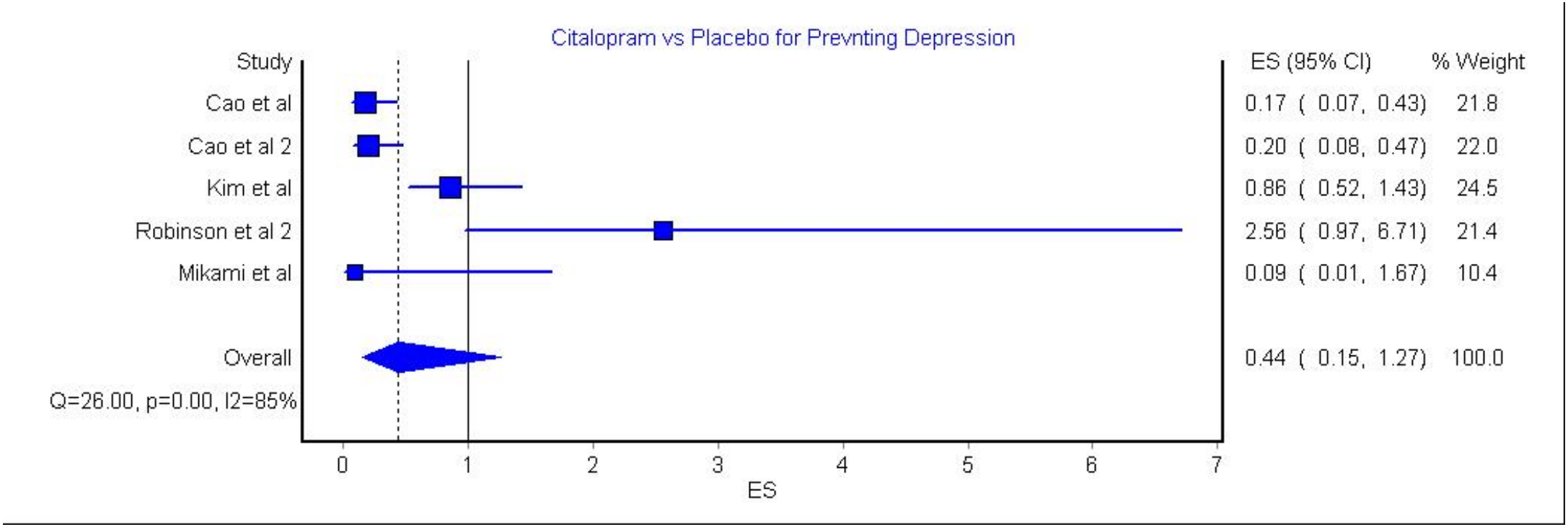
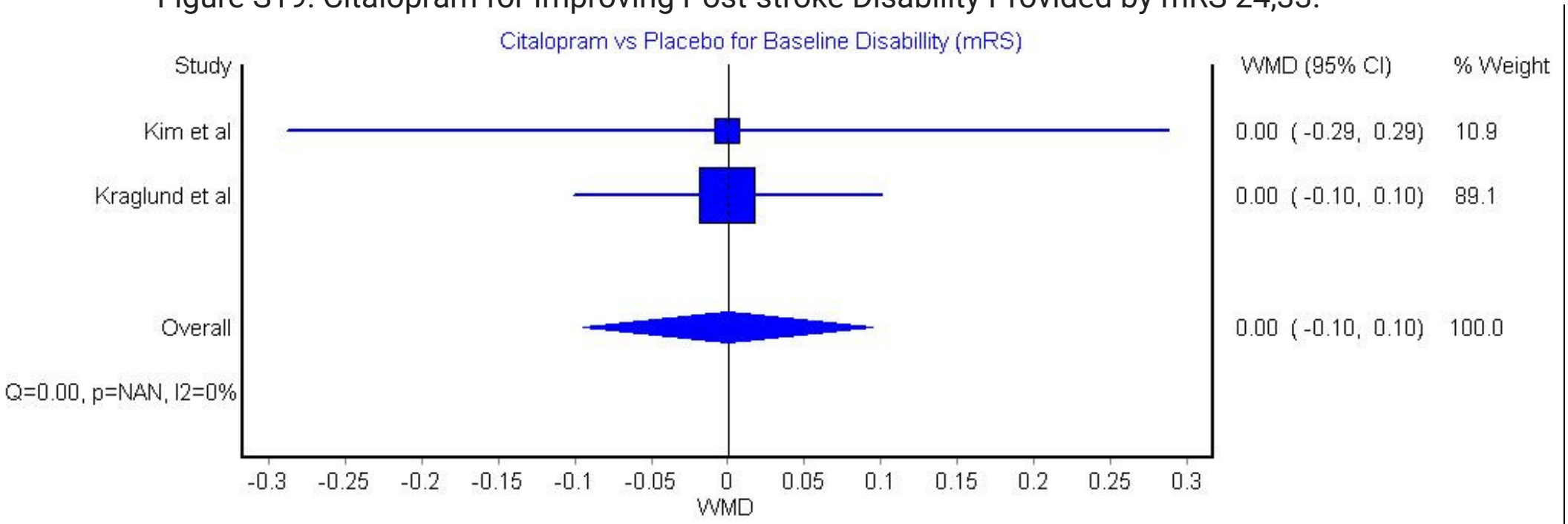


