Received: 22 July 2023 | First decision: 7 September 2023 | Accepted: 22 December 2023

DOI: 10.1111/apt.17867

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: Cause-specific and all-cause mortality trends across different coeliac disease phenotypes

Stiliano Maimaris[1,2] | Annalisa Schiepatti[1,2] | Federico Biagi[1,2]

[1]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

[2]Gastroenterology Unit of Pavia Institute, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy

Correspondence
Annalisa Schiepatti, Istituti Clinici Scientifici Maugeri, IRCCS, Gastroenterology Unit of Pavia Institute, Via Salvatore Maugeri 10, 27100 Pavia, Italy.
Email: annalisa.schiepatti01@universitadipavia.it

Summary

Background: Data on mortality in coeliac disease are contrasting.

Aims: To systematically review the literature on all-cause and cause-specific mortality in coeliac disease compared to the general population, and evaluate differences across clinical phenotypes, geographical regions, and over time.

Methods: We searched PubMed and Embase from 1 January 1970 to 31 December 2022 for eligible studies reporting on all-cause and cause-specific mortality in coeliac disease compared to the general population or controls. The protocol was registered on Open Science Framework (https://doi.org/10.17605/OSF.IO/852DN).

Results: We included 25 studies. All-cause mortality (HR 1.16, 95% CI 1.05–1.27, $I^2=89\%$), mortality due to malignancies (HR 1.21, 95% CI 1.08–1.36, $I^2=65\%$) and respiratory disease (HR 1.39, 95% CI 1.04–1.86, $I^2=76\%$) were increased. Mortality due to non-Hodgkin lymphoma (HR 10.14, 95% CI 2.19–46.88, $I^2=96\%$) was markedly increased. Mortality significantly decreased in recent decades: 1989–2004 (HR 1.61, 95% CI 1.27–2.03, $I^2=91\%$), 2005–2014 (HR 1.16, 95% CI 0.99–1.36, $I^2=89\%$), 2015–2022 (HR 1.19, 95% CI 1.05–1.35, $I^2=93\%$). All-cause mortality was not increased in dermatitis herpetiformis (HR 0.85, 95% CI 0.73–0.99, $I^2=40\%$) and undiagnosed coeliac disease (HR 1.09, 95% CI 0.95–1.25, $I^2=0\%$). Mortality was increased in the UK (HR 1.23, 95% CI 1.03–1.47, $I^2=91\%$) but not Scandinavia (HR 1.01, 95% CI 0.91–1.13, $I^2=81\%$). Limitations include high heterogeneity and lack of data for many countries.

Conclusion: Mortality in coeliac disease is increased, predominantly due to malignancies—particularly non-Hodgkin lymphoma—although differing significantly across disease phenotypes. Mortality of patients with coeliac disease has significantly decreased in recent decades. These results may influence diagnosis and management.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Yuan. The Handling Editor for this article was Professor Peter Gibson, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Coeliac disease is a chronic immune-mediated enteropathy triggered by dietary gluten in genetically predisposed individuals with an estimated prevalence of 1% in the general population and heterogeneous clinical manifestations.[1] The clinical phenotype can vary from silent screen-detected forms to mild forms characterised by extra-intestinal manifestations such as dermatitis herpetiformis to severe malabsorption or even complicated forms of coeliac disease.[1,2] Avoidance of dietary gluten was identified in the early 1950s as providing symptomatic benefit to coeliac patients and later recognised as the leading factor in preventing poor long-term outcomes in coeliac disease.[1,3]

Although the efficacy of a gluten-free diet (GFD) was already understood by the 70s and 80s, significantly improving prognosis,[3] the first studies on mortality in coeliac disease performed in the late 20th century showed significantly increased mortality compared to the general population, largely due to the development of pre-malignant/malignant complications.[4,5] These complications include enteropathy-associated T-cell lymphoma, B-cell lymphomas, small bowel carcinoma, ulcerative jejuno-ileitis, and refractory coeliac disease (type I and type II). While these complications are rare, they have a very poor prognosis.[1,6] However, it has been shown that the risk of developing these complications is not uniform among coeliac patients, with those diagnosed with classical symptoms and/or at an older age (>45 years) at greater risk, while those diagnosed with non-classical and silent forms at a younger age having a very low risk.[6–8] A recent multicenter study also showed an increased risk of developing complications among patients with seronegative coeliac disease.[9]

In the first two decades of this century, interest on mortality in coeliac disease has been maintained and many further studies were performed. Interestingly, an increased mortality in coeliac patients has not been always confirmed. Some findings were in accordance with significantly increased mortality,[10–13] while others reported either no increase or only a minor increase in mortality.[14–16] These results are therefore difficult to interpret uniformly with the only unequivocal finding being that coeliac patients are at increased risk of lymphoproliferative diseases.[10–17] Factors that may explain these differences include differences in study design, study time period, clinical form of coeliac disease being studied, age group under study, and country.

To date, the only systematic review and meta-analysis on all-cause and cause-specific mortality in coeliac disease dates back to 2012 and was based on only a small number of studies. This meta-analysis showed a clearly increased risk of lymphoproliferative malignancies in coeliac disease and found a small increase in all-cause mortality.[17] However, this study did not investigate whether mortality differed among the various clinical forms of coeliac disease. This is a relevant point as there is significant evidence suggesting that long-term outcomes may differ significantly among different forms of coeliac disease.[6–10,18,19]

Therefore, we aimed to perform a systematic review and meta-analysis of the literature to investigate: (i) all-cause and cause-specific mortality in coeliac disease compared to the general population; (ii) how mortality risk varies among different clinical forms of coeliac disease; (iii) whether age at diagnosis influences mortality risk in coeliac disease; (iv) how mortality in coeliac disease has varied over time and (v) whether geographical differences in mortality exist. We also aimed to review factors possibly related to all-cause/cause-specific mortality.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We conducted a systematic review of the literature in accordance with the PRISMA guidelines.[20] The study protocol was prospectively registered on Open Science Framework (https://doi.org/10.17605/OSF.IO/852DN). PubMed and Embase were searched for studies reporting on mortality in coeliac disease and/or dermatitis herpetiformis from January 1, 1970 to December 31, 2022. The following terms were used in the search: (coeliac disease OR coeliac disease OR dermatitis herpetiformis) AND (mortality OR survival OR death OR prognosis). Text words, MeSH/Emtree terms, as well as word variations, were considered for the search. The bibliographies of selected studies and reviews were also hand-searched to identify other relevant studies not detected by our database search. No language restrictions were used during the search. Additional details on the search strategy for each database are provided in supplementary materials.

