

# Mortality in celiac disease

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**Abstract** | Although the prevalence rates of celiac disease tend to be very similar in different Western populations, mortality rates for this disease vary widely. In this Review we focus on the papers that have addressed this issue so far. We evaluated mortality rates in different forms of celiac disease, such as symptomatic celiac disease, unrecognized celiac disease, dermatitis herpetiformis and refractory celiac disease. We also evaluated the role of possible protective factors, such as adherence to a gluten-free diet, early diagnosis and severity of clinical presentation. Finally, we noticed that the mortality rate for celiac disease seems to be higher in Southern than in Northern Europe and seems to correlate with 'national' gluten consumption. To explain these differences, we propose a hypothesis that links mortality rates to the amount of gluten consumed not only after but also before the diagnosis of celiac disease.

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## Introduction

Celiac disease is a very common chronic enteropathy that affects many people in the Western world. Patients with celiac disease are genetically predisposed to it, and it is triggered by gluten, the protein fraction of wheat flour, which is the cornerstone of traditional diets in these countries. Although a gluten-free diet reverses the condition in most patients, the mortality rate is increased in patients with celiac disease.

The first paper to describe mortality in patients with celiac disease was published almost 25 years ago.<sup>1</sup> Since then 21 further papers have addressed this issue.<sup>2–22</sup> However, in spite of this high publication rate, these papers report conflicting results; the overall mortality rates reported vary from 0.52 (that is, a reduced mortality rate)<sup>13</sup> to 3.9.<sup>19</sup>

The discordance of these results should not surprise us. Firstly, these papers differ widely from each other for epidemiological reasons; some of the studies are population-based while others are cohort studies. Moreover, some of the papers are an extension or evolution of previous ones, as is the case for the two studies performed in Scotland by Logan and colleagues,<sup>2,15</sup> and the three Finnish papers published by Collin and colleagues (one included patients with celiac disease diagnosed at the University of Tampere, Finland, another included patients with dermatitis herpetiformis diagnosed at the same university, and the third included patients with celiac disease or dermatitis herpetiformis diagnosed in Tampere—the patients described in the first two papers are also included in the third paper).<sup>4,5,13</sup> Although the study published by Corrao *et al.*<sup>8</sup> is not an extension of the study published by Cottone *et al.*,<sup>7</sup> the Sicilian patients described by Cottone *et al.* were all included in the study by Corrao *et al.*<sup>8</sup>

Secondly, the studies differ from each other for clinical reasons. The patients studied can be categorized into four

different groups: patients with symptomatic celiac disease, patients with unrecognized celiac disease, patients with dermatitis herpetiformis and patients with refractory celiac disease.

The studies published so far are extremely heterogeneous, and it would be very difficult to perform a formal meta-analysis. As such, it is most useful to consider the mortality rates for these different groups separately. In addition, most information is available for patients with symptomatic celiac disease so that is where the main discussion of this Review is focused.

## Symptomatic celiac disease

Mortality in patients with symptomatic celiac disease—that is, patients in whom celiac disease is suspected and diagnosed because of symptoms—has been evaluated in 10 studies that were performed in five different countries.<sup>1,2,4,7,8,10,11,13–15</sup> All 10 of the papers published agreed that the standard mortality rate was increased compared with that for the general population. The lowest reported mortality rate was 1.26 in Finland<sup>13</sup> and the highest reported was 3.8 in Sicily (Figure 1).<sup>8</sup>

## Causes

The causes of the increased mortality were evaluated in all of the studies performed.<sup>1,2,4,7,8,10,11,13–15</sup> Increased mortality in patients with celiac disease was found to mainly be a result of gastrointestinal malignancies—mainly non-Hodgkin lymphoma and small bowel cancer—that developed as a complication of celiac disease. Increased mortality due to autoimmune conditions (such as rheumatoid arthritis and diffuse diseases of connective tissue),<sup>10</sup> ischemic heart disease,<sup>13</sup> and violence<sup>15</sup> was also reported.

