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Prevalence of celiac disease in patients with type 1 diabetes: a systematic review and meta-analysis

ABSTRACT

Background. Celiac disease (CD) is more prevalent among type 1 diabetes (T1D) patients compared to the general population and can be accompanied by hypoglycemia episodes in T1D patients. Studies worldwide have reported CD prevalence with large variability. This study aimed to estimate the pooled prevalence of CD in T1D patients.

Methods. PubMed, Web of Science, Science Direct, and Scopus were searched without time limitation using the keywords: Celiac Disease, Gluten Enteropathy, Gluten-Sensitive Enteropathy, Wheat Hypersensitivity, Tissue Transglutaminase Antibody, Endomysial Antibody Disease, Diabetes Mellitus, and IDDM. Random-effects inverse variance-weighted model, subgroup analysis, and meta-regression were implemented. Heterogeneity was examined using Cochran's Q test and I^2 statistics.

Results. A pooled analysis of 55 articles with total sample size 71,853 revealed that the CD prevalence in patients with T1D was 5.08% (95% CI: 4.44%, 5.73%) with large heterogeneity (I^2 = 84%). To account for publication bias, using trim-and-fill method, the pooled prevalence was 4.0% (95% CI: 3.38%, 4.73%). The prevalence of CD was higher in Asia (6.53%, 95% CI: 4.89%, 8.16%) compared to USA (4.89%, 95% CI: 3.85%, 5.93%) and Europe (4.76%, 95% CI: 3.78%, 5.74%). In addition, studies conducted after 2008 reported pooled prevalence (6.37%, 95% CI: 5.25%, 7.49%) significantly higher than those conducted before 2008 (4.14%, 95% CI: 3.19%, 5.09%). Studies with quality score 10 had significantly higher prevalence (7.0%, 95% CI: 5.04%, 8.96%) compared with quality score 7 (3.66%, 95% CI: 2.61%, 4.70%).

Conclusion. CD is highly prevalent in T1D patients. Studies from Asia, those published after the year 2008, and studies with quality score 10 had higher pooled CD prevalence. Therefore, early screening for CD in T1D patients is important to prevent complications of CD.

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Keywords: type 1 diabetes, celiac disease, prevalence, meta-analysis

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Introduction

Celiac disease (CD) is a chronic autoimmune disease and small bowel enteropathy that is caused by environmental (gluten intolerance) and genetic (human leukocyte antigen (HLA) genes) factors [1]. CD is a common cause of malabsorption in children that is observed in both sexes and at any age and ranges from an asymptomatic form to active malabsorption [2]. Symptoms of Celiac disease include vitamin deficiency, malabsorption and malnutrition, diarrhea, constipation, vomiting, anorexia, and abdominal distension [3]. Given that untreated CD may be accompanied by iron deficiency, anemia, growth retardation, osteoporosis, short stature, neuropsychiatric disorders, lymphoma,

and fertility problems, early screening of high-risk groups for this disease is of high importance [4, 5]. A lifelong gluten-free diet is recommended for these patients so that possible risks can be avoided in the long term [4]. For a long time, the relationship between CD and diabetes has received attention from researchers, and the prevalence of CD in diabetic patients has been increasing; this increased prevalence is attributed to human leukocyte antigen alleles DR3 that is involved in both conditions [6, 7]. Picarelli [8] also maintains that there is a strong association between CD and diabetes for which the prevalence of CD is 20 times higher in diabetic patients compared to the healthy population. Co-occurrence of CD and diabetes can be accompanied by episodes of hypoglycemia and problems in controlling diabetes and delayed diagnosis of this disease can lead to developmental problems in children with diabetes [3]. Given that some patients may have no symptoms, continued consumption of foods high in gluten can aggravate the complications of CD [9].

On the other hand, severe watery diarrhea is common in diabetic patients, and if this symptom is observed in a patient, they should be tested for CD, and if the test result is positive, a biopsy should be required [10]. Many cases of CD in patients with T1D, even in the presence of intestinal lesions, are without typical gastrointestinal symptoms (the iceberg concept); in these cases, CD may remain undiagnosed. Therefore, early identification and treatment of these patients have an important role in preventing the symptoms and reducing long-term complications [11, 12]. Therefore, determining the overall prevalence of CD in patients with T1D can provide researchers and healthcare providers with useful information on this disease.

The present systematic review and meta-analysis are aimed to estimate the pooled prevalence of CD and to identify significant factors that influence the pooled prevalence in patients with T1D according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [13].

Material and methods

Search strategy

Search for articles was performed by two independent researchers in the following databases: PubMed, Web of Science, ScienceDirect, and Scopus, without time limitation. In addition, the following keywords and their possible combinations were used in the search process: CD, Gluten Enteropathy, Gluten-Sensitive Enteropathy, Wheat Hypersensitivity, tissue transglutaminase antibody, endomysial antibody disease, Diabetes Mellitus, IDDM. In order to access more articles, reference lists and discussions were also reviewed. The search strategy in PubMed was as follows:

("Celiac Disease"[Mesh] OR Celiac disease*[tiab] OR celiac*[tiab] OR Gluten Enteropathy*[tiab] Gluten-Sensitive Enteropathy*[tiab] OR Wheat Hypersensitivity*[tiab] OR tissue transglutaminase antibody*[tiab] OR tissue transglutaminase ab[tiab] OR anti endomysial antibody*[tiab] OR endomysial antibody disease*[tiab]) AND ("Diabetes Mellitus, Type I"[Mesh] OR Diabetes mellitus type I [tiab] OR IDDM[tiab]) NOT (Diabetes Mellitus, Type II [Mesh] OR NIDDM[tiab])

Selection of studies and data extraction

The inclusion criteria were as follows: observational studies reporting the frequency or prevalence of CD in diabetic patients, biopsy as the diagnostic criterion for CD, and published in English. Studies with low methodological quality (i.e. with a high level of bias), interventional studies, reviews, qualitative studies, case reports, and letters to the editor were excluded from the analysis. Two authors independently screened the articles by reviewing titles and abstracts, and in the next step, reviewed the complete texts according to the inclusion and exclusion criteria. In addition, the following information was extracted for each article: name of the first author, year of publication, mean age of participants, sample size, location of study, and the number of patients with celiac disease diagnosed by biopsy. Any disagreement between the two authors would be resolved through discussion.

