Down Syndrome Is Associated with Elevated Risk of Celiac Disease: A Nationwide Case-Control Study

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Objective To provide risk estimates for celiac disease (CD) in Down syndrome (DS) compared with the general population.

Study design In this nationwide Swedish case-control study, we examined the risk of CD in individuals with DS born between 1973 and 2008. Study participants consisted of 2 populations: 11 749 patients with biopsy-verified CD (villous atrophy [VA], equivalent to Marsh grade III) who were identified through histopathology reports from the 28 pathology departments in Sweden and 53 887 population-based controls matched for sex, age, calendar year of birth, and county of residence. We used prospectively recorded data from Swedish health registers to identify individuals with DS. ORs were calculated using conditional logistic regression.

Results Of the 11 749 individuals with CD, 165 had a diagnosis of DS (1.4%) compared with 55/53 887 controls (0.1%). This corresponded to an OR of 6.15 (95% CI = 5.09-7.43) for subsequent CD in individuals with DS compared with the general population. The association between DS and CD was not affected by maternal age at delivery, infant sex, or presence of type 1 diabetes mellitus in the child.

Conclusions We found a sixfold increased risk of CD in individuals with DS. This study adds precision to the previously reported association between DS and CD. *(J Pediatr 2013;163:237-42)*.

Celiac disease (CD) is a life-long disease prevalent in 1%-2% of the Western population,[1] and is associated with an increased risk of both lymphoma[2] and overall mortality.[3] CD is increasingly diagnosed through screening of genetic risk groups (eg, first-degree relatives to patients with CD). Genetic susceptibility to CD is shared between human leukocyte antigen (HLA) genotypes on chromosome 6p21 and a high number of genes outside the HLA loci.[4]

Down syndrome (DS, trisomy 21) is the most common chromosomal abnormality in the Western world, with an incidence in the US of 1 in 691 live births.[5] Individuals with DS suffer increased risks of several diseases, including congenital heart defects and autoimmune diseases.[6] The improved survival in DS seen in recent decades has in part been attributable to early detection and treatment of these comorbid conditions.[7]

Although several studies have found a high prevalence of CD in DS,[8,9] there is no consensus that all patients with DS should be screened for CD.[10-13] Although the American Academy of Pediatrics recommends CD screening in children with DS suffering from CD-related symptoms,[11] The Celiac Disease Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends testing for CD also in asymptomatic children with DS.[12] In Sweden, there are no national guidelines for CD screening in DS, and clinicians are instead advised to have a high awareness of CD-related manifestations and, if present, offer testing with CD serology. This lack of consensus with regard to CD screening in DS may partly be explained by the considerable inconsistency in prevalence rates of CD in patients with DS (range 0%[14] to 19%[15]). Additionally, population-based studies on CD and DS are lacking.

The aim of this study was to examine the association between CD and DS in a nationwide Swedish case-control study consisting of 11 749 patients with CD and 53 887 age- and sex-matched controls.

Methods

DS

Through any of the following *International Classification of Diseases* (ICD) codes (ICD-8: 759,30 and 310-315,51; ICD-9: 758A; ICD-10: Q90), 3 independent national health registers were used to identify individuals with DS: the Swedish

CD	Celiac disease
DS	Down syndrome
HLA	Human leukocyte antigen
ICD	*International classification of disease*
VA	Villous atrophy

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National Patient Register,[16] the Medical Birth Register,[17] and the Register of Congenital Malformations.[18]

The Swedish National Patient Register[16] was launched in 1964 and currently more than 99% of all hospital discharges are registered. Since 1973, the Swedish Medical Birth Register[17] encompasses data on virtually all pregnancies. The National Register of Congenital Malformations[18] has collected data on severe malformations since 1964. According to the National Board of Health and Welfare, holder of the national health registers in Sweden, the combined data from multiple registers enable a close to complete identification of individuals with DS.[18] Validation studies[16-18] have concluded that these registers are of high quality, although the accuracy of the DS diagnosis has not been evaluated.

