Supplementary tables

Table S1. MOOSE Checklist.

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4, 5
3	Description of study outcome(s)	4, 5
4	Type of exposure or intervention used	4, 5
5	Type of study designs used	4, 5
6	Study population	4, 5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	NA
13	List of citations located and those excluded, including justification	Fig. 1
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7, 8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	MS: 7,8;
22	Assessment of heterogeneity	8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7 - 9
24	Provision of appropriate tables and graphics	Table 1, Fig. 2-4; Tables S3, S4, Fig. S1-S10
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig. S1-S8
26	Table giving descriptive information for each study included	Table 1

27	Results of sensitivity testing (eg, subgroup analysis)	Fig. 4; Table S4, Fig. S8
28	Indication of statistical uncertainty of findings	Main MS: 14; supplement: 13-17 (Fig. S1-S8)
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	16; Fig. S9, S10
30	Justification for exclusion (eg, exclusion of non-English language citations)	Fig. 1
31	Assessment of quality of included studies	16, Table 1
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16, 17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	17
34	Guidelines for future research	13, 14, 17
35	Disclosure of funding source	18

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.
MOOSE: Meta-analysis Of Observational Studies in Epidemiology; MS: manuscript; NA: not available.

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this pairwise meta-analysis is reported at step #17.

#	Research strategy
1	asthma*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
2	comorbidity*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
3	real*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
4	observational*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
5	cross-sectional*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
6	retrospective*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
7	prospective*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
8	cohort*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
9	children*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
10	pediatric*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
11	COVID-19.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
12	SARS-CoV-2.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
13	3 or 4 or 5 or 6 or 7 or 8
14	9 or 10
15	11 or 12
16	1 and 2 and 13
17	16 not (14 and 15)

Table S3. ORs and 95%CI for the significant association between comorbidities and asthma reported by single studies that, therefore, did not need to be meta-analyzed.

	Study and reference	OR mean (95%CI)
Allergic and rheumatological disorders:		
Allergic conjunctivitis	Toppila–Salmi et al., 2019 (1)	2.63 (2.22 – 3.11)
Allergic reaction	Iribarren et al., 2012 (2)	2.54 (2.44 – 2.64)
Allergic urticaria	Iribarren et al., 2012 (2)	2.39 (2.01 – 2.85)
Anaphylactic shock	Iribarren et al., 2012 (2)	1.84 (1.76 – 1.92)
Angioneurotic edema	Iribarren et al., 2012 (2)	2.70 (2.47 – 2.96)
Eczema or psoriasis	Weatherburn et al., 2017 (3)	3.30 (3.14 – 3.48)
Rheumatological disease	Weatherburn et al., 2017 (3)	1.46 (1.41 – 1.50)
Cardiovascular disorders:		
Hypertensive cardiopathy	Bourdin et al., 2019 (4)	4.24 (2.06– 8.90)
Pulmonary embolism	Cazzola et al., 2011 (5)	1.53 (1.29 – 1.81)
Pulmonary hypertension	Bozek et al., 2016 (6)	2.14 (1.22– 3.88)
Gastrointestinal disorders:		
Inflammatory bowel disease	Weatherburn et al., 2017 (3)	1.47 (1.37 – 1.58)
Viral hepatitis	Weatherburn et al., 2017 (3)	1.60 (1.31 – 1.95)
Diverticular disease	Weatherburn et al., 2017 (3)	1.64 (1.58 – 1.70)
Chronic colitis	Bozek et al., 2016 (6)	1.69 (1.11 – 2.59)
Ulcer	Kim et al., 2019 (7)	1.94 (1.88 – 2.00)
Constipation	Weatherburn et al., 2017 (3)	1.61 (1.56 – 1.67)
Metabolic disorders:		
Thyroid disorders	Weatherburn et al., 2017 (3)	1.50 (1.46 – 1.54)
Musculoskeletal disorders:		
Lower leg fracture or surgery	Chung et al., 2014 (8)	1.29 (1.17 – 1.42)
Psychiatric and neurological disorders:		
Blindness	Weatherburn et al., 2017 (3)	1.19 (1.09 – 1.29)
Alzheimer's disease	Chen et al., 2014 (9)	2.62 (1.96 – 3.49)
Anorexia or bulimia	Weatherburn et al., 2017 (3)	1.42 (1.29 – 1.57)
Learning disability	Weatherburn et al., 2017 (3)	1.28 (1.16 – 1.43)
Phobia	Goodwin et al., 2003 (10)	2.24 (1.52 – 3.25)
Epilepsy	Weatherburn et al., 2017 (3)	1.33 (1.24 – 1.42)
Deafness	Weatherburn et al., 2017 (3)	1.25 (1.21 – 1.29)
Suicidal ideation	Goodwin et al., 2003 (11)	2.25 (1.30 – 3.81)
Somatoform disorder	Goodwin et al., 2003 (10)	1.70 (1.24 – 2.31)
Affective disorder	Goodwin et al., 2003 (10)	1.45 (1.06 – 1.97)
Respiratory disorders:		
Bronchiectasis	Weatherburn et al., 2017 (3)	4.89 (4.48 – 5.34)
Pneumonia	Carter et al., 2019 (12)	1.40 (1.33 – 1.48)
Nasal congestion	Sundbom et al., 2013 (13)	3.30 (2.96 – 3.67)
Other disorders:		
Prostate disorders	Weatherburn et al., 2017 (3)	1.17 (1.10 – 1.25)
Cataract	Bourdin et al., 2019 (4)	2.37 (1.82 – 3.10)

95%CI: 95% confidence interval; OR: odds ratio.

