Suicide risk with selective serotonin reuptake inhibitors and other new-generation antidepressants in adults: a systematic review and meta-analysis of observational studies

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Supplementary Material

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1. Search strategy

Searching databases: Medline, PsycINFO, Web of Science, PsycARTICLES and SCOPUS.

In: text, abstract, keywords.

1. antidepressants
2. antidepressant agents second generation
3. selective sorotonin reuptake inhibitor
4. serotonin norepinephrine reuptake inhibitor
5. #1 OR #2 OR #3 OR #4
6. citalopram
7. escitalopram
8. fluoxetine
9. fluvoxamine
10. paroxetine
11. sertraline
12. desvenlafaxine
13. duloxetine
14. levomilnacipran
15. milnacipran
16. venlafaxine
17. vilazodone
18. vortioxetine
19. nefazodone
20. trazodone
21. reboxetine
22. bupropion
23. mianserin
24. mirtazapine
25. agomelatine

26. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27. suicide
28. suicide attempted
29. self-harm
30. #27 OR #28 OR #29
31. #5 OR #26
32. #30 AND #31

Limits: age = **18 and older**; language = **english**; publication year = **1990-2020**

2. Pubmed search term

((((("antidepressants"[Title/Abstract] OR "antidepressive agents second generation"[Title/Abstract]) OR "selective serotonin reuptake inhibitors"[Title/Abstract]) OR "serotonin norepinephrine reuptake inhibitors"[Title/Abstract]) OR ((((((((((((((((((("citalopram"[Title/Abstract]) OR "escitalopram"[Title/Abstract]) OR "fluoxetine"[Title/Abstract]) OR "fluvoxamine"[Title/Abstract]) OR "paroxetine"[Title/Abstract]) OR "sertraline"[Title/Abstract]) OR "desvenlafaxine"[Title/Abstract]) OR "duloxetine"[Title/Abstract]) OR "levomilnacipran"[Title/Abstract]) OR "milnacipran"[Title/Abstract]) OR "venlafaxine"[Title/Abstract]) OR "vilazodone"[Title/Abstract]) OR "vortioxetine"[Title/Abstract]) OR "nefazodone"[Title/Abstract]) OR "trazodone"[Title/Abstract]) OR "reboxetine"[Title/Abstract]) OR "bupropion"[Title/Abstract]) OR "mianserin"[Title/Abstract]) OR "mirtazapine"[Title/Abstract]) OR "agomelatine"[Title/Abstract])) AND (("suicide"[Title/Abstract] OR "suicide attempted"[Title/Abstract]) OR "self-harm"[Title/Abstract])

3. Quality (risk of bias) assessment scale

The following scale was adapted from the literature[1 2] and was also applied in the previous meta-analysis by Barbui et al.[3]

Domains	Categories	Scoring
Population framework	Defined geographic area	2
	Hospital / Insurance database	1
	Convenience sample	0
Study design	Cohort	2
	Case-control	1
Demographic data	Complete description	1
	Inadequate description	0
Clinical data	Complete description	1
	Partial description	0
Outcome data	Complete description	2
	Partial description	1
	Inadequate description	0
Covariate adjustment	>3 variables	2
	1-3 variables	1
	None	0

4. Qualitative synthesis of unique medical conditions

Haukka et al.[4] conducted a register-based cohort study in patients with schizophrenia in Finland (n=1611; mean age: 38; 51% men). In this cohort there was no clear association between exposure to any antidepressant and suicides (RE=0.97, 0.58-1.61). With respect to suicide attempt, the risk was slightly increased in the group exposed to antidepressants (RE=1.25, 1.06-1.47). By contrast, Tiihonen et al.,[5] based on a largely overlapping sample derived from the same Finnish healthcare registries (n=2588; mean age: 38; 62% men), reported a considerably reduced suicide risk with any antidepressant (RE=0.15, 0.03-0.77). Reutfors et al.[6] also focused on suicides in patients with schizophrenia. In this case-control study based on healthcare registries from Sweden (n=168; mean age: 30; 57% men), there was no clear association between exposure to SSRI and suicide (RE=0.68, 0.23-2.0). In a case-control study based on Korean healthcare registries (n=296; mean age: 40; 78% men), Park et al.[7] found an increased risk of suicide for patients with epilepsy exposed to any antidepressant (RE=7.2, 1.5-34.1). Finally, in a cohort study from the USA based on the Veterans Affairs database (n=294,952; mean age: 80; 97% men), Seyfried et al.[8] reported an increased risk of suicide in patients with dementia exposed to any antidepressant (RE=2.11, 1.57-2.84).

5. Characteristics of studies included in the meta-analysis

Reference (country)	Study design	Population framework (sample size)	Age range (mean)	Males	Indication and exposure description	Adjustment or matching variables	Outcome definition	Ascertainment of exposure	Financial conflicts of interest	Quality score
Bilen 2011 (Sweden)[9]	Cohort	Stockholm emergency department register and Swedish healthcare registers (n=1524)	18-92 (40)	35%	Emergency department visit due to deliberate self-harm Any AD vs. unexposed	>3	Suicide attempt according to ICD-10, including suicide	Prescription registry	No	7
Bjorkenstam 2013 (Sweden)[10]	Cohort	Swedish Causes of Death Register (n=5913)	13+ (50)	71%	Any indication SSRI vs. unexposed	>3	Suicide according to ICD-10	Prescription registry	No	9
Carlsten 2009 (Sweden)[11]	Case-control	Gothenburg Institute of Forensic Medicine (cases), Tax Register (controls) (n=238)	65+ (75)	55%	Any indication SSRI, any AD vs. unexposed	>3	Suicide death according to coroner's report	Post-mortem forensic analysis (cases), psychiatric interview (controls)	No	8
Castelpietra 2017 (Italy)[12]	Case-control	Social and Health Information System of the Friuli Venezia Giulia region (n=5256)	?	65%	Any indication SSRI, SNRI, TCA, other AD vs. unexposed	>3	Suicide according to ICD-9	Prescription registry	Yes	8
Chartrand 2012 (USA)[13]	Cohort	National Epidemiologic Survey on Alcohol and Related Conditions (n=2864)	18+ (40)	33%	Depression Any AD vs. unexposed	>3	Suicide attempt according to structured interview	Structured interview	No	7
Cheung 2015 (Netherlands)[14]	Cohort	Integrated Primary Care Information database (n=27,712)	10+ (50)	39%	Any indication and depression SSRI, other AD, TCA vs. unexposed (AD discontinued)	>3	Suicide attempt according to ICD-9/10, including suicide	Medical records	No	9

Coupland 2011 (UK)[15]	Cohort	UK General Practices database (n=60,746)	65-100 (75)	33%	Depression SSRI, other AD, TCA vs. unexposed	>3	Suicide attempt according to ICD-9/10	Primary care medical records	No	9
Coupland 2015* (UK)[16]	Cohort	UK General Practices database (n=238,963)	20-64 (40)	39%	Depression SSRI, other AD, TCA vs. unexposed	>3	Suicide and suicide attempt according to ICD-9/10	Primary care medical records	No	9
Didham 2005 (New Zealand)[17]	Case-control	Dunedin General Practitioners Research Unit database and New Zealand health record databases (n=57,361)	10-102 (46)	32%	Any indication SSRI, TCA vs. unexposed	1-3	Suicide and suicide attempt according to ICD-9	Computerized clinical records	No	6
Eikelenboom 2019 (Netherlands)[18]	Cohort	Netherlands Study of Depression and Anxiety (n=1713)	18-65 (42)	31%	Depression Any AD vs. unexposed	>3	Suicide attempt according to structured interview	Inspection of medication boxes	No	9
Erlangsen 2009 (Denmark)[19]	Cohort	Danish Register of Medicinal Product Statistics (n=217,123)	50+ (?)	36%	Any indication Any AD vs. unexposed (AD discontinued)	>3	Suicide according to ICD-9	Pharmacy prescription registry	No	9
Gibbons 2007 (USA)[20]	Cohort	Veterans Health Administration database (n=226,866)	18+ (57)	92%	Depression SSRI, other AD, TCA vs. unexposed	0	Suicide attempt according to ICD-9, including suicide or self-inflicted injury	Prescription registry	Yes	6
Leon 1999 (USA)[21]	Cohort	National Institute of Mental Health Collaborative Depression Study (n=643)	17+ (38)	36%	Any affective disorder Fluoxetine vs. unexposed (AD discontinued)	>3	Suicide attempt according to psychiatric interview and medical records, including suicide	Structured interview and medical records	Yes	7
Martinez 2005 (UK)[22]	Case-control	UK General Practices database (n=37,652)	10-89 (40)	80% (Sui); 43% (SA)	Depression Any AD vs. unexposed (AD discontinued)	>3	Suicide and suicide attempt according to ICD-9/10	Primary care medical records	No	7

Olfson 2006 (USA)[23]	Case-control	Medicaid administrative database (n=3397)	19-64 (37)	26% (Sui); 59% (SA)	Depression SSRI, other AD, TCA vs. unexposed	>3	Suicide attempt according to ICD 9, suicide according to ICD 10	Prescription registry	Yes	8
Olfson 2008 (USA)[24]	Case-control	Medicaid administrative database (n=1078)	19-64 (32)	32%	Depression SSRI, other AD vs. unexposed	>3	Suicide attempt according to ICD-9	Prescription registry	Yes	8
Olmer 2012# (Israel)[25]	Case-control	Beer Yaakov mental health centre (n=206)	22-84 (49)	67%	Depression SSRI, other AD, TCA vs. unexposed	>3	Suicide attempt according to clinical evaluation	Medical charts	No	7
Rahman 2014 (Sweden)[26]	Cohort	Swedish healthcare registers (n=46,745)	18-64 (50)	34%	Disability pension due to common mental disorder Any AD vs. unexposed	>3	Suicide and suicide attempt according to ICD-10	Prescription registry	No	8
Rahme 2008 (Canada)[27]	Cohort	Quebec Health Care Fund administrative database (n=128,229)	65+ (75)	30%	Any indication and depression SSRI, other AD vs. unexposed (AD discontinued)	0	Suicide death according to coroner's report (ICD-9/10)	Prescription registry	Yes	8
Raja 2009# (Italy)[28]	Case-control	Italian psychiatric intensive care unit (n=1362)	18+ (43)	52%	Admission to psychiatric intensive care unit Any AD vs. unexposed	0	Suicide attempt according to clinical evaluation	Medical charts and interviews	No	5
Sondergard 2007 (Denmark)[29]	Cohort	Danish Medicinal Product Statistics and health registries (n=31,422)	18-101 (56)	33%	Depression SSRI, other AD, TCA vs. unexposed	1-3	Suicide death according to ICD-10	Prescription registry	Yes	9
Spittal 2019 (Australia)[30]	Case-control	Queensland Corrective Services and Australian Institute of Health and Welfare databases (n=572)	18+ (30)	17%	Any indication Any AD vs. unexposed	>3	Suicide according to ICD-9/10	Detention and case-management records	No	5

