Prevalence of celiac disease in patients with short stature: A systematic review and Meta-analysis

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ABSTRACT

Aim/ Background

Short stature is a common extra-intestinal manifestation of celiac disease (CeD). We conducted a systematic review and meta-analysis to assess the global prevalence of CeD in patients presenting with short stature.

Methods

We searched Medline and EMBASE databases for the keywords 'celiac disease, coeliac disease, anti-gliadin, tissue transglutaminase antibody, anti-endomysial antibody, short stature and growth retardation'. All the studies published from January 1991 to May 2020 were included. Patients without any prior evaluation for short stature were classified as all-cause short stature; while prior evaluated patients, where no cause was found for short stature, were classified as idiopathic short stature. Diagnosis of CeD was based on the European Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines. A random-effects model was used to pool the data.

Results

Seventeen studies screening 3759 patients (1582 with all-cause short stature and 2177 with idiopathic short stature) were included. The pooled seroprevalence of CeD based on positive anti-tissue transglutaminase antibody, anti-endomysial antibody was 11.2% (95% CI 4.0-21.2%;I^2=86%) and 9.7% (95% CI 2.7-20.2%;I^2=95%) for all-cause and idiopathic short stature, respectively. Similarly, pooled prevalence of biopsy-confirmed CeD was 7.4% (95% CI 4.7-10.6%;I^2=76%) and 11.6% (95% CI 4.1-22.2%;I^2=97%), for all-cause and idiopathic short stature, respectively. There was an overall severe risk of selection bias and significant heterogeneity in the pooled results.

Conclusions

Approximately 1 in 14 patients with all-cause short stature and 1 in 9 patients with idiopathic short stature had biopsy-confirmed CeD. Therefore, evaluation for CeD may be prudent in all patients with short stature.

Key words: idiopathic short stature, prevalence, Growth retardation, Enteropathy, Small intestine

INTRODUCTION

Celiac disease (CeD) is a chronic small intestinal immune mediated enteropathy which is precipitated by dietary exposure to gluten in genetically susceptible individuals.(1) With an estimated global prevalence of 0.7%, it is amongst the most prevalent autoimmune afflictions worldwide.(2,3) The spectrum of clinical manifestations of CeD varies and ranges from the classical manifestations such as chronic diarrhea, malabsorption to non-classical extra-intestinal manifestations such as iron-deficiency anemia, isolated growth failure, dermatitis herpetiformis and liver diseases.(4,5) Many of these extra-intestinal manifestations can occur in the absence of gastrointestinal manifestations. Hence, the diagnosis of CeD may be missed in patients presenting predominantly with non-classical manifestations unless we keep a high index of suspicion.

Short stature or growth failure is a complex clinical entity, its detection depends upon astute growth monitoring. A delay in the diagnosis of the cause of growth failure may preclude effective and timely management which can lead to long-term adverse consequences.(6,7) In most of the cases, short stature is attributable to constitutional and familial growth delays, however a significant proportion of the cases are secondary to readily treatable conditions.(8) Short stature is amongst the most common extra-intestinal manifestations of CeD.(9) A diagnosis of CeD and institution of gluten-free diet (GFD) in patients is associated with early catch-up growth for the initial 2-3 years.(10–12) Also, early diagnosis and compliance with GFD results in rapid recovery and patients may achieve normal adult height.(13–15) This suggests missed diagnosis of CeD can have significant therapeutic and prognostic implications in patients with short stature.

The extent to which CeD contributes to patients presenting with short stature is unclear. In a review, van Rijn reported that 1.7-8.3% of patients with short stature without prior endocrinological evaluation, have CeD as the cause of short stature.(16) Furthermore, in patients who had undergone evaluation for the cause of short stature, 18.6-59.1% of them had underlying CeD. Overall, the exact prevalence of CeD in short stature is not well known. It is unclear if the prevalence of CeD in short stature varies with gender and screening methods used. We therefore conducted a systematic review and meta-analysis to estimate the pooled prevalence of CeD in patients being evaluated for short stature.

METHODS

Search strategy

We searched MEDLINE and EMBASE databases up to 20th May 2020, for studies evaluating the causes of short stature. We used the key words "(*short stature, growth retardation) and (celiac disease or coeliac disease or anti-endomysial antibody or tissue transglutaminase antibodies or gliadin*)". Search strategy is detailed in the **appendix**. As the first modern guidelines for CeD were given by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in the year 1990, all studies from 1991 to 2019 were reviewed for inclusion.(17) Studies published after 1991 but recruiting patients before 1991 were excluded. The review was conducted and is reported according to the Preferred Reporting Items for Systematic Reviews And Meta-Analysis (PRISMA) guidelines.(18)

Study screening and selection

Two reviewers (ADS and NF) screened the titles and abstracts of potentially eligible studies from the above-mentioned platforms. Full-text articles were assessed for inclusion based on the following eligibility criteria: studies evaluating patients with short stature that performed baseline serological testing and/or small intestinal biopsies to assess for CeD. Studies which did not report clearly the number of patients subjected to serological and/or intestinal biopsy testing, and those that did not describe the criteria used for the diagnosis of CeD were excluded. We only considered articles published in the English language. Review articles, conference abstracts and case-series were excluded as it is difficult to perform quality assessment on these articles. Studies performed in gastroenterology clinics or only in patients referred for suspected CeD were considered to be at a very high-risk of selection bias. They were excluded.

