The Relationship Between Child Mortality Rates and Prevalence of Celiac Disease

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ABSTRACT

Objectives: Some evidence suggests that prevalence of celiac disease in the general population is increasing over time. Because the prognosis of celiac disease was a dismal one before discovering the role of gluten, our aim was to investigate a possible relationship between children under-5 mortality rates and prevalence rates of celiac disease.

Methods: Thanks to a literature review, we found 27 studies performed in 17 different countries describing the prevalence of celiac disease in schoolchildren; between 1995 and 2011, 4 studies were performed in Italy. A meta-analysis of prevalence rates was performed. Prevalence was compared between specific country under-5 mortality groups, publication year, and age.

Results: In the last decades, under-5 mortality rates have been decreasing all over the world. This reduction is paralleled by an increase of the prevalence of celiac disease. The Spearman correlation coefficient was −63%, 95% confidence interval −82% to −33% ($P < 0.001$). So, the higher the mortality rate, the lower the prevalence of CD. This finding is confirmed by the meta-analysis of the 4 studies conducted in Italy over time.

Conclusions: The under-5 mortality rate seems to influence the prevalence of celiac disease in the general population. In the near future, the number of patients with celiac disease will increase, thanks to the better environmental conditions that nowadays allow a better survival of children with celiac disease.

Key Words: celiac disease/epidemiology, children, endomysial antibodies, gliadin, mortality, tissue transglutaminase

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What Is Known

- Some evidence suggests that prevalence of celiac disease in the general population is increasing over time.
- At the same time, child mortality has been reducing.

What Is New

- The increased prevalence of celiac disease is paralleled by a reduction of mortality rates.
- The number of patients with celiac disease will increase all over the world, thanks to the better environmental conditions that allow a better survival of children.

Celiac disease (CD) is a chronic gluten-induced enteropathy very common in the general population (1). Although its high prevalence in the Western world is nowadays widely recognized, this has not always been the case. Until the early 1980s, CD was considered to be rare and affecting only children. Since then, the number of diagnosed patients has been progressively increasing. This was considered to be due to better medical awareness of this condition and, most important, to the introduction in the 1980s of serological screening (2,3). Although increased awareness and serological tests must have certainly played a major role in increasing the number of diagnosed patients, in the last few years, some articles provided results that were considered evidence of a real increase of the prevalence of CD in the general population over time (4–6). Moreover, CD is no longer limited to Western Caucasian countries and is nowadays emerging in populations in which it was considered to be virtually absent until a few years ago (7).

Catassi et al (6) showed that the prevalence of CD in the American adult general population increased from 1 of 501 in 1974 to 1 of 105 in 2001. Similar results were also obtained in Finland, where the prevalence of CD in the general population rose from 1.05% in 1978 to 1980 to 1.99% in 2000 to 2001 (4). These results are certainly suggestive of a real increase of the prevalence of CD over time.

In 1939, Hardwick (8) studied the prognosis of children affected by CD. It should be noted that, although all these diagnoses were made on the basis of clinical criteria only, in 1968 duodenal biopsies proved that these diagnoses were correct in 90% of the cases (9). The prognosis of these children was a dismal one. At the time of study, 26 children out of 73 (36%) had already died and only 17 out of 73 (23%) were still alive 3 years after the diagnosis. Notably, no death had occurred in children younger than 12 months (8). Certainly, this situation must have persisted for a long time. Dicke et al (10) discovered the role of gluten in CD just after the end of the Second World War and published it in 1953. Although some case reports proved the efficacy of a gluten-free diet in celiac patients in the early 1950s (11,12), an article published in 1960 concluded that ''the elimination of gluten from the diet has little if any influence on the histopathological abnormalities'' (13). This suggests that it must have taken a long time for Dicke's discovery to be acknowledged and adopted in everyday clinical practice.

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In the study performed by Catassi et al (6), 3316 of the 3511 healthy subjects who donated blood for scientific purposes in 1974 were at least 20 years old. That means that the majority of them were born and had grown up much earlier than Dicke's discovery. So, how many celiac children belonging to this cohort can have survived until the 1970s to be included in Catassi et al's (6) and Lohi et al's studies (4)? Since their prognosis in the pre-Dicke era must have been similar to that described by Hardwick (8) in 1939, we believe that not many of them survived that long.

Based on this observation, we think that mortality could have had an important role in determining the prevalence of CD in the general population, not only at different times but also in different countries. Our aim was therefore to study a possible relationship between prevalence of CD and mortality.

