REVIEW

Anxiety and Depression Among Adults and Children With Celiac Disease: A Meta-Analysis of Different Psychiatry Scales

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Background: Celiac disease (CD) is an autoimmune disorder in which genetically susceptible individuals cannot digest gluten (wheat) and its homologs such as Scalin (rye) and Hordein (barley).

Aim: This systematic review and meta-analysis aimed to investigate the measures of associations between CD and psychiatric disorders, specifically anxiety and depression, and explore the relationship between adherence to a Gluten-Free Diet (GFD) and the psychiatric aspects of the disease.

Methods: We searched PubMed, Scopus and Web of Science for articles investigating anxiety and depression in CD patients. The following inclusion criteria were implemented: Primary research articles (either observational or experimental) that include participants with a CD diagnosis -confirmed either serologically, with anti-endomysial antibodies, anti-tissue transglutaminase antibodies, or with duodenum biopsy, whether on a GFD or not,—who have depression or anxiety symptoms identified through self-report or clinician-administered scales.

Results: CD patients are at a higher odds of developing anxiety, as the odds ratio was (OR: 2.26, 95% CI: [1.10, 4.67]) and depression symptoms (OR: 3.36, 95% CI: [1.36, 8.32]). Results of both State-Trait Anxiety Inventory Y-1 and Y-2 improved after 1 year of GFD with mean difference of 3.48, 95% CI: (0.26, 6.71), and MD: 3.45, 95% CI: (1.39, 5.52), respectively.

Conclusion: Anxiety and depression are prevalent among adults and children CD patients as they are observed to have high odds of anxiety and depression as expressed by various scales. It is reported that GFD is associated with decreased levels of anxiety and depression, however, further studies are required to confirm these findings and to investigate the main mechanism of psychiatric disorders among CD patients.

Psych Res Clin Pract. 2024; 6:124–133; doi: 10.1176/appi.prcp.20230076

Celiac disease (CD) is an autoimmune disorder that affects genetically susceptible individuals, rendering them unable to digest gluten found in wheat and related grains such as rye and barley. Recent trends indicate a growing prevalence of CD among both pediatric and adult populations (1.4%), likely due to improved diagnostic methods and targeted screening efforts (1–5). While the classic CD symptoms include duodenal villous atrophy, malabsorption, failure to thrive, and diarrhea (6, 7). However, non-classical manifestations have increasingly come to light. Some patients only discover they have CD through screening investigations prompted by high-risk factors, such as abdominal pain, altered bowel habits like constipation, anemia, short stature, and other symptoms (8). Adult-onset non-classical CD can also manifest alongside comorbid conditions, including type 1 diabetes mellitus, cancers, skin disorders, gynecologic problems, and

HIGHLIGHTS

- Patients with celiac disease (CD) have a higher risk of developing Anxiety and depression.
- Gluten-Free Diet was associated with lower levels of depression and anxiety.
- In addition to physical health care and dietary interventions, mental healthcare should be available and integrated into the care plans for patients with CD.

neuropsychiatric illnesses (9). In the 21st century, the pooled incidence of CD among females was 17.4 per 100,000 person-years, compared with 7.8 among males (10).

The primary treatment for CD is a lifelong commitment to a GFD (11, 12). While some suggest that adhering to a GFD can improve gastrointestinal symptoms and potentially alleviate psychiatric disorders (5). There is an opposing view that GFD may negatively impact the quality of life for CD patients and increase the risk of psychiatric comorbidity (5, 13). Numerous studies have explored the link between CD and psychiatric disorders (14–17). We can generally divide their theories into two schools; specific and non-specific mechanisms (17). Specific mechanisms involve biological processes that point to overlapping pathologies, such as the proposed "gut-brain" relationship (15, 17, 18). While non-specific mechanisms encompass the social and emotional consequences of a CD diagnosis (13).