Quality assessment

At this stage, two independent authors examined the methodological quality of the studies based on the 10 items of the Strengthening The Reporting of Observational Studies in Epidemiology (ESTROBE) checklist (title and abstract, objectives and hypotheses, study environment, inclusion criteria, sample size, statistical methods, descriptive data, interpretation of findings, limitations, and funding); higher scores on this checklist indicate better methodological quality. Articles were divided into three groups according to their methodological quality scores: poor (4 or below), moderate (4 to 7), and good (over 7) [14].

Data analysis

Estimation of the pooled prevalence of CD and its 95% confidence interval (CI) was carried out using a random-effects model with Hartung-Knapp adjustment [15]. The variance for each study was calculated with the weight for each study equals the inverse of the variance and the estimator for τ^2 following DerSimonian and Laird's method [16]. Heterogeneity among the studies was assessed using Cochran Q statistic and I^2 [17]. Confidence intervals for the prevalence of each study and the pooled prevalence were calculated

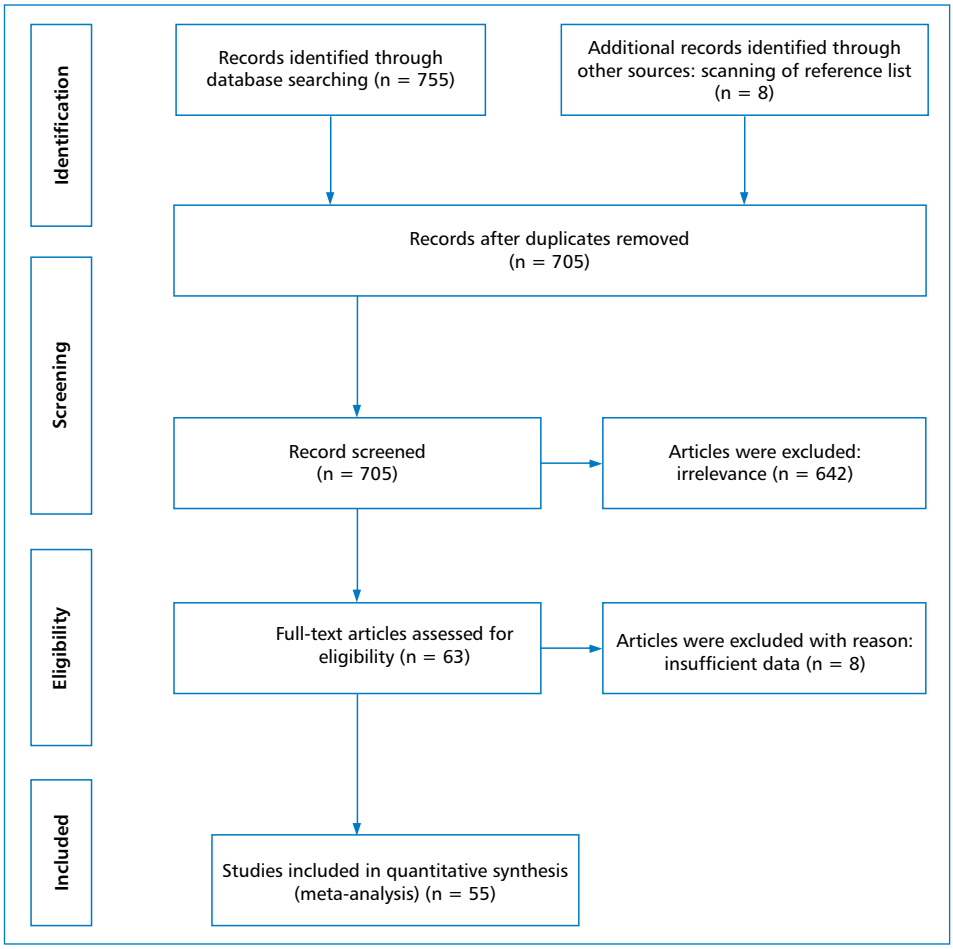

Figure 1. Screening and selection process of articles based on PRISMA guidelines

by the Clopper-Pearson method [18, 19]. Publication bias was evaluated by funnel plot, the asymmetry of which was tested with both the non-parametric test (rank correlation test) Begg's rank test [20], and Egger's regression test [21]. In order to see the effect of each study on the pooled estimate of the prevalence, sensitivity (influential or leave-one-out method) analysis was conducted using a random-effects model. Subgroup analysis and meta-regression were conducted to test the effect of some variables on the pooled estimate of the prevalence of CD. Finally, in case of the presence of publication bias, the trim-and-fill technique [22, 23] will be used to generate an unbiased estimate of the pooled prevalence of CD. Data analysis with all computations was conducted using Stata Version 12, the R statistical software [24] and the R packages meta [25] and metafor [26].

Results

A total of 763 articles were retrieved from international databases. After the removal of duplicate articles, titles and abstracts of 705 non-duplicate articles were examined. In the screening stage, 642 unrelated articles were excluded, and full texts of 63 articles were examined in terms of eligibility. Finally, 55 articles were included in the analysis. The flowchart of selecting and screening articles based on the PRISMA guidelines is presented in Figure 1.

The final analysis included 55 studies with a total sample size of 71,853. Table 1 presents data extracted from the studies included in the final analysis. The Cochran Q test for heterogeneity ($Q = 337.47$, $DOF = 54$, $PV < 0.0001$, $\tau^2 = 3.459$, $H^2 = 5.25$ and $I^2 = 84.0\%$) indicated that significant heterogeneity exists, and hence a random-effects model was implemented with inverse variance method. According to the random-effects model, the pooled estimate of the prevalence of CD is 0.0508 [95% CI: 0.0444, 0.0573] and its forest plot is presented in Figure 2.