CD and Matched Controls

Individuals with CD were identified using the computerized registers of all regional pathology departments in Sweden (n = 28).[19] In this study, CD was defined as small-intestinal villous atrophy (VA, Marsh grade 3).[20] An earlier evaluation has shown that 95% of Swedish individuals with VA have CD.[19] A detailed account of the data collection process has been published elsewhere.[19]

In the current study, we used the same original dataset described in our previous study on mortality.[3] In short, we identified 29 096 individuals with CD (VA) diagnosed between 1969 and 2008. However, because data were restricted to computerized biopsy reports, most of the biopsies originate from 1990 and later. The government agency Statistics Sweden then matched each individual with CD with up to 5 controls from the general population by age at diagnosis, sex, calendar period of birth, and county of residence. Controls were sampled from all Swedish residents in whom the regional pathology registers did not indicate prior duodenal or jejunal biopsy. After matching, 29 096 individuals with CD and 144 522 controls were linked to the Swedish Medical Birth Register (Figure). Through this linkage, we identified 12 738 individuals born in Sweden 1973 and onwards with a later diagnosis of CD. However, because we restricted our analyses to individuals with complete pregnancy and birth data, the final analyses were based on 11 749 individuals with CD and 53 887 controls.

This study was approved by the Research Ethics Committee of Karolinska Institutet.

Statistical Analyses

We used conditional logistic regression analysis to estimate ORs and 95% CIs for CD in individuals with DS. Each stratum (1 individual with CD and up to 5 controls matched for age at diagnosis, sex, calendar period of birth, and county of residence) was analyzed separately before a summary OR was calculated. Through this internal stratification process, our study design takes into account the different years in which the 3 national health registers with information of DS were introduced. In our main analysis, we examined the OR for CD in individuals with DS. We also studied the risk of CD according to sex.

Maternal age at delivery is associated with DS[21] but may also influence the risk of CD[22] in offspring. In a subanalysis, we therefore examined the association between DS and CD based on maternal age at delivery. Because both CD serology monitoring and the awareness of CD have increased in recent years, we examined whether the calendar period of birth (1973-1984, 1985-1996, and 1997-2007) affected the

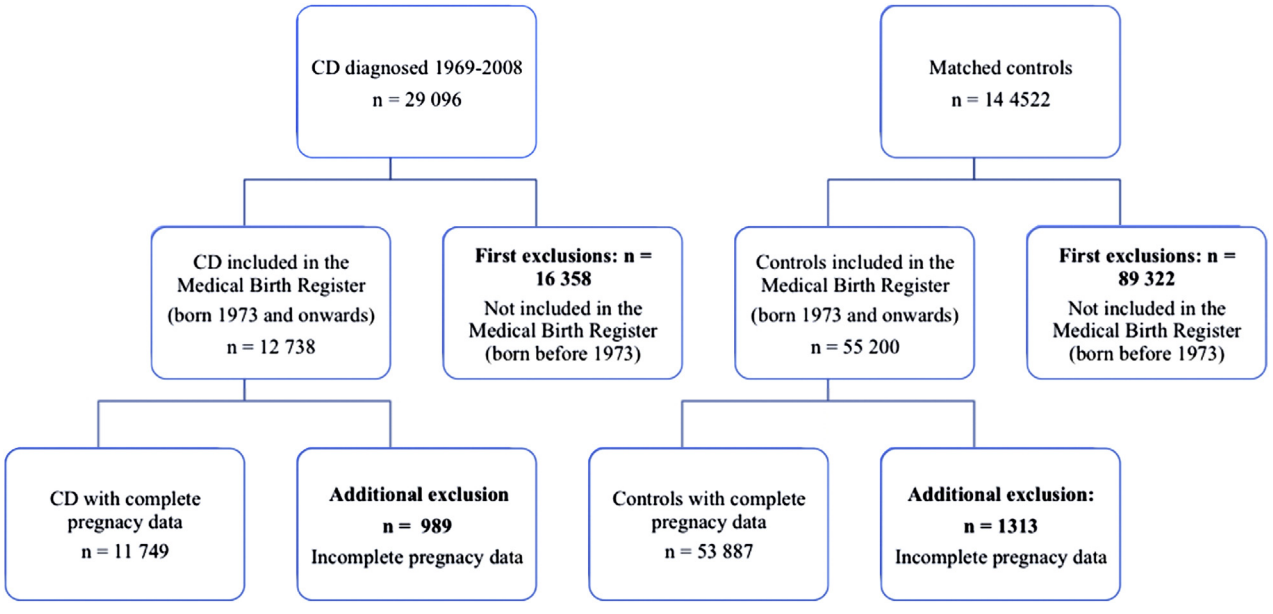

Figure. Flow chart of the exclusion criteria.