

Prevalence of Celiac disease in Saudi Arabia: Meta-analysis

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Abstract

Aim: Meta-analysis for the prevalence of celiac disease (CD) in Saudi Arabia (SA).

Methods: The related articles were retrieved by database and journal search. The relevant data from each article were analyzed by using the statistical package for social science (IBM SPSS Inc) and by using the Comprehensive Meta-analysis program (CMA).

Results: Only seven related articles were found; comprised of three groups: A- Four articles discussing the prevalence in the general population; Meta-analysis for these four articles showed that seroprevalence of CD (one serology at least) (by fixed model) was 2.7% (95% CI = 2.4–3.0) with no heterogeneity ($I^2 = 0.00$), while the prevalence of Biopsy-Proven CD (for two articles) was 1.4% (95% CI = 1.2–1.7) with high heterogeneity ($I^2 = 59.3$). B- One article reported the prevalence in at-risk population as 6.9% and 18.4% for the biopsy-proven CD and the seroprevalence respectively. C- Two letters to the editor commenting that the prevalence (1%) reported (in one of the two articles of group A) for biopsy-proven CD was misleading due considering the patients that refused endoscopy as negative histology.

Conclusion: The current study represents the first and only meta-analysis concerning the prevalence of CD in SA. Prevalence of biopsy-proven CD (1.4%) was lower than the seroprevalence (2.7%), but with higher heterogeneity. Refusing endoscopy is common, that may affect the accuracy of prevalence of biopsy-proven CD, if not taken into consideration.

Introduction

Globally celiac disease's prevalence is 0.588%–1%, [1–2] ranging from 0.33% to 2.5% [1]. Initially, prevalence of celiac disease was estimated at about 0.02% [3]. The subsequent increases in prevalence may be due to changes in diagnostic practice [4], in addition to less exposure to bacteria and other pathogens in Western environments [2]. However, data from northern America shows strong variation in CD prevalence between 0.057% in the clinically defined CD and 1% in the serologically proven CD (presence of IgA TG in blood donors) [5]. Keeping in mind that 85% of the affected subjects are undiagnosed due to variation in signs and symptoms [6], CD can be asymptomatic and because many clinicians are unfamiliar with the CD [7].

Studies using serology and biopsy indicate a prevalence of 0.33–1.06% in children (5.66% in children of the predisposed Sahrawi people [8]) and 0.18–1.2% in adults [9]. The prevalence, among adult blood donors in Iran, Turkey and Syria was 0.60%, 1.15% and 1.61% respectively [10].

In Africa, Japan and China CD is rarely diagnosed [11], reflecting a very low prevalence of the genetic risk factors, such as HLA-B8 [12]. But similar risk was reported in Indians and Western Caucasians [10].

Concerning, the primary care populations with gastrointestinal symptoms, the prevalence was about 3% [13].

Concerning the At-risk groups, the prevalence ranging from 5% to 10%, include Down and Turner syndromes, type 1 diabetes, and autoimmune thyroid disease [3]. In the USA, the prevalence was found to be 0.75% in not-at-risk groups, 1.8% in symptomatic people, 2.6% in second-degree relatives and 4.5% in first-degree relatives, with similar profile in Europe [10].

So far, only seven articles concerning the CD prevalence in SA were retrieved by a comprehensive database and journal search [14]. Here,

we present description and Meta-analysis for the literatures concerning the prevalence of celiac disease in Saudi Arabia.