Table S4. ORs and 95%CI for the significant association between comorbidities and severe asthma reported by single studies that, therefore, did not need to be meta-analyzed.

	Study and reference	OR mean (95%CI)
Psychiatric and neurological disorders:		
Bipolar disorder	Goodwin et al., 2003 (10)	6.16 (2.10 – 15.2)
Phobia	Goodwin et al., 2003 (10)	3.56 (1.37 – 7.96)
Panic disorder	Goodwin et al., 2003 (10)	2.79 (1.30 – 5.46)
Anxiety	Goodwin et al., 2003 (10)	2.30 (1.44 – 3.60)
Depression	Bourdin et al., 2019 (4)	1.96 (1.61 – 2.38)
Panic attack	Goodwin et al., 2003 (10)	3.16 (1.84 – 5.24)
Respiratory disorders:		
COPD	Varsano et al., 2017 (14)	19.27 (15.87 – 23.41)
Allergic rhinitis	Luyster et al., 2012 (15)	11.71 (5.33 – 26.98)
Metabolic disorders:		
Dyslipidaemia	Bourdin et al., 2019 (4)	1.23 (1.02 – 1.48)
Obesity	Bourdin et al., 2019 (4)	4.06 (2.99 – 5.51)
Cardiovascular disorders:		
Cardiovascular comorbidities	Bourdin et al., 2019 (4)	2.38 (1.97 – 2.88)
Other disorders:		
Anaemia	Bourdin et al., 2019 (4)	1.82 (1.36 – 2.41)
Cataract	Bourdin et al., 2019 (4)	2.37 (1.82 – 3.10)

COPD: chronic obstructive pulmonary disorder; OR: odds ratio; 95%CI: 95% confidence interval.

