Supplementary material

# The beneficial and harmful effects of duloxetine versus placebo for adults with major depressive disorder: A systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

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Siddiqui F, *et al. BMJ Open* 2025; 15:e082853. doi: 10.1136/bmjopen-2023-082853

## Contents

## Search strategies for 'Duloxetine for major depressive disorder'

**(Faiza Siddiqui)**

**Searches performed 23 January 2023**

| | |
|---|---|
| **Total number of records identified:** | **4715 records** |
| **Number of duplicates excluded:** | **1314 records** |
| **Number of records in final list:** | **3401 records** |
| **Number of new records sent to authors:** | **173 records** |

**Cochrane Central Register of Controlled Trials (2023, Issue 1) in the Cochrane Library (23 January 2023) (867 hits)**

#1 MeSH descriptor: [Duloxetine Hydrochloride] explode all trees
#2 (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)
#3 #1 or #2
#4 MeSH descriptor: [Depressive Disorder, Major] explode all trees
#5 MeSH descriptor: [Depressive Disorder] this term only
#6 MeSH descriptor: [Seasonal Affective Disorder] explode all trees
#7 MeSH descriptor: [Dysthymic Disorder] explode all trees
#8 MeSH descriptor: [Depression] explode all trees
#9 MeSH descriptor: [Affective Symptoms] this term only
#10 (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 #3 and #11

**MEDLINE Ovid (1946 to 23 January 2023) (597 hits)**

1. exp Duloxetine Hydrochloride/
2. (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3. 1 or 2
4. exp Depressive Disorder, Major/
5. Depressive Disorder/

6. exp Seasonal Affective Disorder/
7. exp Dysthymic Disorder/
8. exp Depression/
9. Affective Symptoms/
10. (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
14. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
15. 12 and (13 or 14)

**Embase Ovid (1974 to 23 January 2023) (2253 hits)**

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2. (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3. 1 or 2
4. exp major depression/
5. depression/
6. exp seasonal affective disorder/
7. exp dysthymia/
8. emotional disorder/
9. (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10
12. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.ne.
13. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
14. 11 and (12 or 13)

**PsycINFO (EBSCOhost; 1806 to 3 June 2022) (438 hits)**

S14 S12 AND S13
S13 TX (random* or blind* or placebo* or trial*)

S12 S3 AND S11
S11 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
S10 TX (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))
S9 MA affective symptoms
S8 MA depression
S7 MA dysthymic disorder
S6 MA seasonal affective disorder
S5 MA depressive disorder
S4 MA Depressive Disorder, Major
S3 S1 OR S2 Expanders - Apply equivalent subjects
S2 TX (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)
S1 MA Duloxetine

**LILACS (VHL Regional Portal; 1982 to 23 January 2023) (20 hits)**
((duloxetin* OR cymbalta* OR irenka* OR ariclaim OR xeristar OR yentreve OR duzela OR c-pact OR combac OR delok OR deneurone OR detine OR dimorex OR dlx OR dulane OR dulex OR dulife OR dulojoy OR dulok OR dulomax OR dulonix OR dulot* OR dulox* OR dultin OR dulx OR dumore OR duonex* OR dureep OR dutin* OR duxet OR duzac OR duzela OR dxt OR neuroxetin OR nudep OR sylonex OR symbal OR sympta OR ulozet OR verlox)) AND ((mdd OR depress* OR ((affective OR adjustment OR dysthym* OR mood) AND (disorder* OR disease* OR symptom*)) OR dysthymia OR alexithymia OR (involutional AND (melancholia OR paraphrenia* OR psychos*)) OR (emotion* AND disturbance*))) AND ( db:("LILACS"))

**Science Citation Index Expanded (Web of Science; 1900 to 23 January 2023) and Conference Proceedings Citation Index – Science (Web of Science; 1990 to 23 January 2023) (978 hits)**
#5 #3 AND #4
#4 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)
#3 #2 AND #1
#2 TS=(MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))
#1 TS=(duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)

Supplementary table S2: Summary of serious adverse events in the included trials.

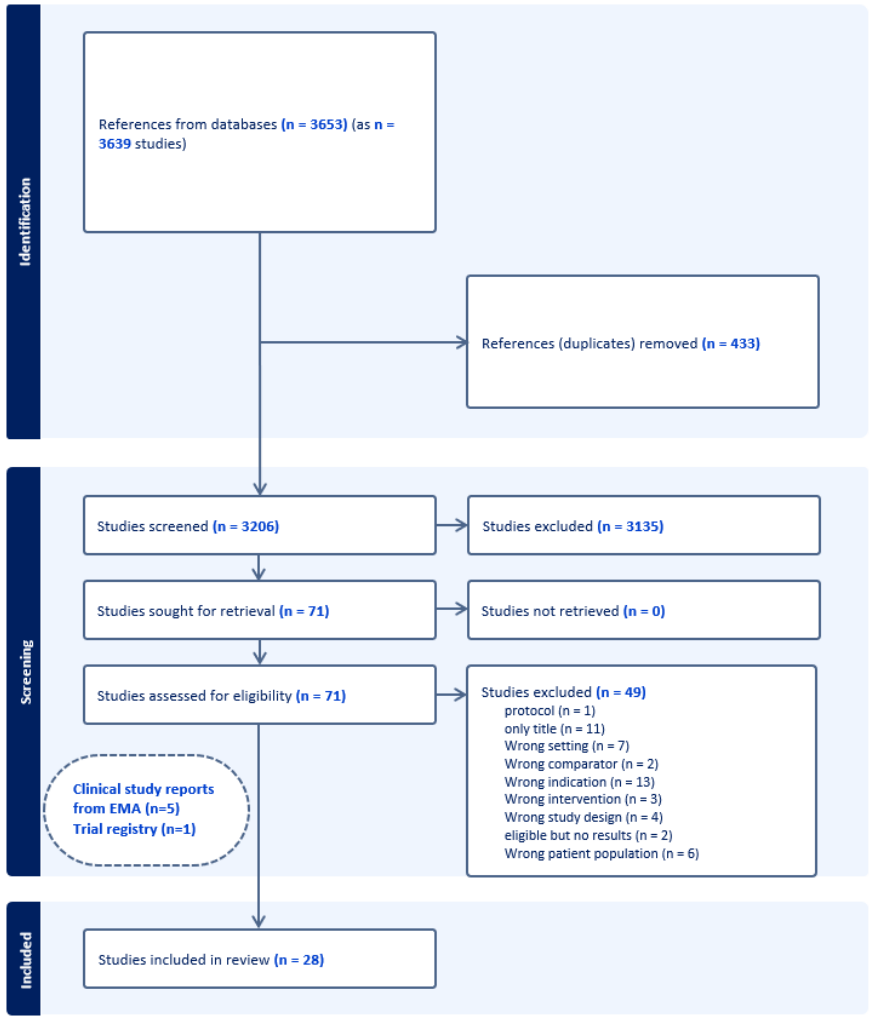
| Trial | Participants receiving duloxetine | | Participants receiving placebo | |
|---|---|---|---|---|
| | Types of SAEs | Proportion of participants with SAEs | Types of SAEs | Proportion of participants with SAEs |
| Baldwin 2012 | Middle ear effusion, serotonin syndrome | 2 out of 155 | Serotonin syndrome, adenomyosis, pulmonary embolism | 3 out of 148 |
| Boulenger 2014 | Suicidal behavior and self harm, intentional overdose, vaginal haemorrhage | 3 out of 147 | | 0 out of 158 |
| Detke 2002 A | | 0 out of 123 | Umblical hernia, emphysema with pneumonia, chest pain | 3 out of 122 |
| Detke 2002 B | Breast carcinoma | 1 out of 128 | | 0 out of 139 |
| Goldstein 2004 B | Accidental injury falling from a horse, suffering a concussion and a subsequent seizure. | 1 out of 91 | | 0 out of 45 |
| Katona 2012 | Prostate cancer, suicide attempt | 2 out of 151 | Hip fracture, bile duct cancer, depression, transient ischemic attack | 4 out of 145 |
| Mahableshwarkar 2013 | Myocardial infarction, panic attack | 2 out of 150 | Elective abortion, worsening of depression | 2 out of 151 |
| Mahableshwarkar 2015 B | Craniocerebral injury | 1 out of 207 | Acute myocardial infarction, worsening of depression | 2 out of 191 |
| Nierenberg 2007 | Not specified | 3 out of 273 | Not specified | 2 out of 137 |

| | | | | |
|---|---|---|---|---|
| Oakes 2012 A | Not specified | 6 out of 257 | Suicide attempt, others not specified | 3 out of 127 |
| Oakes 2012 B | Ruptured cerebral aneurysm, suicide attempt | 2 out of 261 | Suicide, others not specified | 7 out of 131 |
| Perahia 2006 B | Major depression | 1 out of 103 | | 0 out of 50 |
| Raskin 2007 | Not specified | 1 out of 207 | Not specified | 4 out of 104 |
| Tourian 2009 | Suicide attempts | 2 out of 157 | Accidental injury, asthma | 2 out of 161 |
| F1J-MC-HMAI (A) | Suicide attempt | 1 out of 130 | | 0 out of 41 |
| F1J-MC-HMAI (C) | Suicide attempt | 1 out of 131 | Suicide attempt | 1 out of 41 |
| F1J-MC-HMAQ b (B) | | 0 out of 82 | Infectious colitis, food poisoning | 2 out of 75 |
| 11918A | Not specified | 1 out of 133 | Not specified | 1 out of 136 |
| F1J-MC-HMAT a (B) | Cardiopulmonary arrest leading to death | 1 out of 84 | Hospitalization due to exacerbation of asthma | 1 out of 45 |
| F1J-MC-HMAH | Maniac episode, overdose | 9 out of 89 | Accidental injury, hostility, overdose | 8 out of 88 |

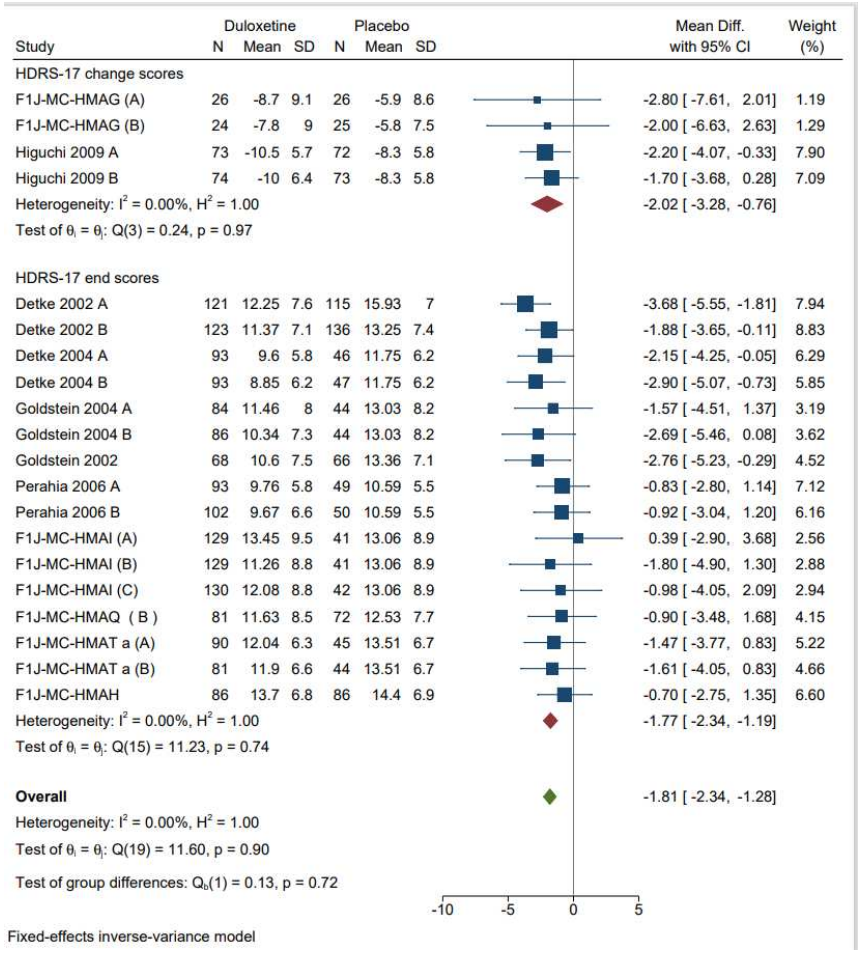
Supplementary Table S3: Meta-analysis of individual non-serious adverse events.

| Non-serious adverse events | No of trials | n* duloxetine group | N** duloxetine group | n* control group | N** control group | RR¤ | 95% CI | P-value | NNH |
|---|---|---|---|---|---|---|---|---|---|
| Nausea | 30 | 957 | 3982 | 244 | 2856 | 2.92 | 2.38-3.58 | <0.0001 | 6.46 |
| Dry mouth | 30 | 627 | 3982 | 222 | 2856 | 2.05 | 1.67-2.52 | <0.0001 | 12.54 |
| Somnolence | 26 | 306 | 3110 | 96 | 2249 | 2.4 | 1.81-3.18 | <0.0001 | 17.95 |
| Sweating | 27 | 252 | 3521 | 55 | 2517 | 2.88 | 1.95-4.26 | <0.0001 | 20.11 |
| Dizziness | 30 | 399 | 3982 | 156 | 2856 | 1.88 | 1.49-2.38 | <0.0001 | 21.94 |
| Yawn | 11 | 45 | 1569 | 1 | 1177 | 5.54 | 2.32-13.22 | 0.0001 | 35.93 |
| Appetite decreased | 9 | 83 | 1469 | 18 | 1129 | 3.33 | 1.8-6.15 | 0.0001 | 24.66 |
| Insomnia | 25 | 304 | 3113 | 133 | 2097 | 1.64 | 1.27-2.11 | 0.0001 | 29.21 |
| Anorexia | 15 | 100 | 1671 | 22 | 1043 | 2.85 | 1.6-5.06 | 0.0004 | 25.81 |
| Constipation | 28 | 359 | 3628 | 132 | 2507 | 1.79 | 1.3-2.47 | 0.0004 | 21.6 |
| Withdrawal syndrome | 1 | 49 | 334 | 24 | 250 | 2.09 | 1.35-3.24 | 0.0009 | 19.72 |
| Vomiting | 22 | 135 | 2556 | 39 | 1799 | 2.28 | 1.4-3.71 | 0.0009 | 32.11 |
| Diarrhea | 30 | 376 | 3982 | 203 | 2856 | 1.38 | 1.12-1.71 | 0.0028 | 42.83 |
| Fatigue | 13 | 143 | 2284 | 48 | 1609 | 2.06 | 1.28-3.3 | 0.0029 | 30.51 |
| Libido decreased | 13 | 54 | 1671 | 13 | 1043 | 2.37 | 1.22-4.61 | 0.0111 | 50.37 |
| Vasodilatation | 13 | 55 | 1287 | 16 | 851 | 2.08 | 1.11-3.89 | 0.0215 | 41.78 |
| Back pain | 20 | 62 | 2128 | 65 | 1514 | 0.64 | 0.42-0.95 | 0.0288 | -72.48 |
| Hyperventilation | 3 | 0 | 460 | 4 | 196 | 0.14 | 0.02-0.82 | 0.0299 | -49 |
| Pain | 16 | 64 | 1782 | 77 | 1264 | 0.65 | 0.43-0.97 | 0.0352 | -40 |
| Breast pain | 8 | 3 | 1055 | 8 | 600 | 0.33 | 0.11-0.99 | 0.048 | -95.33 |

