




# BMJ Open Strength of the association between Turner syndrome and coeliac disease: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Coeliac disease (CD) is a genetic autoimmune disorder characterised by a permanent sensitivity to the gluten contained in some grains. Certain patient groups are considered high risk for the development of CD, including, but not limited to, those with chromosomal disorders such as Turner syndrome (TS). Here, we present a protocol for a systematic review and meta-analysis that aims to comprehensively summarise the literature, and quantitatively estimate the weighted strength of the association between TS and CD.

**Methods and analysis** Our protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 guidelines. We will search PubMed, Scopus, Web of Science and Embase databases for relevant articles. Variant and broad search terms will be selected for identifying epidemiological studies reporting on the crude and/or adjusted association between TS and CD. Retrieved citations will be screened, and data from the eligible research reports against specific eligibility criteria will be extracted. We will then assess the risk of bias associated with the eligible studies using the Newcastle-Ottawa Scale. The overall weighted strength of the pooled association will be quantified using the random-effects model.

**Ethics and dissemination** This review will use data from published literature; hence, ethical approval will not be needed. The resulting review will be the first to produce a comprehensive synthesis of the strength of the association between TS and CD. The results will be disseminated through a peer-reviewed journal as well as in local and international conferences and symposiums. Results dissemination would help healthcare providers and policy-makers to make informed decisions regarding the diagnosis and management of CD in high-risk individuals. **PROSPERO registration number** CRD42019131881, dated 3 September 2019.

## INTRODUCTION

In recent decades, there has been a dramatic increase in the prevalence of coeliac disease (CD), worldwide.<sup>1 2</sup> A recent meta-analysis found that the global prevalence of CD was 1.4% based on serological testing, and 0.7% based on small intestinal biopsy. According

## Strengths and limitations of this study

- To ensure all relevant evidence is captured, this review will include all observational studies reporting an association between Turner syndrome and the development of coeliac disease and the review will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2009 guidelines.
- To have a highly sensitive and specific database search strategy, an expert librarian in designing search strings for systematic review and meta-analysis studies will be involved.
- Citations screening, eligible studies identification, data extraction and risk-of-bias assessment will be performed by at least two well-trained reviewers to ensure avoiding and minimising selection and data extraction bias to the lowest level possible.
- In the event of high heterogeneity in measures of association between Turner syndrome and coeliac disease, and contingent on the availability of enough estimates of association—the source of heterogeneity through subgroup as well as univariate and multivariate metaregression analyses will be explored; otherwise, the review might be reported narratively.

to that meta-analysis, the prevalence of CD varied by location. In South America, the prevalence of CD was 4.0%; in Africa and North America, it was 0.5%, in Asia 0.6% and in Europe and Oceania 0.8%.<sup>3</sup>

CD is a genetically based autoimmune disorder characterised by a permanent sensitivity to gluten-containing grains, such as wheat, barley and rye, and their derivatives.<sup>4</sup> The key genetic factor associated with CD is the human leucocyte antigen (HLA) with more than 90% of patients with CD carrying either the HLA-DQ2 or HLA-DQ8 genotypes.<sup>5</sup> The consumption of gluten or repeated gastrointestinal infections early in life in genetically susceptible individuals are

believed to trigger and drive the induction of intraepithelial lymphocytes in the small intestine, leading to villous atrophy.<sup>6–8</sup> The classical clinical manifestations of patients with CD are usually diarrhoea, weight loss or failure to thrive. However, they may present with non-classical signs and symptoms, such as anaemia, abdominal pain, osteomalacia and osteoporosis, short stature, lymphoma, liver disease and neurological and psychological symptoms.<sup>9 10</sup>

Although screening for CD is not recommended for the general population currently, certain patient groups are considered high risk for the development of CD; screening is recommended for such groups.<sup>11 12</sup> Different high-risk groups have been identified by multiple studies; among these groups are first-degree relatives of patients with CD, patients with immune-mediated conditions including type 1 diabetes mellitus and autoimmune thyroid disease or patients with selective IgA deficiency, and those with genetic disorders such as Down, Turner and Williams syndrome.<sup>13–15</sup> A meta-analysis showed that 1.6% of patients with autoimmune thyroid disease have CD.<sup>16</sup> Another meta-analysis revealed that around 1 in 31 patients with iron deficiency anaemia had histological evidence of CD,<sup>17</sup> and approximately 2.0% of people with osteoporosis had biopsy-verified CD.<sup>18</sup>

Turner syndrome (TS) is a chromosomal disorder that affects around 1 in 2500 live female births. It is the most commonly observed X chromosome-related genetic disorder in females, and is characterised by short stature, ovarian dysfunction, cardiovascular disease and an increased risk of autoimmune diseases such as diabetes type 1 and CD.<sup>19</sup> Several studies have demonstrated that CD is more commonly observed in patients with TS than those in the general population.<sup>20–24</sup> Therefore, it has been recommended that patients with TS be monitored for CD.<sup>11</sup>