According to linear regression and rank correlation tests for publication bias or asymmetry in the funnel plot, results indicated that there is a publication bias

Table 1. Characteristics of the selected studies (n = 55)

Reference	Year	Mean age	Country	Screening test	Male	Number screened	Screen positive	Biopsy	Number biopsied	Frequency	Prevalence
Sahin [27]	2020	11.6 ± 3.7	Turkey	tTG	–	273	23	+	21	12	4.4
Odeh [28]	2019	12 ± 3.9	Jordan	tTG	–	538	89	+	69	49	9.1
Punales [29]	2019	14.3 ± 5.9	Brazil	tTG	–	873	60	+	62	49	5.6
Slae [30]	2019	–	Israel	Unknown	175	314	31	+	16	18	5.7
Paruk [31]	2019	26.4 ± 11.4	South Africa	tTG, EMA	90	202	65	+	53	12	5.9
Velasco Benitez [32]	2018	11 ± 3.6	Colombia	tTG	83	155	13	+	13	4	4.5
Singh [33]	2017	–	India	tTG		126	43	+	40	17	13.5
Craig [34]	2017	–	UK	–	27573	52721	–	+	–	1835	3.5
Bianchi [35]	2016	–	Italy	–		1563	–	+	–	145	9.4
Srivastava [36]	2016	–	India	tTG	52	103	14	+	13	4	3.8
Dogan [37]	2015	–	Turkey	EMA	264	425	15	+	14	10	2.3
Joshi [38]	2015	–	India	tTG	–	71	11	+	6	5	7
Honar [39]	2013	10.3 ± 4.7	Iran	tTG	34	83	12	+	4	4	4.8
Bybrant [40]	2013	–	Sweden	tTG, EMA	–	847	81	+	81	65	7.7
Al–Sinani [41]	2013	10.8 ± 4	Oman	tTG, EMA	53	91	16	+	14	5	5.5
Picarelli [8]	2013	46.9 ± 10.1	Italy	tTG, EMA	43	94	13	+	13	13	13.8
Saadah [42]	2012	10.7	Saudi Arabia	tTG	195	430	91	+	83	48	11.2
Al–Hussain [43]	2012	8.5 ± 2.8	Saudi Arabia	tTG, EMA	44	106	26	+	21	12	11.3
Mansour [44]	2011	23.4 ± 7.6	Iraq	tTG, EMA	37	62	9	+	8	7	11.2
Bhadada [2]	2011	13.7 ± 7.3	India	tTG	93	189	21	+	21	21	11.1
Djurić [5]	2010	10.8	Serbia	tTG	51	121	9	+	7	7	5.8
Uibo [45]	2010	10.6	Estonia	tTG, EMA	155	271	11	+	10	9	3.3
Fallahi [46]	2010	–	Iran	tTG	45	96	6	+	6	6	6.2
Sari [47]	2010	12 ± 4.7	Turkey	tTG	18	48	10	+	8	3	6.2
Ergür [48]	2010	9.4 ± 2.9	Turkey	IgA, EMA	19	38	–	+	–	3	7.8
Narula [49]	2009	–	UK	EMA, tTG	–	556	22	+	17	17	3
Salardi [50]	2008	8.1 ± 4.3	Italy	EMA	–	329	29	+	23	22	5.5
Remes–Troche [51]	2008	28.9	Mexic	EMA	22	84	9	+	7	5	5.9
Poulain [52]	2007	6 ± 4.2	France	EMA, tTG	–	950	–	+	–	15	1.6
Goh [53]	2007	12.1	UK	IgA, IgG	58	113	7	+	7	5	4.4
Tanure [54]	2006	–	Brazil	IgA, AGA	112	236	29	+	19	6	2.6
Aygun [55]	2005	–	Turkey	EMA	54	122	9	+	3	3	2.5
Baptista [11]	2005	10.6 ± 4.3	Brazil	EMA, IgA	52	104	9	+	9	5	4.8

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Table 1 (cont.). Characteristics of the selected studies (n = 55)

Reference	Year	Mean age	Country	Screening test	Male	Number screened	Screen positive	Biopsy	Number biopsied	Frequency	Prevalence
Sanchez-Albisua [56]	2005	12 ± 5	Germany	EMA	120	281	18	+	12	9	3.2
Mahmud [57]	2005	17.9 ± 11.6	USA	EMA, tTG	191	392	158	+	11	11	7
Bouguerra [58]	2005	28.4 ± 10.7	Tunis	EMA, tTG	172	384	14	+	8	8	2.3
Cerutti [59]	2004	11.8 ± 4.2	Italy	EMA	1934	4322	–	+	–	292	6.8
Crone [60]	2003	14.8	Austria	EMA	83	157	16	+	16	9	5.7
Arato [61]	2003	11.6	Hungary	EMA	117	205	24	+	17	17	8.3
Al–Ashwal [62]	2003	10 ± 4	Saudi Arabia	IgA	69	123	10	+	10	6	4.9
Guvenc [63]	2002	–	Turkey	EMA	49	100	8	+	6	4	4
Spiekerkoetter [64]	2002	–	Germany	tTG	108	205	13	+	8	7	3.4
Barera [65]	2002	8.2 ± 4.6	Italy	EMA	159	273	15	+	10	9	3.6
Hansen [66]	2001	–	Denmark	EMA, tTG	56	106	10	+	9	9	8.5
Aktay [67]	2001	–	USA	EMA	113	218	17	+	14	10	4.6
Gillett [7]	2001	12.9	Canada	EMA	125	233	19	+	18	18	7.7
Schober [68]	2000	–	Austria	EMA	210	403	12	+	12	6	1.5
Vitoria [69]	1998	10.5±3.2	Spain	AGA, EMA	–	93	16	+	7	6	6.5
Roldan [70]	1998	15.5 ± 5.4	Spain	IgA	–	177	16	+	7	7	3.9
Acerini [6]	1998	13.8	UK	EMA, AGA	97	167	11	+	10	8	4.8
Fraser–Reynolds [71]	1998	–	Canada	EMA	–	236	19	+	17	12	5.1
Talal [72]	1997	–	USA	IgA	–	185	9	+	5	4	2.7
Rensch [73]	1996	–	USA	EMA	–	47	3	+	3	3	6.4
Saukkonen [74]	1996	–	Finland	AGA	–	776	–	+	–	19	2.4
Sigurs [75]	1993	–	Sweden	IgA		436	19	+	18	10	2.3

tTG: anti-tissue transglutaminase antibody; EMA: anti-endomysial antibody; AGA: anti gliadin antibody

