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1 **Article type:** Original article

2 **The prevalence and odds of anxiety and depression in children and adults with**
3 **hidradenitis suppurativa: systematic review and meta-analyses**

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29 Abstract

30 *Background:* Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder. Previous
31 studies have yielded divergent results on the prevalence of depression and anxiety in HS patients.

32 *Objective:* The aim of this meta-analysis was to provide a pooled estimate of the prevalence and
33 odds of depression/anxiety in HS patients.

34 *Methods:* Search for and extraction of relevant literature without restrictions from five databases
35 (Cochrane Database, EMBASE, PubMed, PsychINFO, Science Direct) were performed. Pooled
36 meta-analyses were made by using random-effects models.

37 *Results:* Meta-analyses of 28 studies of depression in HS and 12 of anxiety showed a prevalence
38 of 21% of depression [17-25] and 12% of anxiety [6; 17] in HS patients, with very wide variations
39 in both cases. Analysis of case-control studies showed an association between depression and
40 HS (OR 1.99 [1.63; 2.43]) and between anxiety and HS (OR 1.97 [1.65; 2.35]).

41 *Limitations:* The results of this meta-analysis are conditioned by the limitations of the studies
42 included and by differences in patient population, methodological approach and data available.

43 *Conclusion:* Patients with HS have a high burden of depression and anxiety. Our results show that
44 clinicians need to be vigilant to the presence of depression or anxiety and to refer patients when
45 appropriate.

46

47

48 Capsule summary

49 • How does this article integrate into what was already known?

50 Divergent results on psychiatric prevalence in patients with hidradenitis suppurativa have been
51 published.

52 • How does it change practice?

53 These meta-analyses show a positive significant association between hidradenitis suppurativa
54 and depression/anxiety.

55 • That is, what does the article mean to the practice of dermatology and what should you do
56 as a result of having read this article? What should change in the way you practice?

57 Dermatologists should screen for depression/anxiety in hidradenitis suppurativa patients and
58 refer them for psychiatric evaluation and appropriate treatment when necessary.

59

60 **Introduction**

61 Hidradenitis suppurativa (HS) is a chronic follicular occlusive disease involving the
62 folliculopilosebaceous unit. Clinically, patients have recurrent inflamed follicular lesions, nodules
63 and abscesses leading to draining sinus tract formation and severe scars in the intertriginous
64 areas.

65 The association between certain chronic inflammatory skin diseases and psychiatric disorders has
66 been widely studied. Systematic reviews or meta-analyses of the prevalence of depression or
67 anxiety in psoriasis, alopecia areata (AA) and atopic dermatitis (AD) have been published¹⁻⁴. A
68 recent meta-analysis showed a positive significant association between HS and the risk of
69 suicide⁵. Previous observational and registry studies on the prevalence of depression and anxiety
70 in patients suffering from HS yielded divergent results⁶. A meta-analysis proposed prevalence
71 rates of anxiety and depression respectively based on 4 and 10 observational studies in adult
72 patients with HS⁷. First the exact magnitude of the association between HS and anxiety is still
73 unknown, since the 4 studies included failed to establish an odds ratio. Second, the limited number
74 of studies failed to test many factors that could affect prevalence. Third, numerous further studies
75 have been published recently and hence a new meta-analysis would provide more accurate
76 results. We aimed to make, therefore, a pooled estimate of the prevalence and odds of
77 depression/anxiety in HS patients and to study the relationship between variations in prevalence
78 and study characteristics.

79

80 **Materials and methods**

81 **Literature search**

82 The search for and extraction of relevant literature from five medical databases (Cochrane
83 Database, EMBASE, PubMed, PsychINFO, Science Direct) were conducted by two authors (IJ,
84 FR) from inception to May 2019 using the following search terms: *hidradenitis suppurativa* OR
85 *acne inversa* AND *depression* OR *anxiety* OR *generalized anxiety disorder* OR *phobia* OR *panic*
86 *disorder* OR *panic* OR *obsessive compulsive disorder* OR *OCD*. No limits were set on language,
87 year of publication, age of study participants or study size. All articles were screened according to
88 title and abstract independently by two authors (IJ, FR). Additionally, studies were sought for by
89 screening reference lists of previous key or review articles. Recommendations of the Preferred
90 Items for the Reporting of Systematic Reviews and Meta-Analysis (PRISMA) were followed⁸. In
91 France, ethics approval is not required for this type of research.

92 Only articles with full text access were retained, those with access only to an abstract were
93 excluded. The full-text articles were independently assessed for inclusion by LC and FR. If several
94 papers analyzed data from the same cohort, we included the article with the most complete data.
95 All disagreements between the reviewers were adjudicated by consensus between three authors
96 (FR, LC, IJ).

97

98 **Data extraction**

99 Two of the authors extracted and tabulated data and checked for accuracy (LC, FR). The data
100 collected were sociodemographic (proportion of female included, mean age), medical (mean
101 duration of HS, Hurley stage, proportion of smokers, number of patients/controls with
102 depression/anxiety) and methodological (prospective or retrospective study, number of patients
103 included, method of depression/anxiety assessment, presence of controls).

