Turner Syndrome and Celiac Disease: A Case-Control Study

Karl Mårild, MD, PhD, a,b Ketil Størdal, MD, PhD, a,c Anna Hagman, MD, PhD, d Jonas F. Ludvigsson, MD, PhD b,e

abstract

OBJECTIVE: Turner syndrome (TS) is the most common sex chromosome abnormality in females. Previous research has indicated a high prevalence of celiac disease (CD) in TS, but data have mostly been limited to case series at tertiary centers. We aimed to examine the risk for CD in individuals with TS compared with the general population.

METHODS: This Swedish nationwide case-control study included individuals with CD and controls born in 1973-2006. The study consisted of 2 groups: (1) 7548 females with biopsy-verified CD (villous atrophy; Marsh stage 3) diagnosed until January 2008 according to histopathology report data from all 28 Swedish pathology departments and (2) 34 492 population-based controls matched by gender, age, calendar year of birth, and county of residence. TS, diagnosed by the end of 2009, was identified using prospectively recorded data from 3 nationwide health registries. Odds ratios (ORs) for CD were calculated using conditional logistic regression.

RESULTS: Of the 7548 females with CD, 20 had a diagnosis of TS (0.26%) compared with 21 of 34 492 controls (0.06%), corresponding to an OR of 3.29 (95% confidence interval [CI] 1.94–5.56) for CD in individuals with TS. The risk of CD in females with TS ranged from twofold (OR 2.16; 95% CI 0.91–5.11) in the first 5 years of life to a more than fivefold increase in females aged >10 years at CD diagnosis (OR 5.50; 95% CI 1.53–19.78). The association between TS and CD was largely unaffected by concurrent type 1 diabetes.

CONCLUSIONS: Females with TS are more likely to develop CD. This study supports active case-finding for CD in TS.
Celiac disease (CD) is an autoimmune disease prevalent in 1% to 2% of Western populations.¹ CD is increasingly diagnosed through an active case-finding approach, implying systematic serological testing for CD in genetic risk groups, such as first-degree relatives of CD patients.² Genetic susceptibility to CD is shared between the HLA (chromosome 6p21) genotype and a number of loci predominantly in noncoding regions outside the HLA loci.³

Turner syndrome (TS) (complete or partial chromosome X monosomy) is the most common sex chromosome abnormality in females, with a worldwide incidence of ~1 in 2500 live-born females.⁴ Classic manifestations of TS include short stature, ovarian failure, cardiovascular disease, and an increased risk of several autoimmune diseases, such as hypothyroidism⁵,⁶ and type 1 diabetes.⁷

Since the 1970s, several reports have indicated an association between TS and CD.⁷–¹⁶ However, most data have been limited to case series at specialist centers for TS and have yielded inconsistent estimates for CD prevalence in TS (range, 2%¹³ to 9%⁹,¹⁵). Only two previous studies have provided population-based relative risk estimates for CD in individuals with TS. Although Jørgensen et al.¹⁰ found a nonsignificant threefold increased relative risk of CD in patients with TS, Goldacre and Seminog⁷ reported a rate ratio of 14.0 (95% confidence interval [CI] 10.2–18.8). Contemporary medical guidelines support active case-finding for CD in TS.²,⁴,¹⁷

The objective of this study was to examine the association between CD and TS in a nationwide Swedish case-control study consisting of 7548 females with CD and 34,492 matched controls. We hypothesized that TS would be associated with an increased risk of CD.

**METHODS**

**Study Population: Individuals with Celiac Disease and Matched Controls**

In 2006 to 2008, we searched the computerized registries of Sweden’s 28 pathology departments to identify individuals with CD, defined as having small-intestinal villous atrophy (Marsh stage 3).¹⁸ An earlier evaluation showed that 95% of Swedish individuals with small-intestinal villous atrophy have CD.¹⁹

After the exclusion of individuals with data irregularities, we identified 29,096 individuals born in 1885 to 2007 with CD diagnosed in 1969 to 2008 (ie, time of first biopsy showing villous atrophy).²⁰ The individuals with CD were then matched for age at celiac diagnosis (or corresponding date of inclusion as a control), gender, calendar year of birth, and county of residence with ≤5 controls from the Swedish Total Population Register. For example, a girl living in the county of Norrbotten who was diagnosed with CD in 2007 at the age of 10 years was matched with five 10-year-old girls who were living in Norrbotten in 2007. After matching, the 29,096 individuals with CD and 144,522 controls were linked to the Medical Birth Register, which identified 11,749 individuals with CD and 53,887 controls born between 1973 (start of registry) and 2006. Finally, after restricting our study sample to females, 7548 individuals with CD and 34,492 matched controls were included in the study (Fig 1).