Swanson 2015 (USA)[31]	Cohort	Medicaid administrative database (n=28,493)	12-55 (25)	0%	Depression Any AD vs. unexposed (AD discontinued)	>3	Suicide attempt according to ICD-9	Prescription registry	No	8
Termorshuizen 2016 (Netherlands)[32]	Cohort	Achmea Health Insurance Database and registers of Statistics Netherlands (n=232,561)	? (49)	36%	Any indication Any AD vs. unexposed (AD discontinued)	0	Suicide and suicide attempt according to DSM-10	Prescription registry	No	4
Tiihonen 2006 (Finland)[33]	Cohort	Finnish National Hospital Dicharge register (n=15,390)	10-100 (39)	49%	Hospitalized with diagnosis of suicide attempt SSRI, other AD, TCA vs. unexposed	>3	Suicide and suicide attempt according to ICD-10	Outpatient pharmacy prescription registry	Yes	9
Valuck 2016 (USA)[34]	Cohort	IMS Health Life-Link database (n=52,355, excluding general population sample)	19-98 (42)	33%	Depression SSRI, SNRI, TCA vs. unexposed	>3	Suicide and suicide attempt according to ICD-9	Prescription registry	Yes	8
Wang 2015 (Sweden)[35]	Cohort	Swedish healthcare registers (n=21,096)	16-64 (37)	40%	Depression Any AD vs. unexposed	>3	Suicide and suicide attempt according to ICD-10	Prescription registry	No	9

*Risk estimate for other AD vs. unexposed was requested from the lead-author (Carol Coupland) and generously provided by email

#Risk estimates for any antidepressant vs. unexposed were calculated based on the data from the contingency table

SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin Norepinephrine Reuptake Inhibitor; TCA: Tricyclic antidepressants; other AD: non-SSRI new-generation antidepressants, including SNRI and atypical AD (e.g. mirtazapine, bupropion); Any AD: any new-generation antidepressant, including SSRI, SNRI and atypical AD

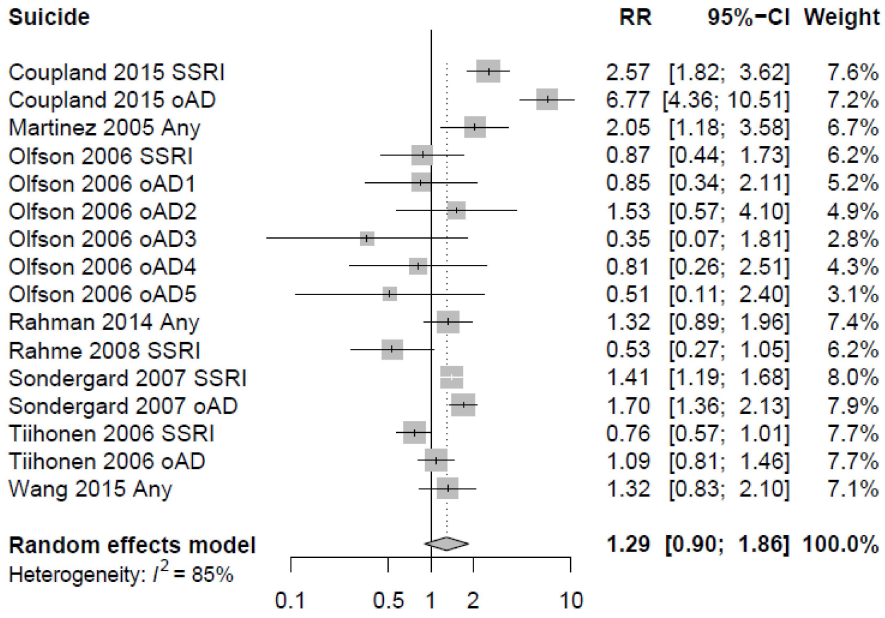
6. Quality ratings of studies included in the meta-analysis

	Population framework	Study design	Demographic data	Clinical data	Outcome data	Covariate adjustment
Bilen 2011	1	2	1	0	1	2
Bjorkenstam 2013	2	2	1	0	2	2
Carlsten 2009	2	1	1	0	2	2
Castelpietra	2	1	0	1	2	2
Chartrand 2012	2	2	0	0	1	2
Cheung 2014	1	2	1	1	2	2
Coupland 2011	1	2	1	1	2	2
Coupland 2015	1	2	1	1	2	2
Didham 2005	1	1	1	0	2	1
Eikelenboom 2019	2	2	1	1	1	2
Erlangsen 2009	2	2	0	1	2	2
Gibbons 2007	1	2	0	1	2	0
Leon 1999	0	2	0	1	2	2
Martinez 2005	1	1	0	1	2	2
Olfson 2006	1	1	1	1	2	2

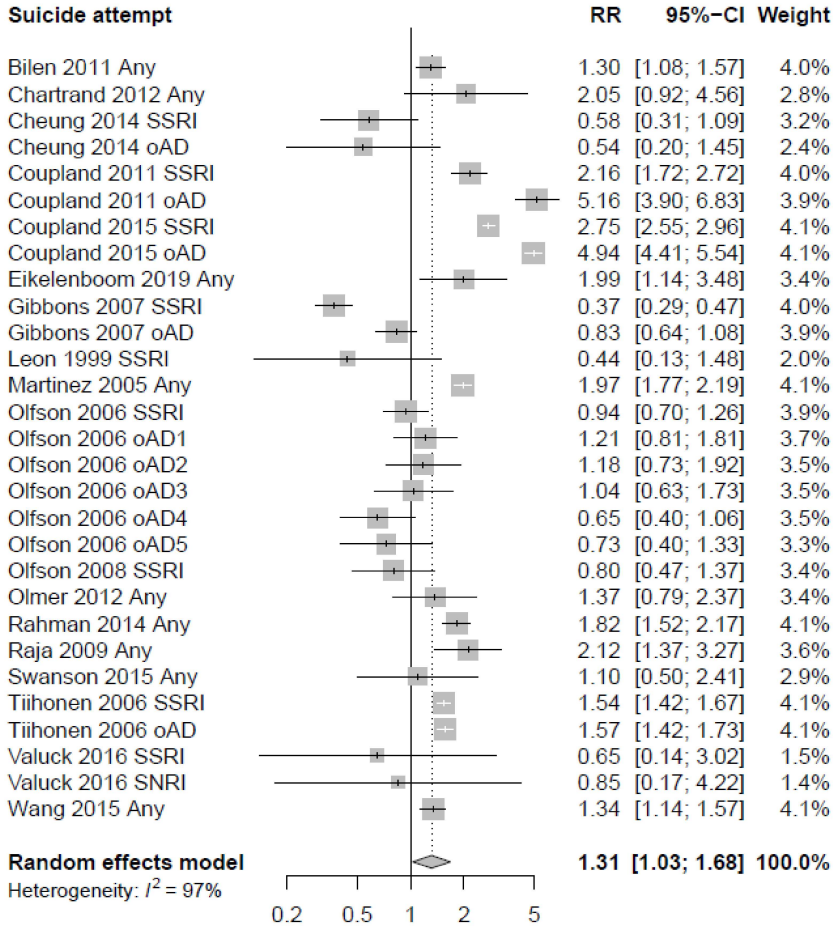
Olfson 2008	1	1	1	1	2	2
Olmer 2012	1	1	0	1	2	2
Rahman 2014	2	2	1	0	1	2
Rahme 2008	2	2	1	1	2	0
Raja 2009	1	1	0	1	2	0
Sondergard 2007	2	2	1	1	2	1
Spittal 2019	1	1	0	0	1	2
Swanson 2015	1	2	1	1	1	2
Termorshuizen 2016	1	2	0	0	1	0
Tiihonen 2006	2	2	1	0	2	2
Valuck 2016	1	2	1	1	1	2
Wang 2015	2	2	1	0	2	2

7. Forest plots for main results

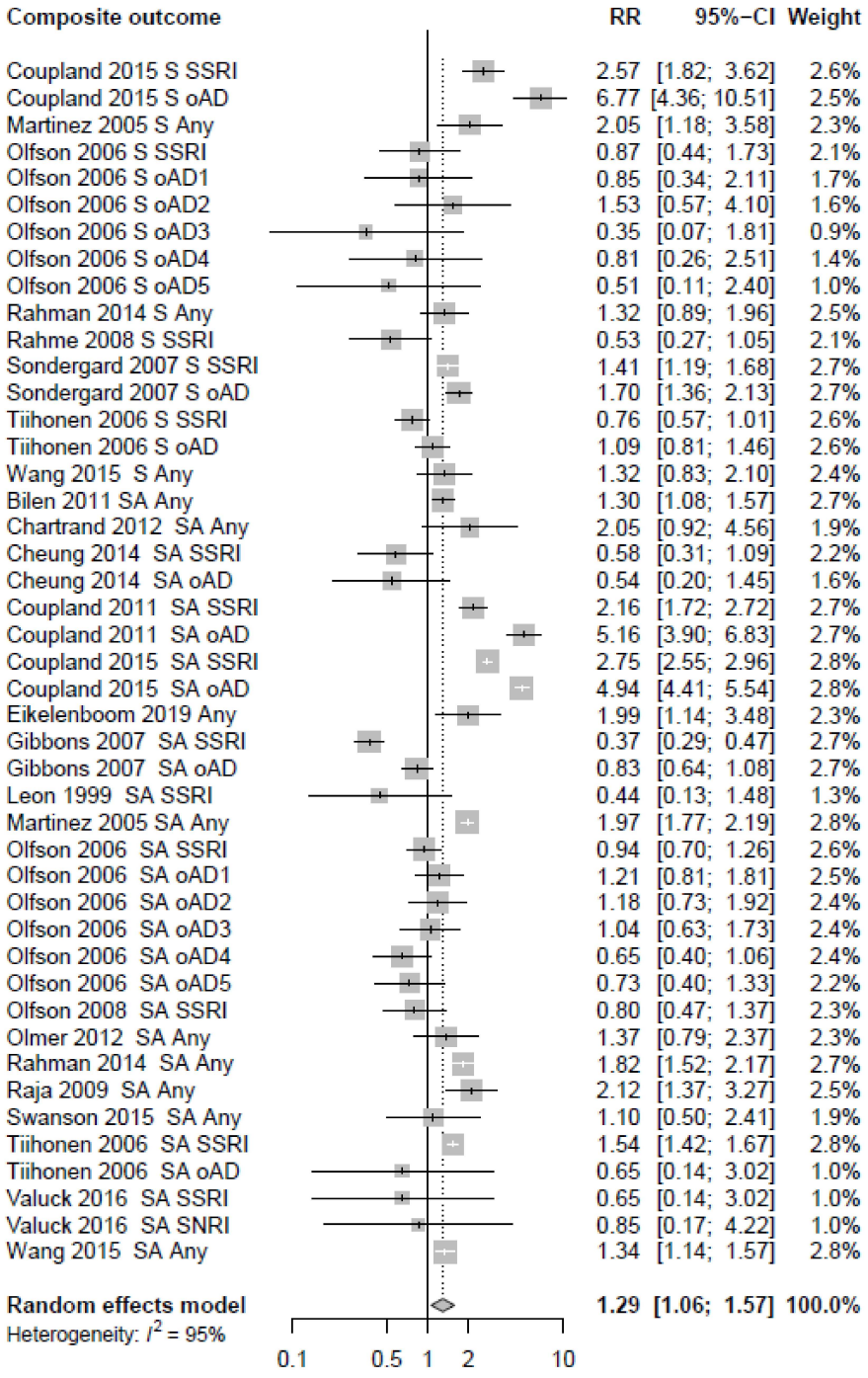
Supplementary Figures 1-3: Suicide risk in patients with depression (including other affective disorders and anxiety disorders). SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; oAD: other (non-SSRI) new-generation antidepressant (includes SNRI and atypical antidepressants); oAD1: venlafaxine; oAD2: mirtazapine; oAD3: bupropion; oAD4: trazodone; oAD5: nefazodone; S: Suicide; SA: Suicide attempts; RR: relative risk estimate