2.2 | Inclusion and exclusion criteria

The flowchart in Figure 1 summarises studies included and excluded. Studies meeting the following criteria were included: (i) full papers on journals in English language reporting outcomes on all-cause mortality and/or cause-specific mortality in coeliac disease or dermatitis herpetiformis compared to general population data or control subjects drawn from the general population; (ii) well-defined criteria for diagnosis of coeliac disease, for clinical studies, and/or case-finding methods/criteria for detection of coeliac individuals for other study types; (iii) reported outcomes as mortality hazard ratios (HR) or standardised mortality ratios (SMR), with corresponding 95% confidence intervals (95% CI), or provided sufficient data for these to be calculated; (iv) matching/adjustment in analyses for at least patient age and sex; (v) primarily enrolled patients diagnosed after 1960 when knowledge of the GFD became widespread.[3] For the purpose of all analyses except the one comparing mortality across different forms of coeliac disease, data on patients with dermatitis herpetiformis were pooled with those affected by all other forms of coeliac disease. For cause-specific

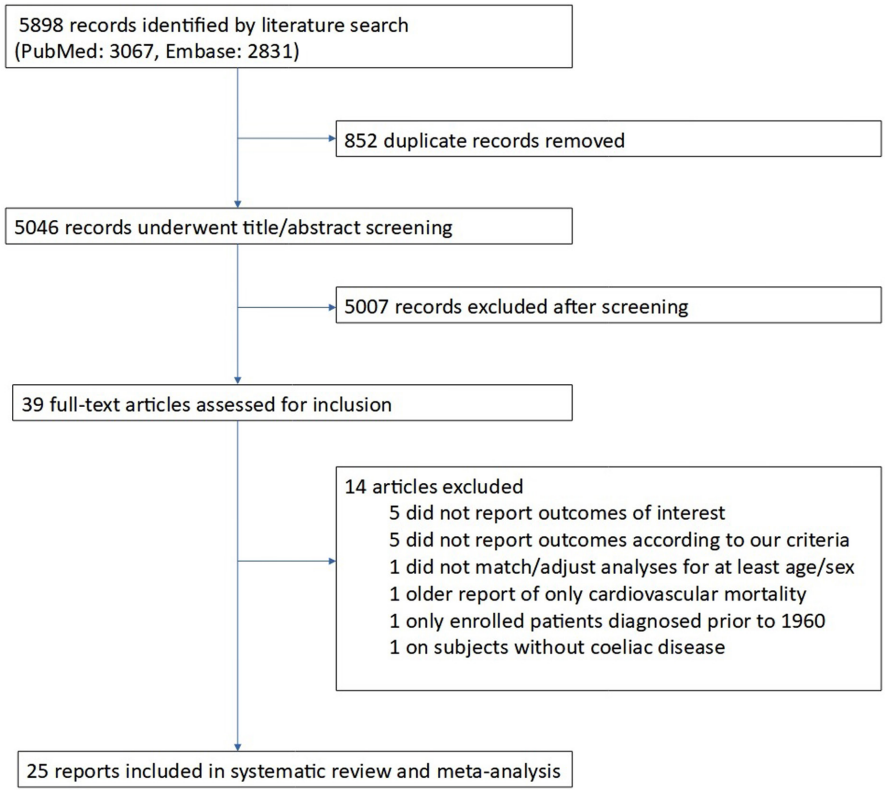

FIGURE 1 Study selection flowchart.

mortality, we considered the following disease categories: all malignant neoplasms, lymphoproliferative neoplasms, non-Hodgkin lymphoma, cardiovascular diseases, respiratory diseases, and infectious diseases. Studies not meeting these criteria were excluded. If a specific population was studied by two or more papers, leading to overlapping samples, only the most updated study was included to avoid data duplication. An exception to this was made for the analysis comparing all-cause mortality in coeliac disease at different time periods, for which all relevant studies were included, as they investigated mortality in coeliac disease at different time periods.

2.3 | Study selection and data extraction

Two reviewers (S.M., A.S.) independently screened titles and abstracts to identify potentially relevant studies which then underwent full-text screening by at least two reviewers. Disagreements were resolved by discussion and/or assistance from a third reviewer (F.B.). For each eligible study, the following data were extracted: study characteristics (authors, study design, publication year, enrollment period, duration of follow-up, geographical location), study population (age at diagnosis of coeliac disease, age at study enrolment, sex ratio, coeliac disease/dermatitis herpetiformis diagnostic criteria or case-finding criteria, sample size), outcome measures (all-cause and/or cause-specific mortality risk estimates and corresponding 95% CI, matching/adjustment criteria, and observed and expected number of deaths). For studies with multiple analyses conducted with different variables adjusted for, the most adjusted analysis was preferred. For studies reporting outcomes separately for different groups of patients, these were also extracted separately.

2.4 | Risk of bias and quality assessment

The Newcastle-Ottawa scale was used to evaluate study quality. This scale evaluates studies using an 8-item rating scale covering three main aspects: selection of study groups (0–4 stars), comparability (0–2 stars), and ascertainment of the outcome of interest (0–3 stars), for a maximum score of nine stars. For the comparability assessment, one star was given for matching/adjusting for age and sex, and one further star was given if additional relevant factors were adjusted for. We considered follow-up adequate if <10% of subjects were lost to follow-up.

2.5 | Study outcomes and statistical analysis

We evaluated the following outcomes: (i) all-cause mortality; (ii) cause-specific mortality from cardiovascular diseases, all malignant neoplasms, lymphoproliferative neoplasms, non-Hodgkin lymphoma, respiratory diseases, and infectious diseases; (iii) all-cause mortality across different clinical forms of coeliac disease (any diagnosed form of coeliac disease, classical, non-classical, and silent forms of coeliac disease, dermatitis herpetiformis, and undiagnosed coeliac disease)[1,2]; (iv) all-cause mortality according to age at diagnosis of coeliac disease; (v) all-cause mortality in coeliac disease according to time period (<2005; 2005–2014; 2015–2022); (vi) all-cause

TABLE 1 Characteristics of studies included in meta-analysis of all-cause and cause-specific mortality in coeliac disease.

Study and country	Population (age at diagnosis)	Source data	Forms of CD studied	Diagnostic method	Deaths/CD patients, *N*	Study period	Comparison group[a]	Variable matching/ adjustment	All-cause mortality risk estimate (95% CI)
2022 Koskinen,[27] Finland	Children and adults, median 39 years	Medical records	Any diagnosed CD	Duodenal histology, Skin biopsy DIF (DH)	376/1392	Enrollment: 1960–2000 Followed-up until 2020	Matched controls	Age, sex, residence	HR 0.96 (0.85–1.08)
2021 Schneider,[28] UK	Adults (37–73 years), mean 56 years	UK Biobank	Any diagnosed CD	Unspecified (ICD codes)	229/2482	Enrollment: 2006–2010 Followed-up until 2020	Control subjects	Age, sex, BMI	HR 1.56 (1.37–1.79)
2020 Lebwohl,[16] Sweden	Children and adults, mean 32 years	Registry (ESPRESSO)	Any diagnosed CD	Duodenal histology	6596/48929	Enrollment: 1967–2017 Followed-up until 2017	Matched controls	Age, sex, calendar year, county, educational status, country of birth, comorbidities	HR 1.14 (1.11–1.18)
2020 Koskinen,[14] Finland	Adults (20–79 years), median 50 years	Finnish Social Insurance Registry	Any diagnosed CD	Duodenal histology, Skin biopsy DIF (DH)	884/12803	Enrollment: 2005–2014 Followed-up until 2017	Matched controls	Age, sex, residence	HR 1.01 (0.94–1.09)
2020 Kårhus,[29] Denmark	Adults (≥15 years), mean 49 years	8 population-based cohorts (stored serum)	Undiagnosed CD	DGP and/or TTA	41/169	Enrollment: 1964–2006 Followed-up until 2017	Control subjects	Age, sex, smoking, alcohol, BMI	HR 1.17 (0.85–1.61)
2019 Quarpong,[30] Scotland	Children and adults, adults: mean 45 years, children: mean 1.6 years	Lothian celiac registry	Any diagnosed CD	Duodenal histology	237/602	Enrollment: 1961–1983 Followed-up until 2016	General population	Age, sex, calendar year	SMR 1.43 (1.25–1.62)
2018 Holmes,[31] England	Children and adults, mean 46 years	Medical records	Any diagnosed CD	Serology plus duodenal histology	284/2174	Enrollment: 1958–2014 Followed-up until 2014	General population	Age, sex, calendar year	SMR 1.57 (1.4–1.77)
2015 Abdul Sultan,[15] UK	Children and adults, average age NR	Clinical Practice Research Datalink Database	Any diagnosed CD	Unspecified (CPRD database)	773/10825	Enrollment: 1990–2012 Followed-up until 2012	Control subjects	Age, sex, socioeconomic status	HR 0.94 (0.84–1.01)

