Changes in Infant Feeding
Prevalence of Childhood Celiac Disease and

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OBJECTIVES: Between 1984 and 1996, Sweden experienced an “epidemic” of clinical celiac disease in children <2 years of age, attributed partly to changes in infant feeding. Whether infant feeding affects disease occurrence and/or the clinical presentation remains unknown. We investigated and compared the total prevalence of celiac disease in 2 birth cohorts of 12-year-olds and related the findings to each cohort’s ascertained infant feeding.

METHODS: A 2-phase cross-sectional screening study was performed in which 13,279 children from 2 birth cohorts participated: children born during the epidemic (1993) and children born after the epidemic (1997). Previously diagnosed cases were reported and confirmed. Blood samples were analyzed for serological markers and children with positive values were referred for small intestinal biopsy. Infant feeding practices in the cohorts were ascertained via questionnaires. Prevalence comparisons were expressed as prevalence ratios.

RESULTS: The total prevalence of celiac disease was 29 in 1000 and 22 in 1000 for the 1993 and 1997 cohorts, respectively. Children born in 1997 had a significantly lower risk of having celiac disease compared with those born in 1993 (prevalence ratio: 0.75; 95% confidence interval: 0.60–0.93; P = .01). The cohorts differed in infant feeding (specifically, in the proportion of infants introduced to dietary gluten in small amounts during ongoing breastfeeding).

CONCLUSIONS: A significantly reduced prevalence of celiac disease in 12-year-olds indicates an option for disease prevention. Our findings suggest that the present infant feeding recommendation to gradually introduce gluten-containing foods from 4 months of age, preferably during ongoing breastfeeding, is favorable.

 abstract

WHAT’S KNOWN ON THIS SUBJECT: Celiac disease is increasing in several countries and has emerged as a public health problem. Infant feeding has been suggested to affect celiac disease development and/or clinical expression. However, evidence-based complementary feeding strategies are limited.

WHAT THIS STUDY ADDS: Significant difference in celiac disease prevalence between 2 cohorts of 12-year-olds indicates an option for disease prevention. The cohorts differed in infant feeding, and our findings suggest that gradual introduction of gluten in small amounts during ongoing breastfeeding is favorable.

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KEY WORDS
celiac disease, prevalence, infant feeding

ABBREVIATIONS
CI—confidence interval
EMA—endomysial antibodies
IgA—immunoglobulin A
tTG—tissue transglutaminase antibodies
*a Drs Ivarsson and Myléus contributed equally to this work.

Drs Ivarsson, Carlsson, Danielsson, Stenhammar, and Hernell designed the study; Dr Ivarsson was responsible for the overall supervision of the study. All authors participated in the development of the study protocol and the performance of the study; Drs Carlsson, Karlsson, Stenhammar, Danielsson, and Ivarsson were each responsible for one of the study sites; Clinical evaluations were primarily performed by Drs Webb, van der Pals, Karlsson, Högborg, Hammarroth, and Sandström. Dr Halvarsson performed all blinded histopathological evaluations, Dr Rosén performed quality control on the clinical data; Dr Norström was responsible for the database; Data analyses were performed by Drs Norström and Myléus; Drs Myléus and van der Pals wrote the first draft of the manuscript; and all authors participated in data interpretation and critical revision of the manuscript and approved its final version.

(Continued on last page)
Celiac disease is one of the most common chronic diseases in childhood, affecting ~1% of the population, although a substantial variation in prevalence has been reported. Prerequisites for developing celiac disease are genetic susceptibility (HLA-DQ2 or DQ8 haplotype) and dietary exposure to wheat gluten or related prolamins. Serologic markers indicative of the disease are widely used, but ascertainment of small intestinal enteropathy is often regarded as the diagnostic gold standard. In infancy, celiac disease frequently presents with gastrointestinal symptoms, malnutrition, and failure to thrive, but its onset can occur throughout life with variable clinical presentation. Because mild symptoms are common, the majority of individuals with celiac disease remain undiagnosed. Celiac disease is associated with morbidity and increased mortality, especially when untreated. Currently, the only effective treatment is a strict gluten-free diet.