Methods

Strategy for systematic search and study selection

The related articles were retrieved by database and journal search. The selection process (inclusion/exclusion) of the pertinent studies was described in detail in our previous analytical review in this journal [14]. Using different key words (“celiac disease in Saudi Arabia”, “celiac disease in Saudi children” and “prevalence of celiac disease in Saudi Arabia”), an electronic literature search was conducted via PubMed (US National Library of Medicine, with no specific period), Ovid, EBSCO and scholar Google; in addition to few related articles obtained through the library of king Fahd research centre of King Abdulaziz University, and directly from the editorial department of the two local journals (Saudi Journal of Internal Medicine and Journal of King Abdulaziz University Medical Science). All the retrieved articles were checked for matching (duplication) via their titles, author(s) and year of publication. Selection of the pertinent studies was achieved via two processes. After matching (for duplication), articles that were concerned with celiac disease in Saudi Arabia were selected (first selection) and

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Key words: Saudi Arabia, Celiac disease prevalence, Coeliac disease prevalence, Celiac disease epidemiology, Celiac disease seroprevalence, Celiac disease meta-analysis, Heterogeneity

Received: July 24, 2018; **Accepted:** August 14, 2018; **Published:** August 16, 2018

their data were recorded using statistical package for social science (IBM SPSS Inc), Version 20. Chicago. Articles that are concerned with the prevalence discipline were further selected (second selection) and kept as a separate SPSS file that was used in this study.

Statistical analysis

Analysis of data was performed using statistical package for social science (IBM SPSS Inc), Version 20, Chicago; and by using the Comprehensive Meta-analysis program (CMA), Version 3. software program (Biostat, USA). Heterogeneity was calculated using I squared (I^2). I^2 values of 0%, <25%, 25% to 49% and > 50% denoted no, low, moderate, and high heterogeneity, respectively. The results were illustrated in tabulated form, diagrams and figures.

Results

Selection and characterization of the pertinent studies (Figure 1 & Table 1)

As described above, after matching (for duplication), data from articles (74 articles) that were concerned with celiac disease in Saudi Arabia (Figure 1) were recorded using statistical package for social science (IBM SPSS Inc), Version 20. Chicago. Articles that are concerned with celiac prevalence (7 articles) were selected and kept as a separate SPSS file that was used in this study. Characterization of these studies with their serological/biopsy pattern are shown in Table 1. The seven related articles were comprised of three groups (Figure 1): A- Four articles discussing the prevalence in the general population

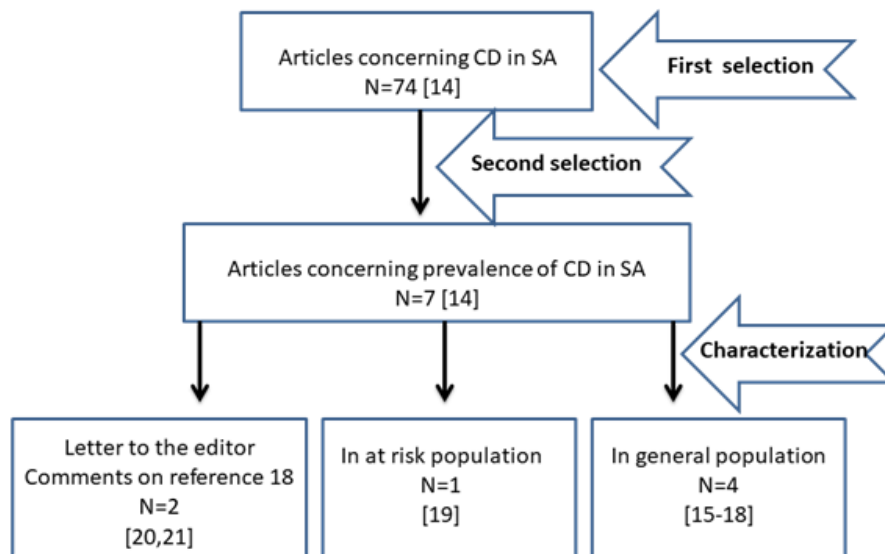


Figure 1. PRISMA flow-diagram showing the selection process of pertinent studies

Table 1. Characterization of identified studies on prevalence of celiac disease (CD) in Saudi Arabia, with their serological/biopsy pattern*