Supplementary figures

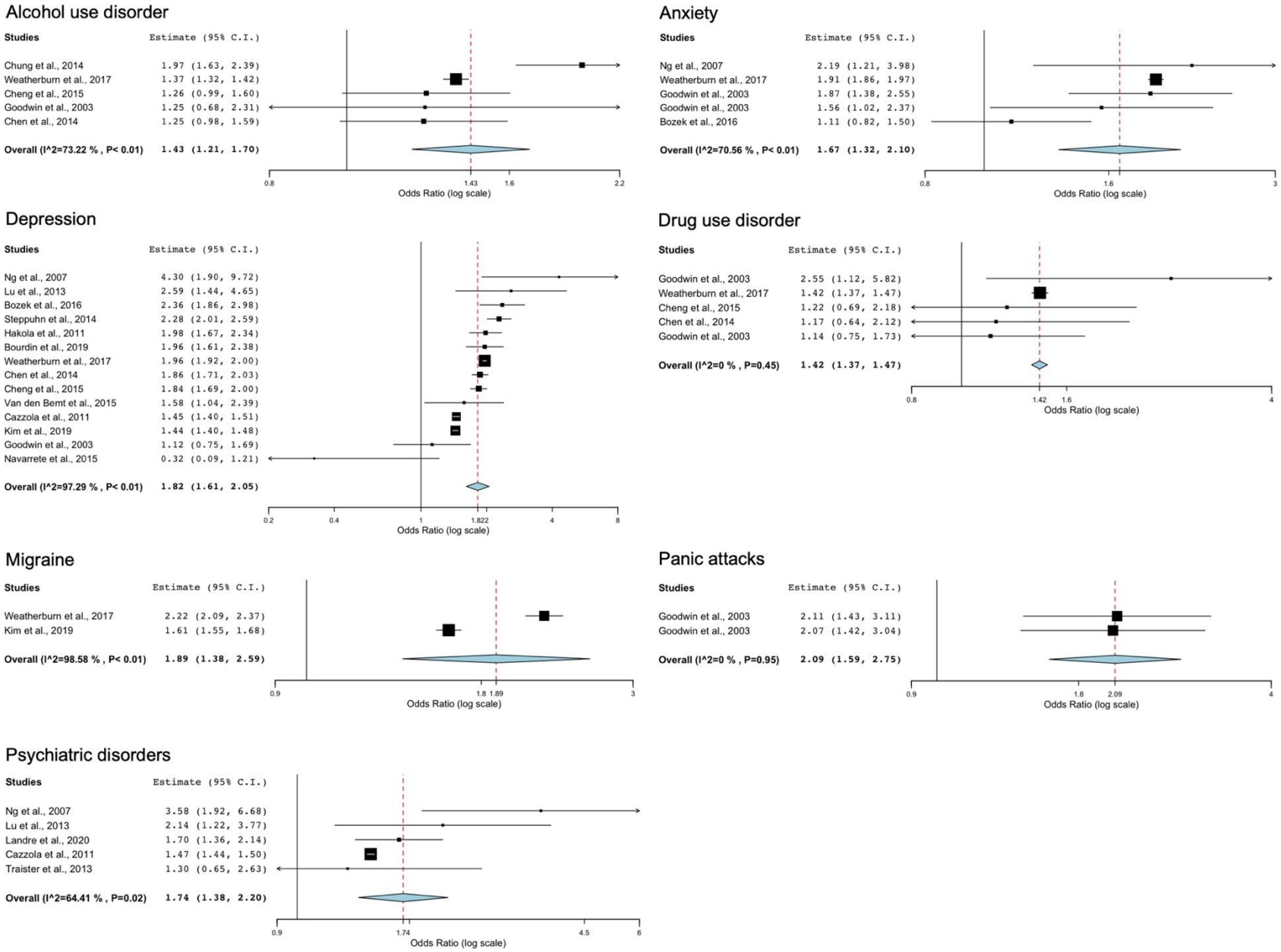

Figure S1. Forest plots for the association between significant psychiatric and neurological disorders and asthma.

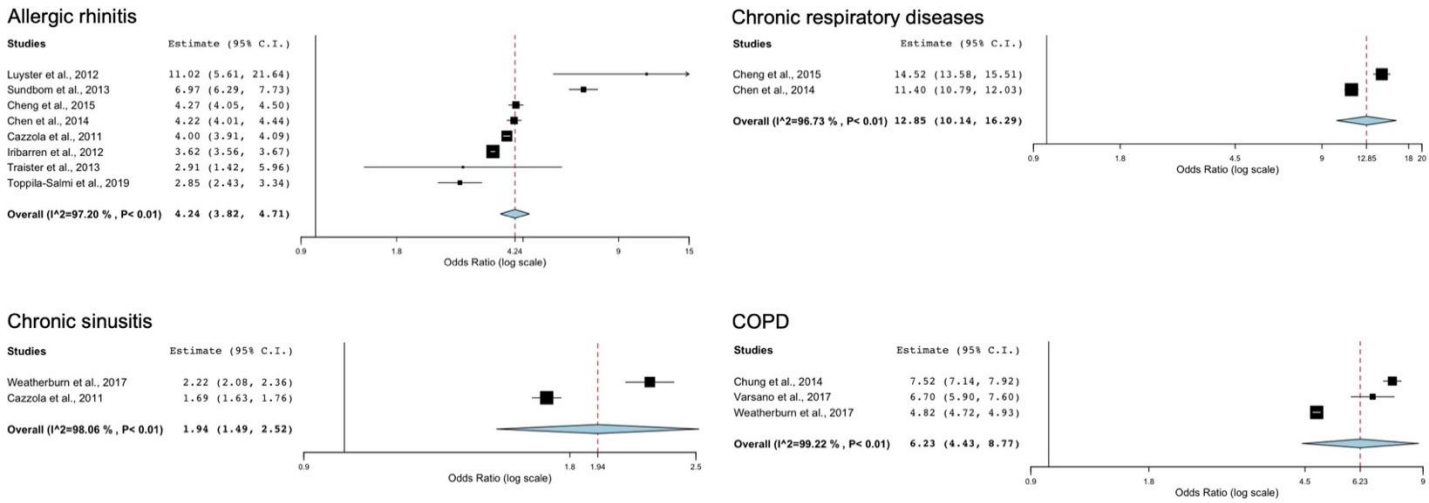

Figure S2. Forest plots for the association between significant respiratory disorders and asthma. COPD: chronic obstructive pulmonary disease.

