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Adverse pregnancy outcomes in women with celiac disease: a systematic review and meta-analysis

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Abstract

Background The aim of this meta-analysis was to evaluate the risk of adverse pregnancy outcomes in women affected with celiac disease (CD), and to further estimate the impact of early disease diagnosis and subsequent adherence to a gluten-free diet (GFD) on obstetric complications.

Methods A systematic search for English language observational studies was conducted in Medline, Scopus, and the Cochrane Library, from inception till April 2022, to identify relevant studies reporting on the incidence of adverse pregnancy outcomes in women with CD. Odds ratios (OR) and relative risks (RR) with 95% confidence intervals (CIs) were used to combine data from case-control and cohort studies, respectively. The quality of the included studies was assessed using the Newcastle-Ottawa scale.

Results In total, 14 cohort and 4 case-control studies were included and our analysis demonstrated that the risk for spontaneous abortion (RR 1.35, 95%CI 1.10-1.65), fetal growth restriction (RR 1.68, 95%CI 1.34-2.10), stillbirth (RR 1.57, 95%CI 1.17-2.10), preterm delivery (RR 1.29, 95%CI 1.12-1.49), cesarean delivery (RR 1.10, 95%CI 1.03-1.16) and lower mean birthweight (mean difference -176.08, 95%CI -265.79 to -86.38) was significantly higher in pregnant women with CD. The subgroup analysis demonstrated that only undiagnosed CD increased risk for fetal growth restriction, stillbirth, preterm delivery and lower mean birthweight, whereas early diagnosis of CD was not linked to any adverse pregnancy outcomes.

Conclusions Undiagnosed CD is associated with a higher risk of adverse pregnancy outcomes. Early CD diagnosis and appropriate management with GFD may ameliorate these associations.

Keywords Celiac disease, pregnancy, complications, outcomes, perinatal

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Introduction

Celiac disease (CD), also known as gluten-sensitive enteropathy, is an immune-mediated inflammatory disorder of the small intestine; it is triggered by exposure to dietary gluten, derived from wheat, barley and rye, in genetically susceptible individuals, with an approximated worldwide seroprevalence rate of 1.4% [1]. The female-to-male ratio of CD based on serological screening is 1.5:1 and its diagnosis can be quite challenging, since most cases are asymptomatic, while the clinical manifestations among symptomatic individuals are quite heterogeneous [2].

The pathogenesis of CD commences with a change in the intestinal mucosa's barrier function, enabling dietary gluten peptides to infiltrate the subepithelial lymphatic tissue and initiate the disease's adaptive and innate immune responses [3]. Histological alterations of intestinal villi, accompanied by nutritional malabsorption, induce the development of many complications in pregnancy, such as nutritional deficiencies and anemia, as well as immune-mediated impairment of the physiologic processes that occur during the implantation of an embryo and/or during the development of the placenta [4].

Initially, abnormalities regarding reproduction were linked to untreated CD; in 1970 Morris *et al* reported 3 cases of infertile women who became pregnant after adopting a gluten-free diet (GFD) [5]. Thenceforth, a causal relationship between CD and infertility has been established [6]. Furthermore, the risk of adverse pregnancy outcomes in women with CD and the impact of GFD during pregnancy on risk-reduction have been under clinical investigation. Several observational studies and a couple of meta-analyses have assessed the association between CD and adverse pregnancy outcomes [4,7], yet the exact risk estimate of obstetric complications in pregnant women with the disease remains ambiguous because of methodological differences and heterogeneity across studies, while the adherence of pregnant women to a strict GFD is an important factor that has not been fully elucidated.

The aim of this study was to evaluate the risk of adverse pregnancy outcomes in women with CD and to further analyze whether early CD diagnosis and subsequent adherence to a GFD during pregnancy have an impact on the risk of obstetric complications, compared to pregnant women with CD on a gluten-unrestricted diet.

Materials and methods

This systematic review is reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [8,9]. The study protocol was registered with PROSPERO international prospective register of systematic reviews (protocol number: CRD42021267062). The present meta-analysis was performed based on data from previously published studies; therefore, no ethical approval or patient consent were required.

Search strategy

A systematic literature search of Medline, Cochrane Library and Scopus was conducted from inception till 12th April 2022, to identify studies reporting on the risk of adverse pregnancy outcomes in women with CD. Key questions were formulated according to the PICO method: "Do pregnant women diagnosed with CD have an increased risk for adverse pregnancy outcomes compared to pregnant women without CD?" Text words and, if applicable, database subject heading fields (e.g., Medical Subject Headings), were used to perform the searches: "celiac disease," "CD," "coeliac disease," "gluten enteropathy," "pregnancy," "premature," "obstetric," "complication," "preterm delivery," "spontaneous miscarriage," "spontaneous abortion," "preeclampsia," "gestational hypertension," "stillbirth," "cesarean delivery," "postpartum hemorrhage," "gestational diabetes," "placental abruption," "small for gestational age", and "fetal growth restriction". Furthermore, we examined the references of each of the retrieved studies to identify further articles that met our criteria. We did not utilize any search software. The search was filtered for human and English language studies only. The title and abstract of studies identified in the original search were reviewed by 2 independent authors (KA, a gastroenterologist, and AS, an obstetrician/gynecologist) to eliminate studies that did not answer our research question, based on predetermined inclusion and exclusion criteria. The complete text of the included articles was then examined to see whether it provided any relevant information. The coefficient of agreement between the 2 reviewers for article selection (k ¼ 0.86, 95% confidence interval [CI] 0.79-0.95) was excellent. Conflicts in study selection were resolved by consensus, referring back to the original article and, if agreement could not be reached, a third author (IT, a biostatistician) was consulted and settled the differences.

Selection criteria

Studies in this meta-analysis had to be observational cohort or case-control studies that met the following inclusion criteria: 1) diagnosed CD according to serology testing and/or endoscopic duodenal biopsy [10]; 2) reported incident cases of at least 1 of the following obstetric complications: spontaneous abortion (SA), fetal growth restriction (FGR), preeclampsia, stillbirth, preterm delivery (PTD), cesarean delivery, postpartum hemorrhage and 5-min Apgar score <7; 3) included a non-CD population for which the aforementioned event rates were calculated (or could be inferred as expected event rates from a reference population); 4) reported relative risk (RR), rate or risk ratio, odds ratio (OR), with 95%CI or provided raw data for their calculation. Peer-reviewed observational controlled data (case-control and cohort studies) from hospitals, referral centers and population-based studies were included. Cross-sectional studies, studies without a control group, meta-analyses, review articles, short surveys, letters to the editor, notes, case reports, pilot studies and conference abstracts were excluded. In addition, studies that did not contain primary data were excluded and duplicates of studies were removed. The selection was not limited by the number of participants in each study.

Data extraction

Two investigators (KA and AS) reviewed and abstracted the data independently onto a standard pre-determined data extraction form. The following data were collected from the studies: first author and year of publication, study design, period study conducted, origin of study population, type of exposure (CD and control population), *a priori* outcomes of interest alongside their frequencies, total number of participants in each group (CD pregnant women vs. non-CD pregnant women), as well as any confounding factors reported in each study. FGR was defined as sonographic estimated fetal weight <10th percentile for gestational age and PTD was defined as birth after <37 weeks of pregnancy. Authors were contacted in case of missing data in any of the eligible studies. If more than

one published study came from the same population, only data from the most recent comprehensive report were included.

Outcome measures

The primary analysis focused on assessing the relative risk of predefined adverse pregnancy outcomes in pregnant women diagnosed with CD, compared with non-CD pregnant women originating from the general population, hospital or referral center. In addition, based on information available from individual cohort studies, we performed a subgroup analysis assessing the risk of predefined adverse pregnancy outcomes amongst pregnant women with diagnosed CD and those with undiagnosed CD, compared to the general population of healthy pregnant women. This analysis aimed to examine the impact of early CD diagnosis and subsequent adherence to a GFD during pregnancy on the risk of obstetric complications. The populations with sufficient information about the time of diagnosis in relation to pregnancy were subdivided into early diagnosed and undiagnosed CD groups. Whenever the same control group was utilized in a study for both the "early diagnosed" and "undiagnosed" CD study groups, the control group was equally subdivided into 2 study subgroups for the analysis [11,12].

Quality and risk of bias assessment of the studies

Two investigators (KA and AS) independently assessed the included studies. The quality was assessed using the Newcastle-Ottawa scale [13]. This scale is based on a "star system" that ranges from 0-9, with 0 being the lowest possible quality, and judges study quality according to 3 perspectives: selection of the study groups (4 questions), comparability of the groups (1 question) and ascertainment of the outcome of interest (3 questions). Each question was rated with a maximum of one star except for "comparability of the groups", for which separate stars were awarded for controlling maternal age and/or any other additional covariate (maximum 2 stars). The risk of bias was assessed with the Quality In Prognosis Studies (QUIPS) tool. The Cochrane Prognosis Methods Group recommends it for assessing risk of bias in prognostic factor studies [14]. Six important domains should be critically appraised when evaluating validity and bias in studies of prognostic factors: (1) study participation [15]; study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) study confounding; and (6) statistical analysis and reporting [16]. The different domains contain between 3 and 7 prompting items to be rated on a 4-grade scale (yes, partial, no, unsure). Finally, based on their assessments of the included items, the rater gives an overall, decisive judgment of the risk of bias within each domain. This risk is classified into 3 levels (serious, moderate, and low risk of bias) [14]. Any disagreements between the 2 investigators were resolved by re-evaluating the original study.

