Meta-Analysis

Risk of obesity during a gluten-free diet in pediatric and adult patients with celiac disease: a systematic review with meta-analysis

Michele Barone,* Andrea Iannone,* Fernanda Cristofori, Vanessa Nadia Dargenio, Flavia Indrio, Elvira Verduci, Alfredo Di Leo, and Ruggiero Francavilla

Context: *Obesity is a significant risk factor for many pathological conditions. Whether a gluten-free diet (GFD) is a risk factor for overweight or obesity remains controversial.* ***Objective:*** *The primary aim of this study was to assess the prevalence of body mass index (BMI) categories at disease presentation and the variation in BMI category from underweight/normal to overweight/obese and vice versa during a GFD.* ***Data Sources:*** *PubMed, Scopus, and Web of Science databases were searched through February 2021 for retrospective, cross-sectional, and prospective studies reporting BMI categories at disease diagnosis and during a GFD.* ***Data Extraction:*** *Data were extracted by 2 reviewers independently. Disagreements were resolved by consensus; a third reviewer was consulted, if necessary. Risk of bias was assessed with the Cochrane ROBINS-I tool.* ***Data Analysis:*** *Subgroup analysis based on age (pediatric/adult patients), study design (prospective, cross-sectional, retrospective), and duration of GFD was performed.. Forty-five studies were selected (7959 patients with celiac disease and 20 524 healthy controls). The mean BMI of celiac patients at presentation was significantly lower than that of controls ($P < 0.001$). During a GFD, the mean BMI increased significantly (mean difference = 1.14 kg/m^2 [95%CI, 0.68–1.60 kg/m^2]; $I^2 = 82.8\%$; $P < 0.001$), but only 9% of patients (95%CI, 7%–12%; $I^2 = 80.0\%$) changed from the underweight/normal BMI category to the overweight/obese category, while 20% (95%CI, 11%–29%; $I^2 = 85.8\%$) moved into a lower BMI category.* ***Conclusion:*** *Most celiac patients had a normal BMI at presentation, although the mean BMI was significantly lower than that of controls. A GFD does not increase the risk of becoming overweight/obese, especially in children. The quality of several studies was suboptimal, with moderate or high overall risk of bias and heterogeneity.*

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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy characterized by a lifelong intolerance to gluten in genetically predisposed people, with an estimated prevalence of 1 in 100 people.[1] The presentation of CD has changed dramatically over time. Previously thought to be a rare condition characterized by diarrhea and malabsorption, it now represents one of the most common autoimmune disorders[2]. During the last 2 decades, a progressive shift of clinical presentation in favor of so-called atypical extraintestinal symptoms, even among asymptomatic patients with normal weight or even overweight and obesity,[3] has been identified by screening programs.[4]

A lifelong, strict gluten-free diet (GFD) is the mainstay for treating CD and preventing complications.[5] However, there are a number of concerns about the health consequences of following a GFD, particularly the possibility that a GFD could promote overweight or obesity.[6] A large amount of data has been published, with some studies showing a compensatory effect of a GFD in underweight patients who experience a recovery of weight to reach their ideal weight, while other studies have instead demonstrated a propensity toward weight gain and obesity. Two recent systematic reviews, one with a meta-analysis,[7,8] have shown an increase in mean body mass index (BMI) during follow-up without a change in BMI category. However, the literature search for these reviews ends in 2018; moreover, both studies were limited to adult populations, and neither one considered BMI categories.

In the present systematic review with meta-analysis, the literature was systematically reviewed to assess whether patients with CD have a lower BMI at presentation than nonceliac individuals and to understand the influence of a GFD on BMI. Moreover, a subgroup analysis was performed to assess the role of study design (retrospective or prospective), length of follow-up, and, for the first time, age at diagnosis (adults vs children).

METHODS

This systematic review with meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (see Appendix S1 in the Supporting Information online).[9]

Inclusion criteria

The PICOS (Population, Intervention, Comparison, Outcome, Study design) strategy was used to define search strategies and establish the inclusion criteria (Table 1).

Observational studies (retrospective, cross-sectional, or prospective) that included both pediatric and adult populations with CD, without any restrictions on the size or location of the study, were included. Studies reporting body weight categories or the body weight of all study participants, expressed as the mean ± standard deviation (SD) or the median and interquartile range at disease diagnosis or before and during a GFD, were included.

Abstracts and conference papers were excluded a priori. Reports investigating patients affected by CD and other comorbidities (genetic diseases, diabetes, etc) were excluded.

Search strategy and study selection

The PubMed, Scopus, and Web of Science Core Collection (Clarivate Analytics) databases were searched systematically from database inception through January 2021. The literature search was limited to articles published in English in peer-reviewed journals in order to select studies that underwent a rigorous international peer-review process. The search strategies are described in detail in Appendix S2 in the Supporting Information online.

Study selection was performed independently by 2 authors for both the adult (M.B. and A.I.) and the pediatric (F.C. and V.N.D.) populations, in 2 stages. In the initial search, title and abstracts were evaluated according to the eligibility criteria, with a high degree of inter-rater agreement between authors (Cohen $\kappa = 0.87$ for adults and $\kappa = 0.89$ for pediatric studies). Afterward, full-text articles were selected (Cohen $\kappa = 0.93$ for adults and $\kappa = 0.91$ for pediatric studies). Disagreements were resolved by consensus, and a third reviewer (A.D.L.) was consulted, if necessary.

Data collection

A datasheet (Microsoft Excel) approved by 2 authors (M.B. and R.F.) was used to collect all data. Data regarding study characteristics, populations examined, and outcomes were extracted by 2 authors (A.I. and F.C.) independently. When additional information was needed, corresponding authors were contacted by email to obtain further data.

In adults, 4 categories of body weight were identified on the basis of BMI cutoff values: underweight (BMI $< 18.5\,kg/m^2$), normal weight (BMI ≥ 18.5 up to $24.9\,kg/m^2$), overweight (BMI ≥ 25 up to $29.9\,kg/m^2$), and obese (BMI $\geq 30\,kg/m^2$).[10] In pediatric patients, body weight categories were identified by centiles of

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Population	Children and adults with CD, in any country
Intervention	Evaluation of the risk of obesity before and after a GFD
Comparison	Risk of obesity was compared between patients with CD and the general population, if available, and between pediatric and adult patients with CD
Primary outcome	Prevalence of BMI categories at disease presentation and the change in BMI category (ie, BMI increase, BMI reduction, or no change in BMI) from underweight/normal to overweight/obese and vice versa during a GFD
Secondary outcomes	a. Mean BMI at disease diagnosis vs mean BMI after a GFD; b. Impact of study design (prospective, cross-sectional, or retrospective), duration of follow-up (< 2 years, > 2 years), and age (adults vs children) on the results; c. Mean BMI and prevalence of overweight/obesity in patients at CD diagnosis vs healthy controls
Study design	Retrospective, cross-sectional, and prospective studies, without restriction on their size or location. Studies reporting body weight categories and/or the body weight of all study participants, expressed as mean ± SD or median and interquartile range, at the diagnosis of CD or before and after a GFD

Abbreviations: BMI, body mass index; CD, celiac disease; GFD, gluten-free diet; SD, standard deviation.

BMI, which were adjusted by age and sex or *z* scores, depending on the definition used by the authors.[11–13] In the present systematic review, only BMI categories (underweight, normal weight, overweight, and obese) were used.

Outcome measures

The primary outcome was the prevalence of BMI categories at disease presentation and the variation of BMI category (ie, BMI increase, BMI reduction, or BMI unchanged) from underweight/normal to overweight/obese and vice versa during a GFD. Three secondary outcomes were also examined: (1) the difference between mean BMI at disease diagnosis and mean BMI during a GFD; (2) the effect, if any, of study design (prospective, cross-sectional, retrospective), duration of follow-up (≤ 2 years, > 2 years), and age (adults vs children) on the results, as determined by subgroup analysis; and (3) the prevalence of overweight/obesity and the mean BMI in patients at CD diagnosis compared with healthy controls.

Risk-of-bias assessment

Two reviewers (F.C. and V.N.D.) evaluated the methodological quality of primary studies independently, using the ROBINS-I tool for nonrandomized studies.[14] Any discrepancies in data extraction or quality assessment were resolved by discussing and involving a third experienced arbitrator (A.I.).

Data synthesis and statistical analysis

Dichotomous variables were expressed as a proportion with a 95%CI, while continuous variables were expressed as the mean ± standard deviation. Proportions with 95%CIs in individual studies were calculated using the Freeman-Tukey double arcsine transformation, allowing the inclusion of values close to the margins.[15] If only the median and interquartile range were reported for continuous outcomes, the mean and standard deviation were estimated.[16,17] When comparing celiac patients and healthy controls, relative risks (RRs) or weighted mean differences (WMDs) with 95%CIs were estimated for dichotomous or continuous outcomes, respectively. Additionally, WMDs with 95%CIs were calculated to compare BMI values in CD patients at diagnosis and in healthy controls.

