



Celiac Disease Is Associated with Childhood Psychiatric Disorders: A Population-Based Study

Agnieszka Butwicka, MD, PhD^{1,2}, Paul Lichtenstein, PhD¹, Louise Frisén, MD, PhD^{3,4}, Catarina Almqvist, MD, PhD^{1,5}, Henrik Larsson, PhD^{1,6}, and Jonas F. Ludvigsson, MD, PhD^{1,7,8,9}

Objectives To determine the risk of future childhood psychiatric disorders in celiac disease, assess the association between previous psychiatric disorders and celiac disease in children, and investigate the risk of childhood psychiatric disorders in siblings of celiac disease probands.

Study design This was a nationwide registry-based matched cohort study in Sweden with 10 903 children (aged <18 years) with celiac disease and 12 710 of their siblings. We assessed the risk of childhood psychiatric disorders (any psychiatric disorder, psychotic disorder, mood disorder, anxiety disorder, eating disorder, psychoactive substance misuse, behavioral disorder, attention-deficit hyperactivity disorder [ADHD], autism spectrum disorder [ASD], and intellectual disability). HRs of future psychiatric disorders in children with celiac disease and their siblings was estimated by Cox regression. The association between previous diagnosis of a psychiatric disorder and current celiac disease was assessed using logistic regression.

Results Compared with the general population, children with celiac disease had a 1.4-fold greater risk of future psychiatric disorders. Childhood celiac disease was identified as a risk factor for mood disorders, anxiety disorders, eating disorders, behavioral disorders, ADHD, ASD, and intellectual disability. In addition, a previous diagnosis of a mood, eating, or behavioral disorder was more common before the diagnosis of celiac disease. In contrast, siblings of celiac disease probands were at no increased risk of any of the investigated psychiatric disorders.

Conclusions Children with celiac disease are at increased risk for most psychiatric disorders, apparently owing to the biological and/or psychological effects of celiac disease. (*J Pediatr* 2017;184:87-93).

Celiac disease is an immune-mediated disorder triggered by gluten exposure in genetically predisposed individuals¹ and histopathologically characterized by small intestinal inflammation and villous atrophy. The overall prevalence of celiac disease is 1%-2% in the general population and 0.3%-2.9% in the childhood population.² In adults, numerous studies have testified to the extraintestinal manifestations of celiac disease, describing decreased quality of life,³ fatigue,⁴ neurologic complications,⁵ and psychiatric disorders. Psychiatric outcomes in adulthood, such as mood disorders⁶ and suicide,⁷ but not psychotic disorders,^{8,9} appear to be associated with celiac disease.

Psychiatric disorders in adults with celiac disease may emerge before or after the diagnosis of celiac disease.⁶ Depending on the temporal relationship, several causal mechanisms have been proposed to explain the relationship between the conditions.³ Although psychiatric disorders developing after a diagnosis of celiac disease are often associated with impaired quality of life and difficulty adapting to the chronic nature of celiac disease,¹⁰ psychiatric disorders occurring before the diagnosis of celiac disease may be attributed to active celiac disease, resulting in cerebral hypoperfusion,¹¹ the presence of proinflammatory cytokines,¹² and low folate levels.¹³

These factors may be expected to be particularly harmful in childhood, when mental abilities are still developing. A systematic review by Lionetti et al examined the effect of celiac disease on the increased risk of neurologic conditions, such as headache and neuropathy in children with celiac disease.¹⁴ Independently, genetic background may underlie a potential association between celiac disease and psychiatric disorders. If shared genetics is also a factor, then these phenomena might be expected to be apparent in children.

From the ¹Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; ²Department of Child Psychiatry, Medical University of Warsaw, Warsaw, Poland; ³Child and Adolescent Psychiatry Research Center; ⁴Department of Clinical Neuroscience, Karolinska Institute; ⁵Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Stockholm, Sweden; ⁶Department of Medical Sciences; ⁷Department of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden; ⁸Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK; and ⁹Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Supported by the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social and Medical Sciences framework (340-2013-5867). A.B. received grants from the Polish Ministry of Science and Higher Education (903/MOB/2012/0 and IP2012 006972). L.F. received financial support from the Swedish Research Council (523-2011-3807), the Karolinska Institute Foundation, and the Magnus Bergvall Foundation. J.L. was supported by grants from the Swedish Research Council (522-2009-1951), the Swedish Society of Medicine, and the Swedish Celiac Society. H.L. has served as a speaker for Eli-Lilly and Shire and has received a research grant from Shire; all outside the submitted work. P.L. has served as a speaker for Medice. The other authors declare no conflicts of interest.

ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
ICD	International Classification of Diseases
PAR	Swedish National Patient Register
RR	Relative risk

0022-3476/\$ - see front matter. © 2017 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.jpeds.2017.01.043>

Little is known about psychiatric morbidity in children with celiac disease. In a previous study reported by Ludvigsson et al, children with celiac disease were found to be at greater risk for later autism spectrum disorder (ASD), but previous ASD was not associated with celiac disease.^{15,16} To date, neither other psychiatric disorders nor the family background of this association have been systematically examined in epidemiologic studies in children with celiac disease.