Supplementary Figure 1

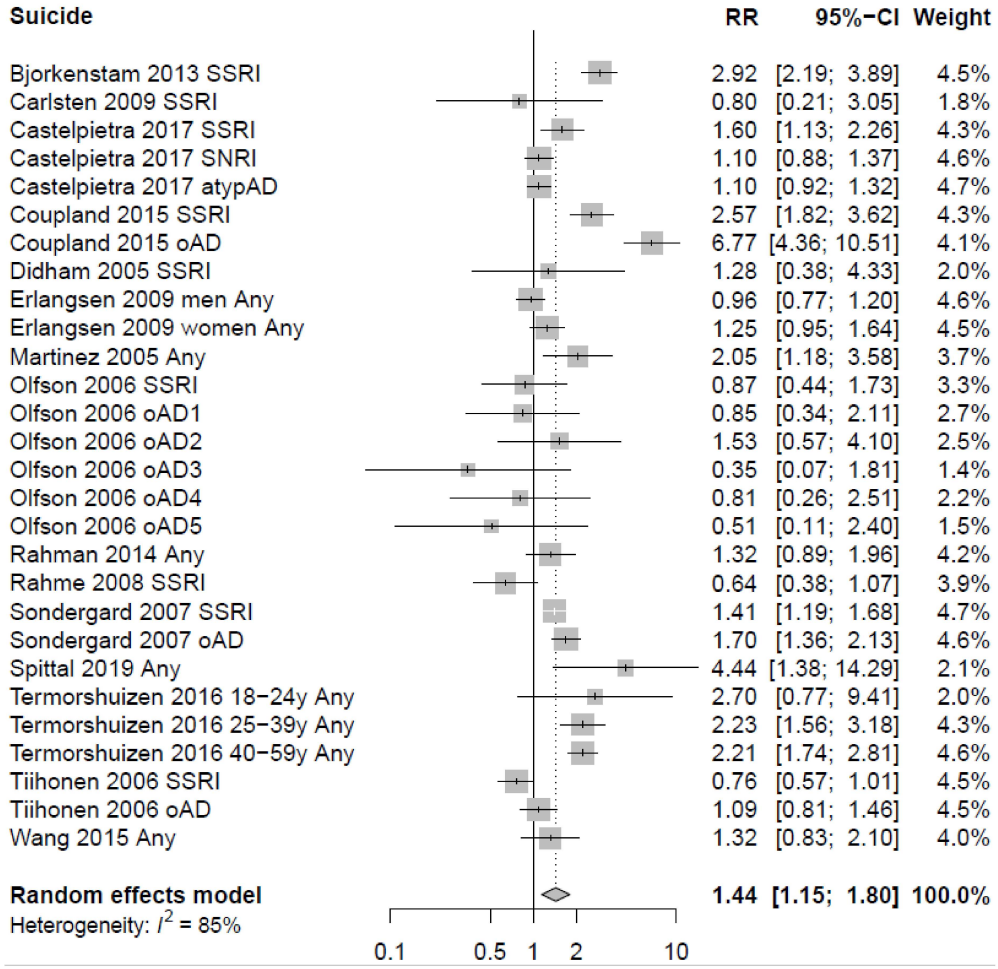


Supplementary Figure 2

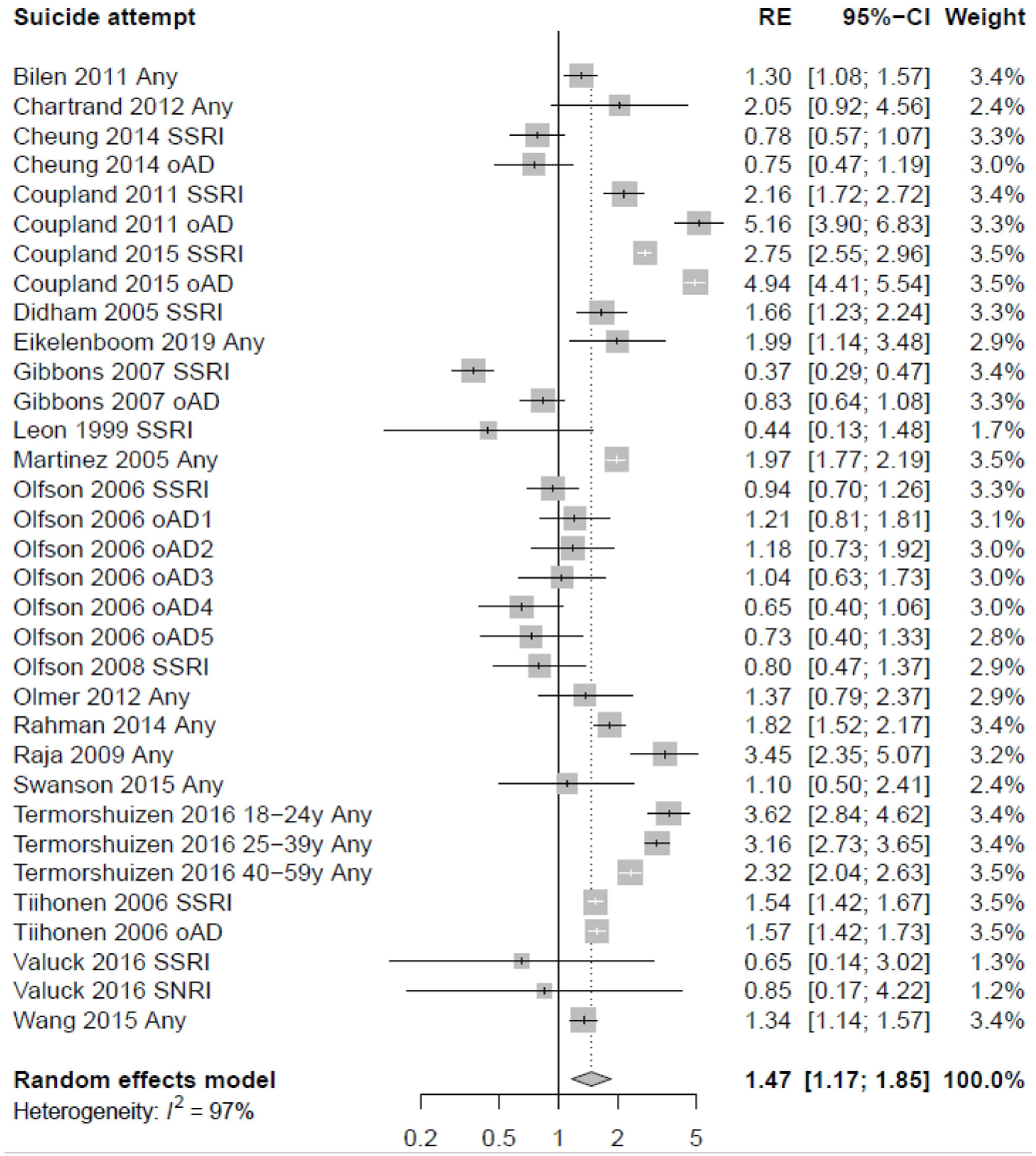


Supplementary Figure 3

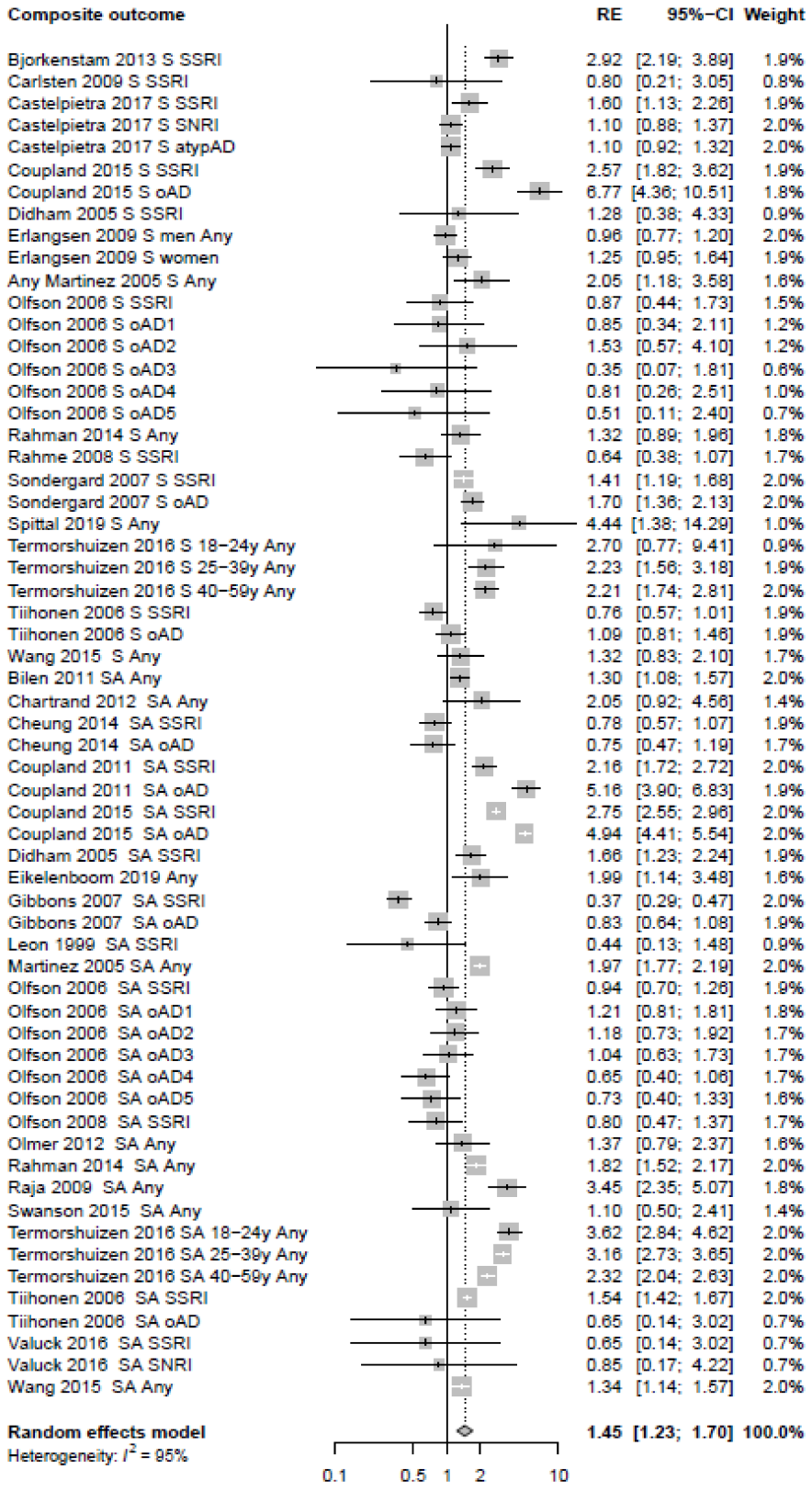
Supplementary Figures 4-6: Suicide risk in patients with any treatment indication (including depression and any unspecified psychiatric and non-psychiatric condition). SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; atypAD: atypical antidepressant; oAD: other (non-SSRI) new-generation antidepressant (includes SNRI and atypAD); oAD1: venlafaxine; oAD2: mirtazapine; oAD3: bupropion; oAD4: trazodone; oAD5: nefazodone; S: Suicide; SA: Suicide attempts; RR: relative risk estimate



Supplementary Figure 4



Supplementary Figure 5



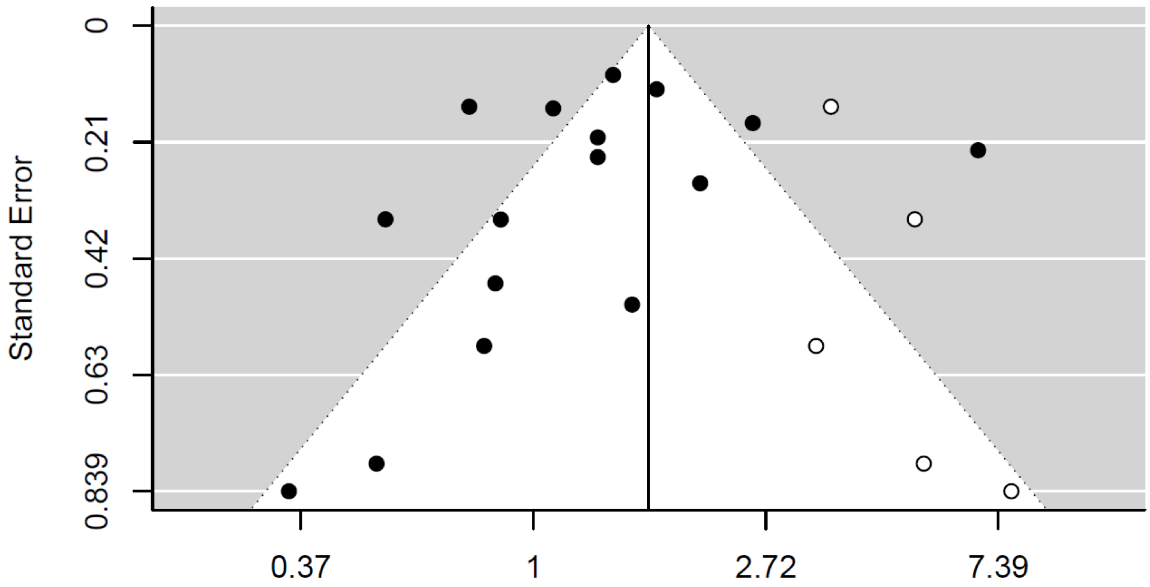
Supplementary Figure 6

8. Assessment of publication bias

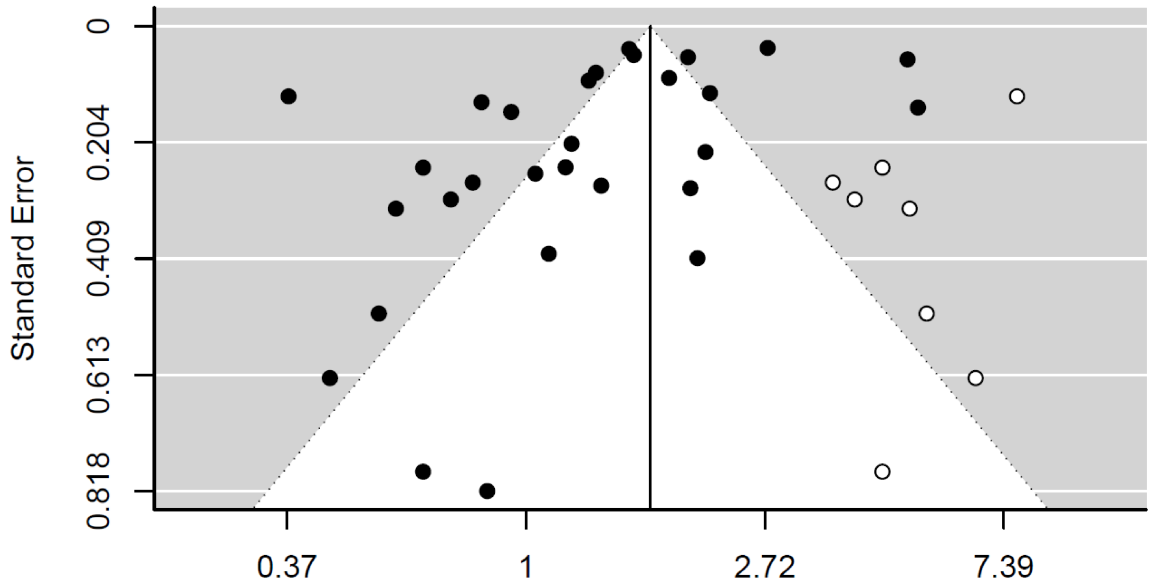
We examined possible publication bias through visual inspection of funnel-plots and formally tested for funnel-plot asymmetry using the mixed-effects version of Egger's test.[36] This test statistic is derived from a mixed-effects meta-regression of the standard error on the study effect sizes. Due to previously described low power of detecting funnel-plot asymmetry, Egger suggests a significance level of $p<0.1$ for evaluating publication bias. As inspection of funnel-plot asymmetry can be challenging, we prespecified in the protocol that we would mainly base our analysis of publication bias on the trim-and-fill method.[37]

Funnel-plots display standard error on the y-axis and the effect estimate on the x-axis. This allows for estimation of asymmetry given the hypothesized normal distribution around a true effect with larger variance and larger standard error in smaller sample size (lower part of the funnel) and smaller standard error in larger studies (upper part of the funnel). Overall, the investigated studies are large and have small standard errors (estimates cluster in the upper part of the plot). Visual inspection reveals funnel-plot asymmetry, as published studies (black circles) cluster on the left part of the summary effect estimate. We additionally display estimates for missing studies (white circles) imputed with trim-and-fill method.

