**Supplementary Material**

*for*

**Growth and pubertal timing in boys with adult-diagnosed celiac disease: A population-based longitudinal cohort study**

*by*

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# SUPPLEMENTARY TABLES

##  Supplementary Table 1. Previous literature on impact on growth from adult-diagnosed celiac disease (CD).

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| **First author** (year of publication) | **Country** | **Design** | **Data on growth** | **Participants**  | **Main findings** |
| *CD*n= CD patients [male patients] | *Comparators* (external/internal comparison group) A |
| **Bardella** (2000)(1) | Italy | Cross-sectional | Directly measured at clinical visits | Adult tertiary care patients, most diagnosed as children, now in clinical, histological and biochemical remission. n=71 [20 men] | Age- and sex-matched healthy controls (internal group) | Men with CD were shorter than their peers (175cm [CD] vs 178 cm [controls]; *P=0.05*); women with CD had a comparable (non-significantly different) adult height as their controls (163 cm [CD] vs 162 cm [controls]). Patients with CD had a significantly lower BMI compared with controls (Men, 22 kg/m2 [CD] vs 24 kg/m2 [controls]; women, 21 kg/m2 [CD] vs 22 kg/m2 [controls]).  |
| **Bodé** (1991) (2) | Denmark | Cross-sectional | Self-reports from a mailed survey | Members of the Danish Coeliac Society diagnosed with CD after puberty and at the time of survey at least 20 years of age.n=160 [54 men] | Directly measured growth C in the population-based Copenhagen Heart Study (external group) | Men and women with CD weighed considerably less (-12 and -7 kg, respectively), had a significantly lower BMI but were not significantly shorter than comparators; in fact, women with CD tended to be somewhat taller than women without CD (P>0.10). Growth differences were unrelated to the presence of GI symptoms prompting the diagnosis of CD, or to whether clinical symptoms of CD started before vs. after puberty.  |
| **Cacciari** (1991) (3) | Italy | Cross-sectional | Not explicitly reported, but likely directly measured at clinical visits | Adult patients diagnosed in adulthood (n=95) or childhood (n=23) attending clinics in Bologna, Emilia-Romagna, Italy. n=118 [32 men] | Mean height of adult residents in that geographical area (external group) | As compared with comparators, no significant differences in adult height in patients with CD irrespective of whether diagnosed in adulthood or childhood or whether associated with GI complaints or not. Results were consistent across sexes. |
| **Cosnes** (2002) (4) | France | Cross-sectional | Not explicitly reported, but likely directly measured at clinical visits | Adult patients n=184 [56 men] | Age- and sex-matched controls (internal group) | Patients with CD were significantly shorter compared with controls (Men, 171 cm [CD] vs 176 cm [controls]; women, 160 cm [CD] vs 163 cm [controls]); short stature was more prevalent among those with symptomatic, adult-diagnosed disease, compared with groups of adults with paucisymptomatic CD, children diagnosed with CD or with disease-free matched controls  |
| **Esmaeilzadeh**(2016) (5) | Iran | Cross-sectional | Directly measured in the clinic | Adult patients who in 2008-2014 were referred to a tertiary CD clinic.n=219 [54 men] | Age-matched disease-free controls (internal group) | Patients with CD were significantly shorter compared with controls (Men, 169 cm [CD] vs 171 cm [controls]; women, 155 cm [CD] vs 158 cm [controls]) and had a significantly lower BMI (Men, 22 kg/m2 [CD] vs 26 kg/m2 [controls]; women, 24 kg/m2 [CD] vs 27 kg/m2 [controls]). |
| **Haapalahti** (2005) (6) | Finland | Cross-sectional  | Directly measured at clinical research visits | CD diagnosed at age 16-25 years from a cohort of schoolchildren studied for risk factors for type 1 diabetes. Cases identified by screening stored blood samples n=26 [8 men] | Healthy cohort controls (age 16-21) screening negative for CD (internal group) | Women with adult-diagnosed CD were shorter than the female controls (162 vs. 167 cm; P=0.04), whereas no significant difference was found for men with or without adult-diagnosed CD (178 versus 177 cm). Both men and women with adult-diagnosed CD had non-significantly higher BMI compared with controls.  |
| **Pärnänen** (2012) (7) | Finland | Cross-sectional | Self-reports and, to a lesser extent, direct measurements | Adult patientsB born in 1920-1989. One in five identified via screening in CD research programs, otherwise by clinical case ascertainment not further defined. n=1084 [271 men] | Growth data from a nationally representative, cross-sectional postal survey: “Health Beha- viour and Health among the Finnish Adult Population” (external group) | Overall no significant differences in final height between patients with adult-diagnosed CD and general population controls. Sub-analyses revealed that, among patients born in 1948-1961, men with GI symptoms at the time of diagnosis and women with a screening-detected CD were significantly shorter than their peers. Conversely, women born in 1920-1989 and presenting with GI symptoms were significantly taller than female controls.  |
| **Sonti** (2013) (8) | USA  | Cross-sectional | Direct measurements of growth from a prospectively maintained clinical database | Patients at a referral center for CD in New York, NY, mostly diagnosed after the year of 2000n=585 [162 men] | Self-reported growth data from white adults of the 2009-2010 NHANES survey (external group) | While men with CD were significantly shorter than their peers (169 cm [CD] vs 177 cm [comparators], P<0.01), women with CD were significantly taller (166 cm [CD] and 163cm [controls], P<0.01). Marked lower BMI for CD patients (both men and women with CD, BMI 23 kg/m2) compared with NHANES data (both men and women in NHANES, BMI 29 kg/m2). |
| **Weiss** (2008) (9) | Israel | Cross-sectional | Retrospective self-reports | Members of the Israeli Celiac Association and patients at a pediatric gastroenterology unitn=290 [83 men] | CDC growth charts of U.S. children (external group) | No significant differences in final height between participants with CD diagnosed in childhood- vs. adulthood (P=0.22 [boys/men] and P=0.68 [girls/women]. For men, but not for women, there were a significant inverse relationship between age at diagnosis and final height (correlation coefficient, R=-0.28; P=0.01).  |