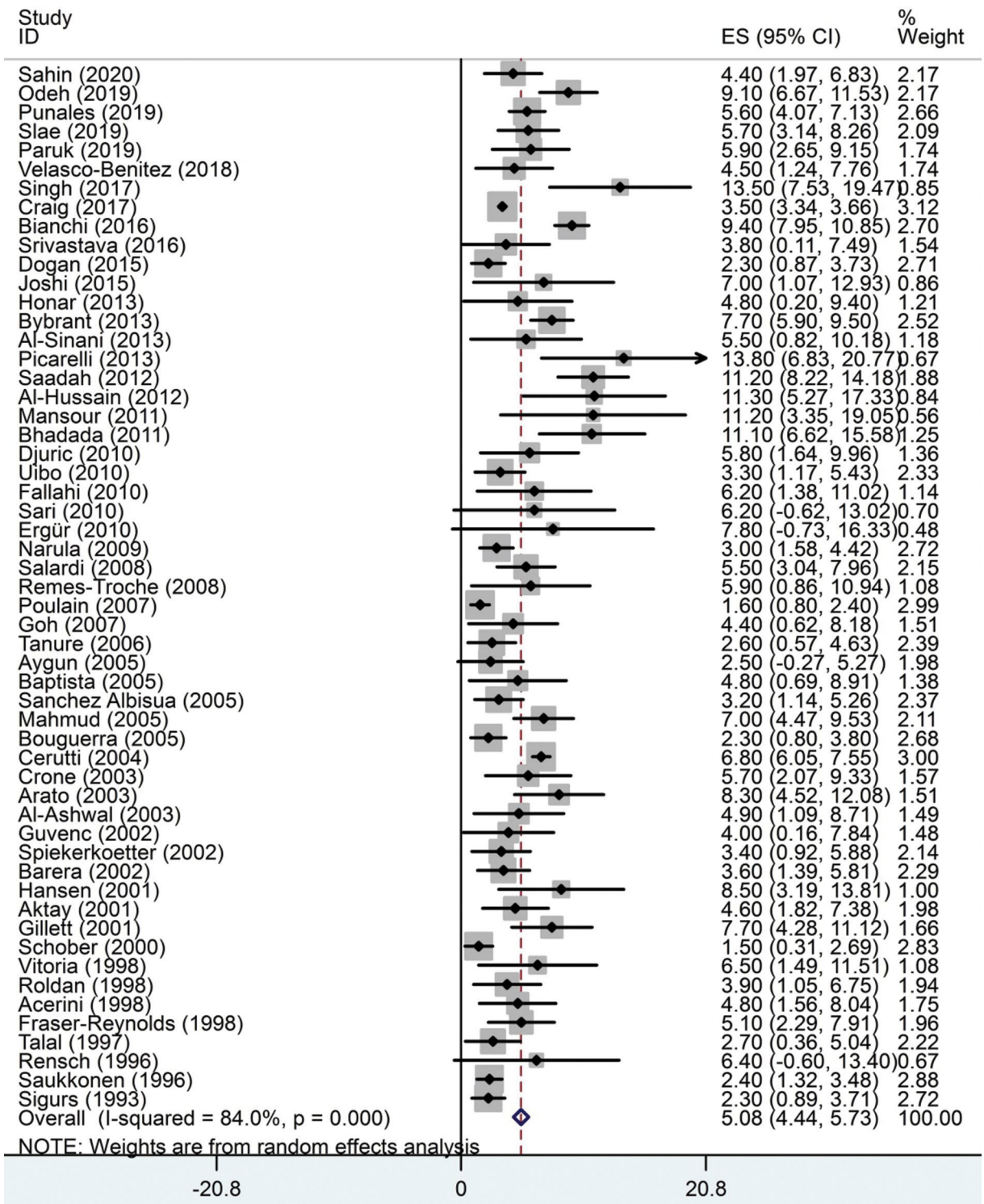

Figure 2. Forest plot of the pooled prevalence of Celiac disease among patients with type 1 diabetes (N = 55 studies)

(linear regression test: t = 3.0, DOF = 50, PV = 0.003, rank correlation test: Z = 4.0, PV = 0.0001). In order to correct for publication bias and produce an unbiased estimate of the prevalence of CD, the trim-and-fill technique (22, 23) was implemented in which 12 additional pseudo studies (total studies is 67) were generated to account for asymmetry. The funnel plot before and after implementing the trim-and-fill technique with pseudo 95% confidence limits is presented in Figure 3. The unbiased pooled estimate of the prevalence of CD

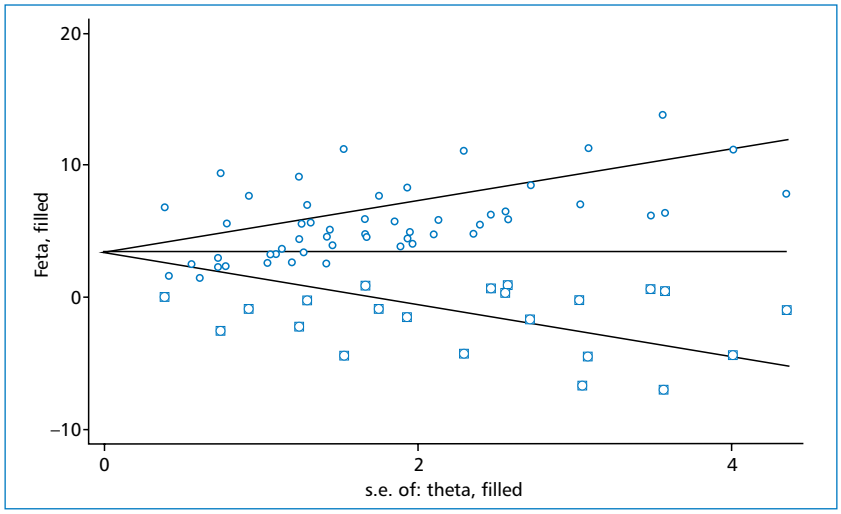

Figure 3. Funnel plot to test for publication bias in estimating the pooled prevalence of Celiac disease before (circles) and after (squares) use of trim-and-fill technique to adjust for publication bias. Squares represent the 22 pseudo studies that have been generated to adjust for publication bias

after implementing the trim-and-fill technique and using the random-effects model was 0.040 [95% CI: 0.0338, 0.0473], with $\tau^2 = 0.356$, H = 3.72; [95% CI: 3.43, 4.04], $I^2 = 92.8\%$ [95% CI: 91.5%, 93.9%], and Q = 912.9, DOF = 66, PV < 0.0001.

