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REVIEW

A meta-analysis of effects of selective serotonin reuptake inhibitors on blood pressure in depression treatment: outcomes from placebo and serotonin and noradrenaline reuptake inhibitor controlled trials

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Zhuoyuan Zhong[1,*]
Limin Wang[2,*]
Xiaojun Wen[3]
Yunyun Liu[4]
Yafei Fan[5]
Zhonglin Liu[5]

[1]Department of Neurology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; [2]Department of Neurology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangdong Neuroscience Institute, Guangzhou, China; [3]Department of Neurology, Guangzhou First Municipal People's Hospital, Guangzhou Medical University, Guangzhou-Birmingham University Brain and Cognition Center, Guangzhou, China; [4]Department of Neurology, the Sixth Affiliated Hospital Sun Yat-sen University, Guangzhou, China; [5]Department of Neurology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

*These authors contributed equally to this work

Correspondence: Zhonglin Liu
Department of Neurology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, 107 Yan Jiang West Road, Guangzhou, Guangdong, China
Tel +86 020 8133 2621
Fax +86 020 8133 2833
Email 13719438236@126.com

Background: Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have been commonly prescribed for depression treatment. However, their effects on blood pressure are unclear.

Materials and methods: Effects on blood pressure of depressive patients in two groups (SSRIs versus placebo and SSRIs versus SNRIs) were evaluated. A search was conducted for double-blind, randomized controlled trials (RCTs) in PubMed, EMBASE, ISI Web of Science, PsycNET, CCRCT, and DARE (up to March 2017). The outcomes were systolic blood pressure (SBP) changes and diastolic blood pressure (DBP) changes from baseline to endpoint or to a certain period of treatment duration. Weighted mean differences (WMDs) and 95% CIs were calculated and pooled using random effects models. The χ^2 test and I^2 statistics were used to assess heterogeneity. Funnel plots, Begg's test, and Egger's test were used to estimate publication bias.

Results: A total of 23 RCTs involving 13,285 participants were included. Patients on SSRIs showed no significant differences in blood pressure changes compared with placebo. In the group of SSRIs versus SNRIs, overall SBP changes and DBP changes revealed statistical significances (WMD 1.5 mmHg, 95% CI −2.15, −0.84, Z=4.46, P<0.00001 and WMD 1.34 mmHg, 95% CI −1.92, −0.75, Z=6.18, P<0.00001). Subgroup analyses on treatment duration and age further evidenced these findings.

Conclusion: It was established that SSRIs did not affect blood pressure, while SNRIs led to a modest increase in SBP and DBP with statistical significance compared with SSRIs.

Keywords: meta-analysis, blood pressure change, depression treatment, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, depression, antidepressant, systolic blood pressure, diastolic blood pressure

Introduction

Major depression manifests kinds of cognitive and biological symptoms, leading to a debilitating condition. Worldwide, 17% of people are likely to experience major depression during their lifetime; it is especially prevalent in patients with cardiovascular disorders.[1] It is well established that depressive patients tend to have unhealthy lifestyles including smoking, physical inactivity, and poor medication adherence. This in turn exacerbates cardiovascular conditions including hypertension and left ventricular hypertrophy.[2] Depressed individuals, whether with a clinical diagnosis

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of depression, have been reported to have a higher occurrence of morbidity and mortality for cardiovascular events.[3] Some studies indicate that low blood pressure (BP) is associated with increased prevalence of depression, as well as with depressive symptom severity, which is independent of age, sex, or cardiovascular disease,[4] even independent of baseline BP or other risk factors usually associated with hypertension. This association is not explained by the use of antidepressants or antihypertensive medications.[5] The Three City Study confirms that both depressed men and women have lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), which are unrelated to antihypertensive or psychotropic agents.[6] In contrast, a meta-analysis suggests anxiety and hypertension are significantly correlated, drawing the conclusion that anxiety is an independent risk factor for incident hypertension.[7] Anxiety and depression are closely linked.[8] A previous review also showed an increased risk of hypertension in depressed patients and an increased risk of depression in hypertensive patients.[9]

Besides controversies regarding the connection between depression and BP level, the role of antidepressants in mood disorders such as anxiety and depression and BP is equivocal. Tricyclic antidepressants have been reported to result in higher mean SBP and DBP, thus making hypertension stage 1 more likely.[10] Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), the second-generation antidepressants, are prescribed for both anxiety and depression, consisting of a tower of strength in treatment of affective disorders. Escitalopram results in a slight decrease in BP without dose effect, though not clinically meaningful.[11] Furthermore, it has been reported that a modest reduction in SBP and DBP could be observed when statistically comparing fluoxetine with placebo during short-term treatment.[12] Effects of venlafaxine and duloxetine on BP have been depicted in previous studies.[13–15] Nevertheless, whether SSRIs increase or decrease BP during the treatment duration of depression and whether significantly different BP variations exist between SSRIs and SNRIs seem ambiguous. It is reported that SSRIs can affect cardiovascular function.[16] SSRIs are rarely associated with cardiac death but cause side effects such as hypotension and mild bradycardia.[17] SNRIs can cause elevation of BP, particularly of DBP. Does antidepressant use act to confound the relationship between psychopathology and BP?

Currently, reports of effects on BP exerted by SSRIs are rather scarce, and there is a lack of detailed analysis investigating effects on BP. Considering that the magnitude of BP changes has not been described elaborately enough with SSRI and SNRI administration, we conducted this meta-analysis in terms of BP change, providing directly perceived clinical evidence. In this context, we reported BP changes during SSRI treatment for depression compared with placebo and SNRIs, respectively.

Materials and methods

Data search

All randomized, double-blind clinical trials which compared SSRIs with SNRIs or placebo in treatment of depression were searched and assessed for inclusion. A computerized search was performed in PubMed, EMBASE, ISI Web of Science, PsycNET, CCRCT, and DARE (up to March 2017) for original research articles. Reference lists of relevant studies and reviews were further examined to reveal additional studies. Search terms included "fluoxetine", "citalopram", "escitalopram", "fluvoxamine", "sertraline", "paroxetine", "placebo", "venlafaxine", "duloxetine", "milnacipran", "major depressive disorder" (MDD), "depression", and "randomized controlled trial" (RCT). The comparison interventions were placebo treatments or SNRIs. Detailed data including changes of SBP and DBP were carefully examined. We excluded open-label trials and studies with insufficient information about BP.

Patients

The inclusion criteria for patients were: a) outpatients or inpatients meeting the diagnostic standard of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) or text revision (DSM-IV TR) diagnosis of MDD, and b) single episode or recurrent MDD. There was no age restriction. Exclusion criteria were: a) past or current presence of seizure disorder; b) depression with psychotic feature, diagnosis of schizophrenia, schizoaffective disorder, and bipolar disorder; c) posttraumatic stress disorder; d) uncontrolled hypertension; e) female patients who were pregnant or lactating; and f) a history of alcohol or substance dependence or abuse.

Data extraction and quality assessment

For each trial, we extracted data recorded in a standardized Excel file, including the first author, year of publication, sample size, population age, treatment duration, medication doses, and checked by a third investigator. Two investigators extracted the data and trial quality information from the studies selected for inclusion in the meta-analysis independently to evaluate eligibility. If the studies were approved to meet inclusion criteria by both reviewers, the trials were included in the analysis. Any inconsistencies were reviewed

and resolved by discussion and consensus. Outcome variables were the effects of individual BP changes.

For each eligible trial, risks of bias were assessed in detail, according to the bias assessment of the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.10). Treatment agents, blinding, and randomization were demonstrated in detail according to the primary trials.

Statistical analysis

We calculated continuous outcomes using weighted mean differences (WMDs) with 95% CIs, since each study used the same outcome for the studied adverse effects, and this preserves the original BP change, which is intuitively interpreted (eg, a WMD of 5 means a 5 mmHg difference in BP between the two groups). The inverse variance statistical method and random effects model were applied to calculate pooled data. When SDs were not reported, they were derived from other available data or we contacted authors to supply the statistics. In the absence of data from authors, we used the average SDs of other studies with the same medication.[18]

We evaluated study heterogeneity by χ^2 test and I^2 statistics, with statistical significance set at χ^2 $P<0.1$ and $I^2>50\%$ indicating heterogeneity. We conducted sensitivity analyses by reestimating pooled WMD by omitting one study at a time to evaluate the influence of each individual study on the overall meta-analysis. Furthermore, for comparing SSRIs with SNRIs, we conducted subgroup analyses based on treatment durations (long-term and short-term) and different ages (≥18 years and <18 years) to clarify potential sources of heterogeneity.

Publication bias was assessed by conducting Begg's test and Egger's test. If *Pr* or *P*-value was <0.05, publication bias of the meta-analysis was considered representative of statistical significance. Data were processed by using the computer program Review Manager (version 5.3. the Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2014) chiefly, and STATA (version 12.0; StataCorp LP, College Station, TX, USA) was used in the quantitative assessment of publication bias and sensitivity analyses as supplement.

Results

The initial search yielded 1,824 abstracts, of which 628 full texts were inspected, as outlined in Figure 1. There were 23 non-duplicated trials[19–41] comparing SSRI intervention with placebo or SNRIs included for this meta-analysis, after excluding other interventions and those with lack of analyzable data about BP or length of intervention shorter than 4 weeks. Except for four studies based on children and teenagers,[26,29,30,40] all other trials included adults. There were 15 trials available for analysis of comparing SSRIs with placebo. One study included patients with MDD combined with a history of acute myocardial infarction or unstable angina.[20] Two trials were about MDD combined with coronary artery disease[28] or depressive disorders combined with acute coronary syndrome,[33] respectively. Considering the fact that comorbid cardiovascular diseases were in a steady state, antihypertensive and other cardiovascular medications were prescribed on stable doses for study duration, the previously mentioned three trials were included in the analysis. A total of 18 trials comparing SSRIs with two SNRIs were included. No qualified studies on fluvoxamine and milnacipran were identified. There were six trials including different medication doses or durations; thus, those data of identically designed studies were all included in the analysis. In all, the group of SSRIs versus placebo included 4,662 patients and 8,623 patients in the SSRIs versus SNRIs group. Table 1 outlines the main characteristics of the 23 RCTs. Figure 2 presents the summary of the risk of bias of each individual study.