This systematic review and meta-analysis aimed to investigate the measures of associations between CD and psychiatric disorders, specifically anxiety and depression, and explore the relationship between adherence to a GFD and the psychiatric aspects of the disease.

METHODS

Search Strategy

A systemic search was carried out to find relevant articles. We searched the following databases: PubMed, Scopus, and Web of Science. The search was carried out from inception until May 23, 2023, using the following search terms: anxiety, depression, CD, and gluten. No filters were applied, and reference lists of included papers were searched to identify further relevant papers that were not identified during the search.

Study Screening and Selection

The following inclusion criteria were developed: Primary research articles (either observational or experimental) that include participants with a CD diagnosis -confirmed either serologically, with anti-endomysial antibodies or anti-tissue transglutaminase antibodies, or with duodenum biopsy, whether on a GFD or not,—who have depression or anxiety symptoms identified through self-report or clinician-administered scales. First, articles were screened by title and abstract by four independent authors in a blinded fashion. Articles that did not meet the inclusion criteria were excluded, and any differences were settled by the first author. Full texts of articles that met the inclusion criteria were retrieved and screened by two independent reviewers and conflicts were settled by the first author.

Quality Assessment

We assessed the quality of case-control studies using New Castle Ottawa scale (NOS) (19), studies with a score of 7–9 were of high quality, 4–6 of moderate quality and 1–3 of low quality. Quality assessment of cross-sectional and cohort studies was assessed using National Institute of Health (NIH) tool (20), studies with a score of more than 8 are considered of good quality, 5–8 of fair quality and less than 5 are of poor quality.

Data Extraction and Statistical Analysis

Data were extracted from each study by four independent reviewers, with conflicts settled by the first author. Extracted data included: study design, country of study, the study population, sample size and characteristics (age and sex), and the number of subjects suffering from anxiety or depression. Furthermore, we collected the reported scores of The State-Trait Anxiety Inventory (STAI), Zung Self-Rating Depression Scale (SDS), Hospital Anxiety and Depression Scale (HADS), Children's Depression Inventory (CDI), and other scales, for both celiac patients and controls.

Statistical Analysis

We conducted the meta-analysis by pooling the results using Review Manager V. 5.4 software. Random effect model was utilized in pooling with a p-value of 0.05 and a confidence level of 95%. The analysis for dichotomous variables was done using event and total to calculate the odds ratio, while that of continuous variables was done using mean difference. Heterogeneity between studies was assessed using I^2 statistical test. A value of $p < 0.05$ was statistically significant. We used Open meta-analyst software for sensitivity analysis using leave-one-out method and to calculate the overall mean of different scales.

RESULTS

Search Strategy and Screening

Our search strategy resulted in a total of 1857 records. After removing duplicates, 922 articles were available for screening. After title and abstract screening, 60 articles entered the full-text screening resulting in a total of 18 articles (21–38) to be included in our meta-analysis (Figure 1).