To unravel the effect of the region of the publication, subgroup analysis was conducted and its forest plot is presented in Figure 4. The pooled estimate of the prevalence of CD was 0.0653 (95% CI: 0.0489, 0.0816) for Asia (19 studies), 0.0476 (95% CI: 0.0378, 0.0574) for Europe (21 studies), and 0.0489 (95% CI: 0.0385, 0.0593) in the USA (11 studies). For Africa and Australia, both had only two studies and hence were not further assessed as regions.

As for year of publication, studies published before 2008 (27 studies) had pooled prevalence estimate of 0.0414 (95% CI: 0.0319, 0.0509) with Q = 147.12, DOF = 26, PV < 0.001, $I^2 = 82.3\%$, $\tau^2 = 4.31$, while studies published after 2008 (28 studies) has pooled prevalence estimate of 0.0637 (95% CI: 0.0525, 0.0749) with Q = 190.31, DOF = 27, PV < 0.001, $I^2 = 85.8\%$, $\tau^2 = 5.72$ with forest plot for year of publication presented in Figure 5. Furthermore, subgroup analysis was conducted for quality of studies score. Studies with quality score of 7 produced a pooled prevalence of 0.0366 (95% CI: 0.0261, 0.0470) with Q = 20.18, DOF = 11, PV = 0.043, $I^2 = 45.5\%$). Studies with quality score of 8 produced a pooled prevalence of 0.0467 (95% CI: 0.0360, 0.0573) with Q = 87.55, DOF = 22, PV < 0.001, $I^2 = 74.9\%$). Studies with quality score of 9 produced a pooled prevalence of 0.0563 (95% CI: 0.0415, 0.0711) with Q = 116.78, DOF = 11, PV < 0.001, $I^2 = 90.6\%$), while studies with quality score of 10 produced a pooled prevalence of 0.070 (95% CI: 0.0504, 0.0896) with Q = 33.38, DOF = 7, PV < 0.001, $I^2 = 79.0\%$). The forest plot for the subgroup analysis of the quality of study score is presented in Figure 6.

Meta-regression was conducted to test the effect of publication year, region of study, sample size, the average age of participants, and quality of study score with results presented in Table 2. Results indicated that publication year and quality of study score had a significant effect on the pooled prevalence of the CD while participants' average age, region of study, and sample size were not significant. In particular, meta-regression indicated that the pooled prevalence of CD for publications before the year 2008 was 0.0414 (95% CI: 0.0319, 0.0509) which is significantly lower (PV = 0.006) compared to the pooled prevalence of 0.0637 (95% CI: 0.0525, 0.0749) for studies published after the year 2008. Using dummy indicator variables, meta-regression results indicated that compared to studies with a quality score of 10, studies with quality scores 7 and 8 had a significantly lower pooled prevalence of CD with PV = 0.012 and 0.024, respectively. Using dummy indicator variables for the region of publication, meta-regression indicated that compared to the pooled prevalence in Asia, the pooled prevalence for Europe is marginally significantly smaller with PV = 0.065 while other regions are not significantly smaller.

In order to shed more light on publication bias and narrow down its source, studies were stratified by year of publication (before 2008 or after 2008), quality of study score (scores = 7, 8, 9, and 10), and region of