	Author(s) and date of article [ref] (region(s))	Age ranges (mean) /year	Cohort	Seroprevalence (F/M) (156/82=1.9)	Prevalence of Biopsy-Proven CD	Serology with/without biopsy?
1	Al-Hussaini A, et al. 2017 [15] (Riyadh)	6-15	7930 Students	221/7930=2.78 (81/38)	Biopsy and/or ESPHAN criteria (119/7930=1.5%)	TTG-IgA, EMA-IgA, and biopsy
2	Khayyat YM. 2012 [16] (Blood bank/Jeddah)	14-78 (35)	204 (Blood bank)	3/204=1.5 (1/2)	Not performed	TTG-IgA
3	Aljebreen AM, et al. 2013 [17] Aseer, Al-Qaseem, Madinah	16-18	1167 students from the 10th to 12th grades	26/1167= 2.2% (17/9)	Biopsies were not available	IgA and IgG EMA
4	Al Hatlani MM. 2016 [18] Students Eastern Province	6-18	1141 Students	32/1141=3% (17/15)	1% (misleading [20,21]) -Cohort without those who refused biopsy (1141-22=1119)→ Prevalence (10/1119=0.9%)	IgA-tTG and IgG-tTG and biopsy Biopsy was performed for 10 of whom were antibody positive. All 10 were biopsy positive.
5	Al-Hakami AM 2016 [19] Asseer	1-79	315 Aseer Central Hospital	58/315= 18.4 (40/18)	6.9 % (misleading) Cohort without those who refuse biopsy (315-18=287) →Prevalence (22/297=7.4%). (40 with endoscopy and 22 positive)	tTG-IgA, EMA-IgA, and biopsy Only 40 (whom tested positive for IgA-tTG) tested for biopsy
6	Al-Mendalawi MD 2016 [20]	None/ comments	None/ comments	None/comments	None/comments	None/comments
7	Almadi MA, Aljebreen AM. 2016 [21]	None/ comments	None/ comments	None/comments	None/comments	None/comments

*Studies 1-4 were in general population and were considered for the Meta-analysis; study 5 was in at risk population; studies 6 and 7 were letters to the editor with comments on study 4.

(articles [15-18]), B- One article reported the prevalence in at-risk population (article [19]) and C- Two letters to the editor (articles [20] and [21]). Age wise, these studies covered different age groups (Table 1): children and adolescents (6-15 years) (Table 1; article 1); adolescents and adults (14-78 years) (Table 1; article 2); adolescents (16-18years) (Table 1; article 3); children and adolescents (6-18 years) (Table 1; article 4); children and adolescents and adults (1-79 years) (Table 1; article 5). Table 1 also illustrates the different cohorts and prevalence for both seropositivity and biopsy-proven conditions.

Cohort for prevalence of biopsy-proven CD

Refusing endoscopy by some patients was a common feature which was found in two studies [18,19]. Al Hatlani [18] reported a seroprevalence of 3% (32/1141=2.8) and that only 10 of the 32 who were seropositive underwent an endoscopy with positive histological findings and with prevalence of Biopsy-Proven CD of 1% (10/1141=0.87%). However, Al-Mendalawi [20] and Almadi [21] commented that the prevalence (1%) reported for biopsy-proven CD was underestimated due to considering the patients that refused endoscopy as negative histology [21]. Likewise, Al-Hakami 2016 [19] reported a seroprevalence of 18.4% (58/315) and that only 40 of the 58 who were seropositive underwent an endoscopy (18 refused) of which 22 were biopsy-positive with a prevalence of Biopsy-Proven CD of 6.9% (22/315); which would also be misleading due to the same reason, and due to the fact that the sensitivity and specificity are high for both the tTG-IgA test (98% and 98% respectively) and for EMA test (95% and 99% respectively) [22,23]. It would sound more logically if the 18 patients (who refused endoscopy) were omitted from the total number (315-18=297) and calculate the prevalence accordingly which would be 7.4% (22/297). Similarly, for the 22 who refused endoscopy [18]; the cohort would be (1141-22=1119) and the rate would be (10/1119=0.9%).

Thus, for the prevalence of Biopsy-Proven CD in both articles (table 1; articles 4 and 5) we used the cohort after detracting those that refused endoscopy (22 in article [18] and 18 in article [19]). The used cohorts were 1119 and 297 respectively.