METHODS

A literature search was performed to select articles describing the prevalence of CD in pediatric general populations. More precisely, a literature search was started by entering the following query on *http://www.ncbi.nlm.nih.gov/pubmed/advanced*: (''1990'' [Publication Date]: ''3000'' [Publication Date]) AND ''Celiac Disease/epidemiology'' [MAJR]). These criteria are the same ones we previously used (1). We then took into account only studies published as full papers, based on at least 400 pediatric subjects who were studied first with endomysial/tissue transglutaminase antibodies and then duodenal biopsies in those found to be antibody positive. At least 2/3 of the positive subjects had to have undergone a biopsy for the article to be taken into account. No selection was performed on the basis of geography or language. Duplicate and triple publications were eliminated. Thanks to this strategy, 26 studies performed in 17 different countries were found (14–39). The biopsy-proven prevalence rates of CD provided by the articles were taken into account.

Child mortality estimates, generated in 2015 by the United Nations Inter-agency Group for Child Mortality Estimation, were downloaded from *http://www.childmortality.org* for each of the 17 countries where prevalence of CD was studied. More precisely, since Hardwick (8) showed that 23 of 26 deaths (88%) occurred in children aged between 1 and 5 years and that nobody died before the age of 1 year, under-5 mortality (U5M) rates were considered. Since the mean age of the screened subjects varied, we applied the following formula to choose a corresponding U5M rate year.

Year of data collection (or year of submission if data collection was not specifically mentioned) − mean age of screened children + 5. For example in Tommasini et al's article (27): 1999 (year of data collection) − 9 (mean age of screened children) + 5 = 1995.

To compare U5M rates and prevalence rates of CD, we performed 2 studies, an International, ''horizontal'' one and an Italian, ''vertical'' one. In the international study, the 26 articles were divided to get them equally distributed using tertiles of U5M rates: <8/1000 (14–22); between 8 and 21 (23–31); >21 (32–39). This was an a priori decision.

The Italian study is a simple attempt to study the evolution of the prevalence of CD in one single country. As far as we know, Italy is the only country where 4 screening studies were performed between 1995 and 2011. We must point out that in the article published by Catassi et al (40) in 1995 children were screened with antigliadin antibodies as the first step. Anyway, this article had to be included to have at least 4 articles. Analysis of these data was performed using Stata 14.2 (StataCorp, College Station, TX). Pooled metanalytic random effects estimates of prevalence were computed. A between group heterogeneity test was performed to compare estimates across age, publication year and U5M groups. The Spearman correlation coefficient between U5M and CD prevalence (with 95% confidence interval [95% CI]) was computed.

RESULTS

Figure 1 shows that pooled metanalytic prevalence of CD was 0.86% (1/116), 95% CI 0.61% to 1.13%. Heterogeneity $\chi^2 = 283.9$, $P < 0.001$. No differences were found on the basis of publication year (<2000 vs ≥2000, $P = 0.24$) or age of screened children (≤5 vs 6–10 vs >10, $P = 1.00$).

International Study

Figure 2 shows the relationship between prevalence of CD and corresponding U5M rate in the simplest way; the Spearman correlation coefficient was −63%, 95% CI −82% to −33% ($P < 0.001$). The higher the mortality rate, the lower the prevalence of CD. More precisely, the right horizontal oval groups together developing countries where U5M rates are high and the prevalence of CD is low. On the contrary, the left vertical oval groups together Western countries with low mortality rates and a highly variable prevalence of CD. This seems to suggest that once mortality is low, other factors must have a role in determining a different prevalence of CD.

Figure 3 shows that the metanalytic prevalence rates of CD in the 3 subgroups of U5M rates were 1.29% (U5M <8/1000), 0.83% (8–21), and 0.48% (>21). The test for heterogeneity between groups was statistically significant ($P = 0.003$).

Italian Study

Figure 4 shows the relationship between prevalence of CD in the 4 Italian studies in the last 25 years and corresponding U5M rates. Although there are only 4 of them, once again the higher the mortality rate, the lower the prevalence of CD. The Spearman correlation coefficient was −100% with a linear decrease of the prevalence.

DISCUSSION

A great deal of evidence suggests that the prevalence of CD has increased considerably over time, not only in terms of clinically diagnosed patients but also in terms of patients found through screening of the general population.