104

105 **Risk of bias**

106 Three authors (FR, LC, IJ) assessed the risk of bias for all studies with a specific instrument that
107 has high interrater agreement in assessment of risk of bias in studies measuring disease
108 prevalence⁹. Disagreements between the reviewers were adjudicated by consensus between
109 three of the authors. We included all studies irrespective of their risk of bias.

110

111 **Statistical analysis**

112 Statistical analysis was performed with Stata software (version 13, StataCorp, College Station,
113 TX). Study characteristics were summarized and reported as mean and standard-deviation for
114 continuous parameters, and percentage for categorical variables.

115 The meta-analysis took into account between- and within-study variability. To address the non-
116 independence of data caused by study effect, random-effects models¹⁰ were preferred over the
117 usual statistical tests to evaluate the prevalence of anxiety and depression. For stratified analyses
118 according to the diagnostic tool used and for comparison between cases and controls, the same
119 statistical approach was adapted. Results were expressed as prevalence and 95% confidence
120 intervals. Heterogeneity in the study results was assessed by examining forest plots and using I^2
121 statistic, which is the most common metric for measuring the magnitude of between-study
122 heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically
123 considered low for 25%, modest for 25% to 50%, and high for 50%¹¹. Publication bias was
124 assessed by funnel plots and confidence intervals. When possible (sufficient sample size), meta-
125 regressions were proposed to study the relationship between variations of prevalence and study

126 characteristics such as assessment method, risk of bias, number and age of patients included,
127 proportion of smokers and Hurley stage 3 patients included, and study design (prospective or
128 retrospective). Results were expressed as regression coefficients (Estimated Coefficient [EC] and
129 95%CI).

130 Finally, to verify the robustness of the results, sensitivity analyses were made excluding studies
131 that were not evenly distributed around the base of the funnel. A sensitivity analysis was also
132 performed to study the prevalence estimate only for those studies for which a case-control
133 comparison was possible, to ensure representativeness in terms of prevalence of this subsample.

134

135 **Results**

136 A total of 356 and 120 articles on depression and anxiety, respectively, were identified. After
137 screening of the titles and abstracts and removal of duplicates, 65 and 33 articles, respectively,
138 remained and were submitted to full-text review. Of these articles, 37 on depression and 21 on
139 anxiety were excluded. A total of 28 and 12 articles were included in the meta-analysis for
140 depression and anxiety, respectively (Figure 1).

141

142 **HS and Depression**

143 The 28 studies selected for the meta-analysis of the prevalence of depression are given in Table
144 1¹²⁻³⁹.

145 The meta-analysis revealed a high prevalence of depression in HS patients (21% [17-25]) with
146 very wide variations ($I^2 = 99.7\%$). Prevalence varied according to the diagnostic tool used, from
147 10% [5-15] in studies based on medical records and the ICD/DSM classification to 31% [26-36] in
148 those involving self-administered questionnaires (Figure 2). These results were confirmed by a
149 meta-regression analysis, which indicated that prevalence was significantly higher in surveys with
150 self-administered questionnaires (EC 0.21 [0.12;0.30], $p < 0.001$). Variations between the studies
151 can also be explained by study design, with retrospective studies recording a lower prevalence
152 than prospective ones (EC -0.09 [-0.19;-0.01], $p = 0.035$) and by patient numbers, with studies
153 including more than 500 patients recording a lower prevalence of depression (EC -0.15 [-0.25;-
154 0.05], $p = 0.005$). In contrast, patient age, proportion of smokers, proportion of Hurley stage 3
155 patients and bias risk had no effect on prevalence.

156

157 Analysis of the 10 case-control studies, comprising 78 129 patients and 14 086 989 controls,
158 showed an association between depression and HS (OR 2.01 [1.67-2.48]) (Supplementary Figure
159 1). Even after exclusion of one study (using a self-administered questionnaire) for funnel plot

160 publication bias (Supplementary Figure 2) the association was still present (OR 1.99 [1.63-2.43])
161 (Figure 3). Sensitivity analysis showed that the prevalence of depression in patients from the case-
162 control studies was close to that observed in our meta-analysis (17% [10-24] before exclusion of
163 the biased article and 15% [8-23] after exclusion).

164

165 **HS and Anxiety**

166 The 12 studies selected for the meta-analysis of the prevalence of anxiety are listed in Table
167 1^{20,21,26,27,29,32-36,39,40}.

168 The meta-analysis showed anxiety to have a prevalence of 12% [6-17] in HS patients with very
169 wide variations ($I^2 = 99.9\%$). Prevalence varied according to the diagnostic tool used, from 6% [1-
170 11] in studies based on medical records and the ICD/DSM classification to 25% [13-36] in those
171 using self-administered questionnaires. (Figure 4). These results were confirmed by a meta-
172 regression analysis, which indicated that prevalence was significantly higher in surveys with self-
173 administered questionnaires (EC 0.19 [0.05;0.32], $p=0.011$). Variations between the studies can
174 also be explained by study design, with retrospective studies recording a lower prevalence than
175 prospective ones (EC -0.16 [-0.28;-0.04], $p=0.012$). Patient age, sample size, proportion of
176 smokers included and bias risk had no effect on prevalence.