Table 2. Mean of seropositivity* and biopsy- proven positivity**

		Mean	Minimum	Maximum	Std. Deviation	Number of studies
Seropositivity CD	seropositivity	70.25	3.00	221.00	101.25	4
	Cohort	2610.50	204.00	7930.00	3574.51	4
Biopsy-proven CD	Biopsy positivity	64.00	10.00	118.00	76.36	2
	Cohort	4524.50	1119.00	7930.00	4816.10	2

*Rate of seropositivity (70 /2610=2.68%)

** Rate of biopsy-proven positivity (64/4524=1.4%)

Table 1a. Data for Meta-analysis of seropositivity prevalence

	Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
1	Al-Hussaini A, et al. 2017	0.028	7930	0.028	-3.547	0.068
2	Khayat YM 2012	0.015	204	0.015	-4.185	0.576
3	Al-Jebreen AM, et al. 2013	0.022	1167	0.022	-3.794	0.200
4	Al Hatlani MM 2016	0.030	1141	0.030	-3.476	0.174

Table 1b. Prevalence (by fixed and random models) with the heterogeneity

Model	Number of studies	Effect size and 95% internal			Test of null (2-Tail)		Heterogeneity				Tau – squared			
		Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	Df (Q)	P-value	I- Squared	Tau Squared	Standard Error	Variance	Tau
Fixed	4	0.027	0.024	0.031	-59.399	0.000	2.808	3	0.422	0.00	0.00	0.024	0.001	0.00
Random	4	0.027	0.024	0.031	-59.399	0.000								

Statistical analysis

SPSS analysis: Table 2 illustrates the cohort's ranges, rates and means for both seropositivity and biopsy-proven positivity. For the general population (articles 1-4 in Table 1); cohort's range was 204 – 7930 with a mean of 2610 and standard deviation of 3574.51 (Table 2). The mean of seropositivity in the general population (articles 1-4 in Table 1) was 70.00 individual with a range of 3-221 and standard deviation of 101.00. Cohort after detracting those that refused endoscopy (in article 4 in Table 1) was 1119. Thus, the cohorts' mean for studies with prevalence of the biopsy-proven CD (articles 1 and 4 in Table 1) was 4524 (1119 and 7930) with standard deviation of 4816 (Table 2); the mean of biopsy positivity in this type of cohort (for articles 1 and 4 in Table 1) was 64.00 individual (10 and 118) with standard deviation of 76 (Table 2). Rate of seropositivity was 2.68% (70 /2610), while the rate of biopsy-proven positivity was 1.4% (64/4524).

Meta-analysis

Meta-analysis was performed using the Comprehensive Meta-analysis program (CMA). Meta-analysis was performed for the four articles discussing the prevalence in the general population (articles 1-4; Table 1). The Meta-analysis of seropositivity prevalence (Tables 1a and 1b; & Figures 1a and 1b) showed that CD prevalence (by fixed model) for serologically proven CD (one serology at least) was 2.7% (95% CI = 2.4–3.1) with no heterogeneity ($I^2 = 0.00$). While Meta-analysis for prevalence of biopsy-proven positivity (for two articles) (Tables 2a and 2b & Figure 2a and 2b) was 1.4% (95% CI = 1.2–1.7) with high heterogeneity ($I^2 = 59.3$).

Discussion

The Meta-analysis (for four articles) showed that seroprevalence of CD in SA (one serology at least) (by fixed model) is 2.7% (95% CI = 2.4%–3.0%) with no heterogeneity ($I^2 = 0.00$), while the prevalence of Biopsy-Proven CD (for two articles) is 1.4% (95% CI = 1.2%–1.7%) with high heterogeneity ($I^2 = 59.3$).