Figure S19: Citalopram for Improving Post-stroke Disability Provided by mRS 24,33.



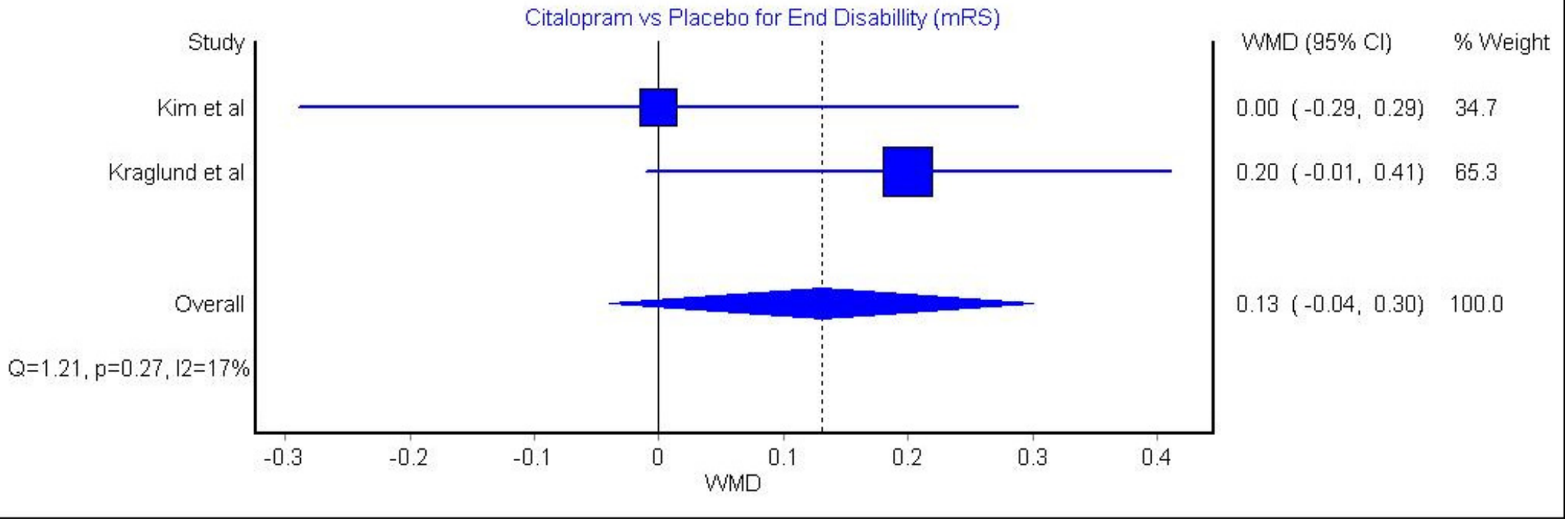


Figure S20: Citalopram for Improving Post-stroke Disability as a Binary Variable 20,24.