Data from individual studies were pooled using the DerSimonian and Laird random-effects model.[18] Heterogeneity among primary studies was assessed using the I^2 statistic, with cutoff points of $< 25\%$, 25%–50%, 50%–75%, and $> 75\%$ indicating little, low, moderate, and high heterogeneity.[19]

Preplanned subgroup analyses were performed by population age (pediatric vs adult), study design (prospective, cross-sectional, or retrospective) and duration of follow-up (≤ 2 years vs > 2 years). Publication bias was explored by funnel plots. All statistical analyses were conducted and all graphics created using Stata software, version 14.0 (StataCorp, College Station, TX).

RESULTS

The flow diagram of the literature search process is shown in Figure 1. After full-text analysis, 45 studies, 22 in pediatric patients[20–41] and 23 in adults,[42–64] met the eligibility criteria and were included in the meta-analysis (Table 2).[20–64]

Five studies included 2 cohorts of patients and reported the results separately for each cohort[34,46,51,53,54]; therefore, individual cohorts were

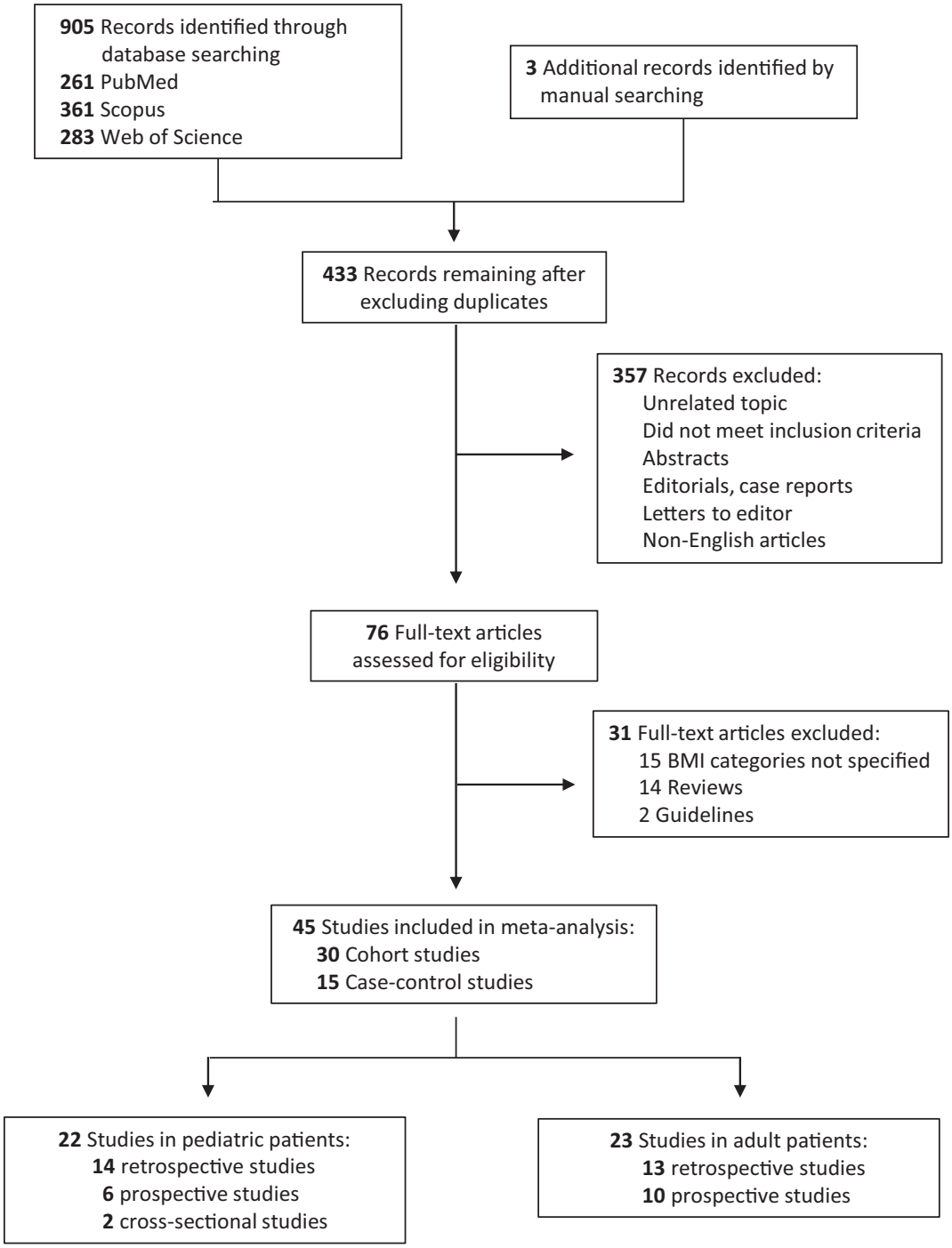

Figure 1 **Flow diagram of the literature search process.**

considered separately. Thirty-four studies (76%) reported the distribution of CD patients in all BMI categories at diagnosis,[20–24,26–33,36–38,40–45,48–50,52,55,57,59–64] 5 studies (11%) reported only data on obese patients together or not with overweight patients,[25,34,35,47] and the remaining 6 studies (13%) reported data as either mean BMI ± SD[46,53,56,58] or median and interquartile range.[33,54] Categories of BMI during a GFD were reported in 22 studies (50%),[22–24,26–31,33,34,36,37,39–43,55,57,59,61] with a period of observation ranging from 1 to 12.6 years.

Altogether, the 45 selected studies, published between 1997 and February 2021 (39 after 2010), included a total of 7959 CD patients from different geographic areas (25 from Europe, 10 from the United States, 4 from Israel, and 2 each from Iran, India, and Australia).

Table 2 **Main characteristics of the studies included in the meta-analysis**

Reference	Sample size (CD patients)	Sample size (controls)	Age (years)	Sex (M/F)	Study design	Duration of follow-up[a]
Pediatric studies						
Almallouhi et al (2017)[20]	93	Absent	< 18	38/55	Retrospective	5 y
Ballestero-Fernández et al (2019)[21]	70	67	< 18	35/35	Cross-sectional	> 1 y
Brambilla et al (2013)[22]	150	288	8.0[b]	47/103	Retrospective	4.4 (0.5–12.6) y[c]
Capriati et al (2016)[23]	445	Absent	6 (3.5–9.3)[c]	154/291	Retrospective	20 (12–28.5) mo[c]
Dehghani et al (2017)[24]	44	Absent	3–12[d]	14/30	Retrospective	2 y
Forchielli et al (2019)[25]	79	Absent	7.9 ± 3.8[e]	52/27	Prospective	1 y
Grandone et al (2015)[26]	280	Absent	5.1 ± 3.8 [e]	115/165	Retrospective	3.2 ± 1.2 y[e]
Levran et al (2018)[27]	40	15	4–15.7[d]	19/21	Prospective	26.6 ± 16.1 mo[e]
Livshits et al (2017)[28]	390	407	7.1 ± 4.3[e]	116/224	Retrospective	13 ± 7 mo[e]
Mackinder et al (2014)[29]	23	Absent	10.7 ± 2.9 [e]	11/12	Retrospective	2 y
Maggio et al (2007)[30]	14	Absent	11 (5.5–13.8)[f]	3/11	Prospective	12 mo
Norsa et al (2013)[31]	114	Absent	10.4 ± 4.1[e]	38/76	Prospective	> 1 y
Nwosu et al (2013)[32]	40	50	7.5 ± 2.7[e]	14/26	Retrospective	NA[g]
Reilly et al (2011)[33]	318	Absent	8.3 (1.1–19.5)[h]	137/181	Retrospective	35.6 (95%CI, 31.3–39.9) mo
Sansotta et al (2020)[34] (Italian cohort)	125	125	7.3[i]	32/93	Retrospective	4.1 (0.5–12.6) y[c]
Sansotta et al (2020)[34] (American cohort)	140	140	8.4[i]	47/93		3.2 (0.5–8.8) y[c]
Shahraki et al (2018)[35]	225	Absent	7.4 ± 3.8 [e]	86/139	Retrospective	NA[g]
Siddh et al (2016)[36]	50	50	< 18	20/30	Prospective	≤ 6 mo
Valletta et al (2010)[37]	149	Absent	6.2 (0.7–17)[f]	57/92	Retrospective	4.5 (1–16.3) y[f]
van der Pals et al (2014)[38]	239	12 227	< 18	102/137	Cross-sectional	NA[g]
Venkatasubramani et al (2010)[39]	143	Absent	8.3 (1-17)[h]	NA	Retrospective	1 y
Villanueva et al (2020)[40]	65	Absent	5.1 ± 3.6 [e]	NA	Retrospective	2 y
Zifman et al (2019)[41]	109	Absent	6.8 ± 3.4 [e]	45/64	Prospective	1 y
Studies in adults						
Agarwal et al (2021)[42]	44	Absent	29.5 ± 11.3 [e]	18/26	Prospective	1 y
Barone et al (2016)[43]	39	39	35 (25–45)[f]	9/30	Retrospective	24.3 (20.2–35.6) mo[c]
Capristo et al (2005)[44]	18	22	31.4 ± 7.8[e]	0/18	Prospective	20.6 ± 1.2 mo
Cheng et al (2010)[45]	369	Absent	≥ 18	121/248	Prospective	2.8 ± 2.7 y[e]
Choung et al (2020)[46] (classical)	62	Absent	44.7 ± 15.5e	19/43	Retrospective	6.7 ± 3.7 ye
Choung et al (2020)[46] (nonclassical)	60	Absent	45.4 ± 14.4[e]	21/39		
Ciccone et al (2019)[47]	185	Absent	36[b]	42/143	Retrospective	7 (1–36) y[f]
Dickey & Kearney (2006)[48]	371	Absent	> 20	114/257	Retrospective	≤ 24 mo
Kabbani et al (2012)[49]	679	Absent	52.4 ± 16.0 [e]	163/516	Retrospective	39.5 (1–345) mo[f]
Lanzini et al (2006)[50]	44	53	33 ± 2[e]	10/34 (P) 45/8 (C)	Prospective	≤ 12 mo
Newnham et al (2016)[51] (cohort 1)	52	Absent	40 (18–71)[h]	35/57	Prospective	1 y
Newnham et al (2016)[51] (cohort 2)	40	Absent	48 (18–71)[h]			5 y
Olén et al (2009)[52] (female cohort)	174	Absent	18–50[d]	174	Retrospective	NA[g]
Olén et al (2009)[52] (male cohort)	70	Absent	18–50[d]	70		
Passananti et al (2012)[53] (cohort 1)	55	Absent	35.1 ± 11.3[e]	0/55	Prospective	≤ 24 mo
Passananti et al (2012)[53] (cohort 2)	55	Absent	35.1 ± 8.7[e]	0/55	Prospective	≤ 60 mo
Saukkonen et al (2017)[54] (cohort 1, with anemia)	38	Absent	49 (16–79)[f]	4/34	Prospective	12 mo
Saukkonen et al (2017)[54] (cohort 2, without anemia)	125	Absent		48/77		