Data synthesis and statistical analysis

The Cochrane Collaboration's Review Manager Software (version 5.4) was used to perform data analysis. In the analysis of case-control studies, the ORs (95%CI) were calculated for each of the endpoints, whereas in the analysis of cohort studies, RRs (95%CI) were calculated for every single endpoint for CD pregnant women in comparison with controls. We used 2 approaches to analyze heterogeneity between study-specific estimates. First, the Cochran Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect. Because this test is underpowered to detect moderate degrees of heterogeneity, the presence of statistically significant heterogeneity across the studies was evaluated by utilizing a P-value <0.10. Second, to estimate which proportion of the total variation across studies was caused by study-related factors (clinical setting, methodological or statistical differences) rather than chance, the I^2 statistic was calculated, where $I^2=100\%\times(Q-df)/Q$ representing the magnitude of the heterogeneity—moderate: 30-60%, substantial: 50-90%, considerable: 75-100% [17,18]. In all analyses, dichotomous outcomes were pooled using the Der Simonian and Laird random-effects model, as it suited our analysis given the heterogeneity generally observed between observational studies. A probability level of 0.05 was considered statistically significant for all tests (excluding heterogeneity). Funnel plots and Egger's test were used through the R studios to test for publication bias.

Results

Eligible studies

The search strategy identified 1427 articles (Supplementary Fig. 1) After the removal of duplicates and screening of titles, abstracts and keywords, 28 papers underwent full-text review. During this process, 9 articles were excluded because of irrelevant outcomes [19-27]. One study was excluded because it neither provided risk estimates for the outcomes of interest nor offered data for calculations [28]. The remaining 18 studies [29-46], published between 1990 and 2021, fulfilled the selection criteria. Our meta-analysis included 14 cohort studies and 4 case-control studies, the general characteristics and results of which are described in Tables 1 and 2.

Quality and risk of bias assessment of the included studies

Based on the Newcastle-Ottawa scale [13], 2 studies were rated as 9-star, 6 studies as 8-star, 9 studies as 7-star, and 1 study as 6-star (Table 1). All studies provided a clear definition of the diagnosis of CD, including the details of confirmation based on serology testing and/or endoscopic duodenal biopsy. The risk of bias according to the QUIPS tool for every individual study will be depicted next to the forest plots. A letter was assigned

Table 1 Characteristics of the studies included in the meta - analysis regarding the risk for adverse pregnancy outcomes of women with celiac disease

Author [ref.], year	Study period	Journal	Location	Study design	Data source (setting)	Outcomes assessed	Celiac group	Control group	Celiac disease	Controls	Subgroup analysis (early diagnosed – undiagnosed)	Quality evaluation
Pogacar *et al* [44], 2019	2007	European Journal of Obstetrics and Gynecology and Reproductive Biology	Slovenia	Retrospective case–control	The Slovenian Celiac Society	CS, SA, FGR, PD, SB, LBW	Women with CD confirmed via serological testing and small intestinal biopsy	Healthy women without CD	144	71	- -	7
Elliott *et al* [33], 2019	1999 - 2014	The Journal of Maternal - Fetal and Neonatal Medicine	USA	Retrospective cohort	The Healthcare Cost and Utilization Project - Nationwide Inpatient Sample	PRE, CS, PH, PD, FGR	Pregnant women with ICD - diagnosed CD	Pregnant women without ICD - diagnosed CD	2755	14,510,832	ICD - diagnosed CD prior to delivery related discharge -	7
Martinelli *et al* [40], 2000	1999	Gut	Italy	Prospective cohort	A single obstetrics - gynecology clinic	PD, CS, SB, 5 - min Apgar score <7, LBW	Pregnant women with CD diagnosed via serological testing and small intestinal biopsy	Pregnant women with a negative CD test	12	206	- No diagnosis or treatment for more than 10 years and with positive antibody test	7
Martinelli *et al* [39], 2010	2008	BMC Gastroenterology	Italy	Case - Control	Participants of the Apulian Section of the Italian Association of Celiac Disease	FGR, SA	Women with CD diagnosed via serological testing and small intestinal biopsy	Age - matched women without CD	31	93	- -	9
Molteni *et al* [42], 1990	1990	Clinical Gastroenterology	Italy	Case - Control	A single clinic	SA	Women with CD confirmed via small intestinal biopsy	Healthy controls or women with IBD	54	54	- -	7

(*Contd...*)

Table 1 (*Continued*)

Author [ref.], year	Study period	Journal	Location	Study design	Data source (setting)	Outcomes assessed	Celiac group	Control group	Celiac disease	Controls	Subgroup analysis (early diagnosed – undiagnosed)	Quality evaluation
Abecassis *et al* [31], 2019	1991 - 2014	Journal of Clinical Medicine	Israel	Retrospective cohort	The Soroka University Medical Center	PRE, PD, GH, CS, LBW, 5 - min Apgar score <7	Women with CD confirmed via small intestinal biopsy	Women without CD	212	24,347	- -	8
Moleski *et al* [41], 2015	2014	Annals of Gastroenterology	USA	Retrospective cohort	The Jefferson Celiac Center	SA, PD, CS	Women with CD confirmed via small intestinal biopsy	Women without CD	245	488	- -	6
Sheiner *et al* [45], 2005	1988 - 2002	European Journal of Obstetrics & Gynecology and Reproductive Biology	Israel	Retrospective cohort	The Soroka University Medical Center	SA, FGR, PH, 5 - min Apgar score <7	Women with ICD - diagnosed CD	Women without ICD - diagnosed CD	48	143,663	CD already diagnosed and women on GFD -	7
Khashan *et al* [36], 2009	1979 - 2004	Human Reproduction	Denmark	Retrospective cohort	The Danish Medical Birth Register	PD	Women with ICD - diagnosed CD	Women without CD	1451	1,502,891	ICD - diagnosed CD at least 90 days before gestation ICD - diagnosed after birth	7
Celdir *et al* [32], 2021	2006 - 2011	The American Journal of Gastroenterology	USA	Retrospective cohort	The Rochester Epidemiology Project	LBW, PD, 5 - min Apgar score <7, PRE	Women with CD diagnosed with positive serological testing	Age - and sex - matched healthy controls	117	250	- CD diagnosis with antibody test and retrospective analysis of medical records	8

(*Contd...*)

Table 1 (*Continued*)

Author [ref.], year	Study period	Journal	Location	Study design	Data source (setting)	Outcomes assessed	Celiac group	Control group	Celiac disease	Controls	Subgroup analysis (early diagnosed – undiagnosed)	Quality evaluation
Ludvigsson *et al* [38], 2005	1964 - 2001	Gastroenterology	Sweden	Retrospective cohort	The Swedish National Board of Health and Welfare	FGR, LBW, PD, CS	Women with ICD - diagnosed CD	Women without a diagnosis of CD	2071	2,815,329	ICD - diagnosed CD prior to birth ICD - diagnosed CD after birth	7
Nørgård *et al* [43], 1999	1977 - 1992	The American Journal of Gastroenterology	Denmark	Retrospective cohort	The Danish Medical Birth Registry	LBW, PD, FGR	Women with ICD - diagnosed CD	Women without a diagnosis of CD	127	126	ICD - diagnosed CD prior to the manifestation of an adverse perinatal outcome ICD - diagnosed CD following manifestation of an adverse perinatal outcome	8
Greco *et al* [34], 2004	2001 - 2002	Gut	Italy	Retrospective cohort	A single obstetrics - gynecology clinic	PD, SA, FGR, LBW	Women with CD diagnosed with positive serological testing	Seronegative women	79	4997	Treated with negative antibody test No diagnosis, no treatment and positive antibody test	7
Tata *et al* [46], 2005	1987 - 2002	Gastroenterology	UK	Retrospective cohort	The General Practice Research Database	CS, PRE, PH, SB	Women with ICD - diagnosed CD	Age - matched women without CD	1521	7732	- -	8

(*Contd...*)

Table 1 (*Continued*)

Author [ref.], year	Study period	Journal	Location	Study design	Data source (setting)	Outcomes assessed	Celiac group	Control group	Celiac disease	Controls	Subgroup analysis (early diagnosed – undiagnosed)	Quality evaluation
Kotze *et al* [37], 2020	2000 - 2017	Arquivos de Gastroenterologia	Brazil	Retrospective cohort	A single gastroenterology clinic	SA	Women with CD diagnosed with positive serological testing and small intestinal biopsy	Healthy age - matched controls	214	286	CD diagnosis and monitoring for at least 5 years -	8
Grode *et al* [35], 2018	1977 - 2016	Human Reproduction	Denmark	Retrospective cohort	The Danish National Patient Register	SA, SB	Women with ICD - diagnosed CD	Age - and sex - matched women without CD	2159	21,634	ICD - diagnosed CD prior to manifestation of an adverse perinatal outcome ICD - diagnosed CD following manifestation of an adverse perinatal outcome	9
Sultan *et al* [29], 2014	1977 - 2012	The American Journal of Gastroenterology	UK	Retrospective cohort	The Clinical Practice Research Datalink	PH, PRE, CS, LBW, PD, SB	Pregnant women with ICD - diagnosed CD	Pregnant women without CD	892	363,038	ICD - diagnosed CD prior to birth ICD - diagnosed CD after birth	8
Sher *et al* [30], 1994	1975 - 1989	Digestion	UK	Case - control	Hospital records from the city of Leicestershire	SB	Women with CD diagnosed with small intestinal biopsy	Age - and sex - matched women without CD	68	68	- -	7

CD, celiac disease; SA, spontaneous abortion; FGR, fetal growth restriction; PRE, preeclampsia; SB, stillbirth; PD, preterm delivery; CS, cesarean section; PH, postpartum hemorrhage; LBW, low birth weight

Table 2 Results of the meta - analysis regarding obstetric complications and pregnancies with celiac disease compared to healthy pregnancies, alongside results of the subgroup analyses regarding the impact of early diagnosis of celiac disease on the course of the pregnancy

Variables	Studies	Study group	Control group	RR	95%CI	I^2; P value	Early diagnosed CD group			Undiagnosed CD group		
							RR	95%CI	I^2	RR	95%CI	I^2
SA	7	920/7978	7202/78,241	1.35	1.10 - 1.65	62%; 0.02	1.38	0.85 - 2.24	69%	1.07	0.98 - 1.17	0%
FGR	5	201/5105	364,192/17,466,900	1.68	1.34 - 2.10	39%; 0.16	1.49	0.98 - 2.25	60%	1.94	1.37 - 2.73	40%
Stillbirth	5	51/9891	1818/443,192	1.57	1.17 - 2.10	0%; 0.97	1.31	0.71 - 2.41	0%	1.73	1.16 - 2.56	0%
PTD	9	582/8012	1,197,460/19,437,859	1.29	1.12 - 1.49	58%; 0.02	1.09	0.96 - 1.24	15%	1.41	1.17 - 1.69	30%
Cesarean delivery	9	1367/8090	4,169,957/17,953,735	1.10	1.03 - 1.16	10%; 0.35	1.03	0.87 - 1.21	44%	1.14	0.98 - 1.32	29%
Postpartum hemorrhage	4	183/5216	411,727/15,025,256	1.11	0.96 - 1.27	0%; 0.69						
Preeclampsia	4	183/5216	511,846/14,882,102	1.04	0.88 - 1.23	0%; 0.60						
5 - min Apgar score <7	4	10/503	6483/387,848	1.40	0.46 - 4.22	62%; 0.05						

CD, celiac disease; SA, spontaneous abortion; FGR, fetal growth restriction; PTD, preterm delivery, RR; relative risk, CI; confidence interval; I^2, heterogeneity

to every domain of the tool: A for Study Participation, B for Study Attrition, C for Prognostic Factor Measurement, D for Outcome Measurement, E for Study Confounding, and F for Statistical Analysis and Reporting.