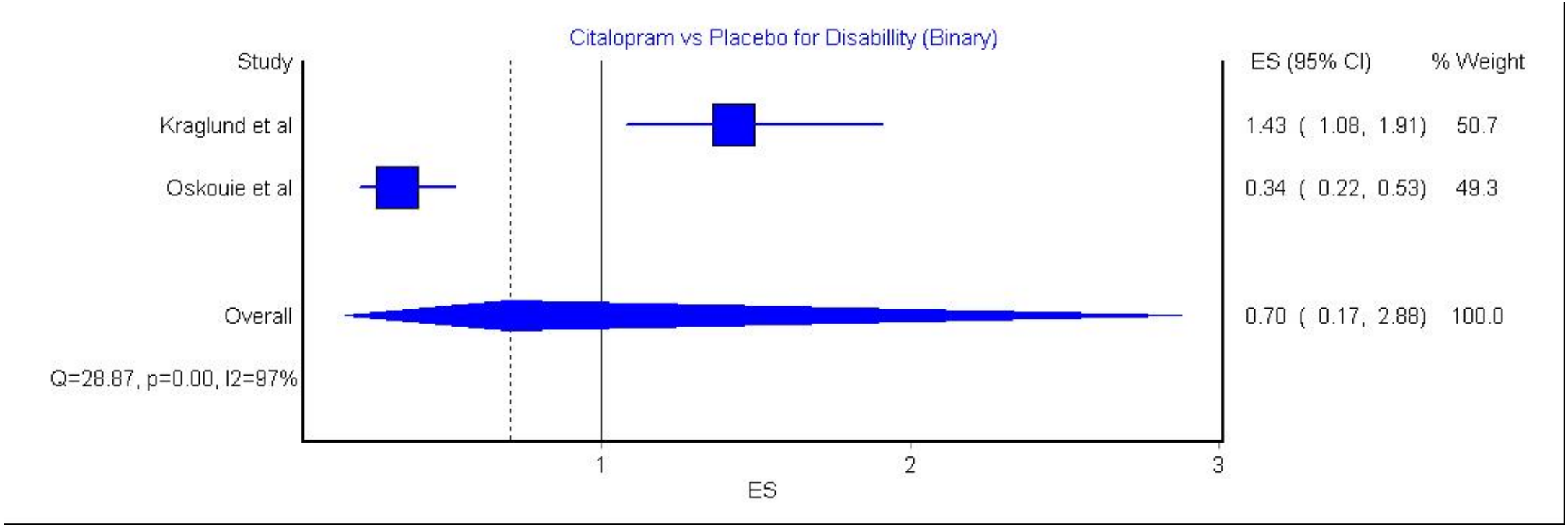
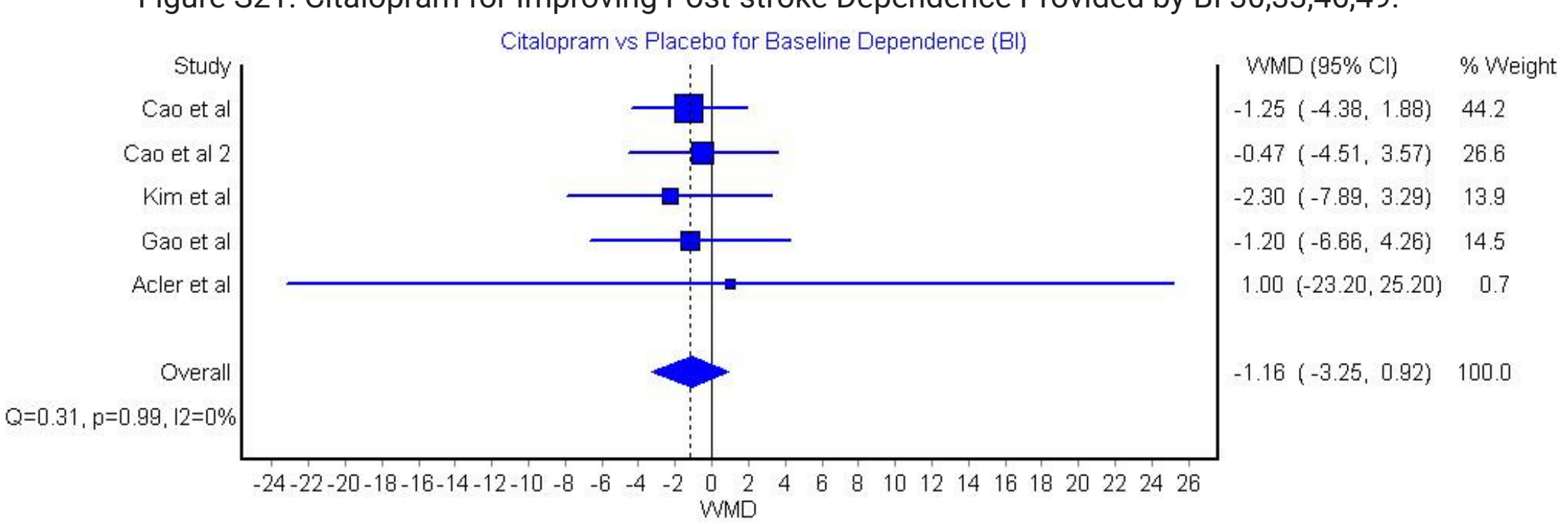