Sweden experienced an “epidemic” of celiac disease (1984–1996) in children aged <2 years. A fourfold increase in incidence of clinically detected disease, followed by a comparable decrease 1 decade later, was confirmed through the National Swedish Childhood Celiac Disease Register. The epidemic has been attributed to differences between the epidemic and postepidemic birth cohorts regarding infant feeding.

Both breastfeeding and aspects of gluten introduction have been associated with celiac disease risk. However, whether infant feeding affects the disease occurrence or the clinical presentation and/or age at disease onset remains unknown. Thus, the relationship between infant feeding and celiac disease risk, as well as between infant feeding and other autoimmune diseases and allergies, remains controversial, and evidence-based complementary feeding strategies are limited. We investigated and compared the total prevalence of celiac disease, including both clinically and screening-detected cases, in 2 birth cohorts of 12-year-olds from the epidemic and postepidemic period, respectively, and related the findings to each cohorts’ ascertained infant feeding.

**METHODS**

**Study Design**

The study was undertaken within the Centre for Global Health Research at Umeå University, with support from the Swedish Council for Working Life and Social Research. We performed a 2-phase cross-sectional screening study called ETICS (Exploring the Iceberg of Celiacs in Sweden), which is part of the PreventCD European project. The screenings were school-based, performed in 2005–2006 and in 2009–2010, and included 2 birth cohorts of 12-year-olds, 1 representing the epidemic birth cohorts (born in 1993) and the other representing the postepidemic cohorts (born in 1997). Characteristics of the birth cohorts regarding infant feeding and celiac disease are summarized in Table 1. The multicenter study covered the same geographic areas of Sweden, and each of the 5 sites included a major city with municipalities in the surrounding suburbs and countryside.

Clinically detected celiac disease (ie, celiac disease diagnosed within routine clinical care before the study) was reported at enrollment, and the other children were screened for celiac disease. Prevalence comparisons were based on the same screening protocol. Informed consent was obtained from all participating families. The study was approved by the Regional Ethical Review Board of Umeå University, Umeå, Sweden.

**Characteristics of the Study Population**

From the 1993 cohort, 10,041 children were invited, with 7567 (75%) participating and 7208 (72%) blood sampled. Corresponding numbers for the 1997 cohort were 8284 invited, with 5712 (68%) participating and 5424 (65%) blood sampled. The larger sample size in the 1993 cohort was due to a larger birth cohort in 1993 (Table 1). The proportion of participating girls was similar in both cohorts (48% girls in the 1993 cohort vs 49% girls in the 1997 cohort, $P = .99$).

**Screening Strategy**

Blood samples from all children without clinically detected disease were analyzed for serologic markers. Anti-tissue-transglutaminase antibodies (tTG) of

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of the Swedish Birth Cohorts With Respect to Infant Feeding and Celiac Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children***</td>
<td>117,997</td>
</tr>
<tr>
<td>Infant feeding recommendation regarding introduction of gluten-containing foods</td>
<td>X</td>
</tr>
<tr>
<td>From age 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>In small amounts, from age 4 to 6 mo</td>
<td>38</td>
</tr>
<tr>
<td>Average daily flour consumption from milk- and cereal-based follow-on formulas (g/child/d)</td>
<td>77</td>
</tr>
<tr>
<td>Proportion of infants breastfed</td>
<td>63</td>
</tr>
<tr>
<td>4 mo of age (%)</td>
<td>5.4/1000</td>
</tr>
<tr>
<td>6 mo of age (%)</td>
<td>Exclusively or partially breastfed. Statistically significant difference between cohorts at both ages ($P &lt; .001$). National Board of Health and Welfare (<a href="http://www.socialstyrelsen.se">www.socialstyrelsen.se</a>).</td>
</tr>
<tr>
<td>Statistically significant difference between cohorts ($P &lt; .008$).</td>
<td></td>
</tr>
</tbody>
</table>

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* Statistics Sweden (www.scb.se).

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** In children below 2 y of age.