Analysis of dichotomous outcomes

Spontaneous abortion

Seven studies (5 cohorts) [34,35,37,40-42,44] were analyzed, including 7978 pregnant women with CD and 78,241 non-CD pregnant women; SA was detected in 11.5% (n=920) vs. 9.2% (n=7202), respectively. A statistically significant positive correlation was found between the risk for SA and CD (RR 1.35, 95%CI 1.10-1.65). This association was also observed in the analysis of the cohort studies alone. The heterogeneity was high in the overall analysis, as well as among the cohort studies (Fig. 1).

FGR

We evaluated data from 5 cohort studies [33,34,38,43,45], with 5105 pregnant women with CD and 17,466,900 controls; FGR was detected in 3.9% (n=201) vs. 2.1% (n=364,192), respectively. A significant correlation between CD in pregnancy and FGR was observed (RR 1.68, 95%CI 1.34-2.10). The heterogeneity was moderate (Fig. 2).

Preeclampsia

Based on data from 4 cohort studies [29,32,33,46], among 5399 pregnancies of women with CD and 14,882,102 control pregnancies, there were 134 (2.5%) and 511,846 (3.4%) cases of preeclampsia, respectively. The association between CD pregnancies and the risk for preeclampsia was not statistically significant (RR 1.04, 95%CI 0.88-1.23). There was no indication of heterogeneity among the included studies (Supplementary Fig. 2)

Stillbirth

In 4 cohort studies and 2 case-control studies [29,30,35,39,44,46], including 10,011 pregnancies in the CD group and 443,354 cases in the control group, the incidence of stillbirth was 0.58% (n=58) in the study group compared to 0.41% (n=1,819) in the control group. The analysis showed a statistically significant correlation between CD and stillbirth (RR 1.57, 95%CI 1.17-2.10). No indication of heterogeneity was found. The subgroup analysis among cohort studies demonstrated similar results (Supplementary Fig. 3).

Preterm delivery

Nine cohort studies [29,31-33,36,38,40,41,43] evaluated the risk of PTD among women with CD. Overall, the study group consisted of 8012 and the control group of 19,437,859 cases, with

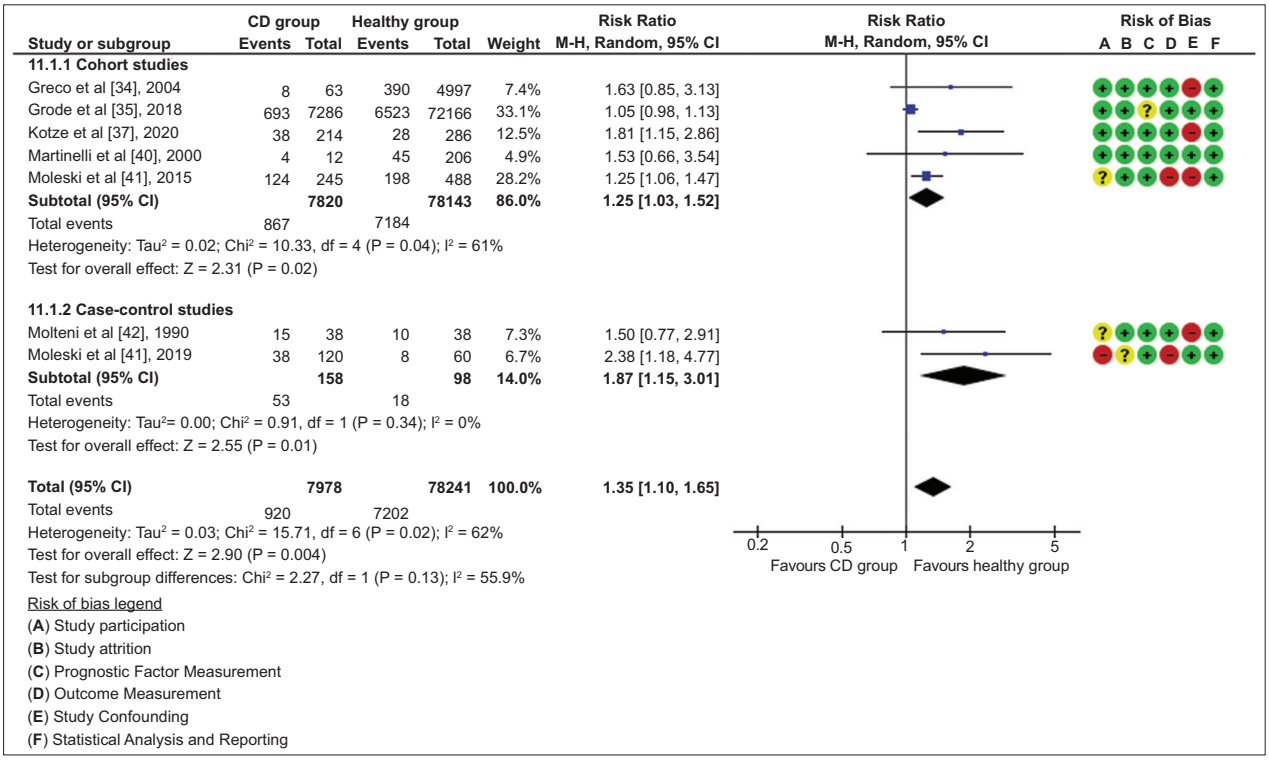

Figure 1 Forest plot demonstrating the relative risk for spontaneous abortion of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval

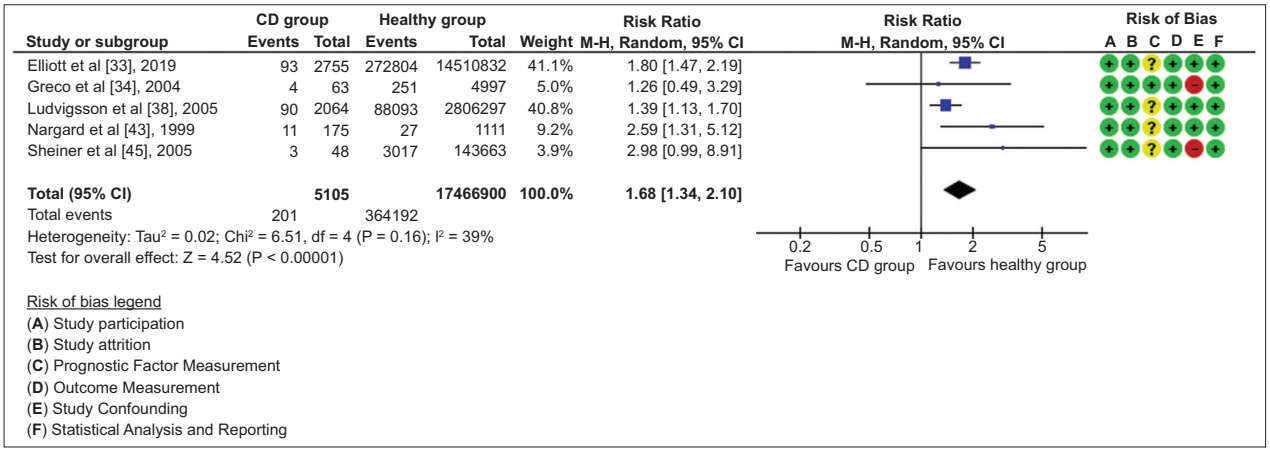

Figure 2 Forest plot demonstrating the relative risk for fetal growth restriction of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval

582 (7.3%) and 1,197,460 (6.2%) events of PTD respectively. A statistically significant association was identified between CD and PTD (RR 1.29, 95%CI 1.12-1.49). Substantial heterogeneity was found among the studies (Supplementary Fig. 4).

Cesarean delivery

The meta-analysis of eight cohort and one case-control study [31-34,38,41,44,46], showed that 1367 (16.9%) out of 8090 women suffering from CD and 4,169,957 (23.2%) women of 17,953,735 in the control group, underwent cesarean delivery. A statistically significant association between CD and cesarean delivery was observed (RR 1.10, 95%CI 1.03-1.16). The correlation remained in the subgroup of cohort studies. The heterogeneity was low, both in the overall analysis and in the cohort studies subgroup (Supplementary Fig. 5).

Postpartum hemorrhage

In this analysis of 4 cohort studies [29,33,45,46], 5216 cases with CD and 15,025,256 controls were included and postpartum hemorrhage occurred in 183 (3.5%) and

411,727 (2.7%) cases, respectively. No statistically significant correlation was observed between CD pregnancies and the incidence of postpartum hemorrhage (RR 1.11, 95%CI 0.96-1.27). There was no indication of heterogeneity among the studies (Supplementary Fig. 6).