177

178 Analysis of the 7 case-control studies (all retrospective), comprising 77 712 patients and 100 994
179 135 controls, showed an association between anxiety and HS (OR 1.97 [1.65-2.35]) (Figure 5).
180 The results were similar irrespective of the diagnostic tool used. Sensitivity analysis showed that
181 the prevalence of anxiety in patients from the case-control studies was close to that observed in
182 our meta-analysis (9% [2-16]).

183

184 **Discussion**

185 **Main findings**

186 This study demonstrated a positive and significant association between HS and depression and
187 anxiety. Additionally, it shows that the prevalence of both depression and anxiety varies according
188 to the assessment method used (with prevalence being higher in studies using self-administered
189 questionnaires), and study design (with prevalence being lower in retrospective studies).

190

191 **Interpretation**

192 Our meta-analysis was based on 28 studies of depression in 93935 patients and 12 studies of
193 anxiety in 78326 patients. A previous paper analyzed depression in 10 studies involving 40307

194 patients (9 full text articles and 1 abstract) and anxiety in 4 studies involving 15533 patients (3 full
195 text articles and 1 abstract)⁷. Of the 19 full text additional articles of depression incorporated in the
196 present meta-analysis, 7 included controls, 11 were retrospective and used medical records, and
197 8 were prospective and based on self-administered questionnaires. The number of patients per
198 study ranged from 17 to 32625. Of the 9 full text additional articles of anxiety incorporated in the
199 present paper, 6 were retrospective and used medical records and 3 were prospective and based
200 on self-administered questionnaires. The number of patients per study ranged from 17 to 24266.
201 Among the additional studies analyzed, 7 on depression and 5 on anxiety comprised pediatric
202 patients. The inclusion of these publications provided an accurate and reliable estimate of the
203 prevalence rates of depression /anxiety and their association with HS, and enabled us to assess
204 various factors likely to affect prevalence such as sample size, study design and patient age.

205
206 We observed a higher overall prevalence of depression (21%) among patients with HS than in the
207 general population^{41,42}. This overall prevalence of depression is slightly higher than that obtained
208 in the paper of Machado *et al.* (17%). We determined a pooled OR for depression (1.99) that is
209 close to that obtained by Machado⁷ (1.84).

210
211 We observed a higher overall prevalence of anxiety (12%) among patients with HS than that
212 obtained in a previous paper (5%)⁷. The 4 studies included by Machado *et al.* did not allow
213 calculation of OR for anxiety. In our study the OR determined was 1.97, showing a positive and
214 significant association between HS and anxiety.

215
216 There are several possible explanations of the increased association between HS and depression
217 or anxiety. Pain, malodorous sweating and decaying scars impair social and professional activity
218 and affective and sexual life. HS significantly reduce quality of life^{6,43}, particularly in terms of mental
219 health ⁴⁴. This is why a specific quality of life scale currently in development, the HS-QoL-v2⁴⁵,
220 includes items on emotional consequences such as depression and anger. In addition, HS has
221 been associated with cigarette smoking and comorbidities such as inflammatory bowel diseases,
222 cardiovascular diseases and obesity, which are themselves associated with depression and
223 anxiety^{6,43}. Last, there is some evidence that inflammation could be a contributor to
224 depression/anxiety comorbidity in inflammatory skin diseases⁴⁶.

225
226 We observed a high heterogeneity across studies for which we suggest several explanations. A
227 major reason for the variation in prevalence rates for both depression and anxiety is the manner

228 in which depression/anxiety is evaluated. The highest prevalence rates were seen in studies using
229 self-report instruments, which are likely to overestimate the prevalence of depression or anxiety.
230 This tendency has been observed in the community⁴¹, in other chronic medical illnesses^{47,48}, in
231 psoriasis and atopic dermatitis^{1,2,4} and in the paper of Machado *et al.*⁷. The appropriateness and
232 different cut-off scores of the diagnostic tools to assess clinically significant symptoms could also
233 have contributed to the very wide variations. More importantly, screening tools, compared to
234 methods that use a formal diagnosis of depression/anxiety, can only reveal probable
235 depression/anxiety. A structured clinical psychiatric interview represents the gold standard.

236 Meta-regression analyses showed that variations can also be attributed to study design and the
237 number of patients included in the studies, with lower prevalence being found in retrospective
238 surveys and in studies involving 500 patients or more. These two factors are closely linked to the
239 method of assessment since retrospective studies are based on medical records and allow
240 inclusion of more patients. We know that the prevalence rates in studies based on medical records
241 are lower than in those using self-report instruments. In addition, the risk of false-negatives in
242 these studies should not be underestimated: if there is not sufficient information about
243 depression/anxiety or if the patient has not been assessed, the uncollected data will not be
244 recorded.

