Original Research Paper

Mortality in people with Coeliac Disease: Long-term follow-up from a Scottish cohort

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Abstract

Background:

Few studies have determined the very long-term mortality risks in adult and childhood-diagnosed coeliac disease.

Objective:

We quantified mortality risks in coeliac disease and determined whether age at diagnosis, or time following diagnosis modified these risks.

Methods:

Standardised mortality ratios (SMRs) were determined using data from a cohort of 602 coeliac patients assembled between 1979 and 1983 from Lothian, Scotland, and followed up from 1970 until 2016.

Results:

All-cause mortality was 43% higher than in the general population. Excess deaths were primarily from haematological malignancies (SMR, 4.77) and external causes (SMR,

2.62) in adult and childhood-diagnosed cases respectively. Mortality risks declined steadily with time in adult-diagnosed cases (SMR, 4.85 in first year compared to 0.97, 25 years post-diagnosis). Beyond 15 years, this group had a significantly reduced risk of any malignancy (SMR, 0.57 [95% CI: 0.33-0.92]). In contrast, for childhood-diagnosed cases an increased risk existed beyond 25 years (SMR, 2.24).

Conclusions:

Adult-diagnosed coeliac patients have a temporary increased mortality risk mainly from malignant lymphomas and a decreased risk of any malignancy beyond 15 years post-diagnosis. In contrast, childhood-diagnosed cases are at an increased risk of mortality mainly from external causes, and have long-term mortality risks that requires further investigation.

Key summary

Established knowledge on subject

- Coeliac disease is associated with increased risk of mortality mainly from specific malignancies.
- Increased mortality risks in coeliac disease are greatest during the first few years of diagnosis.

Significant findings of current study

- Adult-diagnosed coeliac disease patients have no significant excess risk of all-cause mortality beyond 25 years after diagnosis, with the confidence intervals around the standardised mortality ratio excluding a greater than 25% increase.
- Adult-diagnosed coeliac disease patients have a reduced risk of death from any malignancy more than 15 years after diagnosis.
- Childhood-diagnosed coeliac disease patients have a long-term mortality risk that merits further investigation.

Introduction

Coeliac disease (CD) patients are reported to have a higher mortality risk than the general population, although the reported magnitude of this increase in risk varies widely.[1-8] There is consensus that these increased mortality risks are observed predominantly within a few years of diagnosis (1-4 years).[1,4-6] Owing to limited follow-up, the majority of studies have not been able to assess whether these risks persist for long periods (>20 years) after diagnosis. Furthermore, studies have focused entirely on adults[1,4] or included considerably more individuals diagnosed in adulthood (>85%) than in childhood,[3,6,9] with many[1,3,4] but not all[9] reporting them to be at an increased risk of mortality primarily from lymphatic malignancies. Only a few studies[3,5] have included children or assessed mortality risks in patients diagnosed in childhood, and these have been limited by short follow-up times[5] and a focus on inpatients,[3] who are more likely to have worse outcomes.

To our knowledge, the first study to have sufficient follow-up time to assess the difference in mortality risks between childhood and adulthood-diagnosed CD and the long-term trends in these risks was that carried out by Solaymani-**Dodaran** et al.[10] on a cohort of CD patients followed up from 1970 to 2004 (Lothian cohort). Their finding of an increase in long-term mortality in childhood-diagnosed cases, including an excess mortality particularly from external causes has not been corroborated. Evidently, further

research is needed to ascertain the magnitude of mortality risks associated with the disease and the very long-term (>20 years) changes in these risks. An additional 10 years of mortality data on the Lothian cohort enabled us to explore mortality risks further, and with greater statistical power; we aimed to quantify the overall and cause-specific mortality risks in adult and childhood-diagnosed CD, and determine whether these risks persist more than 25 years following diagnosis.

