Prevalence of Celiac Disease in Patients With Turner Syndrome: Systematic Review and Meta-Analysis

Ghada S. M. Al-Bluwi1, Asma H. AlNababteh2, Linda Östlundh3, Saif Al-Shamsi1 and Rami H. Al-Rifai2*

1Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates; 2Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates; 3National Medical Library, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates

Introduction: Celiac disease (CD) is a multifactorial autoimmune disorder, and studies have reported that patients with Turner syndrome (TS) are at risk for CD. This systematic review and meta-analysis aimed to quantify the weighted prevalence of CD among patients with TS and determine the weighted strength of association between TS and CD.

Methods: Studies published between January 1991 and December 2019 were retrieved from four electronic databases: PubMed, Scopus, Web of Science, and Embase. Eligible studies were identified and relevant data were extracted by two independent reviewers following specific eligibility criteria and a data extraction plan. Using the random-effects model, the pooled, overall and subgroup CD prevalence rates were determined, and sources of heterogeneity were investigated using meta-regression.

Results: Among a total of 1,116 screened citations, 36 eligible studies were included in the quantitative synthesis. Nearly two-thirds of the studies (61.1%) were from European countries. Of the 6,291 patients with TS who were tested for CD, 241 were diagnosed with CD, with a crude CD prevalence of 3.8%. The highest and lowest CD prevalence rates of 20.0 and 0.0% were reported in Sweden and Germany, respectively. The estimated overall weighted CD prevalence was 4.5% (95% confidence interval [CI], 3.3–5.9, I^2, 67.4%). The weighted serology-based CD prevalence in patients with TS (3.4%, 95% CI, 1.0–6.6) was similar to the weighted biopsy-based CD prevalence (4.8%; 95% CI, 3.4–6.5). The strength of association between TS and CD was estimated in only four studies (odds ratio 18.1, 95% CI, 1.82–180; odds ratio 4.34, 95% CI, 1.48–12.75; rate ratio 14, 95% CI, 1.48–12.75; rate ratio 42.5, 95% CI, 12.4–144.8). Given the lack of uniformity in the type of reported measures of association and study design, producing a weighted effect measure to evaluate the strength of association between TS and CD was unfeasible.
Celiac disease (CD), also known as celiac sprue and gluten-sensitve enteropathy, is a multifactorial autoimmune disorder arising from the interaction of diverse genetic and environmental factors (1, 2). In patients with CD, the consumption of gluten-containing grains such as wheat, barley, and rye leads to an inappropriate adaptive immune response (3, 4). Although several genes have been reported to contribute to the predisposition to CD, more than 90% of patients with CD carry the HLA-DQ2 or HLA-DQ8 haplotypes (5). Glutin consumption or repeated gastrointestinal infections in early life in genetically predisposed individuals are considered to trigger and regulate the induction of intraepithelial lymphocytes in the small intestines, leading to villous atrophy (6–8). In turn, histological changes leading to CD result in a variety of clinical manifestations. In adults, the classical clinical manifestations include chronic diarrhea, unintentional weight loss, constipation, malabsorption, and iron deficiency anemia (9). However, 50% of patients with CD present with nonclassical or atypical signs and symptoms, such as anemia, abdominal pain, osteoporosis, osteomalacia, short stature, lymphoma, liver disease, and neurological and psychological symptoms (10, 11). In pediatric patients, CD may present with unexplained growth failure, delayed puberty, chronic diarrhea, and anemia (12) and increases the risk of depression, anxiety, eating disorders, autistic spectrum disorder, and attention-deficit/hyperactivity disorder (13).

Globally, the estimated population-based prevalence of CD is approximately 1% (14). The prevalence of CD ranges from 0.8% in Europe and Oceania to 4.0% in Africa (15). The considerable increase in the prevalence of CD worldwide observed in recent decades (16, 17) has been mainly due to the increased availability of screening tests with improved sensitivity and specificity (18–20). According to current guidelines, screening for CD is not recommended for the general population but is recommended for specific patient groups who are considered at high risk for CD (21, 22), such as relatives of patients with CD as well as patients with insulin-dependent diabetes; autoimmune thyroid disease; selective IgA deficiency; and genetic disorders, including Down syndrome, Williams syndrome, and Turner syndrome (TS) (12, 23, 24).