Definitions

Short stature was defined as height less than the two standard deviation score or below the 3rd percentile of the accepted height for that age.(19,20) Patients who had never been evaluated for the cause of short stature were categorized as 'all-cause short stature' while those who were undiagnosed despite previous evaluation were defined as 'idiopathic short stature'. All patients having positive either IgG/ IgA anti-tissue transglutaminase antibody (anti-tTG-ab), IgA anti-endomysial antibody (anti-EMA) were considered as seropositive and the pooled number of this was used to define seroprevalence of CeD. CeD

was diagnosed on the basis of the following criteria: combination of a positive celiac serological test such as IgA anti-tTG-ab, anti-EMA or IgA anti-Gliadin antibody (IgA AGA) along with demonstration of villous abnormalities of ≥ modified Marsh grade 2. (21) If the serological data was negative or unavailable but there was presence of a villous abnormalities of ≥ modified Marsh grade 2 along with demonstration of clinical or histological response to GFD, the patients were diagnosed with CeD.(17) Patients having modified Marsh grade 1 villous abnormalities were considered as potential CeD. Studies which performed intestinal biopsies only for patients who screened positive on serology testing, were considered to have a sequential strategy for diagnosing CeD. Studies where all patients were subjected to intestinal biopsy irrespective of the serological findings were considered to have a parallel strategy for diagnosing CeD.

Data extraction

Data was extracted in duplicate by two reviewers (ADS and NF) using templates adapted from the Cochrane collaboration.(22) We extracted information on study and population characteristics, the country and continent where the study was conducted, proportion of patients having biopsy-confirmed CeD, grade of villous abnormalities as assessed by Marsh grading of the biopsies, presence of co-morbidities such as hypothyroidism and growth hormone deficiency amongst the biopsy confirmed CeD patients. The method of diagnosis used (sequential serology followed by biopsy or parallel serological testing and biopsy) was also noted. Any disagreements in study selection and data extraction were resolved through consensus between the reviewers (ADS, NF) and the corresponding author (GKM).

Risk of bias assessment

Risk of bias of all the included studies was assessed independently by each reviewer using the Risk of Bias tool for the prevalence studies developed and validated by Hoy et al.(23) The studies were evaluated on the basis of nine items and were rated on a binary scale. The first four domains assessed the external validity of the study by observing for selection and non-response biases. The remaining five items evaluated the parameters affecting the internal validity of the study like measurement bias, case definitions etc. Based on these parameters, the study was considered to have low, moderate or high risk of bias.

Statistical analysis

Weighted pooled prevalence was calculated for the study outcomes of seroprevalence and prevalence of CeD. The inter-study heterogeneity was estimated using Chi-square and I^2 statistics. Studies with I^2 <30%, 30-50%, 50-75% and >75 % were considered to have low, moderate, substantial and considerable heterogeneity, respectively.(24) We used the Freeman–Tukey double-arcsine transformation for variance stabilization of the proportions. Subgroup analyses were performed to identify and explain potential sources of heterogeneity. Meta-regression analysis was performed for the variables of age, gender, screening strategy, and type of serology used. For subgroup and meta-regression analysis, all studies were combined for the outcome of biopsy-proven CeD only. The *a priori* hypotheses to explain heterogeneity were that it was due to differences in diagnosing CeD like sequential testing versus parallel testing, region of the study, study design, type of serology used and the gender of the subject. Analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) using the "robumeta"(25) and "metafor" (26) packages.

RESULTS

Study selection

Our literature search retrieved 1162 article titles, of which 71 were found eligible for full-text review and eligibility assessment. The eligibility criteria were fulfilled by 17 studies and they were finally included in the systematic review and meta-analysis.(27–43) The reasons for excluding the remaining studies are summarized in **Figure 1**. In case of multiple publications by the same group of authors involving the same group of patients (28,44), the paper with better quality and with detailed reporting of methods and results was included in the final analysis.(28) Studies with unclear methodology, such as lack of adequate description of screening methods (45–48), inclusion of patients having failure to thrive and not short stature (49), and studies where diagnosis of CeD was not definitive (50), were excluded. Studies utilizing only IgA AGA for serology testing were excluded from analysis for seroprevalence of CeD.(27,30,37) As these studies used parallel testing strategy and all the included patients were biopsied, they were included for the analysis of biopsy-proven CeD.

Characteristics of included studies

We extracted data from 17 studies including a total of 3759 patients. All the studies except for the study by Hill et. al (35) were hospital-based, and single-center studies. The characteristics of the studies are summarized in **Table 1.** The mean age of patients ranged from 6.4 years to 16.8 years, and there was a male preponderance (45%-73%). All-cause short stature was evaluated in six studies comprising of 1582 patients (28,33,36,39,40,43) while the remaining 11 studies included 2177 patients with idiopathic short stature.(27,29–32,35,37,38,41,42,51) In six studies evaluating idiopathic short stature, the respective investigators had biopsied all the screened patients (27,29,30,32,34,37); in the remaining 11 studies, patients underwent duodenal biopsies sequentially once they were found to be seropositive for CeD.(28,31,33,35,36,38–43) IgA AGA were used by three studies (27,30,37), rest of the studies used anti-tTG-ab(28,29,33,34,40,41) or anti-EMA.(32,35,38,42) None of the studies reporting seroprevalence of CeD in patients with short stature used anti-deamidated gliadin peptide antibodies for screening. Study by Singh et al had 432 included patients of which only 285 patients were sequentially screened for CeD.(40) Only these 285 patients were considered for the pooled calculation of prevalence in the meta-analysis.