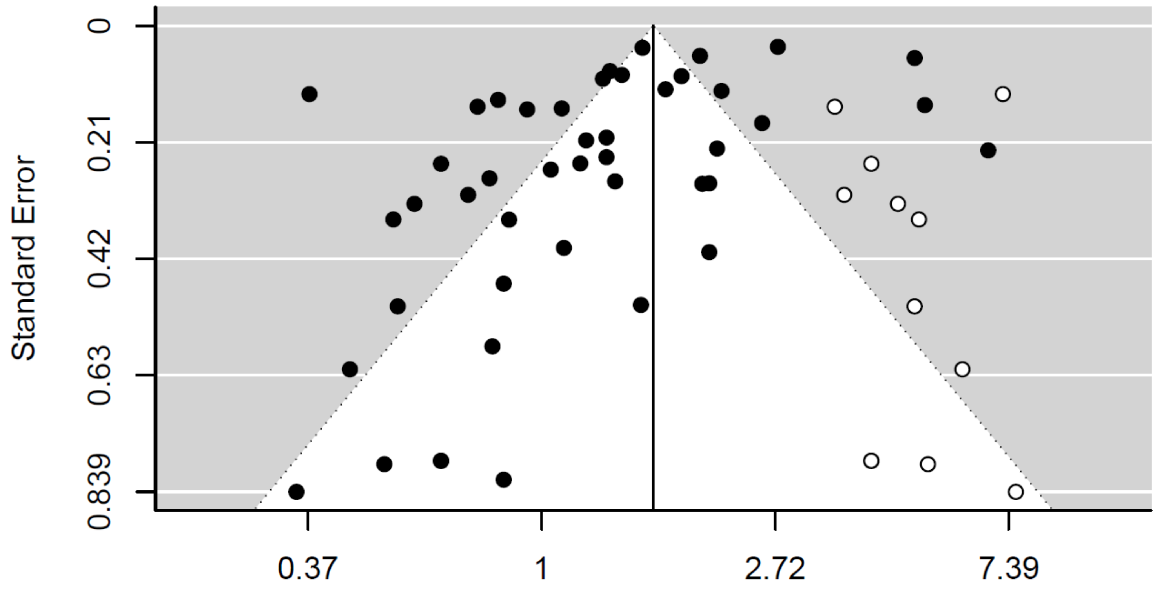
9. Funnel plots for main results



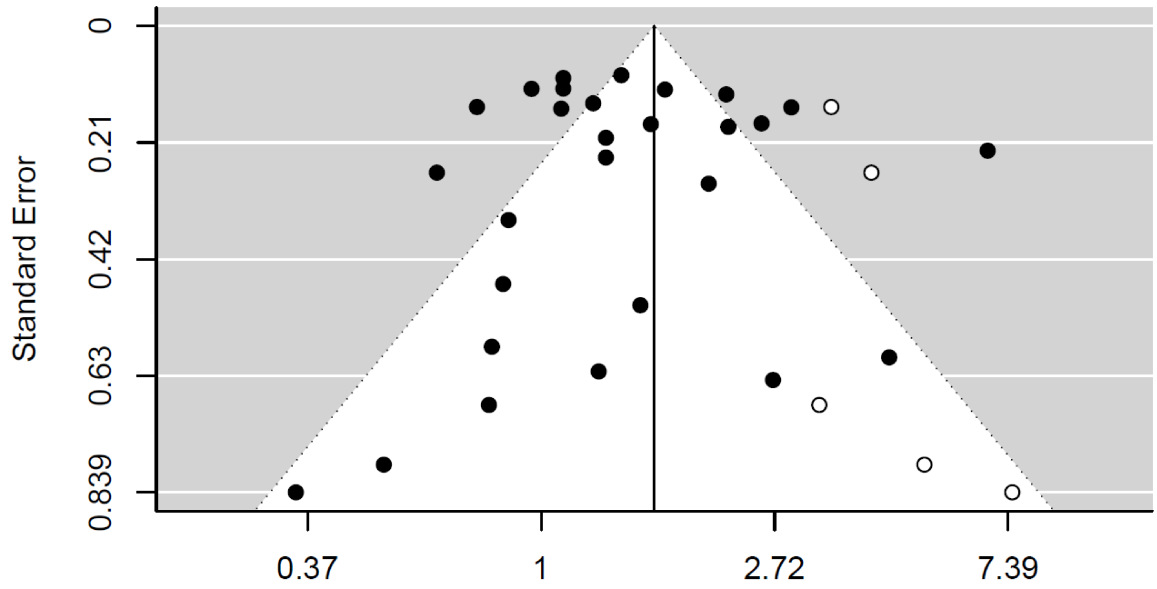
Supplementary Figure 7: Risk of suicide with any new-generation antidepressant in studies of depression; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-1.95, df=14, p=0.072



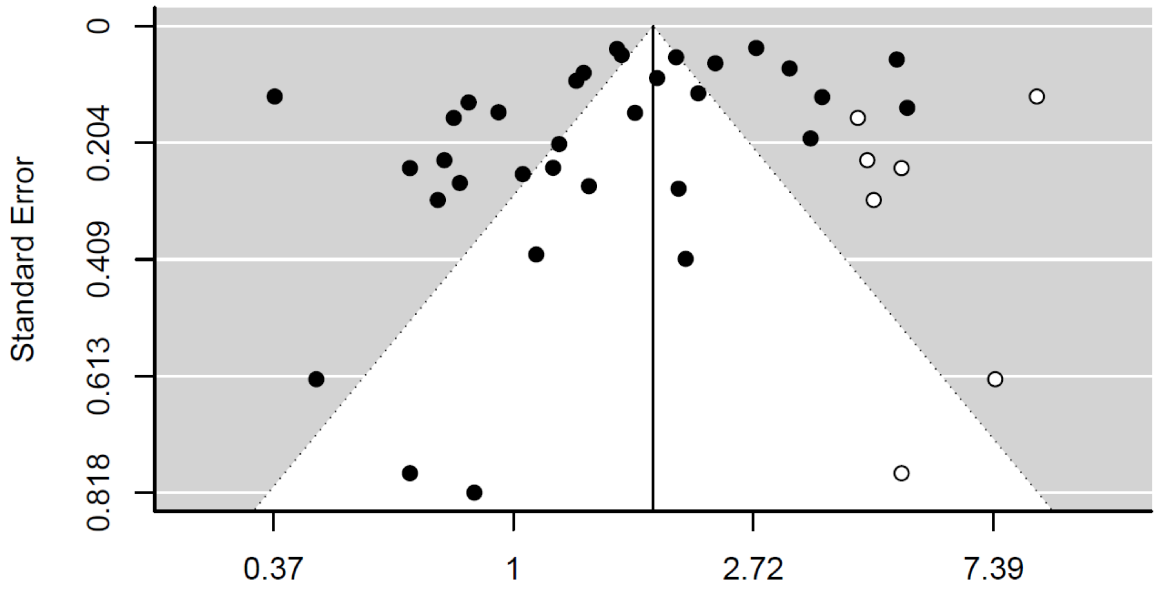
Supplementary Figure 8: Risk of suicide attempt with any new-generation antidepressant in studies of depression; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-2.66, df=27, p=0.013



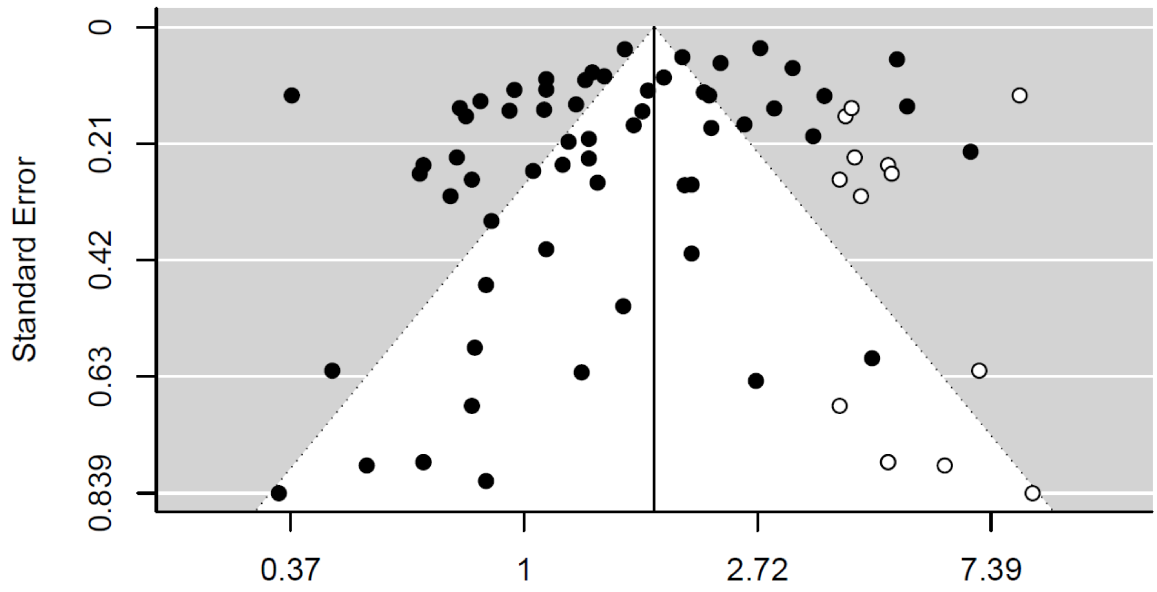
Supplementary Figure 9: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of depression; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-3.35, df=43, p=0.002



Supplementary Figure 10: Risk of suicide with any new-generation antidepressant in studies of all treatment indications; Visual inspection suggests asymmetry, but Egger's test for funnel-plot asymmetry indicates no publication bias, t=-1.02, df=26, p=0.319



Supplementary Figure 11: Risk of suicide attempt with any new-generation antidepressant in studies of all treatment indications; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-2.60, df=31, p=0.014



Supplementary Figure 12: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of all treatment indications; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-2.67, df=59, p=0.010

10. Sensitivity analysis without outlier effects

For the detection of possible outlier effects we formally tested for possible influential data points by calculating studentized residuals.[38] Plotting studentized residuals revealed possible outliers (studentized residuals >2) for the otherAD effect estimates in both studies by Coupland et al.[15 16] and for the SSRI effect estimate in Gibbons et al.[20] Therefore, we repeated all analyses without these outlier effect estimates.

The summary effect estimates for depression without potential outliers were as follows:

The risk of suicide with any new-generation antidepressant was RR=1.18, 0.90-1.54 (for SSRI, RR=1.09, 0.51-2.33; for otherAD, RR=1.09, 0.71-1.68). The funnel-plot was asymmetrical (t=-2.17, df=13, p=0.049) and the trim-and-fill method suggested that 5 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.43, 1.05-1.96. Study fCOI was a significant moderator (Q=6.78, df=1, p=0.009); the risk estimates were considerably smaller in studies with fCOI (RR=1.00, 0.75-1.34) as compared to studies without fCOI (RR=1.75, 1.01-3.03).

The risk of suicide attempt with any new-generation antidepressant was RR=1.27, 1.05-1.53 (for SSRI, RR=1.17, 0.68-2.00; for otherAD, RR=1.00, 0.77-1.30). The funnel-plot was asymmetrical (t=-3.36, df=24, p=0.003) and the trim-and-fill method suggested that 7 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.49, 1.21-1.85. Study fCOI was a significant moderator (Q=7.66, df=1, p=0.006); the risk estimates were considerably smaller in studies with fCOI (RR=1.03, 0.84-1.27) as compared to studies without fCOI (RR=1.59, 1.21-2.08).

The risk of suicide and suicide attempt combined with any new-generation antidepressant was RR=1.22, 1.05-1.42 (for SSRI, RR=1.15, 0.80-1.65; for otherAD, RR=0.98, 0.81-1.19). The funnel-plot was asymmetrical (t=-4.11, df=39, p<0.001) and the trim-and-fill method suggested that 12 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.45, 1.22-1.74. Study fCOI was a significant moderator (Q=19.13, df=1, p<0.001); the risk estimates were considerably smaller in studies with fCOI (RR=0.92, 0.77-1.10) as compared to studies without fCOI (RR=1.93, 1.42-2.62).