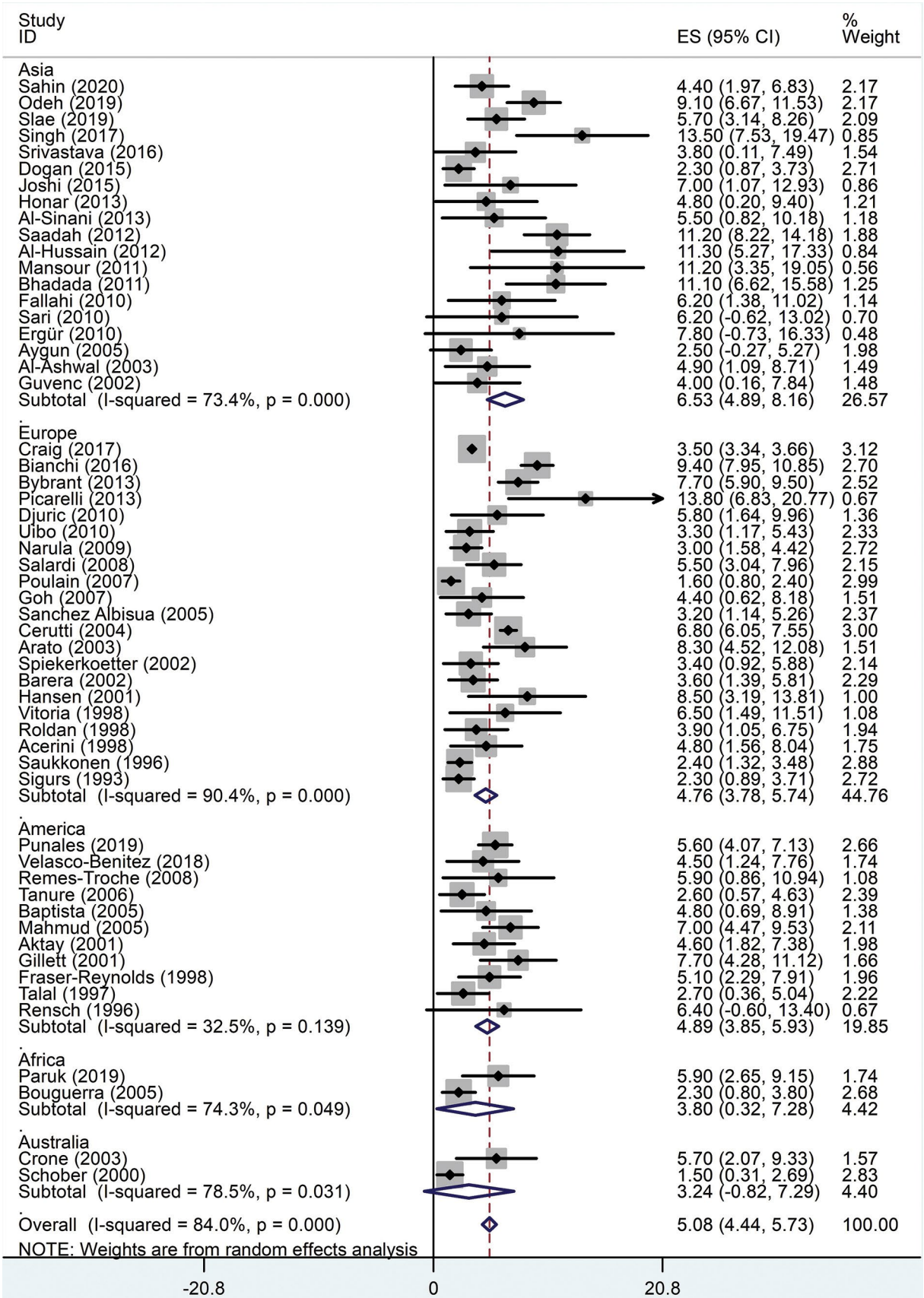

Figure 4. Results of subgroup analysis by place of publication using a random-effects model (N = 55 studies)

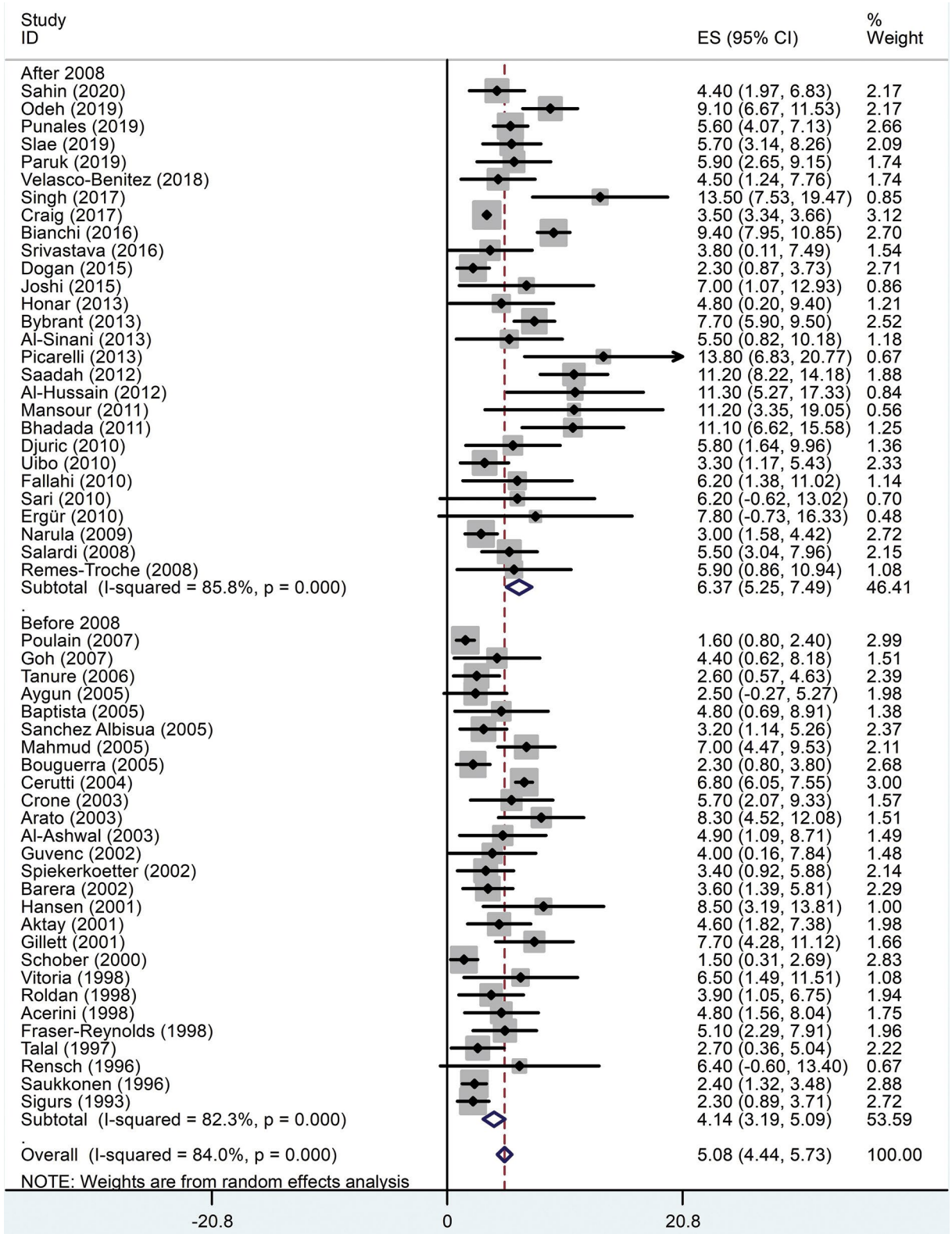

Figure 5. Results of subgroup analysis by year of publication (Before 2008 vs. After 2008) using the random-effects model (N = 55 studies)

publication (Asia, Europe, USA, ignoring Africa and Australia as each has only two studies) and publication bias was tested for each stratum. For the region of publication, results indicated that only studies published in Asia (19 studies) had publication bias (Egger's test: bias = 0.0227, PV = 0.017). For the year of publica-