Bias assessment of the included studies

Risk of bias was assessed for each study. All the studies used the accepted definitions for CeD and short stature. Majority of the studies were from tertiary care/referral centers thus not representing the general population of short statured children in community. In addition, many studies had not performed/ reported random or consecutive sampling which further adds to selection bias. Most of the studies had significant risk of selection bias. As selection bias can have a major role in the reported prevalence of a study, the overall risk of bias was considered high in the studies **(Table 2).**

Outcomes

Seroprevalence and prevalence of biopsy-confirmed CeD in patients with all-cause short stature

Three studies evaluating patients with all-cause short stature reported the seroprevalence of CeD.(28,33,43) Of 469 patients included in the analysis, 61 were seropositive for CeD. Thus, the pooled seroprevalence of CeD in patients with all-cause short stature was 11.2% (95% CI 4-21.2%; I^2=86%) (**Figure 2)**. Of 1582 patients of all-cause short

stature evaluated in six studies (28,33,36,39,40,43), 123 were found to have biopsy-confirmed CeD, resulting in a pooled prevalence of 7.4% (95% CI 4.7-10.6%; I^2= 76%) (**Figure 3**).

Seroprevalence and prevalence of biopsy-confirmed patients with CeD in patients with Idiopathic short stature

Amongst the studies on idiopathic short stature, Bozzola et al. did not report the seroprevalence of the included patients.(31) Of 944 patients included from 7 studies, 79 were seropositive for CeD, thus the pooled seroprevalence was 9.7% (95%CI=2.7-20.2%; I^2=95%) (**Figure 2).**(29,32,35,38,41,42,51) There was significant heterogeneity amongst the studies evaluating seroprevalence of CeD in idiopathic short stature. All the studies were included to calculate the pooled prevalence of biopsy-proven CeD. Amongst 2177 patients with idiopathic short stature evaluated in 11 studies (27,29–32,35,37,38,41,42,51), 145 were found to have biopsy confirmed CeD, resulting in a pooled prevalence of 11.7% (95% CI 4.1-22.2%; I^2=97%) (**Figure 3**).

Subgroup and meta-regression analyses

Subgroup analyses and meta-regression was performed to explain the heterogeneity. The proportion of males in the study population negatively influenced the prevalence of CeD (estimate -0.009, 95% CI [-0.01, -0.0003], p value=0.04,). On meta-regression, age distribution of the study population, type of serology used, type of study (retrospective or prospective) did not affect the overall prevalence of CeD. All the various subgroups evaluated are summarized in **Table 3.** Studies which sequentially biopsied on seropositive short stature patients had a prevalence of 4.5% (95% CI 3-6.2%; I^2=91.7%)(28,31,33,35,36,38–43), while studies which biopsied all the included patients were found to have a much higher prevalence of CeD i.e. 33.8% (95% CI 18.2-49.4%; I^2=91.9%).(27,29,30,32,34,37) On meta-regression analysis, studies which sequentially screened patients with serology followed by biopsy negatively impacted the overall pooled prevalence of CeD (estimate: -0.19, 95% CI [-0.32, 0.06], p value=0.003). The number of studies evaluating the seroprevalence were limited to assess regional distribution or the trend over time.

DISCUSSION

In this systematic review and meta-analysis including 3759 patients with short stature, we observed that 1 in 14 patients of all-cause short stature and 1 in 9 patients of idiopathic short stature have biopsy-confirmed CeD. The prevalence of CeD in this subset of patients was not affected by the mean age of the patients, or the type of serological tests performed. There was significant heterogeneity in the reported studies. Our findings suggest that CeD is an important cause for short stature and especially in patients presenting with idiopathic short stature. These patients must be evaluated for CeD, even when other clinical conditions are suspected.

To the best of our knowledge, this is the first systematic review and meta-analysis to report the global pooled prevalence of CeD in patients with short stature. While a systematic literature search was not done, Van Rijn et al. had collated the data of CeD in patients with short stature, and reported a prevalence of CeD varying from 1.7% to 8.3% in patients who had never been evaluated for short stature and a prevalence of 18.6% to 59.1% in patients in whom prior endocrinological causes had been excluded.(16) Most of the studies included in the review by Van Rijn et al were conducted before the standard definition of CeD was available.(17) A recent systematic review evaluated the prevalence of CeD in patients with short stature in Saudi Arabia.(52) They found an overall pooled seroprevalence of 16.1% and biopsy proven prevalence of 6.75% in their studies. Of the five included studies in the above review, only one study was included in our review.(29) Three of the studies were excluded as the number of patients subjected to the screening of celiac disease was unclear(46–48), and one study was only an abstract.(53) Also, no quality assessment of the included studies was performed.