Figure S21: Citalopram for Improving Post-stroke Dependence Provided by BI 30,33,46,49.



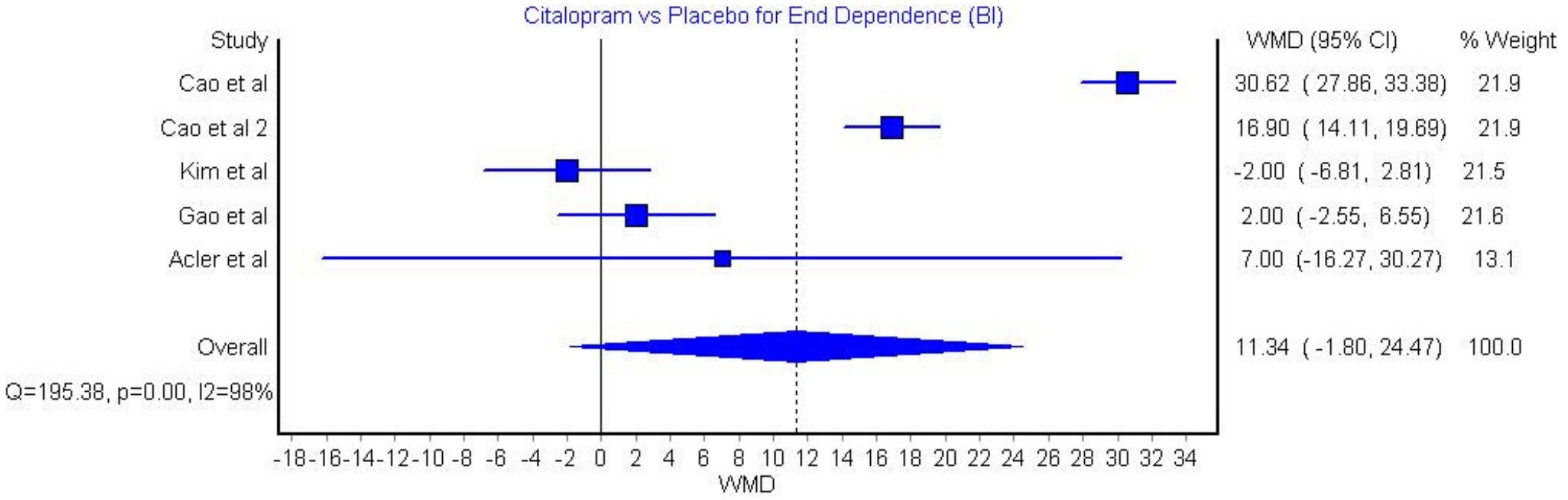
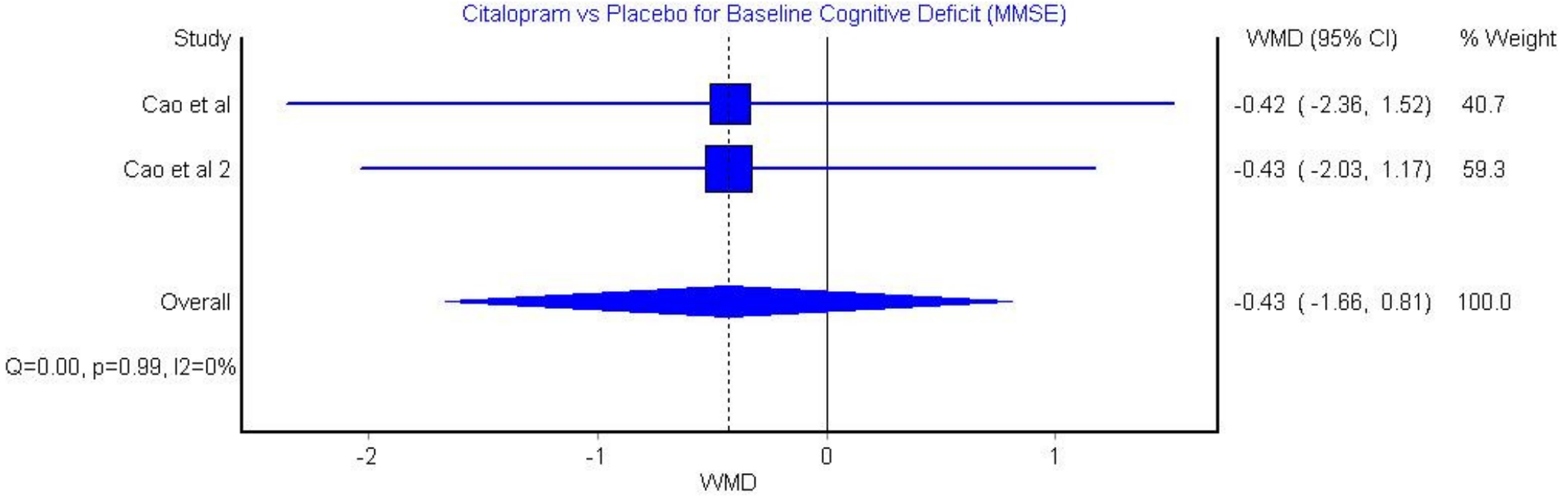