TABLE 1 (Continued)

Study and country	Population (age at diagnosis)	Source data	Forms of CD studied	Diagnostic method	Deaths/CD patients, *N*	Study period	Comparison group[a]	Variable matching/ adjustment	All-cause mortality risk estimate (95% CI)
2012 Hervonen,[18] Finland	Children and adults, mean 43 years	Medical records	DH	Skin DIF	77/476	Enrollment: 1970–2009 Followed-up until 2010	General population	Age, sex, calendar year	SMR 0.7 (0.55–0.87)
2011 Canavan,[32] England	Adults (45–76 years), average age NR	Cambridge GP Health Survey (stored serum)	Undiagnosed CD	TTA + EMA	13/87	Enrollment: 1990–1995 Followed-up until 2009	Control subjects	Age, sex, smoking, socioeconomic group	HR 0.98 (0.57–1.69)
2010 Godfrey,[19] USA	Adults (>50 years), median 63 years	Rochester Epidemiology Project (stored serum)	Undiagnosed CD	TTA + EMA	NR/127	Enrollment: 1995–2001 Last follow-up not reported	Matched controls	Age, sex	HR 0.8 (0.45–1.41)
2009 Lohi (a),[33] Finland	Adults (30–99 years), mean 49 years	Mini-Finland Health Survey (stored serum)	Undiagnosed CD	TTA + EMA	23/74	Enrollment: 1978–1980 Followed-up until 2005	Control subjects	Age, sex, education, alcohol, smoking, diabetes, other cardiovascular risk factors	HR 0.91 (0.59–1.38)
2009 Lohi (b),[33] Finland	Adults (30–99 years), mean 59 years	Mini-Finland Health Survey (stored serum)	Undiagnosed CD	Double TTA+	128/204	Enrollment: 1978–1980 Followed-up until 2005	Control subjects	Age, sex, education, alcohol, smoking, diabetes, other cardiovascular risk factors	HR 1.18 (0.99–1.42)
2008 Lewis,[34] UK	Children and adults, mean 46 years	Registry (GPRD)	DH	Unspecified (GPRD database)	58/846	Enrollment: 1987–2002 Followed-up until 2002	Matched controls	Age, sex, general practice	HR 0.99 (0.7–1.23)
2007 Anderson,[35] Northern Ireland	Children and adults, mean 45 years	Laboratory records	Any diagnosed CD	EMA	46/490	Enrollment: 1993–1996 Followed-up until 2003	General population	Age, sex	SMR 1.77 (1.26–2.28)

TABLE 1 (Continued)

Study and country	Population (age at diagnosis)	Source data	Forms of CD studied	Diagnostic method	Deaths/CD patients, *N*	Study period	Comparison group[a]	Variable matching/ adjustment	All-cause mortality risk estimate (95% CI)
2004 West,[36] UK	Children and adults, average age NR	Registry (GPRD)	Any diagnosed CD	Unspecified	237/4732	Enrollment: 1987–2002 Followed-up until 2002	Matched controls	Age, sex, general practice	HR 1.31 (1.13–1.51)
2001 Corrao,[10] Italy	Adults, mean 36 years	Medical records	Any diagnosed CD	Duodenal histology	53/1072	Enrollment: 1962–1994 Followed-up until 1998	General population	Age, sex, calendar year	SMR 2.0 (1.5–2.7)
1998 Johnston,[37] Northern Ireland	Adults, mean 60 years	MONICA project (stored serum)	Undiagnosed CD	AGA, ARA, EMA	13/102	Enrollment: 1983 Followed-up until 1994	General population	Age, sex	SMR 0.92 (0.5–1.6)
1993 Swerdlow,[38] England	Adults, average age NR	Medical records	DH	Clinical features, skin biopsy histology, DIF	41/152	Enrollment: 1950–1985 Followed-up until 1989	General population	Age, sex	SMR 0.87 (0.61–1.19)
Older studies with more recent updated reports									
2011 Grainge,[23] England (updated by Holmes 2018)	Children and adults, mean 46 years	Medical records	Any diagnosed CD	Serology+histology	142/1092	Enrolment: 1958–2006 Follow-up until 2006	General population	Age, sex, calendar year	SMR 1.37 (1.16–1.62)
2009 Ludvigsson JF,[24] Sweden (updated by Lebwohl 2020)	Children and adults, mean 30 years	Histological registry	Any diagnosed CD	Duodenal histology	3049/29148	Enrolment: 1969–2008 Followed-up until 2008	Matched controls	Age, sex, calendar year, county	HR 1.39 (1.33–1.45)
2007 Solaymani-Dodaran (a),[25] Scotland (updated by Quarpong 2019)	Children (0–14 years), mean 3 years	Lothian celiac registry	Any diagnosed CD	Duodenal histology	22/285	Enrolment: 1961–1983 Followed-up until 2004	General population	Age, sex, calendar year	SMR 2.62 (1.62–4)
2007 Solaymani-Dodaran (b),[25] Scotland (updated by Quarpong 2019)	Adults (>15 years), mean 45 years	Lothian celiac registry	Any diagnosed CD	Duodenal histology	196/340	Enrolment: 1961–1983 Followed-up until 2004	General population	Age, sex, calendar year	SMR 1.55 (1.33–1.8)

(Continues)

TABLE 1 (Continued)

Study and country	Population (age at diagnosis)	Source data	Forms of CD studied	Diagnostic method	Deaths/CD patients, *N*	Study period	Comparison group[a]	Variable matching/ adjustment	All-cause mortality risk estimate (95% CI)
2006 Viljamaa (a),[26] Finland (updated by Koskinen 2022)	Children and adults, median 39 years	Medical records	Non-DH CD	Duodenal histology	85/781	Enrolment: 1960–2000 Followed-up until 2002	General population	Age, sex, calendar year	SMR 1.26 (1.00–1.55)
2006 Viljamaa (b),[26] Finland (updated by Koskinen 2022)	Children and adults, median 38 years	Medical records	DH	Skin DIF	34/366	Enrolment: 1960–2000 Followed-up until 2002	General population	Age, sex, calendar year	SMR 0.52 (0.36–0.72)
2003 Peters,[11] Sweden (overlap with Ludvigsson 2009 and Lebwohl 2020)	Children and adults, mean 17 years	Swedish inpatient registry	Any diagnosed CD	Not reported (ICD codes)	828/10032	Enrolment: 1964–1993 Followed-up until 1993	General population	Age, sex, calendar year	SMR 2.0 (1.8–2.1)
1999 Cottone,[12] Italy (patients included in Corrao 2001)	Adults, mean 35 years	Medical records	Any diagnosed CD	Duodenal histology	12/228	Enrolment: 1980–1997 Followed-up until 1997	General population	Age, sex	SMR 3.8 (2–7)
1989 Logan,[13] Scotland (updated by Quarpong 2019)	Children and adults, average age NR	Lothian celiac registry	Any diagnosed CD	Duodenal histology	115/653	Enrolment: 1961–1981 Followed-up until 1986	General population	Age, sex, calendar year	SMR 1.9 (1.5–2.2)

Abbreviations: AGA, anti-gliadin antibodies; ARA, anti-reticulin antibodies; CD, coeliac disease; DGP, deamidated gliadin peptide antibodies; DH, dermatitis herpetiformis; DIF, direct immunofluorescence; EMA, endomysial antibodies; GPRD, general practice research database; HR hazard ratio; ICD, international classification of diseases; NR, not reported; SMR, standardised mortality ratio; TTA, tissue transglutaminase antibodies.

[a]Matched controls: age-sex matched controls from the general population; Control subjects: controls from the general population not matched for age-sex; General population: general population data.