In our study, the seroprevalence (2.7 %) was higher than the global pooled seroprevalence reported by the meta-analysis of Singh *et al.* [24]

Model	Statistics for each study Event rate	Study name	Statistics for each study				Event rate and 95% CI					Weight (Fixed)		Weight (Random)	
			Lower limit	Upper limit	Z-Value	p-Value	-0.05	-0.03	0.00	0.03	0.05	Relative weight	Relative weight		
	0.028	Al-Hussaini A etal 2017	0.025	0.032	-52.111	0.000						77.87		77.87	
	0.015	Khayyat YM 2012	0.005	0.045	-7.265	0.000						1.09		1.09	
	0.022	Al-Jebreen AM etal 2013	0.015	0.032	-19.014	0.000						9.06		9.06	
	0.030	Al Hatlani MM 2016	0.022	0.042	-20.030	0.000						11.98		11.98	
Fixed	0.027		0.024	0.031	-59.399	0.000									
Random	0.027		0.024	0.031	-59.399	0.000									

Figure 1a. Prevalence (by fixed and random models) with statistics and relative weight for each study

Meta Analysis

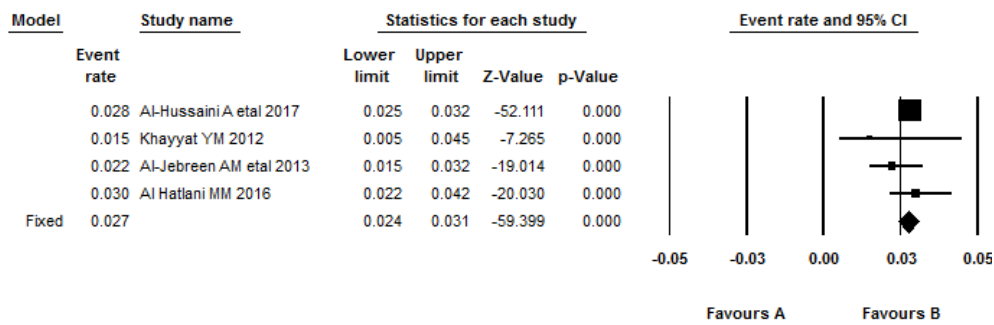


Figure 1b. Forest plot of the Meta analysis of seropositivity prevalence.

Table 2a. Data for Meta-analysis for prevalence of Biopsy proven CD

	Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
1	Al-Hussaini A et al.2017	0.015	7930	0.015	-4.185	0.092
2	Al Hatlani MM 2016	0.009	1119	0.009	-4.701	0.317

Table 2b. Prevalence (by fixed and random models) with the heterogeneity between studies

Model	Number of studies	Effect size and 95% internal			Test of null (2-Tail)		Heterogeneity				Tau – squared			
		Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	Df (Q)	P-value	I- Squared	Tau Squared	Standard Error	Variance	Tau
Fixed	2	0.014	0.012	0.017	-47.643	0.000	2.457	1	0.117	59.305	0.079	0.139	0.036	0.281
Random	2	0.013	0.008	0.020	-17.937	0.000								

Model	Statistics for each study Event rate	Study name	Statistics for each study				Event rate and 95% CI					Residual (Fixed)		Residual (Random)	
			Lower limit	Upper limit	Z-Value	p-Value	-0.02	-0.01	0.00	0.01	0.02	Std Residual	Std Residual		
	0.015	Al-Hussaini A etal 2017	0.013	0.018	-45.295	0.000						1.57		1.00	
	0.009	Al Hatlani MM 2016	0.005	0.017	-14.853	0.000						-1.57		-1.00	
Fixed	0.014		0.012	0.017	-47.643	0.000									
Random	0.013		0.008	0.020	-17.937	0.000									

Figure 2a. Prevalence (by fixed and random models) with statistics and relative weight for each study