Methods

Study participants

Our cohort consisted of CD cases sourced from the Lothian region of Scotland between 1979 and 1983. The Lothian region comprises the administrative districts of West, East and Mid-Lothian and the City of Edinburgh. Its total population in 1979 was estimated at 764,688.[11] Current population estimates indicate little variation in the population statistics, the most recent population estimate being 880,000.[12]

Participants were predominantly resident in the City of Edinburgh, and were identified through: diagnostic records of gastrointestinal units; existing histopathology records; 1961-1977 CD admissions recorded in the Scottish Hospital Inpatient

Statistics; a postal survey of 440 general practitioners; and the region's CD patient support group. Further details of the participants have been published elsewhere.[11,13] We included all participants with at least one small bowel biopsy showing abnormalities typical of CD, some of which were confirmed by a second small bowel biopsy following a gluten withdrawal or gluten challenge (i.e. confirmed CD) and some of which were not (i.e. probable CD). Participants were further classified during enrolment into: childhood-diagnosed (patients diagnosed prior to their 15th birthday) and adulthood-diagnosed (patients diagnosed on or after their 15th birthday) CD cases.[11]

Study design

Follow-up commenced on the later of January 1, 1970 (date of first active tracking of cohort) or the date of clinical diagnosis until the earliest of loss to follow-up, death, or October 20, 2016. Given that participants were recruited into the study between 1979 and 1983, follow-up prior to 1979 was retrospective.

Cohort mortality data

Following an initial search of Scottish National Death Records, participants identified to be alive were flagged in the National Health Service Central Register. Upon death, copies of their death certificates were sent to the study team, who linked information on the underlying causes of death to the cohort participants. The underlying causes of death

were coded using the 8th-10th revisions of the International Classification of Diseases (ICD).

Population mortality data

Mortality rates were determined by applying population mortality estimates for the Lothian region obtained from the National Records of Scotland[12,14] for the years 1974-2016. Population mortality estimates for the years 1970-1973 and cause-specific death estimates for 2016 were unavailable, and were extrapolated from the average mortality estimates for the periods of 1974-1976 and 2013-2015 respectively.

Statistical analysis

Overall and cause-specific mortality

We calculated overall standardised mortality ratios (SMRs) and their 95% confidence intervals (CIs) for the total person-years of follow-up using indirect standardisation, by estimating the number of deaths expected in this amount of person-time when age (5-year bands), gender and year specific mortality rates for the Lothian region were applied to our cohort. We then determined cause-specific SMRs for causes of death where we had population data (appendix), using the same approach. Overall and cause-specific SMRs were calculated for the whole cohort and separately for adult and childhood-diagnosed cases.

Mortality risks by time since diagnosis

To determine whether mortality risks in the cohort were modified by the length of time following diagnosis, we calculated overall SMRs for the following times: first year of diagnosis, 0-4 years, 5-9 years, 10-14 years, 15-24 years and 25 years or more post-diagnosis and cause-specific SMRs for the following times: < 15 years following diagnosis and ≥ 15 years following diagnosis.

Sensitivity analysis

To determine whether conclusions made were dependent on whether or not CD in the patient had been confirmed, we carried out a sensitivity analysis by repeating the analyses in participants with confirmed CD only.

All analyses were carried out using Stata v. 14.2.

Results

Cohort Characteristics

Our cohort consisted of 602 participants diagnosed with CD between 1943 and 1983 (Table 1) (we excluded 23 participants from the original cohort of 625, who had died before our study start date). Of these, 73% had their diagnosis confirmed by one or

more biopsies following gluten withdrawal or a gluten challenge. 318 (53%) participants were diagnosed as adults at a mean age of 45 years, and 284 (47%) were diagnosed as children at a median age of 1.58 years. Participants contributed to a total follow-up of 19,071 person-years, with childhood-diagnosed cases accounting for a greater percentage of the follow-up time (60%). 205 (64%) adult-diagnosed cases had died before the end of the study period compared with 32 (11%) childhood-diagnosed cases.

Overall and cause-specific mortality risks

The causes of deaths analysed and the average ages at which participants died from these causes are presented in Figures 1 and 2 respectively. We observed an excess of 70.8 deaths (237 observed deaths, 166.2 expected deaths) from all causes in the cohort during the entire study period (Table 2). This represents a relative excess mortality risk of 43% in the cohort compared to the general Lothian population (SMR=1.43; 95% CI 1.25-1.62). Participants diagnosed in childhood had more than double the risk of dying (SMR=2.11; 95% CI 1.44-2.97) compared with a 36% increase in risk in those diagnosed in adulthood (SMR=1.36; 95% CI 1.18-1.56).