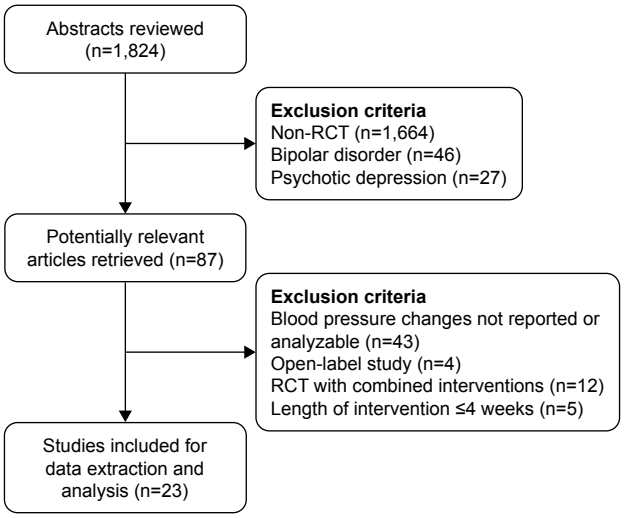

Figure 1 Flow chart of study selection.
Abbreviation: RCT, randomized controlled trial.

BP changes in SSRI groups versus placebo

Differences between individual SSRIs and placebo regarding SBP and DBP changes are summarized in Figures 3 and 4. Overall, SSRI interventions were associated with a pooled SBP change of –0.04 mmHg (95% CI –0.68, 0.59) versus placebo (Figure 3), indicating no significant difference with Z=0.14, P=0.89. Subgroup difference test revealed no significant difference: χ^2=3.46, df=4, P=0.48, I^2=0%.

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Study	Design	Main inclusion criteria	Mean age (SD), years (SSRI placebo or SSRIs/placebo/SNRIs)	Duration (weeks)	Intervention, number, and doses	
					Treatment	Comparison
Lenox-Smith and Jiang 2008[19]	RCT, double-blind	MDD	Citalopram 43 (11.2) Venlafaxine 42 (10.8)	12	Citalopram (20–60 mg/d), N=205	Venlafaxine (75–300 mg/d), N=199
Glassman et al 2002[20]	RCT, double-blind	MDD and AMI or UA	Sertraline 56.8 (11.1) Placebo 57.6 (10.4)	16	Sertraline (50–200 mg/d), N=186	Placebo, N=183
Nierenberg et al 2007[21]	RCT, double-blind	MDD	Escitalopram 43.3 (13.0) Placebo 42.5 (12.3) Duloxetine 41.1 (11.6)	8	Escitalopram (10 mg/d), N=274	Duloxetine (60 mg/d), N=273, placebo, N=137
Coleman et al 2001[22]	RCT, double-blind	Major depression	Fluoxetine 37.1 (18–76)[a] Placebo 36.7 (19–62)	8	Fluoxetine (20–60 mg/d), N=154	Placebo, N=152
Nemeroff et al 2007[23]	RCT, double-blind	MDD	Fluoxetine 37.9 (11.5) Placebo 40.4 (11.7) Venlafaxine 40.1 (11.1)	6	Fluoxetine (20–60 mg/d), N=101	Venlafaxine (75–225 mg/d), N=96, placebo, N=101
Oslin et al 2003[24]	RCT, double-blind	Depressive disorder	Sertraline 83.8 (9.8) Venlafaxine 81.2 (10.8)	10	Sertraline (25–100 mg/d), N=25	Venlafaxine (75–150 mg/d), N=27
Goldstein et al 2004[25]	RCT, double-blind	Depression	Paroxetine 40 (11) Placebo 57 (64) Duloxetine (40 mg/d) 48 (56) Duloxetine (80 mg/d) 56 (62)	8	Paroxetine (20 mg/d), N=87	Duloxetine (40 mg/d), N=86, Duloxetine (80 mg/d), N=91, placebo, N=89
Brent et al 2008[26]	RCT, double-blind	MDD	Different SSRIs 16.0 (1.6) Venlafaxine 15.8 (1.5)	12	Different SSRIs (paroxetine, citalopram, fluoxetine), (20–40 mg/d), N=168	Venlafaxine (150–225 mg/d), N=166
Sheehan et al 2009[27]	RCT, double-blind	MDD	Fluoxetine 37.8 (11.1) Placebo 39.9 (13.0) Venlafaxine 41.7 (12.8)	6	Fluoxetine (60–80 mg/d), N=99	Venlafaxine (225–375 mg/d), N=94, placebo, N=95
Lesperance et al 2007[28]	RCT, double-blind	MDD and CAD	Citalopram 57.9 (9.15) Placebo 58.4 (9.16)	12	Citalopram (20–40 mg/d), N=142	Placebo, N=142
Emslie et al 2014[29]	RCT, double-blind	MDD	Fluoxetine 13.0 (3.2) Placebo 13.1 (2.9) Duloxetine (60 mg/d) 12.9 (2.9) Duloxetine (30 mg/d) 12.9 (2.9)	10	Fluoxetine (20–40 mg/d), N=112	Duloxetine (60 mg/d), N=105, Duloxetine (30 mg/d), N=114, placebo, N=117
Emslie et al 2015[30]	RCT, double-blind	MDD	13.1[b]	10	Fluoxetine (20–40 mg/d), N=226	Duloxetine (60–120 mg/d), N=332, placebo, N=220
Croft et al 1999[31]	RCT, double-blind	MDD	Sertraline 36.0 (19–61)[c] Placebo 37.4 (19–64)	8	Sertraline (50–200 mg/d), N=119	Placebo, N=121
Nelson et al 2006[32]	RCT, double-blind	MDD	Paroxetine 43.2 (11.9) Placebo 42.9 (12.5) Duloxetine 43.4 (12.2)	8	Paroxetine (20 mg/d), N=359	Duloxetine (40–120 mg/d), N=736, placebo, N=371
Kim et al 2015[33]	RCT, double-blind	Depressive disorders and ACS	Escitalopram 60.1 (10.9) Placebo 58.5 (10.6)	24	Escitalopram (5–20 mg/d), N=108	Placebo, N=109
Keller et al 2007[34]	RCT, double-blind	MDD	10 w: Fluoxetine 40.0 (11.6) Venlafaxine 39.6 (12.2) 34 w: Fluoxetine 40.9 (11.5) Venlafaxine 40.4 (12.0)	10 34	Fluoxetine (20–60 mg/d) (10 w, N=266), (34 w, N=185)	Venlafaxine (75–300 mg/d), (10 w, N=781), (34 w, N=530)
Detke et al 2004[35]	RCT, double-blind	MDD	Paroxetine 42.0 (10.6) Placebo 43.7 (12.2) Duloxetine (80 mg/d) 43.1 (11.1) Duloxetine (120 mg/d) 44.7 (10.7)	8 24	Paroxetine (20 mg/d), (8 w, N=85; 24 w, N=70)	Duloxetine (80 mg/d), (8 w, N=93; 24 w, N=70) Duloxetine (120 mg/d), (8 w, N=93; 24 w, N=74) placebo (8 w, N=93; 24 w, N=58)
Allard et al 2004[36]	RCT, double-blind	Major depression	Citalopram 72.5 (5.7) Venlafaxine 73.6 (5.9)	8 22	Citalopram (10–20 mg/d), N=75	Venlafaxine (75–150 mg/d), N=73

(*Continued*)

Table 1 (*Continued*)

Study	Design	Main inclusion criteria	Mean age (SD), years (SSRI Placebo or SSRIs/Placebo/SNRIs)	Duration (weeks)	Intervention, number, and doses	
					Treatment	Comparison
Perahia et al 2006[37]	RCT, double-blind	MDD	Paroxetine 45.8 (10.6) Placebo 44.7 (10.1) Duloxetine (80 mg/d) 46.5 (12.7) Duloxetine (120 mg/d) 44.0 (10.8)	8 32	Paroxetine (20 mg/d), (8 w, N=96; 32 w, N=70)	Duloxetine (80 mg/d), (8 w, N=93; 32 w, N=70) Duloxetine (120 mg/d), (8 w, N=102; 32 w, N=80) placebo (8 w, N=99; 24 w, N=70)
Lee et al 2007[38]	RCT, double-blind	MDD	Paroxetine 38.0 (15.27) Duloxetine 39.0 (13.95)	8	Paroxetine (20 mg/d), N=240	Duloxetine (60 mg/d), N=238
Bielski et al 2004[39]	RCT, double-blind	MDD	Escitalopram 37.3 (12.3) Venlafaxine 37.5 (11.6)	8	Escitalopram (20 mg/d), N=97	Venlafaxine (225 mg/d), N=98
Atkinson et al 2014[40]	RCT, double-blind	MDD	Fluoxetine 13.1 (3.3) Placebo 13.3 (3.1) Duloxetine 13.1 (3.0)	10	Fluoxetine (20–40 mg/d), N=114	Duloxetine (60–120 mg/d), N=113, placebo, N=103
Wade et al 2007[41]	RCT, double-blind	MDD	Escitalopram 43.3 (11.6) Duloxetine 44.5 (11.0)	24	Escitalopram (20 mg/d), N=112	Duloxetine (60 mg/d), N=114

Notes: [a]SDs were missing. Age ranges of fluoxetine group and placebo were 18–76 and 19–62 years, respectively. [b]The mean age of randomized patients included in the three groups was 13.1. [c]SDs were missing. Age ranges of sertraline group and placebo were 19–61 and 19–64 years, respectively.
Abbreviations: RCT, randomized controlled trial; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; AMI, acute myocardial infarction; UA, unstable angina; CAD, coronary artery disease; ACS, acute coronary syndrome.