TS is a female genetic disorder involving the X chromosome. Typical phenotypic characteristics of TS include short stature and gonadal dysgenesis (25). Female patients with TS are at high risk of developing autoimmune diseases approximately twice as high as in the general female populations (26). An increased risk of autoimmune diseases including type 1 diabetes mellitus, thyroid disease (27, 28), and CD has been reported in patients with TS (29). According to the guidelines of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition “NASPHGAN” (30), guidelines of the European Society Pediatric Gastroenterology, Hepatology and Nutrition “ESPHGAN” (31), and the guidelines and recommendation of the TS Consensus Group (32, 33), patients with TS are recommended to be screened for CD and other autoimmune disorders. On the other hand, the latest recommendation statement of the US Preventive Services Task Force (34) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for CD in asymptomatic persons including patients who are at increased risk of developing CD such as patients with TS (34). No systematic review to date has evaluated CD in patients with TS. The aim of the present systematic review and meta-analysis was to evaluate the existing literature and provide comprehensive quantitative evidence on the prevalence of CD among patients with TS and on the strength of association between TS and CD.

**INTRODUCTION**

**METHODS**

This systematic review was conducted and reported following the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (35) (Supplementary Table 1). The review followed a previously published protocol (36) that was also registered in PROSPERO (registration number, CRD42019131881). The published protocol was designed to estimate the strength of association between TS and CD. However, given the lack of sufficient and consistent quantitative effect measures, quantifying a pooled weighted measure of effect was unfeasible. Therefore, following the same protocol and search strategy, the present systematic review was slightly modified to quantify the weighted prevalence of CD among patients with TS. To adjust for the change, necessary minor amendments, including the extraction of information on the prevalence estimates, were implemented.

**Search Strategy**

A comprehensive strategy was designed to search four electronic databases: PubMed, Scopus, Web of Science, and Embase. The search string was developed by an expert librarian (Lo) and is available in the published protocol (36) and in Supplementary Box 1, which contains the results and search details for all databases. The literature search was performed in December 2019 with no restrictions on language or region. A publication year filter to encompass the period from January 1991 until the search date was applied. The year 1990 was defined as the start year for the present study based on the publication of

**Conclusion:** Nearly 1 in every 22 patients with TS had CD. Regular screening for CD in patients with TS might facilitate early diagnosis and therapeutic management to prevent adverse effects of CD such as being underweight and osteoporosis.

**Keywords:** celiac disease, Turner syndrome, systematic review, weighted prevalence, meta-analysis
The first modern guidelines for CD diagnosis by the European Society of Gastroenterology, Hepatology, and Nutrition in the same year (37). All records identified in the search were imported to Covidence systematic review software (38), where automatic de-duplication was performed and the references were prepared for blinded screening. A hand search of bibliographies of studies that were deemed eligible and previously published reviews was also performed.

**Eligibility Criteria**

All observational studies, abstracts, and conference papers were considered. To be deemed eligible, an observational study had to provide quantitative or quantifiable information on the prevalence of CD and/or effect measure on the association between TS and CD regardless of the age of patients with TS screened for CD. Further information on the inclusion and exclusion criteria is available in the published protocol (36).

**Study Selection and Data Extraction**

Following the predesigned eligibility criteria, titles and abstracts of the retrieved studies were independently screened by two reviewers (GSM-AB and AH-N) to identify fully as well as potentially eligible studies; the full texts of the identified studies were retrieved and thoroughly assessed for their eligibility. Conflicts between the reviewers were discussed with a third reviewer (RH-A) and resolved by consensus.

Relevant data were extracted from the studies that were deemed eligible. Data extraction was independently performed.