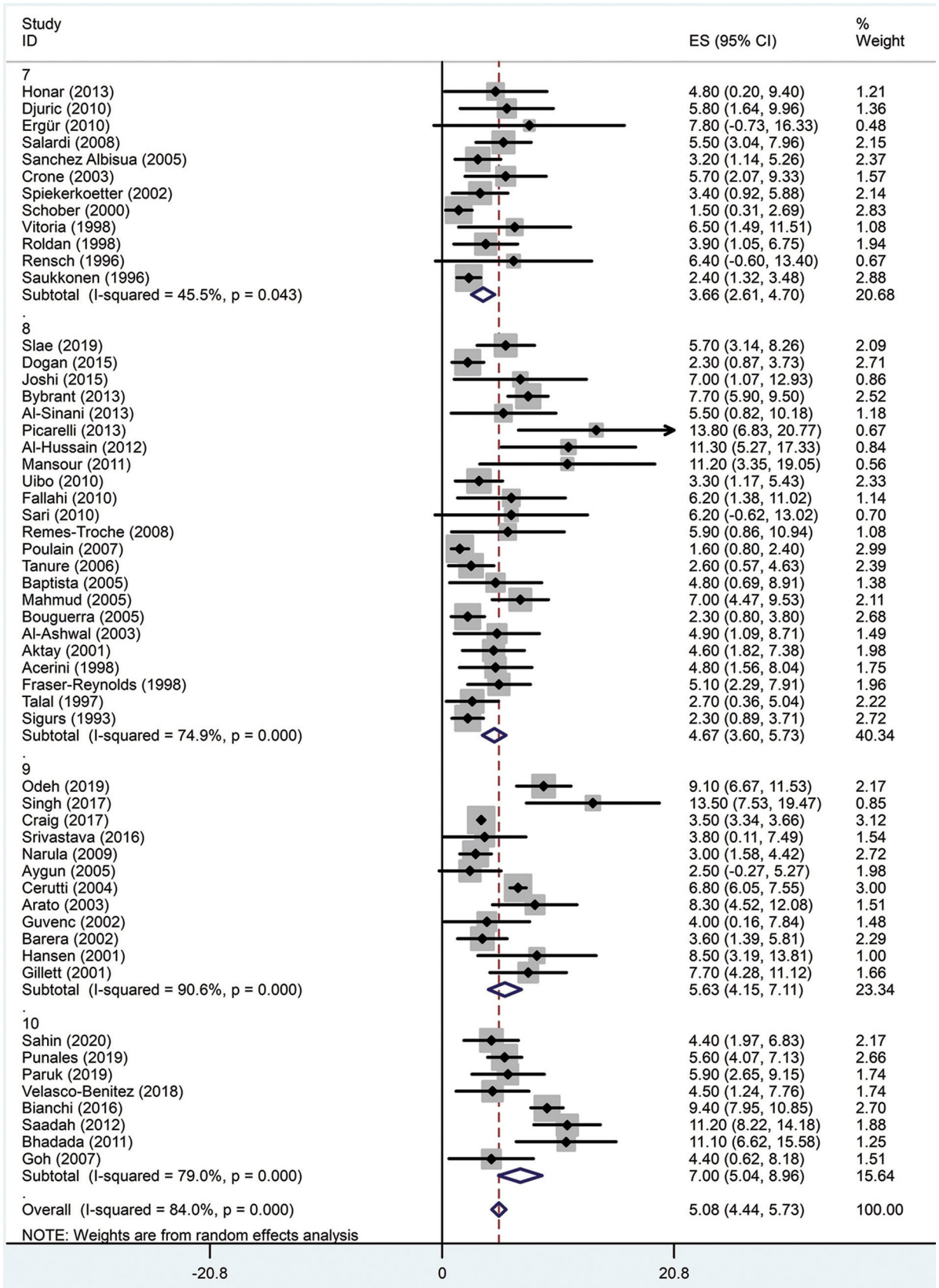

Figure 6. Results of subgroup analysis for quality of study score using a random-effects model (N = 55 studies)

Table 2. Results of meta-regression to investigate the effect of some variables on the pooled prevalence of Celiac disease (N = 55 studies)

Covariate	Estimate	Standard Error	t Value	P-Value
Publication year	0.027	0.0098	2.711	0.006
Place of study				
Asia	0.605	0.396	1.529	0.133
Australia	–0.166	0.543	–0.305	0.762
Europe	0.268	0.391	0.685	0.496
USA	0.181	0.411	0.441	0.662
Sample size	–0.001	0.001	–0.866	0.389
Quality of study score	0.971	0.351	2.77	0.008
Average age	0.0633	0.0792	0.80	0.424

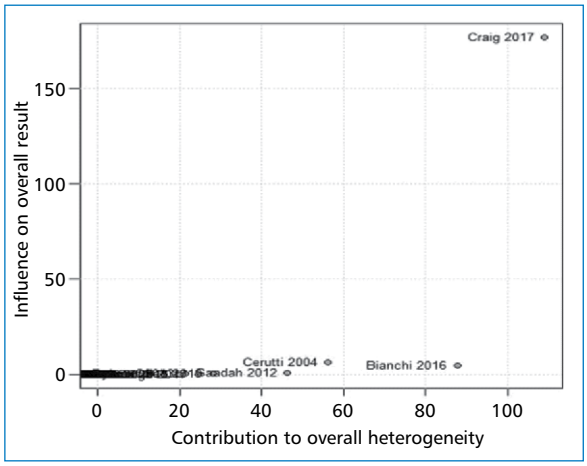

Figure 7. Baujat plot to identify influential studies on the pooled estimate of the proportion of celiac disease

tion, only studies published after 2008 (28 studies) had publication bias (Egger's test: bias = 0.0193, PV < < 0.001). Finally, for quality of study score, studies with quality scores 7 (12 studies, Egger's test: bias = 0.0206, PV < 0.001), 8 (23 studies, Egger's test: bias = 0.0266, PV < 0.001), had publication bias, while the quality of study score of 9 (12 studies, Egger's test: bias = 0.0201, PV = 0.056) and 10 (8 studies, Egger's test: bias = –0.059, PV = 0.795) had no publication bias.