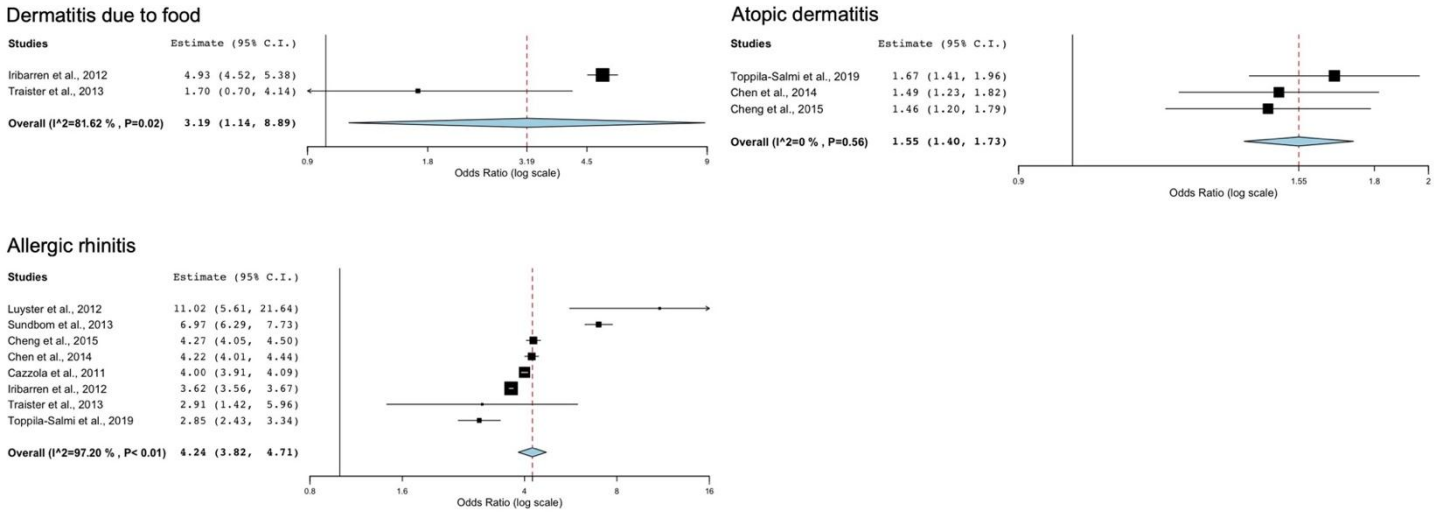

Figure S3. Forest plots for the association between significant allergic disorders and asthma.

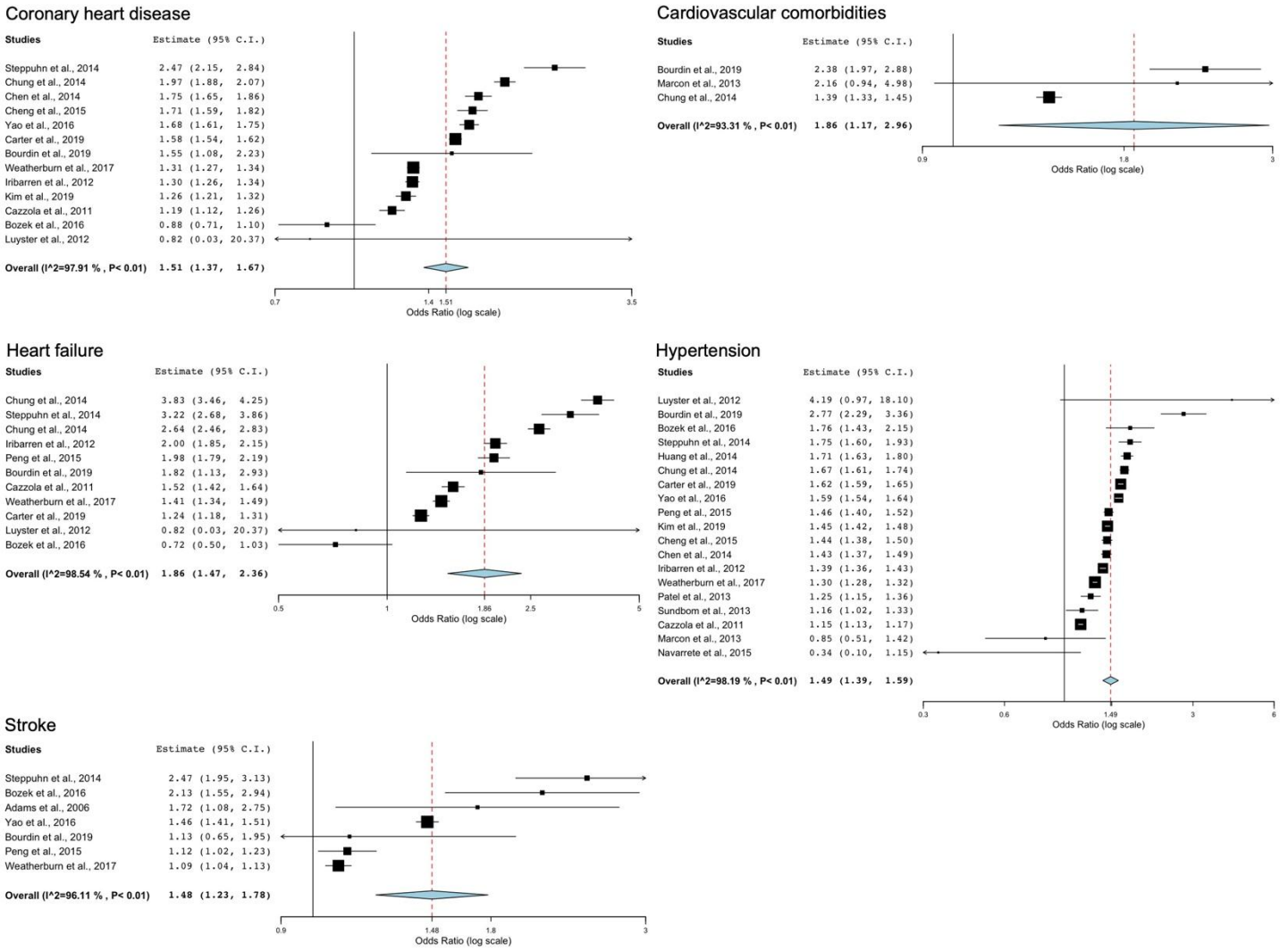

Figure S4. Forest plots for the association between cardiovascular disorders and asthma.