(continued)

Table 2 **Continued**

Reference	Sample size (CD patients)	Sample size (controls)	Age (years)	Sex (M/F)	Study design	Duration of follow-up[a]
Sinniah & Roche (2012)[55]	100	Absent	> 18	NA	Retrospective	NA[g]
Smecuol et al (1997)[56]	15	Absent	41 (19–72)[f]	NA	Prospective	37 (25–49) mo[h]
Stein et al (2016)[57]	157	696	44.3 (37.2–52.9)[c]	NA	Retrospective	4.5–36.2 mo[d]
Tetzlaff et al (2017)[58]	20	20	CD 22.8 (20.4–26.2)[c]	NA	Retrospective	NA[g]
Tortora et al (2015)[59]	98	Absent	> 18	NA	Prospective	1 y
Tucker et al (2012)[60]	187	Absent	54 (18–87)[f]	60/127	Retrospective	NA[g]
Ukkola et al (2012)[61]	698	6325	CD 16–64[d]	181/517	Prospective	1 y
Unalp-Arida et al (2017)[62]	79	Absent	20–80[d]	33/46	Retrospective	NA[g]
Whitehead (2013)[63]	65	Absent	> 18	NA	Retrospective	> 12 mo
Zanini et al (2013)[64]	715	Absent	35 ± 13[e]	209/504	Retrospective	1.6 ± 1.0 y[e]

Abbreviations: C, controls; CD, celiac disease; NA, not assessed; P, patients.
[a]Minimum duration of follow-up: 12 months.
[b]Median.
[c]Median and interquartile range.
[d]Range.
[e]Mean ± SD
[f]Median and range.
[g]Evaluations performed only at diagnosis.
[h]Mean and range.
[i]Mean.

Of these, 14 studies (29%) included 20 524 healthy individuals.[21,22,27,28,32,34,36,38,43,44,50,57,58,61] Twenty-six studies (58%) were retrospective,[20,22–24,26,28,29,32–35,37,39,40,43,46–49,52,55,57,58,60,62–64] 2 (4%) were cross-sectional,[21,38] and 17 (38%) were prospective.[25,27,30,31,36,38,41,42,44,45,50,51,53,54,56,59,61] The sample size ranged from 14 to 715 patients: 22 studies (49%) included 100 individuals or fewer,[20,21,24,25,27,29,30,32,36,40,42–44,46,50,51,55,56,58,59,62,63] 14 studies (31%) included 101 to 250 individuals,[22,31,34,35,37–39,41,47,52–54,57,60] and 9 studies (20%) included more than 250 individuals[23,26,28,33,45,48,49,61,64] (Table 2).[20–64]

BMI category at diagnosis

The evaluation of the pooled prevalence of patients in different BMI categories at CD diagnosis shows that most of the patients (67%) were within the normal BMI range (95%CI, 63%–71%; $I^2 = 90.75\%$), while 14% were overweight (95%CI, 11%–17%; $I^2 = 89.91\%$), 13% were underweight (95%CI, 10%–17%; $I^2 = 93.80\%$), and 6% were obese (95%CI, 4%–8%; $I^2 = 87.15\%$) (Figure 2[20–24,26–43,45,48–50,52,55,57,59–64]). The mean BMI of celiac patients at diagnosis was significantly lower than that of controls ($-1.62\ kg/m^2$; 95%CI, -2.58 to $-0.65\ kg/m^2$; $P < 0.001$) (Figure 3A[38,43,44,50,52,57,58]). In addition, celiac patients had a significantly reduced risk to be in the overweight/obese category compared with controls (RR 0.69; 95%CI, 0.57–0.83; $P < 0.001$) (Figure 3B[22,27,28,32,34,38,57,61,62]).

Subgroup analysis

The subgroup analysis by population age showed that the prevalence of normal weight was significantly higher in pediatric patients than in adult patients (Figure 4A[20–24,26–38,40–43,45,48–50,52,57,59–61,63,64]) (71% [95%CI, 66%–76%] vs 61% [95%CI, 57%–65%]; $P = 0.003$), while no difference was found when comparing adults and pediatric patients in the underweight category. On the contrary, the prevalence of overweight was significantly higher in adults than in pediatric patients (20% [95%CI, 16%–24%] vs 9% [95%CI, 7%–10%]; $P < 0.001$) (Figure 4B[20–23,26–28,30,31,33,36,37,40–43,45,48–50,55,57,59–64]), and a similar difference was observed for the prevalence of obesity (10% [95%CI, 7%–13%] vs 3% [95%CI, 2%–5%]; $P < 0.001$) (Figure 4C[20–23,26–28,30–33,36,37,39–43,45,48–50,55,57,59–64]). The subgroup analysis by study design showed a similar prevalence of underweight patients in retrospective studies (12%; 95%CI, 9%–16%) and prospective studies (16%; 95%CI, 8%–27%), and a significantly lower prevalence in the only 2 cross-sectional studies (5%; 95%CI, 2%–7%) ($P = 0.001$) (see Figure S1A in the Supporting Information online). Accordingly, a higher prevalence of normal-weight patients was observed in cross-sectional studies (82%; 95%CI, 78%–86%) than in retrospective (68%; 95%CI, 64%–72%) or prospective (62%; 95%CI, 53%–70%) studies ($P < 0.001$) (see Figure S1B in the Supporting Information online). No difference was observed for the overweight or obese categories. Funnel plots were used to determine whether publication bias affected the outcomes, resulting in no small-study effects (see Figure S2A–S2E in the Supporting Information online).