245
246 Machado *et al.* showed no effect of risk of bias (with a scale often used for assessing risk of bias
247 despite some limitations⁴⁹⁻⁵¹) nor of patient age on the prevalence of depression (but the studies
248 included had similar age-groups: 34.3 to 45.8 years). However, the use of a specific tool⁹ and the
249 integration of studies including children had no effect on prevalence in our meta-analysis. Other
250 meta-regression analyses failed to explain prevalence variations, but for some factors the lack of
251 data made it impossible to show any difference or to assess their effect on prevalence.

252
253 Prospective studies with large population-based samples based on a structured or semi-structured
254 clinical psychiatric interview with a record of patients' dermatological data would make it possible
255 to assess the specific prevalence of depression and anxiety disorders such as generalized anxiety,
256 social anxiety, panic disorder and agoraphobia stating the prevalence period studied⁵²⁻⁵⁶.

257

258 **Limitations**

259 Our meta-analysis was conditioned by the limitations of the studies included. Most of the studies
260 did not provide sufficient details about the patients enrolled, such as the respective proportions of
261 children and adults, the severity of HS (only 9 of the 28 studies on depression and 2 of the 12 on

262 anxiety mentioned the Hurley stage), smoking, and somatic comorbidities, which in certain
263 patients had known associations with depression or anxiety. In the retrospective studies, data
264 were collected over widely varying periods. In studies of alopecia areata it was observed in 50%
265 of patients that psychiatric disorders preexisted before skin disease onset⁵⁷. In contrast, in the HS
266 studies included in the present work the time elapsed between the onset of depression or anxiety
267 and that of HS was not given. Additionally, owing to lack of information in most of the studies
268 included, we were unable to take into account psychological or pharmacological treatments that
269 can modify mood or anxiety. Last, the variables retrieved from declarative data in some studies
270 also represented a limitation.

271

272 **Conclusion**

273 This study shows that HS patients have a high burden of depression and anxiety. Prospective
274 studies with large population-based samples based on a structured or semi-structured clinical
275 psychiatric interview should now be performed to refine the analysis.

276 For the immediate future, however, our results show that clinicians need to be vigilant to the
277 presence of depression or anxiety and to assess whether patients suffering from the conditions
278 should be referred for psychiatric evaluation and appropriate treatment.

279

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282

283

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Table 1: Description of selected studies

Name	Diagnosis	Assessment Method	Design	Number of patients	Controls	Age	Age category	Female	Smokers	HS duration	Hurley 1 †	Hurley 2 †	Hurley 3 †	Risk of bias
2010 Matusiak ¹⁴	Depression	Self-questionnaire	Prospective	52	-	39.9	Adults	52%	-	10.2	24%	54%	22%	Moderate
2013 Kurek ¹⁵	Depression	Self-questionnaire	Prospective	44	Healthy	34.3	Adults	55%	-	10.0	-	-	-	Moderate
2013 Onderdijk ¹⁶	Depression	Self-questionnaire ICD medical records	Prospective	211	Other ††	43.0	Adults	-	-	16.8	30%	56%	13%	Low
2013 Vazquez ¹⁷	Depression	Medical records	Retrospective	268	-	-	Children and Adults	71%	57%	-	60%	38%	2%	Low
2014 Crowley ¹⁸	Depression	Self-questionnaire	Prospective	154	-	36.3	Adults	71%	55%	11.9	16%	55%	29%	Moderate
2014 Wormald ¹⁹	Depression	Medical records	Prospective	27	-	34.7	Adults	70%	41%	-	-	-	100%	High
2015 Khalsa ²⁰	Depression	ICD medical records	Retrospective	7 901	Other ††	36.2	Adults	75%	-	-	-	-	-	Moderate
2015 Patel ²¹	Depression	Medical records	Retrospective	112	Healthy	-	Adults	84%	36%	-	-	-	-	Moderate
2015 Shavit ²²	Anxiety and Depression	Medical records	Retrospective	3 207	Healthy	39.6	Children and Adults	62%	-	-	-	-	-	Low
2016 Humphries ²³	Anxiety and Depression	Medical records	Retrospective	17	-	36.8	Adults	77%	47%	10.5	-	-	-	High
2016 Santos ²⁴	Depression	ICD medical records	Retrospective	1 177	-	-	Children and Adults	54%	14%	-	-	-	-	Low
2016 Vangipuram ²⁵	Depression	Medical records	Retrospective	283	-	-	Adults	81%	50%	-	46%	36%	19%	Low
2017 Kirby ²⁶	Depression	Self-questionnaire	Prospective	154	-	40.9	Adults	84%	-	-	-	-	-	Moderate
2017 Kluger ²⁷	Depression	Self-questionnaire	Prospective	26	-	44.2	Adults	62%	77%	18.4	50%	42%	8%	High
2018 Garg ²⁸	Anxiety and Depression	Medical records	Retrospective	32 625	Healthy	-	Adults	76%	-	-	-	-	-	Low
2018 Huilaja ²⁹	Anxiety and Depression	ICD medical records	Retrospective	4 372	Healthy	39.6	Children and Adults	59%	-	-	-	-	-	Low
2018 Ingram ³⁰	Depression	Medical records	Retrospective	24 027	Healthy	-	Children and Adults	-	-	-	-	-	-	Low
2018 Kimball ³¹	Anxiety and Depression	DSM 5 medical records	Retrospective	5 357	Healthy	42.2	Adults	72%	-	-	-	-	-	Low
2018 Kjaersgaard Andersen ³²	Depression	Self-questionnaire	Prospective	503	-	41.0	Adults	79%	53%	21.0	-	-	-	Low
2018 Ramos Rodriguez ³³	Depression	ICD medical records	Retrospective	4 369	Other ††	-	Adults	62%	-	-	-	-	-	Moderate