The overall excess mortality was accounted for at least in part by lymphatic and haematopoietic tissue (haematological) malignancies in adulthood-diagnosed cases, and by accidents, suicides and violence (external causes) in childhood-diagnosed cases

(Figure 1). In adult cases there were 13 haematological malignancies (all of which were specifically lymphoma), compared with 2.7 expected, resulting in an SMR of 4.77 (95% CI 2.54-8.16). Childhood-diagnosed cases had an increase in risk of death from external causes (SMR=2.62; 95% CI 1.05-5.40), haematological malignancies (SMR=8.03; 95% CI 1.66-23) and cerebrovascular diseases (SMR=4.42; 95% CI 0.53-16), although the last of these was not statistically significant.

Mortality risks by time since diagnosis

Overall, mortality risks for the entire cohort declined gradually over time (Table 3). This decreasing trend was driven by the results in adult-diagnosed cases. The highest mortality risk for this group was observed in the year following diagnosis (SMR=4.85; 95% CI 2.42-8.68). Within 5 to 9 years post-diagnosis, the excess risks had decreased to 49% (SMR=1.49; 95% CI 0.97-2.18). Beyond 25 years after diagnosis, adulthood-diagnosed CD patients had no significant excess risk, with the confidence intervals around the SMR excluding a greater than 25% increase (SMR=0.97, 95% CI 0.74-1.24). Our analysis of childhood-diagnosed cases was somewhat hampered by a small number of expected deaths during the first 24 years following diagnosis. However, beyond 25 years after diagnosis, those diagnosed in childhood had more than double the mortality risk (SMR=2.24; 95% CI 1.45-3.30).

When cause-specific deaths were analysed in the whole cohort, it appeared that most of the excess deaths from the different causes had been accrued during the first 15 years following diagnosis (Table 4). Among adult-diagnosed cases, there were significantly raised mortality risks in the first 15 years for all malignancy as well as for digestive cancers and haematological malignancies specifically. In contrast, beyond 15 years there was a modest but statistically significant decreased risk of mortality from any malignancy (SMR=0.57; 95% CI 0.33-0.92). In childhood-diagnosed cases, the majority of deaths in the first 15 years were from external causes (SMR=4.89; 95% CI 1.01-14). Beyond 15 years, the increased risks from these causes persisted, although lower than before (SMR=1.95; 95% CI 0.53-4.98). For this group, increased mortality beyond 15 years of diagnosis was strongest for haematological malignancies (SMR=9.44; 95% CI 1.95-28).

Sensitivity analysis

Restricting the analyses to confirmed cases did not produce any substantial differences in the estimates obtained (data not shown). We observed a similar pattern of higher mortality risks in childhood-diagnosed cases, as well as a decreasing trend in mortality risks with increasing time following diagnosis.

Discussion

Key Findings

People diagnosed with CD were at a 43% increased risk of mortality compared to the general population. The largest relative risks of death were from haematological malignancies (>90% of which were specifically lymphoma) in both adult and childhood-diagnosed cases. Mortality risks declined steadily with time since diagnosis, particularly in the adulthood-diagnosed cases. For these, we observed a lower than expected risk of mortality from all malignancies after the first 15 years of diagnosis. We did not have sufficient follow-up at ages where mortality is expected to be high in the childhood-diagnosed cases to be able to make robust conclusions. We are nevertheless confident that beyond 25 years post-diagnosis, CD patients diagnosed as adults are no longer at a higher risk of mortality compared to the general population.

Strengths and Limitations

Our study can boast a number of strengths, one of them being that it was population-based and therefore not prone to selection bias. Another strength is the use of the generally accepted gold standard[15] of biopsies as a means of confirmation of CD. By using death certificates to ascertain the underlying causes of death, we have ensured a

uniform quality of recording of causes of death in the cohort and the general population to which it was compared. We also have long follow-up, allowing us to assess longer-term risks, something impossible for earlier studies.

Supposing that CD truly raises mortality risks, then our estimates may have been underestimated by the inclusion of probable cases, if many of these did not indeed have CD (non-differential misclassification). In this instance, restricting the analyses to confirmed cases would have resulted in higher mortality estimates, at the cost of wider confidence intervals. However, when we restricted the analyses to confirmed cases, we observed slightly lower mortality risks and similar trends in all-cause and cause-specific mortality, implying that our probable cases were likely to be true CD cases. Given that over 70% of our cases were confirmed, we are quite confident that the inclusion of probable cases did not affect our results substantially.