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**FIGURE 1** | PRISMA flow chart of study selection.
| Author, year | Duration of data collection | Country, city | Study design | Sampling method | Study population | Strata | TS type | CD diagnostic method | Sample size | Number of patients with CD | Prevalence (%) | Estimate of association |
|-------------|-----------------------------|---------------|--------------|----------------|-----------------|--------|---------|---------------------|-------------|--------------------------|---------------|----------------------|
| Bonamico et al. (46) | – | Italy, Catania and Rome | Cross-sectional | Unclear | Patients with TS observed at pediatric clinics at the University of Rome and University of Catania | All | Unclear | Biopsy | 37 | 3 | 8.1 | – |
| Ivarsson et al. (47) | – | Sweden | Cross-sectional | Unclear | Patients with TS aged 3–16 years (mean age, 10 years) in a Swedish multicenter trial to promote growth in patients with TS | All | All types | Biopsy | 87 | 4 | 4.6 | – |
| Gillet et al. (48) | 01/12/1998–01/10/1999 | Canada, British Columbia | Cross-sectional | Whole population | Patients with TS followed up at the British Columbia’s Children’s Hospital | All | Unclear | Biopsy | 45 | 1 | 2.2 | – |
| Rujner et al. (49) | – | Poland, Warsaw | Cross-sectional | Unclear | Patients with TS who attended the Outpatient Department of Children’s Memorial Health Institute in Warsaw | All | Unclear | Biopsy | 48 | 2 | 4.2 | – |
| Bonamico et al. (50) | – | Italy, various cities | Cross-sectional | Unclear | Patients with TS aged 7–38 years recruited from various centers in the Northern, Central, Southern, and Insular Italian regions | All | All types | Biopsy | 389 | 25 | 6.4 | – |
| Sakly et al. (51) | – | France, Lyon | Cross-sectional | Unclear | Patients from several Departments of Pediatrics over an 18-month period (Hospices Civils de Lyon, France) | All | Unclear | Sero anti-tTG Abs or AEA positive | 47 | 7 | 14.9 | – |
| Moayeri and Bahreman (52) | 00/10/2002–2004 | Iran, Tehran | Cross-sectional | Unclear | Patients with TS who attended the Pediatric Clinic at Tehran University of Medical Sciences | All | Unclear | Biopsy | 48 | 2 | 4.2 | – |
| Bettendorf et al. (53) | – | Germany | Cross-sectional | Unclear | Patients with TS aged >16 years from 96 German centers recorded until January 2000 in the IGLU database | TS Karyotype | All types | Sero anti-tTG Abs or AEA positive | 120 | 5 | 4.2 | – |
| Ságodi et al. (54) | 1994–2003 | – | – | Unclear | – | All | Unclear | Biopsy | 63 | 5 | 7.9 | – |
| Motenson et al. (55) | – | Denmark | Cross-sectional | Whole population | Danish patients with TS recruited from the National Society of Turner Contact Groups in Denmark, the Medical Department at Aarhus University Hospital, the Pediatric Unit at Hillerød Hospital, and Children’s Hospital at Glostrup Hospital | All | All types | Biopsy | 106 | 5 | 4.7 | – |
### TABLE 1 | Continued