*** Exclusively or partially breastfed. Statistically significant difference between cohorts at both ages ($P < .001$). National Board of Health and Welfare (www.socialstyrelsen.se).
immunoglobulin A (IgA)-type were determined through enzyme-linked immunosorbent assay (Celikey, Phadia GmbH, Freiburg, Germany), and values > 4 U/mL were considered positive. Intermediate values for tTG-IgA (2–4 U/mL) were additionally analyzed for anti-endomysial antibodies (EMA) of IgA type by indirect immunofluorescence technique, with the sample diluted to determine the lowest titer with 1:5 dilution as the cutoff for positivity (The Binding Site, Birmingham, United Kingdom). Children with tTG < 2 U/mL were classified as noncases. Genotyping for HLA alleles encoding for DQ2/DQ8 was performed by oligonucleotide probe hybridization (Eu-DQ test, Eurhospital SpA, Trieste, Italy). Analyses were performed according to the manufacturer’s instructions at the same laboratory, details have been published previously.19,20

Celiac Disease Case Ascertainment

For those who reported clinically detected celiac disease, diagnosis was confirmed by review of histology and serological markers from the National Swedish Childhood Celiac Disease Register12 and/or medical records. Among the children screened, all with positive serological markers were referred to the nearest pediatric clinic for a small intestinal biopsy. Biopsies (4–6 biopsies recommended) were generally taken from both the duodenal bulb and the duodenum distal to the papilla of Vater. Mucosal specimens were classified according to the revised Marsh-Oberhuber classification.21 All biopsies were subjected to a second histopathologic evaluation by 1 pathologist blinded to the previous result. In case of disagreement, a third pathologist evaluated the biopsy.22

Criteria for a celiac disease diagnosis were Marsh III enteropathy or the combination of Marsh I–II enteropathy, HLA-DQ2/DQ8 haplotype, symptoms or signs compatible with celiac disease, and clinical response to a gluten-free diet.

Ascertainment of Infant Feeding

Differences between the cohorts in infant feeding on population level (Table 1) were ascertained via questionnaires sent to all participating families and completed before receiving the screening result. In total, 67% of the participants responded with complete information on breastfeeding duration and age at gluten introduction.

Statistical Analyses

Our prespecified null hypothesis was the same total celiac disease prevalence in the 2 birth cohorts. The acceptable limit for a type I error was set at 5% (α = .05), and for a type II error, it was set at 10% (β = .10), corresponding to a statistical power (1-β) of 90%. Considering an assumed difference in prevalence between the cohorts of 0.5%, a sample size of ~5000 participants from each cohort was necessary. Prevalence was reported as cases per 1000 individuals with a 95% confidence interval (CI) and percentages. Prevalence comparisons between cohorts were calculated by using the traditional log-transformation method (Open Access program WinPepi 11.8)24 and expressed as prevalence ratios with a 95% CI and P values. Comparisons for proportions and medians were performed by using the χ² test and the Mann-Whitney U test, respectively. A 95% CI not including 1.0 or a 2-tailed P value < .05 was defined as statistically significant.

RESULTS

Comparison Between Birth Cohorts

The screening procedure, depicted in Fig 1, revealed a total celiac disease prevalence of 29 in 1000 in the 1993 cohort, including both clinically and screening-detected cases20 and 22 in 1000 in the 1997 cohort. A significantly lower risk for celiac disease in children born after the celiac disease epidemic (1997) compared with during the epidemic (1993) was observed (prevalence ratio: 0.75; 95% CI: 0.60–0.93; P = .01; Fig 2). Comparison between birth cohorts of clinically detected cases resulted in a prevalence ratio of 0.88 (95% CI: 0.45–1.0; P = .07), which was not statistically significant. We found a significantly lower prevalence of positive serological markers in the 1997 cohort compared with the 1993 cohort (prevalence ratio: 0.74; 95% CI: 0.58–0.94; P = .01), and the difference remained in biopsy-verified cases (prevalence ratio: 0.78; 95% CI: 0.6–1.0; P = .06), although it did not reach statistical significance (Fig 2). There was no difference between the birth cohorts in the proportion of clinically vs. screening-detected cases (30% vs 28% clinically detected cases; P = .59). Among the clinically detected cases there was a significantly lower median age at diagnosis for the birth cohort of 1993 than the cohort of 1997 (1.7 vs 5.5 years; P = .04). Considering both cohorts together, celiac disease was more common among girls than boys (prevalence ratio: 1.6, 95% CI: 1.3–2.0; P < .001), but the difference was more pronounced in the 1997 cohort (prevalence ratio: 1.8 vs 1.4; Table 2).