The summary effect estimates for all treatment indications without potential outliers were as follows:

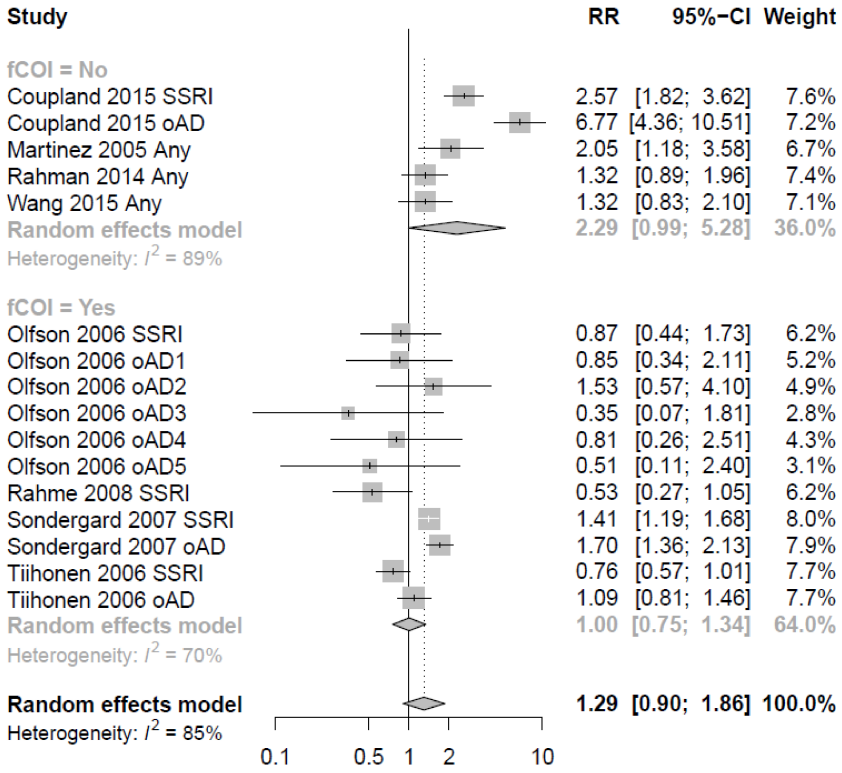
The risk of suicide with any new-generation antidepressant was RR=1.36, 1.12-1.64 (for SSRI, RR=1.33, 0.86-2.04; for otherAD, RR=1.12, 0.86-1.46). The funnel-plot was not found to be asymmetrical (t=-1.02, df=25, p=0.316), but the trim-and-fill method suggested that 3 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.44, 1.17-1.79. Study fCOI was a significant moderator (Q=10.30, df=1, p=0.001); the risk estimates were considerably smaller in studies with fCOI (RR=1.08, 0.88-1.33) as compared to studies without fCOI (RR=1.77, 1.36-2.31).

The risk of suicide attempt with any new-generation antidepressant was RR=1.43, 1.18-1.74 (for SSRI, RR=1.27, 0.82-1.96; for otherAD, RR=1.00, 0.78-1.28). The funnel-plot was asymmetrical (t=-2.98, df=28, p=0.006) and the trim-and-fill method suggested that 9 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.77, 1.43-2.19. Study fCOI was a significant moderator (Q=15.30, df=1, p<0.001); the risk estimates were considerably smaller in studies with fCOI (RR=1.03, 0.84-1.27) as compared to studies without fCOI (RR=1.83, 1.44-2.33).

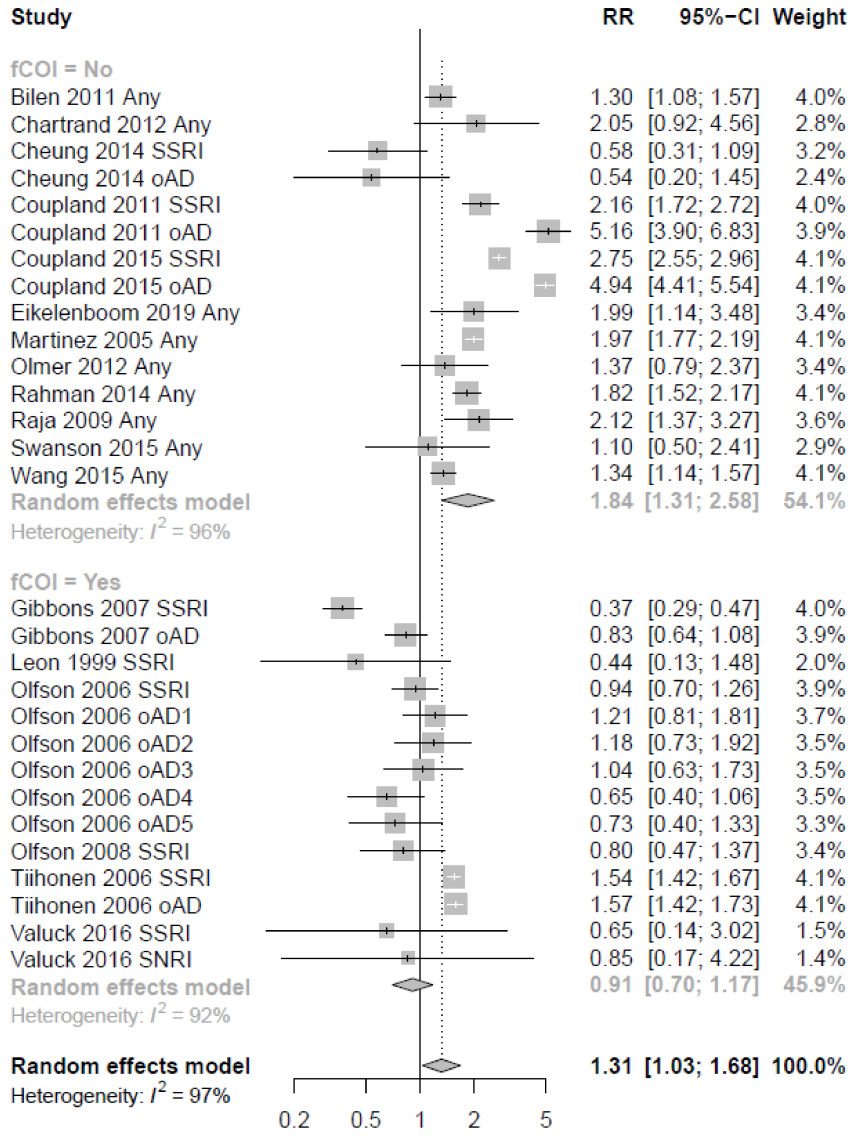
The risk of suicide and suicide attempt combined with any new-generation antidepressant was RR=1.39, 1.22-1.59 (for SSRI, RR=1.30, 0.99-1.71; for otherAD, RR=1.01, 0.87-1.17). The funnel-plot was asymmetrical (t=-2.93, df=55, p=0.005) and the trim-and-fill method suggested that 12 studies were missing; the summary effect estimate with the missing studies imputed was RR=1.60, 1.37-1.86. Study fCOI was a significant moderator (Q=29.64, df=1, p<0.001); the risk estimates were considerably smaller in studies with fCOI (RR=1.03, 0.90-1.17) as compared to studies without fCOI (RR=1.81, 1.53-2.15).

11. Forest plots for fCOI subgroups

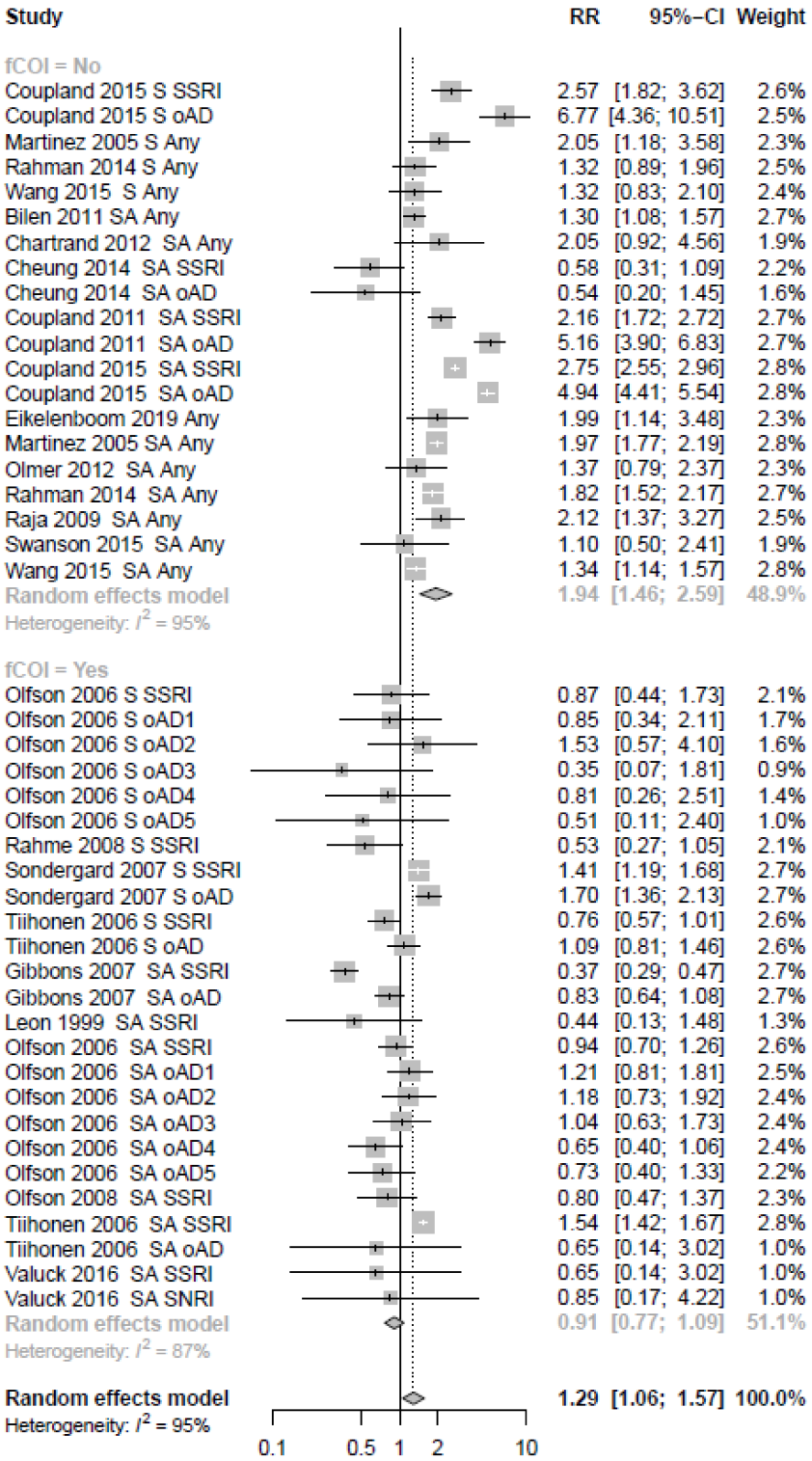
In studies of depression, study fCOI was a significant moderator of suicide risk estimates (Q=6.35, df=1, p=0.012); studies with fCOI (RR=1.00, 0.75-1.34) reported considerably lower risk estimates than studies without fCOI (RR=2.29, 0.99-5.28). Study fCOI also had a significant effect on suicide attempt risk estimates (Q=12.86, df=1, p<0.001); studies with fCOI (RR=0.91, 0.70-1.17) reported considerably lower risk estimates than studies without fCOI (RR=1.84, 1.31-2.58). The same pattern was found in studies on antidepressants for any treatment indication. Study fCOI had a significant effect on suicide risk estimates (Q=11.36, df=1, p<0.001). Studies with fCOI reported no increased risk (RR=1.08, 0.88-1.33), but studies without fCOI did (RR=1.98, 1.43-2.76). Study fCOI was also a significant moderator of suicide attempt risk (Q=21.97, df=1, p<0.001); no clear effect was shown in studies with fCOI (RR=0.91, 0.70-1.17), but studies without fCOI revealed significantly increased risk (RR=2.05, 1.57-2.67). The forest plots are shown below.