A pooled DBP change in SSRIs versus placebo group was 0.08 mmHg (95% CI −0.43, 0.60), with no statistical significance, Z=0.32, P=0.75 (Figure 4). There was no significant difference in DBP changes among subgroups: χ^2=1.01, df=4, P=0.91, I^2=0%.

BP changes in SSRIs versus SNRIs groups

Twenty-eight studies reported BP changes in SSRIs versus SNRIs. In the pooled analysis, overall SBP changes and DBP changes revealed statistically significant differences (WMD −1.5 mmHg, 95% CI −2.15, −0.84, Z=4.46, P<0.00001, Figure 5, and WMD −1.34 mmHg, 95% CI −1.92, −0.75, Z=6.18, P<0.00001, Figure 6). There was a low level of heterogeneity across all studies in SBP changes (I^2=39%, P=0.02, Figure 5), while a medium level of heterogeneity was detected in DBP changes (I^2=54%, P=0.0004, Figure 6).

Short-/long-term duration

SBP changes between SSRIs and SNRIs in short-term duration (≤8 weeks) and long-term duration (>8 weeks) differed statistically (WMD −1.51 mmHg, 95% CI −2.44, −0.58, Z=3.18, P=0.001 and WMD −1.46 mmHg, 95% CI −2.42, −0.49, Z=2.95, P=0.003) (Figure 5). Significant differences were observed in DBP changes in short-/long term duration (WMD −1.10 mmHg, 95% CI −1.82, −0.39, Z=3.04, P=0.002 and WMD −1.49 mmHg, 95% CI −2.37, −0.61, Z=3.31, P=0.0009) (Figure 6). Tests for subgroup differences of SBP and DBP changes revealed no significant difference: χ^2=0.01, df=1, P=0.94, I^2=0% and χ^2=0.44, df=1, P=0.51, I^2=0%.

Different ages

A significant difference in SBP changes resulting from age (<18 or ≥18 years) was observed when comparing SSRIs with SNRIs (WMD −1.31 mmHg, 95% CI −2.31, −0.31, Z=2.56, P=0.01 and WMD −1.51 mmHg, 95% CI −2.31, −0.70, Z=3.68, P=0.0002) (Figure 7). DBP changes resulting from age between SSRIs and SNRIs showed a statistical difference (WMD −1.84 mmHg, 95% CI −3.66, −0.01, Z=1.97, P=0.05 and WMD −1.24 mmHg, 95% CI −1.85, −0.63, Z=3.96, P<0.0001) (Figure 8). Tests for subgroup differences of SBP and DBP changes revealed no significant difference: χ^2=0.09, df=1, P=0.76, I^2=0% and χ^2=0.37, df=1, P=0.54, I^2=0%.

Publication bias and sensitivity analysis

We assessed the possibility of publication bias in the articles, which compared the effects on BP in groups of SSRIs versus placebo and SSRIs versus SNRIs. The funnel plot of Begg illustrated a symmetrical distribution of the points, suggesting a lack of publication bias. No obvious publication bias was found by Begg's test and Egger's test (Figure 9). Sensitivity analyses by reestimating pooled WMD when excluding one study at a time showed similar results (Figures 10 and 11).

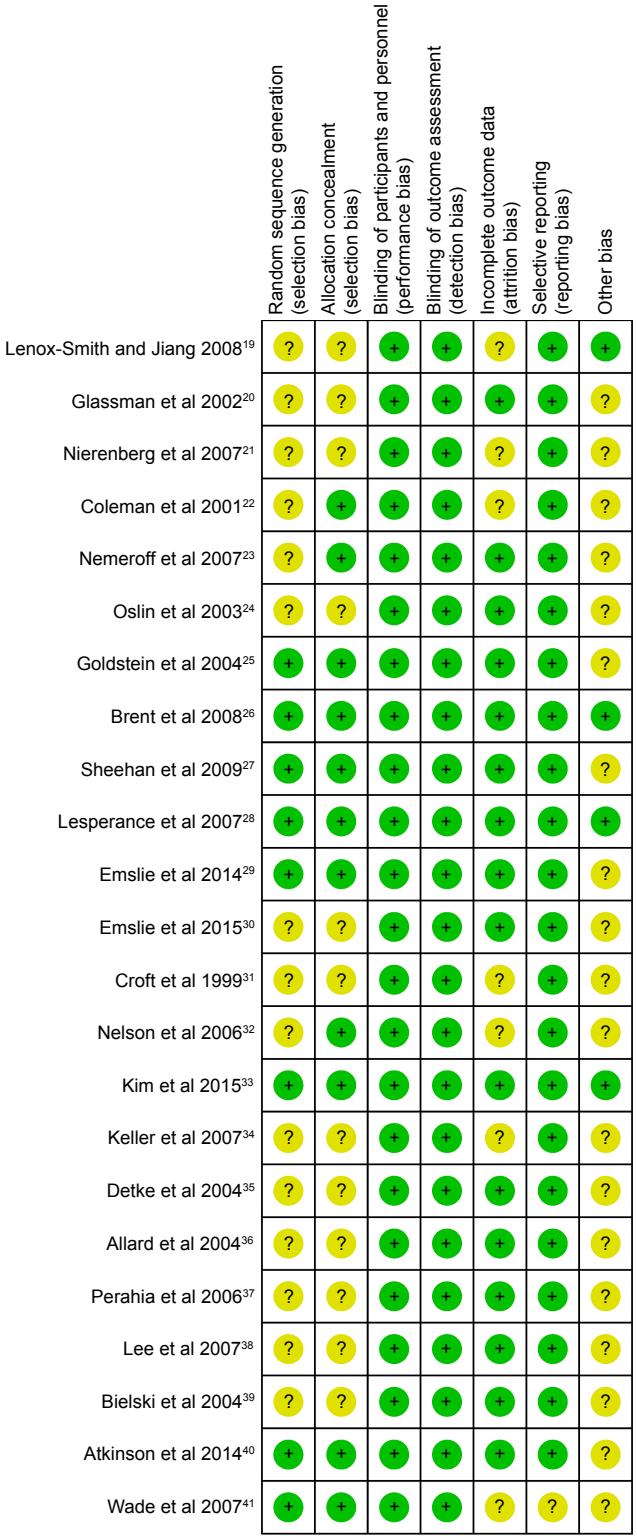

Figure 2 Assessment of risk of bias for each individual trial. ?, unclear risk of bias; +, low risk of bias.

Discussion

The main purpose of this meta-analysis was to critically evaluate the effects of SSRIs and SNRIs on BP in quantification. As illustrated in our randomized, double blind meta-analysis, WMDs varied little among five kinds of SSRIs when compared with placebo. A test on the subgroups revealed no statistical difference, indicating little difference in BP among the five kinds of SSRIs. SSRIs might not cause more apparent fluctuation of BP than placebo. In terms of definite BP changes, each SSRI may be associated with <3 mmHg variation during the period of trials, which showed no close connection with management of BP, at the same time suggesting that SSRIs might be safe in regard to BP. Furthermore, it is reported that depressive disorder is associated with average lower levels of SBP and DBP[6] and less hypertension.[10]

With regard to changes in BP caused by SSRIs versus SNRIs, WMDs were significantly different, though the exact numerical values were small with variations of <3 mmHg. A conclusion that fluctuations in BP were not significantly different in groups of SSRIs compared with placebo may be drawn from our meta-analysis, it may be inferred that SNRIs could lead to higher BP than SSRIs. Both in short-term and long-term duration, SNRIs were associated with escalation of SBP and DBP to some extent. These findings are consistent with conclusions drawn in the previous reports focusing on venlafaxine.[13,14] Mean BP[13] and supine DBP[14] increase with incremental doses of venlafaxine. Incidence of clinically significant increases in BP can be lower at doses below 200 mg daily,[13] and only doses above 300 mg/day lead to statistical and clinical significance of the incidence of elevated supine DBP.[14] A previous study reported that duloxetine at supratherapeutic doses increases supine SBP and DBP by maxima of ~12 mmHg and 7 mmHg above baseline, respectively.[15] Doses of venlafaxine and duloxetine in the included trials of our analysis varied between 75–375 mg/d and 40–120 mg/d, respectively. Because of the paucity of eligible studies and dose modulations, analysis for different doses of medications was not conducted. Nevertheless, it is reliable to highlight that greater BP changes are associated with SNRIs compared to SSRIs; thus, clinicians should monitor BP periodically throughout treatment with venlafaxine and duloxetine.