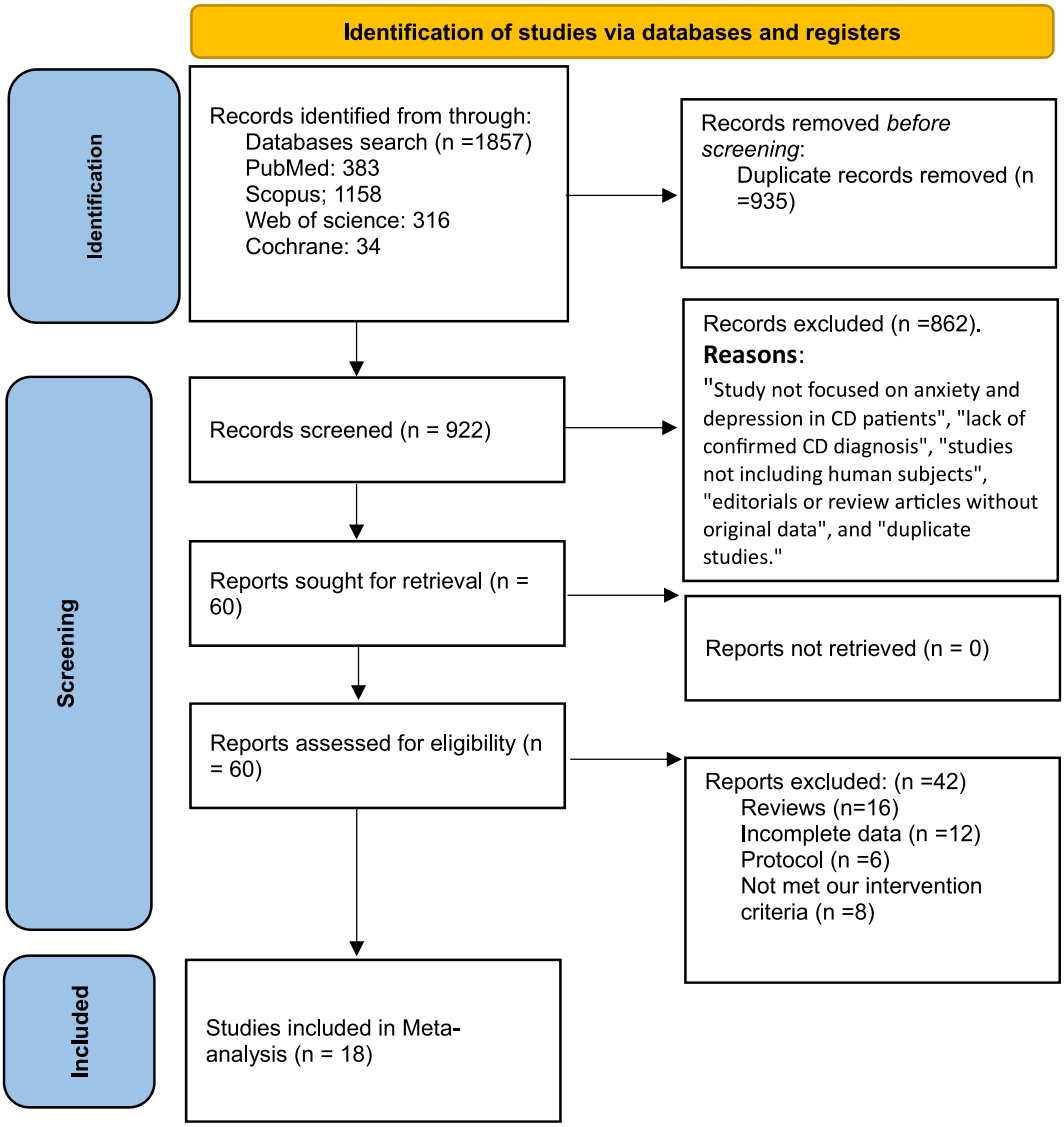
Quality Assessment of Included Studies

Using the NOS scale for case-control studies, eight of the included studies (21–28) were of high quality, one (29) of moderate quality and one (30) with low quality (Table 1). Regarding cross-sectional studies evaluated by the NIH tool, four studies (31–34) were of good quality and two (35, 36) were of fair quality while the two cohort studies, one (37) was of good quality and the other (38) was of fair quality (Table 2). Study criteria and baseline characteristics of the included patients in each study are summarized in Table 3.

Meta-Analysis of Anxiety and Depression Among CD Patients

Anxiety in Celiac Disease Patients. Celiac patients are at a higher odds of developing anxiety, among six studies, the

FIGURE 1. PRISMA flow diagram of the included studies and screening process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



odds ratio was (OR: 2.26, 95% CI: [1.10, 4.67]). However, this was accompanied by a statistically significant heterogeneity, which was solved by subgroup analysis into adults and children subgroups, and the heterogeneity became insignificant (Figure 2).