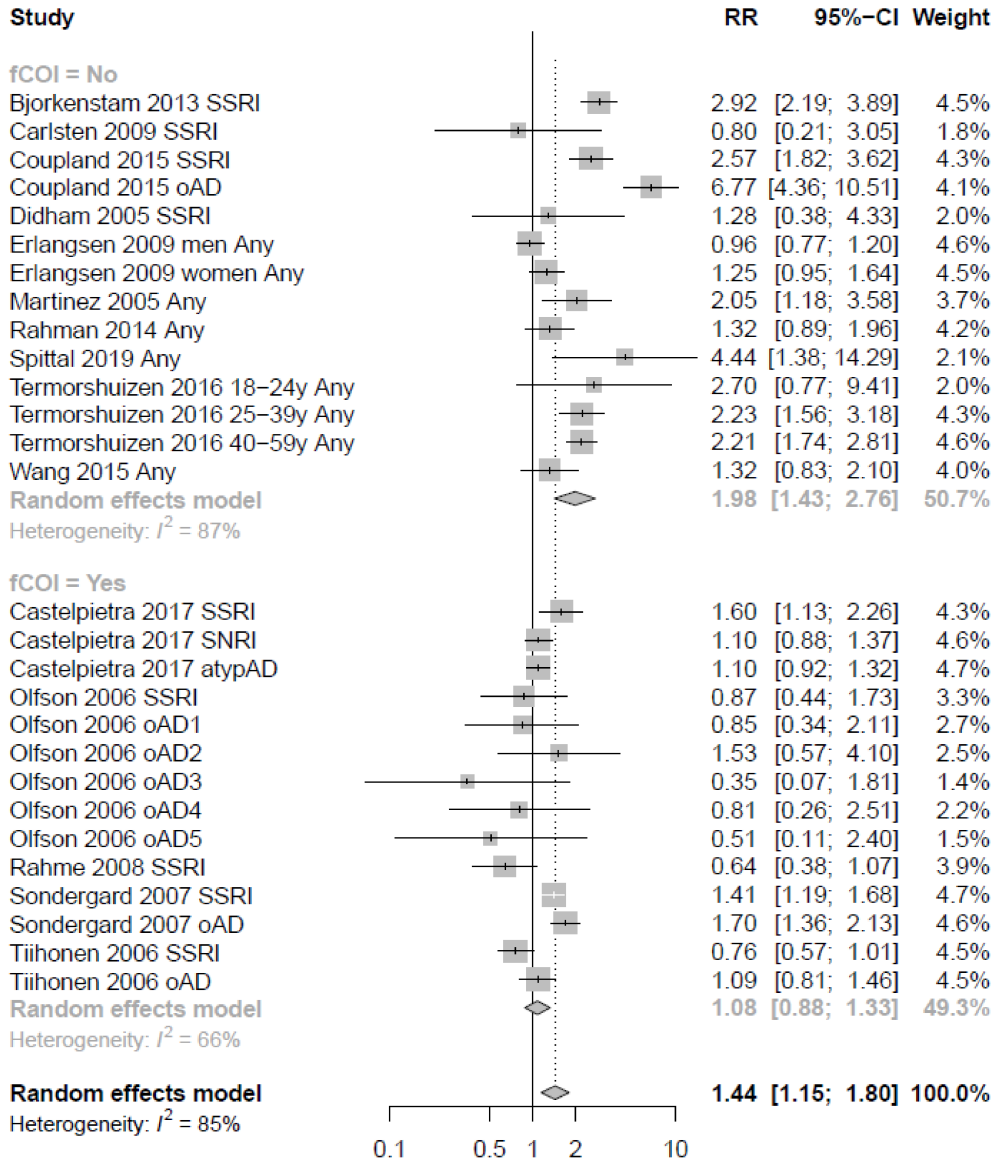
Supplementary Figure 13: Risk of suicide with any new-generation antidepressant in studies of depression; test for subgroup difference, Q=6.35, df=1, p=0.012



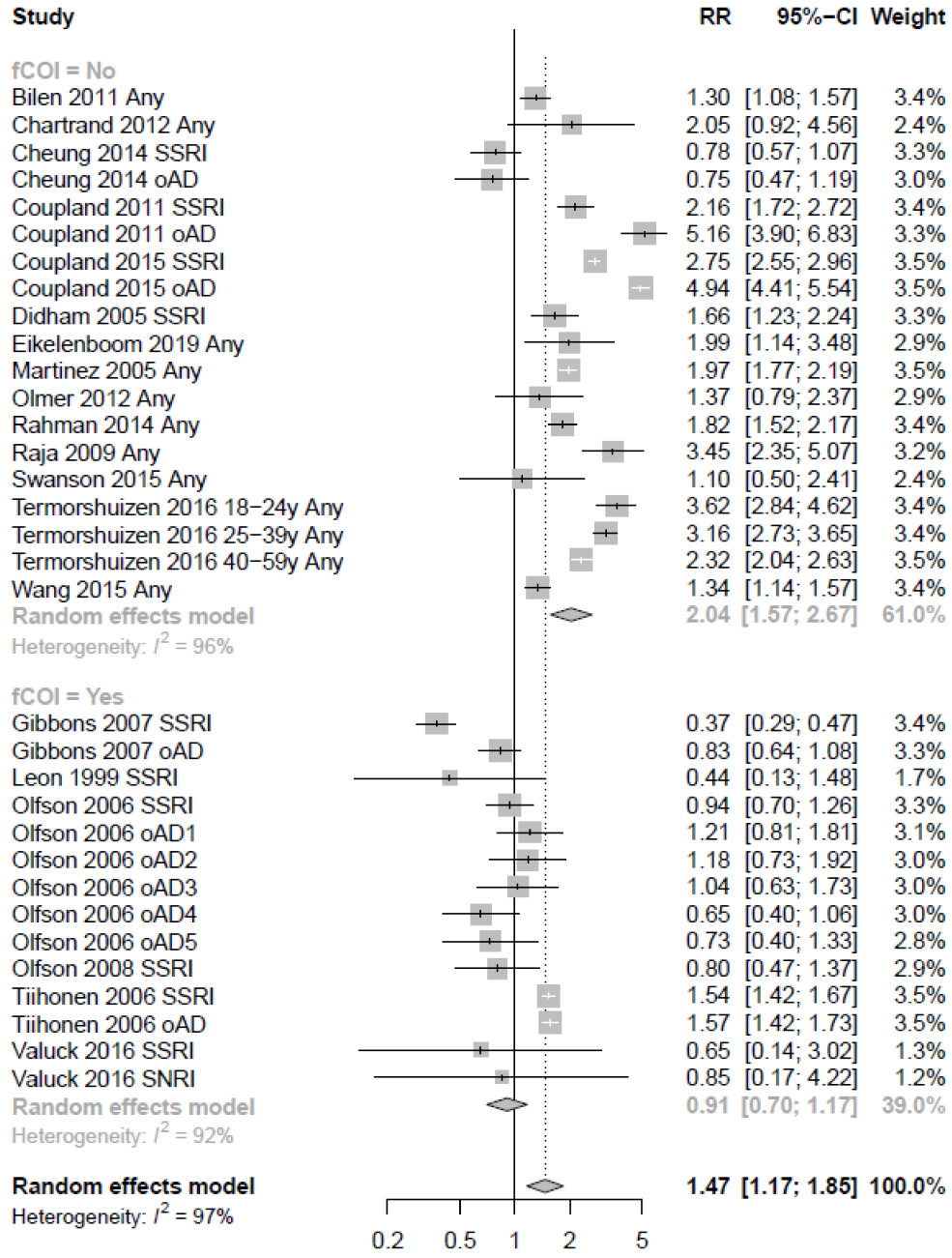
Supplementary Figure 14: Risk of suicide attempt with any new-generation antidepressant in studies of depression; test for subgroup difference, Q=12.86, df=1, p<0.001