BMI, body mass index; CD, celiac disease; CDC, Centers for Disease Control and Prevention; GI, gastrointestinal; GFD, gluten-free diet; NHANES, National Health and Nutrition Examination Survey.

A Internal comparison group refers to a control group of participants without CD drawn from the same source population as cases with CD; conversely, an external comparison group is identified from a source population distinct from the one from which cases with CD were identified. B Only one-third of patients with CD were on a GFD. C Comparators weighted wearing normal indoor clothing. The papers included in this table were identified using a PubMed search on August 7, 2019, for: (celiac disease[Title/Abstract] OR coeliac disease[Title/Abstract]) AND (height[Title/Abstract] OR body mass index[Title/Abstract]) AND (adult[Title/Abstract] OR puberty[Title/Abstract]). Out of 86 listed papers we, based on abstract and title, included seven studies reporting original data on to the impact of height and/or BMI in adult-diagnosed CD (i.e., diagnosed after puberty) as compared with a control group; hence, we did not include case series without a control group. From the reference lists of these seven papers we identified two additional relevant studies, by Haapalahti *et al.* (6) and Cosnes *et al.* (4)

# SUPPLEMENTARY METHODS

## Formation of study sample: The BEST cohort

This study is based on the BMI Epidemiology Study (BEST) cohort which takes advantage of growth data in centrally stored school healthcare records in Gothenburg, Sweden’s second largest city, to study the association of growth with disease development.(10) Since the early 20th century, the health and wellbeing of Swedish children have been monitored by the school healthcare, starting at the time of compulsory school attendance (at age seven years for the study cohort) throughout the school years. This program includes vaccinations and direct measurements of height and weight performed by trained school nurses. From the early 1950s (coinciding with childhood measurements from ≈ birth year 1943), 98.5% of all pupils nationwide were covered by school healthcare. (11)

As described in Supplementary Figure 1 (flowchart), due to missing data, the study cohort represents some 75% out of those in the source population. In order to better understand the potential impact on our growth estimates from missing data, we have previously compared body mass index (BMI) from military conscription among those with vs. without stored school healthcare record data. (12) That analysis revealed an almost identical BMI at military conscription among participants and non-participants (BMI mean [SD]: Included participants 21.13 [2.53] kg/m2; Non- participants 21.15 [2.57]; non-significant using t-test), indicating that the study cohort is representative for all boys born in 1945-1961 in Gothenburg, Sweden.