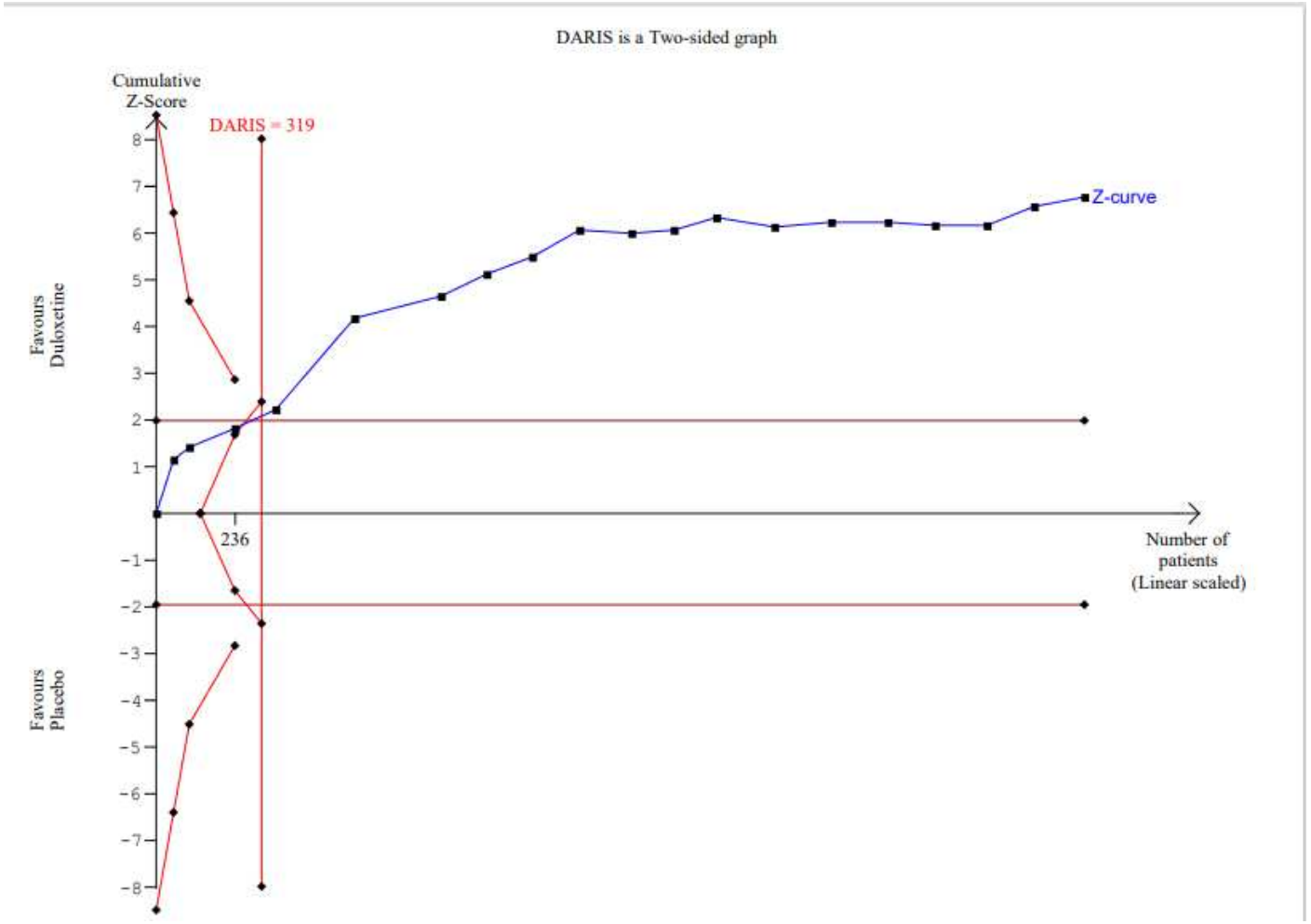
*n= no of events
**N= no analyzed
¤ RR= relative risk



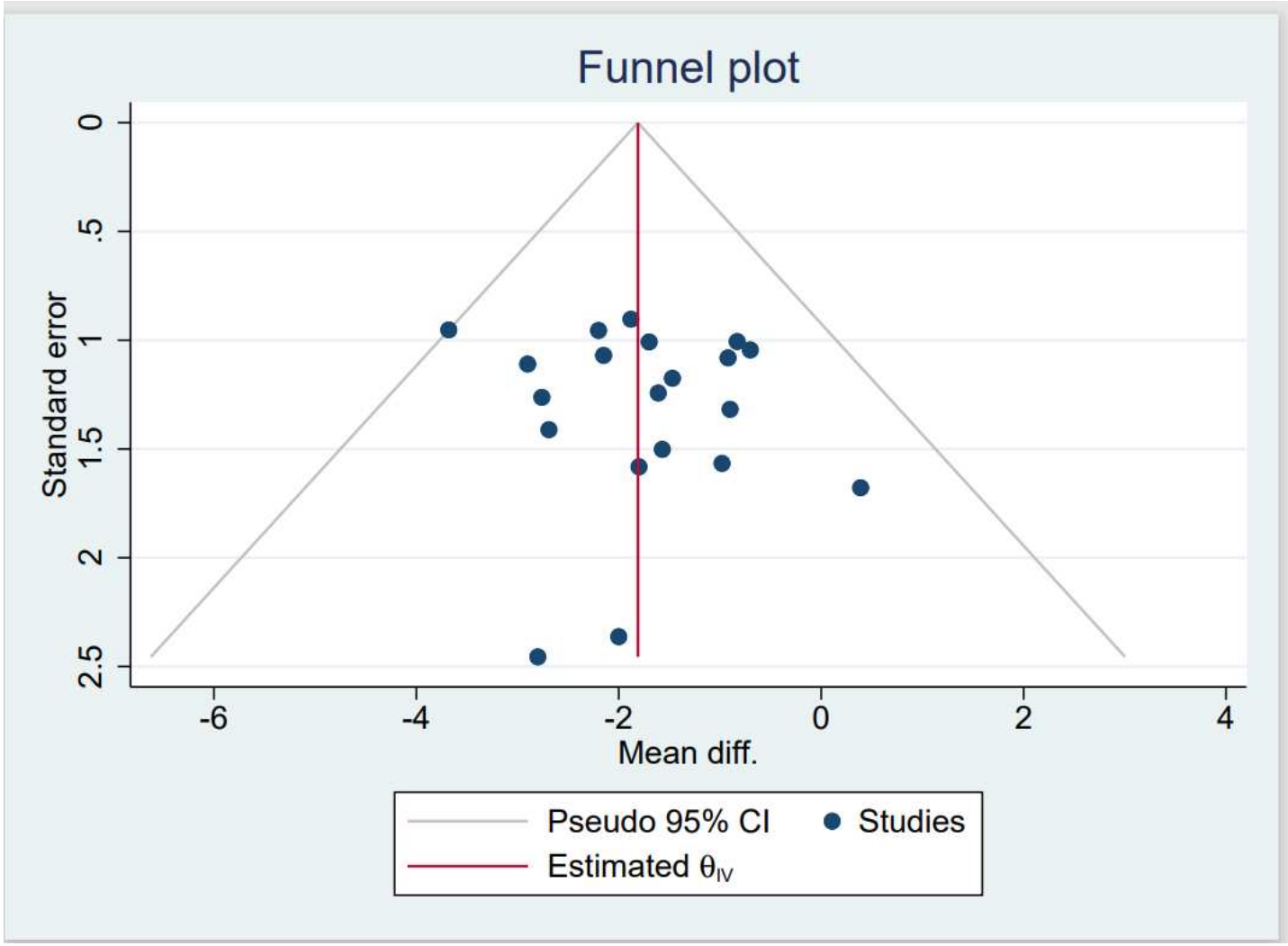

Supplementary Fig S1: PRISMA flow chart.



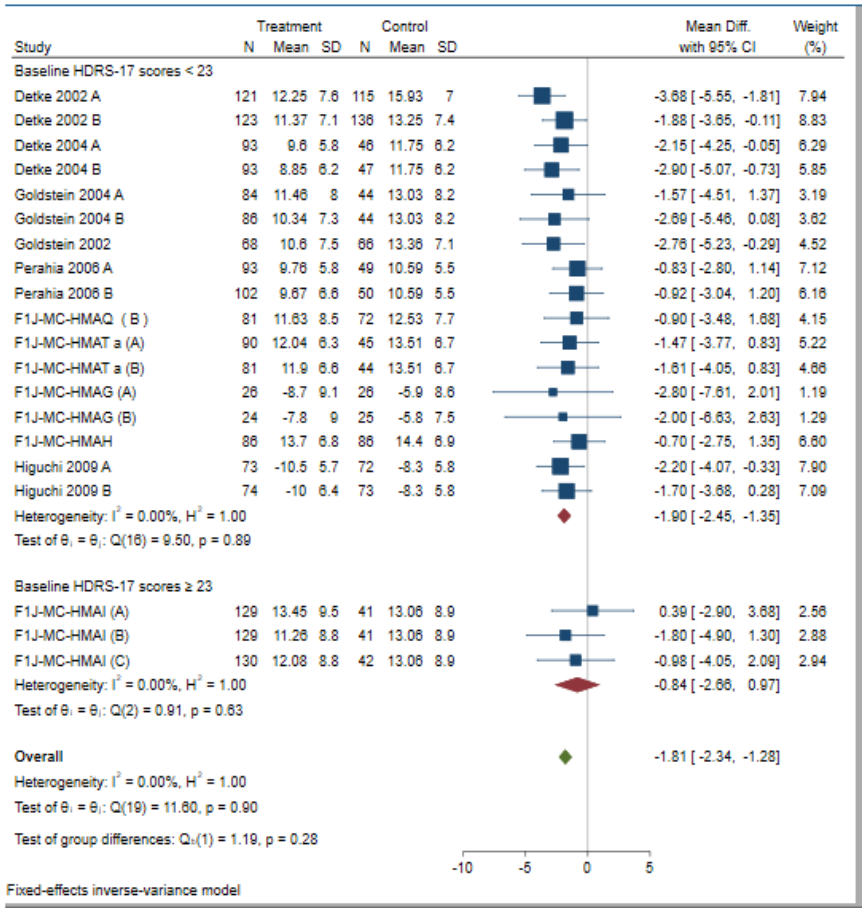

Supplementary Fig S2: Meta-analysis of duloxetine vs. placebo for the outcome HDRS-17 scores.



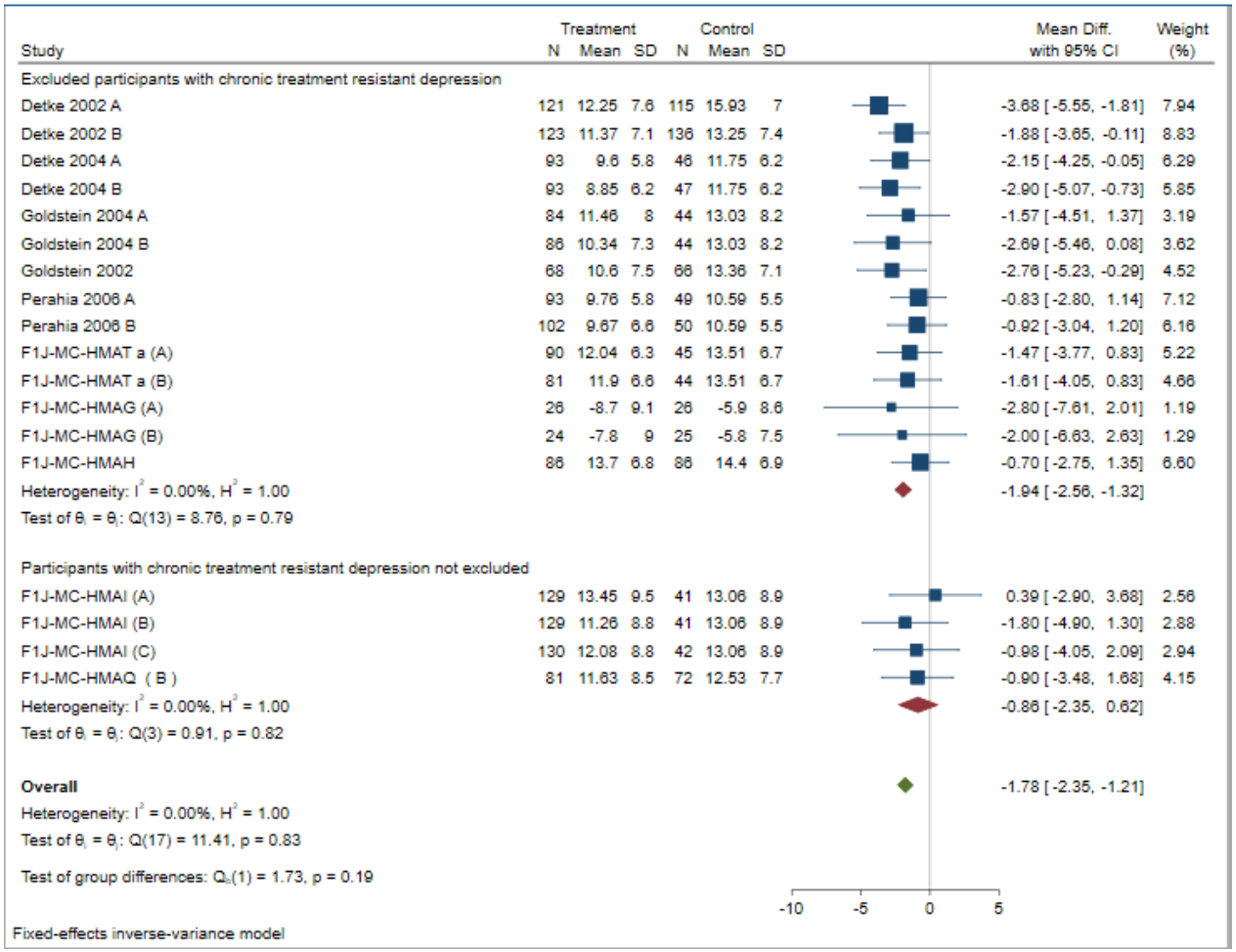

Supplementary Fig S3: Trial Sequential Analysis of duloxetine vs. placebo for the outcome HDRS-17.