The standard definition of short stature (height below 2 standard deviation) may include many normal individuals, patients with familial short stature and constitutional growth delays.(54,55) A considerable number of patients with all-cause short stature were found to have underlying celiac disease and this number was even higher in patients with idiopathic short stature. This group of patients may have been missed during the initial stages of the evaluation, as many patients with CeD and short stature do not have any gastrointestinal symptoms.(10,56) As the more common causes of short stature were prior excluded in patients with idiopathic short stature, there could have been higher suspicion to test for CeD in these patients. This could have also influenced the higher prevalence in this

patient population. Malabsorption secondary to the villous atrophy is the most likely contributor to short stature in these patients. However, it is also postulated that the ongoing inflammatory process especially elevation of pro-inflammatory cytokines like IL-6, TNF-α, IL-1 results in the dysregulation of growth hormone secretion.(57–59) Also, delayed detection of CeD has been associated with shorter adult heights as compared to normal population.(60,61) This further emphasizes the significance of timely detection of CeD in this subset of the population.

We identified several factors that could influence the prevalence of CeD among children with short stature. Considering that the prevalence of CeD is higher in females (2,62,63), the meta-regression analysis showed the proportion of males in the screened populations negatively influenced the reported prevalence of CeD in the studies. The differences in the proportion of males and females in studies investigating the prevalence of CeD in patients with short stature could have affected the prevalence of CeD in this population. Another reason for heterogeneity was the method of diagnosis of CeD. Studies which performed duodenal biopsies in all the included patients (27,29,30,32,34,37) had a higher prevalence of CeD as compared to the studies with a sequential diagnostic strategy. These studies where duodenal biopsies were performed in all patients included patients with idiopathic short stature which could have contributed to the increased prevalence of CeD. The studies with sequential biopsies included patients with idiopathic as well as all-cause short stature. Furthermore, relying on single serology as the sole screening strategy in high-risk populations may underestimate the prevalence of CeD. This is due to a significant intra and inter-test variation in the diagnostic accuracies of commercially available IgA tTG-ab assays. A recent validation study showed that the false-negative rate for commercially available IgA tTG-ab assays could be as high as 24%.(64) A significant proportion of CeD patients may be missed if a single negative IgA–anti-tTG result is relied on to screen patients for CeD. Also around 2% CeD patients may have seronegative CeD in presence of normal IgA levels which can be diagnosed by duodenal biopsies. (65,66) These observations and the high yield of CeD testing in idiopathic short stature, we suggest pursuing upper endoscopy in all cases of idiopathic short stature even if serological screening is negative. Otherwise, a screening strategy with more than one IgA anti-tTG-ab assays can also be considered to ensure the test is not false negative.

We found that studies which included small number of subjects (n <200) yielded a much higher prevalence as compared to studies which included a larger number of subjects (n >200) (17.2% vs 3.9%, P value- 0.006). The study with the smallest number of patients (n=49) showed the prevalence of CeD to be as high as 59.2% (30) as compared to the study which included the largest number of subjects (n=1066) which showed a prevalence of 1.1%.(31) This might be due to selection bias and referral bias in smaller studies. The largest study utilized anti-EMA for testing which may have resulted in the some false negative tests due to the test's low sensitivity as compared to anti-tTG antibodies.(67) Also, the study screened asymptomatic children without diarrhea or anemia. This could have further lowered the prevalence of CeD in this group of patients which was similar to the disease prevalence in the general population. (2)

The recent update in the diagnosis of CeD on the basis of serology alone may further enhance the evaluation of the patients with short stature.(68) Per the recent ESPGHAN guidelines, a patient with anti-tTG-ab levels ≥10 times upper limit of normal along with positive anti-EMA on a second blood draw can be diagnosed with CeD. This suggests that CeD can be diagnosed without duodenal biopsy in a subset of patients with short stature. However, it is important to note that in patients not meeting the abovementioned criteria, duodenal biopsy should be performed to confirm the diagnosis. Also, duodenal biopsy may improve the yield of diagnosis in patients with high clinical suspicion like those with short stature and concomitant anemia or chronic diarrhea or with idiopathic short stature even when the serological tests are negative.

Strengths of the present systematic review include inclusion of a large number of studies drawn from two large databases. This allowed us to the appraise the present evidence on the prevalence of CeD in patients with short stature. It also afforded us to evaluate the seroprevalence and prevalence of CeD in patients with all-cause short stature and idiopathic short stature. To explain the heterogeneity of the pooled results, subgroup analysis and meta-regression was performed. A thorough assessment of the various factors which could influence the results was done.

Limitations of the study included high-risk of bias for many of the included studies thereby lowering the quality of the studies that described the prevalence of CeD in patients with short stature. There was no uniformity in the patient screening and selection process. Most of the studies were conducted at tertiary care centers, hence there is an inherent risk of referral bias in these study populations and they may not be truly reflective of the prevalence

in the general population. As the mean age of the patients was 6.4 to 16.8 years, the data is more relevant to the children and adolescents with short stature. These shortcomings should be considered while interpreting the results of this meta-analysis.

In conclusion, approximately 1 in 14 patients with all-cause short stature and 1 in 9 patients with idiopathic short stature have biopsy-confirmed CeD. However, the results should be interpreted with caution given significant heterogeneity in pooled analysis and high selection bias as most of the studies were from tertiary care centers. The results of present systematic review and meta-analysis supports the screening of patients with short stature for celiac disease.