## Gluten-free diet

Although the protective effect of adhering to a strict gluten-free diet against the development of cancer was

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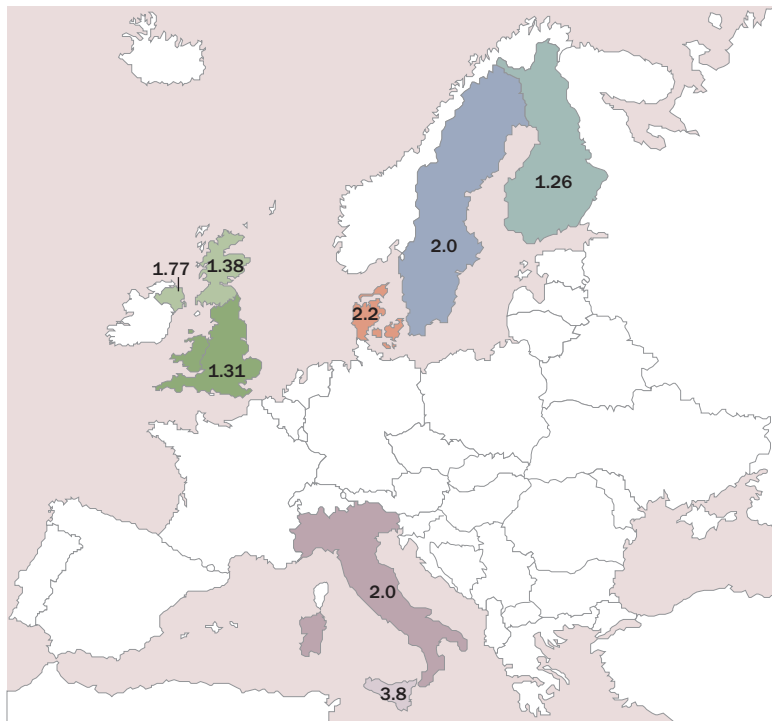
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## Competing interests

The authors declare no competing interests.

## Key points

- Mortality rates in patients with celiac disease are increased compared with the general population
- Reported mortality rates vary between studies
- Increased mortality in patients with celiac disease is mainly due to malignancies
- Overall, mortality rates decrease over time from diagnosis
- Early diagnosis and a strict gluten-free diet are protective



**Figure 1** | The standard mortality rate for symptomatic celiac disease in the European countries studied so far: Finland,<sup>13</sup> Sweden,<sup>10</sup> Denmark,<sup>1</sup> whole of Italy (including Sicily),<sup>8</sup> Sicily,<sup>7</sup> whole of the UK (including Scotland and Northern Ireland),<sup>11</sup> Scotland,<sup>15</sup> and Northern Ireland.<sup>14</sup>

shown more than 20 years ago,<sup>23,24</sup> the relationship between compliance with a gluten-free diet and mortality has been specifically analyzed in only two papers.<sup>1,8</sup> The work of Corrao and colleagues revealed that compliance with a gluten-free diet correlates with mortality.<sup>8</sup> In patients adhering to a strict gluten-free diet, the standard mortality rate was not increased compared with the general population; the standard mortality rate was doubled in patients who were considered to be unlikely to follow a strict gluten-free diet and was six times higher in patients definitely not on a strict gluten-free diet. By contrast, Nielsen *et al.* reported that mortality rates were increased in both patients complying with a gluten-free diet (3.2,  $P < 0.005$ ) and in patients not complying with a gluten-free diet (4.5,  $P < 0.005$ ).<sup>1</sup> However, the study by Nielsen and colleagues included only 98 patients, 25 of whom were considered to be affected by a refractory form of celiac disease, which introduces an obvious selection bias that could account for the lack of difference in mortality rates. Adherence to a strict

gluten-free diet was said to be protective in three other papers but the issue was not specifically investigated in these studies.<sup>4,10,13</sup>