5-min Apgar score <7

In this analysis of 4 cohort studies [31,32,40,45], including 503 pregnancies with CD and 387,848 control pregnancies, the 5-min Apgar score was <7 in 2% (n=10) and in 1.7% (n=6483), respectively. There was no indication of an elevated risk for 5-min Apgar score <7 in the study group compared to the control group (RR 1.40, 95%CI 0.46-4.22). The heterogeneity was significant (Supplementary Fig. 7).

Analysis of continuous outcomes

Mean birthweight (BW)

Four cohort studies and one case-control study reported on mean BW [34,36,39,43,45], consisting of 1829 and 1,652,997 cases in the study and control groups respectively. Pregnancies of mothers with CD had a statistically significant correlation with lower mean BW (mean difference [MD] -176.08, 95%CI -265.79 to -86.38). Substantial heterogeneity was observed among the studies, whether the case-control study was included in the analysis or not (Supplementary Fig. 8).

Subgroup analyses

In total, 11 studies offered relevant data and were included in the subgroup analysis (Table 1). No statistically significant risk was observed among the early diagnosed and the undiagnosed CD groups with spontaneous abortion, compared to the control group (Fig. 3). A statistically significant positive correlation with FGR was identified solely among the undiagnosed CD (RR 1.94, 95%CI 1.37-2.73) (Fig. 4), while only women with undiagnosed CD had an higher risk for stillbirth compared to healthy controls (RR 1.73, 95%CI 1.16-2.56) (Supplementary Fig. 9). The undiagnosed CD subgroup had an elevated risk of PTD compared to controls (RR 1.41, 95%CI 1.17-1.69), whereas no indication of elevated risk was observed for the early diagnosis subgroup with regard to PTD; a significant difference among the subgroups of undiagnosed versus early diagnosed CD was identified (P=0.02) and the initial heterogeneity was also minimized (Supplementary Fig. 10). No greater risk of cesarean delivery was detected in either the early diagnosed or the undiagnosed CD group compared to healthy controls (Supplementary Fig. 11). Interestingly, the undiagnosed subgroup had a lower mean BW compared to healthy controls (MD -280.53, 95%CI -456.13 to -104.93), while no difference was found among the early diagnosed and the healthy control group; a significant difference was noted in the subgroups of undiagnosed vs. early diagnosed CD (P<0.001) (Supplementary Fig. 12). All subgroup analyses regarding the impact of early diagnosis of CD on the course of the pregnancy are summarized in Table 2.

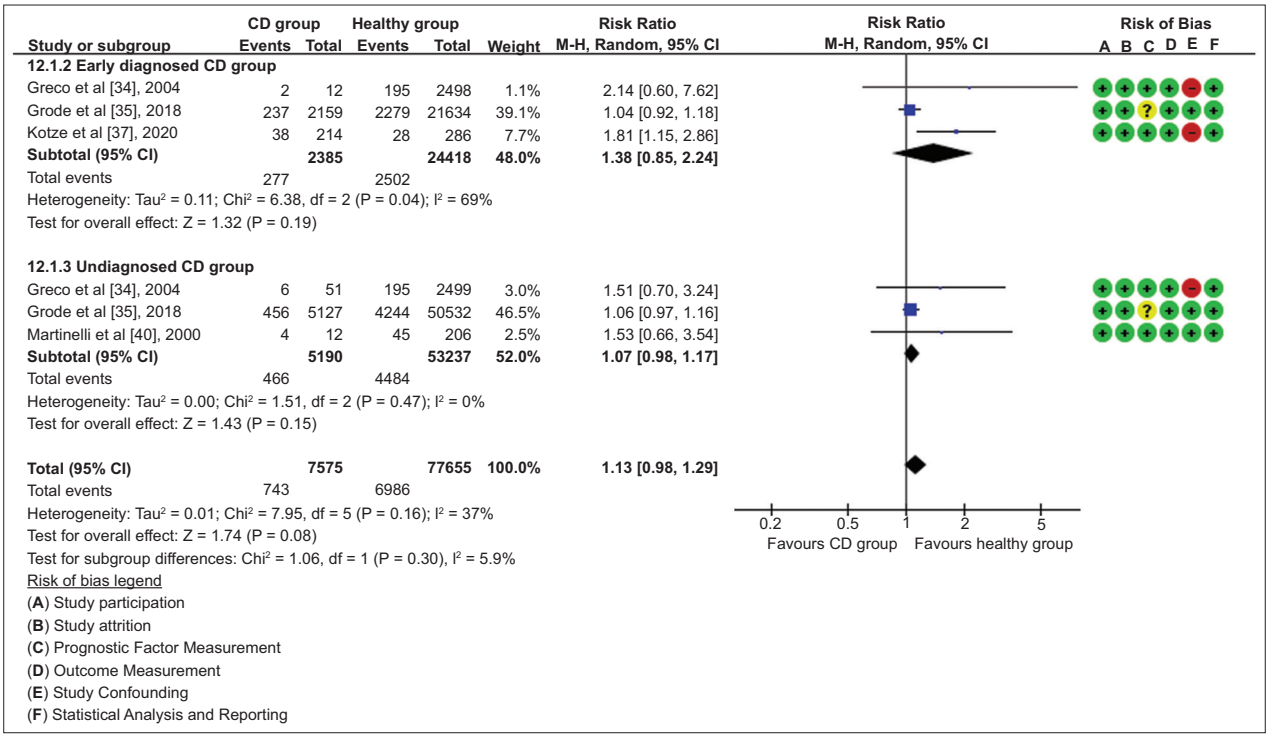

Figure 3 Subgroup analysis on spontaneous abortion based on the time of celiac disease diagnosis
CI, confidence interval

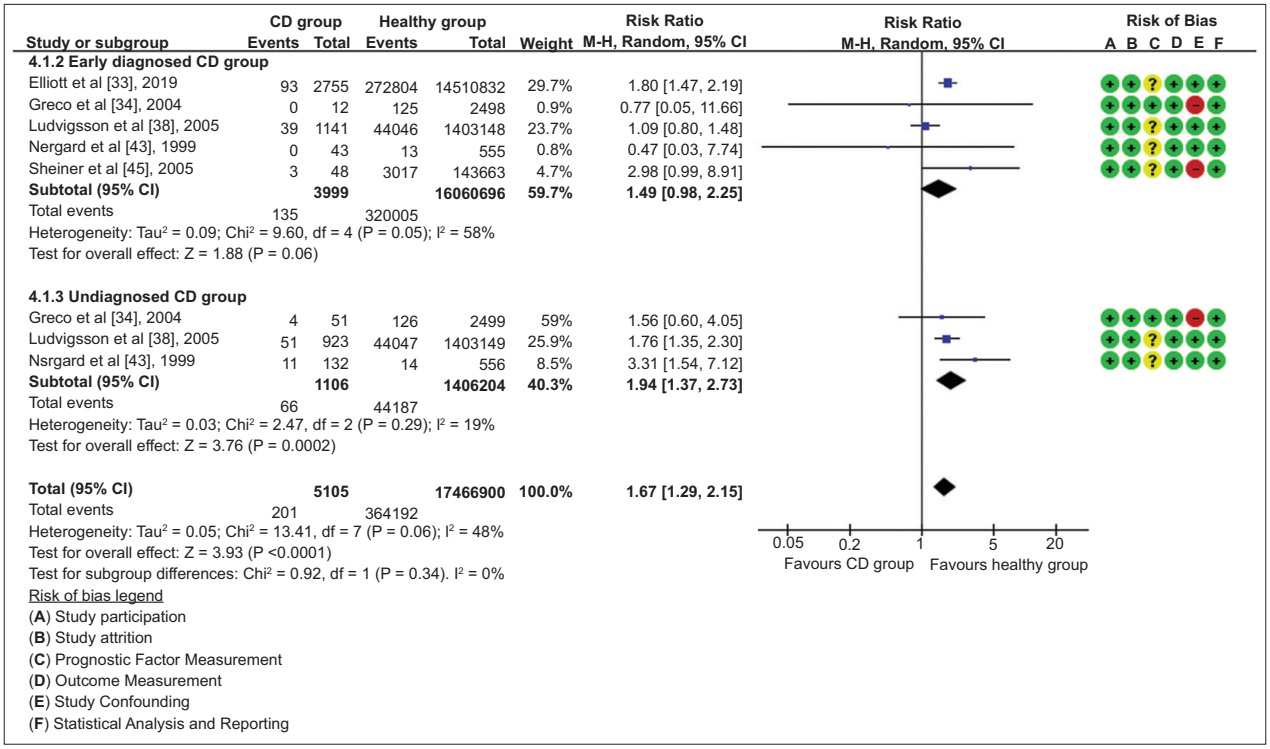

Figure 4 Subgroup analysis on fetal growth restriction based on the time of celiac disease diagnosis
CI, confidence interval

Publication bias

PTD was the outcome included in the majority of the included studies, so it was tested for publication bias (Supplementary Fig. 13,14). The funnel plot in which the individual studies were scattered symmetrically on the vertical axis showed no indication of publication bias, while Egger's test confirmed this (P=0.12). It should be noted, however, that the PTD meta-analysis contained only 9 studies. Thus, both the funnel plot and Egger's test may have lacked the statistical power to detect publication bias (Supplementary Fig. 15).

Discussion

This meta-analysis, which evaluated pooled data from all currently available observational studies assessing the risk of adverse pregnancy outcomes in women with CD, showed that the risk of spontaneous abortion, FGR, stillbirth, PTD, cesarean delivery and lower BW was significantly higher in the CD group, compared to the non-CD control group (Table 2). Moreover, we found that only pregnant women without an early diagnosis of CD were at higher risk for FGR, stillbirth, PTD, and lower mean BW.