Meanwhile, the subgroup analysis revealed the adults' anxiety chance among four studies (OR: 3.60, 95% CI: [2.70, 4.79]) as well as the children's (OR: 1.19, 95% CI: [1.07, 1.32]) among two studies, which shows the prevalence of anxiety in CD patients whether adults or children (Figure 2).

Analysis of the STAI-Y1 revealed that children CD patients are associated with increased scores of anxiety among three studies (MD: 4.58, 95% CI: [−0.15, 7.5]). We observed statistically insignificant results in adults as well as the total results (Supplemental Figure 1), therefore, we performed a leave-one-out analysis by eliminating the "Addolorato et al. 2001" study, after which results confirmed there to be a higher anxiety susceptibility in CD patients (MD: 5.19, 95% CI: [2.46, 7.92]) (Supplemental Figures 2 and 3).

The STAI-Y2 analysis also showed statistically insignificant results in the adults' subgroup but there was a statistically significant increase in STAI-Y2 in children with CD compared to control (Supplemental Figure 4). However, we observed statistically significant overall heterogeneity, so sensitivity analysis using leave-one-out analysis was done by discarding the "Addolorato et al. 2001" study, so heterogeneity decreased among results (Supplemental Figures 5 and 6).

Analysis of the anxiety section of the HADS among three studies showed significant results (MD: 2.06, 95% CI:

TABLE 1. Newcastle-Ottawa Scale tool for quality assessment of case-control studies.

Study ID	Is the case definition adequate? (★)	Representativeness of the cases	Selection of the controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Quality level
Addolorato et al. (21)	★	★	★	★	★★	-	★	★	High
Addolorato et al. (22)	★	★	★	★	★	-	★	★	High
Brottveit et al. (23)	★	★	-	★	★★	-	★	★	High
Esenyel et al. (24)	★	★	★	★	★	-	★	★	High
Carta et al. (25)	★	★	★	★	★★	★	-	★	High
Garud et al. (26)	★	★	-	★	★★	-	★	★	High
Ciacci et al. (30)	★	★	★	★	★★	-	★	★	Low
Fidan et al. (29)	★	★	★	★	★	-	★	★	Moderate
Lebwohl et al. 2020 (27)	★	★	-	★	★★	-	★	★	High
Kara et al. 2018 (28)	★	★	★	★	★	-	★	★	High

TABLE 2. National Institute of Health tool for quality assessment of cohort and cross-sectional studies.[a]

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality
Jafari et al. (32)	Yes	Yes	NR	Yes	NR	Yes	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Good
Mazzone et al. (31)	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	No	Yes	No	Yes	Yes	Good
Häuser et al. (35)	Yes	Yes	Yes	Yes	Yes	No	No	NA	No	No	Yes	NA	No	Yes	Fair
Alkhayyat et al. (38)	Yes	Yes	No	No	No	No	No	No	Yes	No	Yes	No	Yes	NR	Fair
Butwicka et al. (37)	Yes	Yes	Yes	Yes	Yes	No	NR	No	Yes	Yes	Yes	No	Yes	NR	Good
Fera et al. (34)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	NR	NR	Good
O'Shaughnessy et al. (36)	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	No	Yes	No	NR	NR	Fair
Canova et al. (33)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	No	No	NR	Good

[a] Q1: Was the paper's goal or research question stated clearly? Q2: Was the study population precisely defined and specified? Q3: Was the participation rate of those who were eligible at least 50%? Q4: Were all the participants chosen or enlisted from the same or comparable populations (including the same time period)? Were predetermined criteria for inclusion and exclusion in the study implemented consistently to every participant? Q5: Were estimates of the variance and effects, or descriptions of the power, provided? Q6: Were the exposure(s) of interest measured before the outcome(s) being examined for the analysis in this paper? Q7: Was the timeframe long enough for a relationship between exposure and result, if one existed, to be fairly anticipated? Q8: Did the study look at different exposure levels in relation to the outcome for exposures that can vary in amount or level (e.g., categories of exposure, or exposure measured as continuous variable)? Q9: Were all study participants exposed to the same exposure measures, which are independent variables, in a way that was uniformly defined, valid, and reliable? Q10: Were the exposure(s) evaluated multiple times over time? Q11: Were the dependent variables (outcome measures) accurately described, dependable, and applied uniformly across all study participants? Q12: Were the outcome judges unaware of the participants' exposure status? Q13: After the baseline, was the loss to follow-up 20% or less? Q14: Were significant confounding factors that might have affected the association between the exposure(s) and outcome(s) measured and statistically adjusted?