| Author, year | Duration of data collection | Country, city | Study design | Sampling method | Study population | Strata | TS type | CD diagnostic method | Sample size | Number of patients with CD | Prevalence (%) | Estimate of association |
|--------------|-----------------------------|---------------|-------------|----------------|------------------|--------|---------|----------------------|-------------|---------------------------|----------------|------------------------|
| Frost et al. (56) | – | UK, London | Cross-sectional | Consecutive | Women with karyotypically proven TS who attended the Adult Turner Clinic at University College Hospital, London | All | All types | Biopsy | 256 | 12 | 4.7 | – |
| Dias et al. (57) | – | Brazil, Brasilia | Cross-sectional | Unclear | Patients with TS followed up at the Clinical Genetic Unit of Brasilia University Hospital | All | All types | Biopsy | 56 | 2 | 3.6 | – |
| Nabhan and Eugester (58) | 00/00/2000–00/00/2010 | USA, Indiana | Cross-sectional | Whole population | Girls followed up for TS at the Endocrine Clinic at Riley Hospital for Children in Indianapolis, Indiana | All | All types | Sero anti-tTG Abs or AEA positive | 77 | 4 | 5.2 | – |
| Freriks et al. (59) | 00/05/2005–00/06/2009 | Netherlands, Nijmegen | Cross-sectional | Consecutive | Adult women with TS at a multidisciplinary care unit for adult women with TS | All | All types | Sero anti-tTG Abs or AEA positive | 150 | 3 | 2.0 | – |
| Bakalov et al. (60) | 00/01/2000–00/03/2009 | USA, Bethesda | Cross-sectional | Consecutive | Patients with TS at the Clinical Center of the National Institutes of Health (NIH) recruited primarily through notices on the internet and the NIH home page | All | All types | Medical records | 224 | 6 | 2.7 | RR, 42.5 (95% CI, 12.4–144.8) |
| Nadeem and Roche (61) | – | Ireland, Dublin | Cross-sectional | Unclear | Patients with TS who visited the Department of Pediatrics, University of Dublin | All | All types | Biopsy | 32 | 3 | 9.4 | – |
| Goldacre and Seminog (62) | 1999–2011 | UK, England | Retrospective | Unclear | A cohort of female patients hospitalized with TS | All | Unclear | Medical records | 2,459 | 45 | 1.8 | RR, 14 (95% CI, 1.48–12.75) |
| Yesilkaya et al. (63) | 00/09/2013–31/01/2014 | Turkey | Cross-sectional | Unclear | Patients with TS aged 0–18 years who were followed in 35 different centers in different regions of Turkey | All | All types | Biopsy | 698 | 18 | 2.6 | – |
| Rutigliano et al. (64) | – | Italy | Cross-sectional | Unclear | A cohort of 31 children with TS | All | All types | Medical records | 31 | 4 | 12.9 | – |
| Hirschfield et al. (65) | – | Canada, Ontario | Cross-sectional | Consecutive | Patients with TS aged 8–18 years enrolled from two pediatric TS clinics in Ontario | All | All types | Biopsy | 63 | 4 | 6.3 | – |
| Gawlik et al. (66) | – | Poland, Silesia | Case-control | Consecutive | Patients with TS treated at the Department of Pediatric Endocrinology | All | Unclear | Unclear | 37 | 3 | 8.1 | – |
| Stocklasova et al. (67) | – | Czech Republic | Cross-sectional | Unclear | A cohort of 286 Czech females with TS followed up at pediatric tertiary centers and later at adult tertiary centers in the Czech Republic | All | All types | Biopsy | 286 | 25 | 8.7 | – |
| Farquhar et al. (68) | 01/02/2015–01/07/2018 | Canada, Toronto | Cross-sectional | Whole population | Patients with TS evaluated at a multidisciplinary TS clinic at a university-based ambulatory hospital in Toronto | All | All Types | Medical records | 122 | 11 | 9.0 | – |