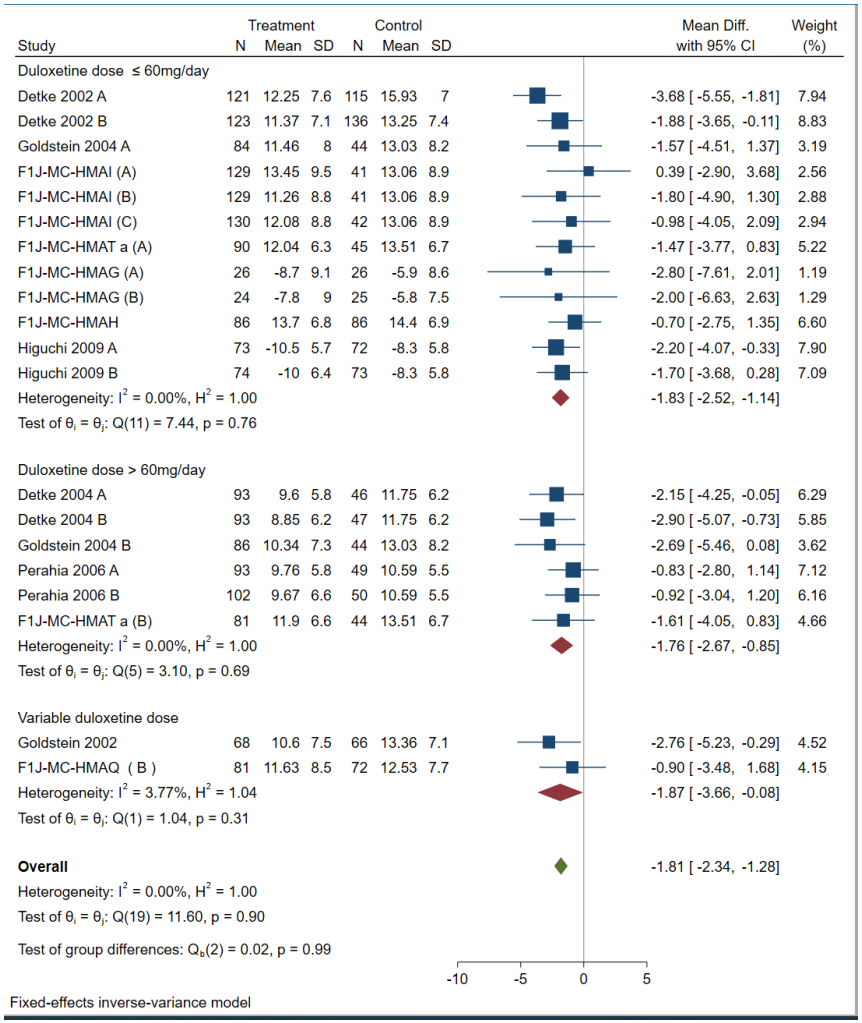

Supplementary Fig S4: Funnel plot of duloxetine vs. placebo for the outcome HDRS-17 scores.



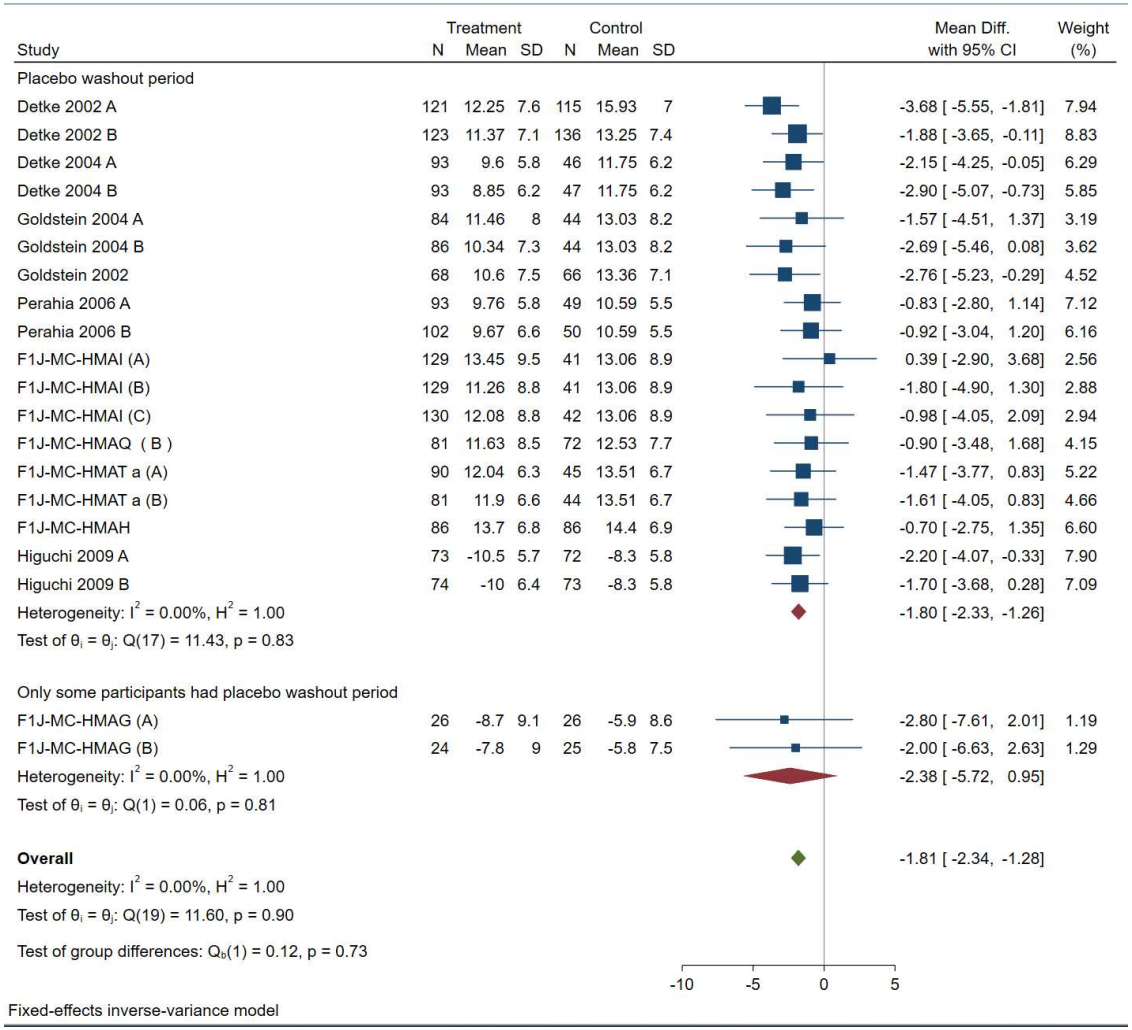

Supplementary Fig S5: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for baseline HDRS-17 scores.



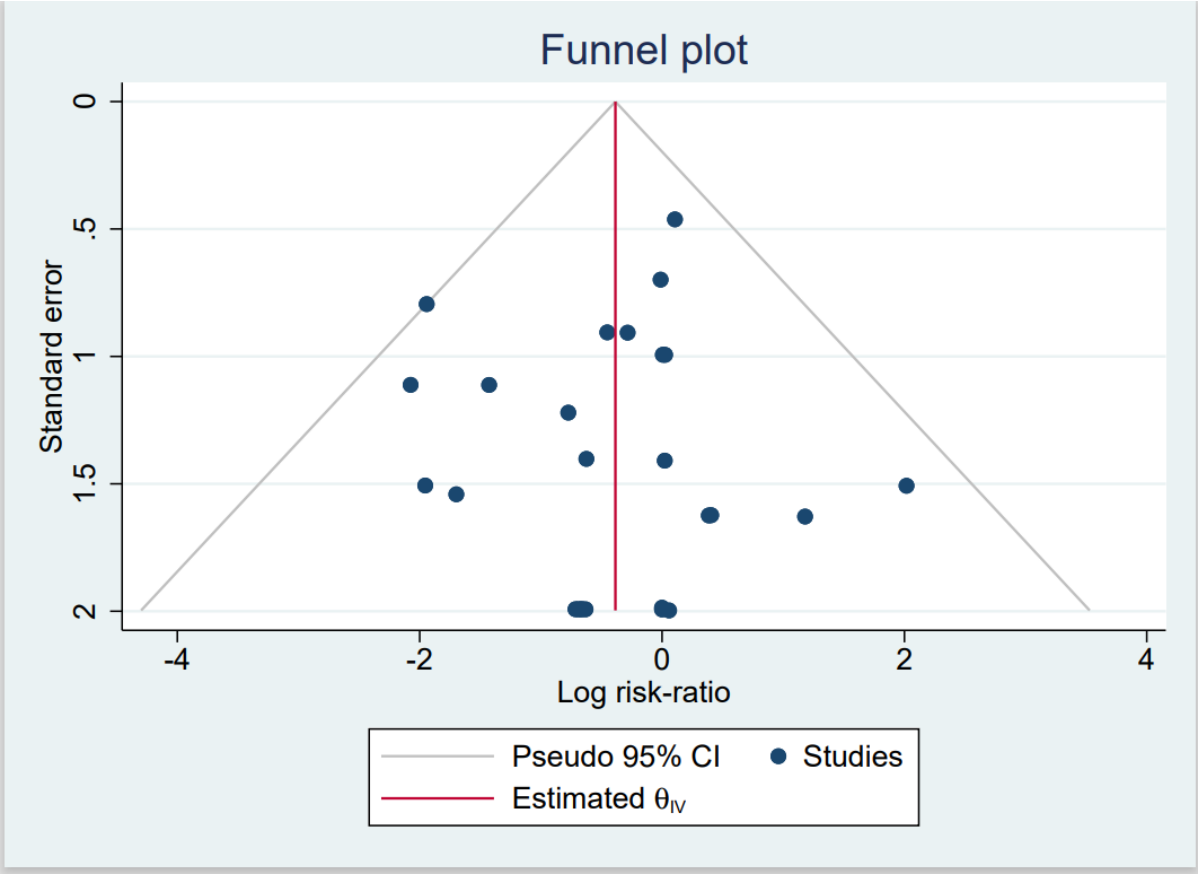

Supplementary Fig S6: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for chronic or treatment resistant depression.



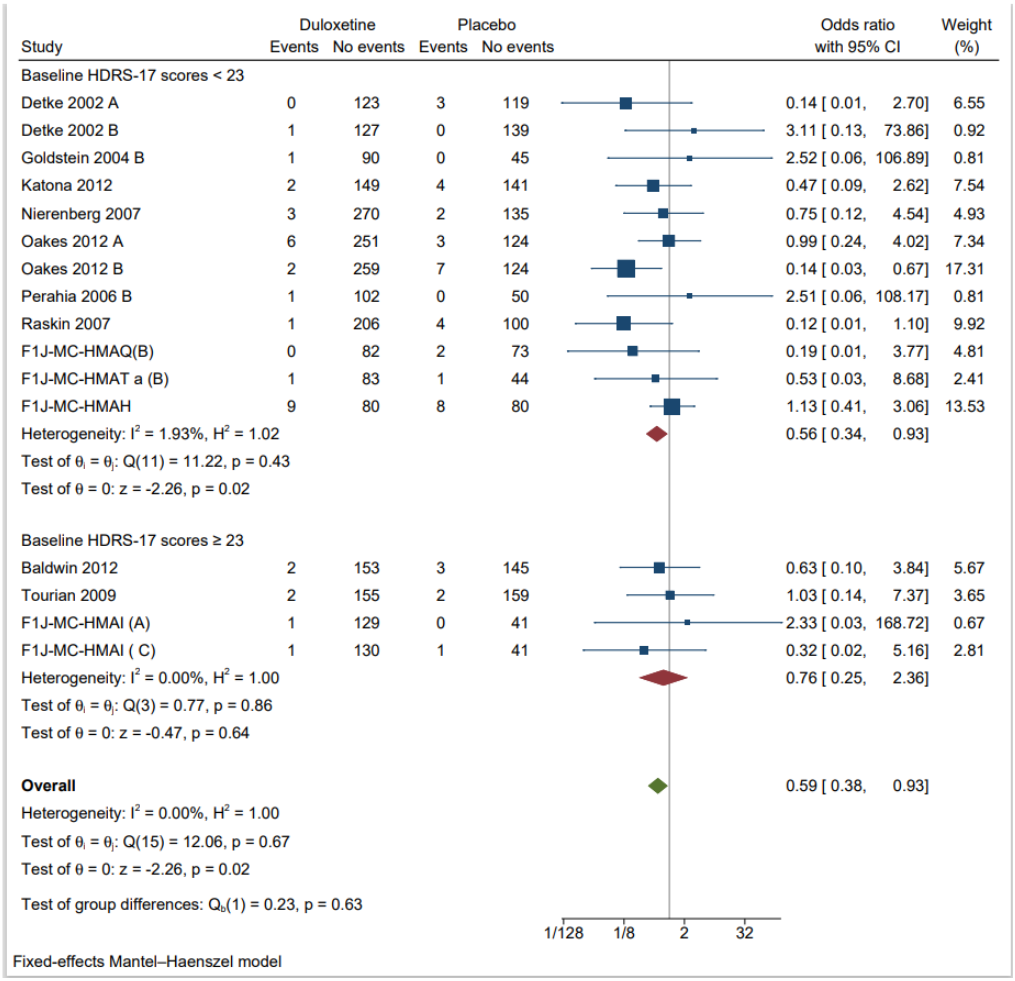

Supplementary Fig S7: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for duloxetine dose.



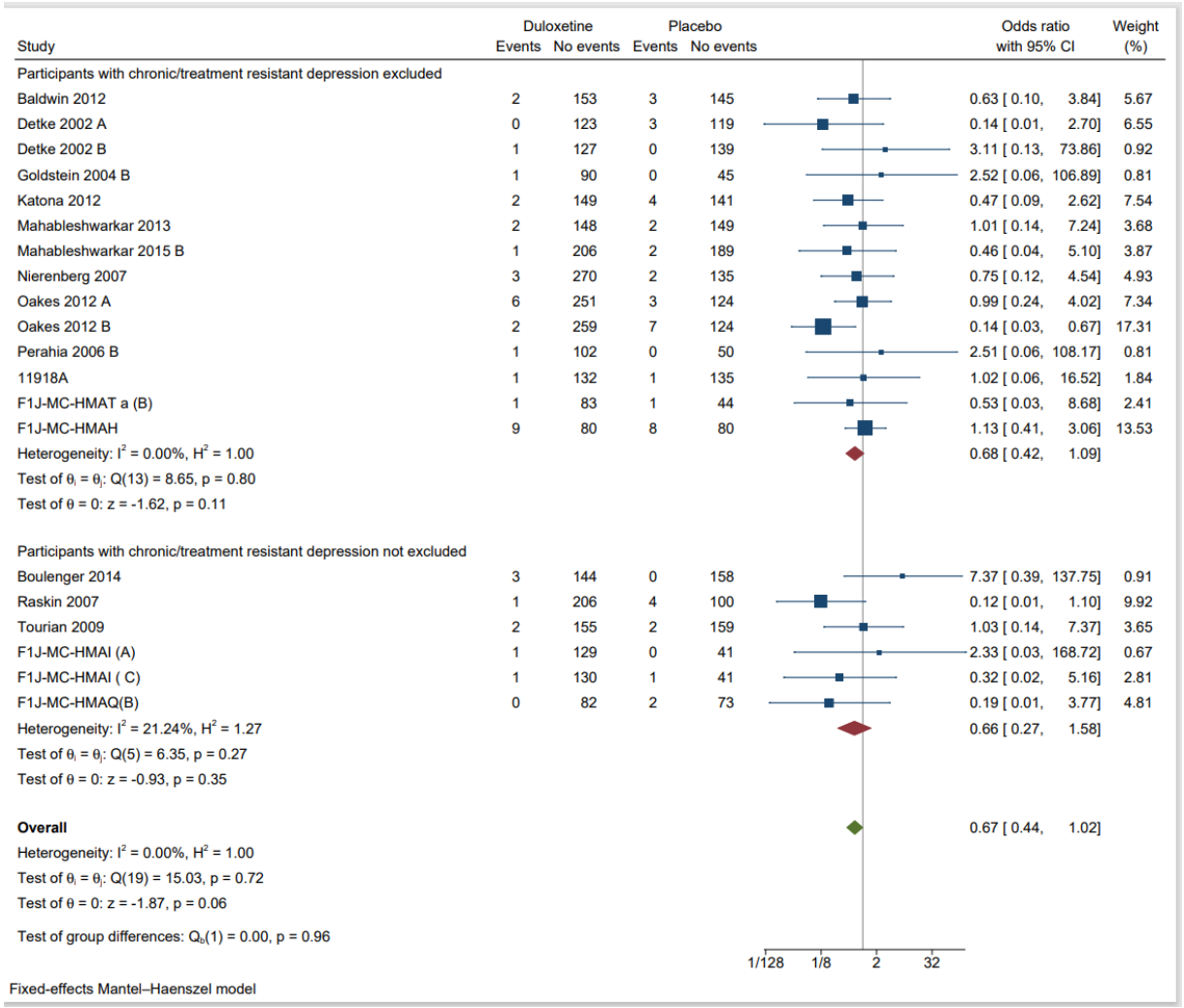

Supplementary Fig S8: Subgroup analysis of placebo washout period on HDRS-17.