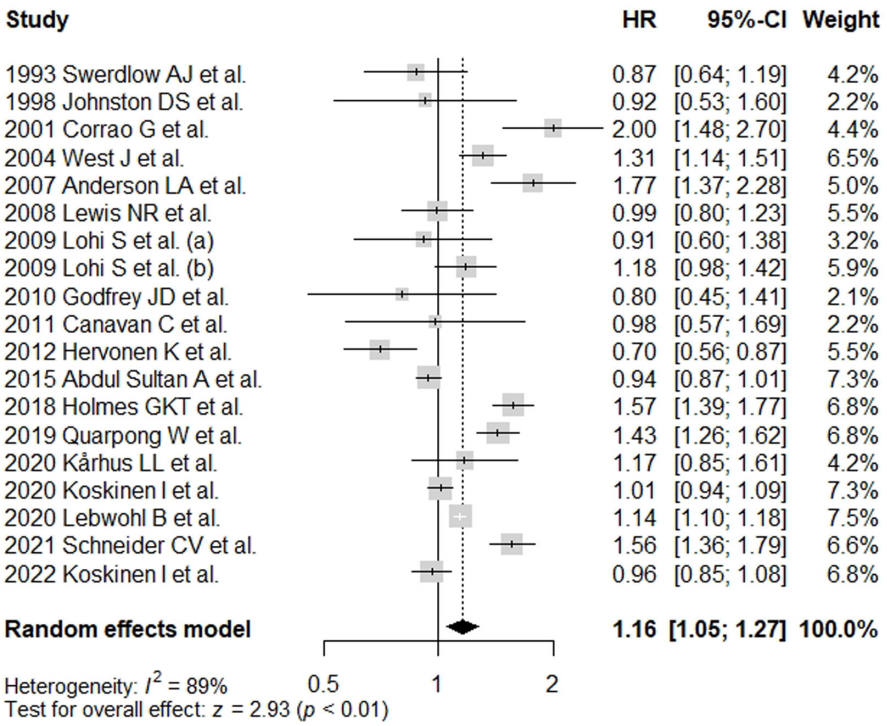

FIGURE 2 Forest plot showing meta-analysis of all-cause mortality in coeliac disease compared to the general population.

TABLE 2 Pooled estimates of cause-specific mortality in coeliac disease.

Cause of death	Data sources (study references)	Total coeliac patients, *N*	Pooled HR (95% CI)	Heterogeneity (I^2, %)
All causes	10, 14–16, 18, 19, 27–38	87,738	1.16 (95% CI 1.05–1.27)	89
All malignancies	10, 14, 16, 18, 19, 27–33, 35, 36, 38	75,965	1.21 (95% CI 1.08–1.36)	65
Lymphoproliferative malignancies	14, 18, 27–29, 33, 36	22,765	3.14 (95% CI 2.38–4.14)	39
Non-Hodgkin Lymphoma	10, 14, 27, 35	15,757	10.14 (95% CI 2.19–46.88)	96
Respiratory disease	10, 14, 16, 18, 27, 28, 31, 33, 38	69,758	1.39 (95% CI 1.04–1.86)	76
Cardiovascular disease	10, 14, 16, 18, 27–33, 35, 38	71,106	1.04 (95% CI 0.93–1.15)	52
Infectious diseases	14, 27, 38	14,347	2.14 (95% CI 0.53–8.66)	71

Abbreviations: HR, hazard ratio; *N*, number of patients.

mortality in different geographical regions. All-cause mortality was considered the primary outcome.

Statistical analysis was performed using R version 4.1.2 (R Core Team, 2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/. From each eligible study all-cause and/or cause-specific mortality risk estimates and 95% CI were extracted. HRs and SMRs with corresponding 95% CI were log-transformed and pooled for random-effects meta-analysis with inverse variance weighting and then back-transformed for data interpretation. For the purpose of our analysis, we considered HRs and SMRs as approximately equivalent, as has been done previously.[21] For the analysis concerning age at diagnosis, as studies did not use homogeneous age categories, we grouped and pooled data according to which of the following categories was the closest match: children (age ≤18 years), young adults (age 19–44 years), older adults (age ≥45 years).[6–8] A post-hoc analysis was performed to investigate cause-specific mortality in patients with dermatitis herpetiformis. Between-study heterogeneity was evaluated by visual inspection of forest plots and the I^2 statistic, and classified as low (I^2 < 30%), moderate (I^2 = 30%–49%), substantial (I^2 = 50%–74%), and high (I^2 ≥ 75%). Pre-planned and post-hoc subgroup analyses were conducted (χ^2, p < 0.1 for significance) and where post-hoc pairwise comparisons between subgroups were made, p-values were adjusted for multiplicity using the Benjamini–Hochberg method. Publication bias was investigated by funnel plot visual inspection and Egger's test. We conducted the following sensitivity analyses: (i) The overall all-cause mortality analysis was repeated after individual exclusion of outliers (the studies with the most extreme results on the forest plot) to evaluate for undue influence on our results by a single outlier study; (ii) we also repeated all analyses using fixed-effects models to further investigate for possible small-study effects on our pooled mortality risk estimates and evaluate the robustness of our results[22]; (iii) a post hoc analysis comparing the all-cause mortality outcomes reported by studies

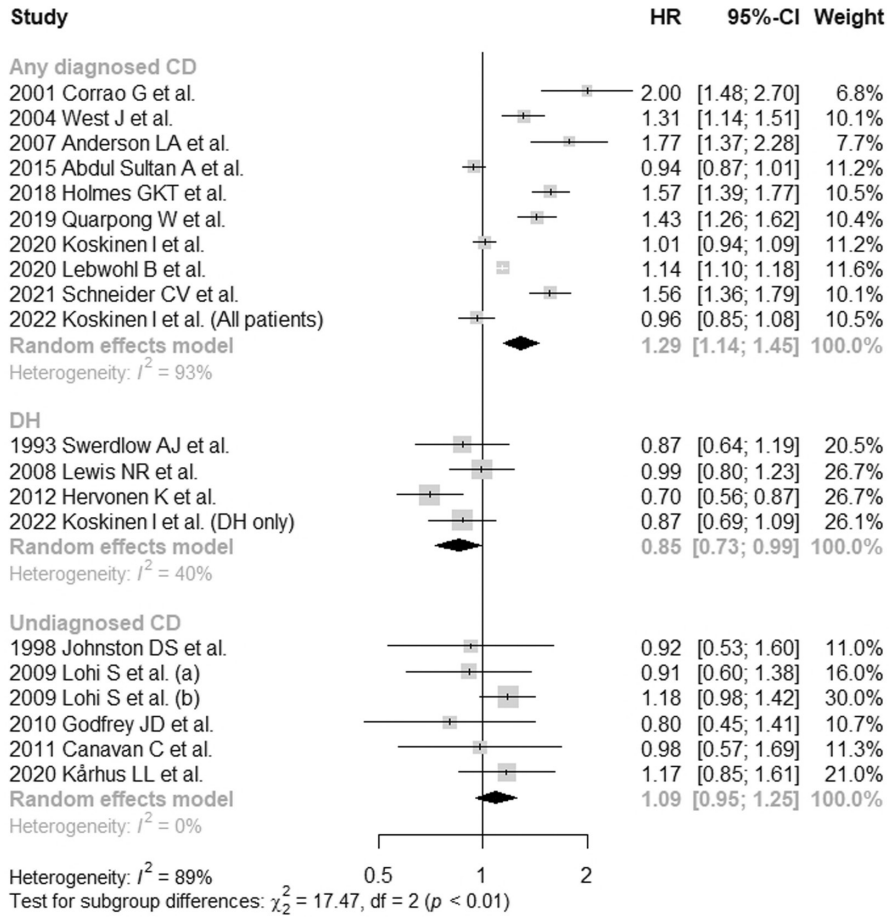

FIGURE 3 Forest plot showing subgroup analysis of all-cause mortality according to the clinical form of coeliac disease.