Depression is associated with reductions in heart rate variability[42] and might be related to low cardiac vagal control,[43] as well as central autonomic dysfunction, a shift of autonomic balance toward sympathetic predominance, leading to cardiovascular somatic symptoms of depression such as higher heart rate and BP lability.[11,42,44] Some studies support the hypothesis that depression is associated with lower BP.[4–6,43] However, how BP changes when depressive symptoms are ameliorated still remains obscure. Antidepressant agents, such as SSRIs and SNRIs,

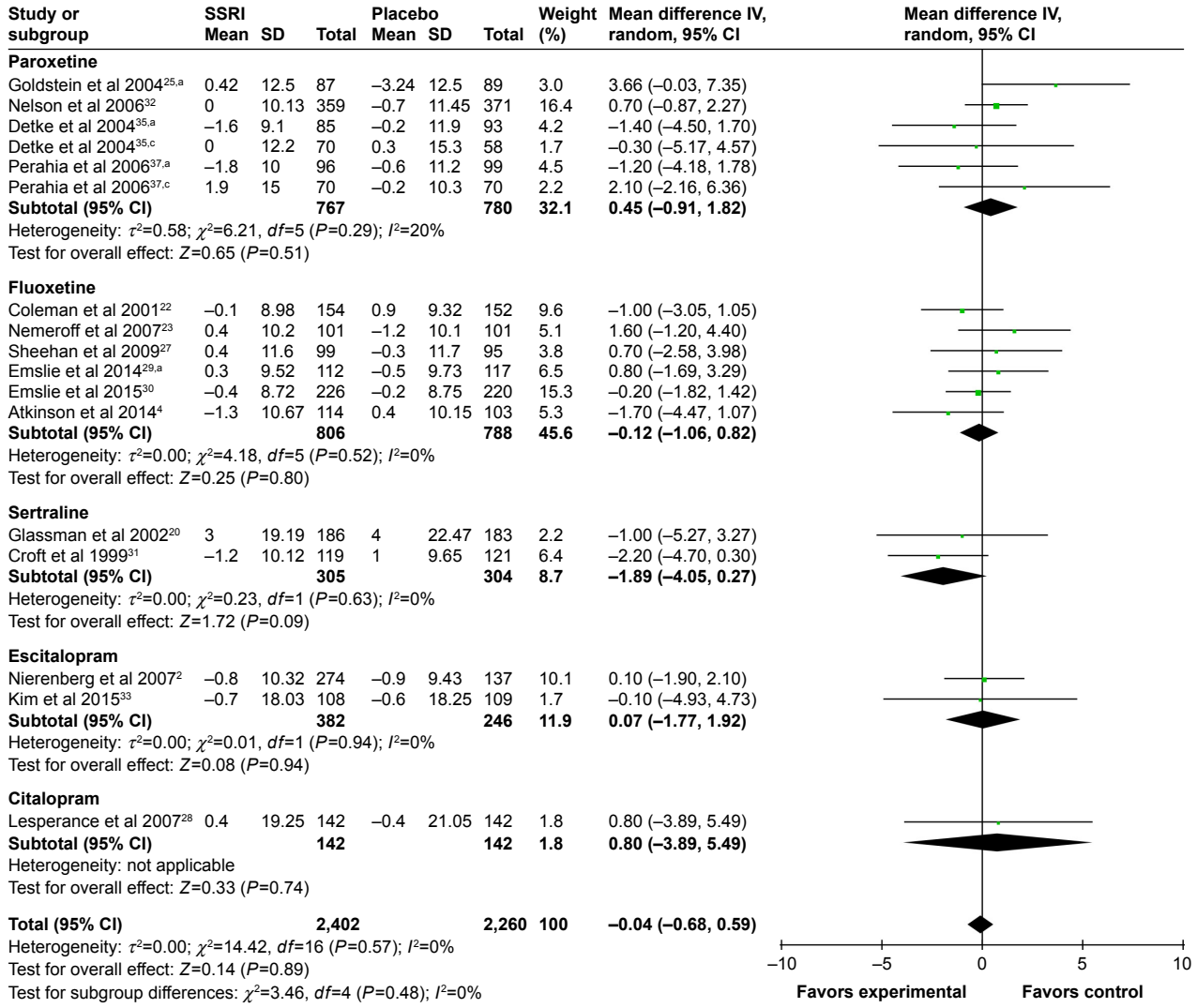

Figure 3 A forest plot of RCTs comparing SSRI group with placebo group for change in systolic blood pressure.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor.

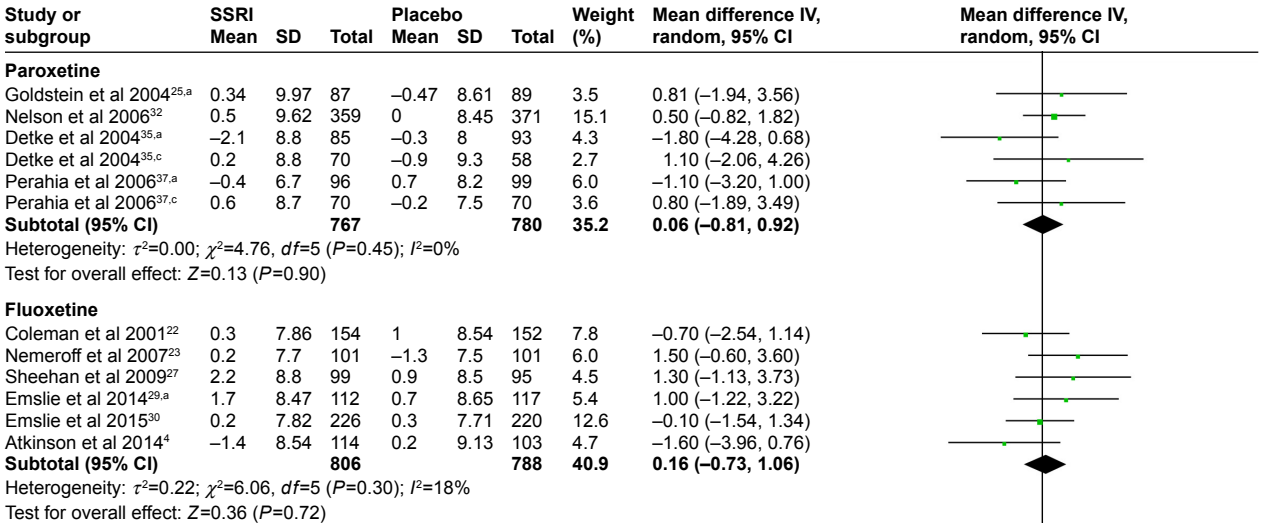

Figure 4 (*Continued*)

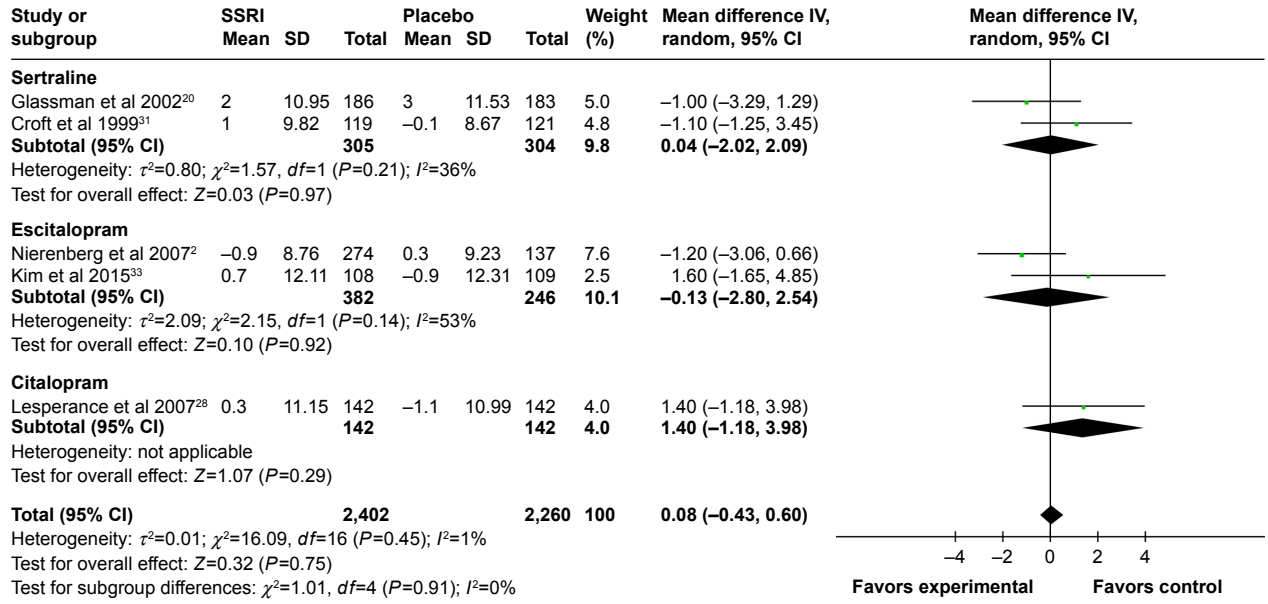

Figure 4 A forest plot of RCTs comparing SSRI group with placebo group for change in diastolic blood pressure.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor.