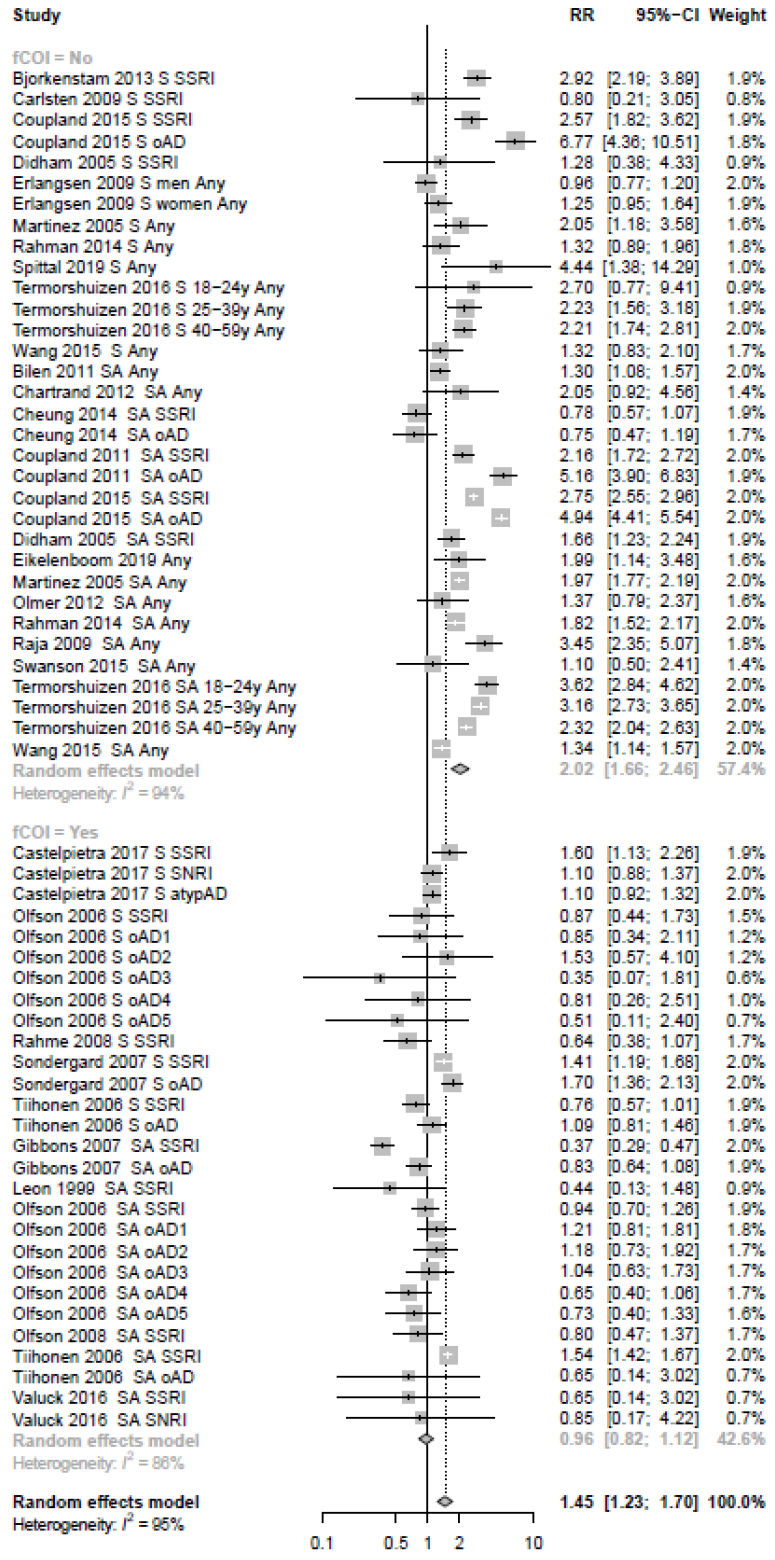
Supplementary Figure 15: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of depression; test for subgroup difference, Q=21.87, df=1, p<0.001



Supplementary Figure 16: Risk of suicide with any new-generation antidepressant in studies of all treatment indications; test for subgroup difference, Q=11.36, df=1, p<0.001

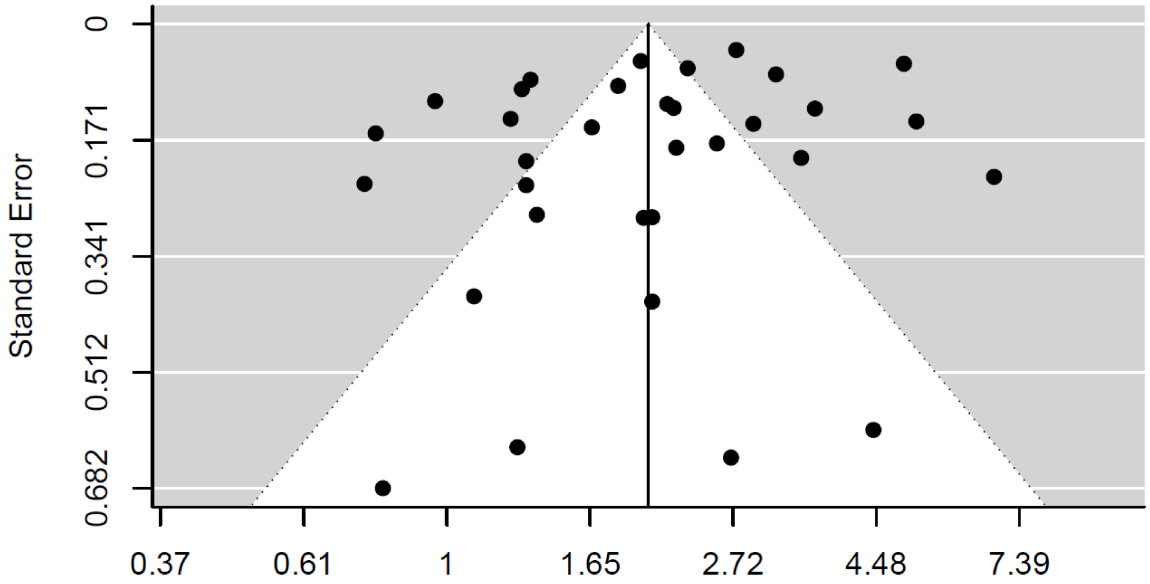


Supplementary Figure 17: Risk of suicide attempt with any new-generation antidepressant in studies of all treatment indications; test for subgroup difference, Q=21.97, df=1, p<0.001

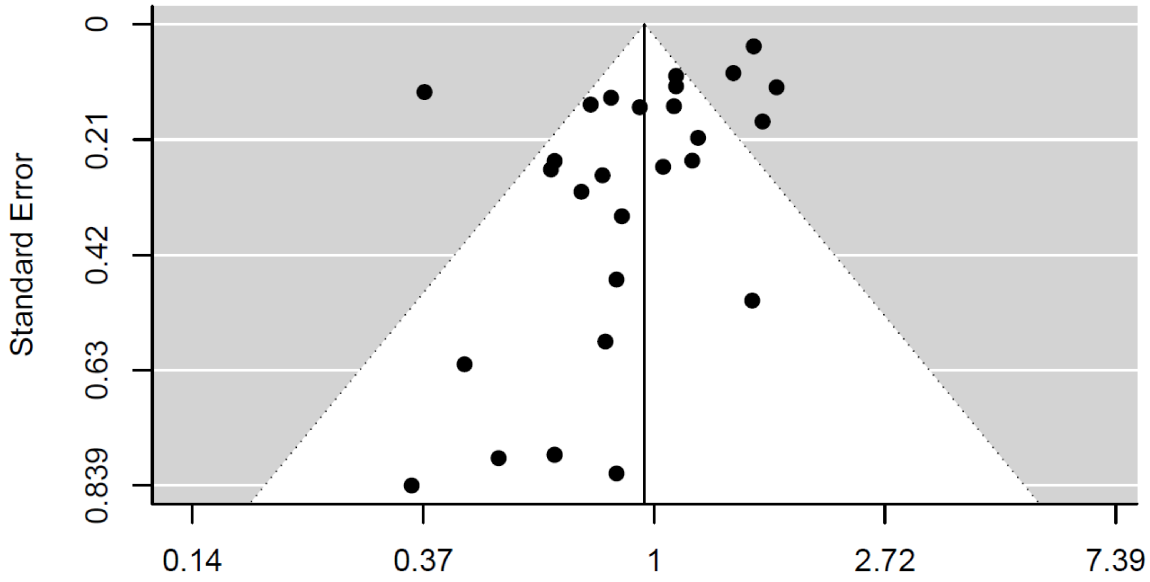


Supplementary Figure 18: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of all treatment indications; test for subgroup difference, Q=37.17, df=1, p<0.001

12. Funnel plots for fCOI subgroups



Supplementary Figure 19: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of all treatment indications without fCOI; Visual inspection and Egger's test for funnel-plot asymmetry indicate no publication bias, t=-0.8456, df=31, p=0.404



Supplementary Figure 20: Risk of suicide and suicide attempt combined with any new-generation antidepressant in studies of all treatment indications with fCOI; Visual inspection and Egger's test for funnel-plot asymmetry indicate publication bias, t=-2.1368, df=26, p=0.042

13. Impact of fCOI in meta-regression models

		Not adjusted for fCOI			Adjusted for fCOI		
		B	SE (B)	p	B	SE (B)	p
Drug class	SSRI	-0.46	0.19	0.02	0.12	0.18	0.51
	oAD	-0.36	0.19	0.01	0.40	0.20	0.05
	Any unspecified	reference			reference		
	Omnibus Test	*F(2,58)=3.39*		*0.04*	*F(2,57)=2.44*		*0.10*
Main treatment indication	Depression	-0.20	0.17	0.24	0.05	0.14	0.71
	Any unspecified	reference			reference		
	Omnibus Test	*F(1,59)=1.41*		*0.24*	*F(1,58)=0.14*		*0.71*
Location	North America	-0.79	0.15	0.00	-0.43	0.17	0.02
	Europe	reference			reference		
	Other	-0.03	0.30	0.91	-0.18	0.28	0.52
	Omnibus Test	*F(2,58)=13.9*		*0.00*	*F(1,59)=3.22*		*0.05*
Older adult sample (≥65 years)	No	reference			reference		
	Yes	0.21	0.33	0.53	0.14	0.26	0.61
	Missing	-	-	-	-		
	Omnibus Test	*F(1,56)=0.40*		*0.53*	*F(1,55)=0.27*		*0.61*
Study Design	Cohort	0.28	0.13	0.16	-0.02	0.14	0.90
	Case-control	reference			reference		
	Omnibus Test	*F(1,59)=2.99*		*0.09*	*F(1,58)=0.02*		*0.90*
Study quality	High (≥7 points)	-0.34	0.20	0.08	-0.11	0.16	0.50
	Low (<7 points)	reference			reference		
	Omnibus Test	*F(1,59)=3.09*		*0.08*	*F(1,58)=0.47*		*0.50*
Covariate adjustment	Yes	-0.20	0.21	0.34	-0.08	0.16	0.63
	No	reference			reference		
	Omnibus Test	*F(1,59)=0.93*		*0.34*	*F(1,58)=0.24*		*0.63*
fCOI	Yes	-0.77	0.13	0.00			
	No	reference					
	Omnibus Test	*F(1,59)=36.1*		*0.00*			

Supplementary Figure 21: Result of meta-regression analyses adjusting subgroup differences for fCOI. Estimates are regression coefficients (B) with standard errors (SE), calculated with the R‘s metafor package. The omnibus tests for the subgroups are italicised. SSRI: selective serotonin reuptake inhibitor; oAD: other new-generation antidepressant (includes all non-SSRI new-generation antidepressants); fCOI: financial conflict of interest.

14. References

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