With regard to a previous meta-analysis [7], we further evaluated 2 important pregnancy outcomes: spontaneous abortion and cesarean delivery; they proved to be significantly associated with CD pregnancies. Notably, most of the individual observational studies reported no statistically significant results regarding spontaneous abortion [34,35,40,42] and cesarean delivery [32-34,38,41], while the meta-analysis detected 35% and 10% higher risk for pregnancies with CD, respectively. The increased risk of pregnancy complications could be attributed to nutrient deficiencies [43] or the potential compromise of placental function by gliadin and/or maternal CD antibodies [47]. The older age among women with CD could be potentially attributed to related infertility issues [35].

Interestingly, after stratifying the analyses for current management of the disease, we further demonstrated that only women with undiagnosed CD had a high risk for obstetrical complications such as FGR, stillbirth, PTD, and low BW, compared to the general pregnant population. These findings are unique and highlight the protective role of early CD diagnosis and possible subsequent adherence to GFD in minimizing the risk for adverse pregnancy outcomes. It is noteworthy that GFD adherence among CD patients can be up to 90% [48].

Our results provide comprehensive and convincing support for a hypothesis published in the literature, suggesting that undiagnosed CD is associated with a greater risk for adverse obstetric outcomes compared to women with known CD under GFD [49]. The findings are also in accordance with the general non-pregnant population; the

adoption of a GFD can lead to the eradication of circulating transglutaminase antibodies within months and to complete healing of the small intestine in 66% of adult patients within 5 years of diagnosis [50]. Therefore, these patients should be made aware of the potential negative effects of active CD and the importance of adherence to a strict GFD, in order to ameliorate their health condition and associated complications.

Our study's main strength lies in the fact that this is the first meta-analysis to distinguish between women in early diagnosed and undiagnosed CD groups and assess the risk of pregnancy outcomes. Furthermore, to our knowledge, no previous meta-analysis on this issue included such a large sample size. Statistical heterogeneity among the studies was low, and our subgroup analyses managed to minimize and explain it when high. Moreover, the majority of the included studies were cohort studies and of moderate or good quality. Finally, no indication of publication bias was detected.

Certain limitations of our meta-analyses should also be acknowledged. The main issue derives from the limitations of the included studies: since it is not possible to perform randomized controlled trials exploring the association between CD and adverse pregnancy outcomes, we included only observational studies, most of them retrospective, often susceptible to selection bias and may fail to consider several potential confounders. Additionally, details about the time of diagnosis, the duration of the disease and its severity, were rarely provided altogether. More importantly, only a few of the included studies gave thorough information about the compliance of the study group with a GFD—in most cases, only the early diagnosis was known. If the subgroups had been better defined regarding GFD adherence, the effect measure differences would have possibly been even bigger. It is also worth mentioning that an analysis regarding the risk for adverse pregnancy outcomes based on the maternal serological levels of total immunoglobulin A (IgA) and IgA anti-tissue transglutaminase was not feasible, given the absence of data in the included studies. Finally, most of the included studies did not match the populations for maternal age, although most offered adjusted RRs or ORs.

This meta-analysis confirmed the negative impact of CD on several pregnancy complications. Moreover, there are serious indications that early diagnosis of CD and subsequent GFD can reverse the high risk of FGR, stillbirth, PTD and low BW. These results could further contribute to the development of contemporary maternal medicine guidelines. Finally, adequately conducted prospective cohort studies, matched for maternal age and ideally examining the compliance with the GFD, are warranted to provide more robust data regarding risk differences among certain subgroups.

Summary Box

What is already known:

- Celiac disease (CD) is an immune-mediated inflammatory disorder of the small intestine triggered by exposure to dietary gluten in genetically susceptible individuals
- The risk of adverse pregnancy outcomes in women with CD and the impact of a gluten-free diet (GFD) during pregnancy on risk-reduction have been under clinical investigation
- The exact risk estimate of obstetric complications in women with CD remains ambiguous, while adherence of pregnant women to a strict GFD is an important factor not fully elucidated

What the new findings are:

- The risk of spontaneous abortion, fetal growth restriction, stillbirth, preterm delivery, cesarean delivery, and lower birthweight was significantly higher in the CD group, compared to the non-CD control group
- Only pregnant women with undiagnosed CD were at high risk for fetal growth restriction, stillbirth, preterm delivery and low birthweight; those diagnosed early had no greater risk for the aforementioned outcomes, compared to the general pregnant population
- Early diagnosis of CD minimizes the risk of fetal growth restriction, stillbirth, preterm delivery, and low birthweight, possibly via the adoption of a GFD

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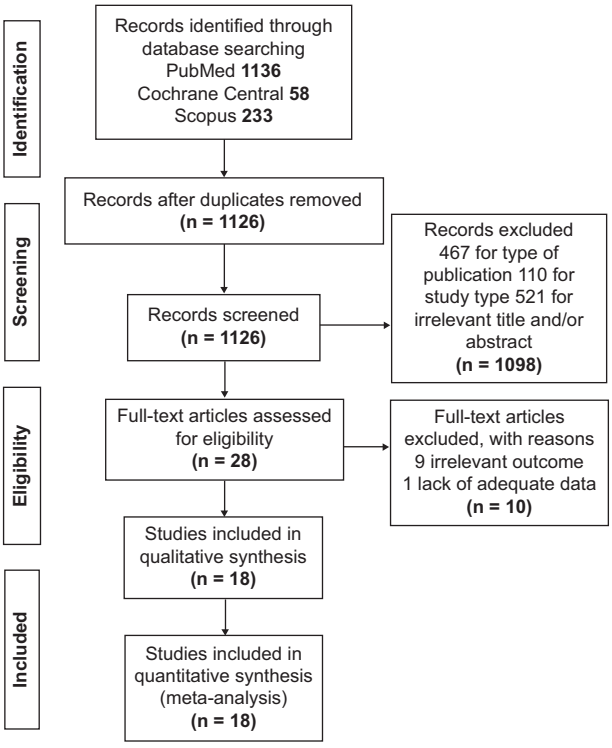
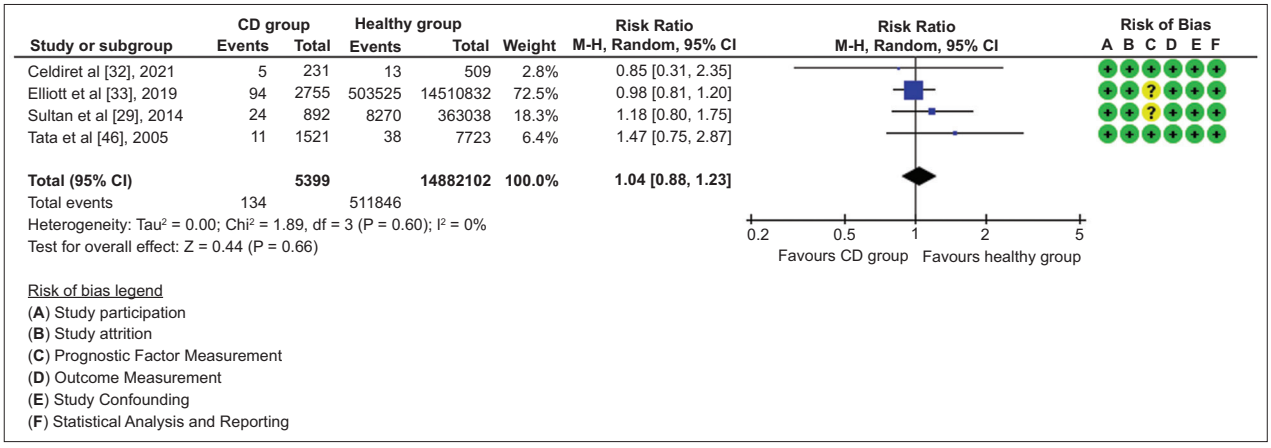
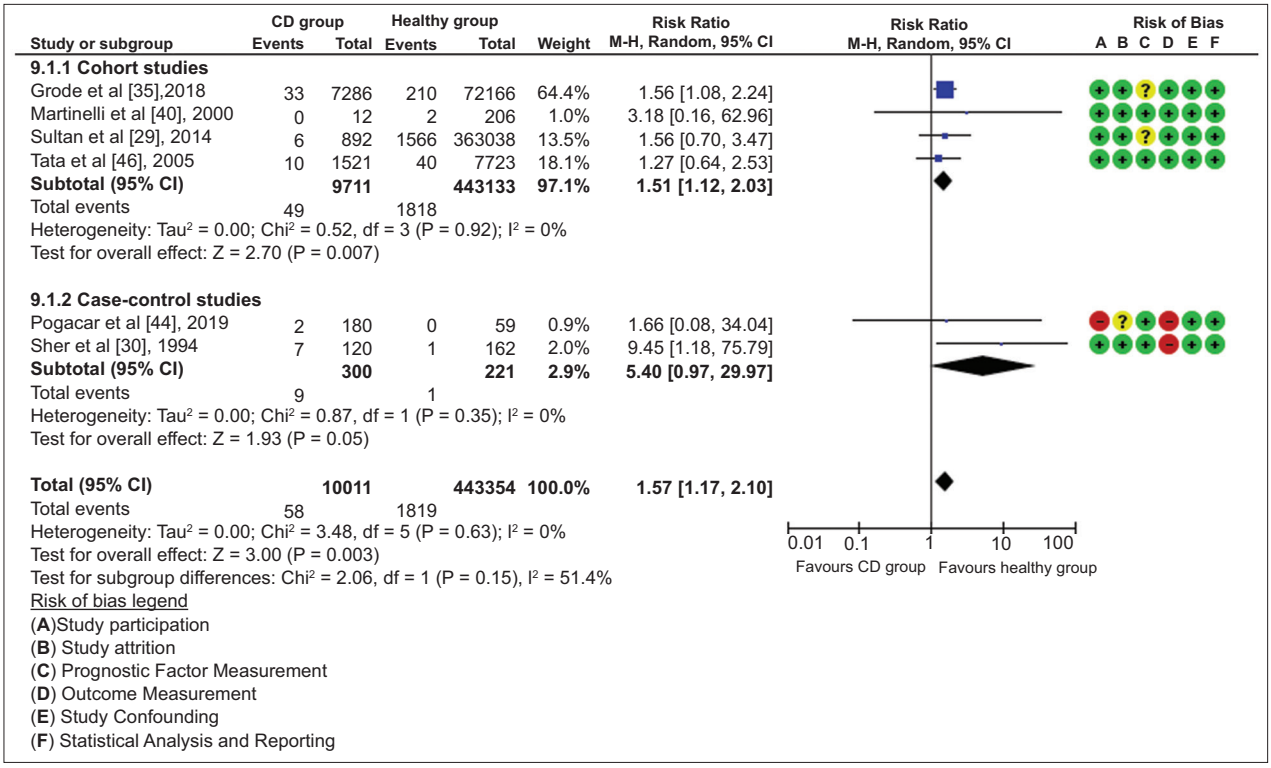
Supplementary material