Screening of the 1993 Cohort

The results from the screening of children born during the epidemic (1993) have been published previously20,22 for comparative purposes, the main findings are summarized in Fig 1 and Table 2. Clinically detected celiac disease was identified in 66 cases, of which all but 1 had their diagnosis confirmed through small intestinal biopsy. The nonbiopsied case had EMA 1/320, family history of celiac disease, and clinical response to a gluten-free diet. Positive tTG-IgA and enteropathy were found in 151 screening-detected cases, all carrying the HLA-DQ2/DQ8 haplotype (Table 2).
Clinically detected celiac disease, ascertained by small intestinal biopsy, was identified in 34 cases, of which 22 were girls and 12 were boys, corresponding to a prevalence of 6.0 in 1000 (95% CI: 4.1–8.3; Fig 1). Positive serological markers were found in 104 children (Table 2), which corresponds to a prevalence of 19 in 1000 (95% CI: 16–23).

Infant Feeding in the Study Population

Duration of breastfeeding was 7 and 9 months in the 1993 and 1997 cohort, respectively ($P < .001$), which is in agreement with the proportion of infants breastfed at 6 months of age in the Swedish population (Table 1). Median age at gluten introduction was 5 months in both cohorts; nevertheless, the proportion of infants with
breastfeeding continuing beyond gluten introduction was significantly larger in the later cohort (70% vs 78% in the 1993 and 1997 cohort, respectively, P < .001). Comparable infant feeding patterns were observed for the celiac disease cases and the respective study population in each cohort (data not shown).

**DISCUSSION**

In 2 cohorts differing in infant feeding, we found a significantly lower celiac disease prevalence in the 1997 cohort compared with the 1993 cohort (2.2% vs 2.9%; P = .01, Fig 2). Our findings suggest that infant feeding affects the risk of developing celiac disease, at least up to the age of 12 years.

Our screening verifies that the epidemic pattern in celiac disease incidence seen in Sweden between 1984 and 199611,13 represents a change in disease occurrence and not only a change in clinical presentation (Fig 2). Previous studies have indicated that infant feeding affects the clinical presentation and/or age at disease onset.25,26 In line with these findings, we found a higher median age at diagnosis among the clinically detected cases born after the epidemics compared to those born before.

The beginning and the end of the Swedish epidemic of celiac disease were preceded by changes in infant feeding recommendations (more specifically, regarding the age for introduction of gluten-containing complementary foods). The changes were implemented through the well-baby clinics that are attended by almost all infants (99%) (www.socialstyrelsen.se). In 1982, the recommendation was changed by postponing the introduction from 4 until 6 months of age, and in 1996 the recommendation was revised again, now recommending that gluten could be introduced from 4 months of age. From the questionnaires completed before knowledge of the screening results, no difference in age at gluten introduction could be observed. However, the recall time was 12 years. Recall bias should not be more prevalent in one of the cohorts compared with the other, and thus nondifferential misclassification bias pulls the result toward null, underestimating or even concealing a potential difference. Our previous case-referent study performed during the epidemic showed that ∼70% of the parents followed the recommendations at that time. Correspondingly, on the basis of a Swedish cohort of children born after the epidemic,27 ∼60% of the parents followed the revised recommendation. Taken together, there might have been a difference in age at gluten introduction, albeit nondetectable after 12 years. Nonetheless, we found a difference between the cohorts in the proportion of infants being introduced to gluten during ongoing breastfeeding, probably a combined effect of the revised infant feeding recommendation and the increase in duration of breastfeeding (Table 1). Concurrently, but independent of the revised feeding recommendations, the gluten content of Swedish milk and cereal-based follow-on formulas was first substantially increased and later decreased again (Table 1).11 The current Swedish infant feeding recommendation, revised as a result of the celiac disease epidemic, entails both the aspects of gluten introduction in small amounts and concomitant breastfeeding. Our findings suggest that this is favorable with respect to celiac disease risk. In both European and US infant populations, equivalent infant feeding practices were recently recommended.28–31