[1.60, 2.52]), in addition to having no notable heterogeneity (Supplemental Figure 7).

Depression in Celiac Disease Patients. The odds of depression were high in CD patients as observed by the included four studies (OR: 3.36, 95% CI: [1.36, 8.32]) (Figure 3). We noticed the heterogeneity to be significant, so by performing sensitivity analysis by leave-one-out method and excluding the "Garud et al." study, the heterogeneity became unremarkable (Supplemental Figure 8).

The depression analysis of the HADS among three studies showed no statistically significant results, however, after sensitivity analysis by leave-one-out of "O'Shaughnessy et al. 2022" study, which only contained 11 celiac patients to 3 healthy subjects, results became statistically significant (MD: 1.58, 95% CI: [0.25, 2.90]) as the scale was noted to be increased in CD patients compared to controls. In addition, no heterogeneity was noted (Supplemental Figures 9 and 10).

Analysis of the Zung-SDS among three studies showed significant results (MD: 7.39, 95% CI: [1.75, 13.03]), but there was considerable heterogeneity between the studies (Supplemental Figure 11).

CDI among three studies demonstrated substantial results (MD: 2.33, 95% CI: [0.79, 3.87]), in addition to having homogeneity between the studies (Supplemental Figure 12).

Effect of Gluten-Free Diet on Anxiety. Among two studies, we analyzed studies that compared the values of the STAI-Y1 scale of patients who were on a GFD for an entire year, after which the value was decreased in those on GFD, proving the value of a GFD for CD patients (MD: 3.48, 95% CI: [0.26, 6.71]). In addition, there was no notable heterogeneity among the studies (Supplemental Figure 13). Results of the STAI-Y2 scale among two studies also improved in patients after a year of consuming GFD (MD: 3.45, 95% CI: [1.39, 5.52]). Heterogeneity was similarly insignificant (Supplemental Figure 14).

Overall Mean of Different Scales Among CD Patients. The overall mean of HADS anxiety scale among the study participants with CD in two studies was found to be 6.168, 95% CI: (4.592, 7.744), CDI among three studies was found to be 6.488, 95% CI: (4.643, 8.334), Zung-SDS: among three studies was reported to be 43.628, 95% CI: (32.839, 54.418), STAI-Y1 in children among three studies: 32.870, 95% CI: (29.532, 36.207), STAI-Y2 in children among three studies: 33.125, 95% CI: (29.475, 36.774), STAI-Y1 in adults among three studies: 43.813, 95% CI: (36.864, 50.761) and STAI-Y2 in adults among four studies: 43.594, 95% CI: (37.456, 49.732) (Supplemental Figures 15–21, respectively).

DISCUSSION

Our study showed the increased odds of anxiety and depression among CD patients. This was assessed using different anxiety and depression scores such as STAI-Y1, STAI-Y2, HADS for anxiety and depression, CDI, and Zung-SDS. It was found that anxiety measured by STAI-Y1 and STAI-Y2 was reduced after 1 year of GFD.

The literature has reported associations between CD and a wide spectrum of psychiatric disorders. According to certain studies (2, 25), depression was a common comorbidity among CD patients, however, other studies found no differences between CD patients and the general population (35, 39). It is believed that persistent symptoms like pain or diarrhea commonly occur before the onset of depression symptoms. It is also reported that the severity of depression symptoms is associated with the severity of Gastrointestinal symptoms (40–42). A GFD has been shown to reduce the symptoms of depression (43, 44).