2018 Thorlacius ³⁴	Anxiety and Depression	ICD medical records	Prospective	7 732	Healthy	45.8	Adults	74%	27%	9.6	-	-	-	Low
2018 Tiri ³⁵	Anxiety and Depression	ICD medical records	Retrospective	153	Healthy	15.6	Children	73%	-	-	-	-	-	Low
2019 Butt ³⁶	Anxiety and Depression	Self-questionnaire	Prospective	229	-	40.8	Adults	83%	-	-	-	-	-	Moderate
2019 Nielsen ³⁷	Anxiety and Depression	Self-questionnaire	Prospective	91	-	-	Adults	81%	-	-	-	-	-	Moderate
2019 Patel ⁴²	Anxiety	Medical records	Retrospective	24 266	Healthy	41.3	Children and Adults	60%	-	-	-	-	-	Low
2019 Pavon Blanco ³⁸	Anxiety and Depression	Self-questionnaire	Prospective	211	-	38.2	Adults	60%	41%	-	21%	29%	50%	Low
2019 Senthilnathan ³⁹	Depression	Self-questionnaire	Prospective	67	-	39.3	Adults	90%	-	-	-	-	-	Moderate
2019 Theut Riis ⁴⁰	Depression	-	Prospective	500	Healthy	36.6	Adults	50%	18%	-	-	-	-	Moderate
2019 Zimman ⁴¹	Anxiety and Depression	Medical records	Retrospective	66	-	37.0	Children and Adults	65%	59%	-	42%	36%	21%	High
Total Anxiety	N= 12	9 medical records ††† 3 self-questionnaires	4 Prospective 8 Retrospective	78 326	7	37.7	1 Children 6 Adults 5 mixed	70%	41%	-	-	-	-	8 Low 2 Moderate 2 High 13 Low
Total Depression	N= 28	18 medical records ††† 9 self-questionnaires	13 Prospective 15 Retrospective	93 935	10	38.1	1 Children 21 Adults 6 mixed	70%	43%	14.8	35%	41%	20%	11 Moderate 4 High

† Hidradenitis suppurativa severity was assessed according to the three Hurley stages.

†† Other controls are patients of other dermatological diseases in two studies and patients with inflammatory bowel disease in one study. Only studies with healthy controls were included in the case-control comparison.

††† The total medical records include medical records with ICD/DSM classification and unspecified medical records in the following ratio: 4/5 for anxiety and 9/9 for depression respectively.

Mean age of patients and mean duration of hidradenitis suppurativa are reported in years.

1 **Figure Legends**

2
3 **Figure 1. Hidradenitis suppurativa. Flow diagram of article selection for the meta-analysis (PRISMA**

4 **2009)**
5 The numbers on the left represent the number of articles on depression and those on the right on anxiety (n

6 = Depression / Anxiety)

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9 **Figure 2. Hidradenitis suppurativa. Meta-analysis of the prevalence of depression according to**

10 **diagnostic tool.**

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13 **Figure 3. Hidradenitis suppurativa. Odds ratio meta-analysis of the association between depression**

14 **and hidradenitis suppurativa.**

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16
17 **Figure 4. Hidradenitis suppurativa. Meta-analysis of the prevalence of anxiety according to diagnostic**

18 **tool.**

19
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21 **Figure 5. Hidradenitis suppurativa. Odds ratio meta-analysis of the association between anxiety and**

22 **hidradenitis suppurativa.**

23

Identification

Records identified through
database search
Cochrane (n = 9 / 4)
Embase (n = 177 / 56)
PsycInfo (n = 0 / 0)
Pubmed (n = 48 / 18)
Science Direct (n= 122 / 42)

Additional records identified
through other sources
(n = 0)

Screening

Records screened
(n = 356 / 120)

Records excluded
(n = 260 / 70)
Duplicates removed
(n = 31 / 17)