Meta Analysis

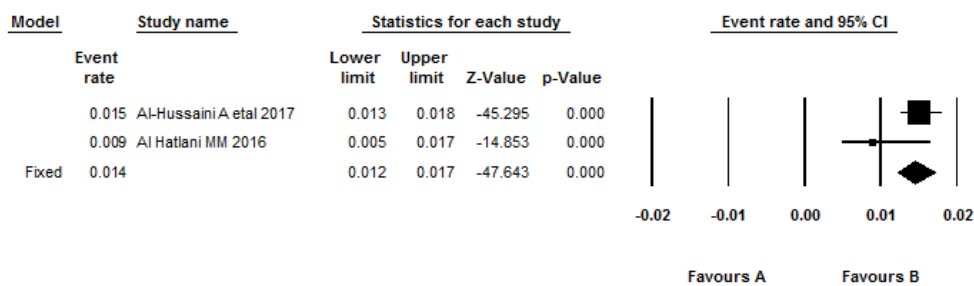


Figure 2b. Forest plot of the Meta-analysis for the prevalence of Biopsy proven positivity

as 1.4% (95% CI, 1.1%–1.7%). In our study the prevalence of biopsy-proven CD (1.4 %) was also higher than the global pooled prevalence of biopsy-proven CD reported by Singh, et al. [24] as 0.7% and by Biagi et al. [25] (0.58%).

The present meta-analysis confirms that the seropositive females are 1.9 times more common than males.

Some limitation was noted. Including the limited number of studies; only four articles for meta-analysis, two studies of them only reported the seroprevalence, but not the prevalence of the biopsy proven, only few studies (two) reported prevalence of biopsy-proven CD, which could not be established properly, mostly because 30-60% of seropositive individuals refused to undergo a biopsy. One article [19] discussed the prevalence in at risk population [19], with seroprevalence of 18.4% (58/315) and 6.9% (22/315) for prevalence of Biopsy-Proven CD, which would be misleading due to considering those who refuse endoscopy as biopsy negative histology, in spite of the fact that the sensitivity and specificity are high for both used tests, tTG-IgA test (98% and 98% respectively) and for EMA test (95% and 99% respectively) [22,23]. Thus, for the prevalence of Biopsy-Proven CD we used the cohort after detracting those that refused endoscopy (18 seropositive individual) in article [19] which gave a prevalence of 7.4%. However, concerning the At-risk groups, the global prevalence ranging from 5% to 10%, include Down and Turner syndromes, type 1 diabetes, and autoimmune thyroid disease [3]. In the USA, the prevalence was found to be 0.75% in not-at-risk groups, 1.8% in symptomatic people, 2.6% in second-degree relatives and 4.5% in first-degree relatives, with similar profile in Europe [10]. It is worth mentioning, that the articles discussing Down syndrome, type 1 Diabetes Mellitus and Short status [14] will be separately analyzed by Meta-analysis.

The highest prevalence was in Al-Qaseem region (3.2%) (8/252) [17] and the Eastern Province (3%) (32/1141) [18], and the least prevalence in Riyadh and Jeddah (1.5%) [15,16]. The factors influencing the regional difference in prevalence of CD were shown to include the HLA and non-HLA genes, patterns of wheat consumption, age at wheat introduction, practices of infant feeding, gastrointestinal infections, the use of antibiotic and proton-pump inhibitor use, and caesarian section rates [26]. It is recommended to search for these factors in different regions in SA, particularly the population prevalence of the HLA-DQ2 haplotype and wheat consumption. These two factors, for examples, are significantly lower in sub-Saharan Africa compared with Northern Africa [27]. However, recently an interesting study was appeared in SA in this concern [28] which reported one of the highest frequencies of CD-predisposing HLA-DQ genotypes among healthy general populations (52.7%) worldwide.

Conclusion

The current study represents the first and only meta-analysis concerning the prevalence of CD in SA. Prevalence of biopsy-proven CD (1.4%) was lower than the seroprevalence (2.7%), but with higher heterogeneity. Refusing endoscopy is common, that may affect the accuracy of prevalence of biopsy-proven CD; a point which must be taken into consideration.

Ethical approval

The collected data were part of a retrospective literature review and analysis, thus a written ethical approval was not obtained before commencing the study.

Disclosures

The current study was not funded or supported by any drug company. This paper is unique and is not under consideration by any other publication and has not been published elsewhere.

Conflicts of Interest

The author declares no conflicts of interest.

Financial support and sponsorship

Nil

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