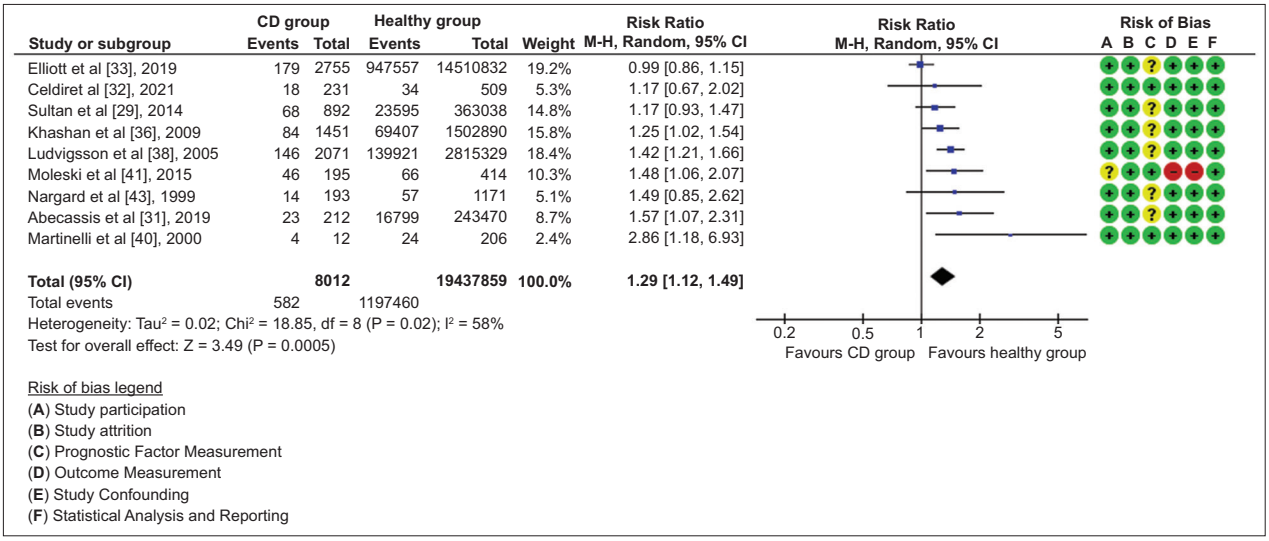
Supplementary Figure 1 Study selection flow diagram presented according to the PRISMA Statement



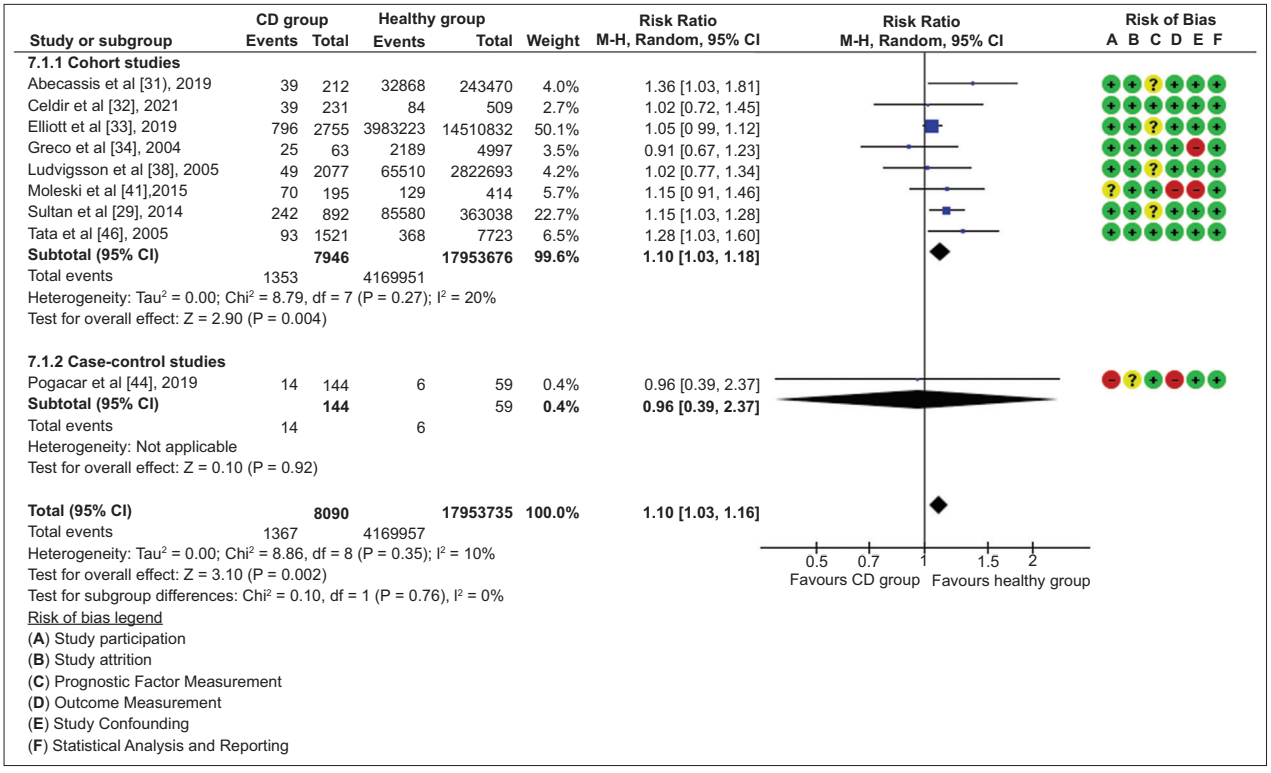
Supplementary Figure 2 Forest plot demonstrating the relative risk for preeclampsia of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



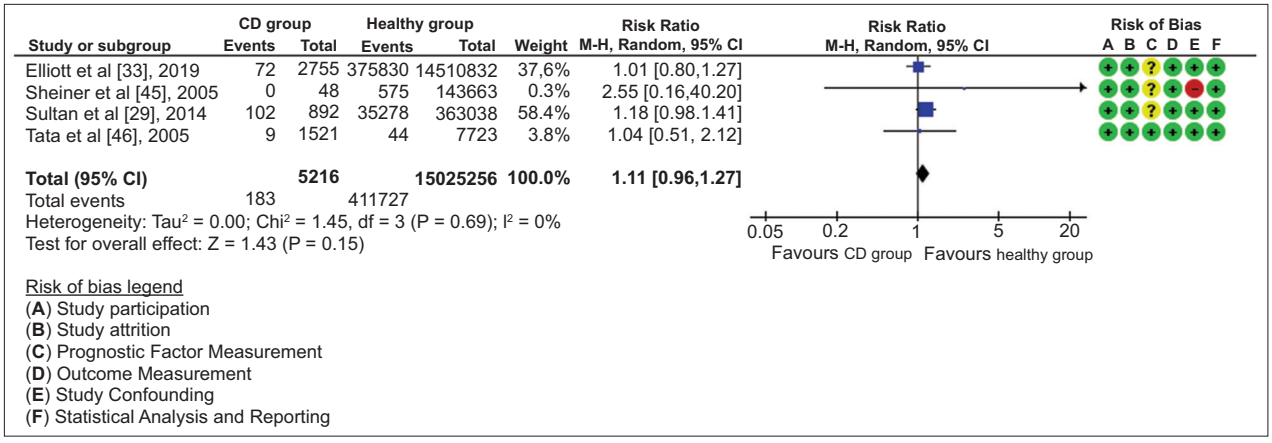
Supplementary Figure 3 Forest plot demonstrating the relative risk for stillbirth of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



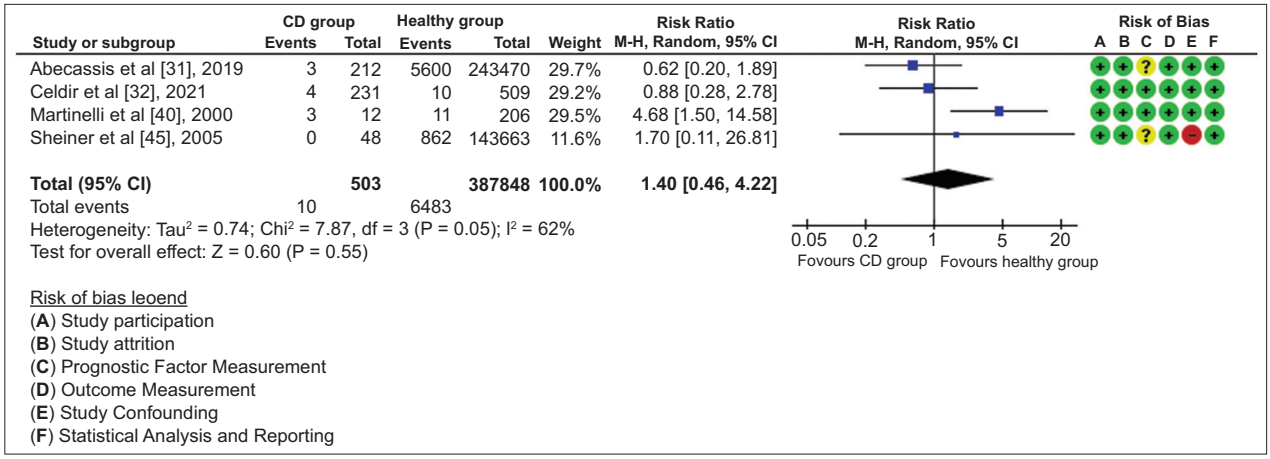
Supplementary Figure 4 Forest plot demonstrating the relative risk for preterm delivery of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