## Clinical presentation

The relationship between standard mortality rate and the severity of the clinical presentation of celiac disease was taken into account in one paper.<sup>8</sup> A standard mortality rate of 2.5 was shown for patients who presented with severe symptoms of malabsorption. The standard mortality rate was not increased for those patients who had only mild symptoms or for those who had no symptoms at all (that is, patients with silent celiac disease). This finding is in agreement with the assumption that a severe clinical presentation is likely to be due to the increased extension of mucosal lesions along the small bowel (causing a greater degree of malabsorption).<sup>25,26</sup>

## Early diagnosis

An early diagnosis (that is, soon after the development of symptoms) has been shown to have a variable effect on mortality rates in patients with symptomatic celiac disease. Six papers have investigated this effect.<sup>1,7,8,10,15,22</sup> An early diagnosis was shown to have a protective effect in two Italian studies,<sup>7,8</sup> and also in a Swedish study of a pediatric population.<sup>10</sup> In contrast to these findings, the Swedish study found that early diagnosis did not have a protective effect on the mortality rate in the adult population.<sup>10</sup> A UK study showed that the mortality rate was increased in the pediatric celiac disease population by a greater extent than in the adult population (standard mortality rate 3.32 versus 1.38).<sup>15</sup>

## Risk over time

The trend of mortality risk over time has been evaluated and the general consensus seems to be that the increased risk of mortality decreases over time from the initial diagnosis. Indeed, in five of the eight papers to consider the risk over time, mortality was shown to decrease substantially after the first year of diagnosis.<sup>7,8,10,11,22</sup> This trend was not shown in the three other papers.<sup>1,13,15</sup> However, in the first of these three papers the results are likely to have been biased by the inclusion of a substantial number of patients who had refractory celiac disease.<sup>1</sup> In the second paper, the overall mortality rate was very low (standard mortality rate 1.26) and so a reduction would have been difficult to detect.<sup>13</sup> By contrast, the third paper, by Solaymani-Dodaran and colleagues, reported some very worrying results.<sup>15</sup> In their study, although mortality was not increased in the first year after diagnosis, a 25-year follow-up showed that long-term mortality was markedly increased. Moreover, the increased mortality was due not only to malignancies, but also to causes that are difficult to attribute directly to celiac disease itself, such as accidents, suicides and violence.

## Unrecognized celiac disease

Although it is difficult to do, four studies have investigated the standard mortality rate of healthy members of

the general population who have unrecognized celiac disease. In each of these studies, serum samples from individuals who gave blood for research purposes were stored and after a few years were tested for celiac antibodies.<sup>6,12,18,19</sup> Information on celiac status was then matched with mortality data. This process represents the only ethically acceptable way to study mortality in individuals with unrecognized, and therefore untreated, celiac disease.

Mortality was reported to not be increased in patients with unrecognized celiac disease in two of the studies.<sup>6,18</sup> It should be noted that these two papers come from the UK and Finland, which are the countries that have the lowest celiac mortality rates detected so far (Figure 1). By contrast, markedly increased mortality in patients with unrecognized celiac disease was found in the other two studies, one from Germany<sup>12</sup> and the other from the USA.<sup>19</sup>

The German study showed that there was a 2.53 age-adjusted hazard ratio for all-cause mortality in patients who were positive for IgA antitissue transglutaminase compared with patients who were negative for these antibodies.<sup>12</sup> The most important excess of mortality was found in the middle age (45–64 years) and old age (65–74 years) groups, a finding that is in line with those from other studies.<sup>7,8</sup> The American study showed that there was an almost fourfold increased hazard mortality ratio (3.9) among individuals who were found to be positive for celiac antibodies compared with those who were found to be negative.<sup>19</sup> Moreover, the authors of the American study suggested that the prevalence of celiac disease in the American general population has increased substantially during the past 50 years. We must note, however, that the highly alarming findings of the American study were obtained by analyzing serum samples taken from more than 9,000 trainees on an air force base, who were, therefore, likely to be members of the US Air Force. If this is indeed the case, then a major selection bias was introduced: military personnel are 'super healthy' and their mortality rates are probably reduced compared with the general population. The mortality rate for those military personnel who were positive for celiac antibodies was probably therefore artificially increased.