The aims of the present study were to examine the risk of psychiatric disorders in children with a biopsy-verified diagnosis of celiac disease, to examine the prevalence of psychiatric disorders before celiac disease is diagnosed in children, and to investigate whether healthy siblings of celiac disease probands are at increased risk of childhood psychiatric disorders.

Methods

Between 2006 and 2008, we contacted Sweden's 28 pathology departments and obtained histological data on individuals who exhibited villous atrophy (Marsh stage 3) in small intestine biopsy specimens analyzed between 1969 and 2008.¹⁷ In this study, we equated villous atrophy with celiac disease. Although we did not have data on celiac serology in all individuals with villous atrophy, a review of patient charts revealed that in a random sample of 81 individuals with available serologic data, 71 (88%) were antibody-positive at the time of biopsy.¹⁸ Data on villous atrophy were retrieved by local information technology personnel and included information on personal identity number,¹⁹ date of biopsy, topography (duodenum or jejunum), and morphology according to the Swedish SnoMed classification. These data have been described in detail previously.¹⁸ After removing duplicates and data irregularities, we had data on a total of 29 096 individuals with villous atrophy. These individuals were identical to those in our earlier study of mortality in celiac disease.²⁰

Because we aimed to examine the association between childhood celiac disease and psychiatric disorders, we restricted our cohort to individuals aged <18 years at the time of biopsy (n = 10 903), born in Sweden in 1973 or later, and living in Sweden at the time of biopsy. The date was restricted to 1973, because that was when the Swedish Patient Registry began recording psychiatric diagnoses.²¹

Childhood Psychiatric Disorders

Childhood psychiatric disorders were defined as psychiatric diagnoses assigned before age 18 years according to relevant International Classification of Diseases (ICD) codes in the Swedish National Patient Register (PAR).²¹ We explicitly examined the following disorders: any psychiatric, psychotic, mood, anxiety, or eating disorder; psychoactive substance misuse; behavioral disorders; attention-deficit hyperactivity disorder (ADHD); ASD; and intellectual disability. (ICD-based definitions are presented in [Table I](#); available at www.jpeds.com.) Most diagnoses included in the PAR have a positive predictive value of 85%-95%, but these figures vary according to diagnosis.²¹

General Population Controls

A control cohort was retrieved from the Swedish Total Population Register, which was provided by Statistics Sweden. For each patient with celiac disease, we randomly selected 100 general population controls (unexposed individuals) matched by sex, year, and county of birth. The unexposed individuals were required to have been born in Sweden in 1973 or later, to have been diagnosed with celiac disease at age 18 years or older, and to have been living in Sweden at the date of the first biopsy of the matched proband.

Siblings

Through the Multi-Generation Register, we identified 12 710 siblings of children with celiac disease. Siblings of celiac disease probands were required to have been born in Sweden in 1973 or later, to have the same parents as the celiac disease proband, and to be free of diagnosed celiac disease at age 18 years. For each sibling of a celiac disease proband, we randomized 100 healthy control siblings from the general population (siblings of individuals without celiac disease) and matched them in terms of sex, year, and county of birth of both siblings. Both siblings of celiac disease probands and their controls were required to be free of celiac disease to age 18 years.

Covariates

Information on parental country of birth was retrieved from the Migration Register provided by the Swedish Migration Board. The highest level of education obtained by either parent was based on data obtained from the Education Registers, the National Censuses for 1970-1985, and the Integrated Database for Labour and Market Research, provided by the government agency Statistics Sweden. The Medical Birth Register administered by Sweden's National Board of Health provided data on gestational age (≤ 31 weeks, 32-36 weeks, ≥ 37 weeks), birth weight (≤ 1499 g, 1500-2499 g, 2500-3499 g, ≥ 3500 g), Apgar score (≤ 6 , ≥ 7) ([Table II](#); available at www.jpeds.com). Missing data were not replaced by any method, but rather were categorized as "unknown" and as such used in subsequent analyses.

Statistical Analyses

In our main cohort study, we estimated the risk for any psychiatric disease and the following psychiatric disorders in children with celiac disease vs the general population controls: psychotic disorders, mood disorders, anxiety disorders, eating disorders, psychoactive substance misuse, behavioral disorders, ADHD, ASD, and intellectual disability. We previously reported data on biopsy analysis-verified celiac disease and ASD,¹⁶ but chose to include these data here to provide a complete assessment of childhood psychiatric disorders and confirm the previous report with current general population control and sibling analyses. HRs were estimated from Cox proportional hazard models stratified on matched sets to account for matching by sex, birth year, and county of birth. The proportional hazards assumption for each variable in the models was assessed by plotting the cumulative hazard functions and plotting Schoenfeld residuals against time.

Download English Version:

<https://daneshyari.com/en/article/5719585>

Download Persian Version:

<https://daneshyari.com/article/5719585>

[Daneshyari.com](https://daneshyari.com)