TABLE 3. Study criteria and baseline characteristics of participants.[a]

Study ID	Country	Sample size		Study design	Age: mean (SD)		Gender (M/F)	
		Cases	Controls		Cases	Controls	Case	Controls
Garud et al. (26)	Israel, USA	600	200	Case-control	51.5	50.39	150/450	50/150
Addolorato et al. (22)	Italy	37	59	Case-control	29.8 (7.4)	31.7 (6.9)	14/23	27/32
Alkhayyat et al. (38)	Jordan	112,340	37,353,470	Cohort	18> years old: *N* (%) = 6290 (5.6) 18–65 years old: *N* (%) = 78,350 (69.7) 65< years old: *N* (%) = 27,700 (24.7)	18> years old: *N* (%) = 6,598,300 (17.7) 18–65 years old: *N* (%) = 22,231,240 (59.5) 65< years old: *N* (%) = 8,523,930 (22.8)	27,230/85,120	16,548,030/20,805,440
Addolorato et al. (21)	Italy	40	50	Case-control	38 (11.3)	35.5 (10.5)	5/35	10/40
Brottveit et al. (23)	Norway	22	40	Case-control	40.5 (12)	37.2 (10.2)	7/15	20/20
Butwicka et al. (37)	Sweden	10,903	1,042,072	Cohort	4.47 (5.6)	4.47 (5.6)	4070/6833	403,859/638,213
Canova et al. (33)	Italy	93	-	Cross-sectional	37.3 (13.2)		17/76	
Carta et al. (25)	Italy	36	144	Case-control	41.1 (15.3)	41.3 (14.9)	11/25	36/108
Ciacci et al. (30)	Italy	30	-	Case-control	39.86 (18.39)	-	8/22	-
Häuser et al. (35)	Germany	441	441	Cross-sectional	46.3	49.9	95/346	95/346
Esenyel et al. (24)	Turkey	30	20	Case control	11.9 (2)	12 (2)	9/21	7/13
Fera et al. (34)	Italy	100	100	Cross-sectional	40.4 (14.1)	52.72 (17.4)	25/75	32/68
Fidan et al. (29)	Turkey	30	30	Case-control	7–11 years: *N* = 13 12–18 years: *N* = 17	11–7 years: *N* = 20 18–12 years: *N* = 10	13/17	13/17
Lebwohl et al. 2020	Sweden	3174	13,286	Case-control	6.6 (5.2)	6.5 (5.2)	7110/12,076	34,891/59,358
Kara et al. 2018	Australia, New Zealand	40	40	Case-control	11.95 (2.76)	11.95 (2.76)	17/23	17/23
O'Shaughnessy et al. (36)	Ireland	11	3	Cross-sectional	45.6 (19.6)	36 (11.3)	3/8	1/2
Jafari et al. (32)	Iran	50	50	Cross-sectional	7–10 years: *N* = 23 11–13 years: *N* = 14 14–16 years: *N* = 13	7–10 years: *N* = 33 11–13 years: *N* = 14 14–16 years: *N* = 3	24/26	23/27
Mazzone et al. (31)	Italy	100	100	Cross-sectional	10.38 (2.71)	11.37 (2.61)	35/65	42/58

[a] Cases are celiac disease patients, controls are people without celiac disease.

FIGURE 2. Subgroup analysis of anxiety among adults and children celiac disease patients.