### Dermatitis herpetiformis

Dermatitis herpetiformis is a gluten-sensitive, blistering, itchy skin disease that is almost invariably associated with celiac disease. However, intestinal lesions tend to be less severe in patients with dermatitis herpetiformis and celiac disease than in patients with celiac disease alone.<sup>27</sup> Mortality in patients with dermatitis herpetiformis was evaluated in four papers. Two of the studies were performed in the UK<sup>3,17</sup> and the other two in Finland.<sup>5,13</sup> The standard mortality rate varied from 0.52 to 0.93 in these studies.<sup>13,17</sup> Although the reduced mortality (0.52) shown by Collin and colleagues is difficult to explain,<sup>13</sup> we conclude that, compared with the general population, mortality is not increased in patients with dermatitis herpetiformis.

### Refractory celiac disease

Refractory celiac disease is a very severe form of celiac disease that does not respond to a gluten-free diet.<sup>28</sup> Refractory celiac disease is further classified into type I and type II on the basis of gamma chain T-cell clonal rearrangement and aberrant T-cell phenotypes. Type II refractory celiac disease predisposes to the most severe complication of celiac disease, that is, enteropathy-associated T-cell lymphoma.<sup>16</sup> Three papers have evaluated survival in patients with refractory celiac disease.<sup>16,20,21</sup> The 5-year survival rate varied from 80% to 96% in patients with refractory celiac disease type I, but it was much lower in patients with refractory celiac disease type II, varying from 44% to 58%. The survival rate dropped to 8% in patients with refractory celiac disease type II who developed enteropathy-associated T-cell lymphoma.<sup>16</sup>

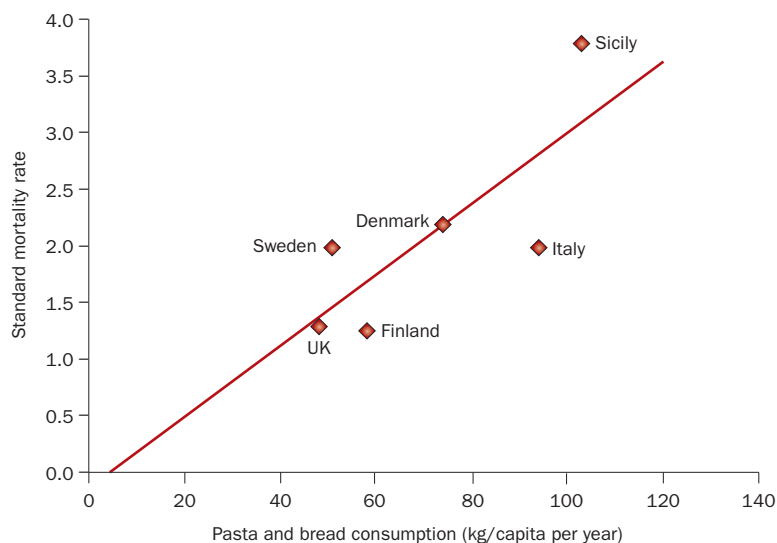
### Understanding the different mortality rates

As mentioned in the introduction and discussed above, the papers published so far on mortality in patients with celiac disease have provided us with conflicting results. Although these papers are very difficult to compare, we believe that the results they report are certainly different, but not necessarily contrasting, for several reasons.

The populations of patients studied vary widely in terms of the extent of their intestinal lesions. The majority of patients who have dermatitis herpetiformis or silent celiac disease are likely to have only mild and limited intestinal lesions, whereas patients who have severe malabsorption are likely to have diffuse intestinal lesions.<sup>25–27</sup> Although this is not always the case when individual patients are considered, these differences are likely to have a considerable impact when whole populations are taken into account and could, therefore, have a role in determining celiac disease mortality.