The hypothesis that early exposures influence celiac disease development is supported by our previous pilot screening study, performed on the same birth cohorts, suggesting a difference in celiac disease prevalence as early as 2.5 years of age.32 Oral tolerance to an antigen develops early in life, and celiac disease can be viewed

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**TABLE 2** Screening outcome and celiac disease ascertainment in 2 birth cohorts of 12-y-olds.

<table>
<thead>
<tr>
<th>Positive serological markers</th>
<th>1993 Cohort n (%)</th>
<th>1997 Cohort n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tTG-IgA &gt;4 U/mL</td>
<td>167 (88)</td>
<td>85 (88)</td>
</tr>
<tr>
<td>tTG-IgA 2–4 U/mL and EMA-IgA &gt;1:5</td>
<td>20 (11)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>187</td>
<td>104</td>
</tr>
<tr>
<td>Girls</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>Small intestinal biopsy evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsh III</td>
<td>139 (92)</td>
<td>88 (89)</td>
</tr>
<tr>
<td>Marsh II</td>
<td>2 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Marsh I and symptoms/signsab</td>
<td>9 (6.0)</td>
<td>1 (1.0)c</td>
</tr>
<tr>
<td>Noninterpretable</td>
<td>1 (0.7)d</td>
<td>0</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>151</td>
<td>89</td>
</tr>
<tr>
<td>Girls</td>
<td>80</td>
<td>57</td>
</tr>
<tr>
<td>HLA genotyping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DQ2</td>
<td>113 (75)</td>
<td>71 (80)</td>
</tr>
<tr>
<td>DQ2/DQ8</td>
<td>23 (15)</td>
<td>8 (9.0)</td>
</tr>
<tr>
<td>DQ8</td>
<td>15 (9.9)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Non-DQ2/DQ8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not available</td>
<td>0</td>
<td>1 (1.0)e</td>
</tr>
</tbody>
</table>

a Data published previously.20,22
b Symptoms/signs include gastrointestinal complaints, tiredness, deviation in weight and/or height, heredity for celiac disease, anemia, and autoimmune disorders.
c Diagnosis based on tTG 3 U/mL, EMA 1/10, Marsh I enteropathy in combination with stomachache.
d Diagnosis based on tTG >100 U/mL because the biopsy was noninterpretable, but parents declined rebiopsy. After gluten-challenge: oral rhagades and additional tTG >100 U/mL.
e Diagnosis based on tTG >100 U/mL and Marsh III enteropathy.
as a failure to develop oral tolerance to gluten, or a later loss of this tolerance. The development of oral tolerance is a complex immunologic process involving interactions between genetic factors and environmental and lifestyle exposures, such as bacterial gut colonization and infant feeding.\(^{18,33}\)

Breastfeeding has been associated with reduced risk for several autoimmune diseases and for allergy.\(^{29}\) With respect to celiac disease, we have previously shown a protective effect of concomitant breastfeeding and introduction of gluten-containing complementary foods,\(^{14}\) an effect also seen in other studies but not in all.\(^{15,17}\) The current study suggests that this protective effect prevails up to 12 years of age. Introducing gluten during ongoing breastfeeding may increase the chance of developing oral tolerance through immune-modulating factors in breast milk and/or influence on the gut maturation and colonization.\(^{33}\) Differences in the microbiota composition between formula-fed and breastfed infants have been shown, which might involve an increased celiac disease risk because differences in gut microbiota between individuals with and without celiac disease have been reported.\(^{34,35}\) Furthermore, breastfeeding has been associated with a reduced risk of gastrointestinal infections,\(^{29}\) an additional risk factor for celiac disease.\(^{36}\)