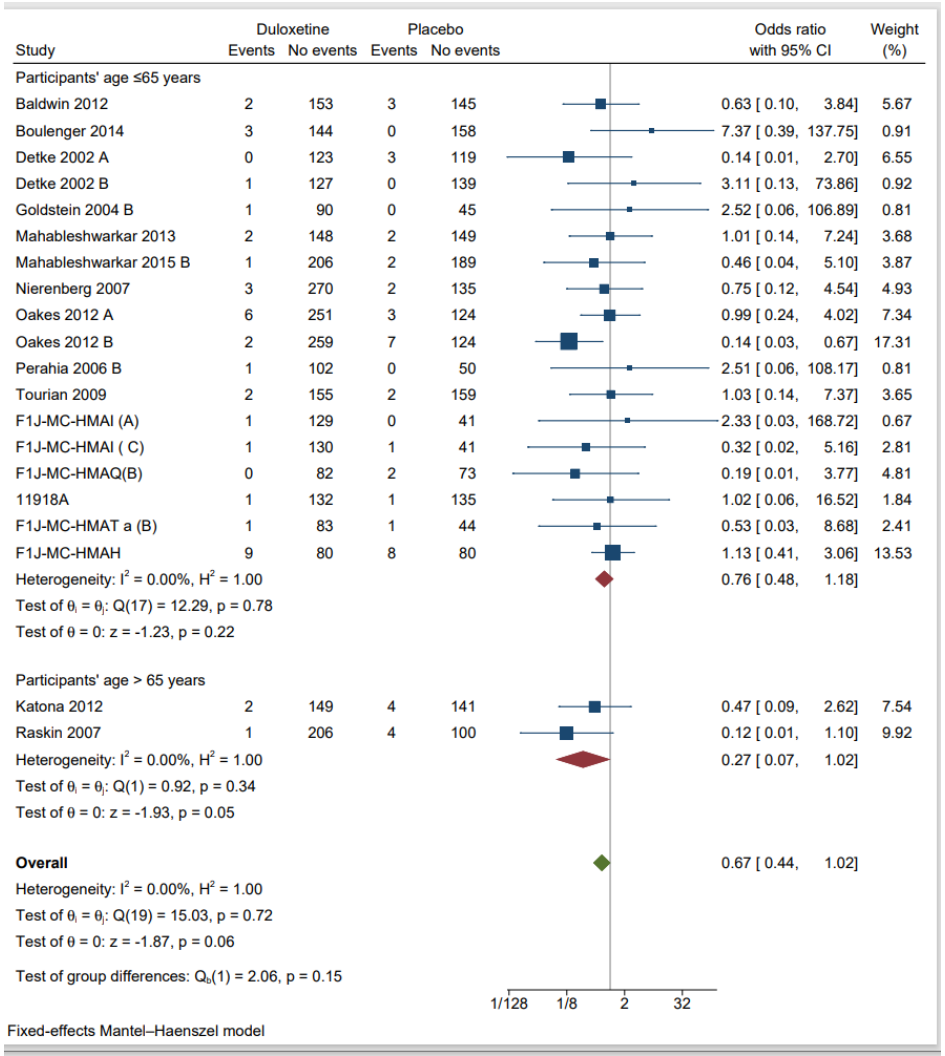

Supplementary Fig S9: Funnel plot of duloxetine vs. placebo for the outcome serious adverse events.



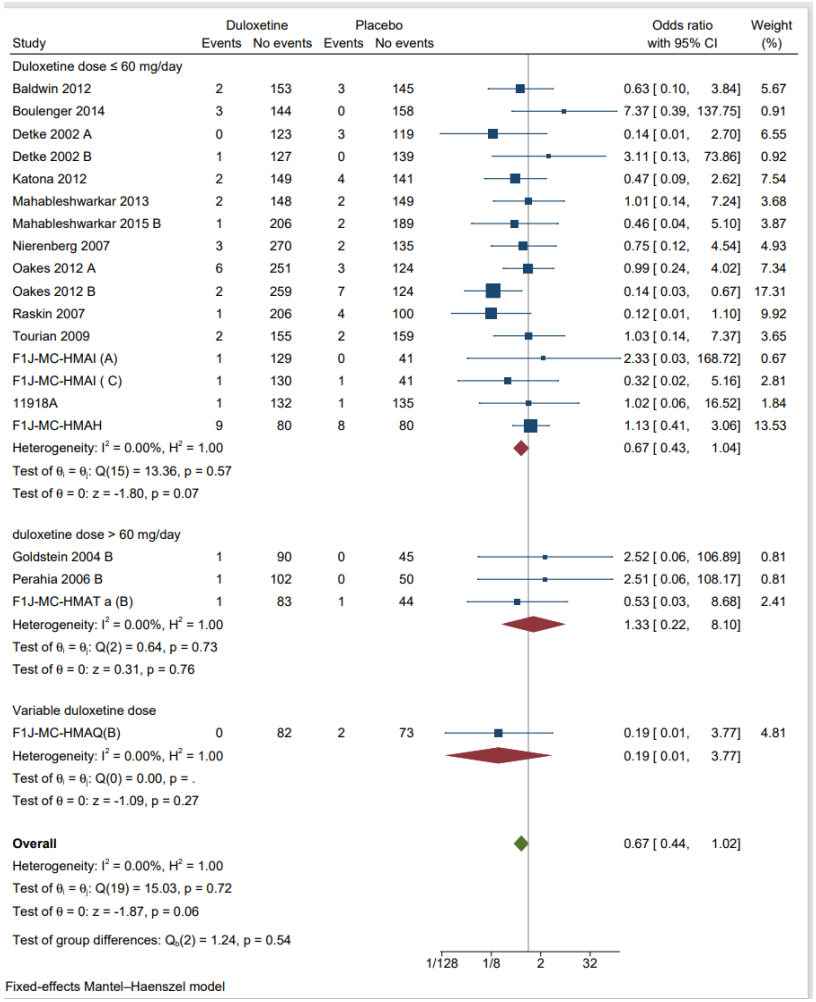

Supplementary Fig S10: Subgroup analysis of baseline HDRS scores on serious adverse events.



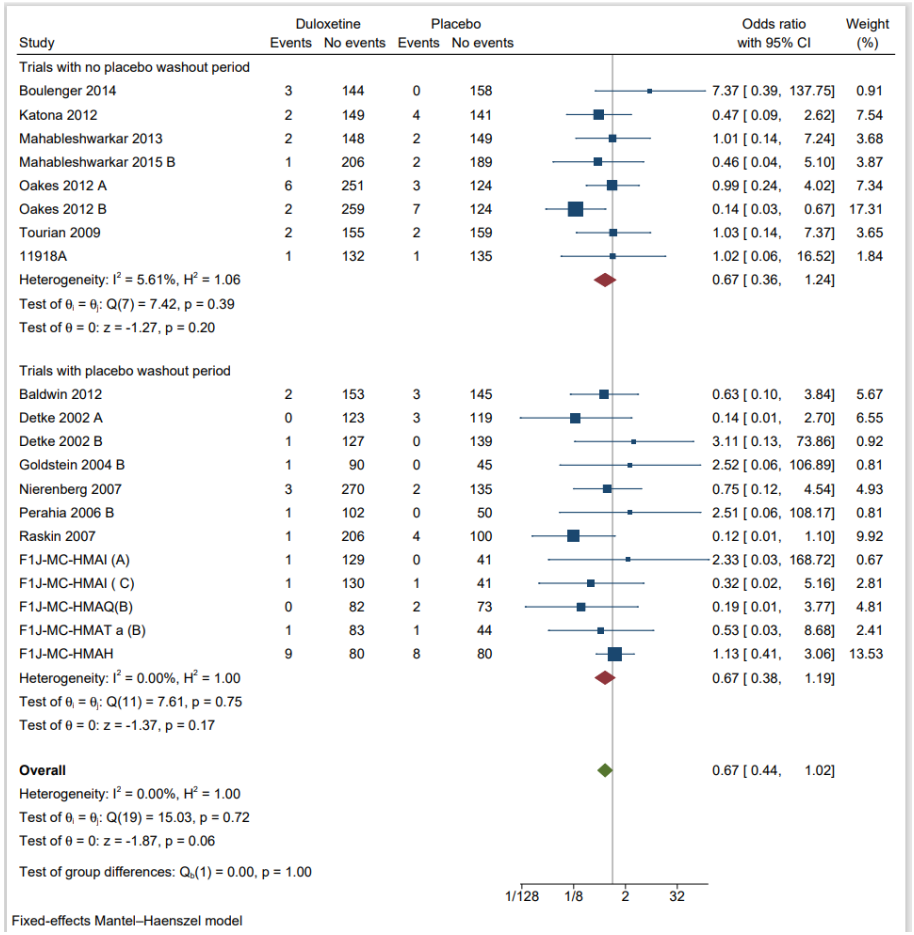

Supplementary Fig S11: Subgroup analysis of chronic treatment resistant depression on serious adverse events.



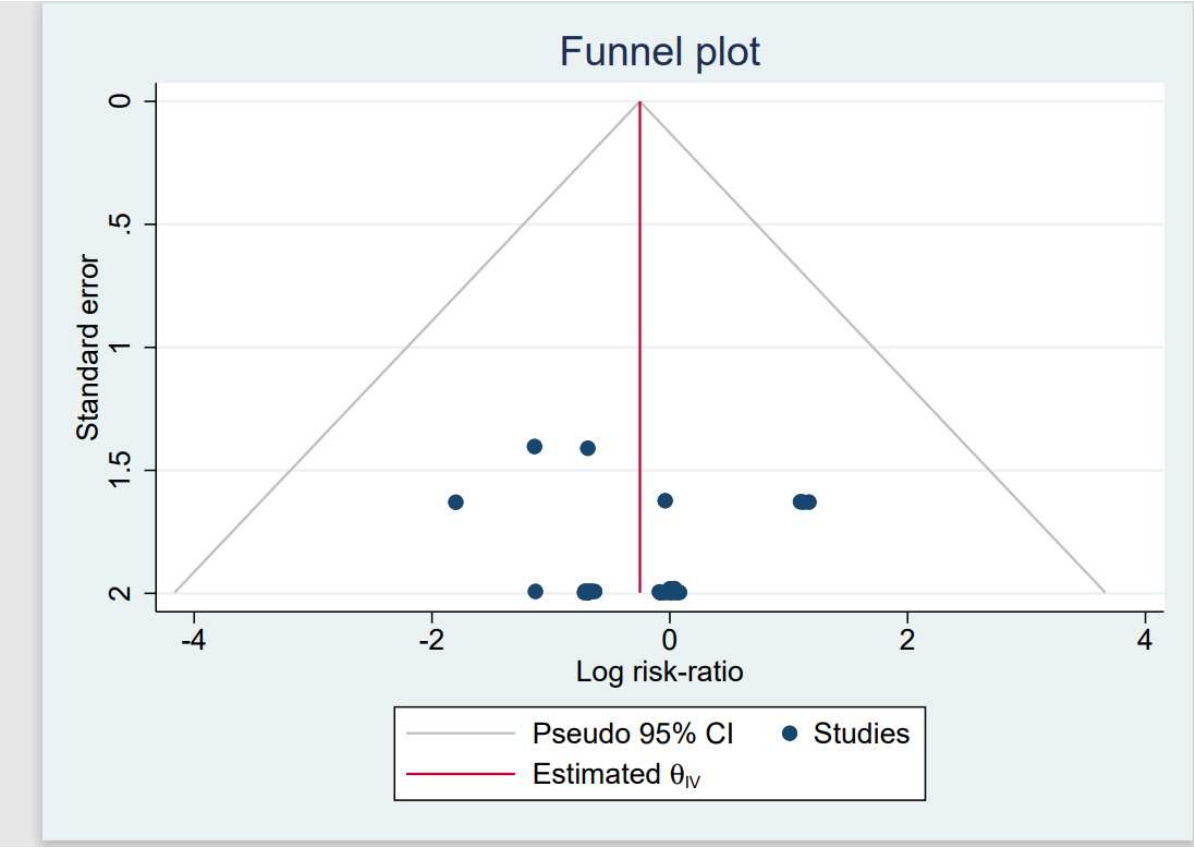

Supplementary Fig S12: Subgroup analysis of participants' age on serious adverse events.



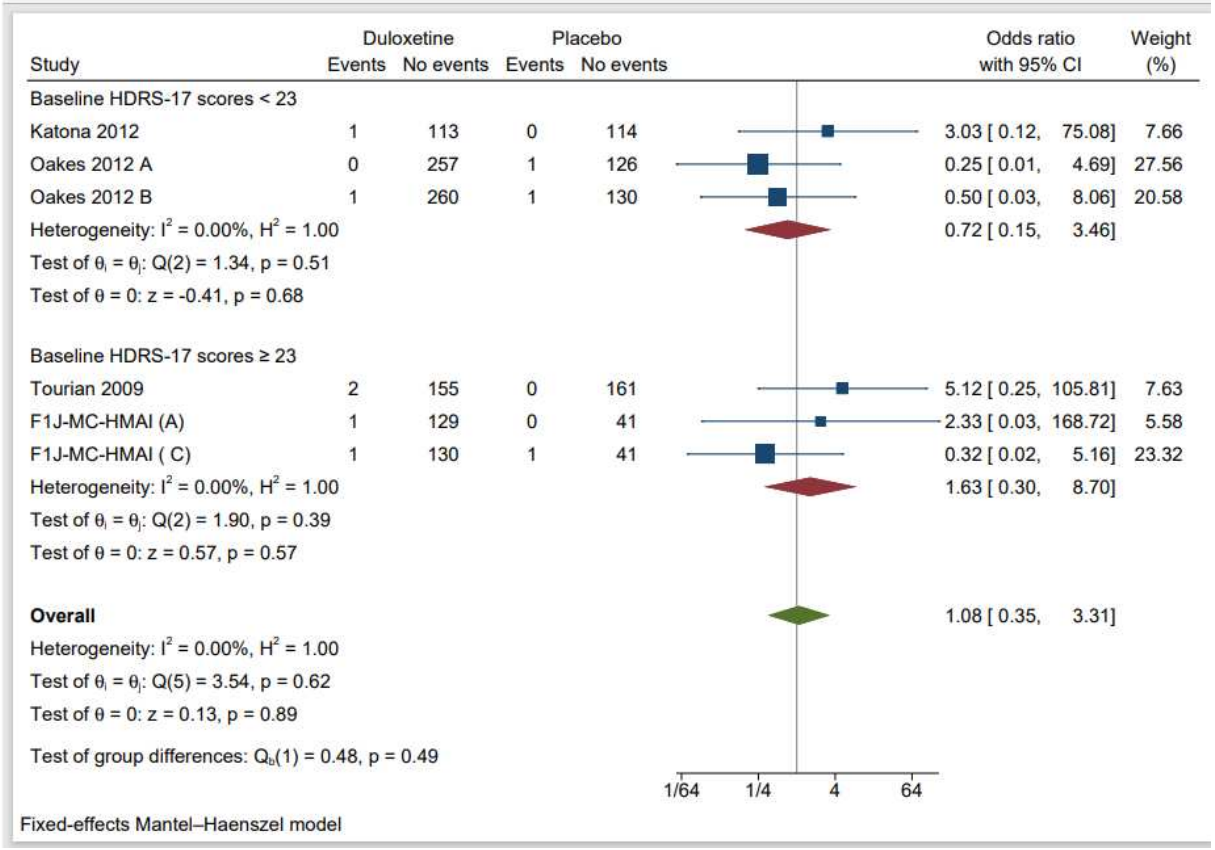

Supplementary Fig S13: Subgroup analysis of duloxetine dose on serious adverse events.