The study population was restricted to individuals registered in the Medical Birth Register, because this registry includes data on TS diagnoses and potential covariates.

**Turner Syndrome**

TS was defined as having a relevant International Classification of Diseases (ICD) code (ICD-8, 759.50 and 310 to 315.54; ICD-9, 758G; ICD-10, Q96) in any of the following 3 nationwide registries: the National Patient Register,²² the Medical Birth Register,²¹ and the Register of Congenital Malformations.²³ TS was identified up until December 31, 2009. All 41 females with TS identified in this study were registered in the National Patient Register; 9 of these were also registered in the Medical Birth Register, and none were recorded in the Register of Congenital Malformations (Supplemental Fig 2, overview of registry linkages).

The National Patient Register started in 1964, became nationwide in 1987, added hospital-based outpatient...
visits in 2001, and currently includes >99% of all somatic inpatient and specialist outpatient care in Sweden.22 The Medical Birth Register encompasses pregnancy and birth data on virtually all births in Sweden since 1973.21 The Register of Congenital Malformations collects data on malformations and chromosomal abnormalities since 1964.23 Validation studies21–23 have concluded that these 3 registries overall hold high-quality data, although the accuracy of the TS diagnosis has not specifically been evaluated.

**Covariates**

Data on socioeconomic position (according to the European Socioeconomic Classification: 6 categories with missing data fitted into a separate category24) and education level (4 a priori categories)24 were retrieved from the government agency Statistics Sweden. For all individuals, we used the highest available parental level of education and socioeconomic position.24 Using data from the Medical Birth Register, we included maternal age at delivery as a potential confounder because advanced maternal age at delivery has been positively associated with offspring TS25 and may also be associated with offspring CD.26

Type 1 diabetes is associated with TS7 and CD.27 In a sensitivity analysis, we therefore estimated the association between TS and CD after excluding individuals with type 1 diabetes. Type 1 diabetes was defined according to relevant ICD codes recorded before age 30 years in the National Patient Register: ICD-8/ICD-9, 250; ICD-10, E10. We used an age cutoff because ICD-8 and ICD-9 do not distinguish between type 1 and type 2 diabetes.28

**Preplanned Subanalyses**

Previous research from Sweden has shown that CD developing at an early age may differ in terms of risk factors from later-onset CD,29 but also that the phenotype of the disease varies with age, perhaps representing different subgroups. For this reason, we explored the association between CD and TS in different age groups at celiac diagnosis (<5, 5 to 10, and >10 years). We also examined whether the calendar period of birth (1973 to 1984, 1985 to 1996, and 1997 to 2006) influenced our results, because the introduction of CD serology as part of the diagnostic workup for CD and an increasing awareness of CD over time might have changed the clinical spectrum of CD. Finally, we examined the association between TS and CD stratified by maternal age at delivery (<25, 25–29, and ≥30 years).

**Statistical Analyses**

We used conditional logistic regression analysis to estimate odds ratios (ORs) as measures of the relative risk of CD in females with TS. Each stratum (1 individual with CD and ≤5 matched controls from the general population) was analyzed separately before a summary OR was calculated.30 This internal stratification process therefore eliminates the effect of gender, age, calendar year of birth, and county of residence on our ORs.

Although TS is a congenital disorder, the age at diagnosis typically varies according to phenotypic presentation from infancy to adulthood.31 Differences in age at TS diagnosis between females with and without CD, and the differences in age at celiac diagnosis among females with and without TS, were tested using Mann-Whitney U test.

Statistical significance was defined as 95% CIs for ORs not including 1.00 and P values <.05. SPSS version 22.0 was used for all statistical analyses.

**Post Hoc Analyses**

Using Wald test, we examined for interactions between TS and age at celiac diagnosis, calendar year of birth, and maternal age at delivery by introducing multiplicative interaction terms in an unconditional logistic regression model.

**Ethics**

This project was approved by the Ethics Review Board of Karolinska Institutet (Stockholm, Sweden).

**RESULTS**

**Background Characteristics**

The average age at celiac diagnosis in this study was 8 years (median age, 4 years), and some 50% of individuals with CD were diagnosed before the year 2000. The median age of the study participants at the end of 2009 (last identification of TS diagnosis) was 17 years. Although ~4% of the children with CD had a history of maternal CD, the percentage was only 0.3% among controls (Table 1). The median age at TS diagnosis was 6 years (range, 0 to 18 years) and did not differ significantly among females with and without CD (P = .16). Among the individuals with TS, the average age at CD diagnosis was 9 years, compared with an average age of 8 years at celiac diagnosis for those without TS (P value for difference in age, .08).