The quantity of gluten that is sufficient to trigger celiac disease is known to be very small.<sup>29</sup> We believe that this could be the reason why the prevalence rates for celiac disease in different Western populations tend to be very similar—around 1 person out of 100.<sup>30</sup> However, it is also well known that there are huge differences in the quantity of gluten-containing products that are consumed every day in different European countries. We believe that this could explain why there are different standard mortality rates in these countries, despite the similar prevalence rates. Indeed, there seems to be a relationship between standard mortality rate and pasta and bread consumption in the six countries where symptomatic celiac disease has been studied (Figure 2). However, we must make it clear that the assumed relationship is based on rough data.<sup>31–33</sup> Furthermore, these data do not take into account the consumption of rye in Northern Europe, which is another common source of gluten in these populations.

If further studies prove that the relationship between standard mortality rate and pasta and bread consumption is real, it would mean that mortality in celiac disease depends not only on compliance with a gluten-free diet—that is, the amount of gluten consumed after the diagnosis of celiac disease—but also on the amount of



**Figure 2** | The relationship between the standard mortality rate for patients with symptomatic celiac disease (Denmark,<sup>1</sup> Sicily,<sup>7</sup> Italy,<sup>8</sup> Sweden,<sup>10</sup> UK<sup>11</sup> and Finland<sup>13</sup>) and pasta and bread consumption<sup>31–33</sup> ( $r=0.66$ ,  $P=0.049$  for Pearson linear regression). The figure suggests that gluten intake due to ‘cultural’ reasons correlates with standard mortality rates for celiac disease.

gluten consumed before the diagnosis of celiac disease. So, parallel to the quantity of gluten that triggers celiac disease, we hypothesize that there is a set quantity of gluten that, once exceeded, complicates celiac disease and thus triggers refractory celiac disease and lymphoma. This so-called ‘lymphoma triggering amount of gluten’ would be the sum of gluten ingested before and after the diagnosis of celiac disease. This hypothesis could explain not only the increased standard mortality rate in patients who do not adhere to a strict gluten-free diet,<sup>8</sup> but also the higher standard mortality rate seen in countries that have a high level of gluten consumption (Figure 2). If the ‘lymphoma triggering amount of gluten’ is exceeded before a diagnosis of celiac disease is made, we hypothesize that the patient will develop a

lymphoma and will probably die very shortly,<sup>16</sup> regardless of how strictly he or she follows a gluten-free diet after diagnosis. Our hypothesis could also, therefore, explain the overall mortality reduction over time found in some studies;<sup>7,8,10,11,22</sup> for patients who have not eaten the ‘lymphoma triggering amount of gluten’ (and will not reach this amount if they follow a gluten-free diet), mortality is similar to that of the general population. Overall mortality therefore reduces over time after the patients who developed lymphoma have died.

**Conclusions**

The mortality rate in patients with celiac disease seems to be associated with both the extent of lesions along the small bowel and the quantity of gluten consumed before and after the diagnosis of celiac disease. If this is proved to be the case, we may have to re-think the way we approach the management of celiac disease. Could the risk of osteoporosis and nutritional deficiencies become the main reasons to support the screening of the general population, as already proposed?<sup>34</sup> What about first-degree relatives, in whom mortality is not increased?<sup>8</sup> Should the strategies for screening be the same in countries where there is high gluten consumption and in countries with low gluten consumption? Would it be possible to treat patients suffering from mild symptoms with a low gluten-containing diet, which would be much easier to follow than a gluten-free diet and could be sufficient to protect against the development of refractory celiac disease and lymphoma? Although we are unable to answer these questions now, we may have to face them in the future.

**Review criteria**

A PubMed search was performed using the following terms: “celiac AND [mortality OR survival]”. There was no date restriction on the papers included for review.

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