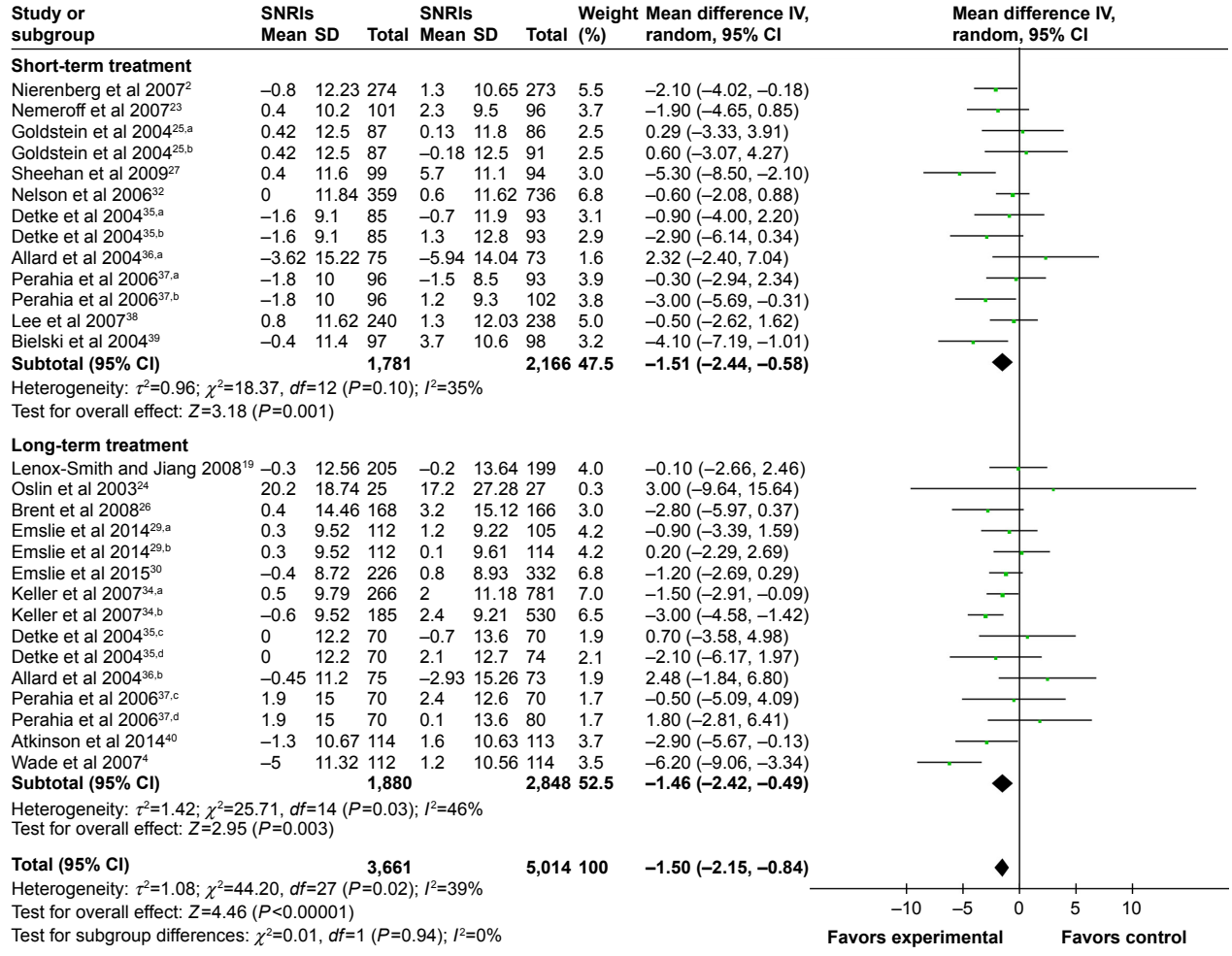

Figure 5 A forest plot of RCTs comparing SSRI group with SNRI group for change in systolic blood pressure change of short-/long-term duration.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

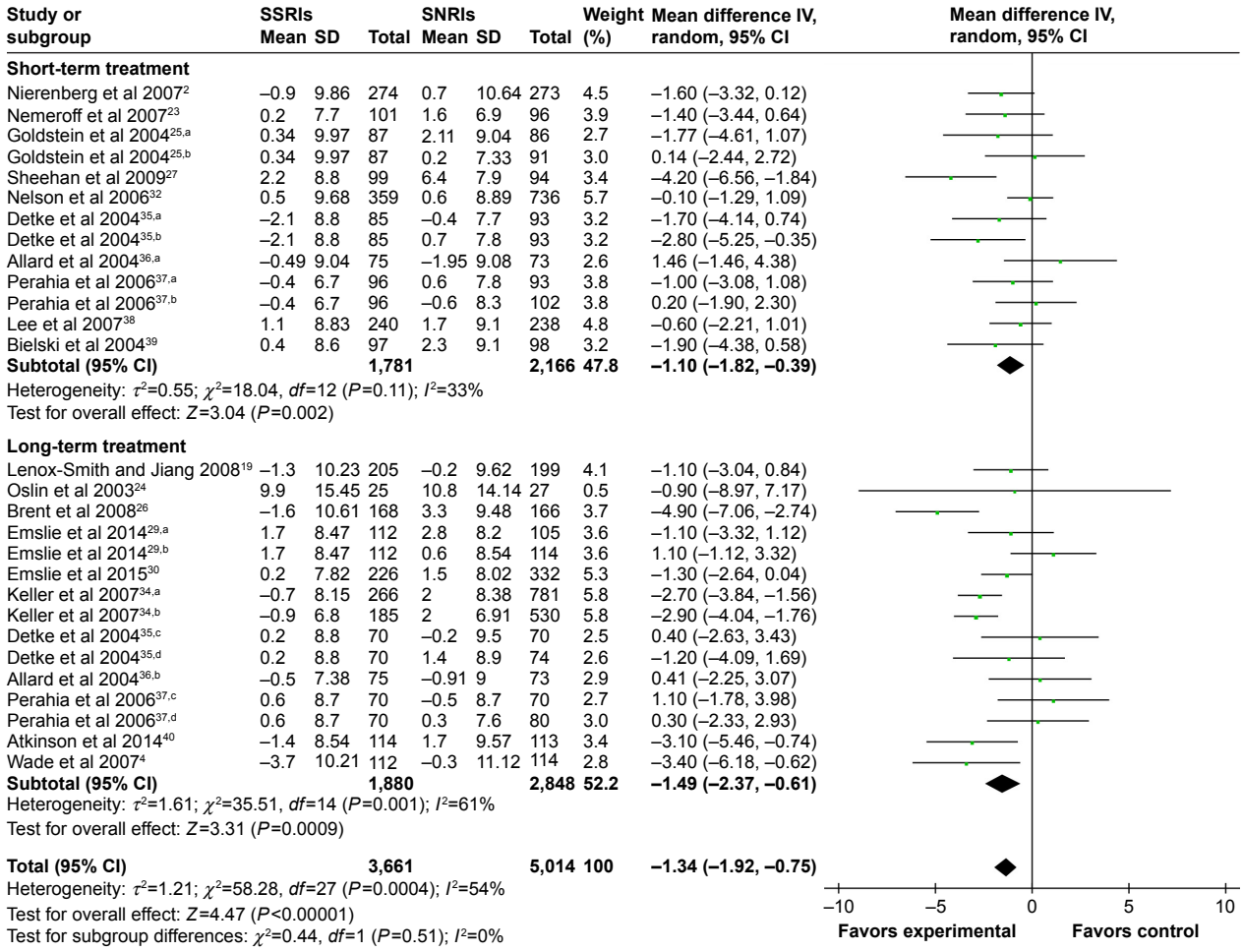

Figure 6 A forest plot of RCTs comparing SSRI group with SNRI group for change in diastolic blood pressure change of short-/long-term duration.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

exert effects such as relieving depressive symptoms,[45] yet antidepressant medications could not reliably change BP through depression amelioration. The roles of depression and antidepressant agents affecting BP are regarded complex, and relevant studies are warranted. There exists some evidence suggesting that both SSRIs and SNRIs are related to the autonomic nervous system. SNRIs can exacerbate the situation that autonomic balance shifts to sympathetic predominance, while SSRIs might not affect the balance.[11,44] Furthermore, sympathetic activity may be attenuated by administration of SSRIs in major depressive patients,[46,47] thus reducing cardiac risk to some degree.[46] Sertraline has been demonstrated to decrease sympathetic tone of patients with depression in conditions of physiological stress,[47] and it may be an appropriate agent for comorbidity of depression and cardiac disease.[48] SNRIs exhibit a broad spectrum of antidepressant activity, resembling SSRIs, as well as show noradrenergic potentiation. Because of noradrenergic potentiation, the SNRIs can elevate BP to some extent. Depression deregulates hypothalamic–pituitary–adrenal axis when depressive people are experiencing psychological stress.[2] As SSRIs and SNRIs improve the stressful condition, we speculate that they can play a role in hypothalamic–pituitary–adrenal axis for long-term treatment, which can affect BP to a certain degree.

In addition, this greater increase in BP from baseline in SNRI-treated patients compared with SSRI-treated patients is consistent with the pharmacological actions, which are actions on both serotonergic and noradrenergic neurotransmission and on serotonergic neurotransmission.[30] A 3 mmHg difference in SBP may be thought not clinically relevant, particularly at older ages. Indeed, even a 2 mmHg lower than usual SBP would involve ~10% lower stroke mortality and about 7% lower mortality from ischemic heart disease or other vascular causes in middle age. Therefore, for the general normotensive population, producing persistent reductions in average BP of just a few mmHg by some widely practicable methods should avoid large absolute numbers