There were other potential limitations. First, around 23% of the study participants lived outside the Lothian region (Fife or the Scottish borders) when diagnosed with CD.[11] However, the demographic characteristics and mortality pattern of people living in Fife and the Scottish borders are generally similar to that of people in the Lothian region.[16] Hence, we do not believe there are significant differences in the characteristics of the participants living within and outside the Lothian region to have rendered the population data used inappropriate. Second, we were unable to adjust for

the effect of certain factors such as socio-economic status, smoking, compliance with gluten-free diets (GFDs), body mass index (BMI), existence of co-morbidities, etc., which may be associated with high mortality risks. Previous studies, however, have found that adjusting for BMI, smoking[6] and education[5] did not remove the effect. Third, approximately half of the deaths in the cohort were from causes that we did not have population data on. We are therefore unable to speculate as to whether people with CD have different mortality risks from causes of death that we have not analysed.

Other Studies

Overall and cause-specific mortality

The 43% raised mortality risk observed is much lower than most of the earlier reports[1,4] and more in agreement with recent studies,[5,6] which have reported modest increases (30-40%) in mortality risks in CD patients. This lends support to the findings of decreased mortality risks with increasing length of time following diagnosis,[4-6] as our current analysis was based on follow-up data more than 15 years following diagnoses in most cases.

We have just a few studies with which to compare our findings of higher risks in childhood than adulthood-diagnosed cases. While two studies[3,5] have similarly reported

high risks in children, they either included young adults[5] or had a shorter follow-up time.[3]

Our finding of excess risks of death from malignant lymphomas in adult and childhood-diagnosed CD is consistent with other studies[1,3,4,7] and our previous observation from this cohort that malignancy itself was raised in CD patients,[17] a finding not supported by all previous research.[18] Previous research has highlighted a reduced risk of breast cancer in CD patients,[6,9] however, with only small numbers of deaths (<5) we were unable to say whether this extends to mortality from breast cancer.

The observed excess deaths in childhood-diagnosed cases from external causes is consistent with prior publications from this cohort[10,11] and reports of causes of death in children in the UK and worldwide.[19] However, it is unclear why childhood-diagnosed CD patients would have significantly more of such deaths than the general population. According to Cinquetti et al.[20] the acceptance of GFDs in children and adolescents can be associated with adverse psychological effects such as depression and anxiety. In addition, there is evidence that hypervigilance to GFDs may have a negative impact on quality of life.[21] This may therefore make such individuals more inclined to intentional self-harm; however, this reasoning is speculative and further research is needed.

Mortality risks with time following diagnosis

Similar to most studies,[1,4,5,11] we have confirmed that the mortality risks in CD patients are greatest during the first few years after diagnosis. It is plausible that at the time of diagnosis, patients in our cohort (all of whom were diagnosed prior to 1984) were more symptomatic and presented with more severe forms of the disease, as has been hypothesized to be the case with patients diagnosed in the pre-serological era.[8,22] This coincides with the recognition that diagnosis at this time was more difficult than what it has become with serology and endoscopic biopsy. This is evidenced from co-existing symptoms at the time of diagnosis among the present cohort.[23] Another possible explanation is that the cases may have presented with illnesses other than CD, leading to an ascertainment bias with respect to CD diagnosis.

Alternatively, it could be argued that CD patients adopt healthier lifestyles after their diagnoses and are therefore less likely to have higher mortality risks than before. As reported in some studies, CD patients are generally less likely than the general population to smoke or be obese[6] and also, they have lower fat intake and better cholesterol profiles,[24,25] all of which are associated with lower mortality risks.

The reduction in all malignancies in adult cases 15 years following diagnosis is an interesting finding which needs further exploration through research. Few studies[9,17,26] have reported a decrease in the incidence of malignancies in CD 10 years or

more following diagnoses, but we are not aware of any study, that corroborates our finding of decreased mortality risk from these causes 15 years after diagnosis. The results may have been driven by a combination of breast cancer and other cancers which share similar biological properties with breast and lung cancers, which some studies have shown CD patients to be protected from.[6,9] Understanding the mechanism of protection of these cancers could provide valuable information on the treatment of cancers in the general population.

The persistent increase in mortality risks in childhood-diagnosed cases more than 25 years after diagnosis is consistent with the earlier report on the cohort,[10] and requires further investigation. A longer follow-up of these cases will enable a better assessment of the risks from diseases that occur in later years in life but this will necessitate several additional decades of follow-up of this cohort for us to be able to estimate these risks with sufficient precision. Therefore, retrospectively collected data available from people with childhood-diagnosed CD in the distant past is likely to offer our best hope of realising this.