Many explanations are possible. A few years ago, we showed that different prevalence rates among different studies were mainly due to different screening strategies (1). This, however, cannot be the case in the present study because we included only studies involving schoolchildren screened with celiac antibodies first and then with duodenal biopsies. Other factors taken into account to explain these different prevalence rates were genetics, gluten consumption, gluten quality, and weaning modalities. Genetics is certainly important at least in some regions, such as Sardinia and in North African Saharawi children (7). The quantity of gluten consumption was considered but although wheat consumption varies a lot in different countries, the consumed quantity is always much higher than the quantity known to trigger CD (41,42). Modifications of gluten content of wheat were also considered, but this does not seem to be an issue (43). Finally, modalities of weaning regarding time of introduction of gluten and its relationship with breast-feeding were extensively studied. The timing of gluten introduction was shown to be responsible for the so called ''Swedish epidemic of CD,'' and breast-feeding does not seem to have any relevant protective role on the induction of CD (44–46).

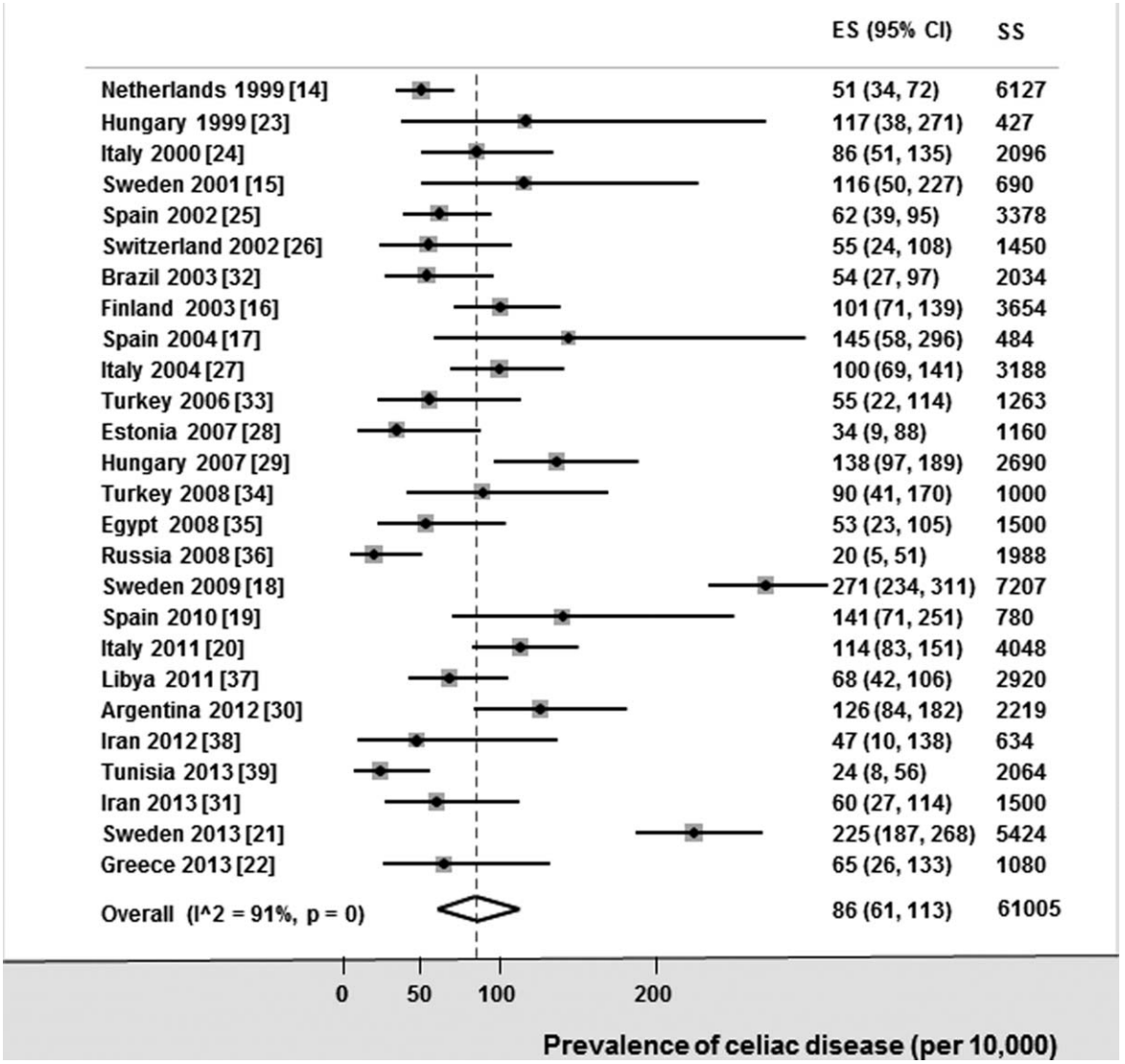

FIGURE 1. Forest plot of the prevalence of celiac disease (per 10,000) in the 26 studies included. ES = estimate, SS = sample size.