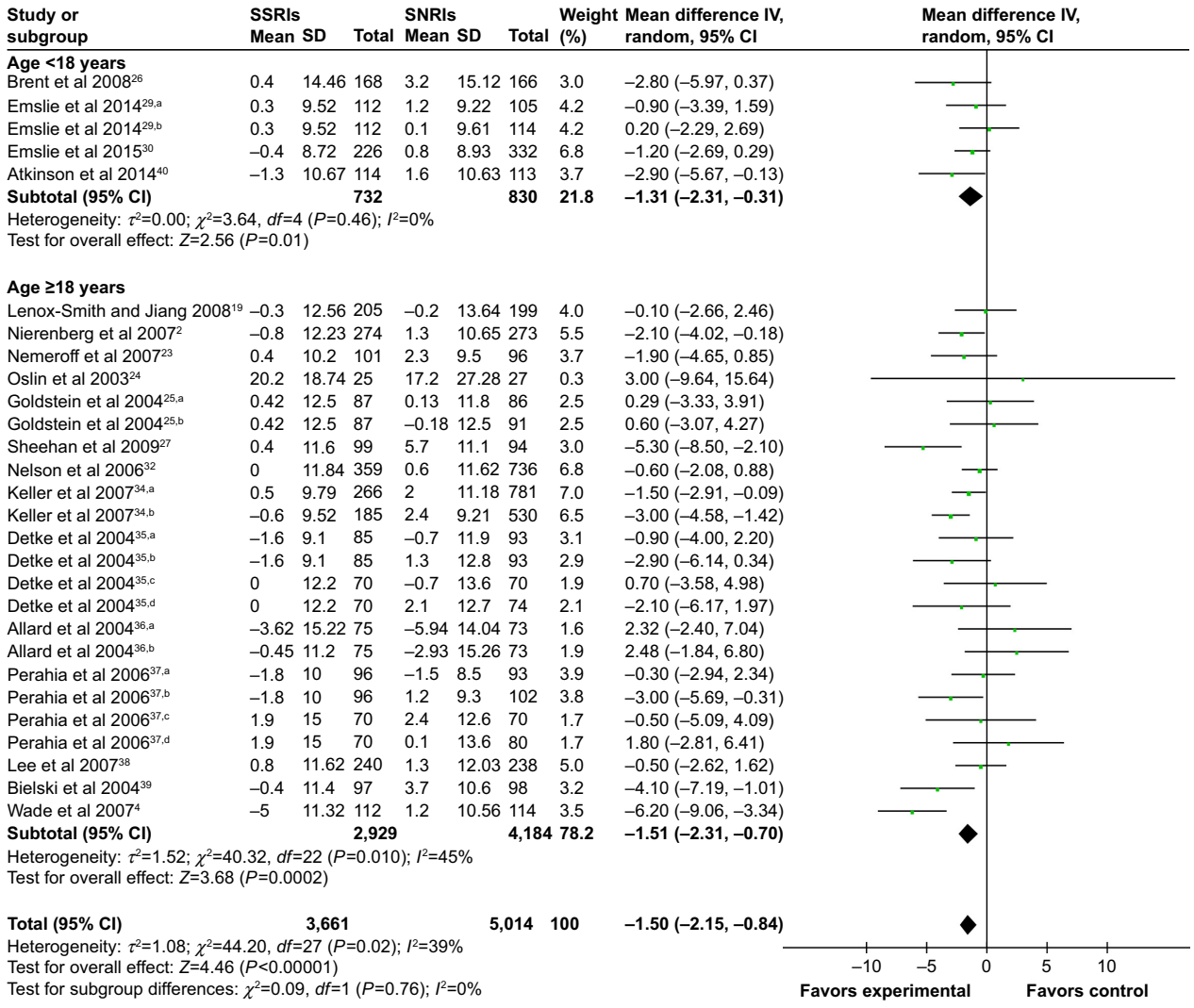

Figure 7 A forest plot of RCTs comparing SSRI group with SNRI group for change in systolic blood pressure change of different ages.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

of premature deaths and disabling strokes.[49] Depression and coronary heart disease (CHD) are well known to be associated, and in that case patients may suffer from both diseases and be at higher risk for myocardial infarction.[42] With the existence of the hypothesis that BP can partly explain the association between cardiovascular disease and psychopathology, SSRIs may be more suitable than SNRIs because of improvement in CHD prognosis for depressive patients with CHD.[50]

The included trials recorded office BP, which showed the incapability to reveal the circadian BP rhythm.[51] There is research indicating that even a mildly depressive mood is associated with larger among-day BP variability (BPV).[52] Moreover, BPV is more sensitive in reflecting depression-associated changes of autonomic function as compared to heart rate variability.[53] Prior studies have shown that a higher morning BP surge is positively correlated with depressive symptoms[54] and is associated with stroke risk independently in older hypertensive patients.[55] Low-frequency component of systolic BPV, a surrogate of sympathetic vasomotor tone, can show blunted response with depressive scores, even in the absence of clinically significant alterations in BP, thus acting as a strong predictor of depressive symptoms. In addition, some studies suggest low-frequency component of systolic BPV may be a potential biomarker of neurovascular functioning, contributing to a better understanding of the interaction between MDD and cardiovascular disease.[56] It has been reported that fluvoxamine has a potency to diminish autonomic cardiac activity, and both pharmacological actions and improvement of depressive mood state could change BP level after antidepressant treatment.[57] However, antidepressant medication studies

Study or subgroup	SSRIs Mean	SD	Total	SNRIs Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Age <18 years								
Brent et al 2008[26]	–1.6	10.61	168	3.3	9.48	166	3.7	–4.90 (–7.06, –2.74)
Emslie et al 2014[29,a]	1.7	8.47	112	2.8	8.2	105	3.6	–1.10 (–3.32, 1.12)
Emslie et al 2014[29,b]	1.7	8.47	112	0.6	8.54	114	3.6	1.10 (–1.12, 3.32)
Emslie et al 2015[30]	0.2	7.82	226	1.5	8.02	332	5.3	–1.30 (–2.64, 0.04)
Atkinson et al 2014[40]	–1.4	8.54	114	1.7	9.57	113	3.4	–3.10 (–5.46, –0.74)
Subtotal (95% CI)			**732**			**830**	**19.6**	**–1.84 (–3.66, –0.01)**
Heterogeneity: τ^2=3.23; χ^2=16.55, *df*=4 (*P*=0.002); I^2=76%								
Test for overall effect: *Z*=1.97 (*P*=0.05)								
Age ≥18 years								
Lenox-Smith and Jiang 2008[19]	–1.3	10.23	205	–0.2	9.62	199	4.1	–1.10 (–3.04, 0.84)
Nierenberg et al 2007[2]	–0.9	9.86	274	0.7	10.64	273	4.5	–1.60 (–3.32, 0.12)
Nemeroff et al 2007[23]	0.2	7.7	101	1.6	6.9	96	3.9	–1.40 (–3.44, 0.64)
Oslin et al 2003[24]	9.9	15.45	25	10.8	14.14	27	0.5	–0.90 (–8.97, 7.17)
Goldstein et al 2004[25,a]	0.34	9.97	87	2.11	9.04	86	2.7	–1.77 (–4.61, 1.07)
Goldstein et al 2004[25,b]	0.34	9.97	87	0.2	7.33	91	3.0	0.14 (–2.44, 2.72)
Sheehan et al 2009[27]	2.2	8.8	99	6.4	7.9	94	3.4	–4.20 (–6.56, –1.84)
Nelson et al 2006[32]	0.5	9.68	359	0.6	8.89	736	5.7	–0.10 (–1.29, 1.09)
Keller et al 2007[34,a]	–0.7	8.15	266	2	8.38	781	5.8	–2.70 (–3.84, –1.56)
Keller et al 2007[34,b]	–0.9	6.8	185	2	6.91	530	5.8	–2.90 (–4.04, –1.76)
Detke et al 2004[35,a]	–2.1	8.8	85	–0.4	7.7	93	3.2	–1.70 (–4.14, 0.74)
Detke et al 2004[35,b]	–2.1	8.8	85	0.7	7.8	93	3.2	–2.80 (–5.25, –0.35)
Detke et al 2004[35,c]	0.2	8.8	70	–0.2	9.5	70	2.5	0.40 (–2.63, 3.43)
Detke et al 2004[35,d]	0.2	8.8	70	1.4	8.9	74	2.6	–1.20 (–4.09, 1.69)
Allard et al 2004[36,a]	–0.49	9.04	75	–1.95	9.08	73	2.6	1.46 (–1.46, 4.38)
Allard et al 2004[36,b]	–0.5	7.38	75	–0.91	9	73	2.9	0.41 (–2.25, 3.07)
Perahia et al 2006[37,a]	–0.4	6.7	96	0.6	7.8	93	3.8	–1.00 (–3.08, 1.08)
Perahia et al 2006[37,b]	–0.4	6.7	96	–0.6	8.3	102	3.8	0.20 (–1.90, 2.30)
Perahia et al 2006[37,c]	0.6	8.7	70	–0.5	8.7	70	2.7	1.10 (–1.78, 3.98)
Perahia et al 2006[37,d]	0.6	8.7	70	0.3	7.6	80	3.0	0.30 (–2.33, 2.93)
Lee et al 2007[38]	1.1	8.83	240	1.7	9.1	238	4.8	–0.60 (–2.21, 1.01)
Bielski et al 2004[39]	0.4	8.6	97	2.3	9.1	98	3.2	–1.90 (–4.38, 0.58)
Wade et al 2007[4]	–3.7	10.21	112	–0.3	11.12	114	2.8	–3.40 (–6.18, –0.62)
Subtotal (95% CI)			**2,929**			**4,184**	**80.4**	**–1.24 (–1.85, –0.63)**
Heterogeneity: τ^2=0.94; χ^2=41.31, *df*=22 (*P*=0.008); I^2=47%								
Test for overall effect: *Z*=3.96 (*P*<0.0001)								
Total (95% CI)			**3,661**			**5,014**	**100**	**–1.34 (–1.92, –0.75)**
Heterogeneity: τ^2=1.21; χ^2=58.28, *df*=27 (*P*=0.0004); I^2=54%								
Test for overall effect: *Z*=4.47 (*P*<0.00001)								
Test for subgroup differences: χ^2=0.37, *df*=1 (*P*=0.54); I^2=0%								

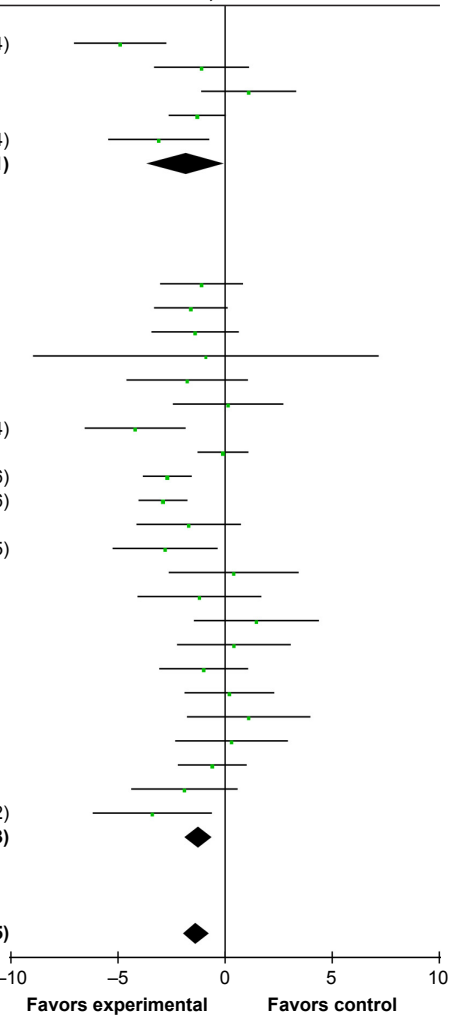

Figure 8 A forest plot of RCTs comparing SSRI group with SNRI group for change in diastolic blood pressure change of different ages.
Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