reporting outcomes as SMRs vs those reporting as HRs was performed, to evaluate the robustness of our approach of pooling SMRs and HRs. p-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of included studies

As shown in Figure 1, a literature search identified 5898 records, from which 25 eligible studies were identified.[10–16,18,19,23–38] Of these, seven were older reports[11–13,23–26] for which updated or more comprehensive reports on the same population of patients were available.[10,16,27,30,31] The remaining 18 eligible studies (shown above in Table 1) were considered for all analyses whereas the seven older studies (shown below in Table 1) were considered only for the analysis comparing mortality in different time periods and excluded from all other analyses to avoid inclusion of duplicate data. Table S1 lists studies excluded after full-text review and reasons for exclusion. Study quality was high overall with Newcastle-Ottawa scale scores ranging from 7 to 9 stars, and a median score of 8 stars (see Table S2). Funnel plot examination (Figure S1) and Egger's test (p = 0.74) revealed no evidence of publication bias. One study[33] reported outcomes only separately for the two subgroups included (Table 1), so they were also included separately for meta-analysis.

3.2 | All-cause and cause-specific mortality

Data on all-cause mortality from 18 studies (87,738 coeliac patients) was pooled. All-cause mortality in coeliac disease was overall slightly but significantly increased compared to the general population (pooled HR 1.15, 95% CI 1.05–1.27; I^2 = 89%), as shown in Figure 2. Table 2 shows pooled estimates of cause-specific mortality. Notably, mortality due to malignancies overall was increased (pooled HR 1.21, 95% CI 1.08–1.36; I^2 = 65%), while mortality due to lymphoproliferative malignancies (pooled HR 3.14, 95% CI 2.38–4.14; I^2 = 39%), and especially non-Hodgkin lymphoma (pooled HR 10.14, 95% CI 2.19–46.88; I^2 = 96%) were markedly increased. Mortality due to respiratory diseases (pooled HR 1.39, 95% CI 1.04–1.86; I^2 = 76%) also showed a significant increase. On the contrary, mortality due to cardiovascular disease (pooled HR 1.04, 95% CI 0.93–1.15; I^2 = 52%) was not significantly increased. Data on mortality due to infectious diseases was inconclusive (pooled HR 2.14, 95% CI 0.53–8.66; I^2 = 71%).

3.3 | Mortality in different clinical forms of coeliac disease

Data on all-cause mortality shown in Figure 2 was further categorised according to the form of coeliac disease being studied, that is, diagnosed coeliac disease (classical coeliac disease, non-classical

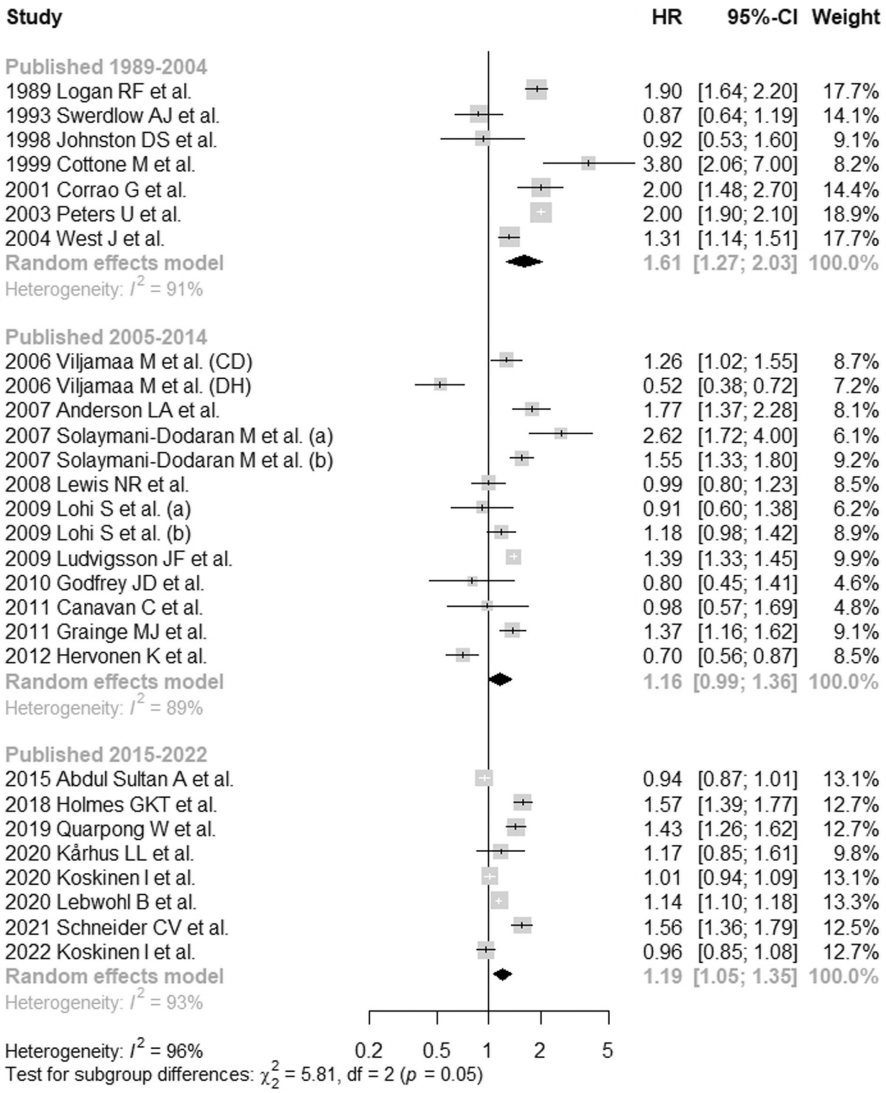

FIGURE 4 Forest plot showing comparison of all-cause mortality in coeliac disease according to study publication date.

coeliac disease, dermatitis herpetiformis, silent coeliac disease) and undiagnosed coeliac disease. Figure 3 shows the results of this subgroup analysis, revealing significant differences among subgroups ($p < 0.001$). Pairwise comparisons between subgroups confirmed significant differences for any diagnosed coeliac disease vs dermatitis herpetiformis (adjusted $p < 0.001$) and dermatitis herpetiformis versus undiagnosed coeliac disease (adjusted $p = 0.02$), and also for any diagnosed coeliac disease vs undiagnosed coeliac disease (adjusted $p = 0.07$). An increase in all-cause mortality was confirmed among patients with any diagnosed form of coeliac disease (pooled HR 1.29, 95% CI 1.14–1.45; $I^2 = 93\%$). On the contrary, all-cause mortality was not significantly increased in undiagnosed coeliac disease (pooled HR 1.09, 95% CI 0.95–1.25; $I^2 = 0\%$) and in dermatitis herpetiformis, where all-cause mortality was slightly reduced (pooled HR 0.85, 95% CI 0.73–0.99; $I^2 = 40\%$). Only one study compared mortality among patients with classical, non-classical and silent coeliac disease and found an increase in mortality only in classical coeliac disease.[10]

Data on cause-specific mortality in patients with dermatitis herpetiformis was reported by only two studies,[18,38] with neither finding an increased mortality from any specific cause of death,[18,38] with the exception of one reporting increased mortality from lymphoproliferative neoplasms.[18] A post-hoc analysis of cause-specific mortality in dermatitis herpetiformis showed reduced mortality from cardiovascular diseases (pooled HR 0.70, 95% CI 0.53–0.92) and no increase in mortality from malignancies overall (pooled HR 0.87, 95% CI 0.62–1.23). Four studies reported outcomes on cause-specific mortality in undiagnosed coeliac disease.[19,28,32,33] However, as the sample size of studies on undiagnosed coeliac disease was generally small, no further analysis on cause-specific mortality in these patients was possible.