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Table 1: Characteristics of the included studies

Author, year, ref	Study Year	Country	Type of Study	Evaluation	Short Stature definition	Number of patients screened	Serology type performed	Number serology performed	Number serology positive	Biopsy strategy	CeD diagnosed
Abd El Dayem, 2010 (27)	2004-07	Egypt	Prospective Study	Idiopathic short stature	< -2.5 SDS	67	IgA anti-AGA	67	18	Parallel	23
Ahmad, 2010 (28)	2006-07	India	Prospective Study	Severe Short Stature	< -3SD	112	anti-tTG-ab	112	23	Sequential	15
Assiri, 2010 (29)	2002-2008	Saudi Arabia	Prospective study	Idiopathic short stature	5th centile	91	IgA anti-tTG-ab	91	10	Parallel	10
Bonamico, 1992(30)	-	Italy	Prospective Study	Idiopathic short stature	< 3rd Percentile, Velocity < -2.5 below average, 25th percentile	49	IgA anti-AGA	49	13	Parallel	29
Bozzola, 2005(31)	-	Italy	Prospective Study	Idiopathic short stature	< 3rd Percentile	1066	Anti-EMA	1066	-	Sequential	12
Dehghani, 2008(33)	2003-2005	Iran	Prospective Study	All-cause short stature	< -2 SDS	72	IgG anti-tTG-ab	72	2	Sequential	2

Hashemi, 2008(34)	2003-2005	Iran	Prospective Study	Idiopathic short stature	< 2nd centile	104	IgA anti-tTG-ab	104	31	Parallel	35
Hussein, 2017(36)	2012-2015	Egypt	Descriptive observational Prospective Study	All-cause short stature	< -2 SDS, <3rd Percentile	637	IgA anti-tTG-ab	-	-	Sequential	42
de Lecea, 1996(32)	-	Spain	Prospective Study	Idiopathic short stature	< 3rd percentile	118	IgA anti-EMA	65	20	Sequential	22
Queiroz, 2004(38)	-	Brazil	Prospective Study	Idiopathic short stature	<3rd percentile	106	IgA anti-EMA	106	6	Sequential	5
Rabbani, 2013(39)	2011	Pakistan	Cross sectional study	All-cause short stature	<-2 SDS/ 3rd Percentile	169	IgA anti-tTG-ab	-	-	Sequential	6
Singh, 2015(40)	2008-2011	India	Retrospective cohort study	All-cause short stature	< -2 SDS, 5 centile, slow velocity	432	IgA anti-tTG-ab	285	36	Sequential	36#
Sisley, 2013(41)	2008-2011	USA	Retrospective chart review	Idiopathic short stature	<3rd percentile	235	IgA anti-tTG-ab	235	3	Sequential	1
Tumer, 2001(42)	-	Turkey	Prospective Study	Idiopathic short stature	< 3rd Percentile	84	IgA anti-EMA	84	7	Sequential	7
Abduljabbar, 2014 (43)	2008-2010	Iran	Prospective Study	All-cause short stature	< 3rd Percentile	307	IgA anti-tTG-ab	307	-	Sequential	22
Hill, 2000	-	USA	Prospective	Idiopathic	<-2 SDS	259	IgA anti-	259	2	Sequential	1

(51)			Study	short stature			EMA				
Oliveira, 1998(37)	1993-1994	Brazil	Prospective Study	Idiopathic short stature	< 3rd Percentile	51	IgA anti-AGA	51	0	Parallel	0

Abbreviations: anti-AGA- Anti-Gliadin antibodies, anti-tTG-ab: anti-tissue transglutaminase antibody, anti-EMA: anti-endomysial antibody, SD: standard deviation, -: not reported.

Footnotes: All the studies were hospital-based studies. Sequential- patients were subjected to intestinal biopsy only if serological tests were positive, All- all the included patients were subjected to biopsy, - Not reported, #Of 432 patients, but only 285 patients underwent consecutive screening for celiac disease with serological tests for detection of celiac disease. 36 patients were diagnosed after the screening while there were 47 total patients with CeD.

Table 2. Risk of Bias assessment of the included studies

Author, year, ref	Center	Was the study population close representative of national population?	Was the sampling frame the true representation of the target population?	Was some form of random sampling or Census taken?	Was the likelihood of non-response minimal?	Was the data collected directly from patients?	Was an acceptable case definition used?	Did the study instrument have reliable validity?	Was same mode of collection used for all subjects?	Were the numerator and denominator for the parameter of interest appropriate?
Abd El Dayem, 2010 (27)	Single	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ahmad, 2010 (28)	Single	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Assiri, 2010 (29)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Bonamico, 1992(30)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Bozzola, 2005 (31)	Single	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dehghani, 2008 (33)	Single	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hashemi, 2008 (34)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Hussein	Single	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

2017 (36)										
de Lecea, 1996 (32)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Queiroz, 2004 (38)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Rabbani, 2013 (39)	Single	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Singh, 2015 (40)	Single	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Sisley, 2013 (41)	Single	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
Tumer, 2001 (42)	Single	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Abduljabbar, 2014 (43)	Single	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Hill, 2000 (51)	Two	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Oliveira, 1998 (37)	Single	Yes	No	No	No	Yes	No	Yes	Yes	Yes