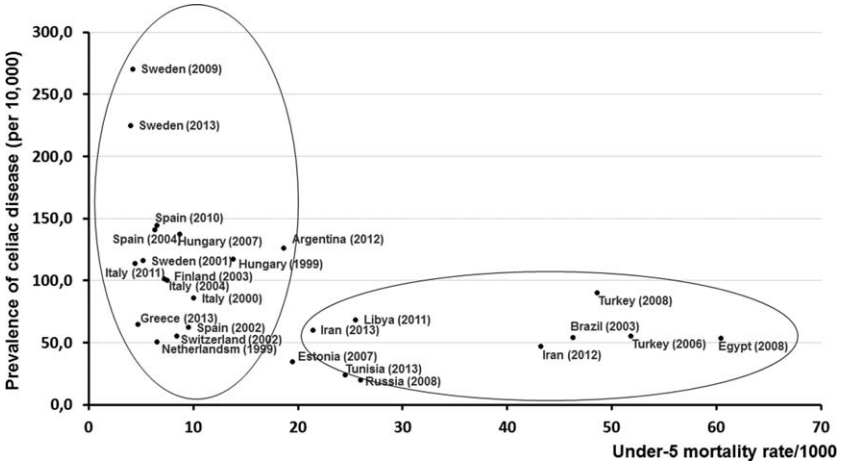

FIGURE 2. Prevalence of celiac disease in the 26 studies performed in schoolchildren from 17 different countries and corresponding under-5 mortality rates. The right oval groups together developing countries in which under-5 mortality rates are very high and prevalence of celiac disease is very low. The left one groups together Western countries with low mortality rates and highly variable prevalence rates of celiac disease.

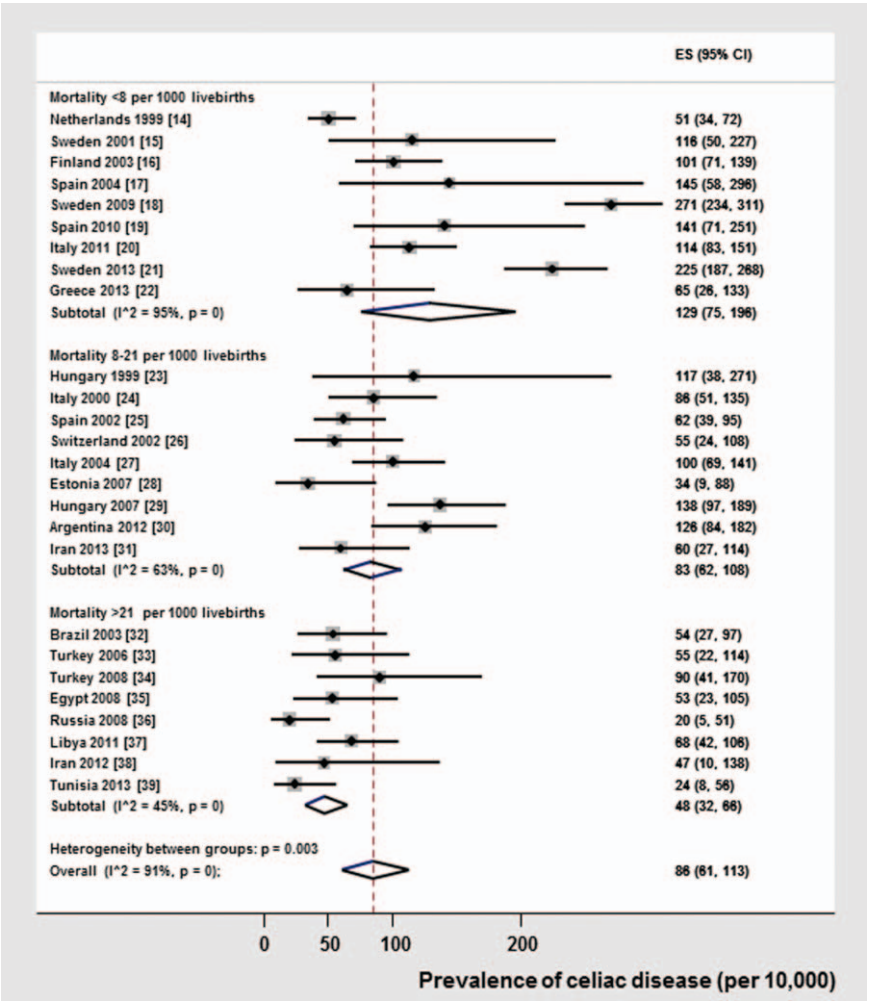

FIGURE 3. Forest plot of the prevalence of celiac disease in the 26 studies stratified by under-5 mortality rates (<8 per 1000 live birth; 8–21 per 1000; >21 per 1000). ES = estimate.