Mortality risks in the Lothian cohort over time

A summary of key findings from all mortality follow-up of the Lothian cohort is provided in Table 5.

Conclusion

Our study indicates that individuals with CD are at a modestly increased risk of mortality compared to the general population. The increased risk, primarily from malignant lymphomas are only temporary in adults and generally decline in the long-term. The increased risk of death from external causes in childhood-diagnosed cases we highlighted in our previous report persisted with this longer-term follow-up and should form the focus of further research.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Ethics Approval

Initial approval was obtained in 1978/1979, with permission from consultants in the Lothian region for the accessing of patient records and review of biopsies. In terms of the long-term follow-up of the study participants, members of the study team who had access to death certificate and other personally identifiable information supplied by National Records of Scotland signed a confidentiality agreement with National Records of Scotland. Other members of the study team only had access to anonymised patient data. The current study was approved by the Division of Epidemiology and Public Health Ethics Committee, University of Nottingham (9/Mar/2017).

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Informed Consent

Not required.

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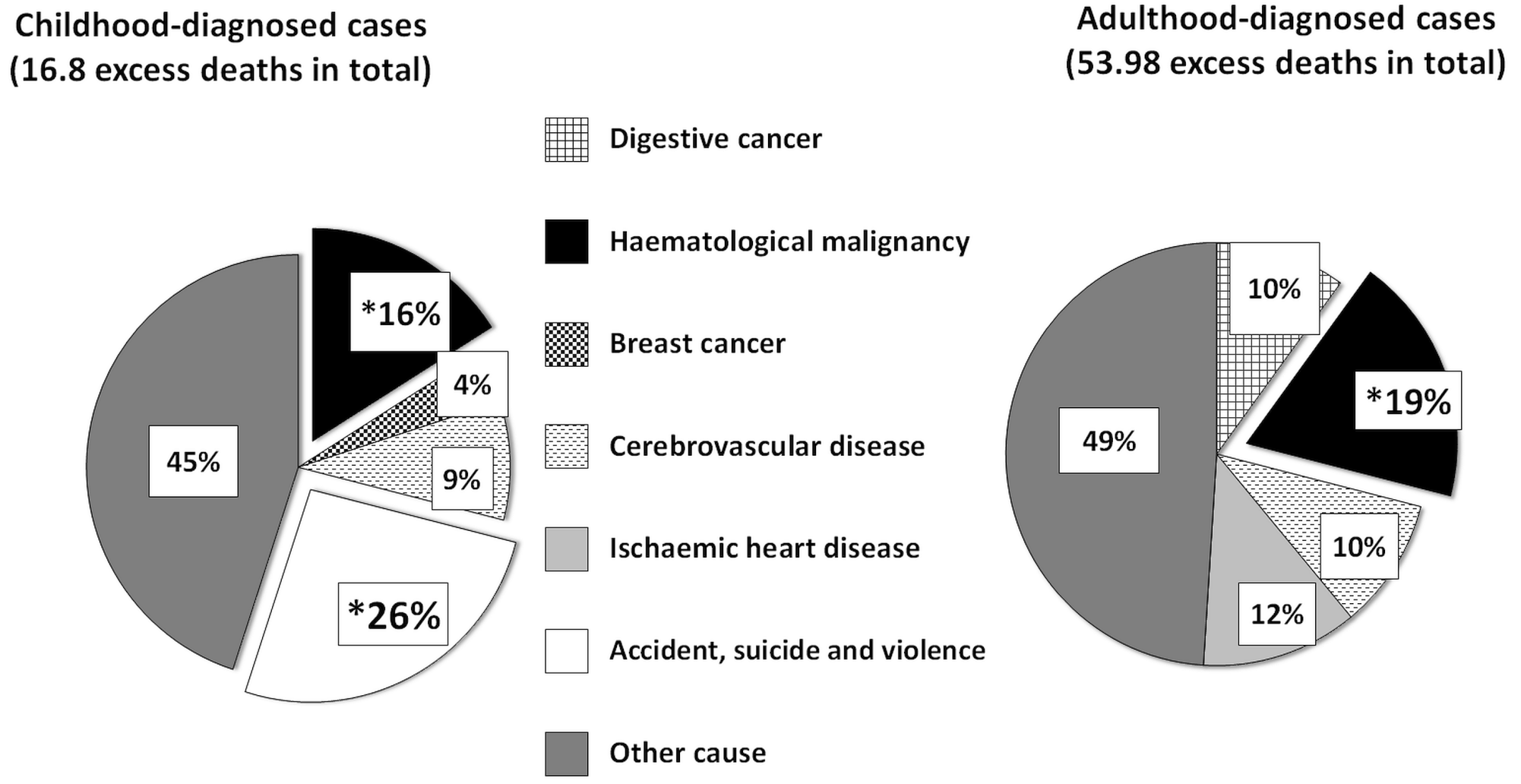
Figure legends