Finally, a sensitivity analysis was conducted in which one study at a time was omitted and the pooled estimate of the prevalence was estimated. A Baujat plot [76] of the contribution to the overall heterogeneity and influence on the overall result was produced and presented in Figure 7. The graph in Figure 7 identified four studies [34, 35, 42, 59] that might have either changed the pooled estimate of the prevalence of I^2 with the study by Craig et al. [34] contributing when deleted the largest heterogeneity decrease in I^2 to 77.7% and overall estimated prevalence to 0.0520. It is worth noting that the study by Craig et al. had a very large sample size (n = 52,721). This is supportive of the presence of heterogeneity and influence on the overall pooled estimate.

In an attempt to identify outlying studies and in order to better understand the influence of some outlying studies on the pooled estimate of the prevalence of CD, a diagnostic plot was produced and presented in Figure 8. The diagnostic plot includes indices for identifying outlying studies like zstudentized residuals, Cooks distance, and difference in fits. The diagnostic plot revealed that the study by Bianchi et al. [35] and Saadah et al. [42] was flagged as outlying studies. A careful look at these studies revealed that these studies produced individual prevalence of 0.093 and 0.112, respectively which are among the highest individual study estimates of the prevalence of CD.

Discussion

In the present systematic review and meta-analysis, a total of 55 articles with a total sample size of 71,853 were examined. The pooled prevalence of CD in patients with T1D was found to be 5.08%; however, after the removal of 4 articles in a sensitivity analysis that had considerable influence on the total prevalence of the disease, a prevalence of a 5.20% was found. Moreover, due to the presence of publication bias, the trim-and-fill technique produced a pooled prevalence of 4.0%. Due to different clinical symptoms of CD, higher prevalence rates may have been estimated for CD. In a study aimed at examining the total prevalence of CD in the general population, Singh et al. found a prevalence of 0.5% that was much lower than the prevalence of disease in diabetic patients [77]. For many years, the comorbidity of the two diseases has received attention from researchers, and this comorbidity has been attributed to similarity in genetic susceptibility to both diseases

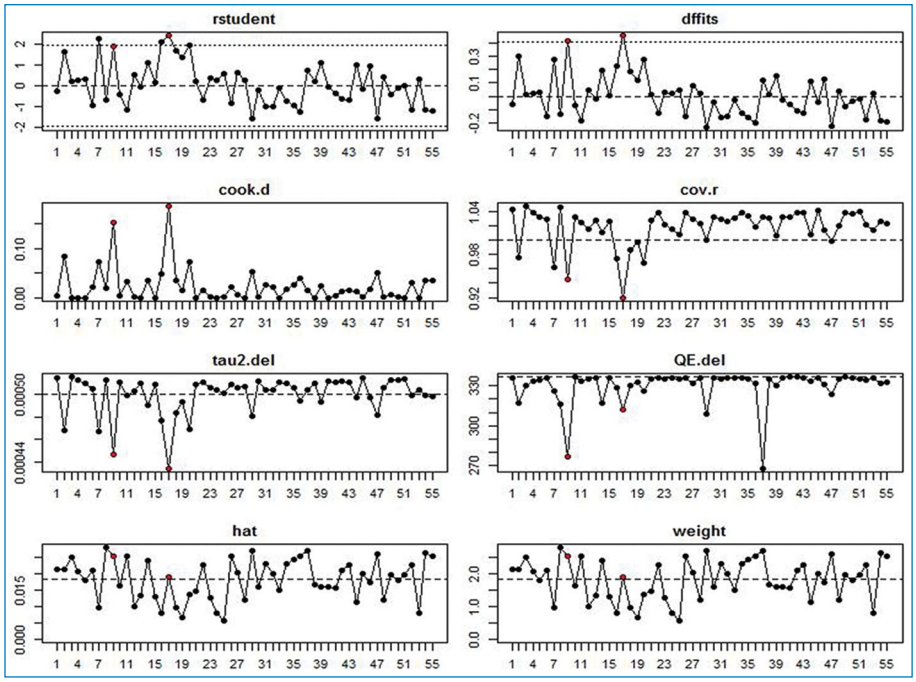

Figure 8. Diagnostic plots for estimating the pooled prevalence of celiac disease using 55 studies and the mixed-effects model identified study 9 [35] and 17 [42] as outlying studies (marked in red dot)

as a result of the DQA10501 and DQB10201HLA [78]. Patients recently diagnosed with diabetes are more vulnerable to Celiac disease than those with long-lasting diabetes; this indicates that the development of both diseases is related to some environmental factors [79].

Results of subgroup analysis showed that the prevalence of CD was higher in Asia (6.53%) than in the US (4.89%) and Europe (4.76%). A previous meta-analysis aimed at assessing the prevalence of CD showed that the highest and lowest prevalence rates for the disease were in Asia (1.8%) and Africa (1.1%), respectively [77]. A systematic review and meta-analysis by Singh et al. [80] showed that the prevalence of Celiac disease was 5% in all groups in Asia. In the present study, among the 19 studies conducted in Asia, 15 were from the Middle-East where wheat is commonly consumed as the staple food, and 4 studies were from India where wheat is eaten by part of the population and rice by another part as the staple food. These differences may be due to different prevalence rates of the HLA-DQ2/HLA-DQ8 haplotype and even due to different patterns of wheat consumption in these populations [81, 82]. Dubé et al. [83] also found that the prevalence of CD in European countries ranged from 3% to 6%; this finding is consistent with our results. The prevalence of CD was higher in the studies conducted after 2008 compared to those conducted before this date (6.37% vs. 4.14%). This finding can be attributed to the fact that screening parameters for CD have changed in recent years, so that older tests have been replaced by more sensitive and specific tests, such as the EMA and the tTG [84].

One of the limitations of this study was that gray literature was not included in the analysis. One of the strengths of this study is the novelty and comprehensiveness of these findings, which can be considered by many researchers.

Conclusion

About 5% to 10% of T1D patients test positive for anti-endomysium antibodies, and a major group of these patients shows abnormalities in biopsy of the intestine. More importantly, some of these patients test negative in the first screening, but they test positive in later screenings [37]; therefore, it is suggested that suspected cases should be repeatedly (and just one time) screened using the EMA antibodies, and biopsy should be considered if needed. CD is highly prevalent in patients with T1D compared to the general population; therefore, performing multiple screenings seems to have an important role in the early diagnosis of CD and preventing its complications in T1D patients.

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Conflict of interest

None.

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