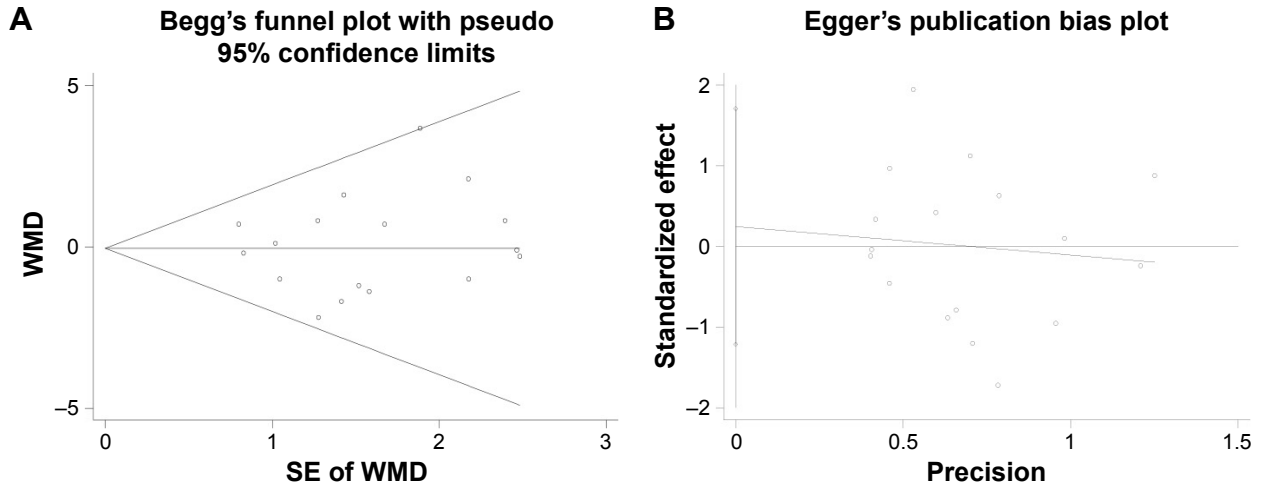

Figure 9 (*Continued*)

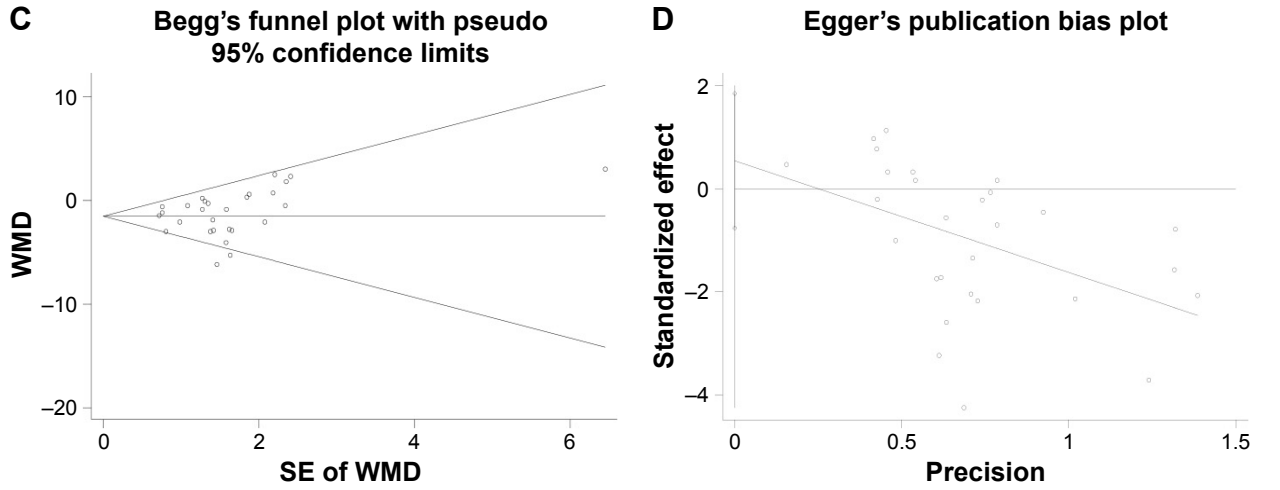

Figure 9 Begg's test and Egger's test identified no publication bias. In the group of SSRI versus placebo: Begg's test: *Z*=0.33, *P*=0.742 (**A**); Egger's test: t=0.36, *P*=0.724 (**B**). In the group of SSRI versus SNRI: Begg's test: *Z*=1.19, *P*=0.236 (**C**); Egger's test: t=0.85, *P*=0.405 (**D**).
Abbreviations: WMD, weighted mean difference; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

on BPV remain scarce, the effect of antidepressants on autonomic nervous system activity is not clear, and relevant study is warranted.

This meta-analysis, however, had some potential limitations. First, the designs of many RCTs met the inclusion criteria, except when the results did not include details about BP; thus, the exclusion of these RCTs and unpublished data may have resulted in bias. Moreover, six included RCTs reported BP changes for different medication doses or durations, and results were all analyzed as an individual trial according to different doses or durations; therefore, overestimation of the treatment effects on BP might happen. Finally, the trials included adults and children or teenagers, and antihypertensive medications were allowed during treatment, which might lead to bias to some extent, although the doses of cardiovascular medication were fixed.

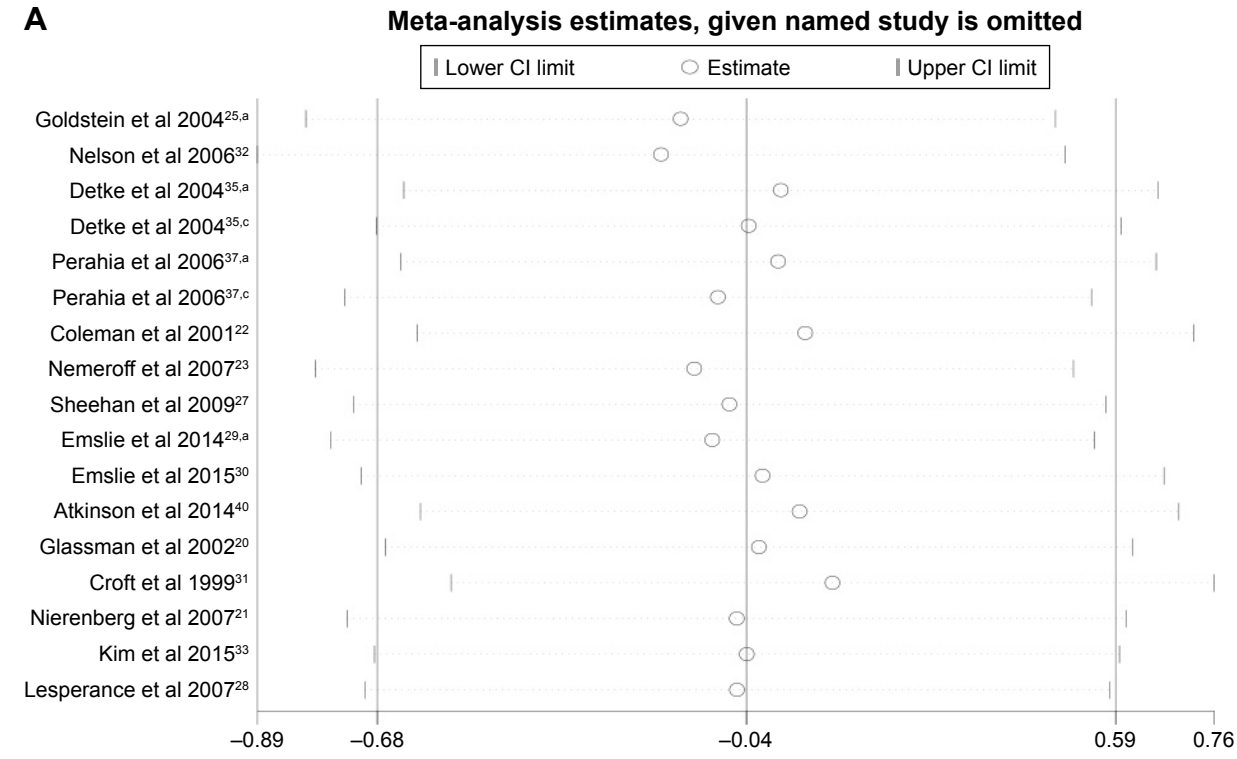

Figure 10 (*Continued*)