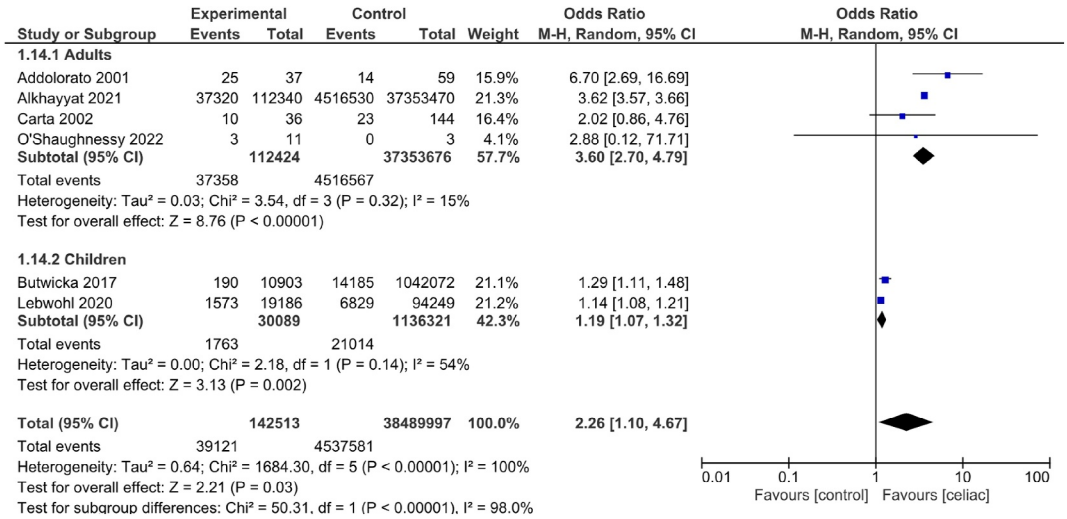
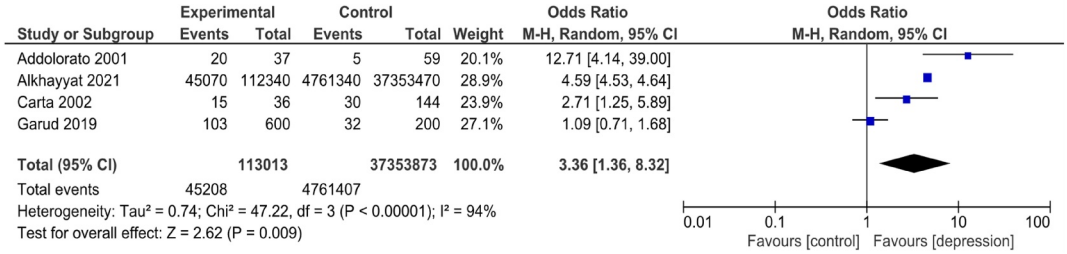


FIGURE 3. Depression among celiac disease patients versus controls.



Other research (45, 46), however, revealed that depression symptoms persisted, probably as a result of dietary restrictions that harm patients' social contacts and lower their quality of life (22). Furthermore, not adhering to a GFD may result in or exacerbate recurrent depression (47).

The purpose of the study was to assess the occurrence of anxiety and depression in CD patients and if there is an effect of GFD. There are several findings in the study that confirm this association in both adults and children. Our results reveal that there is an increased odds of anxiety and depression in patients with CD. This finding is directly in line with previous studies on CD patients (48–50). Also, it has been reported that anxiety and depression can decrease the quality of life in CD patients (51, 52). So, different scales for anxiety and depression (53, 54) are used as a measure to diagnose trait and state anxiety, and to distinguish them from depressive disorders. We found that both STAI and HADS scales for anxiety had high values, indicating higher odds of anxiety, as reported in previous research that showed an increase in mean anxiety scores in CD patients (36). In addition, both HADS and Zung-SDS for depression had high values, indicating higher odds of depression; this is congruent with another study that reported a significant increase in the percentage of depression among CD patients compared to healthy controls (21). We also performed a single-arm meta-analysis on the scales of anxiety and depression in both adults and children with CD, the results showed increased average means in all scales indicating the strong association between these psychological disorders and CD. These resulting values can provide an estimate of the values of these scales in CD patients and can further help diagnose anxiety and depression in CD patients.