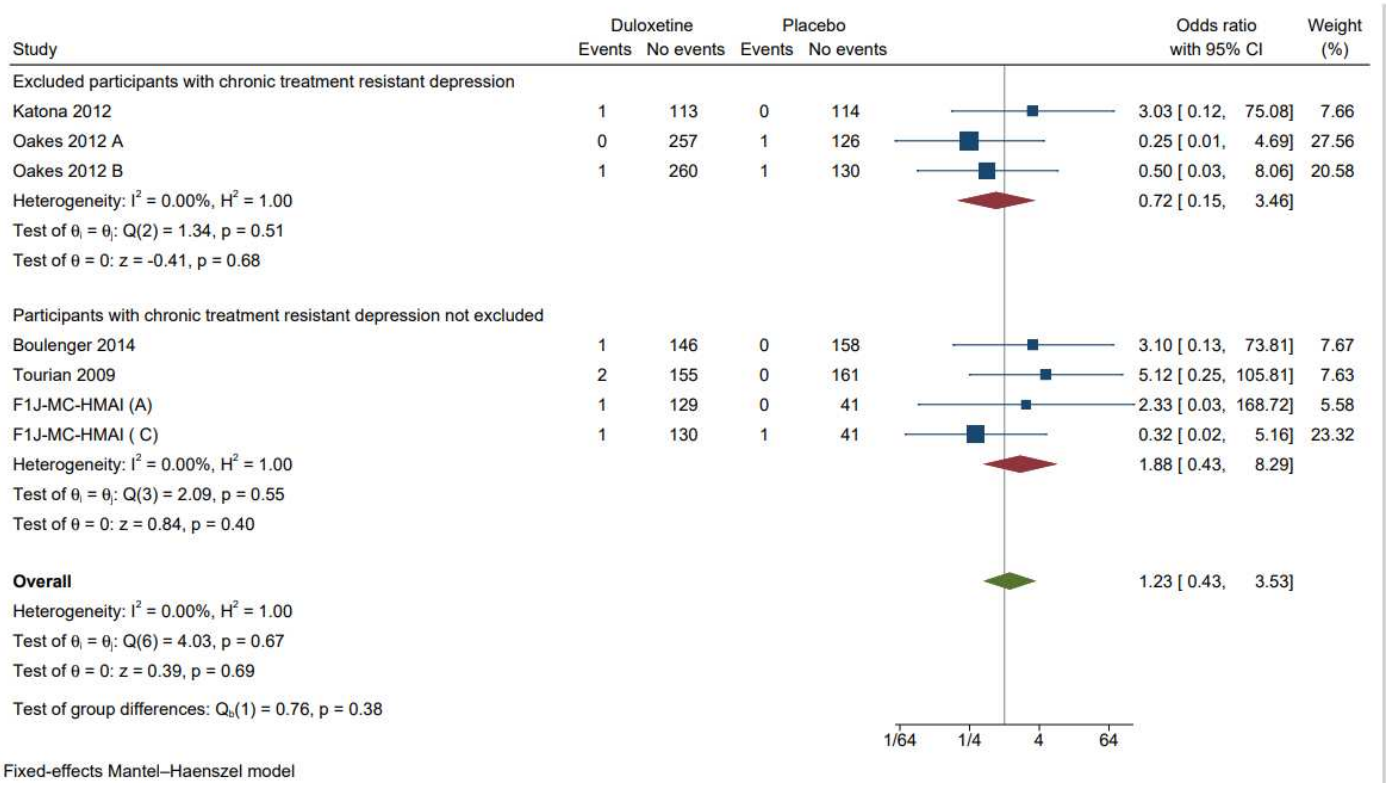

Supplementary Fig S14: Subgroup analysis of placebo washout period on serious adverse events.



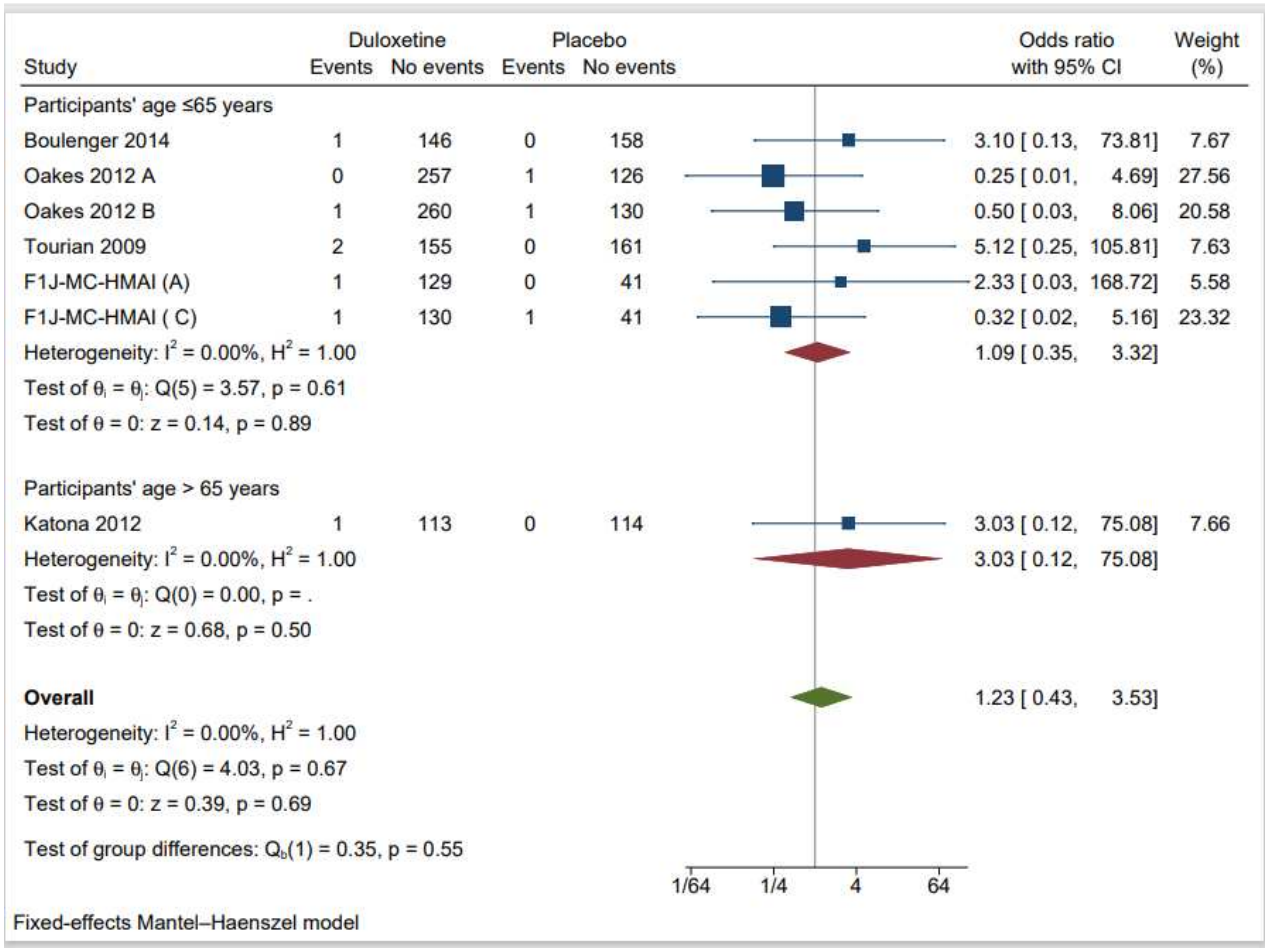

Supplementary Fig S15: Funnel plot duloxetine vs. placebo for the outcome suicide or suicide attempt.



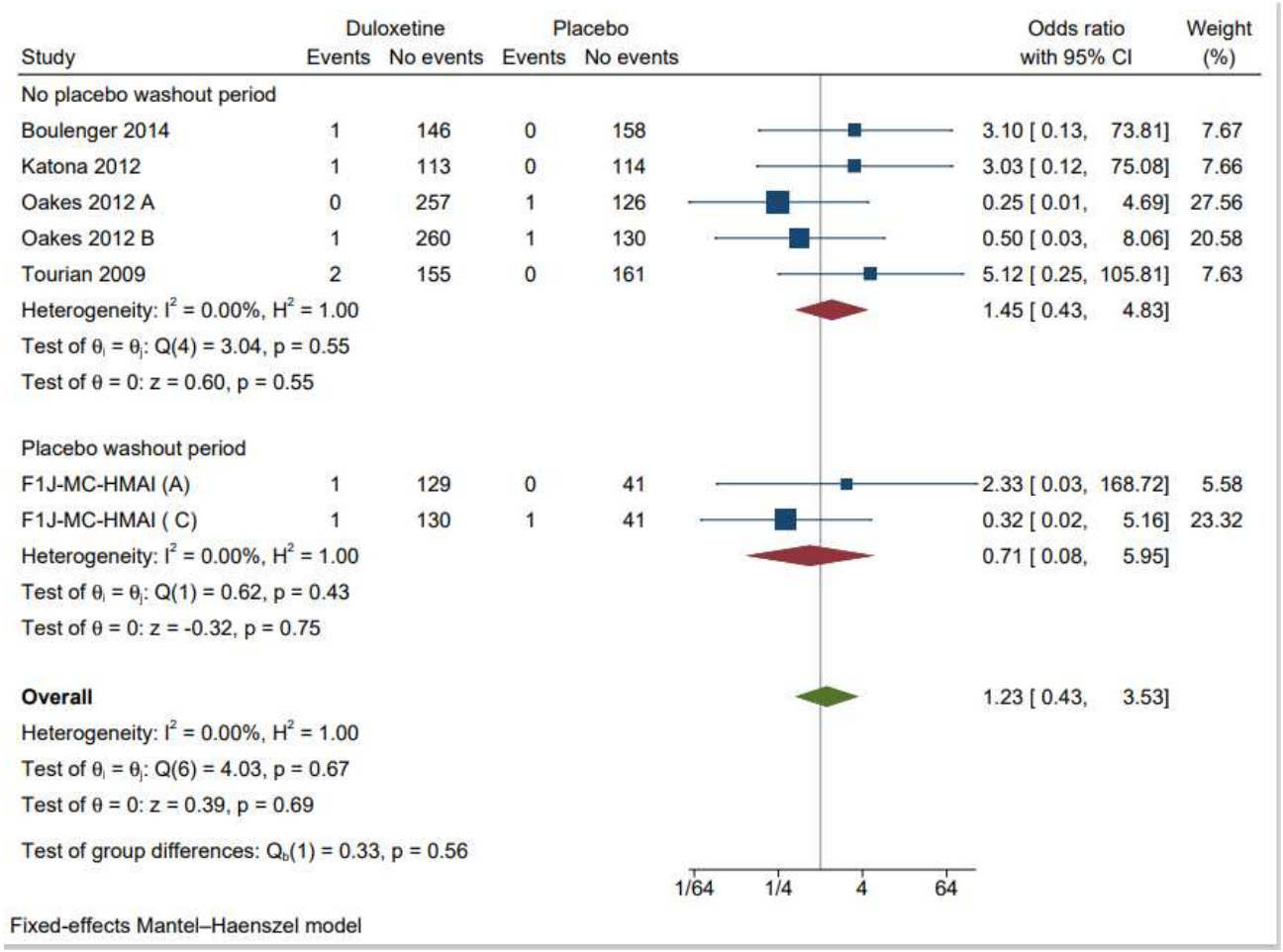

Supplementary Fig S16: Subgroup analysis of baseline HDRS scores on suicide and suicide attempts.



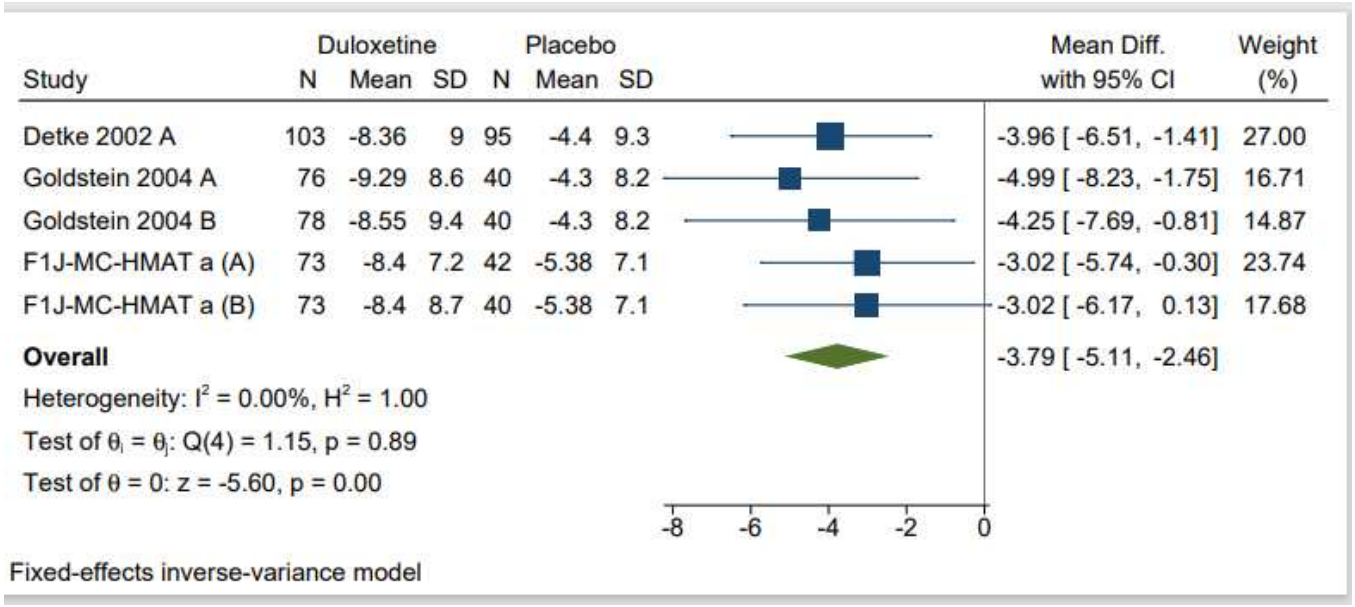

Supplementary Fig S17: Subgroup analysis of chronic treatment resistant depression on suicide and suicide attempts.