**Main Results**

We identified 41 TS individuals (20 had CD and 21 did not have CD). This meant that the prevalence of TS was 0.26% (20 of 7548) in the CD population, compared with 0.06% (21 of 34 492) in the matched control population. This corresponded to an OR of 3.29 for CD in TS (95% CI 1.94–5.56) (Table 2). Adjustment for socioeconomic position and education level yielded essentially unchanged ORs (data not shown). Excluding cases and controls with
type 1 diabetes at some stage in life \((n = 541)\) from our dataset did not substantially affect the association between TS and CD (OR 3.32; 95% CI 1.96–5.62).

**Age at Time of Celiac Diagnosis**

The median time difference between TS diagnosis and CD diagnosis was 1 year, ranging from CD antedating TS diagnosis by 8 years to CD postdating TS diagnosis by 29 years. Thirteen females were diagnosed with TS before their CD diagnosis, whereas 7 females were diagnosed with TS after CD.

The risk of CD in females with TS ranged from an nonsignificantly increased twofold relative risk for children aged <5 years at the time of CD diagnosis (OR 2.16; 95% CI 0.91–5.11) to a more than fivefold increase in females aged >10 years at the time of CD diagnosis (OR 5.50; 95% CI 1.53–19.78; \(P\) value for interaction, .44).

**Calendar Period of Birth**

The ORs for CD were highest for those females born in the years 1973 to 1984 (Table 2) \((P\) value for interaction, .63).

**DISCUSSION**

In this nationwide case-control study, we found an overall threefold increased risk of CD in individuals with TS. The risk ranged from twofold (first 5 years of life) to fivefold (in those aged >10 years at the time of CD diagnosis). This study contributes to the existing literature by adding population-based relative risk estimates for CD in TS, and our results support current recommendations of an active case-finding approach to identify CD in TS patients.

**Strengths and Limitations**

Strengths of this study include its population-based study design and the use of biopsy data to identify CD, enabling us to identify a representative CD population. In contrast, CD identified in inpatient registries often includes those suffering from more severe disease than the average CD patient, which could lead to exaggerated risk estimates. During the study period, biopsy-proven villous atrophy was

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7548</td>
<td>34 492</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calendar year of birth</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973–1984</td>
<td>1734 (22.97)</td>
<td>7063 (20.56)</td>
</tr>
<tr>
<td>1985–1996</td>
<td>4390 (58.18)</td>
<td>20 643 (59.84)</td>
</tr>
<tr>
<td>1997–2006</td>
<td>1424 (18.87)</td>
<td>6756 (19.59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3039 (40.26)</td>
<td>14 473 (41.96)</td>
</tr>
<tr>
<td>1–2</td>
<td>4101 (54.33)</td>
<td>17 785 (51.56)</td>
</tr>
<tr>
<td>≥3</td>
<td>408 (5.41)</td>
<td>2254 (6.48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 1 diabetesb</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>375 (4.97)</td>
<td>166 (0.48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal age at delivery, y</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>2098 (27.80)</td>
<td>8670 (25.14)</td>
</tr>
<tr>
<td>25–29</td>
<td>2912 (38.58)</td>
<td>12 748 (36.96)</td>
</tr>
<tr>
<td>≥30</td>
<td>2538 (33.62)</td>
<td>13 074 (37.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal CDc</th>
<th>CD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>316 (4.18)</td>
<td>114 (0.33)</td>
</tr>
</tbody>
</table>

**TABLE 2** Relative risk of CD in Individuals With TS compared with matched controls from the general population

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total (n)</th>
<th>CD (n) affected (%)</th>
<th>Control (n)</th>
<th>OR; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS</td>
<td>7548</td>
<td>20 (0.26)</td>
<td>34 492</td>
<td>3.29; 1.94–5.56</td>
</tr>
<tr>
<td>Age at time of CD diagnosis, y^a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>3860</td>
<td>6 (0.16)</td>
<td>18 657</td>
<td>11 (0.06)</td>
</tr>
<tr>
<td>5–10</td>
<td>1394</td>
<td>8 (0.57)</td>
<td>6266</td>
<td>6 (0.10)</td>
</tr>
<tr>
<td>≥10</td>
<td>2294</td>
<td>6 (0.26)</td>
<td>9569</td>
<td>4 (0.04)</td>
</tr>
<tr>
<td>Calendar year of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1984</td>
<td>1734</td>
<td>7 (0.40)</td>
<td>7083</td>
<td>4 (0.06)</td>
</tr>
<tr>
<td>1985–1996</td>
<td>4390</td>
<td>9 (0.21)</td>
<td>20 643</td>
<td>15 (0.07)</td>
</tr>
<tr>
<td>1997–2006</td>
<td>1424</td>
<td>4 (0.28)</td>
<td>26 756 (0.03)</td>
<td>4.34; 1.48–12.75</td>
</tr>
<tr>
<td>Maternal age at delivery, y^a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>2098</td>
<td>7 (0.33)</td>
<td>8670</td>
<td>4 (0.05)</td>
</tr>
<tr>
<td>25–29</td>
<td>2912</td>
<td>5 (0.17)</td>
<td>12 748</td>
<td>5 (0.04)</td>
</tr>
<tr>
<td>≥30</td>
<td>2538</td>
<td>8 (0.32)</td>
<td>13 074</td>
<td>12 (0.09)</td>
</tr>
</tbody>
</table>