<40-years old

≥40-years old

(Continued)
TABLE 1 | Continued

| Author, year | Duration of data collection | Country, city | Study design | Sampling method | Study population | Strata | TS type | CD diagnostic method | Sample size | Number of patients with CD | Prevalence (%) | Estimate of association |
|--------------|-----------------------------|---------------|--------------|-----------------|-----------------|--------|---------|----------------------|-------------|--------------------------|----------------|--------------------------|
| Wegiel et al. (69) | 00/00/2001–00/00/2018 | Poland, Silesia | Cross-sectional | Unclear | 134 patients with TS treated at the Department of Pediatric Endocrinology | All | All types | Biopsy | 73 | 2 | 2.7 | – |
| Ouidad et al. (70) | 2015–2017 | Algeria, Algeria | Cross-sectional | Unclear | Children and adolescents with TS | All | All types | Biopsy | 85 | 12 | 14.1 | – |
| Stagi et al. (71) | 06/2003–05/2011 | Italy, Avellino and Florence | Prospective Cohort | Unclear | Patients with TS with a median age of 16.2 years | All | Unclear | Biopsy | 32 | 3 | 9.4 | OR, 18.1 (95% CI, 1.82–180) |
| Kammoun et al. (72) | 01/2007–12/2011 | Tunisia | Cross-sectional | Unclear | Patients with TS | All | All types | Unclear | 37 | 2 | 5.4 | – |
| Berglund et al. (73) | 2003–2008 | Denmark | Cross-sectional | Unclear | Girls and women with TS from the National Society of Turner Contact Groups in Denmark, Aarhus University Hospital, Hillerød Hospital, and Children’s Hospital at Glostrup Hospital | All | All types | Biopsy | 141 | 2 | 1.4 | – |
| Bessahaoui et al. (74) | 2007–2013 | Algeria | Cross-sectional | Unclear | Children with TS observed over a 7-year period | All | All types | Unclear | 33 | 4 | 12.1 | – |
| Avolio et al. (75) | – | USA, Pittsburg | Cross-sectional | Unclear | Patients who presented at the Genetics and/or Endocrine clinic with varying mosaic TS karyotypes for evaluation | All | Mosaic | Medical records | 40 | 1 | 2.5 | – |
| Dumitrescu et al. (76) | – | Romania, Bucharest | Cross-sectional | Unclear | Girls diagnosed with TS at the C. I. Parhon National Institute of Endocrinology | All | All types | Unclear | 93 | 3 | 3.2 | – |
| Elechi et al. (77) | 2008–2017 | England, Nottingham | Cross-sectional | Unclear | Girls with TS who attended the over-12 TS clinic at Nottingham Children’s Hospital | All | All types | Medical records | 28 | 1 | 3.6 | – |
| Grossi et al. (78) | – | Italy, Rome | Cross-sectional | Unclear | Patients with TS recruited from Bambino Gesu Children’s Hospital in Rome | All | All types | Sero anti-TG Abs | 66 | 2 | 3.0 | – |
| Hamza et al. (79) | 00/10/2009–00/11/2010 | Egypt, Cairo | Cross-sectional | Unclear | Patients with TS recruited from the Pediatric Endocrinology Clinic, Children’s Hospital, Ain Shams University | All | All types | Biopsy | 80 | 2 | 2.5 | – |
| Marid et al. (80) | 1997–2006 | Sweden | Case-control Whole population | Unclear | Patients with TS registered in the National Patient Register | All | Unclear | Biopsy | 5 | 1 | 20.0 | OR: 4.34 (95% CI, 1.48–12.75) |
| Sterberg et al. (81) | – | Sweden, Stockholm | Cross-sectional | Unclear | Females with TS in the Stockholm area aged 7–65 years | All | All types | Medical records | 97 | 4 | 4.1 | – |

CI, confidence interval; TS, Turner syndrome; CD, celiac disease; tTG Abs, antibodies against tissue transglutaminase; AEA, anti-endomysium; IGLU, Internationale Genotropin Langzeit-Untersuchung; RR, rate ratio; OR, odds ratio.
by two reviewers (GSM-AB and AH-N) following predefined data extraction parameters described in the published protocol (36), with minor amendments to extract data related to prevalence estimates. Discrepancies between the reviewers were discussed with a third reviewer (RH-A) and resolved by consensus. The following information was extracted from eligible studies: author names; publication year; country and city where the study was conducted; study design, setting, and period; CD diagnostic method; type of TS; number of participants tested for CD; mean or range of age of study participants at the time of CD testing; number of participants who were diagnosed with CD; number of patients with and without TS diagnosed with CD; and crude and adjusted estimates of the association between TS and CD with 95% confidence intervals (CIs), if available. The corresponding authors of the eligible articles were contacted by e-mail if the published information in the article was not sufficient.

Quantitative Evidence Synthesis and Data Analysis

According to our previously published protocol (36), we aimed to estimate the strength of association between TS and CD. However, due to the lack of sufficient studies reporting estimates on the strength of association between the exposure–outcome pair, we aimed to determine the burden of CD, in the form of weighted prevalence, among patients with TS.

Among the patients with TS tested for CD, the weighted CD prevalence and corresponding 95% CI was estimated using the Dersimonian–Laird random-effects model. In the meta-analysis, to estimate the weighted prevalence, variances in the prevalence measures were stabilized using the Freeman–Tukey double arcsine transformation method (39, 40). Measures of heterogeneity, Cochran’s Q statistic, inconsistency I-squared ($I^2$) index, and 95% prediction interval, which estimates the 95% interval in which the true effect size in a new prevalence study will lie, were also computed and reported (41).