Footnotes: overall risk of bias is based on subjective assessment of the study. Adapted from Hoy et al. (23)

Table 3: Subgroup analysis

Scenario	Number of studies (study references)	Pooled prevalence (95% CI)
Study size		
Less than 200 patients	11 (27–30,32–34,37–39,42)	17% (10- 47%)
More than 200 patients	6 (31,35,36,40,41,43)	39% (19-58%)
Study design		
Prospective studies	14 (27–30,32–35,37,41,42)	14% (5-22%)
Retrospective and cross-sectional studies	3 (38,40)	7% (1-12%)
Criteria for intestinal biopsy		
Only if serology positive (sequential)	12 (28,31–33,35,36,38–43)	6% (3-9%)
All included patients (parallel)	5 (27,29,30,34,37)	27% (7-47%)
Type of serological test used*		
Anti-endomysial antibody	4 (27,29,30,34,37)	11% (0- 23%)
Anti-tTG antibody	6 (28,29,33,34,40,41)	12% (4-21%)
Anti-gliadin antibody	3 (27,30,37)	17% (0-35%)
Study region		
Europe	3(30–32)	25.9% (0.48,50.1%)
North America	2(35,41)	0.4% (0, 0.9%)
Middle-eastern countries	7(27,29,33,34,36,42,43)	12.7% (7.5, 18.0%)

South-east Asia	3(28,39,40)	9.6% (2.5, 16.6%)
South America	2(37,38)	4.7% (1.5, 10.6)
Time of publication		
Studies before year 2000	4(30,32,35,37)	18.8% (0,41.4%)
Studies after the year 2000	13(27–29,31,33,34,36,38–43)	8.1% (5.61,10.5%)

Abbreviations: anti-tTG- tissue transglutaminase

*This was the pooled seroprevalence.

APPENDIX

Search strategy

First Search Date: 5 February 2019

Database: Embase <1974 to 2019 February 05>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to February 05, 2019>

Search Strategy:

#9.	('short stature' OR 'growth retardation') AND (('celiac disease'/exp OR 'celiac disease') OR ('anti endomysial' AND antibody) OR 'tissue transglutaminase' OR (non AND tropical AND sprue))	1056
#8.	('celiac disease'/exp OR 'celiac disease') OR ('anti endomysial' AND antibody) OR 'tissue transglutaminase' OR (non AND tropical AND sprue)	34,607

#7.	'short stature' OR 'growth retardation'	71,969
#6.	'growth retardation'	54,073
#5.	'short stature'	20,187
#4.	non AND tropical AND sprue	126
#3.	'tissue transglutaminase'	4,299
#2.	'anti endomysial' AND antibody	450
#1.	'celiac disease'/exp OR 'celiac disease'	33,063

Legends:

Figure 1: PRISMA flow diagram of the study

Figure 2: Forest plot showing the seroprevalence of celiac disease in patients with short stature

Figure 3: Forest plot showing the biopsy-proven prevalence of celiac disease in patients with short stature