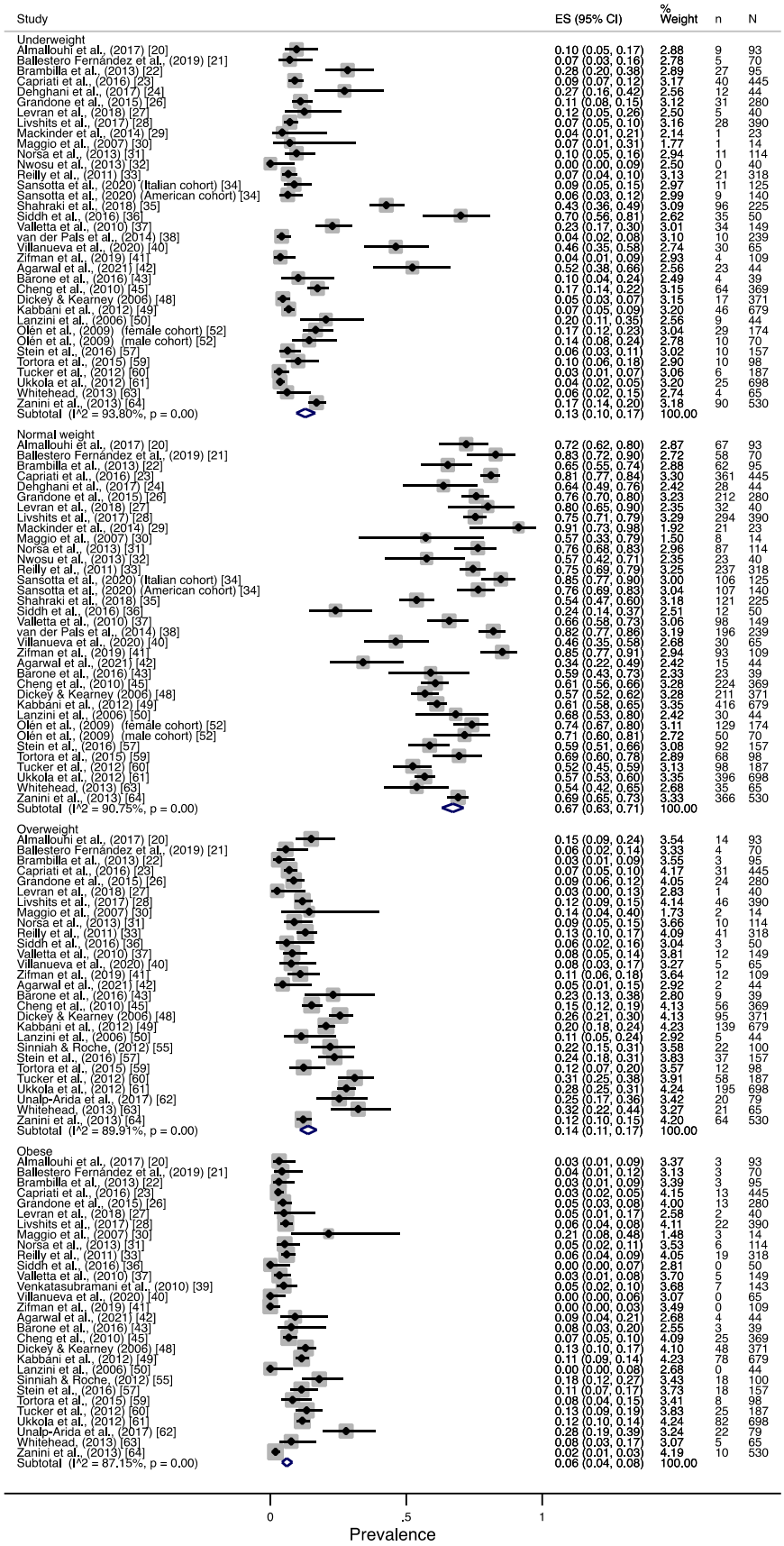

Figure 2 **Pooled prevalence of patients in different body mass index categories at diagnosis of celiac disease**. The effect size (ES) was expressed as prevalence. *Abbreviation*: ES, effect size.

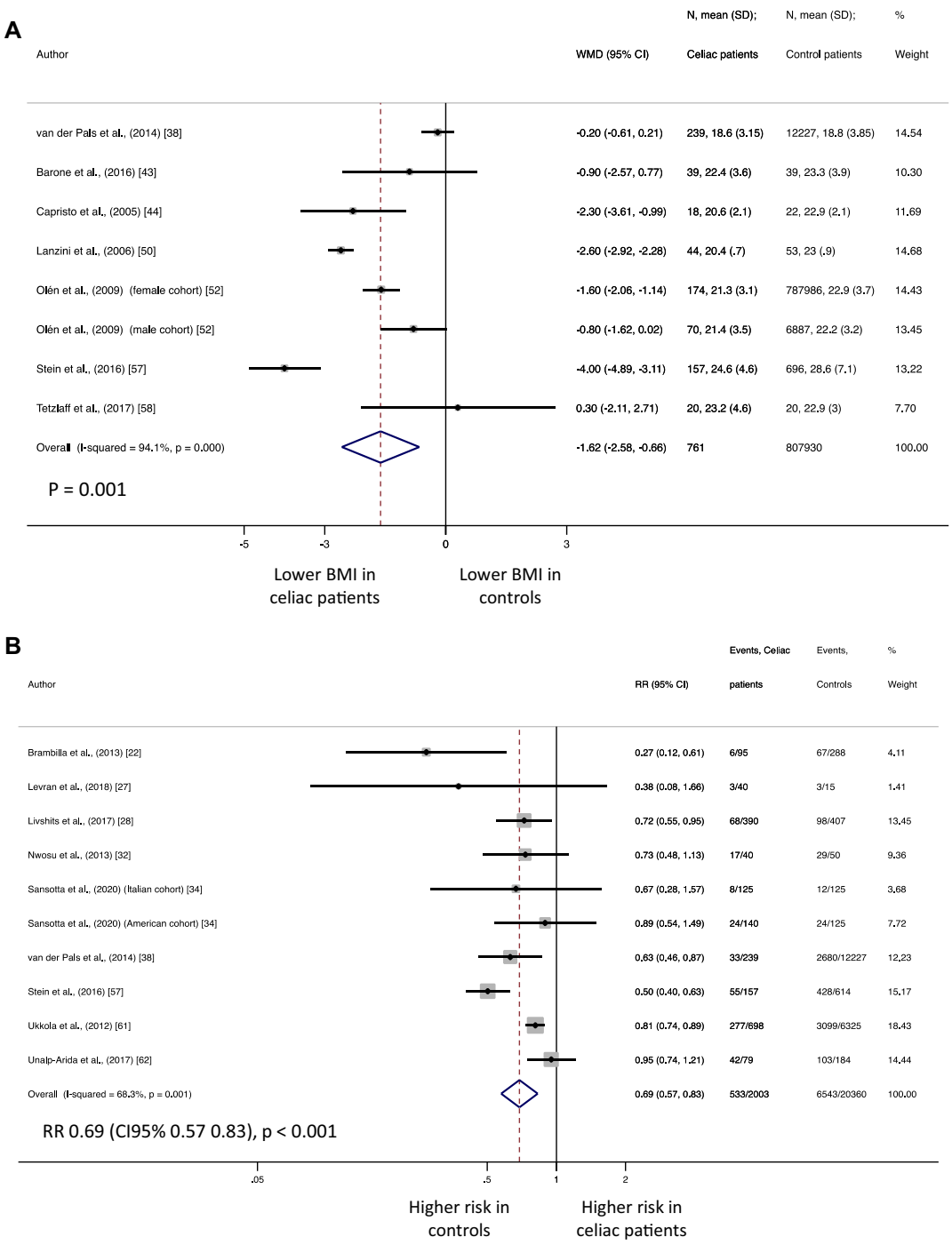

Figure 3 **(A) Mean body mass index (BMI) at diagnosis in patients with celiac disease compared with controls, and (B) risk of patients with celiac disease to be in overweight/obese body mass index category compared with controls.** The effect size was expressed as the weighted mean difference (WMD) (kg/m^2) in (A) and as the relative risk (RR) in (B).

Effect of GFD on BMI category

During a GFD, celiac patients significantly increased their mean BMI compared with that observed at diagnosis (WMD = 1.14 kg/m2; 95%CI, 0.68–1.60 kg/m2; $I2 = 82.8\%$; $P < 0.001$) (Figure 5[36,42–46,49–51,53,54,56,59,64]). The pooled prevalence of patients in different BMI categories during a GFD showed that the percentages of patients in the overweight and obese categories remained similar to those observed at disease presentation, ie, 13% (95%CI, 8%–19%; $I^2 = 93.1\%$) and 7% (95%CI, 4%–10%; $I^2 = 88.3\%$), respectively (see Figure S3 in the Supporting Information online).