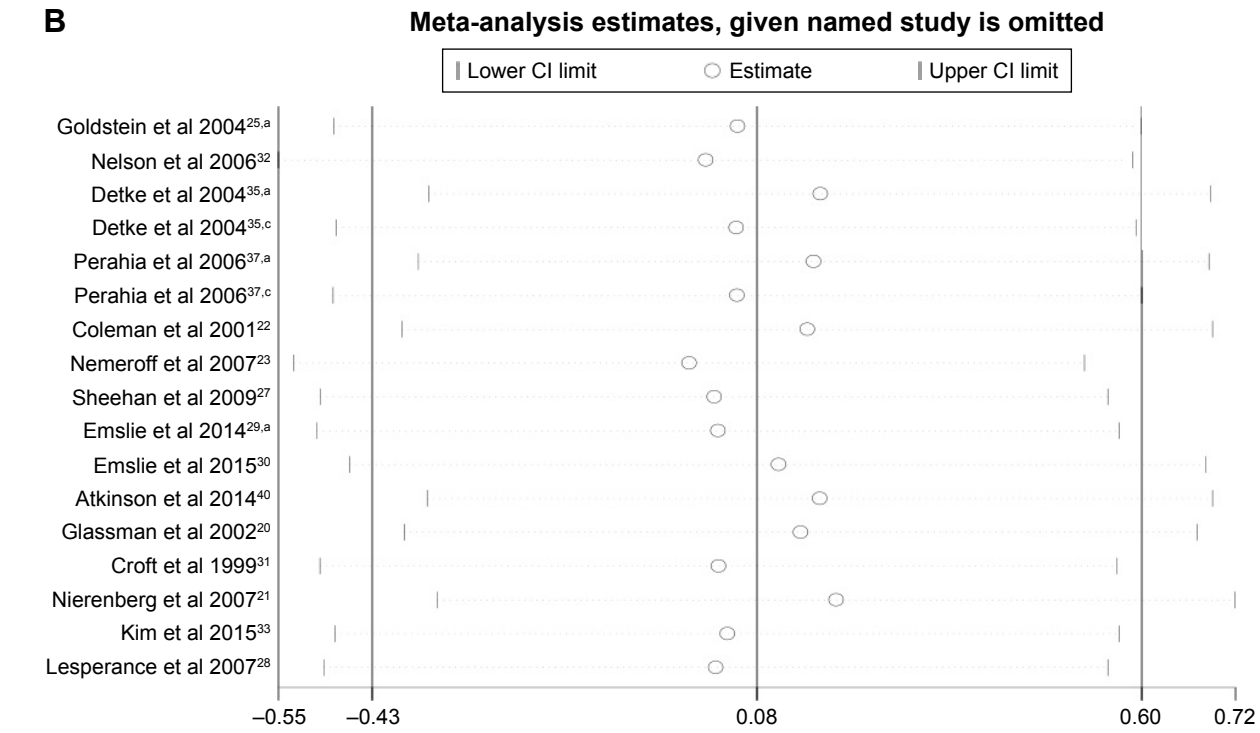

Figure 10 The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of SSRI versus placebo. The pooled WMDs (95% CI) ranged from –0.19 (–0.89, 0.50) to 0.10 (–0.55, 0.76) in systolic blood pressure change (**A**), and from –0.01 (–0.53, 0.52) to 0.19 (–0.34, 0.72) in diastolic blood pressure change (**B**), with all showing no statistical significance.

Notes: (**A**) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus placebo in systolic blood pressure change. (**B**) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus placebo in diastolic blood pressure change.

Abbreviations: SSRI, selective serotonin reuptake inhibitor; WMDs, weighted mean differences.

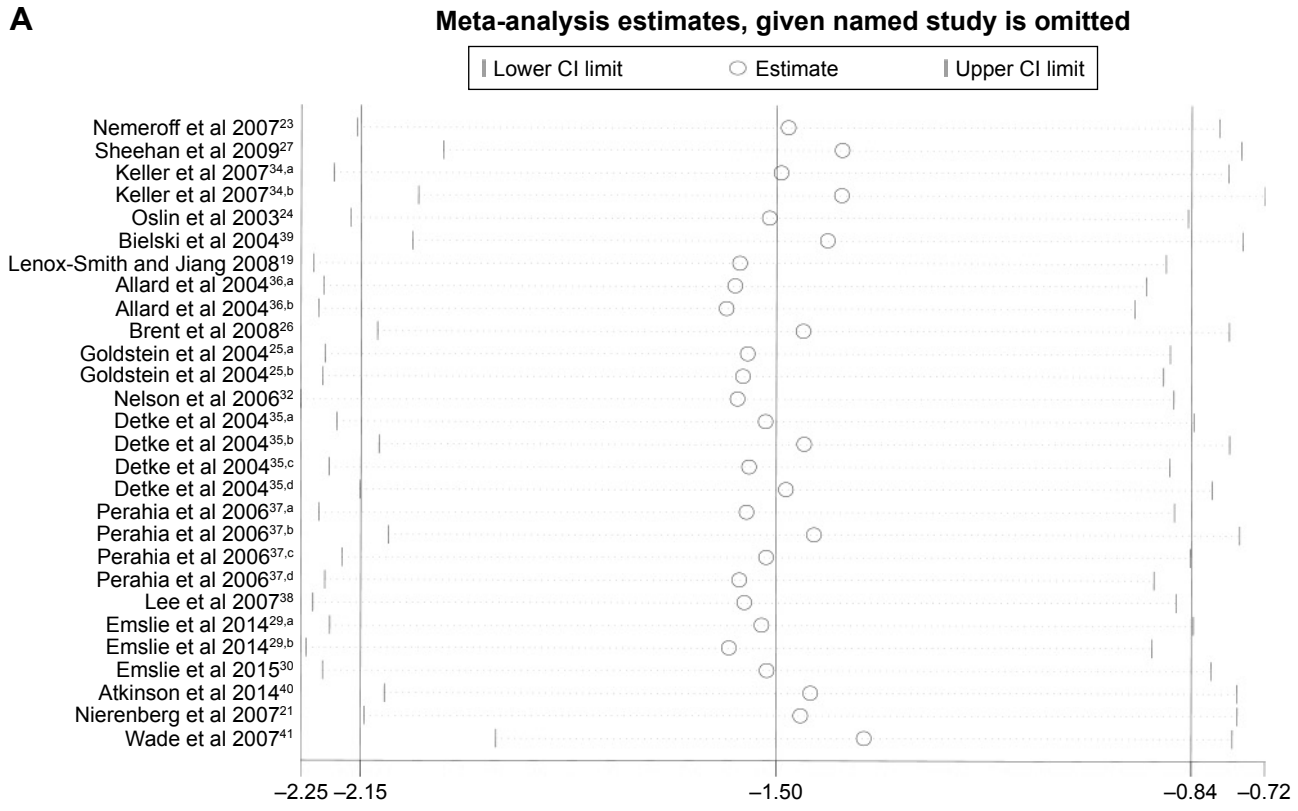

Figure 11 (*Continued*)

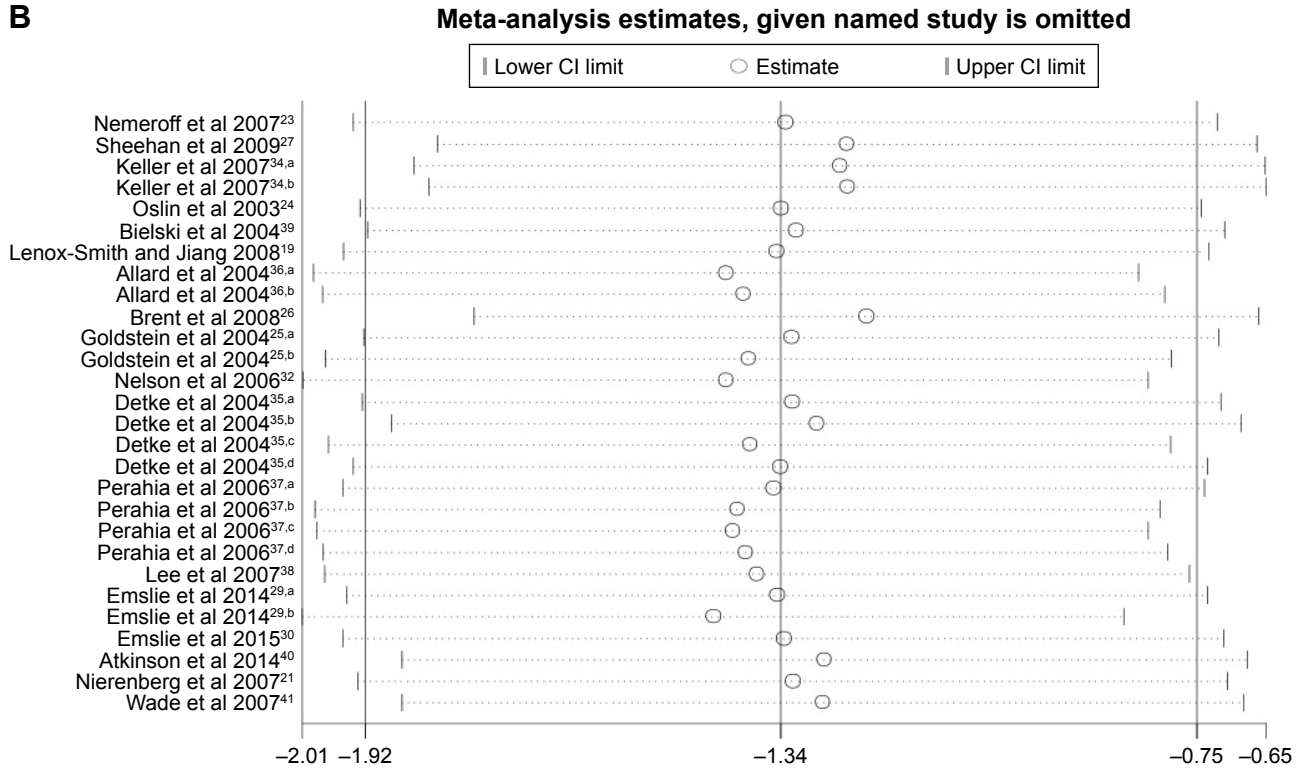

Figure 11 The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of SSRI versus SNRI. The pooled WMDs (95% CI) ranged from −1.58 (−2.22, −0.93) to −1.36 (−1.94, −0.77) in systolic blood pressure change (**A**), and from −1.43 (−2.01, −0.85) to −1.22 (−1.77, −0.67) in diastolic blood pressure change (**B**), with all showing statistical significances.

Notes: (**A**) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus serotonin and noradrenaline reuptake inhibitor on systolic blood pressure change. (**B**) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus serotonin and noradrenaline reuptake inhibitor on diastolic blood pressure change.

Abbreviations: SNRI, serotonin and noradrenaline reuptake inhibitor; WMDs, weighted mean differences.

In summary, SSRIs were not established to affect BP fluctuation in depressive patients as a result of their pharmaceutical characteristics or ameliorating depressive symptoms. SNRIs could result in higher SBP and DBP than SSRIs, although none of them caused sudden substantial BP elevation. While office BP is incapable of reflecting the circadian BP rhythm, future research should be focused on antidepressant medication and BPV.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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