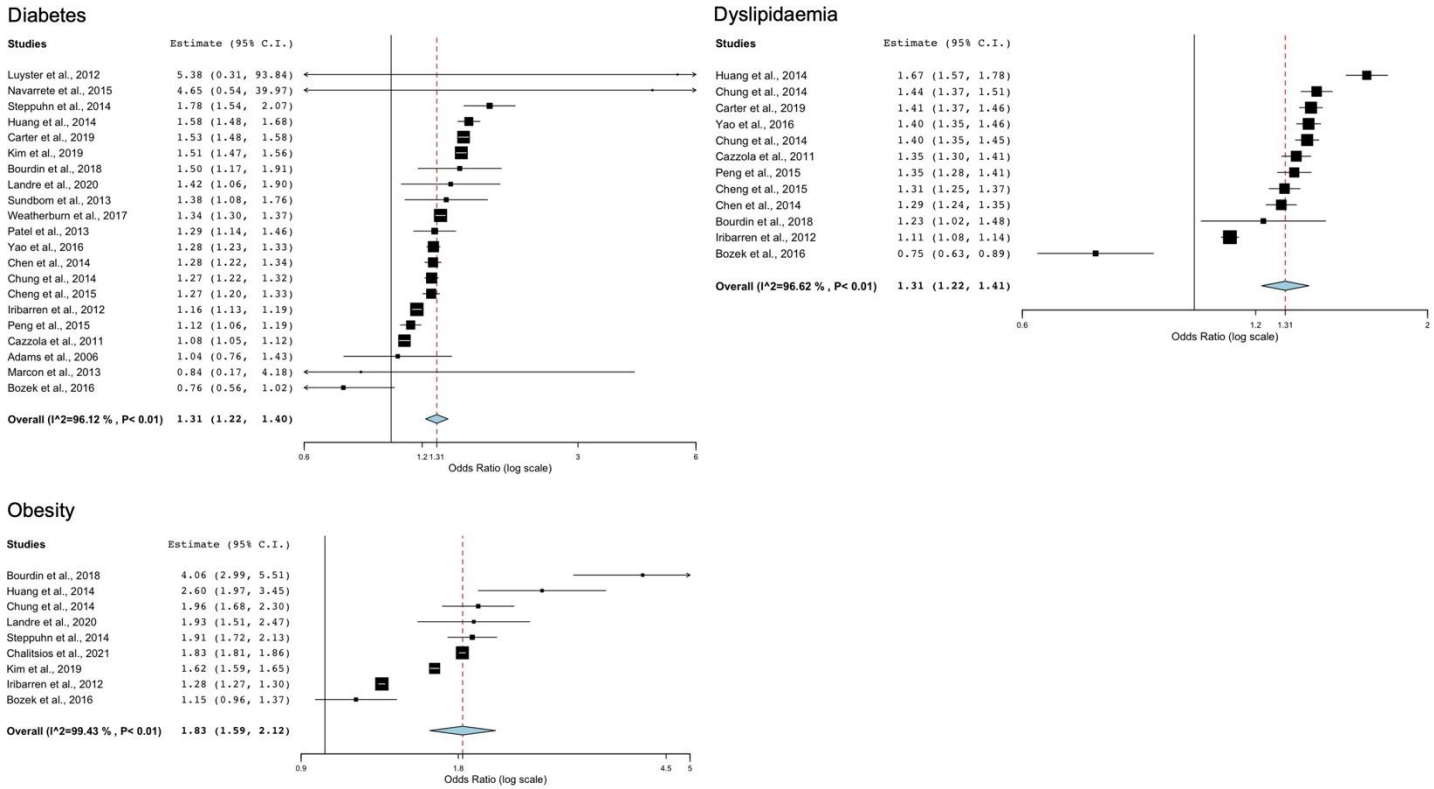

Figure S5. Forest plots for the association between metabolic disorders and asthma.