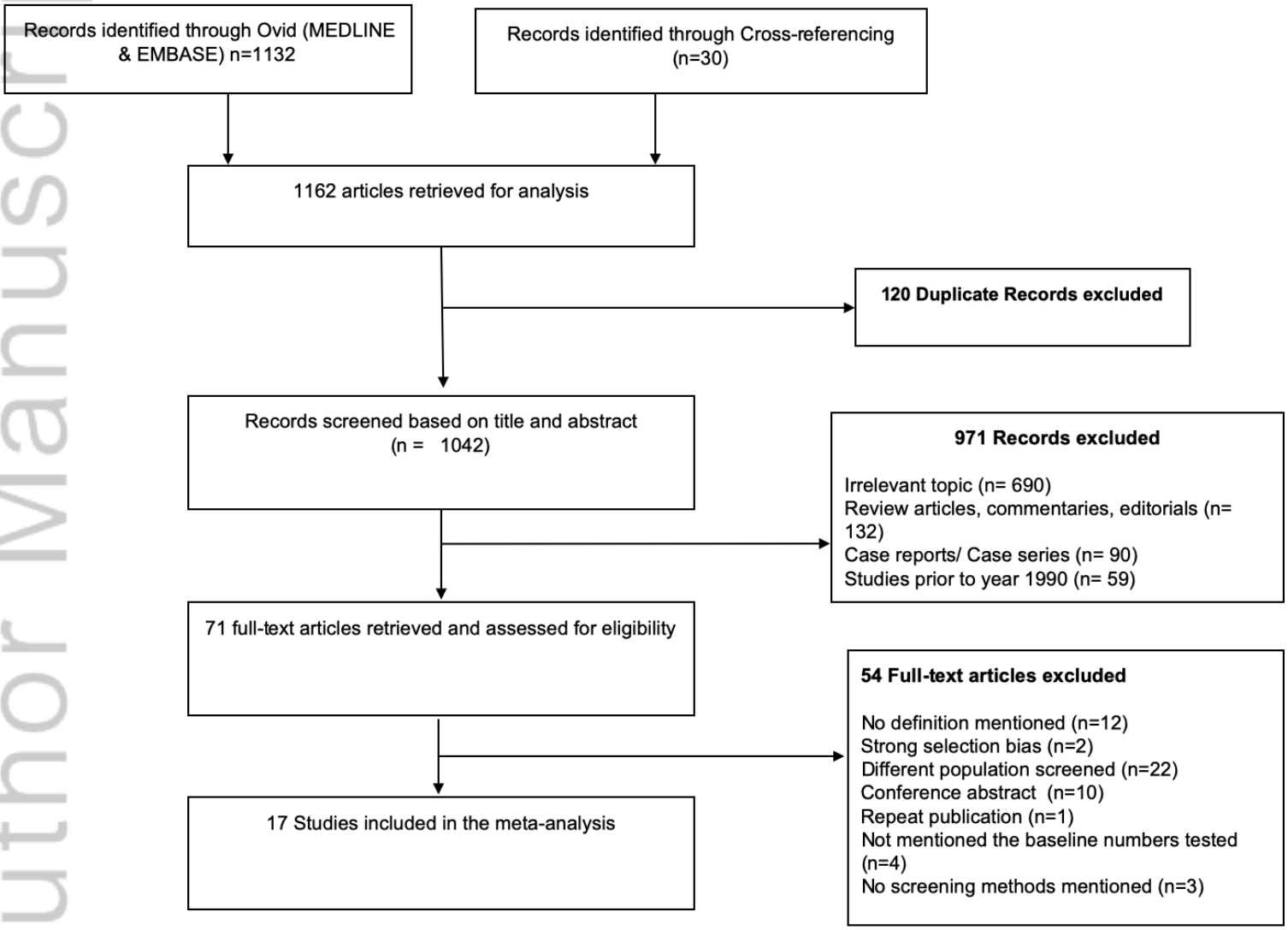
MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	7
2	Hypothesis statement	-
3	Description of study outcome(s)	5,6
4	Type of exposure or intervention used	-
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, title
8	Search strategy, including time period included in the synthesis and key words	6, appendix
9	Effort to include all available studies, including contact with authors	6
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)	6
13	List of citations located and those excluded, including justification	9, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the	6-8

	hypothesis to be tested	
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-8
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	8
24	Provision of appropriate tables and graphics	Tables 1-2,supplement Figs 1,2 supplement
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 2, supplement
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Table 3
28	Indication of statistical uncertainty of findings	11

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Table 2
30	Justification for exclusion (eg, exclusion of non-English language citations)	8,9
31	Assessment of quality of included studies	Table 2ß
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14,15

34	Guidelines for future research	-
35	Disclosure of funding source	15



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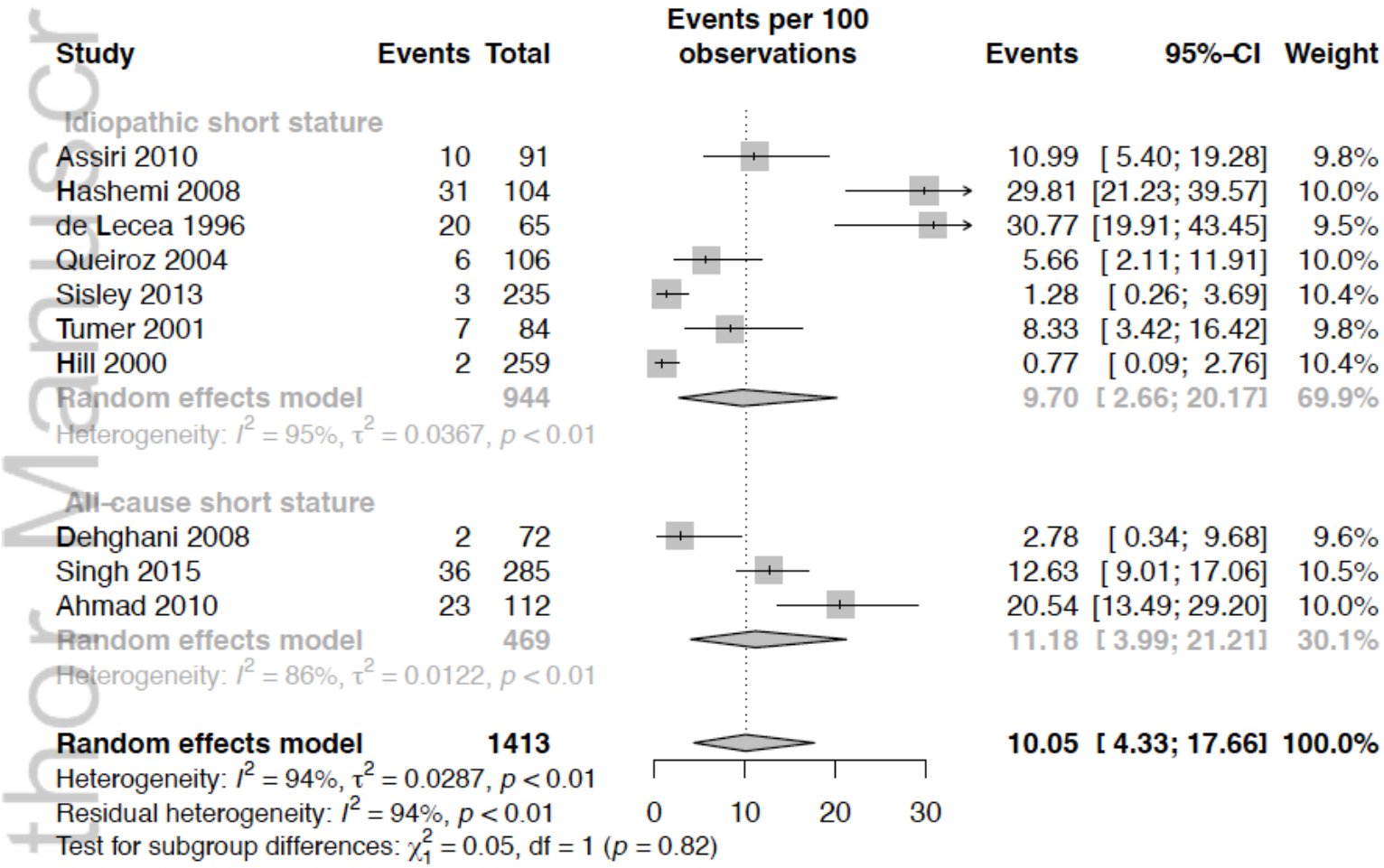