3.4 | Role of age at diagnosis on mortality

Figure S2 shows meta-analysis results when all-cause mortality estimates were categorised according to age at diagnosis. In relative terms, mortality was most increased in coeliac patients diagnosed in childhood (pooled HR 1.63, 95% CI 1.17–2.27; $I^2 = 57\%$). Mortality in older adults showed a small increase (pooled HR 1.11, 95% CI 1.01–1.22; $I^2 = 76\%$), while data on young adults was inconclusive (pooled HR 1.34, 95% CI 0.81–2.20; $I^2 = 86\%$), but was suggestive of

an intermediate risk level between that of children and older adults. Despite substantial/high heterogeneity remaining within subgroups (see Figure S2), subgroup analysis revealed significant differences between these groups ($p=0.08$). Pairwise comparisons showed a significant difference when comparing those diagnosed in childhood to those diagnosed in older adulthood (adjusted $p=0.09$), but not between other subgroups (adjusted $p>0.5$). Our analysis cannot provide comprehensive data regarding excess mortality in these subgroups, but a large Swedish registry-based study also analysed excess mortality rates according to age at diagnosis.[24] This study found the greatest excess in mortality among those diagnosed in older adulthood but very low excess mortality in patients diagnosed in childhood. Specifically, excess mortality rates were 0.2, 1.1, 2.6, and 8.2 deaths per 1000 person-years for patients diagnosed at <20, 20–39, 40–59, and ≥60 years, respectively.[24] This suggests that the relatively large increase in mortality found in those diagnosed in childhood by our analysis was likely due to a small number of excess deaths.

3.5 | Changes in mortality over time

Figure 4 shows a subgroup analysis of all-cause mortality in coeliac disease according to date of study publication including also older reports (total number of reports = 25), revealing significant differences in mortality over time ($p=0.05$). While studies published prior to 2005 showed a significant increase in all-cause mortality (pooled HR 1.61, 95% CI 1.27–2.03; $I^2=91\%$), only a very small increase in mortality was shown by studies published in the periods from 2005 to 2014 (pooled HR 1.16, 95% CI 0.99–1.36; $I^2=89\%$) and 2015–2022 (pooled HR 1.19, 95% CI 1.05–1.35; $I^2=93\%$). Pairwise comparisons between subgroups confirmed a significant difference between the 1989 and 2004 time period versus the 2005–2014 and 2015–2022 periods (both adjusted $p=0.04$), but not for 2005–2014 versus 2015–2022 (adjusted $p=0.78$).

3.6 | Differences in mortality according to geographical location

Data on mortality in coeliac disease compared to the general population was available for only a few countries. Specifically, multiple studies were conducted in the UK[15,28,30–32,34–38] and Scandinavian countries (Finland, Sweden, Denmark),[14,16,18,27,29,33] two were conducted in Italy, one of which was a multicentre study[10] also including the patients described in the other paper[12] and one was conducted in the USA on undiagnosed coeliac disease.[19] Overall, studies conducted in Scandinavian countries showed no increase in mortality (pooled HR 1.01, 95% CI 0.91–1.13; $I^2=81\%$) while in the UK there was overall a slight increase in mortality (pooled HR 1.23, 95% CI 1.03–1.47; $I^2=91\%$). The USA study included only patients with undiagnosed coeliac disease and found no increase in mortality (HR 0.80, 95% CI 0.45–1.41).[19] On the contrary, the Italian multicenter study performed by Corrao et al. more than 20 years ago found a markedly increased mortality risk among coeliac patients (SMR 2.00, 95% CI 1.48–2.70).[10]

3.7 | Sensitivity analyses

To explore whether any outlier studies significantly influenced our results we repeated the overall all-cause mortality analysis after individually excluding these studies. This did not significantly alter the pooled all-cause mortality risk estimate. Repeating analyses using fixed-effects models did not substantially alter mortality risk estimates, further excluding a role of small-study effects on our results. The only noteworthy difference which emerged regarded the analysis of cause-specific mortality due to infectious diseases which, when analysed using a fixed-effects model, showed a significant increase in mortality. However, the point estimate remained very similar and the main difference was narrowing of the 95% CI when a fixed-effect model was used. When comparing studies reporting outcomes as SMRs versus HRs, all-cause mortality estimates did not differ significantly between these two groups ($p=0.32$).

3.8 | Other factors related to mortality

Several studies found that significantly higher mortality was observed in the first years after coeliac disease diagnosis, with a subsequent diminishing of risk over time.[10,12–14,24,25,30,36] One study reported on the role of diagnostic delay on mortality, finding a greater risk in those with a diagnostic delay of more than 12 months.[10] Although all studies on diagnosed coeliac disease were conducted on patients on a GFD, only one study systematically evaluated the impact of poor GFD adherence had on all-cause mortality, finding significantly increased mortality only in patients with poor dietary adherence but not in those with good dietary adherence.[10]

One large registry-based study considered the role of mucosal healing on all-cause mortality, and while an inverse relationship was found between mucosal healing and mortality, this was not confirmed at multivariate analysis.[16] Finally, one study investigated the relationship between the number of HLA-DQ2/DQ8 alleles (0–1 vs 2) and mortality, both in celiac patients and controls, and found no significant relationship with all-cause mortality in either group. However, an increased risk of death from lymphoproliferative disorders was found only in celiac patients with 2 HLA-DQ2/DQ8 alleles (HR 7.6, 95% CI, 1.01–57.25) but not in coeliac patients with 0–1 alleles, or controls irrespective of number of alleles.[28] Among the included studies, none evaluated the role of seronegative coeliac disease or complicated coeliac disease on mortality.

4 | DISCUSSION

This systematic review and meta-analysis on mortality in coeliac disease were based on high-quality studies published over more than

30 years, finding that coeliac disease overall has an increased mortality compared to the general population, mainly due to malignancies, particularly lymphoproliferative disorders, but also due to respiratory disease. Novel findings include a reduction in coeliac disease mortality in recent decades and significant differences in mortality among different forms of coeliac disease.

One major factor contributing to the reduction in mortality in the period after 2005 could be the widespread availability of serological assays for tissue transglutaminase antibodies for coeliac disease,[39] leading to many milder cases of coeliac disease also being diagnosed, while also reducing diagnostic delay. This is supported by the exponential increase in new cases of coeliac disease in this period of time.[40] Legislative and social changes facilitating access to gluten-free foodstuffs in many countries may also have played a role.[41] This also coincided with a reduction in the prevalence of complications among coeliac patients.[42]

Clinically, certain forms of coeliac disease are more severe than others, with complicated forms of coeliac disease having such high mortality rates that they cannot be compared to the general population.[6,8] Our results show that some forms of coeliac disease are not characterised by an increased mortality, specifically dermatitis herpetiformis and undiagnosed coeliac disease. Interestingly, a large epidemiological study previously found that subjects with undiagnosed coeliac disease showed a reduction in several major cardiovascular risk factors compared to controls and better self-reported health status, despite higher rates of osteoporosis and lower haemoglobin values.[43] It may be that these patients are mainly affected by mild forms of coeliac disease, and due to their favourable cardiovascular risk profile do not show an increased mortality. Further studies on this group of patients are warranted as there may be significant implications regarding screening strategies for coeliac disease, both for family members of coeliac patients and the general population. This is relevant as large studies on first-degree relatives of coeliac patients or offspring of coeliac patients have failed to find any significant increase in mortality.[10,44,45]

Mortality in dermatitis herpetiformis may even be reduced compared to the general population, possibly due to a reduced risk of death from cardiovascular disease. One possible contributing factor may be that dermatitis herpetiformis is usually characterised by a mild enteropathy[46] and a low risk of developing complicated forms of coeliac disease.[6,7] Reports suggesting a reduction in cardiovascular risk factors such as tobacco smoking among coeliac patients in general,[43,47] and specifically among patients with dermatitis herpetiformis,[18,48,49] may partly explain the lower risk of cardiovascular death observed among these patients.