^a Defined as time of first biopsy showing villous atrophy (Marsh stage 3) and corresponding age in matched controls.
advocated as the gold standard for CD diagnosis\textsuperscript{32} and was performed by >95% of Swedish pediatricians and adult gastroenterologists before CD diagnosis.\textsuperscript{19} This implies that biopsy records should have a high sensitivity for diagnosed CD. In addition, a previous validation of villous atrophy has shown a positive predictive value of 95% for CD.\textsuperscript{19} Although some individuals in the control group may have had undiagnosed CD, the prevalence of undiagnosed CD should be <2%\textsuperscript{33} and would not affect our estimates more than marginally.

We regard the risk of misclassification of TS as low. Together, the 3 registries used should have high sensitivity for TS.\textsuperscript{34} In our study, all females with TS (n = 41) were identified in the National Patient Register; 9 girls were also registered in the Medical Birth Register, and none were recorded in the Register of Congenital Malformations. However, few TS diagnoses are expected to be found in the latter 2 registries, as these record only TS diagnosed perinatally. Underreporting to the Register of Congenital Malformations might also explain why TS was not identified in this registry.\textsuperscript{34} Although the accuracy of the TS diagnosis per se has not been validated, it is expected to be high given that the positive predictive value for other diagnoses in the Swedish National Patient Register is generally 85% to 95%.\textsuperscript{22}

Regrettably, we lack data on clinical characteristics, including data indicating whether patients with CD were symptomatic or asymptomatic. In addition, in Sweden, the threshold for testing individuals with TS for CD is low. We therefore acknowledge that our estimates might have been somewhat influenced by surveillance bias. Still, it should be noted that the association between CD and TS was not generally recognized until the late 1990s,\textsuperscript{16} meaning that during a large part of our study period, health supervision for children with TS did not include testing for CD. Finally, we acknowledge that TS and CD may be diagnosed at any age and that the confinement of this study to mostly children may have somewhat underestimated our overall OR for CD.

Interpretation of Findings and Previous Literature

This nationwide study on TS and CD yielded 3 main findings. First, there was a considerable, approximately threefold increased risk of CD in individuals with TS compared with the general population. Second, the risk increase for CD was largely unaffected by socioeconomic position or type 1 diabetes. The latter finding implies that the increased risk for CD in TS is not merely related to the CD-prone HLA distribution of patients with type 1 diabetes. Third, although the overall difference between age bands was nonsignificant (P = .44) and should be interpreted with caution, our results suggest a more pronounced risk of CD in females with TS aged >10 years at celiac diagnosis, compared with those diagnosed at a younger age. This finding may reflect the usual latency period before being diagnosed with TS. In our sample, the median age at TS diagnosis was 6 years, which is similar to that found in a previous Swedish study.\textsuperscript{25} The finding of a relatively high risk of CD among females aged >10 years could also reflect the challenges to clinically recognize CD in very young females with TS. Previous research on TS has shown that subclinical CD is common and that those with symptomatic CD, despite a high level of suspicion, frequently face long diagnostic delays.\textsuperscript{11} One potential explanation for this is that classic CD symptoms, such as growth failure,\textsuperscript{35} may be disregarded and attributed to TS alone.\textsuperscript{11}

Over the last decades, the association between CD and TS has gained more widespread recognition.\textsuperscript{16} In the meantime, the emergence of CD-specific serology tests and an increased awareness of CD have meant that more individuals, in particular those outside classic risk groups, are now tested for CD. In spite of this, we found no clear evidence that period-specific changes in case-finding practices significantly influenced the ORs for CD. However, we cannot rule out that we have somewhat underestimated the association between CD and TS among those females born in 1997 to 2006 because of short follow-up of these individuals. Over time, the median age at celiac diagnosis has increased, and it is now common even for older people to receive a diagnosis of CD.\textsuperscript{36} In our study, the children in the youngest age band (<5 years at celiac diagnosis) had the lowest OR for TS, and it is possible that the overall OR for TS would have been even higher had a larger proportion of study participants been adults.