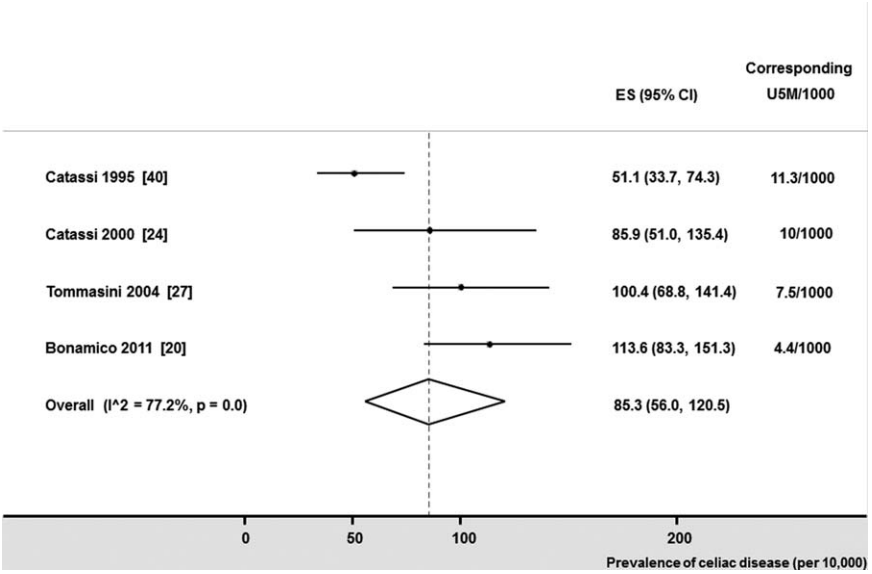

FIGURE 4. Forest plot of the prevalence of celiac disease in the 4 studies performed in Italy over time (vertical study) and corresponding under-5 mortality rates (U5M).

Our results show for the first time that the prevalence of pediatric CD parallels U5M rates. The higher the mortality rate, the lower the prevalence of CD. This was shown not only in the horizontal International study, but also in the vertical Italian one, which further confirms that our theory of an inverse relationship of prevalence of CD and U5M over time holds.

In the past, child mortality was very high all over the world and is nowadays still very high in developing countries. In the last few decades child mortality has, however, dropped. This was obviously much more evident in developing countries but even in Western developed countries a considerable reduction is still present (47). More than 20 years ago, Marsh wrote that ''infection of the gastrointestinal tract must be by far the most common factor to awaken'' CD (48). In the last few decades, not only overall mortality but also gastrointestinal infections and related mortality have decreased considerably all over the world (47). This could have resulted in an improved survival of celiac children, allowing them to be diagnosed afterwards. At the same time, the reduction of gastrointestinal infections could have increased the number of patients with CD by triggering ''celiac autoimmunity,'' as suggested by the hygiene hypothesis that has already been taken into account also for CD (36,49). Interestingly, these 2 mechanisms, that is, reduced mortality of celiac children and the hygiene hypothesis, are not mutually exclusive and could both have a role in increasing the prevalence of CD.

Another factor that must be kept in mind is the general attitude toward gluten. Although nowadays gluten is almost demonized, that was certainly not the case in the 19th and 20th centuries. Flour was the earliest milk modifier and beer and slops, a thin food made from the mash of malt liquors, were cheap and easy to get substitutes for the far more expensive cow's milk (50). In 1865, Liebig patented and marketed ''the perfect food for infants'' consisting of wheat flour, cow's milk, and malt flour. Finally, children suffering from diarrhea were treated with ''barley water'' (50). In Italy, gluten-enriched pasta was very popular and was advertised in magazines and newspapers as the ideal food for weaning, especially in the case of children suffering from diarrhea, malnutrition and anemia. Its production was stopped around 1985 (Nestlé, personal communication to FB).

In conclusion, we think that celiac children born before the discovery made by Dicke, who developed gastrointestinal infections and were fed with gluten could not have had many chances of surviving to be enrolled in a screening study performed 20 or 30 years later. We definitely agree with those authors that suggest that prevalence of CD is increasing over time and that it is appearing in countries in which it was almost nonexistent until a few years ago. This is due, at least partially, to the better environmental conditions that nowadays allow a better survival of celiac children.

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