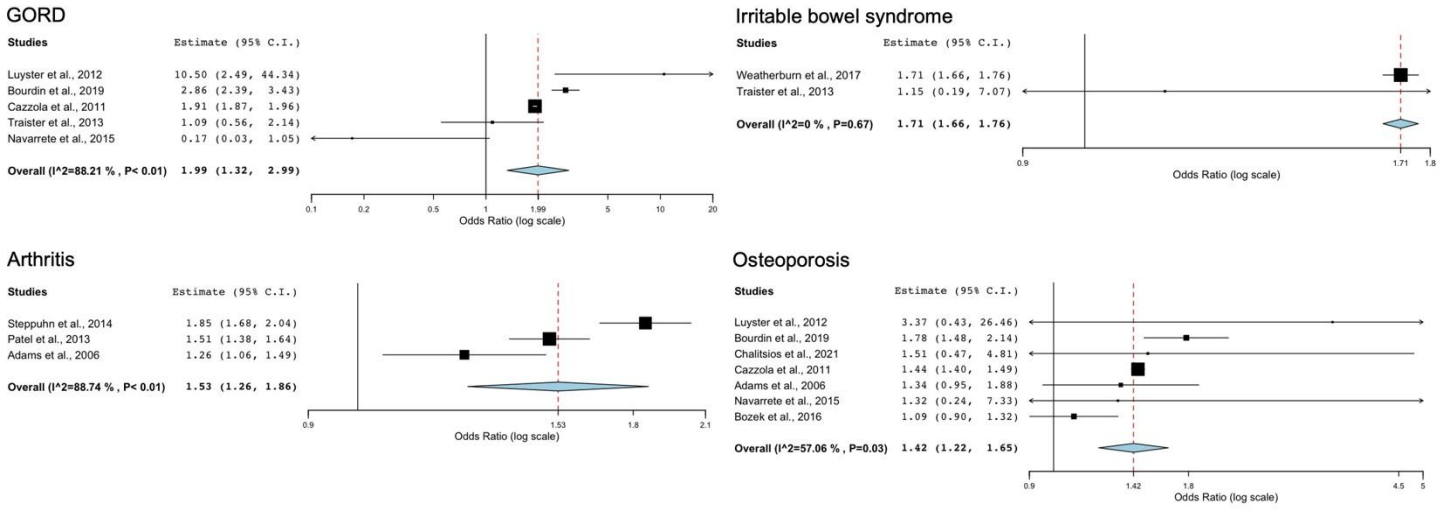

Figure S6. Forest plots for the association of gastrointestinal and musculoskeletal disorders with asthma. GORD: gastroesophageal reflux disease.

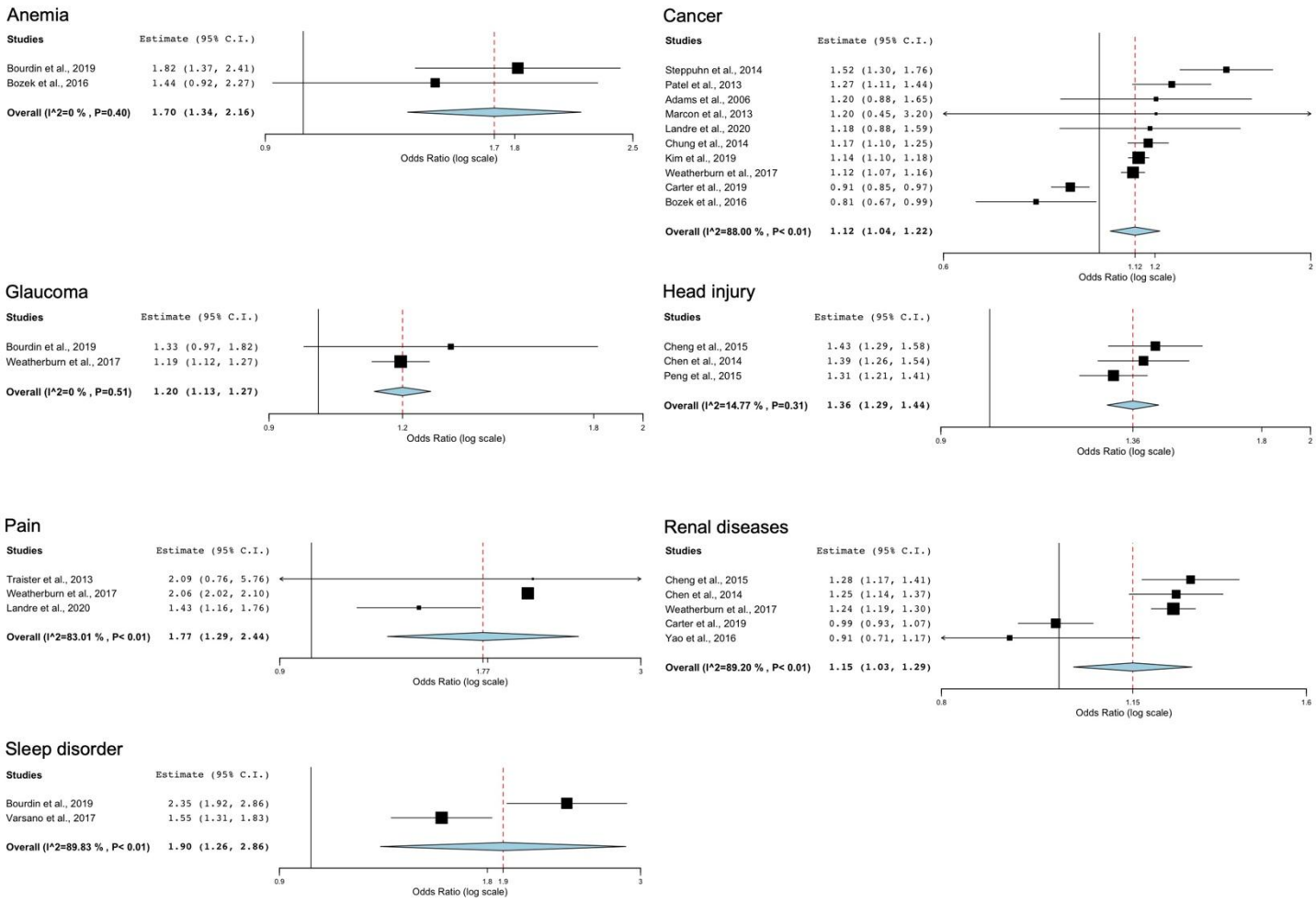

Figure S7. Forest plots for the association between other disorders and asthma.