Figure 1: Proportion of excess deaths from analysed causes

Causes of death analysed in the cohort and the percentage of excess deaths from each of these causes, calculated as number of excess deaths from specific cause/total number of excess deaths x 100%. Definition of symbols used: *Significant number of excess deaths.

Figure 2: Average ages at death from specific causes

Average age of death among participants who died by cause of death.


Childhood-diagnosed cases
(16.8 excess deaths in total)
*16%
4%
9%
*26%
45%
Digestive cancer
Haematological malignancy
Breast cancer
Cerebrovascular disease
Ischaemic heart disease
Accident, suicide and violence
Other cause
Adulthood-diagnosed cases
(53.98 excess deaths in total)
10%
*19%
10%
12%
49%

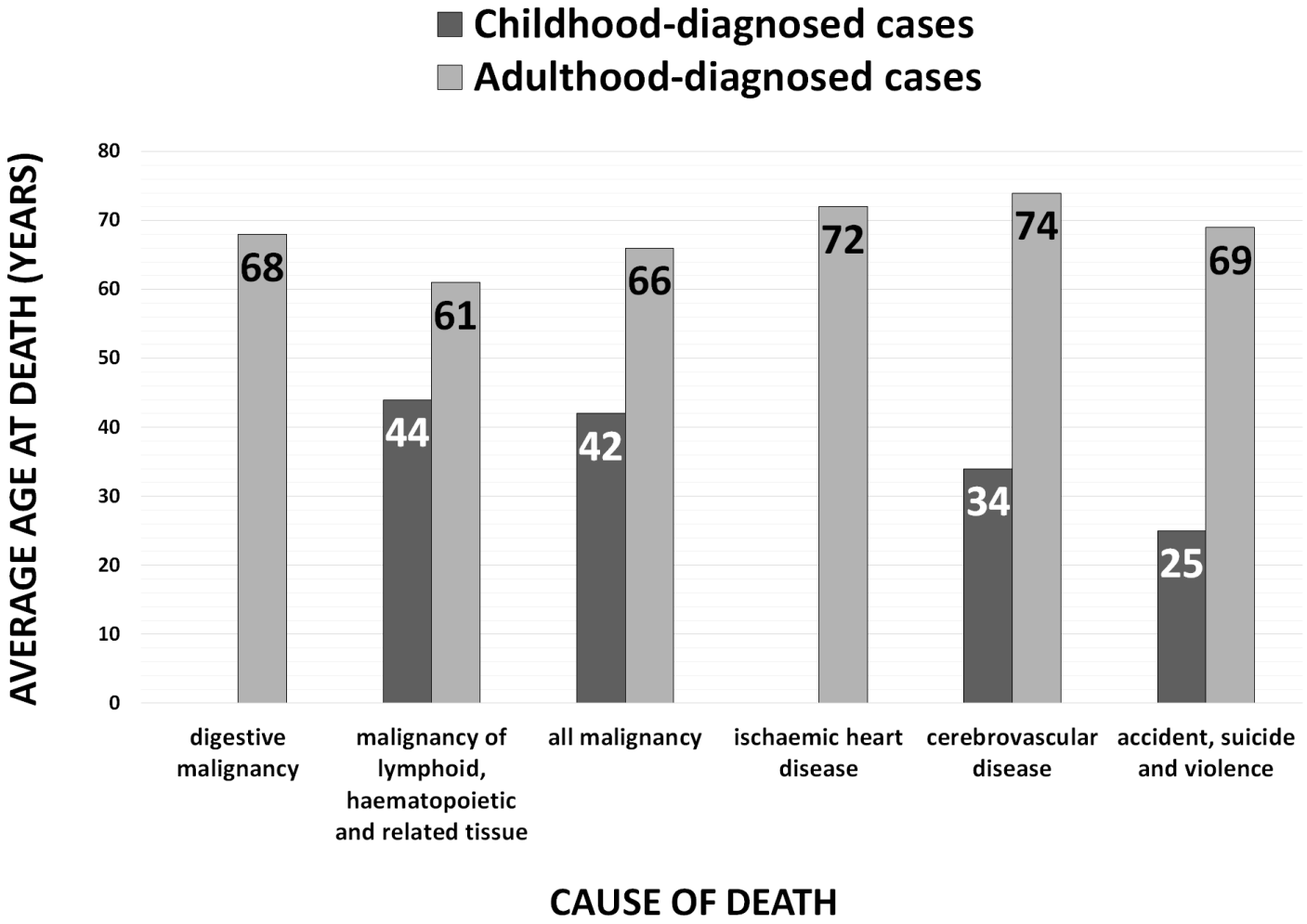

Childhood-diagnosed cases
Adulthood-diagnosed cases
AVERAGE AGE AT DEATH (YEARS)
80
70
60
50
40
30
20
10
0
68
61
44
66
42
72
74
34
69
25
digestive malignancy
malignancy of lymphoid, haematopoietic and related tissue
all malignancy
ischaemic heart disease
cerebrovascular disease
accident, suicide and violence
CAUSE OF DEATH

Table 1: Cohort characteristics

Characteristic	Age at diagnosis		Total
	< 15 years (N= 284)	≥ 15 years (N= 318)	(N=602)
Number of participants, n (%)			
Male	129 (45.42)	105 (33.02)	234 (38.87)
Female	155 (54.58)	213 (66.98)	368 (61.13)
Diagnosis, n (%)			
Confirmed	197 (69.37)	242 (76.10)	439 (72.92)
Probable	87 (30.63)	76 (23.90)	163 (27.08)
Age group at diagnosis (years), n (%)			
0-4	223 (78.52)	-	223 (37.04)
5-9	46 (16.20)	-	46 (7.64)