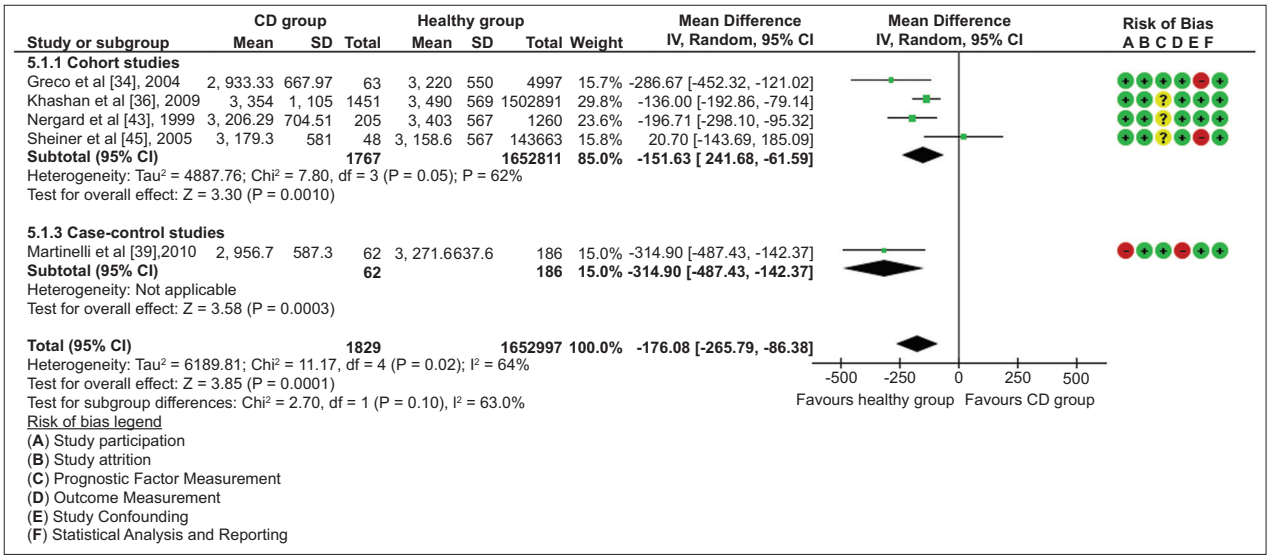
Supplementary Figure 5 Forest plot demonstrating the relative risk for cesarean delivery of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



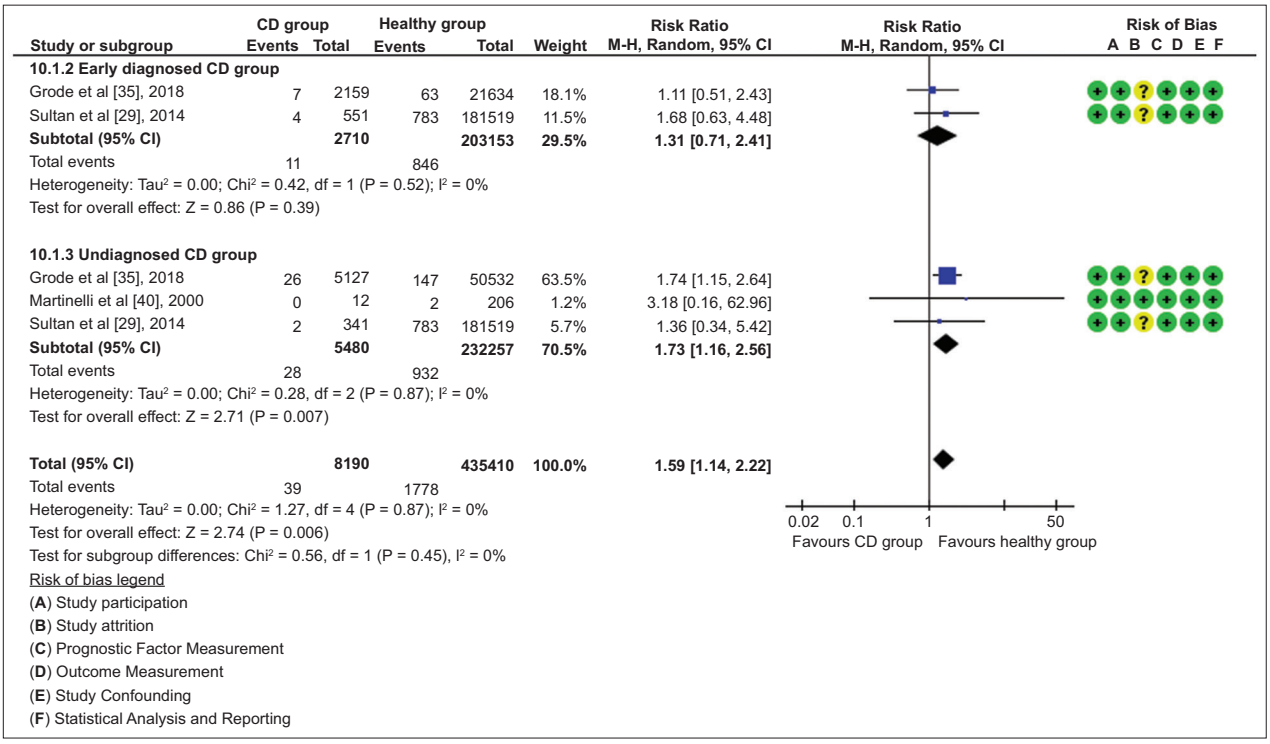
Supplementary Figure 6 Forest plot demonstrating the relative risk for postpartum hemorrhage of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



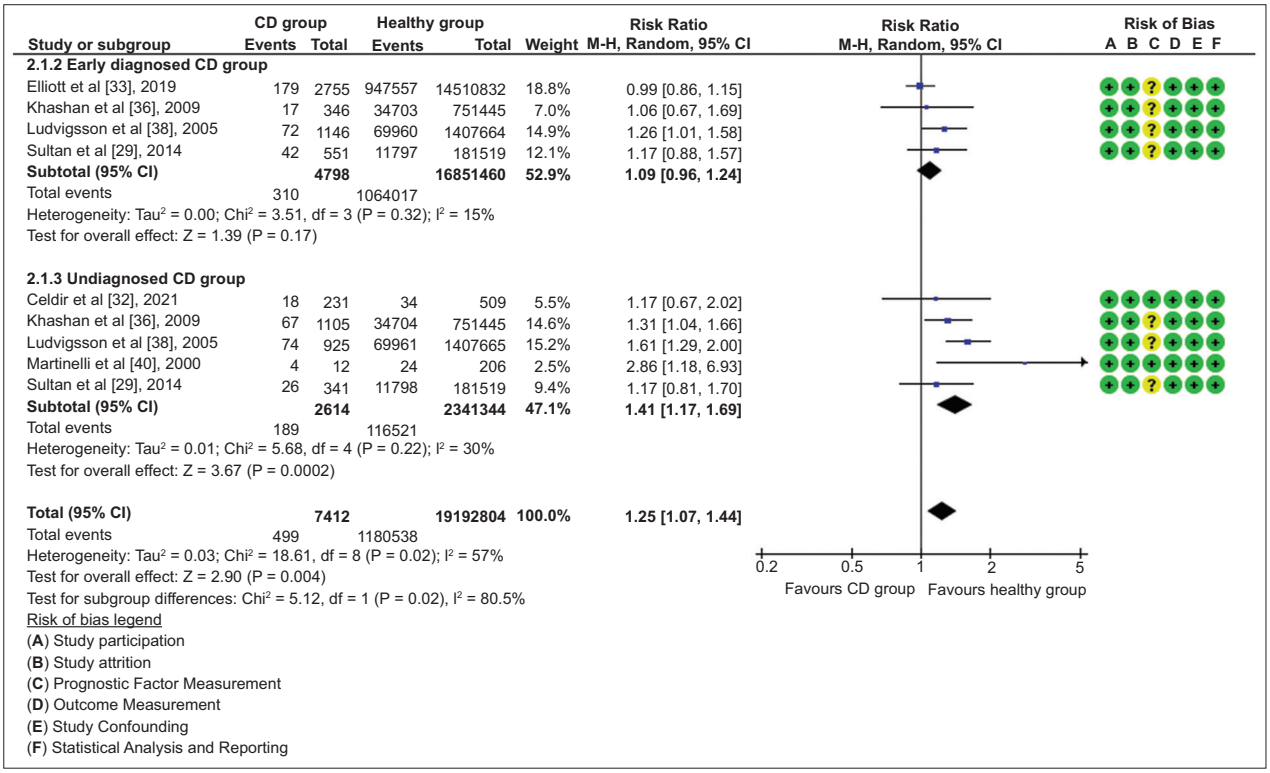
Supplementary Figure 7 Forest plot demonstrating the relative risk for 5-min Apgar score <7 of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