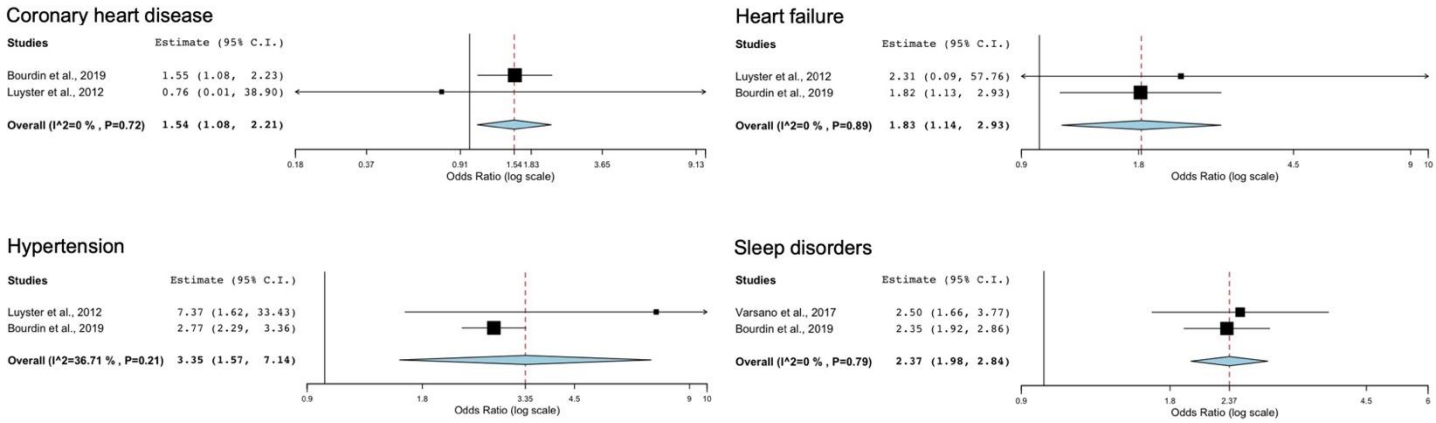

Figure S8. Forest plots for the association between coronary heart disease, hypertension, heart failure, sleep disorders and severe asthma.