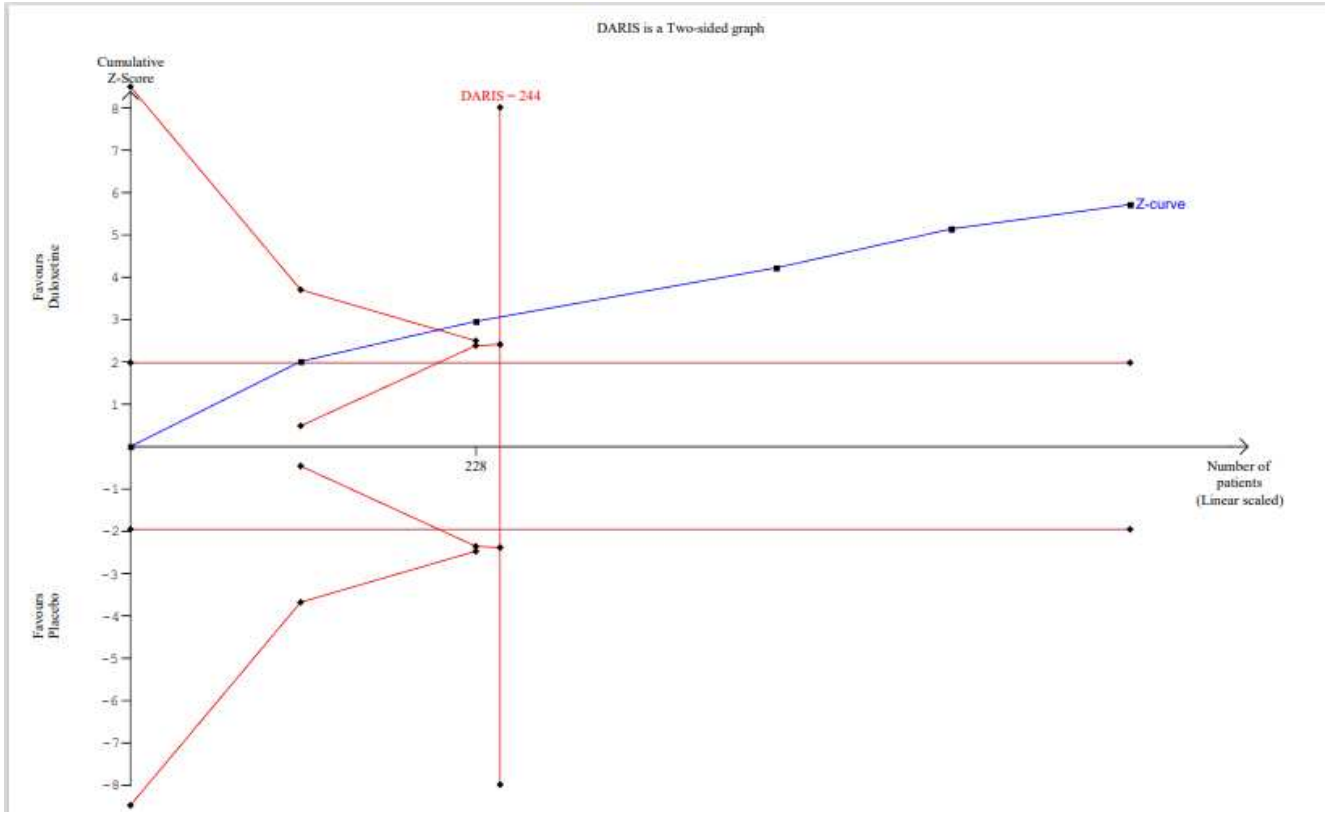

Supplementary Fig S18: Subgroup analysis of participants' age on suicide and suicide attempts.



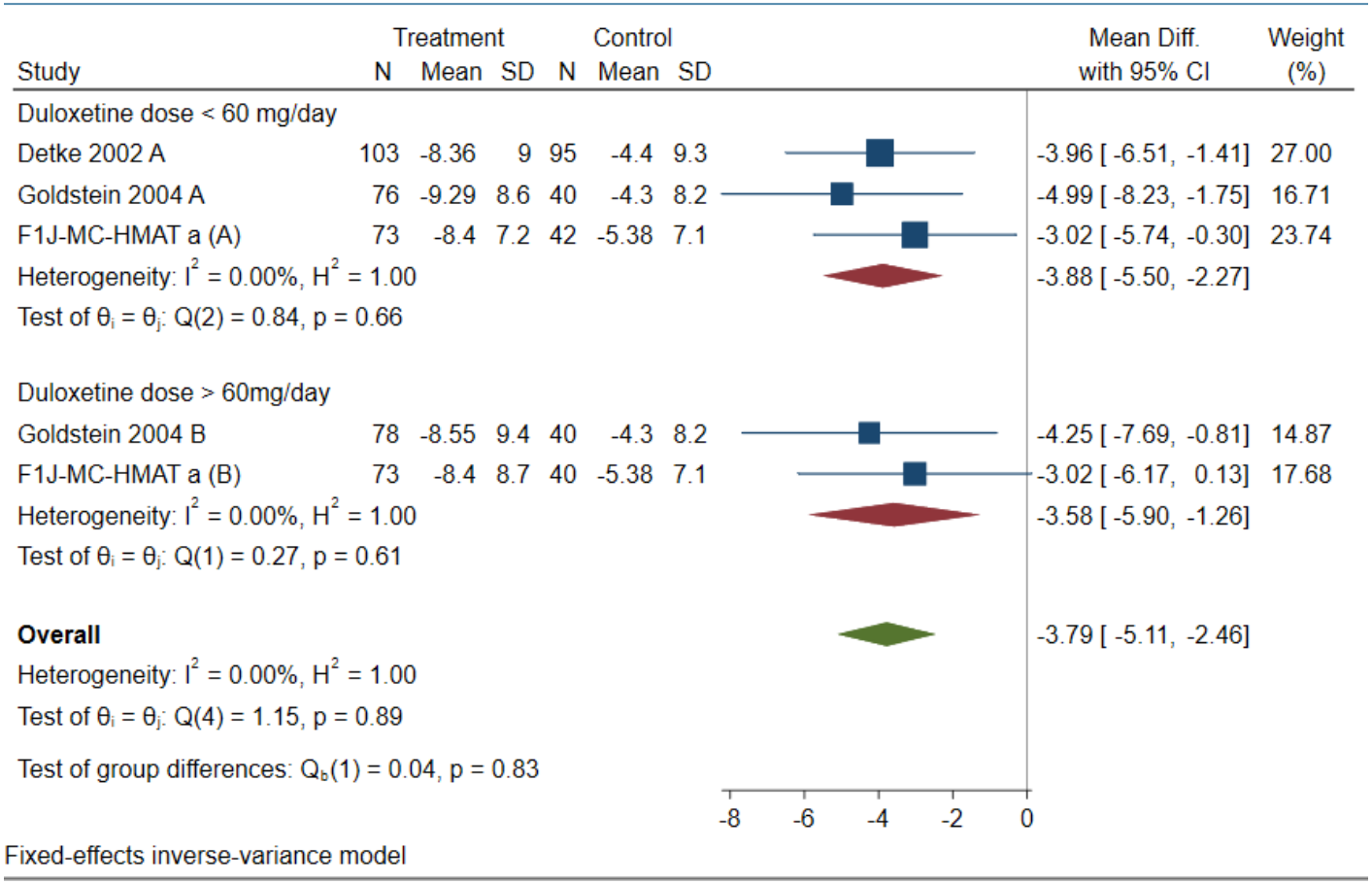

Supplementary Fig S 19: Subgroup analysis of placebo washout period on suicide and suicide attempts.



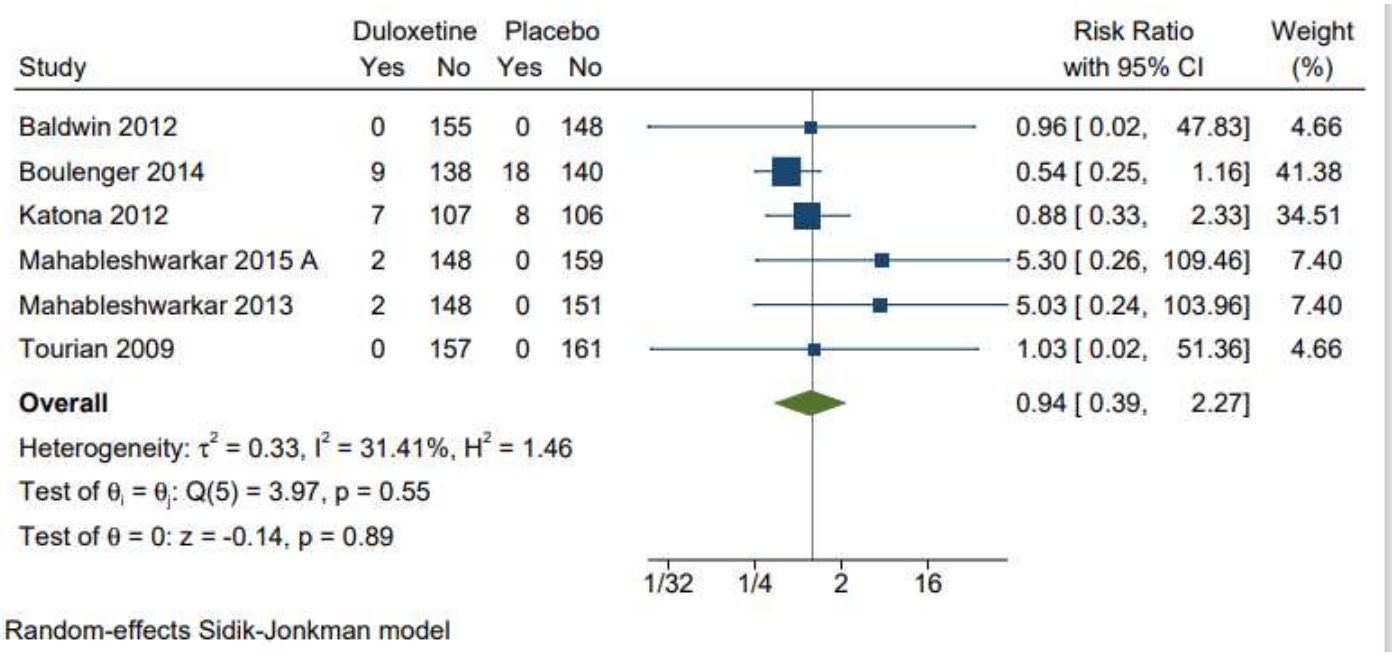

Supplementary Fig S20: Meta-analysis of duloxetine vs. placebo on the outcome quality of life.



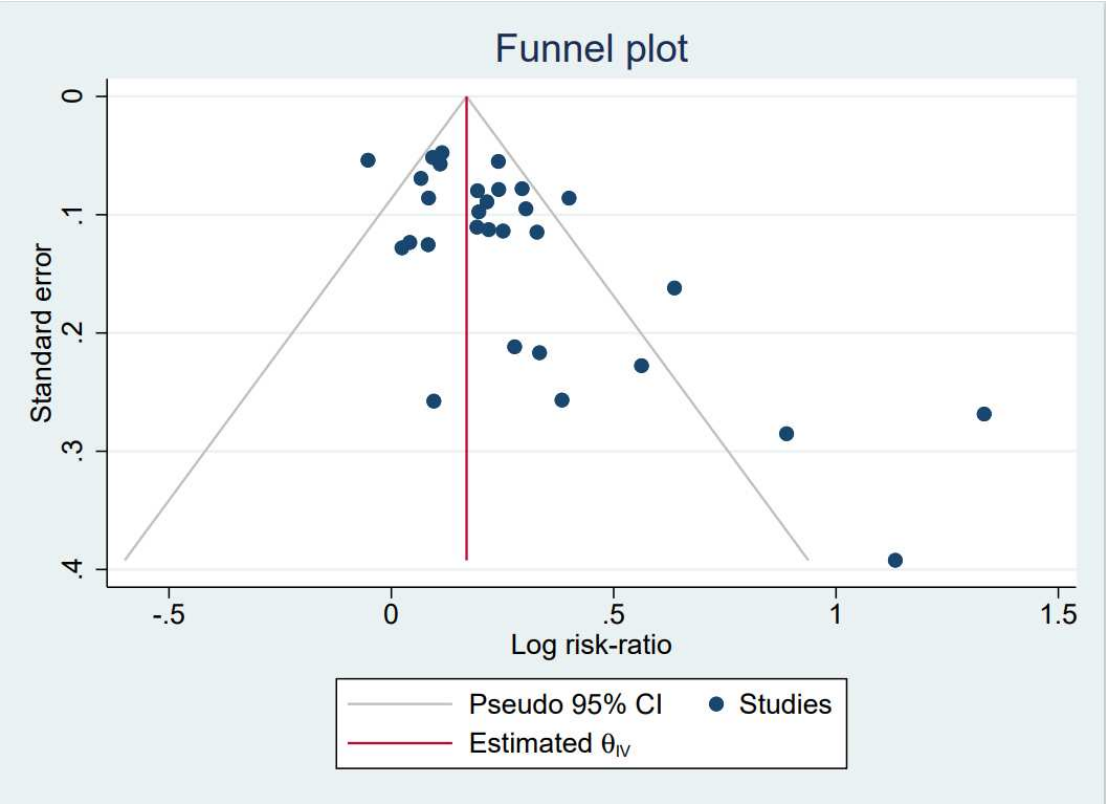

Supplementary Fig S21: Trial Sequential Analysis of duloxetine vs. placebo for the outcome quality of life.