There is a lack of systematic reviews on the strength of association between specific genetic disorders and CD.<sup>25</sup> Estimating the pooled prevalence would reflect only the burden of disease. Furthermore, the prevalence of CD in cases of TS does not provide any information on whether TS increases the risk of CD and by how much. In contrast, a statistical measure of association between TS and the risk of developing CD provides this information directly. Moreover, producing a pooled measure of association would allow and minimise bias in estimating (1) the attributable risk fraction of TS in developing CD among individuals with TS and (2) the population attributable risk fraction of TS in developing CD among the entire population. However, the success of this approach is contingent on the availability of the prevalence estimates. The present protocol describes the methodology for a systematic literature review and quantitative estimation of the strength of the association between TS and CD. The findings of the review will fill a gap in the literature, and may inform the planning and implementation of effective early screening and control programmes for CD among those with TS.

The systematic review that is to be conducted following this protocol aims to narratively summarise all the available literature, and quantify a weighted estimate of the strength of the association between TS and CD, from 1 January 1991 to 1 December 2019.

### Objectives

The specific objectives of the systematic review are as follows:

1. To systematically review and narratively summarise literature reporting the association between TS and CD.
2. To quantitatively summarise the weighted crude and adjusted strength of the association between TS and CD, in the form of relative risk (RR).

### Research question

The present protocol for a systematic review and meta-analysis study will help in answering our research question: ‘Are patients with TS at a higher risk of having CD than those without?’

## MATERIALS AND METHODS

### Protocol and registration

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (online supplementary table 1).<sup>26</sup> The systematic review will be reported according to the PRISMA (2009) statement guidelines,<sup>27</sup> and the Meta-analyses Of Observational Studies in Epidemiology checklist.<sup>28</sup>

### Eligibility criteria

The protocol has been developed in consideration of the participants, exposure, comparator, outcome(s), and type of study (PECO(T)). The PECO(T) statement provides the framework from which studies are identified and selected for inclusion.<sup>29</sup> However, as we are looking for observational studies, we only considered participants, exposure and the outcome of interest.

### Participants

The participants included should be females with a TS diagnosis regardless of age.

### Exposure

TS presence. All TS cases regardless of type (mosaic or classical).

### Outcome

Our outcome of interest is CD regardless of the diagnostic criteria.

### Type of studies

All epidemiological observational studies that report on the calculated association between TS and CD, or that allow for the calculation of the crude and/or adjusted estimate of the association between TS and CD will be included.

### Publication period

In 1990, The European Society of Gastroenterology, Hepatology and Nutrition released the first modern guidelines for CD diagnosis.<sup>30</sup> Therefore, we will consider the year 1990 as the year for the well-defined CD diagnostic criteria. All relevant articles published from January 1991 to December 2019 will be included in this systematic review.

We will exclude all other studies not meeting our eligibility criteria.

### Data sources and search strategy

Four major electronic databases, PubMed, Scopus, Web of Science and Embase, will be used to conduct a literature search to identify eligible publications. The reference lists of the eligible publications will be hand searched to identify further studies that may have been missed.

A comprehensive and sensitive computerised search will be implemented for identifying eligible published studies. We will use specific search terms including variant terms using Boolean operators. To ensure the comprehensiveness of the search strategy, and to avoid potential eligible studies being missed, a predetermined electronic search strategy will be designed by the search team (GSM-AB and S-AS) and a librarian with expertise in designing search terms for systematic reviews. Our designed search strategy is presented in the online supplementary box 1.

### Identification of the eligible studies

All the retrieved search citations will be imported to Covidence software (Covidence, Melbourne, Australia),<sup>31</sup> where all duplicates will be removed automatically.

### Titles and abstract screening

Of the remaining citations, the titles and abstracts will be screened for relevance by at least two independent reviewers. Screened titles and abstracts will be classified into three categories: not relevant, relevant or potentially relevant. A third reviewer will resolve articles that fall in the conflict zone.

### Full-text screening

The full texts of the identified relevant or potentially relevant publications will be thoroughly screened, and independently assessed by at least two reviewers. Additional studies with potential duplicate estimates on the same study subjects will be removed during the full-text screening. Discrepancies between reviewers will be resolved by a third reviewer.

### Data extraction

Relevant data from eligible studies will be extracted into a predefined data extraction form, which will first be piloted using five eligible research reports. The data will be extracted independently by two review investigators. Discrepancies between data extractors will be discussed and resolved for a consensus to be reached. If a consensus cannot be achieved, an expert will be consulted.

The following parameters will be extracted from relevant studies: author names, year of publication, specific country and city in which the study was conducted, study design, setting, study period, CD diagnostic criteria used, type of TS, number of participants tested for CD, mean or range age of the tested study subjects, number of tested subjects found positive for CD, frequency of screening, numbers of patients with and without TS diagnosed with CD, crude and adjusted estimates of the association between TS and CD and their 95% CIs. We will contact the relevant corresponding authors to obtain any missing data.

A complete list of the precoded parameters to be extracted is provided in online supplementary table 2.