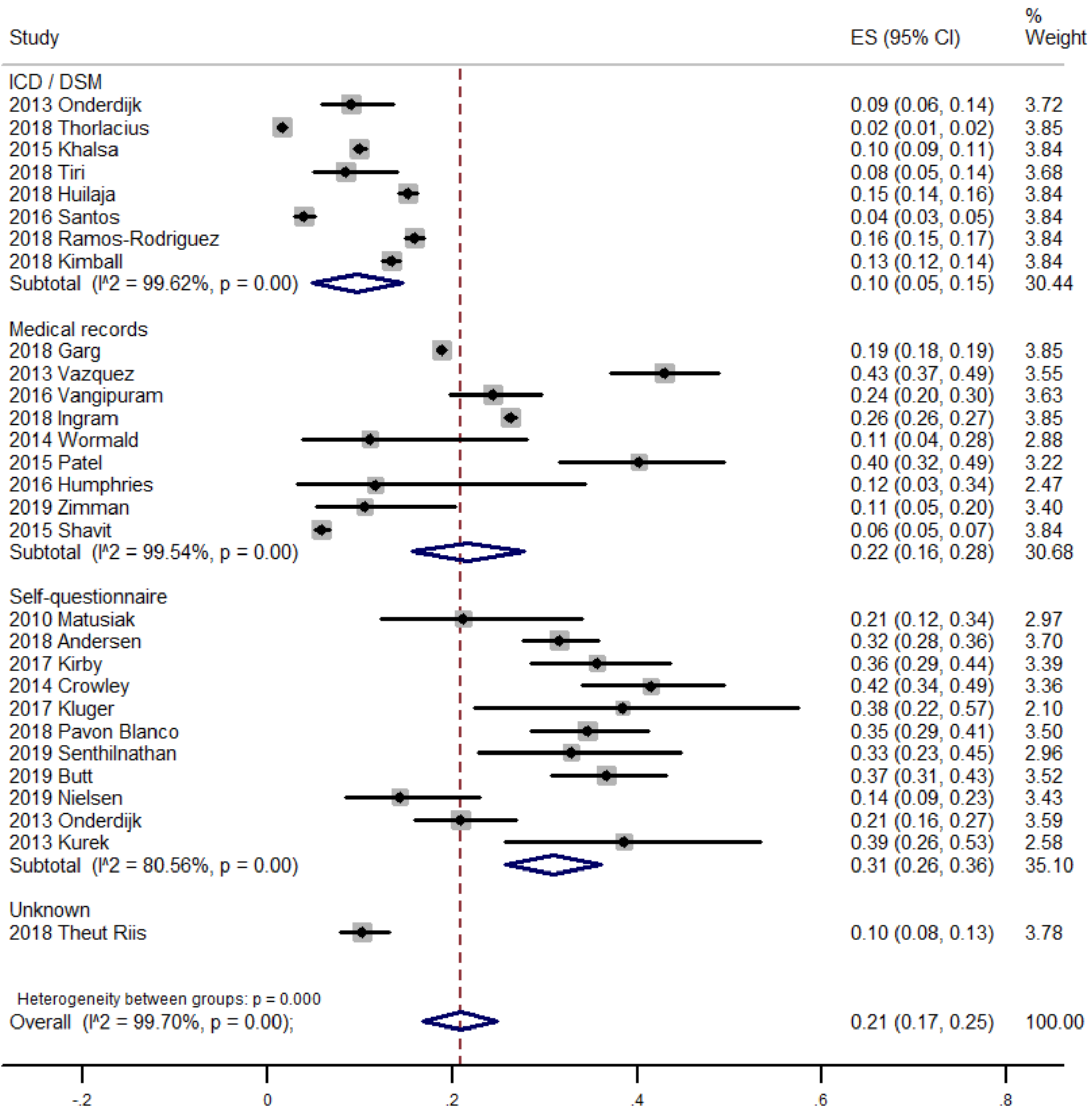
Eligibility

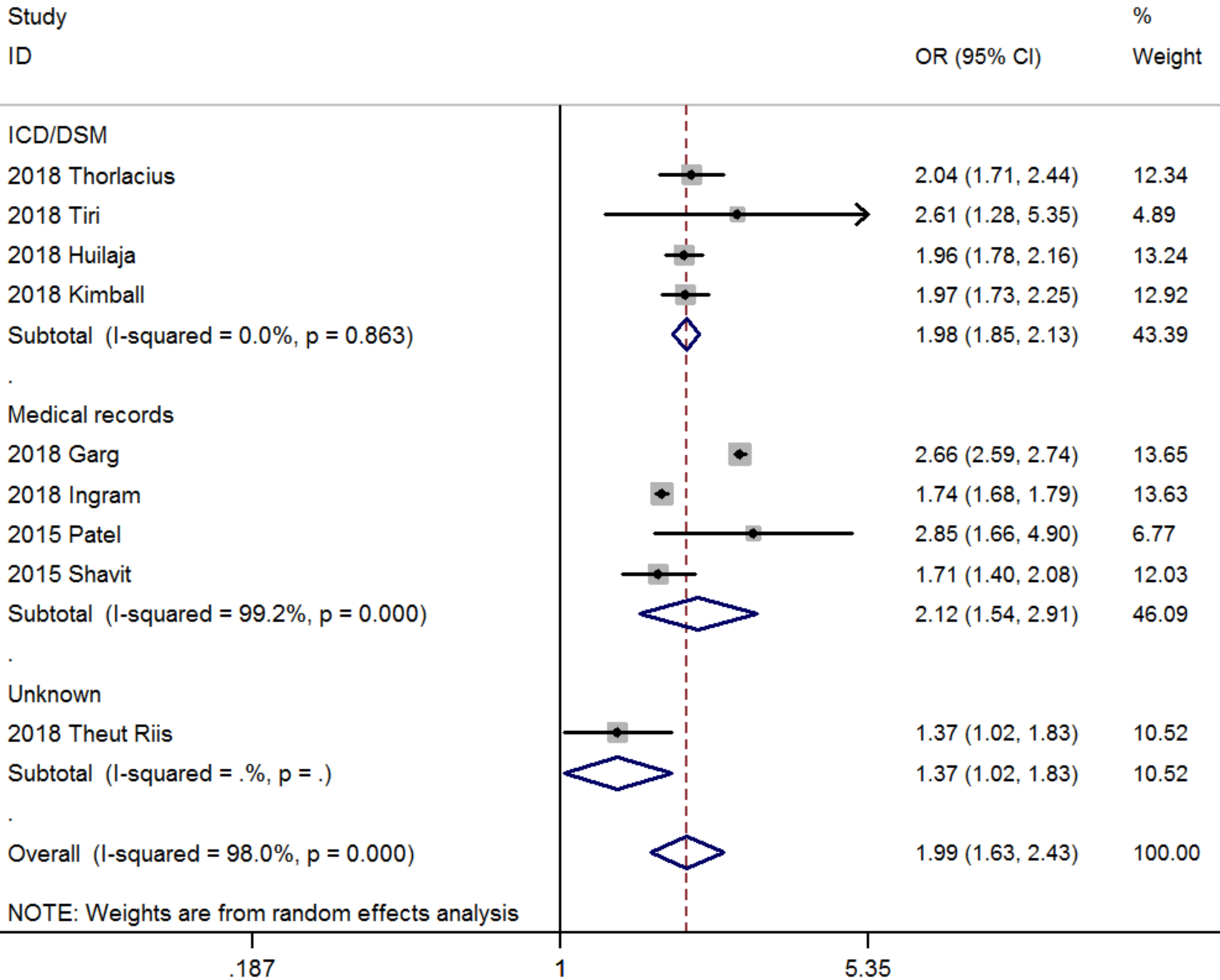
Full-text articles assessed
for eligibility
(n = 65 / 33)