In addition to the overall weighted CD prevalence, the weighted CD prevalence were determined by analyzing subgroups according to TS type, sample size (<50 or ≥50 patients with TS), and CD diagnostic method (medical records, serology, biopsy, or unclear). Additionally, for each subgroup, the number of studies, number of patients with TS tested for CD, number of patients with TS diagnosed with CD, and median CD prevalence with ranges were also reported.

To determine the contribution of sample size and CD diagnostic method to the variability in CD prevalence rates across the studies, univariate and multivariate random-effects meta-regression models were performed. In the multivariate model, a p-value of $≤0.05$ was considered indicative of statistical significance, which contributed to the heterogeneity in prevalence estimates. The number of studies in the reported subcategories was low; therefore, TS type was not used in the meta-regression analysis to preserve sufficient power.

Risk of Bias Assessment

The risk of bias (RoB) of the reviewed individual studies was evaluated using six criteria related to prevalence studies included in the National Heart, Lung, and Blood Institute risk assessment tool (42). The six quality-related criteria assessed whether the study population was clearly specified, participation rate was at least 50%, justification for the recruited sample size was provided, all the participants were selected from the same or similar populations, and the outcome measure was clearly defined, valid, reliable, and implemented consistently across all study participants. The potential answer for each of these criteria was either “yes, no, or an unclear.” For additional quality assessment, we also determined the robustness of the implemented sampling methodology (probability-based, not probability-based, or unclear sampling methodology) as the seventh criterion. Studies were considered to be of high quality if patients with TS tested for CD were selected following probability-based sampling. In the event of insufficient information on any of the quality assessment criteria, the study was categorized as unclear. The overall proportion of individual studies with potentially low RoB across the seven quality criteria was determined. The mean study quality score was also computed based on a maximum quality score of seven.

Quality assessment was independently performed by two reviewers (GSM-AB and AH-N). Any disagreements between the reviewers in the extraction phase or during quality assessment were discussed and resolved by consensus.

Publication Bias

A contour-enhanced funnel plot was constructed to explore the effects of small studies on the pooled CD prevalence. The funnel plot was constructed by plotting each CD prevalence measure against its standard error. Asymmetry of the funnel plot was tested using Egger’s test (43).

The metaprop (44) and metareg packages of Stata v15 software (45) were used for analyses.

RESULTS

Scope of the Review

Among a total of 1,116 citations retrieved from the four databases, 36 research articles that fulfilled the eligibility criteria were included in the quantitative meta-analysis (Figure 1).

Table 1 summarizes descriptive information of the 36 research articles. These articles (29, 46–48, 50–80) were from 19 countries (Italy, Sweden, Canada, Poland, France, Iran, Germany, Denmark, The United Kingdom, Brazil, The United States of America, The Netherlands, Ireland, Turkey, Czech Republic, Algeria, Tunisia, Romania, and Egypt), with the majority of the articles from Europe (47.2%) (29, 46, 47, 49–51, 53, 55, 56, 59, 61, 62, 64, 66, 67, 69, 71, 73, 76–78, 80), Canada (11.1%) (48, 60, 65, 68), and the United States of America (8.3%) (58, 60, 75). The predominantly used CD diagnostic method was biopsy in 55.6% of the research articles. These 36 research articles included 40 studies (single prevalence estimate) on CD prevalence in patients with TS. The TS type was specified in only two articles (53, 75), whereas all TS types were considered in 24 studies.
TABLE 2 | Weighted prevalence of CD in patients with TS.