### Quality and risk-of-bias assessment

Two reviewers will independently assess the quality of the eligible studies. We will assess each study's risk of bias using the Newcastle-Ottawa Scale (NOS) for observational studies.<sup>32</sup> The NOS will be adapted from its original version to make it specific to and suitable for this review.

### Data synthesis

For studies providing an overall adjusted estimate of the association between TS and CD using several models, we will consider the estimate obtained from the model adjusted for the largest numbers of variables. For studies providing stratified crude estimates of the association between TS and CD, the estimate of the association of the total sample will be replaced with that of the pooled stratified measures. A predefined sequential order will be followed when considering stratified measures. Estimates stratified according to age will be prioritised, followed by countries and year. This scheme will prioritise strata with more information on the tested subjects. Otherwise, the overall estimate of the association will be included. One stratification level per included published research report will be considered to avoid double counting.

### Summary measures and synthesis of results: meta-analysis

Using the random-effects model, we will perform meta-analyses of the extracted data for the estimation of the weighted pooled strength of the association between TS and CD and its corresponding 95% CI. The strength of the association will be quantified in the form of RR and adjusted RR. Since we are including all observational studies regardless of the type of the measure of association between TS and CD, we are expecting a lack of uniformity in the reported measures of association in the literature. For instance, some studies might report an odds ratio (OR) while others might report RR. However, to obtain a unified and consistent measure of association across all studies, in the form of RR, all estimates in the form of OR will be converted into RR, following a standard procedure using the following mathematical formula.<sup>33</sup> This will be done for crude and adjusted estimates separately

$$RR = OR / (1 - p_0 + (p_0 \times OR))^{34\ 35}$$

where  $p_0$  is the baseline risk that is calculated using the following formula:

$$\text{Baseline risk} = \text{OR} / (1 + \text{OR})$$

We will use the *metan* command in Stata software (StataCorp)<sup>36</sup> for the performance of a meta-analysis of the crude and adjusted estimates of association, separately. The *metan* command incorporates the Freeman-Tukey double arcsine transformation for the stabilisation of the variances of estimate measures.

As for the adjusted estimates, based on the reported confounders adjusted for in the individual studies, in the subgroup analyses, we will pool estimates together adjusted for the same confounders as long as enough data are available. For example, all estimates adjusted for age will be pooled in one meta-analysis model while those adjusted for age and other chronic diseases will be pooled using a separate meta-analysis model. This would allow us to produce more precise and informative estimates of association.

The effect estimates will be weighted using the inverse variance method.<sup>37</sup> For each pooled estimate and its 95% CI, a forest plot will be created to show the effect estimate and corresponding 95% CI for each study and the overall weighted effect estimate.

The heterogeneity in effect estimates will be evaluated across studies. Specifically, we will conduct Cochran's  $Q$  test and extract several heterogeneity measures, including the estimate of the between-study variance of the true effect sizes using the  $\tau^2$  statistic, the magnitude and the 95% CI of the between-study variation attributed to heterogeneity rather than chance using the  $I^2$  statistic, and the 95% prediction interval that estimates the distribution of the true effect size among the included studies.<sup>38, 39</sup> The  $Q$ -statistic tests for heterogeneity are based on the null hypothesis that all studies share a common effect size. Hypothesis testing will be performed based on a  $p$  value  $< 0.10$ , implying that the studies do not share a common effect size.<sup>38</sup>

#### Assessment of metabias

To assess publication bias, we will examine funnel plots supplemented with formal statistical testing using Egger's test.<sup>40</sup> A funnel plot of effect estimates will be plotted against the sample size.<sup>41</sup> The asymmetry of the funnel plot will be examined by performing an Egger's test.<sup>40</sup>

#### Sources of heterogeneity: metaregression

Random-effects univariate models and multivariable metaregression models will be used for identifying sources of between-study heterogeneity and quantifying their contribution to variability in the effect estimates. In the univariate metaregression models, analyses will be performed based on tested population, study period, CD diagnostic criteria and sample size. All variables with a  $p$  value  $< 0.1$  in the univariate models will be included in the multivariable model. In the final multivariable model, a  $p$  value  $\leq 0.05$  will be considered statistically significant, contributing to heterogeneity in the effect estimates.

All metaregression analyses will be performed using the *metareg* package in Stata/SE V.15.<sup>36</sup>

#### Patient and public involvement

No patients were involved in the design of this protocol or the study to be carried out.

#### Ethics and dissemination

This review will use data from published literature; hence, ethical approval is not needed. The results of this proposed systematic review will be disseminated to health-care providers and policy-makers. The findings may aid in updating relevant guidelines, and help inform clinicians to make decisions regarding the diagnosis and management of CD in high-risk individuals.

**Contributors** GSMA-B, AHA and SA-S conceptualised the research question. All authors contributed equally to protocol drafting and writing. RHA-R designed the analysis plan, critically revised the protocol and approved the final version. All authors read and approved the final manuscript. RHA-R and SA-S are the guarantors of the review.

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