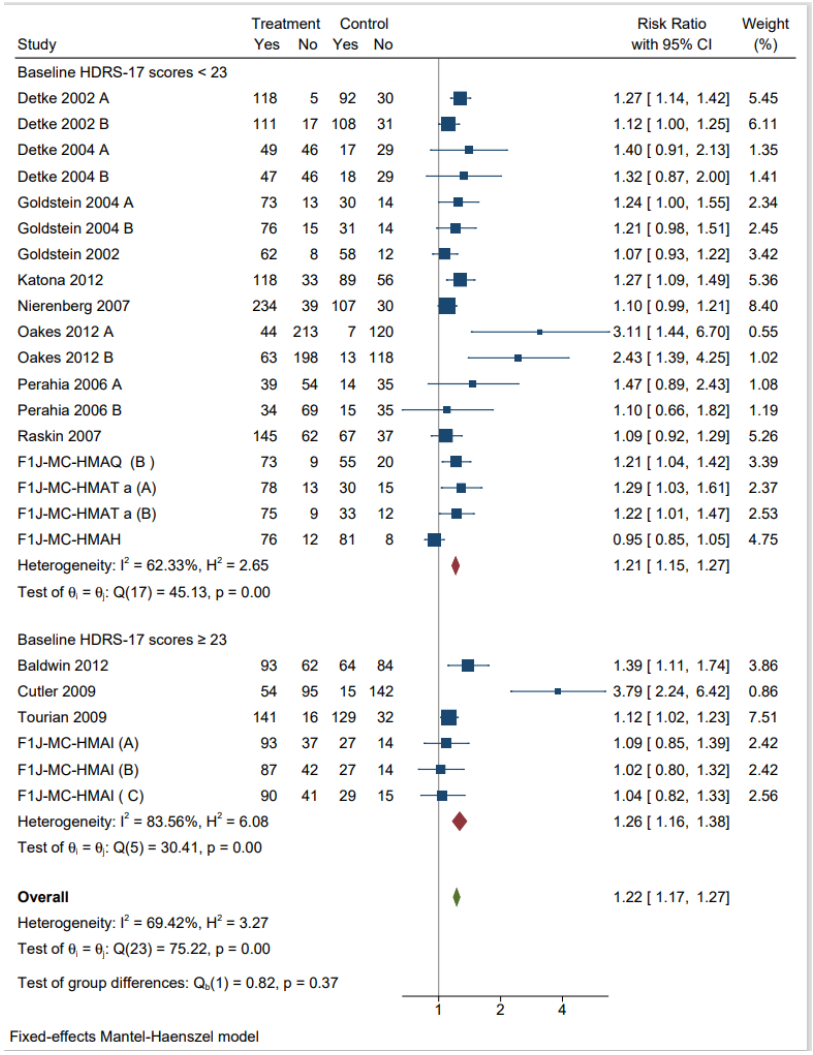

Supplementary Fig S22: Subgroup analysis of duloxetine dose on quality of life.



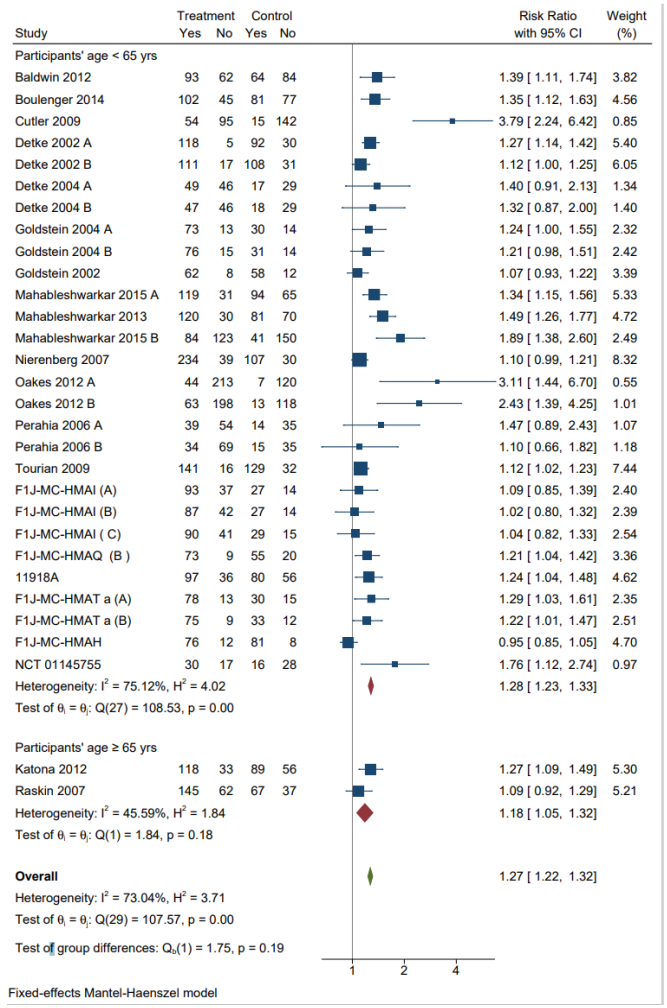

Supplementary Fig S23: Meta-analysis of duloxetine vs. placebo on the outcome suicidal ideation.



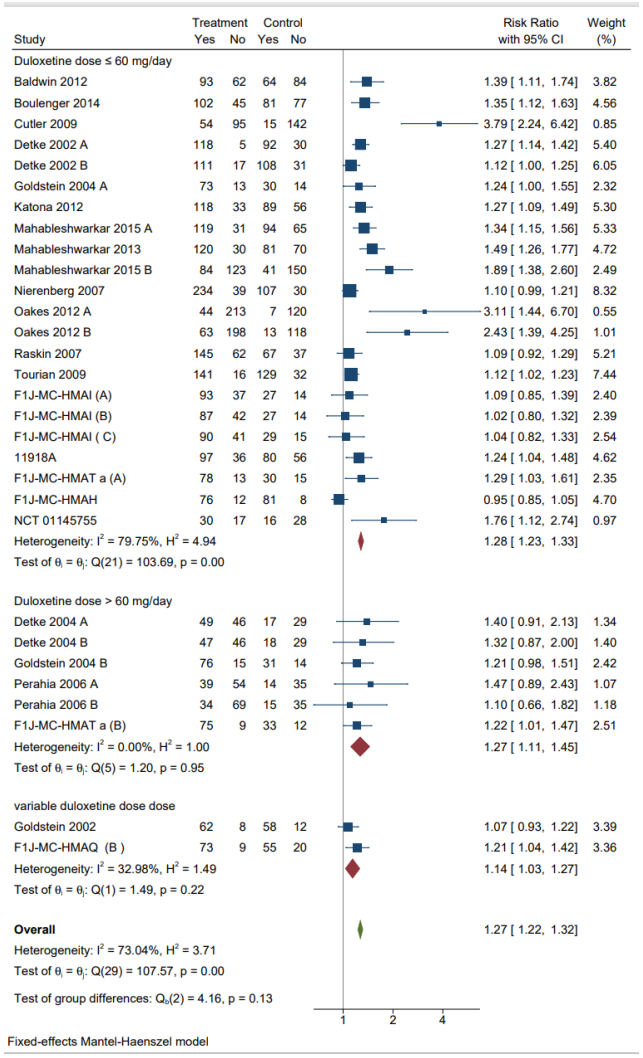

Supplementary Fig S24: Funnel plot duloxetine vs. placebo for the outcome non-serious adverse events.



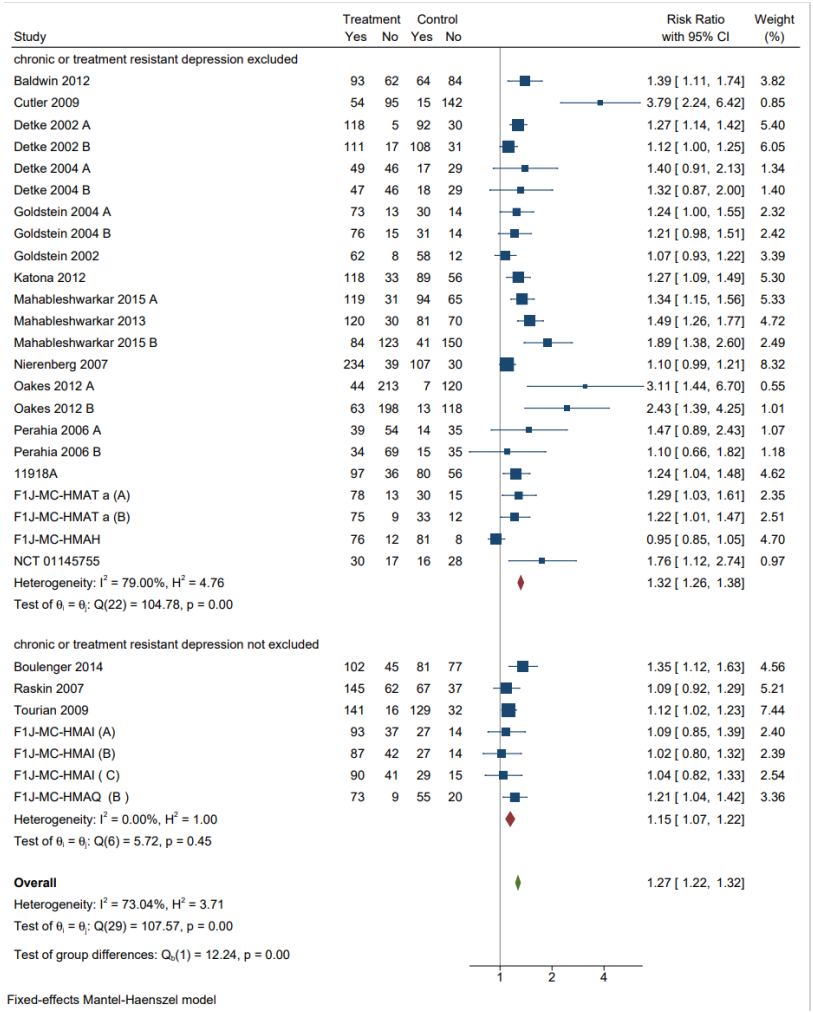

Supplementary Fig S25: Subgroup analysis of baseline HDRS scores on non-serious adverse events.



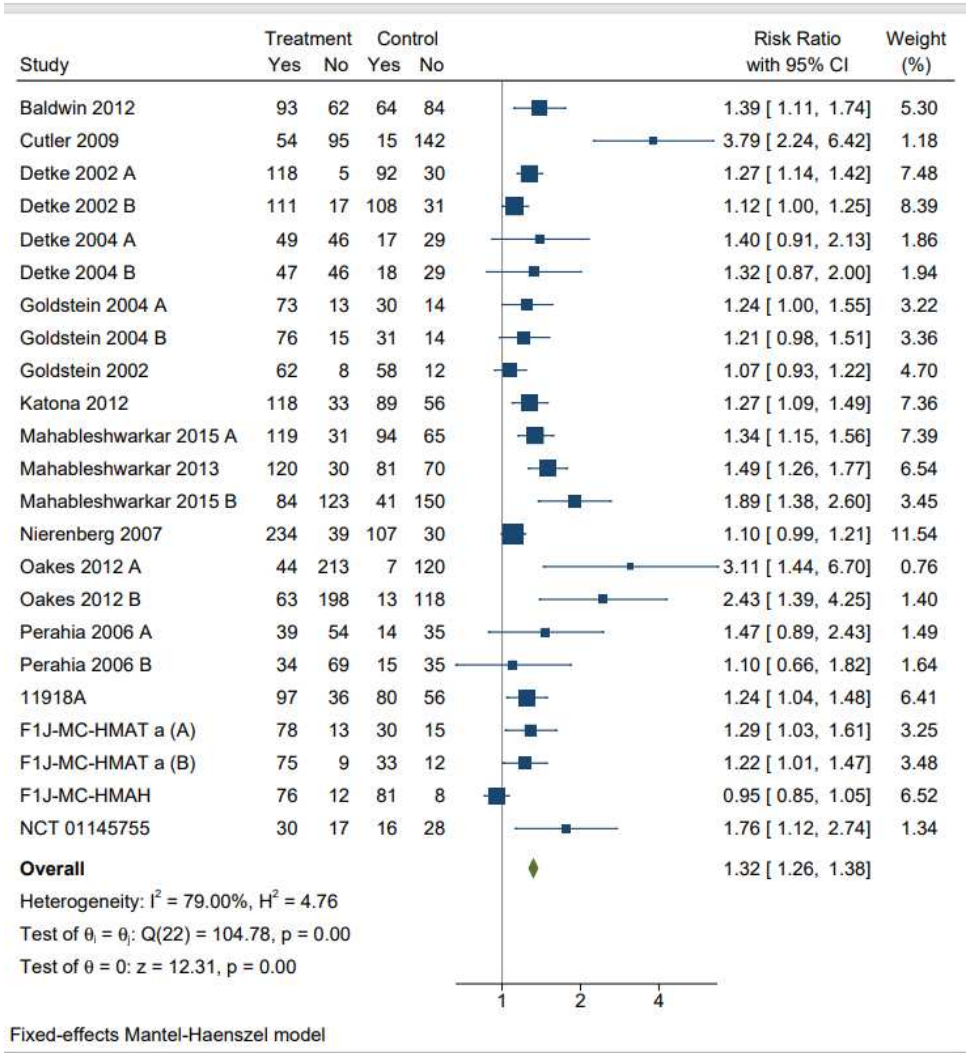

Supplementary Fig S26: Subgroup analysis of participants' age on non-serious adverse events.



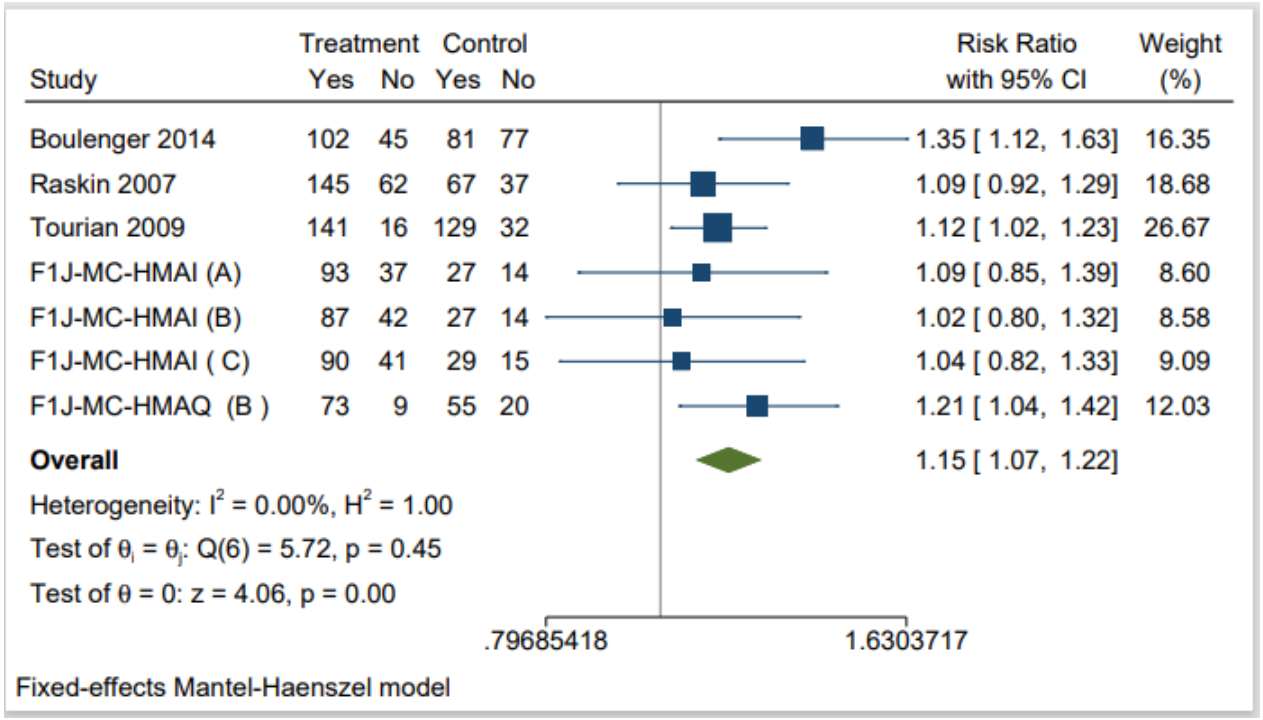

Supplementary Fig S27: Subgroup analysis of duloxetine dose on non-serious adverse events.