Our study sample was restricted to men because Sweden did not during the study period have mandatory female military conscription, which prevented us from retrieving data on young adult BMI and height for women.

## Description of study variables

### *Body mass index*

Body mass index (BMI) at age eight years and at age 20 years were estimated using all paired height and weight measurements in the period between 6.5 and 9.5 years of age and 17.5 to 22 years of age, respectively. The participants had on average 1.9 measurements in the childhood BMI period and 1.3 measurements in the young adult BMI period. All measurements within these age intervals were then used to construct a linear regression model and the data for individual participants were extra- or intrapolated on this regression line to obtain BMI at eight respectively 20 years of age; the age-dependent change was assumed to follow the slope of the fitted models and BMI at age 8/20 years was estimated using the slope of the fitted model. For individuals with more than one BMI measurement between 6.5 and 9.5 years of age, the mean of the BMI estimations at eight years was used; a similar approach was used for repeated BMI measurements at ages 17.5-22.0 years.

The BMI development through puberty was defined as the difference between BMI at 20 years of age and BMI at 8 years of age. Puberty has a great impact on growth, and its timing and development varies between individuals. (13) We therefore chose to define the pubertal period with a rather wide time window in order to avoid the confounding effect of puberty on growth. Hence, the time between 8 and 20 years included not only the complete pubertal period but also time periods of varying length before and after puberty.

### *Height*

Height at age eight years was estimated using all height measurements in the period between 6.5 and 9.5 years of age. All measurements within this age interval were then used to construct a linear regression model which was used to estimate height at eight years. For individuals with more than one height measurement within this age interval, the mean of the height estimations at eight years was used.

For individuals with information on height after age 21 years in the Passport register we used the mean of available heights for each individual (available for 79.9% of the study cohort). For individuals with no information on height after 21 years of age in the Passport register we used height measurements from school healthcare or the Swedish military conscription registry (20.1%). Height measurements in the interval 17.5 to 22 years of age were age-adjusted to 21 years of age. For individuals with several measurements in the interval we estimated and used the mean height at age 21 years.

### *Peak height velocity*

To adequately estimate the age at peak height velocity in an unbiased manner, height measurements before, during, and after the pubertal period are required. We estimated age at peak height velocity according to the Infancy-Childhood-Puberty model(14), modified as previously described (15, 16). Age at peak height velocity was defined as the age at the maximum growth velocity during adolescence and was estimated by the curve-fitting program.

### *Quality control of growth data*

The following steps was used to assure the quality of the collected data on height and weight: *i*) careful transcription of height/weight and dates of measurement from paper school health care records into digital format; *ii*) quality check by another team member (than (*i*)) and correction of erroneously transcribed measurements; *iii*) visual inspection of each growth curve. In addition, biologically implausible values of height and weight were removed from the analyses (i.e., treated as missing), including height measurements that were clearly on a different standardized level before versus after the time of measurement. Finally, we compared the participant’s adult height measurements from school health care and military conscription records when data from both sources were available.

### *Demographic data*

Based on previous literature,(17, 18) and available data, we preselected adjustment variables that may be associated with growth and CD diagnosis. Information on country of birth was retrieved from the Total Population Register maintained by the government agency Statistics Sweden.(19) Country of birth was categorized as Sweden, when the participant and both of his parents were registered as born in Sweden, or categorized as not Sweden (i.e., when the participant, or one or both of his parents were born outside of Sweden, or when data on country of birth were missing). We also retrieved data on the highest attained education level by age 45 years as recorded in the Longitudinal Integration Database for Health Insurance and Labor Market Studies held by Statistics Sweden.(20) From seven predefined education categories, we grouped data into low (=elementary school), middle (=secondary education), and high education level (=post-secondary education).