Most studies that have examined the occurrence of CD in TS have been performed at specialist centers for TS, finding prevalences of biopsy-proven CD between 2%\textsuperscript{13} and 9%\textsuperscript{9,15} There are also considerable differences between the few previously published relative risk estimates for CD among Individuals with TS. Jørgensen et al.\textsuperscript{10} followed a cohort of 798 TS patients from 1980 to 2004 using Danish national health registry data, reporting a standardized incidence ratio of 2.7 for inpatient CD (95% CI 0.2–11.7). However, in that study, only 1 individual with TS developed CD, compared with an expected number of 0.4 among Danish women in general. In contrast, an English registry–based cohort study by Goldacre et al.\textsuperscript{7} including 2459 TS patients requiring hospital admission in 1999 to 2011, reported a rate ratio of 14 for inpatient CD (95% CI 10.2–18.8). The study by Goldacre et al was based on 45 TS patients
developing CD. Our overall OR of 3.29 is consistent with the findings of Jørgensen et al., although their study population differs from ours in size and has an older age distribution. Another distinction compared with the above studies is that our study population consists of both in- and outpatients with CD. Still, it is likely that some of the presented differences in CD prevalences and risk estimates for CD in TS are attributable to chance, as the number of TS patients with CD have been low. Therefore, taken together, the current study and the existing literature quite consistently indicate a positive association between TS and CD.

The mechanisms underlying the TS-associated increased risk of CD, and of autoimmunity in general, remain to be elucidated. It has been suggested that the higher rate of autoimmunity in TS may be related to haploinsufficiency of immunoregulatory genes located on the X-chromosome, such as FOXP3, which encodes a transcription factor critical for the control of regulatory T cells. Although FOXP3 is believed to be implicated in the pathogenesis of several autoimmune diseases, its specific role in CD development is largely unknown. Estrogen deficiency due to ovarian failure or a proinflammatory cytokine profile related to TS are other factors that have been proposed to increase the risk of autoimmunity in TS.

The uncertain long-term benefits of diagnosing asymptomatic CD, and the difficulties in adhering to a gluten-free diet, have meant that CD screening in the general population is controversial. Still, our finding of a markedly increased OR for CD in TS, together with the previously reported dominating subclinical picture of CD in TS and frequent diagnostic delays, argue in favor of continued active case-finding for CD in TS. Such a case-finding strategy may most feasibly include an initial typing of CD-specific HLA phenotypes (HLA-DQ2/DQ8) and, if positive, periodic assessments with CD-specific serology tests to identify those requiring a small-intestine biopsy.

CONCLUSIONS

This large-scale nationwide study found that individuals with TS are at a threefold increased risk of CD. Our results are consistent with the previously reported positive association between CD and TS but add to the literature by providing population-based risk estimates from a population consisting of both in- and outpatients with CD. Our data support the current recommendation of active case-finding for CD in TS.

ABBREVIATIONS

CD: celiac disease
CI: confidence interval
HLA: human leukocyte antigen
ICD: International Classification of Diseases
OR: odds ratio
TS: Turner syndrome

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES


42. Canavan C, Logan RF, Khaw KT, West J. No difference in mortality in undetected celiac disease compared with the general population: a UK cohort study. *Aliment Pharmacol Ther*. 2011;34(8):1012–1019


Turner Syndrome and Celiac Disease: A Case-Control Study
Karl Mårild, Ketil Størdal, Anna Hagman and Jonas F. Ludvigsson
Pediatrics originally published online January 8, 2016;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/early/2016/01/07/peds.2015-2232

Supplementary Material
Supplementary material can be found at:
http://pediatrics.aappublications.org/content/suppl/2016/01/07/peds.2015-2232.DCSupplemental

References
This article cites 45 articles, 8 of which you can access for free at:
http://pediatrics.aappublications.org/content/early/2016/01/07/peds.2015-2232.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
http://classic.pediatrics.aappublications.org/cgi/collection/endocrinology_sub
Gastroenterology
http://classic.pediatrics.aappublications.org/cgi/collection/gastroenterology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Turner Syndrome and Celiac Disease: A Case-Control Study
Karl Mårild, Ketil Størdal, Anna Hagman and Jonas F. Ludvigsson

Pediatrics originally published online January 8, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2016/01/07/peds.2015-2232