| TS type               | Number of studies | Number of patients tested for CD | CD prevalence | Heterogeneity measures |
|-----------------------|-------------------|---------------------------------|---------------|------------------------|
|                       |                   |                                 | Range (%)     | Median (%)             | Weighted prevalence (%) | 95% CI          | Q (p-value) | f (%) | 95% PI (%) |
| Classical             | 1                 | 72                              | 4.2           | –                      | –                       | –              | –           | –     | –       |
| Mosaic                | 2                 | 47                              | 0.0–2.5       | 1.25                   | 0.7                     | 0.0–7.5        | –           | –     | –       |
| Xq                    | 1                 | 7                               | 14.3          | –                      | –                       | –              | –           | –     | –       |
| All types             | 24                | 3,244                           | 1.4–14.1      | 4.9                    | 4.2                     | 1.4–11.5       | 53.2 (<0.001) | 56.7   | 0.0–10.0 |
| Unclear               | 12                | 2,921                           | 1.8–20.0      | 6.0                    | 4.9                     | 3.7–6.4        | 37.2 (<0.001) | 70.4   | 0.0–20.0 |
| Sample size           |                   |                                 |               |                        |                         |                |             |       |         |
| <50                   | 18                | 597                             | 0.0–20.0      | 8.1                    | 5.9                     | 3.9–8.3        | 14.2 (0.8) | 0.0    | 0.0–10.0 |
| ≥50                   | 22                | 5,694                           | 1.4–14.1      | 4.4                    | 4.4                     | 3.1–5.8        | 83.0 (<0.001) | 74.7   | 0.0–10.0 |
| CD diagnostic method  |                   |                                 |               |                        |                         |                |             |       |         |
| Medical records       | 7                 | 2,970                           | 1.8–9.6       | 3.6                    | 3.6                     | 1.6–6.3        | 18.4 (<0.001) | 67.4   | 0.0–10.0 |
| Serology              | 8                 | 460                             | 0.0–1.5       | 3.6                    | 3.4                     | 1.0–6.6        | 11.2 (0.1) | 37.7   | 0.0–10.0 |
| Biopsy                | 20                | 2,630                           | 1.4–20.0      | 5.5                    | 4.8                     | 3.4–6.5        | 42.5 (<0.001) | 55.3   | 0.0–10.0 |
| Unclear               | 5                 | 231                             | 3.2–12.9      | 8.1                    | 6.8                     | 3.1–5.9        | 0.2 (<0.001) | 26.2   | 1.0–20.0 |
| Overalla              | 40                | 6,291                           | 0.0–20.0      | 4.7                    | 4.5                     | 3.3–5.9        | 119.6 (<0.001) | 67.4   | 0.0–10.0 |

CD, celiac disease; TS, Turner syndrome; CI, confidence interval; PI, prediction interval.

*a* Q: Cochran’s Q statistic is a measure assessing the existence of heterogeneity in estimates of CD prevalence.

*b* f: a measure assessing the percentage of between-study variation due to differences in CD prevalence estimates across studies rather than chance.

*c* 95% PI: estimates the 95% CI in which the true CD prevalence estimate in a new study is expected to fall.

dOverall pooled CD prevalence in patients with TS.

Only four research articles (29, 60, 62, 72) reported quantified or quantifiable information on the strength of association between TS and CD, with a heterogeneous study design and type of effect estimates.

CD Prevalence in Patients With TS

The 40 studies that examined CD prevalence tested 6,291 patients with TS, yielding a crude CD prevalence of 3.8% (Table 2). The lowest CD prevalence of 0.0% was reported in a study of seven patients with mosaic TS in Germany (53), whereas the highest CD prevalence of 20.0% was reported in a study of 97 patients with TS registered in the National Patient Register in Sweden (80).

The estimated weighted CD prevalence was 4.5% (95% CI, 3.3–5.9, I², 67.4%; Table 2 and Figure 2). The weighted CD prevalence was similar between studies that included <50 patients with TS (5.9%, 95% CI, 3.9–8.3, I², 0.0%) and those that included ≥50 patients with TS (4.4%, 95% CI, 3.1–5.8, I², 74.7%; Table 2). The analysis according to the CD diagnostic methods used revealed that the highest estimated weighted CD prevalence was obtained from five studies including “unclear” as a diagnostic method (6.8%, 95% CI, 3.1–5.9, I², 26.2%), followed by an estimated weighted CD prevalence of 4.8% (95% CI, 3.4–6.5, I², 55.3%) obtained from 20 studies using biopsy. The 95% CI of the CD prevalence according to the four CD diagnostic method categories was overlapping (Table 2).