## Overview of other data sources

Register linkages were possible using the personal identity number, a 10-digit unique identifier assigned to all Swedish residents.

### *Celiac disease recorded in the National Patient Register*

The National Patient Register started in 1964, became nationwide in 1987, and also includes hospital-based outpatient visits since 2001.(21) It currently records >99% of all somatic inpatient and specialist outpatient care in Sweden. It is mandatory of all Swedish, non-primary care physicians, private as well as publicly funded, to deliver data to the National Patient Register. Reporting to the National Patient Register is also linked to the governmental reimbursement system of healthcare services.(21) The register contains patient-related data (e.g., personal identity number, municipality), data about the caregiver (e.g., department/hospital), administrative data (e.g., date of visit/hospital stay) and medical data including a primary diagnosis (the main condition for visit/admission) and up to seven secondary (additional/contributory) diagnoses of comorbidities or complications related to the care. Similar to other register-based studies,(22) we defined celiac disease (CD) according to at least one entry of any of the following International Classification of Diseases (ICD) codes registered by latest December 31, 2016: ICD-7 (introduced in 1964): 286.00; ICD-8 (introduced in 1968): 269.00, 269.98; ICD-9 (introduced in 1987): 579A; ICD-10 (introduced in 1997): K90.0. We considered both primary and secondary diagnoses of CD.

Using the National Patient Register, this study was likely to identify a large proportion of CD diagnoses within our study population. This is because in Sweden, CD has long been exclusively diagnosed by hospital-based gastroenterologist and pediatric gastroenterologists, who are obliged to report to the National Patient Register, rather than general practitioners. Further, since the 1970s,(23) it has been mandatory to perform minimum one duodenal biopsy before confirming the diagnosis of CD in both children and adults (as of 2012, European guidelines has allowed for a non-biopsy celiac diagnosis in certain children,(24) but not in adults). A duodenal biopsy, and its diagnosis, would be recorded in the National Patient Register when the procedure was associated with an admission (common for those who underwent such a procedure in the earlier half of the study period) or else recorded as a hospital-based outpatient visit (included in the National Patient Registry since 2001). This also means that in this study sample, CD diagnosis was based on a standardized investigation including duodenal biopsy and not merely on symptoms, signs and serological tests, which may in adults not be sufficient for diagnostic purposes.(25)

In 2005, the ICD-10 code for CD were validated among patients with later lymphoma and found to be correct (i.e., positive predictive value for CD) in 86% of reviewed cases.(26) The accuracy of CD diagnosis among patients without other conditions is not known. However, the National Patient Register is regarded to hold high-quality data, with diagnosis of chronic conditions generally having a positive predictive value of 85-95%.(21) Regrettably, we in this study did not have access to medical records to verify the diagnosis of CD. Neither did we have access to data on symptoms or signs of the disease that would have enabled us to classify CD into subtypes based on its mode of presentation.

### *Swedish military conscription registry*

This cohort retrieved data from military conscription. Between 1964 and 2008, military conscription was mandatory for all 18- to 20-year-old Swedish men, with an estimated nationwide coverage of some 97-98% until the mid-90s (exclusions from conscription were generally restricted to men with severe medical conditions or those living in institutions); (27) (28) Importantly, individuals diagnosed with CD have never been exempted from conscription. The conscription was performed in a standardized approach, which besides height and weight measurements, included cognitive and physical assessments.

### *The Passport register*

We collected data on adult height recorded in the nationwide Passport register held by The Swedish Police Authority (data capture: 1991 through 2015). Height (cm) at the time of passport application was typically self-reported and only occasionally measured by a professional. Adult height recorded after 21 years of age was available in the Passport register for 79.9% of our cohort. Height in the Passport register is generally regarded to be of high quality as it aims to enhance accurate identification of the passport applicants. However, while it has previously been used in research, (29) we are unaware of studies validating the accuracy of the data from the Passport register.

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