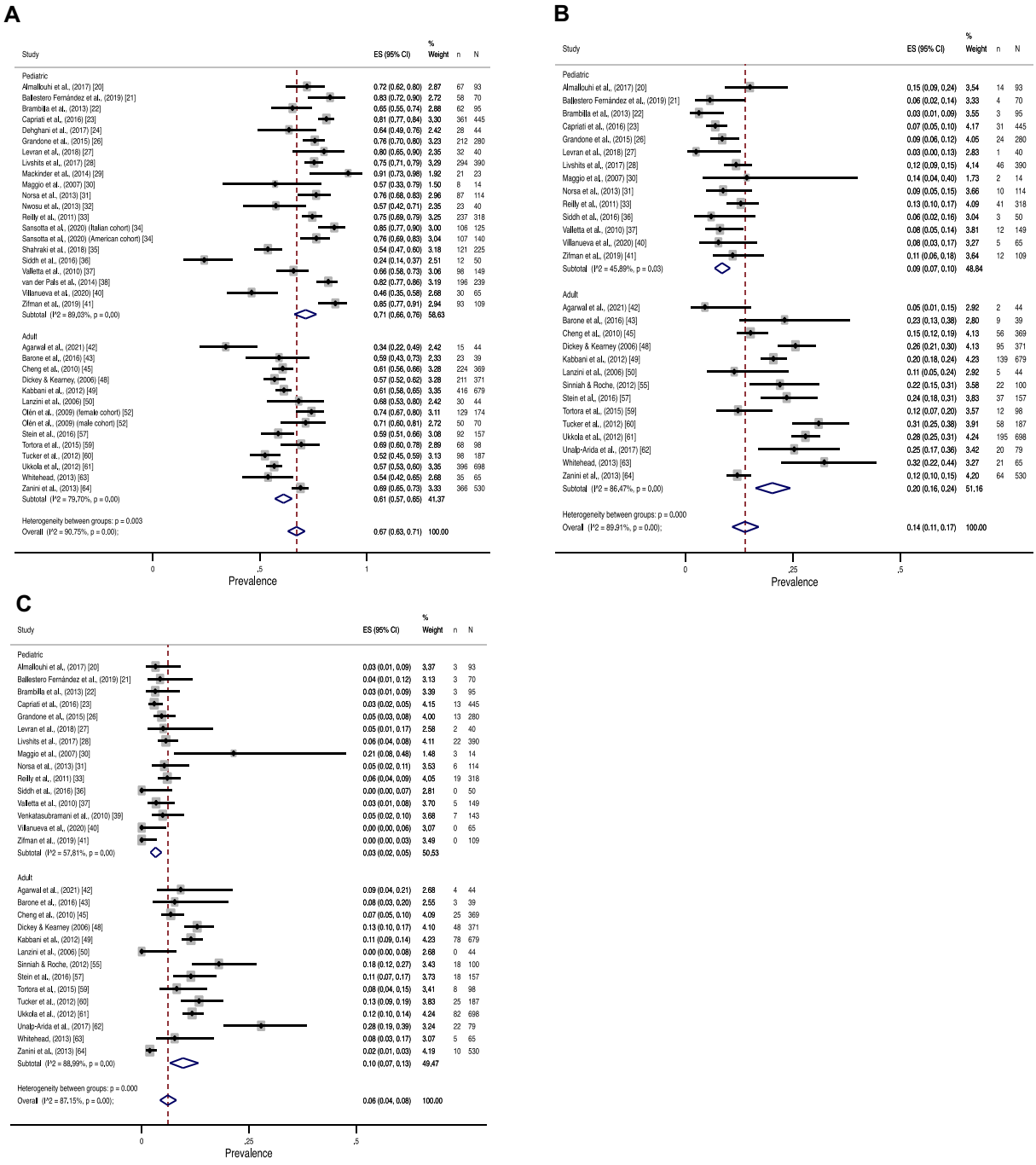

Figure 4 **Pooled prevalence of patients in the (A) normal-weight, (B) overweight, and (C) obese body mass index categories at diagnosis of celiac disease, according to population age (pediatric vs adult patients).** The effect size (ES) was expressed as prevalence.

Interestingly, the subgroup analysis by age showed that the prevalence of normal weight was significantly higher in pediatric patients than in adult patients (76% [95%CI, 70%–81%] vs 55% [95%CI, 50%–60%], $P < 0.001$) (see Figure S4A in the Supporting Information online), whereas the prevalence of overweight and obesity was significantly higher in adults than in pediatric patients, ie, 26% (95%CI, 20%–33%) vs 9% (95%CI, 6%–12%) ($P < 0.001$) and 14% (95%CI, 10%–20%) vs 5% (95%CI, 2%–8%) ($P = 0.002$), respectively (see Figure S4B–S4C in the Supporting Information online).

To further evaluate the risk of developing overweight/obesity during a GFD, a pooled estimate of the change from the underweight/normal BMI category to the overweight/obese BMI category was calculated. Data demonstrated that 9% of the entire study population (95%CI, 7%–12%; $I^2 = 80.0\%$) changed to a higher BMI category; however, this percentage was

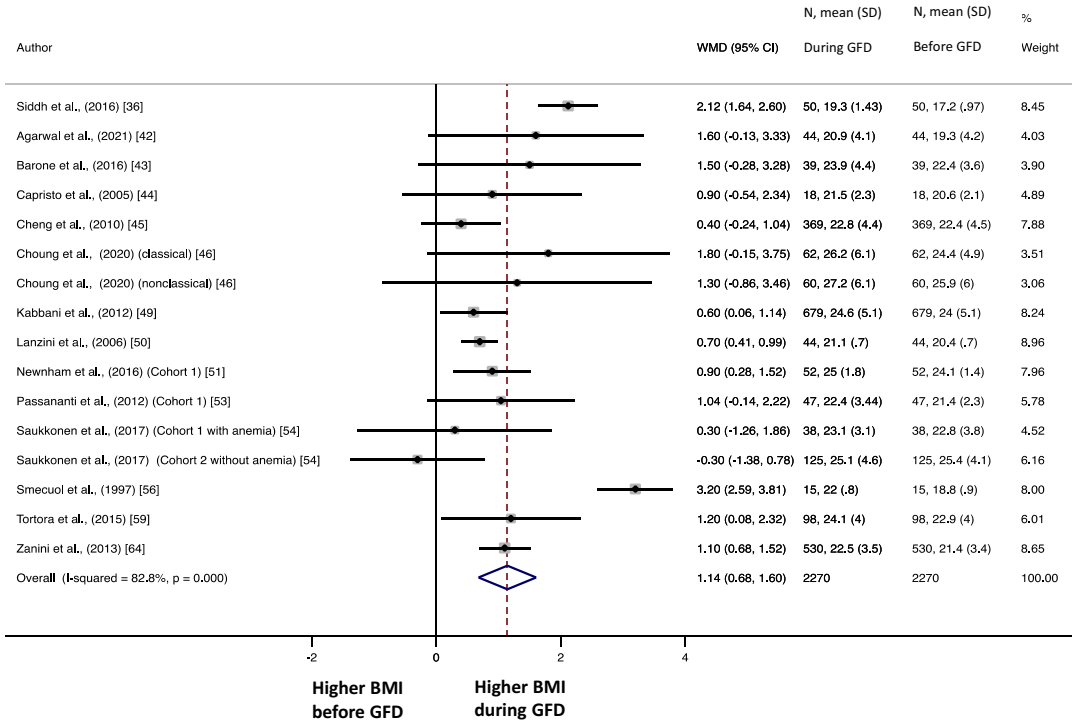

Figure 5 **Comparison of mean body mass index (BMI) at diagnosis and during a gluten-free diet (GFD) in patients with celiac disease.** The weighted mean difference (WMD) was expressed as kg/m^2.

significantly higher in adults than in children (12% [95%CI, 8%–17%] vs 6% [95%CI, 4%–9%]; $P = 0.013$) (Figure 6A [22–24,27–31,33,34,36,43,45,47–50,55,59,61,64]). Conversely, 20% (95%CI, 11%–29%; $I^2 = 85.8\%$) of the entire population changed from the overweight/obese category to the underweight/normal category, with the percentage being significantly higher in the pediatric vs the adult population (34% [95%CI, 17%–54%] vs 8% [95%CI, 5%–12%]; $P < 0.001$) (Figure 6B[22–24,27,28,30,31,33,34,36,39,43,45,48–50,59,61,64]).

It is noteworthy that BMI category changes were more represented in retrospective studies than in prospective studies (26% [95%CI, 14%–41%] vs 9% [95%CI, 2%–19%]; $P = 0.047$) (see Figure S5A in the Supporting Information online) and in trials with a follow-up duration of more than 2 years, although in this case the difference did not reach statistical significance (28% [95%CI, 14%–43%] vs 11% [95%CI, 3%–21%], $P = 0.06$) (see Figure S5B in the Supporting Information online). Finally, funnel plots created to explore potential publication bias showed no small-study effects (see Figure S6A–S6F in the Supporting Information online).

Assessment of study quality and risk of bias

The overall risk of bias in the 22 pediatric studies was low in 10 (45.5%)[22–24,27,28,33–35,37,40] and moderate in 12 (54.5%)[20,21,25,26,29–32,36,38,39,41] (see Figure S7 in the Supporting Information online). In detail, among studies with low risk of bias, reasons for risk of bias were as follows: deviation from intended intervention in 15 (68.2%),[22–29,33–38,40] missing outcomes in 18 (81.8%),[21–24,26–38,40] measurement of outcomes in 10 (45.5%),[20,26,29–32,34,35,37,40] and selection of results in 15 62.8%).[20–24,27,28,30,31,33–35,37,40,41] Among studies with moderate risk of bias, reasons for risk of bias were as follows: deviation from the intended intervention in 7 (31.8%),[20,21,30–32,39] missing outcomes in 4 (18.2%),[20,25,39,41] measurement of outcomes in 12 (54.5%),[21–25,27,28,33,36,38,39,41] and selection of reported results in 6 (27.3%)[26,29,32,36,38,39]. Only 1 study (4.5%)[25] had a critical risk of bias, owing to the selection of reported results. In the 23 studies performed in adults, the overall risk of bias was low in 13 (57%),[42,43,45,46,49,51,54,57,59–62,64] moderate in 5 (22%)[48,52,55,56,63] and high in 5 (21%)[44,47,50,53,58] (Figure S7 in the Supporting Information online). In detail, the risk of bias was low in 13 studies (57%)[42,43,45,46,48,49,51,57,59–62,64] and moderate in 10 studies (43%)[44,47,50,52–56,58,63] that showed deviation from the intended intervention; low in 15 (65%),[42,43,45,46,48,49,51,52,54,57,59–62,64] moderate in 3 (13%),[55,56,63] and high in 5 (22%)[9] that were missing data; low in 12 (52%),[43,45,46,49,51,54,57,59–62,64] moderate in 6 (26%),[42,48,52,55,56,63] and high in 5 (22%)[44,47,50,53,58] that showed bias in measurement of outcomes, and low