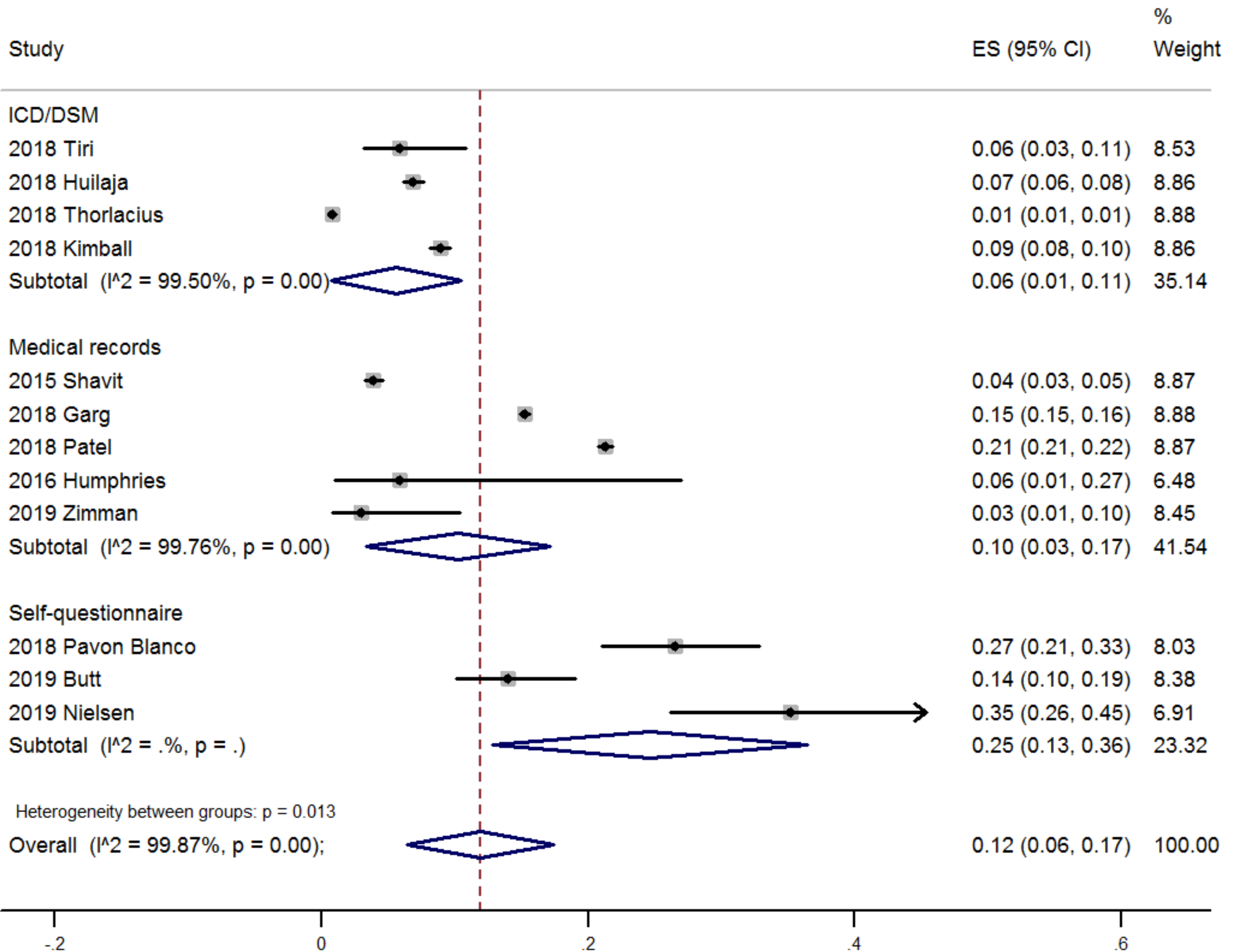
Full-text articles excluded, with
reasons
Irrelevant exposure (n = 5 / 2)
Irrelevant outcome (n = 5 / 8)
Review (n = 2 / 1)
Same population as another
study (n = 2 / 1)
No access (n = 3 / 3)
Congress abstract (n = 20 / 6)