The CDI is a specific scale to measure depression in children (55), our analysis showed high values indicating higher odds of depression in children with CD. This finding is consistent with a previous study that showed significant improvement in depressive symptoms in children with CD (56). However, another study on CD pediatric patients showed no significant difference in depression compared to healthy controls (24).

GFD is considered the most reliable and radical treatment for CD symptoms, as it aids good absorption by improving the structural and functional aspects of the intestinal mucosa and preventing complications of CD which may be malignant or non-malignant (57, 58). For this reason, we analyzed studies that reported the values of the STAI-Y1 and STAI-Y2 scales of patients who were on a

GFD for 1 year to deduce if there is an improvement in symptoms; we found that values improved after GFD, which indicates an improvement in symptoms. Previous research (22) supported these findings regarding anxiety but not depression, as it showed decreased anxiety after 1 year of GFD. It reported an increased prevalence of state anxiety while there was no change in trait anxiety between patients and controls. This indicates that anxiety in CD patients is primarily considered a reactive form, not a personality trait.

Despite the benefits of GFD, on the other hand, a previous study showed that there was a decrease in quality of life in patients on GFD for 10 years, so, it was reported that long-term GFD is insufficient to improve the symptoms of CD patients (57).

Although several studies reported the link between CD and psychiatric disorders, the literature is evermore conflicting due to limitations in knowledge and the need for further different types of studies to strongly prove this association (57, 59). Also, some studies with small sample sizes may make the findings less reliable and less generalizable (21). The included studies showed significant heterogeneity, this could be due to conflicting literature or reflecting that the subject is still under investigation and there is a need for more future research to be carried out.

The observed heterogeneity in our findings regarding the association between CD and psychiatric disorders such as anxiety and depression may be influenced by cultural factors. Cultural norms and values can significantly impact the prevalence, expression, and reporting of these psychiatric symptoms. These differences not only encompass the willingness of individuals to report symptoms and seek help but also extend to diagnostic practices and societal acceptance of both CD and mental health conditions. Additionally, the cultural context can affect dietary habits and the availability of gluten-free options, influencing the ease with which individuals adhere to a GFD and its subsequent impact on mental health.

The study had some limitations, including heterogeneity in the included studies, as the included studies exhibited significant heterogeneity, possibly due to the difference in populations and the assessment scales. However, it was resolved by subgrouping and leave-one-out analysis. We conducted a "leave-one-out" sensitivity analysis to assess the robustness of our meta-analytic findings on the association between CD and anxiety/depression. This sensitivity test, contrary to suggesting correlations, was primarily employed to determine the impact of excluding individual studies on the overall results. The "leave-one-out" sensitivity analysis ensured the reliability of our findings by identifying the influence of individual studies on the overall results, highlighting the impact of study-specific factors such as design and population characteristics on the observed association between CD and psychiatric disorders. By conducting this leave-one-out, heterogeneity was resolved by the removal of the individual studies that caused this heterogeneity. Some studies had small sample sizes, which could potentially impact the reliability and generalizability of their findings. Long-term effects of GFD: while our analysis suggests an improvement in anxiety symptoms after 1 year of a GFD, it's worth noting that only two studies investigated this important concern and after only 1 year, emphasizing the need for further investigation into the long-term effects of GFD on CD patients. Therefore, further longitudinal studies with large sample sizes are recommended to investigate the anxiety and depression in CD patients and the role of GFD in those patients.

In conclusion, the CD is associated with high odds of anxiety and depression in both adults and children. This requires the monitoring of these symptoms and providing mental health care for CD patients. However, extended research is required to understand the specific pathophysiological aspects and the long-term effects of GFD.

CONCLUSION

Anxiety and depression are prevalent among adults and children CD patients as they are observed to have high odds of anxiety and depression as expressed by various scales. It is reported that GFD is associated with decreased levels of anxiety and depression, however, further studies are required to confirm these findings and to investigate the main mechanism of psychiatric disorders among CD patients.

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Received December 7, 2023; revised May 28, 2024; accepted June 6, 2024.

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