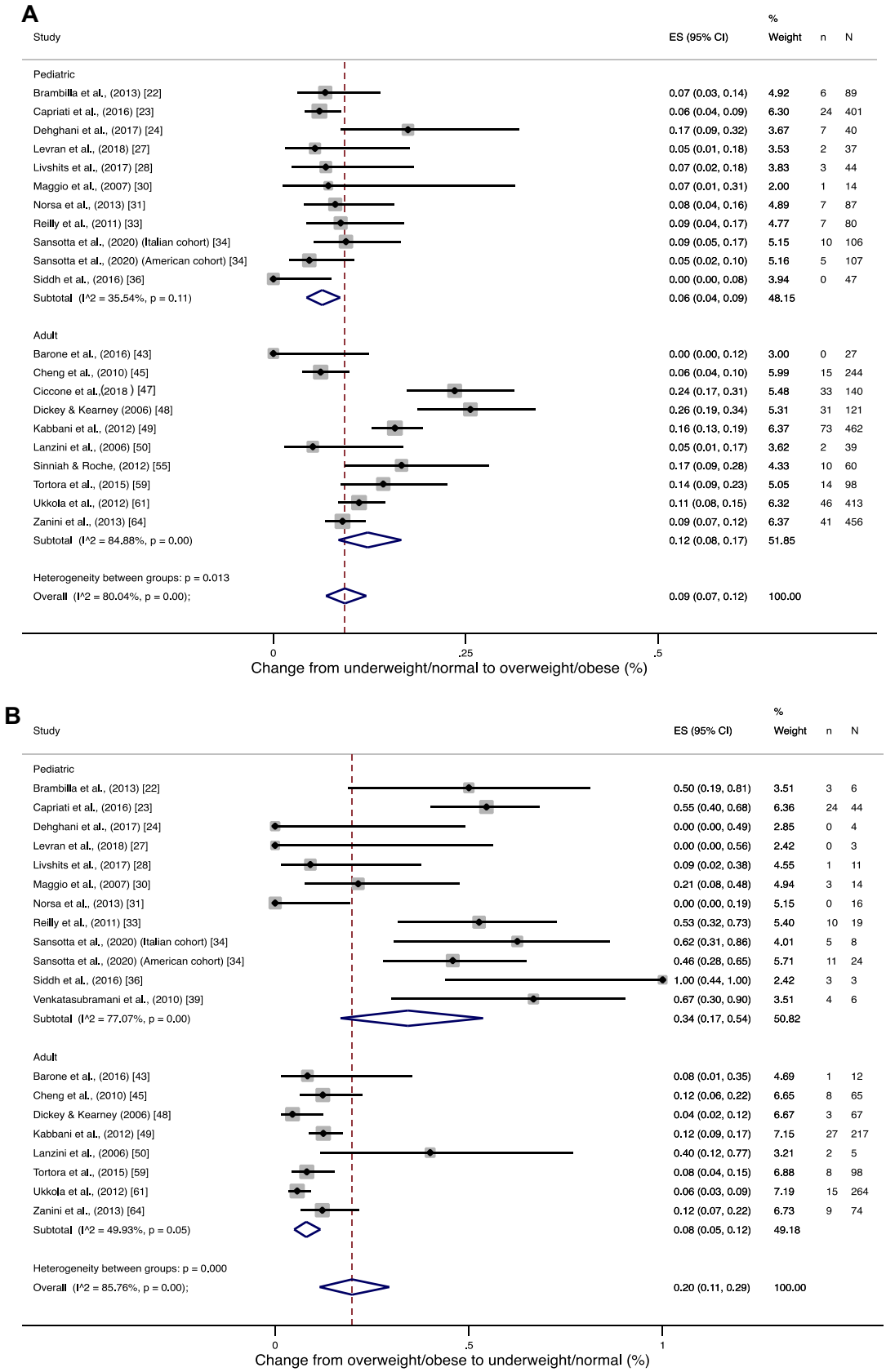

Figure 6 **Pooled estimate of change from (A) underweight/normal body mass index (BMI) category to overweight/obese BMI category and from (B) overweight/obese BMI category to underweight/normal BMI category after a gluten-free diet, according to population age (pediatric vs adult patients).** The effect size (ES) was expressed as percentage change.

in 14 (61%),[43,45,46,48,49,51,52,54–56,59,61,62,64] moderate in 4 (17%),[42,57,60,63] and high in 5 (22%)[44,47,50,53,58] that showed bias in the selection of reported results.

DISCUSSION

The clinical picture of CD has changed profoundly in recent decades. The increased index of suspicion and the adoption of case-finding strategies have contributed to the early recognition of CD, before the onset of classical symptoms. Therefore, increasingly more individuals with CD at diagnosis are within the normal weight range, and the finding of overweight or obesity among has become more common.

In the context of a society moving toward obesity, the GFD is gaining prominence in the scientific literature because of its purported ability to facilitate weight gain. Thus far, however, the literature has produced conflicting results and 2 systematic reviews.[7,8] The only systematic review with a meta-analysis analyzed only an adult population and did not consider variations between BMI categories.[7]

The data presented herein show that most patients with CD were in the normal weight range at diagnosis. Only 13% of patients were underweight at diagnosis, and the prevalence of overweight and obesity was 14% and 6%, respectively. Moreover, although the mean BMI of the CD population increased significantly during a GFD, most patients remained in the same BMI category. These findings highlight 2 clinical implications. The first is that the index of suspicion for CD can no longer be based on body weight alone,[65] confirming findings that the probability of encountering overweight and obese patients at the presentation of disease is increasing over time.[66–68] This change in CD presentation can be explained at least in part by the increased knowledge of the disease and the availability of highly accurate diagnostic tests that allow identification of CD patients, irrespective of clinical presentation.[67,69] The second clinical implication is that a GFD does not cause a significant change in body weight. This finding is of very current relevance, given that celiac patients are concerned about gaining weight, while nonceliac patients follow the GFD with the intent of losing weight. It has become increasingly common to see weight-loss advice on websites that advertise a GFD and use celebrities as examples of those who have benefited from it. It is widely accepted by the scientific community that this advice has no scientific basis, and the results of the present study provide validation of this.

For the first time in the scientific literature, a systematic review comparing adult and pediatric populations with CD has shown the prevalence of normal and underweight BMI to be significantly higher in children and the prevalence of overweight/obese BMI to be significantly higher in adults. This result agrees with the observation that children are more prone to be symptomatic at disease presentation and therefore are more frequently affected by malabsorption, whereas adults more frequently have an atypical or oligosymptomatic presentation.[70] Moreover, after a GFD, an increase in the BMI category was significantly more frequent in adults, while the opposite was observed in children.

Two previous systematic reviews that included only studies in adults have been published. In one, Nikniaz et al[7] performed a meta-analysis, reporting a statistically significant increase in BMI during the follow-up period (standard mean difference = 0.26; 95%CI, 0.17–0.35; $P < 0.001$), although the mean BMI remained in the normal-weight category.[7] In the other, Potter et al[8] focused mainly on the effect of a GFD on cardiovascular risk factors and reported an increase in BMI, though patients remained within the normal-weight category. In agreement with these data, the present meta-analysis shows that the mean BMI of the CD population increased significantly during a GFD (WMD = 1.14 kg/m^2), especially in the pediatric population, and most patients remained in the same BMI category. More interestingly, a reduction of underweight BMI in favor of normal-weight BMI was found, whereas patients in the overweight/obese BMI category remained in the same category after a GFD. In fact, only 9% of celiac patients moved up from an underweight/normal BMI category to an overweight/obese BMI category, whereas 20% changed in the opposite direction, moving from the overweight/obese BMI category to the underweight/normal BMI category. This change of category was significantly higher in the pediatric population than in the adult population.

Finally, consistent with the data at diagnosis, findings during a GFD showed that children were significantly more represented in the normal-weight BMI category than adults and were less represented in the overweight and obese BMI categories. This finding is in line with the World Health Organization's global estimate of overweight and obesity, which shows an increased prevalence of obesity with increasing age.[71]

There are multiple mechanisms involved in body weight increase, depending mainly on energy intake, nutrient absorption, and physical activity. The simplest explanation is that, during a GFD, there is a *restitutio ad integrum* of the gut mucosa, which results in the recovery of absorptive capacities and a subsequent increase in weight. On the other hand, a GFD may be rich in sugar (simple sugars and processed foods with a higher glycemic index)[72] and fat (high intakes of saturated fatty acids and cholesterol) and deficient in fiber,[73] all of which might facilitate an increase in weight.