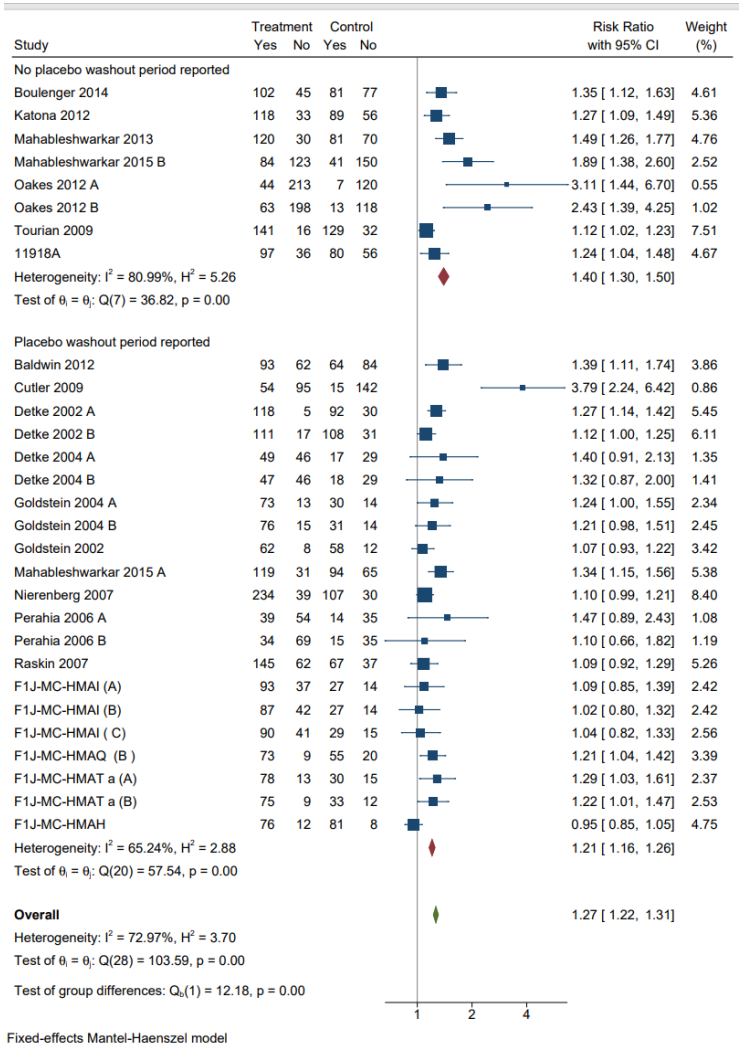

Supplementary Fig S28: Subgroup analysis of chronic treatment-resistant depression on non-serious adverse events.



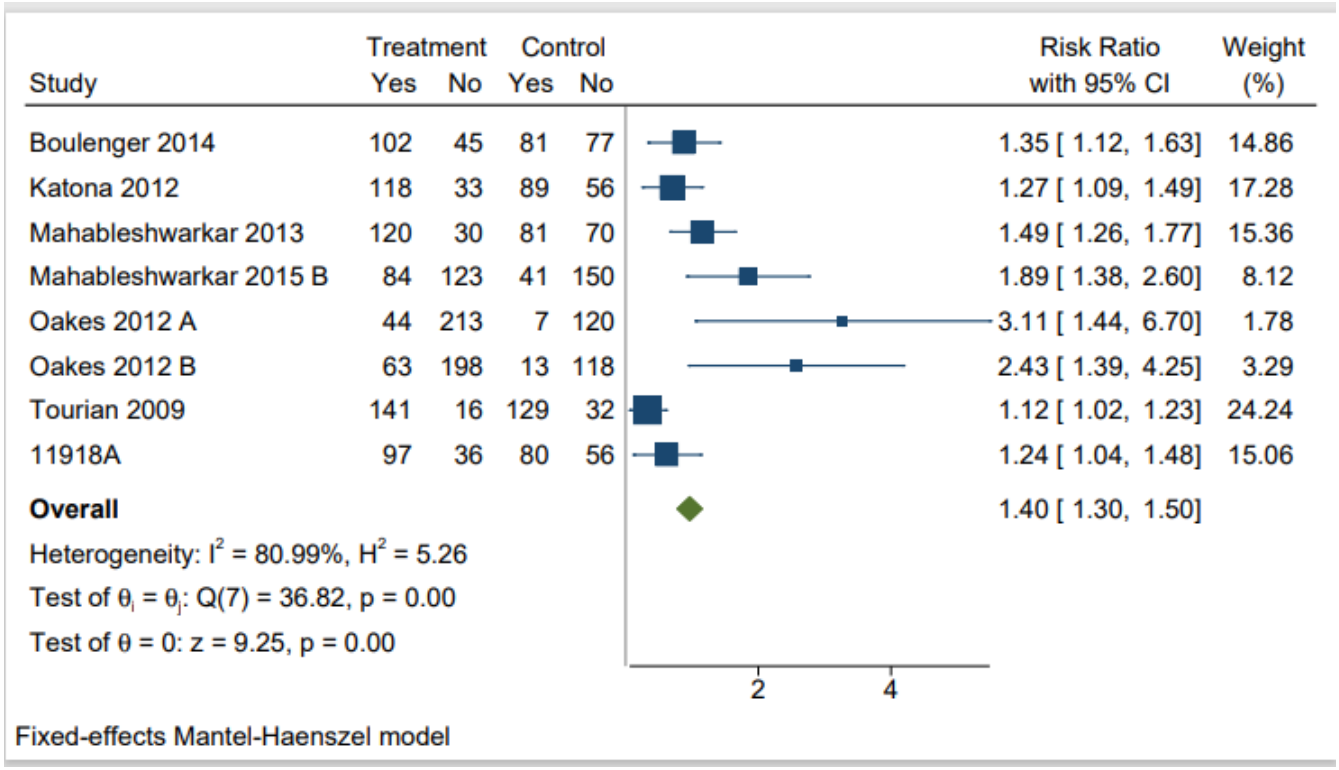

Supplementary Fig S29: Subgroup analysis of for participants without chronic treatment resistant depression on non-serious adverse events.



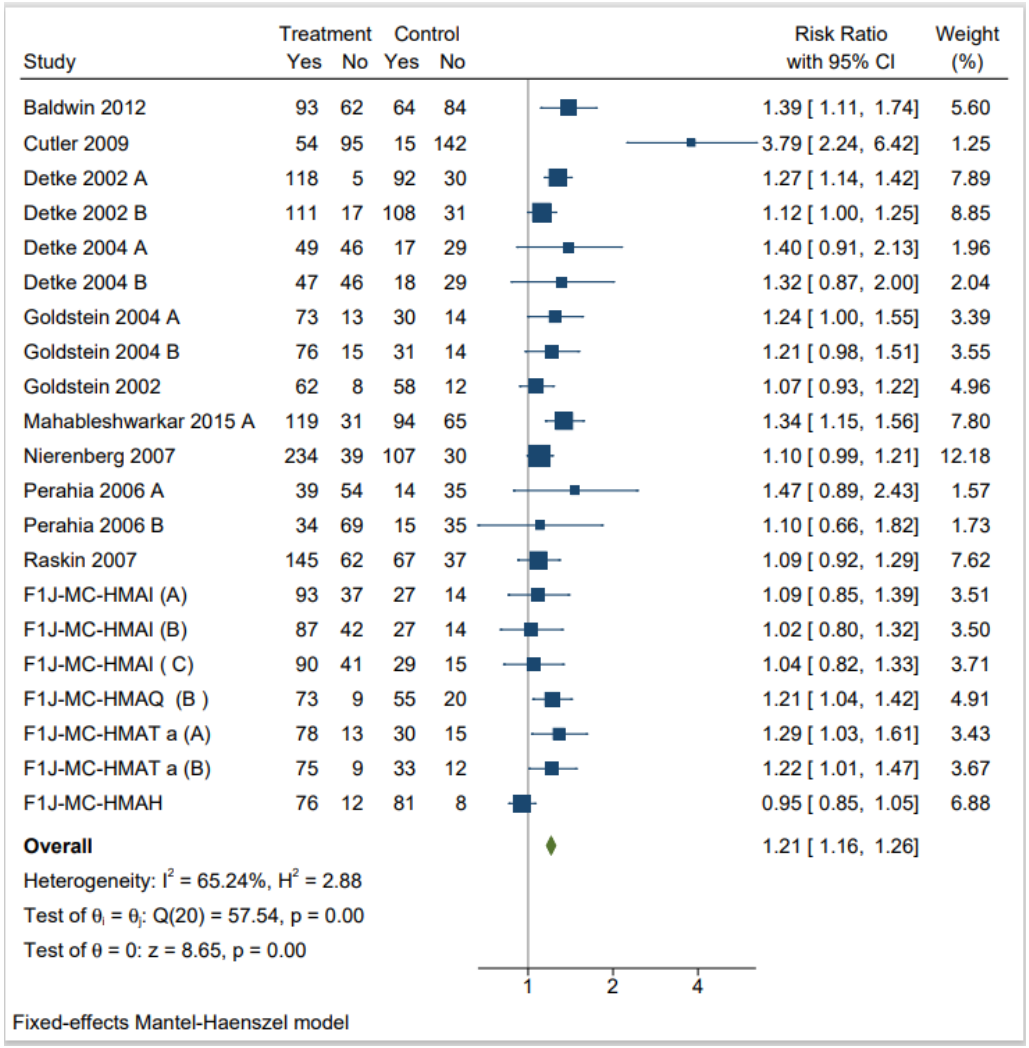

Supplementary Fig S30: Subgroup analysis of participants with chronic treatment resistant depression on non-serious adverse events.




Supplementary Fig S31: Subgroup analysis of placebo washout period on non-serious adverse events.




Supplementary Fig S32: Subgroup analysis of trials without placebo washout period on non-serious adverse events.




Supplementary Fig S33: Subgroup analysis of trials with placebo washout period on non-serious adverse events.

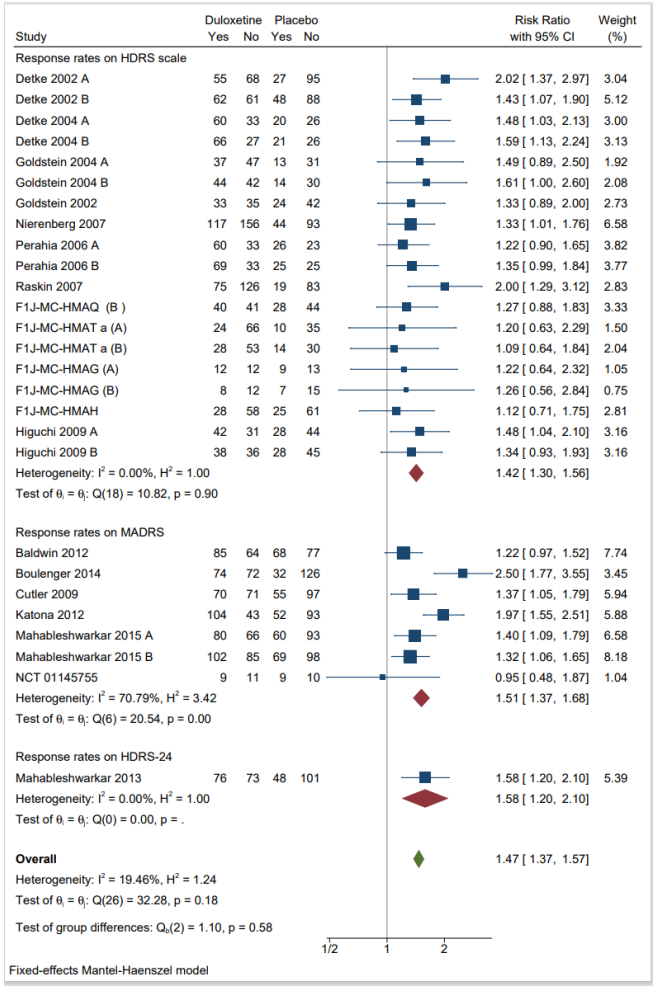
## Exploratory outcomes

### Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale and Beck's Depression Inventory

Twelve trials reported mean change/follow-up scores and SD for HDRS-17.[1-12] Only one trial reported mean change scores and corresponding SD for MADRS (NCT 01145755). However, we specified in the protocol that we will not pool change scores and end scores for standardized mean difference.

### Response

Thirteen trials reported response on HDRS-17 scale,[1-13] six trials on MADRS scale [14-19]and one trial on HDRS-24 scale.[18] Meta-analysis showed beneficial effect of duloxetine on response (RR 1.47, 95%CI, 1.37 to 1.57; P < 0.01; 21 trials) (Fig S34).



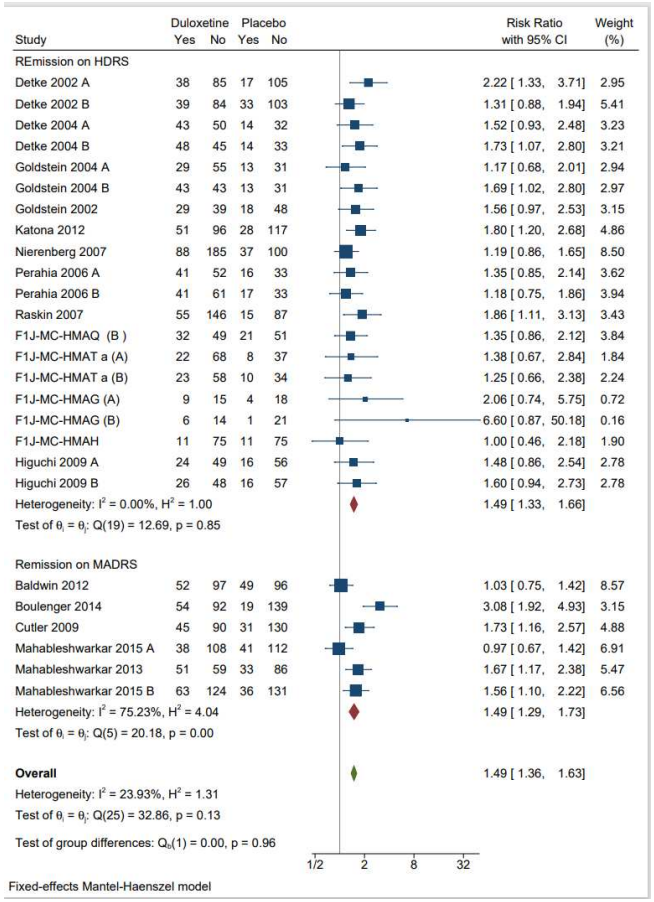

Supplementary Fig S34: Meta-analysis of duloxetine vs. placebo on the outcome response rates.

## Remission

Fourteen trials reported remission on HDRS-17 scale[1-13] and six trials on MADRS scale.[14-19] Meta-analysis of these 17 trials showed beneficial effect of duloxetine on remission (RR 1.49, 95%CI, 1.36 to 1.63; $p < 0.01$; Fig S35).



Siddiqui F, *et al. BMJ Open* 2025; 15:e082853. doi: 10.1136/bmjopen-2023-082853




Supplementary Fig S35: Meta-analysis of duloxetine vs. placebo on the outcome remission rates.

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