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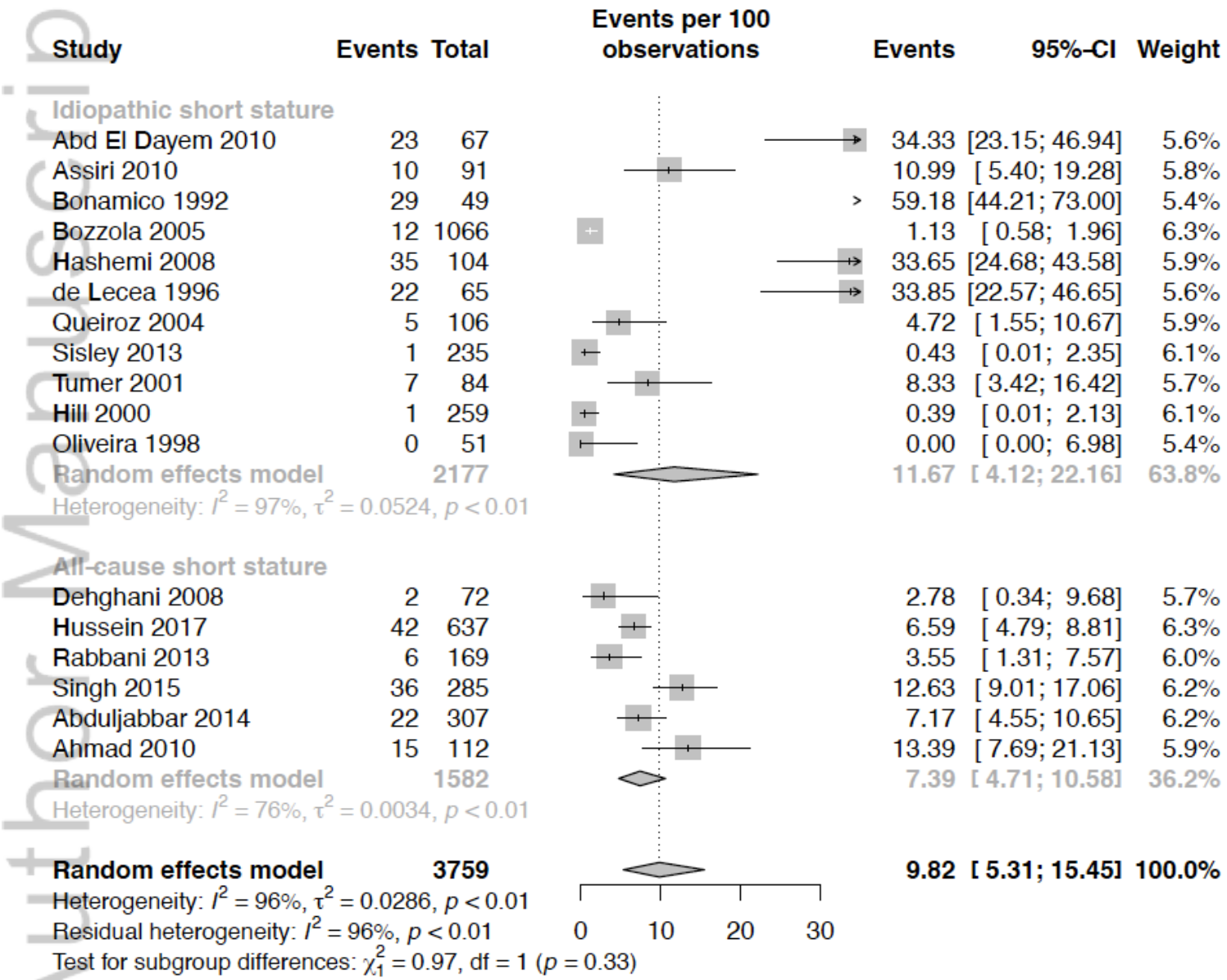

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