Finally, stress-related dietary issues might be responsible for emotional eating, which, as documented for other chronic diseases, is more pronounced in children with CD.[74]

An attempt to understand why a GFD can cause a reduction in body weight might be more challenging. One explanation could be that a GFD restores a state of complete well-being to the patient, who is then able to modify a sedentary lifestyle and regain the ability to be physically active and play sports, resulting in increased caloric consumption. Finally, a different gut microbiota induced by dietary change may play a key role in weight balance.[75]

Strengths and limitations

To the best of knowledge, this is the first meta-analysis that investigates the effect of a GFD on BMI by comparing pediatric and adult patients with CD. In addition, this is the first pooled analysis, conducted in 7959 CD patients and 20 524 healthy individuals, to evaluate the change of BMI category during a GFD. This specific analysis allowed more accurate results to be obtained about the possibility that a GFD may contribute to overweight or obesity. In addition, a subgroup analysis based on the study design (prospective, cross-sectional, or retrospective) and the duration of follow-up (≤ 2 years or > 2 years) was performed.

This meta-analysis included only studies published in English, which could have caused bias. However, this approach ensured that only data extracted from studies that underwent a rigorous international peer-review process were included. The quality of several studies, which had moderate or high overall risk of bias and exhibited heterogeneity for all evaluated outcomes, was suboptimal. The inclusion of patients of different ethnicities with different dietary habits may have played a relevant role in causing the observed heterogeneity. No clear evidence of publication bias was found. Finally, the influences of dietary intake, physical activity, social class, and education level, as well as the confounding variable of disease remission, were not evaluated.

CONCLUSION

The present meta-analysis shows that a GFD does not increase the risk of developing overweight or obesity. Large prospective studies from different geographical areas that examine dietary counseling or the monitoring of dietary habits, assess physical activity, and determine mucosal healing in patients with CD for whom precise anthropometric data are obtained would be helpful to confirm these findings.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA 2020 checklist**

Appendix S2 **Search strategy for the systematic review.**

Appendix S3 **Reference lists for Figures S1A, S1B, S2A–S2E, S3, S4A, S4B, S4C, S5A, S5B, S6A–S6F, and S7.**

Figure S1A **Pooled prevalence of patients in the underweight body mass index (BMI) category at diagnosis of celiac disease, according to study design (retrospective, cross-sectional, or prospective). The effect size (ES) was expressed as a percentage.**

Figure S1B **Pooled prevalence of patients in the normal-weight body mass index (BMI) category at diagnosis of celiac disease, according to study design (retrospective, cross-sectional, or prospective) The effect size (ES) was expressed as a percentage**

Figure S2A–S2E **Funnel plots of different outcomes assessed for publication bias. (A) Mean body mass index (BMI) in celiac disease (CD) patients vs healthy controls; (B) Reduced risk of overweight/obese BMI category in CD patients vs healthy controls; (C) Higher prevalence of normal-weight BMI category in pediatric vs adult patients; (D) Higher prevalence of overweight BMI category in adults vs pediatric patients; (E) Higher prevalence of obese BMI category in adults vs pediatric patients.** *Abbreviations*: ES, effect size; RR, relative risk; se, standard error; WMD, weighted mean difference

Figure S3 **Pooled prevalence of patients in different body mass index (BMI) categories at follow-up.** *Abbreviation*: ES, effect size

Figure S4A **Pooled estimate of prevalence of patients in normal-weight body mass index (BMI) category in pediatric vs adult populations.** *Abbreviation*: ES, effect size

Figure S4B **Pooled estimate of prevalence of patients in overweight body mass index (BMI) category in pediatric vs adult populations.** *Abbreviation*: ES, effect size

Figure S4C **Pooled estimate of prevalence of patients in obese body mass index (BMI) category in pediatric vs adult populations.** *Abbreviation*: ES, effect size

Figure S5A **Pooled estimate of change from overweight/obese to underweight/normal-weight body mass index (BMI) category after a gluten-free diet, according to study design (retrospective vs prospective).** *Abbreviation*: ES, effect size

Figure S5B **Pooled estimate of change from overweight/obese to underweight/normal-weight body mass index (BMI) category after a gluten-free diet, according to duration of follow-up.** *Abbreviation*: ES, effect size

Figure S6A–S6F **Funnel plots of different outcomes assessed for publication bias. (A) Increase in mean body mass index (BMI) during a gluten-free diet (GFD) in celiac disease (CD) patients; (B) Change in BMI category from underweight/normal-weight to overweight/obese in adults vs pediatric patients; (C) Change in BMI category from overweight/obese to underweight/normal-weight in adults vs pediatric patients; (D) Prevalence of normal-weight BMI category in pediatric vs adult patients; (E) Prevalence of overweight BMI category in pediatric vs adult patients; (F) Prevalence of obese BMI category in pediatric vs adult patients.** *Abbreviations*: ES, effect size; se, standard error; RR, relative risk; WMD, weighted mean difference

Figure S7 **Risk of bias in studies conducted in pediatric and adult populations, as assessed by the ROBINS-I tool.**

REFERENCES

1. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther*. 2007;26:1217–1225.
2. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16:823–836.e2.
3. Ghiselli A, Bizzarri B, Gaiani F, et al. Growth changes after gluten free diet in pediatric celiac patients: a literature-review. *Acta Biomed*. 2018;89:5–10.
4. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013;62:43–52.
5. Caio G, Ciccocioppo R, Zoli G, et al. Therapeutic options for coeliac disease: what else beyond gluten-free diet? *Dig Liver Dis*. 2020;52:130–137.
6. Melini V, Melini F. Gluten-free diet: gaps and needs for a healthier diet. *Nutrients*. 2019;11:170.
7. Nikniaz Z, Farhangi MA, Hosseinifard H, et al. Does a gluten-free diet increase body mass index and lipid profile in celiac patients? A systematic review and meta-analysis. *Med J Nutrition Metab*. 2019;12:341–352.
8. Potter MDE, Brienesse SC, Walker MM, et al. Effect of the gluten-free diet on cardiovascular risk factors in patients with coeliac disease: systematic review. *J Gastroenterol Hepatol*. 2018;33:781–791.
9. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269; W64.
10. WHO Expert Committee on Physical Status. Physical status: the use and interpretation of anthropometry , report of a WHO Expert Committee. WHO Technical Report Series no. 854. Published 1995. https://apps.who.int/iris/handle/10665/37003
11. Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. *Natl Health Stat Rep*. 2013;Feb 11:1–3. PMID: 24992748
12. Cacciari E, Milani S, Balsamo A, et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest*. 2006;29:581–593.
13. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85:660–667.
14. Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. Robvis Visualization Tool. https://www.riskofbias.info/welcome/robvis-visualization-tool. Accessed August 1, 2021.
15. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist*. 1950;21:607–611.
16. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785–1805.
17. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. 2003;327:557–560.
20. Almallouhi E, King KS, Patel B, et al. Increasing incidence and altered presentation in a population-based study of pediatric celiac disease in North America. *J Pediatr Gastroenterol Nutr*. 2017;65:432–437.
21. Ballestero Fernández C, Varela-Moreiras G, Úbeda N, et al. Nutritional status in Spanish children and adolescents with celiac disease on a gluten free diet compared to non-celiac disease controls. *Nutrients*. 2019;11:2329.
22. Brambilla P, Picca M, Dilillo D, et al. Changes of body mass index in celiac children on a gluten-free diet. *Nutr Metab Cardiovasc Dis*. 2013;23:177–182.
23. Capriati T, Francavilla R, Ferretti F, et al. The overweight: a rare presentation of celiac disease. *Eur J Clin Nutr*. 2016;70:282–284.
24. Dehghani SM, Ostovar S, Ataollahi M, et al. The effect of gluten-free diet among celiac patients aged 3–12 years old on BMI during 2006 to 2014 at Nemazee Teaching hospital. *Rev Gastroenterol Peru*. 2017;37:323–328. PMID: 29459801
25. Forchielli ML, Diani L, Labriola F, et al. Gluten deprivation: what nutritional changes are found during the first year in newly diagnosed coeliac children? *Nutrients*. 2019;12:60.
26. Grandone A, Marzuillo P, Cirillo G, et al. FTO polymorphism rs9939609 contributes to weight changes in children with celiac disease on gluten-free diet. *J Pediatr Gastroenterol Nutr*. 2015;61:220–223.
27. Levran N, Wilschanski M, Livovsky J, et al. Obesogenic habits among children and their families in response to initiation of gluten-free diet. *Eur J Pediatr*. 2018;177:859–866.
28. Livshits OE, Shauol R, Reifen R, et al. Can celiac disease present along with childhood obesity? *Int J Celiac Dis*. 2017;5:19–23. 10.12691/ijcd-5-1-7
29. Mackinder M, Allison G, Svolos V, et al. Nutritional status, growth and disease management in children with single and dual diagnosis of type 1 diabetes mellitus and coeliac disease. *BMC Gastroenterol*. 2014;14:99.
30. Maggio MC, Corsello G, Iacono G, et al. Gluten-free diet impact on leptin levels in asymptomatic coeliac adolescents: one year of follow-up. *Horm Res*. 2007;67:100–104. 10.1159/000096422
31. Norsa L, Shamir R, Zevit N, et al. Cardiovascular disease risk factor profiles in children with celiac disease on gluten-free diets. *World J Gastroenterol*. 2013;19:5658–5664.
32. Nwosu BU, Snook RI, Maranda L. The relationship between adiposity and stature in prepubertal children with celiac disease. *J Pediatr Endocrinol Metab*. 2013;26:819–824. 10.1515/jpem-2012-0312
33. Reilly NR, Aguilar K, Hassid BG, et al. Celiac disease in normal-weight and overweight children: clinical features and growth outcomes following a gluten-free diet. *J Pediatr Gastroenterol Nutr*. 2011;53:528–531.
34. Sansotta N, Guandalini S, Romano S, et al. The gluten free diet's impact on growth in children with celiac disease in two different countries. *Nutrients*. 2020;12:1547.