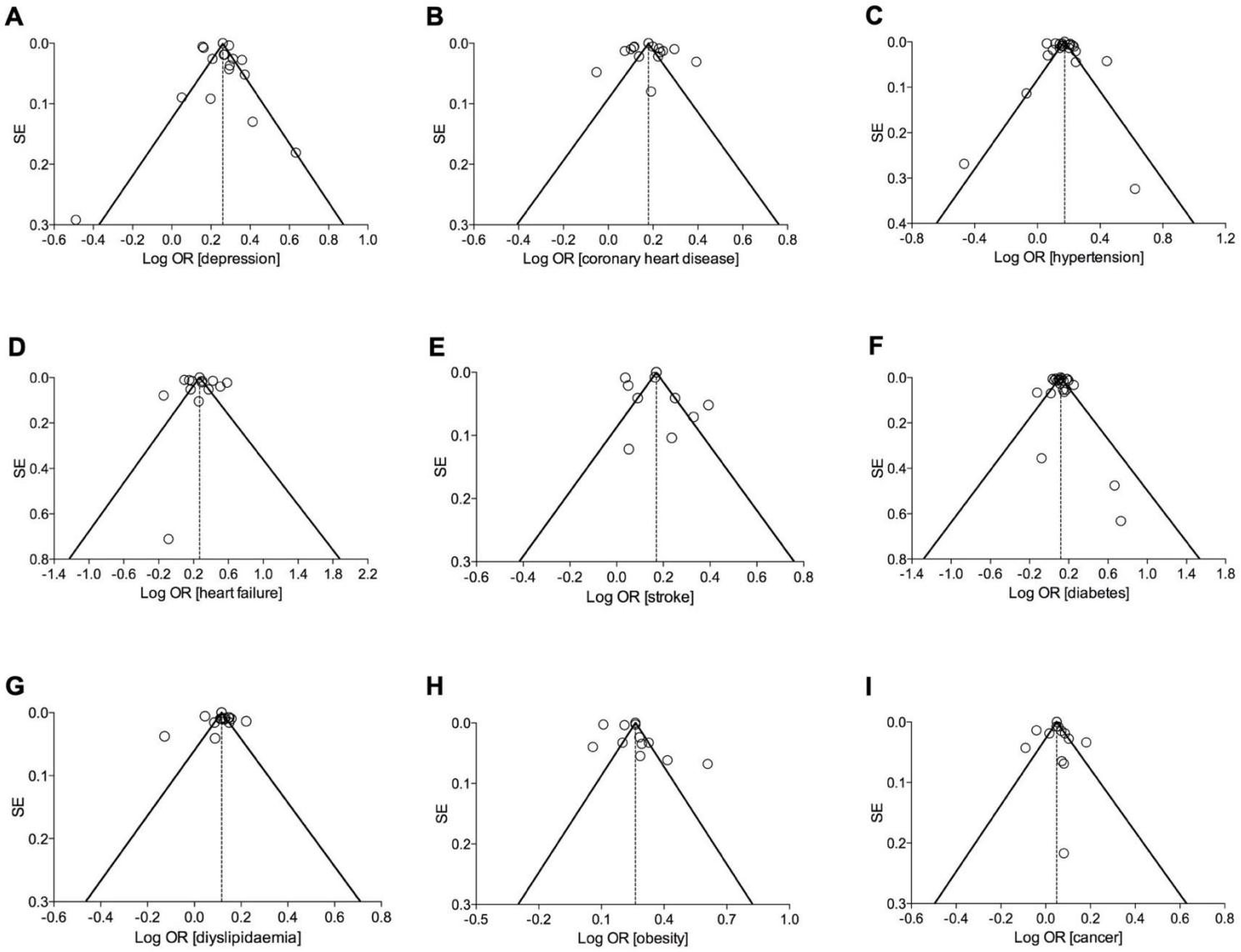

Figure S9. Publication bias assessment via funnel plots analysis for the association of depression (A), coronary heart disease (B), hypertension (C), heart failure (D), stroke (E), diabetes (F), dyslipidaemia (G), obesity (H), cancer (I). OR: odds ratio; SE: standard error.

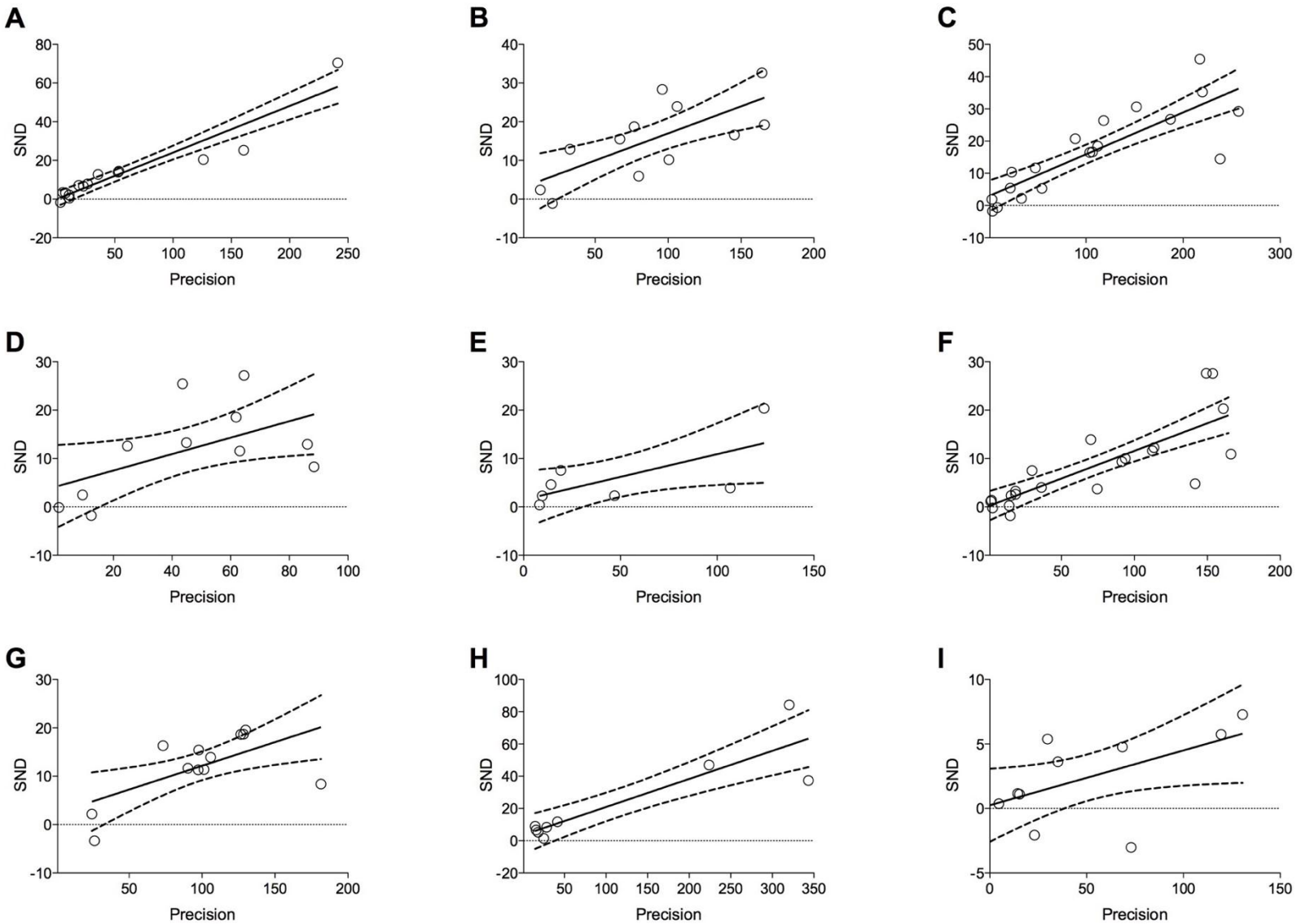

Figure S10. Publication bias assessment via Egger's test for the association of depression (A), coronary heart disease (B), hypertension (C), heart failure (D), stroke (E), diabetes (F), dyslipidaemia (G), obesity (H), cancer (I). SND: standard normal deviation.