Figure S22: Citalopram for Improving Post-stroke Cognitive Functions Provided by MMSE 26,30.



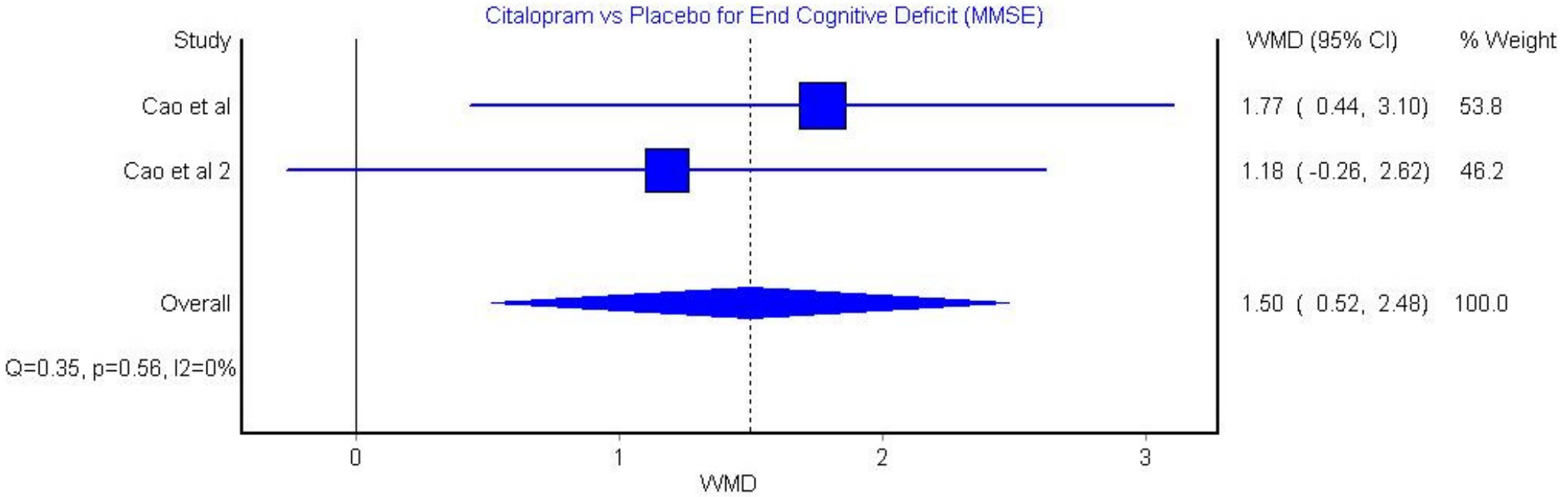


Figure S23: Citalopram for Improving Post-stroke Motor Functions Provided by NIHSS 19,20,33,49.