Age at gluten introduction might be important because it influences the proportion of infants still breastfed at that time and/or there might be a certain age interval that provides a “window of opportunity” with respect to developing oral tolerance.\(^{18,33}\) This window has been suggested to occur between 4 and 6 months of age,\(^{17}\) however, evidence concerning the most favorable age to introduce gluten is still inconclusive. Whether age between 4 and 6 months is preferable for gluten introduction, in contrast to gluten avoidance until 12 months of age, is under investigation in a prospective intervention study. At the 36-month follow-up, the results suggested that delaying gluten introduction delays the celiac disease onset but does not prevent disease development.\(^{17}\)

We have previously shown an increased celiac disease risk associated with gluten consumption in larger compared with smaller amounts 2 weeks after its introduction,\(^{14}\) and this is supported by our current findings because the cohorts differed in the amount of gluten ingested during weaning (Table 1). In agreement, a correlation between national celiac disease prevalence and wheat consumption has been shown,\(^{6}\) and celiac disease cases seem to react to gluten ingestion in a dose-response fashion.\(^{38,39}\) Thus, the evidence to date suggests that the amount of gluten ingested during its introduction affects the possibility of developing oral tolerance. This is undergoing further investigation in an ongoing randomized controlled trial.\(^{19}\)

In both study cohorts, we invited nearly 10% of the total Swedish birth cohort, and the study sites were selected to represent the country from north to south. Participation rate was high in both cohorts with only marginal differences between the sites. The populations in the sites had similar consumption of health resources per capita and unemployment rates as the national population (www.scb.se). For these reasons, we consider the samples representative. The screening-detected cases were ascertained by small intestinal biopsies and HLA-DQ testing. We used criteria for celiac disease that also included minor enteropathy (Marsh I-II). However, restricting the diagnostic criteria to villous atrophy (Marsh III), as proposed in the recent European guidelines,\(^{40}\) did not alter the conclusion (prevalence ratio, 0.79; 95% CI: 0.63–0.98; \(P = .03\)). The cohorts differed in infant feeding, as shown on a population level and ascertained through questionnaires. Because the infant feeding exposure pattern changed in the whole population, the proportion of children with the proposed worst combination (large amounts of gluten after discontinued breastfeeding) decreased, which could be associated with the reduced prevalence in the 1997 cohort. Thus, although the “Swedish population experiment” was not planned, it has many characteristics of an intervention study, and the relationship between infant feeding and celiac disease risk can thus be evaluated on a population level.

In the current study, we have a relatively long follow-up (12 years). It could be hypothesized that exposure after the infant period resulted in the difference in celiac disease prevalence now shown. However, a difference was already suggested at 2.5 years of age,\(^{32}\) and the screenings were performed only 4 years apart (2005–2006 and 2009–2010). To our knowledge, there has not been any major change in environmental- or lifestyle factors during this period, with the exception of infant feeding. In general, the parallel increase in the prevalence of many autoimmune diseases, as well as allergy,\(^{18,41}\) suggests a gradual change in the environment during recent decades with respect to these diseases, resulting in increased disease risk. This could explain the relatively high celiac disease prevalence also revealed in the 1997 cohort (2.2%), but not the significant reduction compared with the 1993 cohort (2.9%).

**CONCLUSIONS**

Celiac disease occurs worldwide, with increasing prevalence in several countries.\(^{4,20,42}\) Consequently, the disease represents a growing public health problem and preventive strategies are...
warranted. We have shown a reduced prevalence of celiac disease in 12-year-olds born in 1997 compared with 1983, indicating that celiac disease can be avoided in some genetically predisposed children, at least up to 12 years of age. Our findings contribute to the evolving evidence base for infant feeding recommendations.

ACKNOWLEDGMENTS

We thank all participating children and their families and the personnel who worked on the study, including research nurses, laboratory personnel and administrative staff, and collaborators within the school health services and pediatric departments. We also thank Associate Professor Hans Stenlund and Professor Stig Wall for their valuable contributions during the planning of the study and interpretation of the results.

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Pediatrics 2013;131;e687
DOI: 10.1542/peds.2012-1015 originally published online February 18, 2013;

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