Although we aimed to also investigate whether mortality differs according to the clinical pattern of coeliac disease at diagnosis,[2] this was limited by a lack of studies reporting mortality outcomes separately for classical, non-classical and silent coeliac disease. Only one Italian multicentre study reported outcomes separately for these subgroups of patients, finding an increase in mortality only in classical coeliac disease, but not in non-classical or silent coeliac disease.[10] This is corroborated by data in the literature suggesting that the clinical pattern of coeliac disease is a major risk factor for the development of complications of coeliac disease, with classical coeliac disease being at greatest risk of complications.[6,7] Therefore, while it is reasonable to think that mortality differs among these forms of coeliac disease, further studies are needed to clarify this.

Regarding cause-specific mortality, the increased mortality from malignancies, especially lymphoproliferative disorders confirms the results of a prior meta-analysis by Tio et al. in 2012.[17] However, prior data on cardiovascular mortality in coeliac disease have been inconclusive. The meta-analysis by Tio et al. found a slightly increased risk of cardiovascular death[17] whereas two subsequent meta-analyses specifically on cardiovascular disease in coeliac disease only found small, but not statistically significant, increases in risk of cardiovascular death.[21,50] Possibly explaining these discrepancies, Tio et al. could only include data from 3 studies in their analysis of cardiovascular death,[17] while we included data from 13 studies in our analysis of cardiovascular death, many of them published after 2012.[10,14,16,18,27–33,35,38]

Regarding differences in mortality among different countries, unfortunately, data were only available for a few countries with most studies being conducted in the UK and Scandinavian countries. It is therefore difficult to draw conclusions on whether geographical differences in coeliac disease mortality exist. Further studies are needed, particularly for most countries in Europe and America, as well as in India and other Asian countries, where coeliac disease is present.[51]

Another interesting point is the role of age at diagnosis. Our results suggest that the greatest increase in mortality risk occurs among those diagnosed in childhood. However, this result must be interpreted with caution. This is well illustrated by data from a large Swedish registry-based study.[24] Although those diagnosed as children show the greatest increase in mortality in relative terms, this translates to only a relatively small increase in excess mortality, whereas the comparatively smaller increase in mortality among coeliac patients diagnosed in older adulthood translates into a much greater increase in excess mortality. Specifically, excess mortality rates for the age at diagnosis categories of <20, 20–39, 40–59, and ≥60 years were respectively 0.2, 1.1, 2.6, and 8.2 deaths per 1000 person-years.[24]

Although the inclusion of a large number of high-quality studies published over more than 30 years without any evidence of publication bias certainly represents a major strength of our study, we must acknowledge some intrinsic limitations. Firstly, although we tried to be as comprehensive as possible, several studies were excluded as they reported outcomes in ways that could not be quantitatively meta-analysed. The wide range of control and reference populations among eligible studies is another intrinsic limitation. Heterogeneity was overall high, and although some of the heterogeneity might be explained by the factors we investigated, including differences in mortality between different clinical forms of coeliac disease being studied, and study time period, significant unexplained heterogeneity remained.

Finally, we could not completely address some important aspects, including the influence on mortality of dietary adherence and rare forms of coeliac disease such as seronegative coeliac disease. The role of GFD adherence on mortality was evaluated by only one study,[10] finding that poor adherence significantly increased mortality. Among the included studies only one evaluated the relationship between mucosal healing and mortality, finding an inverse relationship, but this was not confirmed at multivariate analysis.[16] This is partly in contrast with the results of a recent multicentre study showing significantly increased mortality in patients with persistent atrophy[52] as well as prior evidence suggesting increased mortality in patients with persistent atrophy.[53] Several studies reported higher mortality in the first years after diagnosis, with a subsequent reduction in risk.[10,12–14,24,25,31,37] This could on one hand be due to the beneficial effect of a GFD reducing mortality over time, but the greater mortality observed in the short term may also be partly due to an ascertainment bias, for example, due to testing for coeliac disease more frequently among symptomatic subjects. None of the included studies evaluated the role of seronegative coeliac disease on mortality, although many of them could not due to their study designs. A recent multicentre study reported that patients with seronegative coeliac disease may be at increased risk of mortality compared to conventional seropositive coeliac disease, although a multivariate analysis suggested this may be partly due to late diagnosis in these patients.[9] Further study of these aspects is warranted.

In conclusion, coeliac disease is overall characterised by a small increase in mortality, mainly due to malignancies, particularly non-Hodgkin lymphoma. Novel findings include that mortality in coeliac disease has significantly decreased in recent decades and that mortality is not uniform across different forms of coeliac disease, with dermatitis herpetiformis and undiagnosed coeliac disease not showing an increased mortality. Further studies investigating how mortality compares among other forms of coeliac disease are needed. Finally, data on mortality in coeliac disease is lacking in many countries and need of investigation.

AUTHOR CONTRIBUTIONS

Stiliano Maimaris: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Annalisa Schiepatti:** Conceptualization; data curation; writing – original draft; writing – review and editing. **Federico Biagi:** Conceptualization; supervision; writing – review and editing.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

AUTHORSHIP

Guarantor of the article: Prof. Federico Biagi.

ORCID

Annalisa Schiepatti https://orcid.org/0000-0002-8493-7698
Federico Biagi https://orcid.org/0000-0002-2227-4622

REFERENCES

1. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014;63:1210–28.
2. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PHR, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62:43–52.
3. Sheldon W. Prognosis in early adult life of coeliac children treated with a gluten-free diet. Br Med J. 1969;2:401–4.
4. Whorwell PJ, Alderson MR, Foster KJ, Wright R. Death from ischaemic heart-disease and malignancy in adult patients with coeliac disease. Lancet. 1976;2:113–4.
5. Nielsen OH, Jacobsen O, Pedersen ER, Rasmussen SNS, Petri M, Laulund S, et al. Non-tropical sprue. Malignant diseases and mortality rate. Scand J Gastroenterol. 1985;20:13–8.
6. Biagi F, Marchese A, Ferretti F, Ciccocioppo R, Schiepatti A, Volta U, et al. A multicentre case control study on complicated coeliac disease: two different patterns of natural history, two different prognoses. BMC Gastroenterol. 2014;14:139.
7. Biagi F, Schiepatti A, Maiorano G, Fraternale G, Agazzi S, Zingone F, et al. Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation. Dig Liver Dis. 2018;50:549–52.
8. Biagi F, Gobbi P, Marchese A, Borsotti E, Zingone F, Ciacci C, et al. Low incidence but poor prognosis of complicated coeliac disease: a retrospective multicentre study. Dig Liver Dis. 2014;46:227–30.
9. Schiepatti A, Rej A, Maimaris S, Cross SS, Porta P, Aziz I, et al. Clinical classification and long-term outcomes of seronegative coeliac disease: a 20-year multicentre follow-up study. Aliment Pharmacol Ther. 2021;54:1278–89.
10. Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet. 2001;358:356–61.
11. Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. Arch Intern Med. 2003;163:1566–72.
12. Cottone M, Termini A, Oliva L, Magliocco A, Marrone C, Orlando A, et al. Mortality and causes of death in celiac disease in a Mediterranean area. Dig Dis Sci. 1999;44:2538–41.
13. Logan RF, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology. 1989;97:265–71.
14. Koskinen I, Virta LJ, Huhtala H, Ilus T, Kaukinen K, Collin P. Overall and cause-specific mortality in adult celiac disease and dermatitis Herpetiformis diagnosed in the 21st century. Am J Gastroenterol. 2020;115:1117–24.
15. Abdul Sultan A, Crooks CJ, Card T, Tata LJ, Fleming KM, West J. Causes of death in people with coeliac disease in England compared with the general population: a competing risk analysis. Gut. 2015;64:1220–6.
16. Lebwohl B, Green PHR, Söderling J, Roelstraete B, Ludvigsson JF. Association between celiac disease and mortality risk in a swedish population. JAMA. 2020;323:1277–85.
17. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Aliment Pharmacol Ther. 2012;35:540–51.
18. Hervonen K, Alakoski A, Salmi TT, Helakorpi S, Kautiainen H, Kaukinen K, et al. Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients. Br J Dermatol. 2012;167:1331–7.
19. Godfrey JD, Brantner TL, Brinjikji W, Christensen KN, Brogan DL, van Dyke CT, et al. Morbidity and mortality among older individuals with undiagnosed celiac disease. Gastroenterology. 2010;139:763–9.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

