CORRESPONDENCE

The Prevalence of Celiac Disease in Children and Adolescents in Germany—Results From the KiGGS Study

by Dr. med. Martin W. Laass, Dr. oec. troph. Roma Schmitz, Prof. Dr. med. Holm H. Uhlig, Klaus-Peter Zimmer, Michael Thamm, Prof. Dr. med. Sibylle Koletzko in issue 33–34/2015

The Prevalence is Only Estimated

The prevalence reported in the study is 0.9% (1). The methods and interpretation of the results prompt a certain amount of criticism, however. The title of the article includes the term "prevalence of celiac disease". What was studied in actual fact, however, was the frequency of positive transglutaminase antibodies (tTG-AB), and the prevalence of celiac disease was estimated from this. Celiac disease is an immunologically mediated enteropathy. For a diagnosis without histological confirmation, the ESPGHAN guideline (2012) has recommended a tTG-AB titer above the 10-fold cut-off, and additionally the confirmation of positive endomysium antibodies (EMA-AB). The study determined only the tTG-AB, although JH, co-initiator of the study, the Robert Koch-Institute, which conducted the analysis, pointed out the necessity of also measuring EMA-AB several times. When both antibodies were measured, the sensitivity and specificity in mass screenings were substantially improved (2, 3). When the frequency of the tTG-AB values above the 10-fold cut-off is considered in the present study, the prevalence of celiac disease according to Table 1 is 0.4% (95% confidence interval [CI]: 0.3%; 0.5%), which seems to reflect reality. Such an assessment, while including positive EMA-AB, is also consistent to two cohort studies in German adults, of 0.2% and 0.3% from 2010 (4). A recent Canadian study found biopsy-proofed celiac disease in 13.3% of children with up to threefold-cut-off positive tTG-AB but negative EMA-AB (2). As the maximum specificity of tTG-AB is 95%, 5% of false results are to be expected. The conclusion by the authors of the study (1) that the prevalence of celiac disease of 0.9% is comparable with that in other European countries, is thus not correct, as enormous differences exist in this respect between European countries and further abroad.

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Conflict of interest statement
The authors declare that no conflict of interest exists.

Seropositivity Needs to Be Critically Considered

Laass and colleagues recently reported in *Deutsches Ärzteblatt International* a prevalence of celiac disease of 0.9% in children and adolescents in Germany (1). This prevalence was deduced from the results of antibody measurements in more than 12 000 serum specimens by using a test whose origin was not reported. The conclusion of a celiac disease diagnosis was drawn from seropositivity. The authors assumed a specificity of 95% for their antibody test. However, even if the specificity is much higher (99.5%) the test will yield a number of false positives (n=60 to 65) that will be within the range of cases of seropositive children as reported by the authors (n=98). In the discussion section of the article, the authors attempted to assess the proportions of false positives and false negatives, but this seems speculative—among other reasons, because the comparison was made with results that—as the authors reported—were obtained by using a different testing system (2). The prevalence of celiac disease as reported in the article is consistent with study results from other countries, but deducing a prevalence of celiac disease from seropositivity should be critically considered. The calculated prevalence may represent an upper limit. The lower limit would then result from the number of 47 children whose antibody concentration was above the 10-fold of the cut-off value suggested by the test manufacturer, plus the 8 children with a clinical history. This amounts to a total of 55 children or a prevalence of celiac disease of 0.43%.

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In Reply:

Our correspondents criticize the fact that we used serological data to estimate the prevalence of celiac disease without confirming the diagnosis by using histology or measuring endomysium antibodies (EMA). They suggest only to consider for celiac disease the 47 subjects with transglutaminase antibodies (tTG) concentrations that reach the 10-fold value of the cut-off. Such an approach would lead to a serious underestimate of the prevalence of celiac disease in an epidemiological study. This may be concluded from the data of the Swedish ETICS study (1, 2).

We used this study as a comparator because:

- Like our own study, this is a population-based cross sectional study in children;
- Subjects with tTG values above the cut-off (>5U/mL) underwent biopsy testing, as did those with high normal values (2–5 U/mL); and
- A tTG test from the same manufacturer based on the same antigen was used (ELIA Celikey® tTG-IgA ELISA in the Swedish study and ELIA Celikey® tTG-IgA Immunocap in our cohort; Phadia, now ThermoFisher, Freiburg, Germany).

A total of 192 children met the criteria for biopsy testing, biopsy specimens were taken from 184, and celiac disease was confirmed in 153. Thirteen false positive results (tTG>5 U/mL with normal histology) were offset by 17 false negative results (tTG<5 U/mL in pathological histology findings) (1).

The specificity of the cut-off values of 5 U/mL and 4 U/mL was 99.8% and 99.6%. Additionally, measuring EMA would have increased the specificity only minimally. tTG values above the 10-fold of the normal value were present in only 47 of 153 children with biopsy-confirmed celiac disease.

The retrospective Canadian study reported by Gidrewicz et al. that was cited by Prof Henker indeed showed poorer specificity for tTG antibodies (manufacturers of the test: Euroimmun) (3). However, serological and histological findings were up to six months apart. We do not know how many children had already been put on a gluten-free or low-gluten diet before they underwent biopsy testing.

The cited European multicenter study also raises questions (4). tTG positivity in the two German adult cohorts was 1.4% and 0.5%. The proportion of EMA positivity in subjects positive for tTG varied between 0.14% and 0.9% across the seven cohorts under investigation. This unusually high variance may be due to the varying quality of serum specimens in the cohorts. Any epidemiological screening study of celiac disease will always be subject to limitations, as we discussed in our study. The comparison with the results of the Swedish study, however, supports our conclusions about the prevalence of celiac disease in children and adolescents in Germany. This conclusion was supported during the review process—hence the suggestion by one of the reviewers to include "prevalence of celiac disease" in our title.

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