35. Shahraki T, Shahraki M, Hill ID. Frequency of overweight/obesity among a group of children with celiac disease in Iran. *Prz Gastroenterol*. 2018;13:127–131.
36. Siddh L, Sengar GS, Nagraj N, et al. Body mass index in celiac disease and effect of a gluten-free diet on body mass index. *Int J Adv Med*. 2016;3:813–815.
37. Valletta E, Fornaro M, Cipolli M, et al. Celiac disease and obesity: need for nutritional follow-up after diagnosis. *Eur J Clin Nutr*. 2010;64:1371–1372.
38. van der Pals M, Myléus A, Norström F, et al. Body mass index is not a reliable tool in predicting celiac disease in children. *BMC Pediatr*. 2014;14:165.
39. Venkatasubramani N, Telega G, Werlin SL. Obesity in pediatric celiac disease. *J Pediatr Gastroenterol Nutr*. 2010;51:295–297.
40. Villanueva M, Oyarzún A, Leyton B, et al. Changes in age at diagnosis and nutritional course of celiac disease in the last two decades. *Nutrients*. 2020;12:156.
41. Zifman E, Waisbourd-Zinman O, Marderfeld L, et al. The effect of gluten-free diet on cardiovascular risk factors in newly diagnosed pediatric celiac disease patients. *J Pediatr Gastroenterol Nutr*. 2019;68:684–688.
42. Agarwal A, Singh A, Mehtab W, et al. Patients with celiac disease are at high risk of developing metabolic syndrome and fatty liver. *Intest Res*. 2021;19:106–114.
43. Barone M, Della Valle N, Rosania R, et al. A comparison of the nutritional status between adult celiac patients on a long-term, strictly gluten-free diet and healthy subjects. *Eur J Clin Nutr*. 2016;70:23–27.
44. Capristo E, Farnetti S, Mingrone G, et al. Reduced plasma ghrelin concentration in celiac disease after gluten-free diet treatment. *Scand J Gastroenterol*. 2005;40:430–436.
45. Cheng J, Brar PS, Lee AR, et al. Body mass index in celiac disease: beneficial effect of a gluten-free diet. *J Clin Gastroenterol*. 2010;44:267–271.
46. Choung RS, Lamba A, Marietta EV, et al. Effect of a gluten-free diet on quality of life in patients with nonclassical versus classical presentations of celiac disease. *J Clin Gastroenterol*. 2020;54:620–625.
47. Ciccone A, Gabrieli D, Cardinale R, et al. Metabolic alterations in celiac disease occurring after following a gluten-free diet. *Digestion*. 2019;100:262–268.
48. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol*. 2006;101:2356–2359.
49. Kabbani TA, Goldberg A, Kelly CP, et al. Body mass index and the risk of obesity in celiac disease treated with the gluten-free diet. *Aliment Pharmacol Ther*. 2012;35:723–729.
50. Lanzini A, Magni P, Petroni ML, et al. Circulating ghrelin level is increased in coeliac disease as in functional dyspepsia and reverts to normal during gluten-free diet. *Aliment Pharmacol Ther*. 2006;23:907–913.
51. Newnham ED, Shepherd SJ, Strauss BJ, et al. Adherence to the gluten-free diet can achieve the therapeutic goals in almost all patients with coeliac disease: a 5-year longitudinal study from diagnosis. *J Gastroenterol Hepatol*. 2016;31:342–349.
52. Olén O, Montgomery SM, Marcus C, et al. Coeliac disease and body mass index: a study of two Swedish general population-based registers. *Scand J Gastroenterol*. 2009;44:1198–1206.
53. Passananti V, Santonicola A, Bucci C, et al. Bone mass in women with celiac disease: role of exercise and gluten-free diet. *Dig Liver Dis*. 2012;44:379–383.
54. Saukkonen J, Kaukinen K, Koivisto A-M, et al. Clinical characteristics and the dietary response in celiac disease patients presenting with or without anemia. *J Clin Gastroenterol*. 2017;51:412–416.
55. Sinniah R, Roche E. Letter: rising incidence of obesity in the coeliac population—a malady or maladaptation? *Aliment Pharmacol Ther*. 2012;35:1483.
56. Smecuol E, Gonzalez D, Mautalen C, et al. Longitudinal study on the effect of treatment on body composition and anthropometry of celiac disease patients. *Am J Gastroenterol*. 1997;92:639–643. PMID: 9128314
57. Stein AC, Liao C, Paski S, et al. Obesity and cardiovascular risk in adults with celiac disease. *J Clin Gastroenterol*. 2016;50:545–550.
58. Tetzlaff WF, Meroño T, Menafra M, et al. Markers of inflammation and cardiovascular disease in recently diagnosed celiac disease patients. *World J Cardiol*. 2017;9:448–456.
59. Tortora R, Capone P, De Stefano G, et al. Metabolic syndrome in patients with coeliac disease on a gluten-free diet. *Aliment Pharmacol Ther*. 2015;41:352–359.
60. Tucker E, Rostami K, Prabhakaran S, et al. Patients with coeliac disease are increasingly overweight or obese on presentation. *J Gastrointestin Liver Dis*. 2012;21:11–15.
61. Ukkola A, Mäki M, Kurppa K, et al. Changes in body mass index on a gluten-free diet in coeliac disease: a nationwide study. *Eur J Intern Med*. 2012;23:384–388.
62. Unalp-Arida A, Ruhl CE, Choung RS, et al. Lower prevalence of celiac disease and gluten-related disorders in persons living in southern vs northern latitudes of the United States. *Gastroenterology*. 2017;152:1922–1932.e2.
63. Whitehead C. Obesity and coeliac disease: possible effects of the gluten-free diet. *Gastrointestinal Nurs*. 2013;11:31–36.
64. Zanini B, Mazzoncini E, Lanzarotto F, et al. Impact of gluten-free diet on cardiovascular risk factors. A retrospective analysis in a large cohort of coeliac patients. *Dig Liver Dis*. 2013;45:810–815.
65. Kumral D, Syed S. Celiac disease screening for high-risk groups: are we doing it right? *Dig Dis Sci*. 2020;65:2187–2195.
66. Anania C, Pacifico L, Olivero F, et al. Cardiometabolic risk factors in children with celiac disease on a gluten-free diet. *World J Clin Pediatr*. 2017;6:143–148.
67. Rampertab SD, Pooran N, Brar P, et al. Trends in the presentation of celiac disease. *Am J Med*. 2006;119:e9–e14. 10.1016/j.amjmed.2005.08.044
68. Lo W, Sano K, Lebwohl B, et al. Changing presentation of adult celiac disease. *Dig Dis Sci*. 2003;48:395–398.
69. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. *Pediatrics*. 2009;124:1572–1578.
70. Vivas S, Ruiz de Morales JM, Fernandez M, et al. Age-related clinical, serological, and histopathological features of celiac disease. *Am J Gastroenterol*. 2008;103:2360–2366.
71. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390:2627–2642. 10.1016/S0140-6736(17)32129-3
72. Wild D, Robins GG, Burley VJ, et al. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. *Aliment Pharmacol Ther*. 2010;32:573–581.
73. Sue A, Dehlsen K, Ooi CY. Paediatric patients with coeliac disease on a gluten-free diet: nutritional adequacy and macro- and micronutrient imbalances. *Curr Gastroenterol Rep*. 2018;20:2.
74. Sainsbury K, Halmos EP, Knowles S, et al. Maintenance of a gluten free diet in coeliac disease: the roles of self-regulation, habit, psychological resources, motivation, support, and goal priority. *Appetite*. 2018;125:356–366.
75. Francavilla R, Cristofori F, Vacca M, et al. Advances in understanding the potential therapeutic applications of gut microbiota and probiotic mediated therapies in celiac disease. *Expert Rev Gastroenterol Hepatol*. 2020;14:323–333.