Included

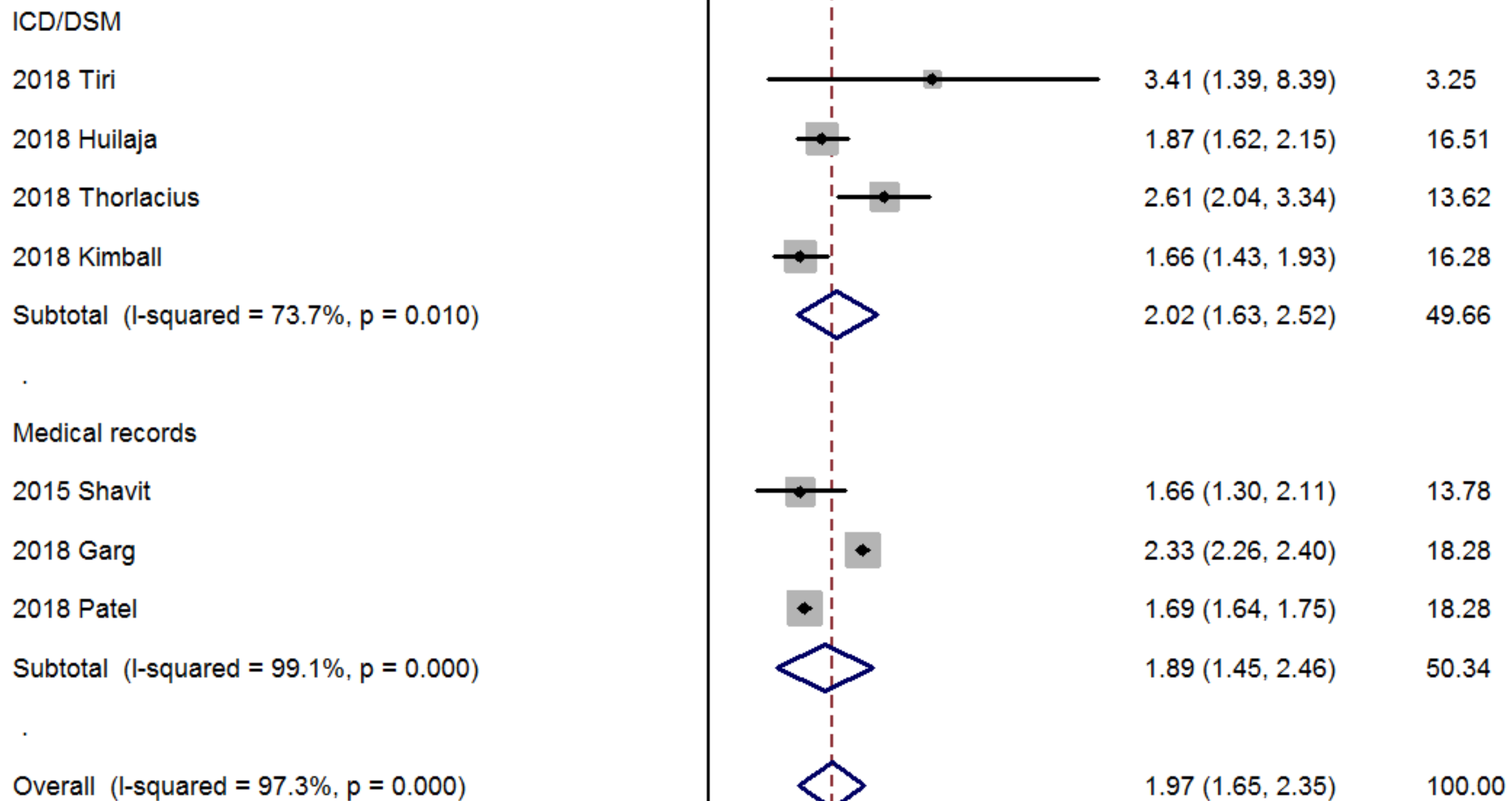
Studies included in
quantitative synthesis
(meta-analysis)
(n = 28 / 12)







Study			%
ID		OR (95% CI)	Weight



NOTE: Weights are from random effects analysis

.119

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8.39