Predictors of Heterogeneity in CD Prevalence

In the univariate meta-regression model, only sample size exhibited a significant association with variability in CD prevalence. The CD prevalence was 40% lower in studies that included ≥50 patients with TS (odds ratio 0.60, p = 0.022) than in studies that included <50 patients with TS. The observed significance in variability remained in the meta-regression model adjusted for the CD diagnostic method (adjusted odds ratio 0.61, 95% CI, 0.39–0.97; Table 3).

Publication Bias in CD Prevalence

The statistical assessment (Egger’s test, p < 0.001) of the funnel plot to determine the potential of publication bias due to the small-study effect suggested that there was asymmetry in the funnel plot, implicating the role of the small-study effect in CD prevalence (Figures 3A,B).

Quality Assessment of the CD Prevalence

Supplementary Table 2 and Supplementary Figure 1 provide the details of RoB assessment using the seven assessment criteria. Briefly, the study population was clearly specified and defined in 72.2% of the reviewed articles, the selection of the TS population from the same or similar populations was clearly mentioned in 75.0% of the articles, and the outcome of CD was clearly defined in 83.3% of the articles. The sample size justification and power calculation were not reported in 86.1% of the articles. Overall,
more than half (55.6%) of the 36 articles were deemed to have low RoB based on at least five of the seven RoB assessment criteria. Of a maximum score of 7, the mean RoB score was 3.8 for the 36 reviewed articles.

**DISCUSSION**

The present systematic review and meta-analysis summarized the burden of CD in patients with TS by evaluating its prevalence. The systematic review included 36 research articles yielding 40 prevalence studies that included a total of 6,291 patients with TS. The meta-analysis revealed that the CD prevalence was 4.5% in patients with TS. The estimated CD burden in patients with TS in the present meta-analysis is similar to that reported by other meta-analyses of different subject cohorts with chronic conditions or genetic disorders, including patients with type 1 diabetes mellitus (5%, 95% CI, 3–7) (81), iron deficiency anemia (3.2%, 95% CI, 2.6–3.9) (82), and irritable...
The strength of this study is the inclusion of studies from four large databases, which yielded a substantial sample size of patients with TS (n = 6,291) screened for CD. The review of the articles and the extraction of data by independent reviewers contributed to reducing the potential human error. Extracting and pooling stratified CD prevalence estimates as well as subgroup analyses according to the CD diagnostic methods also provided more stringent and potentially less biased prevalence estimates. A further strength of this study is the identification of gaps in evidence, specifically the lack of data on the burden of CD in patients with TS from several countries worldwide. Conversely, we acknowledge some limitations that should be considered when interpreting the findings. First, there was lack of uniformity in the CD diagnostic methods among the studies, with the highest prevalence of CD reported in studies with no clear CD diagnostic method, which might have led to over- or under-estimation of CD prevalence. Second, most studies were from Western countries, which might affect the generalizability of the results at the regional, sub-regional, and global levels. Third, the publication bias assessment showed an asymmetry of the funnel plot, which might be a result of the small-study effect.

In conclusion, ~1 in 22 patients with TS had CD. Regular screening of patients with TS for CD will facilitate the early identification of asymptomatic CD, with early and better intervention ultimately leading to improvements in case management and health outcomes. Further studies are needed from countries that lack data on the burden of CD among various patient populations at risk for CD, including those with TS.
FIGURE 3  |  Contour-enhanced Funnel plot (A) and Egger's publication bias plot (B) examining small-study effects on the pooled celiac disease prevalence among patients with Turner syndrome. The estimated bias coefficient is 0.346 with a standard error of 0.077, indicating a p-value of <0.001.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon justifiable requests.

AUTHOR CONTRIBUTIONS

RH-A performed data analysis and interpretation. GA-B and AA drafted the manuscript. RH-A and SA-S critically reviewed the drafted manuscript. All authors conceptualized the study objectives and design and reviewed and approved the final submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.674896/full#supplementary-material
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