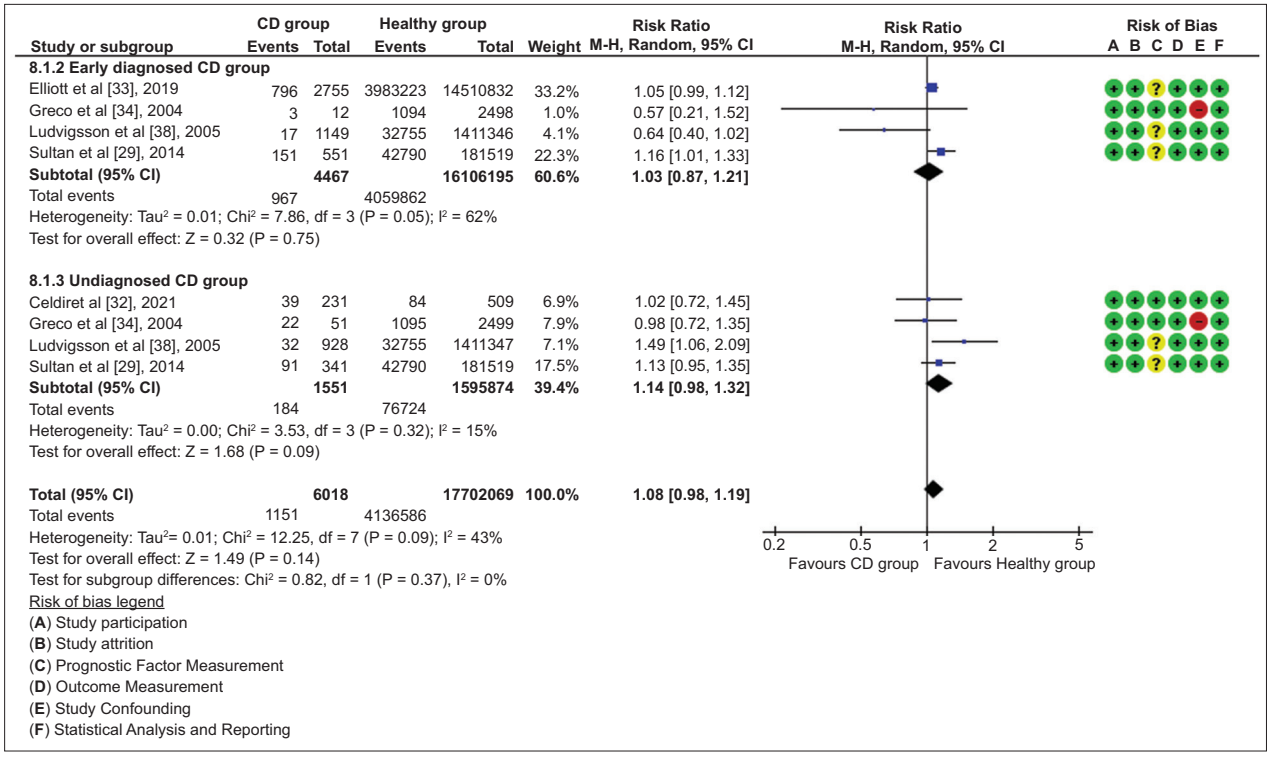
Supplementary Figure 8 Forest plot demonstrating the relative risk for mean birthweight difference of pregnant women with celiac disease compared to a healthy control group
CI, confidence interval



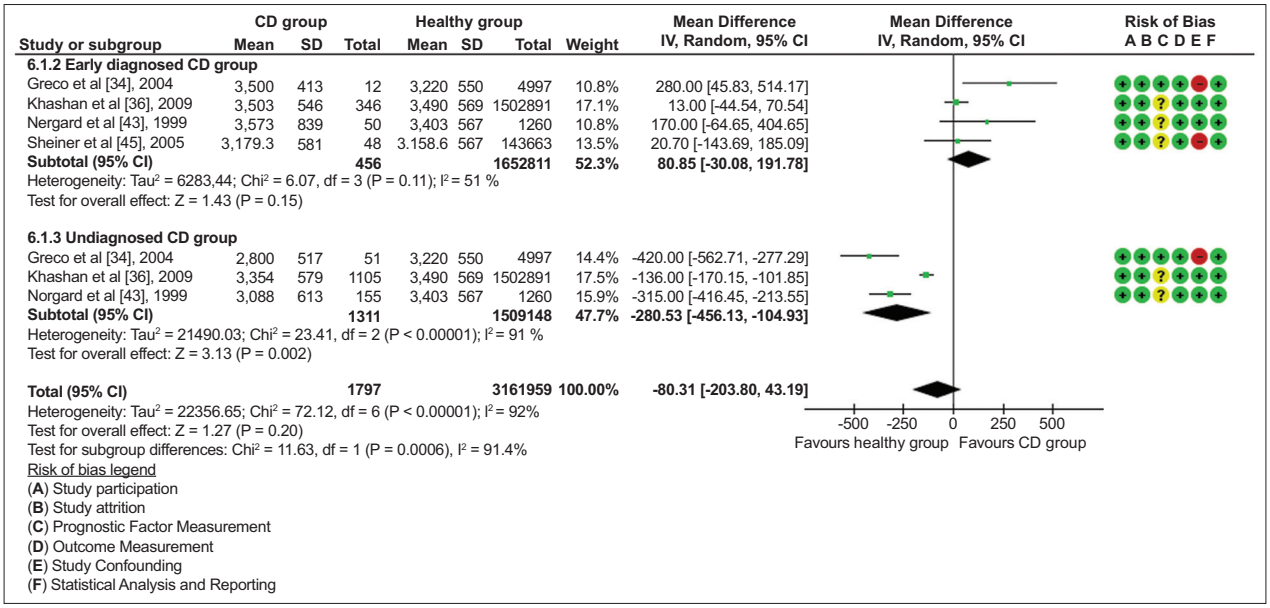
Supplementary Figure 9 Subgroup analysis on stillbirth based on the time of celiac disease diagnosis
CI, confidence interval



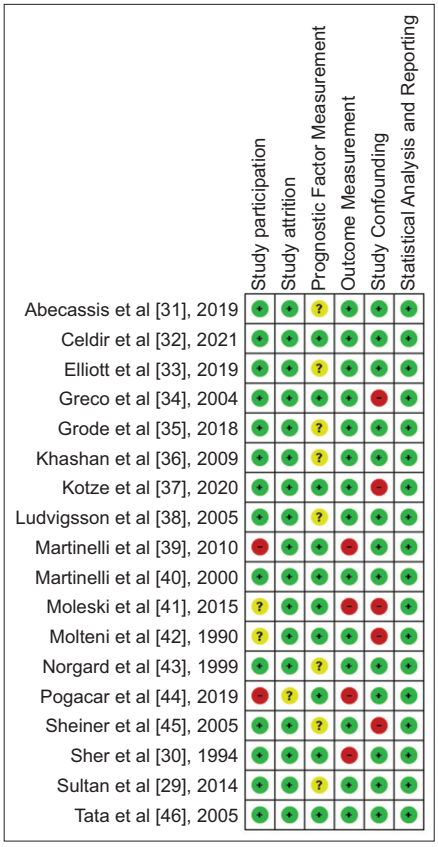
Supplementary Figure 10 Subgroup analysis on preterm delivery based on the time of celiac disease diagnosis
CI, confidence interval



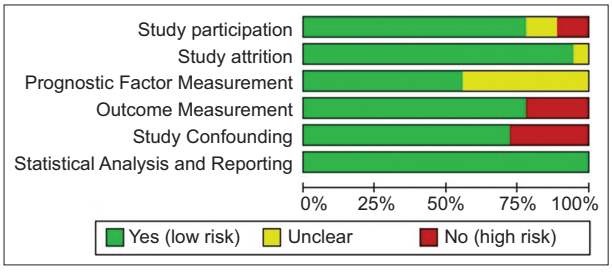
Supplementary Figure 11 Subgroup analysis on cesarean delivery based on the time of celiac disease diagnosis
CI, confidence interval



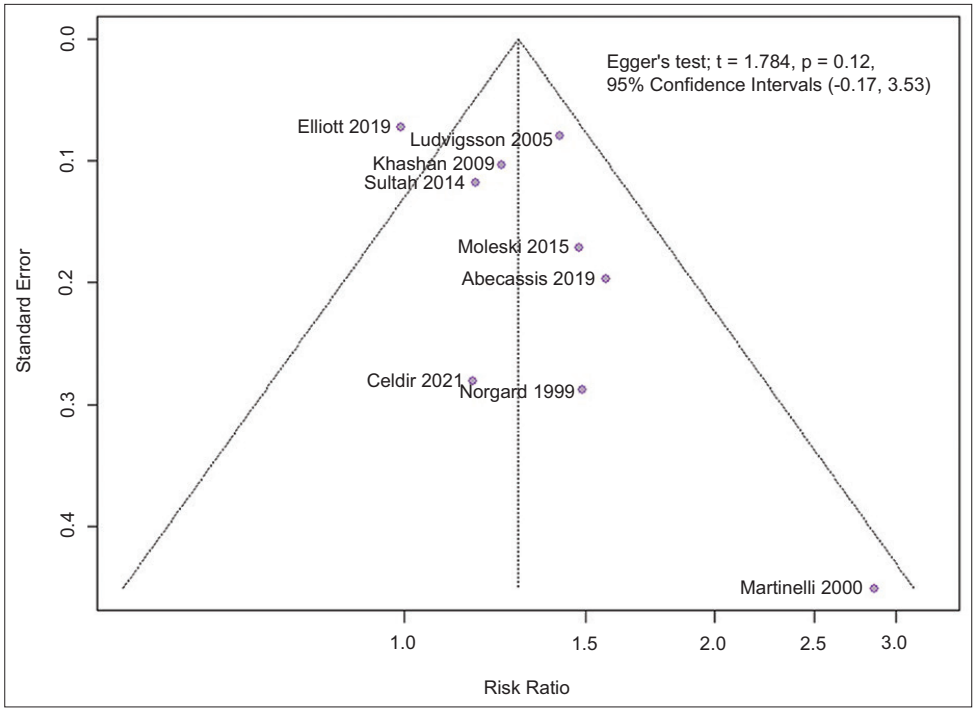
Supplementary Figure 12 Subgroup analysis on mean birthweight difference based on the time of celiac disease diagnosis
CI, confidence interval



Supplementary Figure 13 Risk of bias summary: review of authors' judgments regarding each risk of bias item for each included study



Supplementary Figure 14 Risk of bias graph: review of authors' judgments regarding each risk of bias item presented as percentages across all included studies



Supplementary Figure 15 Funnel plot and Egger's test regarding preterm delivery