21. Emilsson L, Lebwohl B, Sundström J, Ludvigsson JF. Cardiovascular disease in patients with coeliac disease: a systematic review and meta-analysis. Dig Liver Dis. 2015;47:847–52.
22. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. In Cochrane handbook for systematic reviews of interventions version 6.4 (updated august 2023). Cochrane; 2023. Available from www.training.cochrane.org/handbook
23. Grainge MJ, West J, Card TR, Holmes GKT. Causes of death in people with celiac disease spanning the pre- and post-serology era: a population-based cohort study from Derby, UK. Am J Gastroenterol. 2011;106:933–9.
24. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. JAMA. 2009;302:1171–8.
25. Solaymani-Dodaran M, West J, Logan RF. Long-term mortality in people with celiac disease diagnosed in childhood compared with adulthood: a population-based cohort study. Am J Gastroenterol. 2007;102:864–70.
26. Viljamaa M, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. Dig Liver Dis. 2006;38:374–80.
27. Koskinen I, Hervonen K, Huhtala H, Pasternack C, Salmi T, Reunala T, et al. Mortality and causes of death in different celiac disease phenotypes during long-term follow-up. Dig Liver Dis. 2022;54:1502–7.
28. Schneider CV, Kleinjans M, Fromme M, Schneider KM, Strnad P. Phenome-wide association study in adult coeliac disease: role of HLA subtype. Aliment Pharmacol Ther. 2021;53:510–8.
29. Kårhus LL, Skaaby T, Petersen J, Madsen AL, Thuesen BH, Schwarz P, et al. Long-term consequences of undiagnosed celiac seropositivity. Am J Gastroenterol. 2020 Oct;115:1681–8.
30. Quarpong W, Card TR, West J, Solaymani-Dodaran M, Logan RFA, Grainge MJ. Mortality in people with coeliac disease: long-term follow-up from a Scottish cohort. United European Gastroenterol J. 2019;7:377–87.
31. Holmes GKT, Muirhead A. Mortality in coeliac disease: a population-based cohort study from a single Centre in southern Derbyshire, UK. BMJ Open Gastroenterol. 2018;5:e000201.
32. Canavan C, Logan RF, Khaw KT, West J. No difference in mortality in undetected coeliac disease compared with the general population: a UK cohort study. Aliment Pharmacol Ther. 2011;34:1012–9.
33. Lohi S, Mäki M, Rissanen H, Knekt P, Reunanen A, Kaukinen K. Prognosis of unrecognized coeliac disease as regards mortality: a population-based cohort study. Ann Med. 2009;41:508–15.
34. Lewis NR, Logan RF, Hubbard RB, West J. No increase in risk of fracture, malignancy or mortality in dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther. 2008;27:1140–7.
35. Anderson LA, McMillan SA, Watson RG, Monaghan P, Gavin AT, Fox C, et al. Malignancy and mortality in a population-based cohort of patients with coeliac disease or "gluten sensitivity". World J Gastroenterol. 2007;13:146–51.
36. West J, Logan RF, Card TR, Smith C, Hubbard R. Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. Aliment Pharmacol Ther. 2004;20:73–9.
37. Johnston SD, Watson RG, McMillan SA, Sloan J, Love AH. Coeliac disease detected by screening is not silent—simply unrecognized. QJM. 1998;91:853–60.
38. Swerdlow AJ, Whittaker S, Carpenter LM, English JS. Mortality and cancer incidence in patients with dermatitis herpetiformis: a cohort study. Br J Dermatol. 1993;129:140–4.
39. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3:797–801.
40. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. Am J Gastroenterol. 2020;115:507–25.
41. Directive 2003/89/EC of the European Parliament and of the council of 10 November 2003. Off J European Union. 2003;308:15–8. [cited 2023 Mar 1] Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:308:0015:0018:EN:PDF
42. Eigner W, Bashir K, Primas C, Kazemi-Shirazi L, Wrba F, Trauner M, et al. Dynamics of occurrence of refractory coeliac disease and associated complications over 25 years. Aliment Pharmacol Ther. 2017;45:364–72.
43. West J, Logan RF, Hill PG, Lloyd A, Lewis S, Hubbard R, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut. 2003;52:960–5.
44. Zugna D, Richiardi L, Stephansson O, Cnattingius S, Ludvigsson JF. Mortality rate in children born to mothers and fathers with celiac disease: a nationwide cohort study. Am J Epidemiol. 2013;177:1348–55.
45. Emilsson L, Abdul Sultan A, Ludvigsson JF. No increased mortality in 109,000 first-degree relatives of celiac individuals. Dig Liver Dis. 2016;48:376–80.
46. Mansikka E, Hervonen K, Salmi TT, Kautiainen H, Kaukinen K, Collin P, et al. The decreasing prevalence of severe villous atrophy in dermatitis herpetiformis: a 45-year experience in 393 patients. J Clin Gastroenterol. 2017;51:235–9.
47. Wijarnpreecha K, Lou S, Panjawatanan P, Cheungpasitporn W, Pungpapong S, Lukens FJ, et al. Cigarette smoking and risk of celiac disease: a systematic review and meta-analysis. United European Gastroenterol J. 2018;6:1285–93.
48. Lear JT, English JS, Jones PW. Adult coeliac disease, dermatitis herpetiformis and smoking. Gut. 1997;40:289.
49. Smith JB, Smith SB, Zone JJ. Dermatitis herpetiformis and cigarette smoking. Gut. 1998;43:732.
50. Heikkilä K, Koskinen OA, Agarwal A, Tikkinen KAO, Mäki M, Kaukinen K. Associations of coeliac disease with coronary heart disease and cerebrovascular disease: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis. 2015;25:816–31.
51. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16:823–836.e2.
52. Schiepatti A, Maimaris S, Raju SA, Green OL, Mantica G, Therrien A, et al. Persistent villous atrophy predicts development of complications and mortality in adult patients with coeliac disease: a multicentre longitudinal cohort study and development of a score to identify high-risk patients. Gut. 2023;72:2095–102.
53. Rubio-Tapia A, Rahim MW, See JA, Lahr BD, Wu TT, Murray JA. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. Am J Gastroenterol. 2010;105:1412–20.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Maimaris S, Schiepatti A, Biagi F. Systematic review with meta-analysis: Cause-specific and all-cause mortality trends across different coeliac disease phenotypes. Aliment Pharmacol Ther. 2024;59:592–605. https://doi.org/10.1111/apt.17867