9-14	15 (5.28)	-	15 (2.49)
15-24	-	35 (11.01)	35 (5.81)
25-34	-	63(19.81)	63(10.47)
35-44	-	60 (18.87)	60 (9.97)
45-54	-	58 (18.24)	58 (9.63)
55-64	-	71 (22.33)	71 (11.79)
65-74	-	27 (8.49)	27 (4.49)
75-84	-	4 (1.26)	4 (0.66)

Age at diagnosis (years)			
Mean ± SD	2.97 ± 3.14	44.99 ± 15.49	25.17 ± 23.92
Median (IQR)	1.58 (0.91-4.21)	45.46 (31.75-58.50)	21.67 (1.67-46.82)
Year of diagnosis, n (%)			
Prior to 1970	135 (47.54)	93 (29.25)	228 (37.87)
1970-1983	149 (52.46)	225 (70.75)	374 (62.13)
Status at end of study[§], n (%)			
Dead	32 (11.27)	205 (64.47)	237 (39.37)
Alive	228 (80.28)	97 (30.50)	325 (53.99)
Censored[‡]	24 (8.44)	16 (5.03)	40 (6.64)
Follow-up time (person-years)			
Total	11500.79	7570.95	19071.74
Mean follow-up ± SD (per person)	40.50 ± 9.87	23.81 ± 15.46	31.68 ± 15.54

N, total number; n, number within category; SD, Standard deviation
[§]End of study, 26th October, 2016
[‡] Censored, lost to follow up through emigration

Table 2: Overall and cause-specific standardized mortality ratios by age at diagnosis

	Age at diagnosis								
	<15 years (N= 284)			≥15 years (N= 318)			Overall (N= 602)		
Cause of Death	Obs	Exp	SMR (95%CI)	Obs	Exp	SMR (95%CI)	Obs	Exp	SMR (95%CI)
All Cause	32	15.20	2.11 (1.44-2.97)†	205	151.02	1.36 (1.18-1.56)†	237	166.22	1.43 (1.25 - 1.62)†
All malignancy	**8**	**3.74**	2.14 (0.92-4.21)	50	41.57	1.20 (0.89-1.59)	58	45.32	1.28 (0.97-1.65)
Digestive cancer	<5	*	0.00 (0.00-4.53)	16	10.82	1.48 (0.85-2.40)	16	11.63	1.38 (0.79-2.23)
Malignant lymphoma	<5	*	8.03 (1.66-23)†	13	2.73	4.77 (2.54-8.16)†	16	3.1	5.16 (2.95-8.38)†
Breast Cancer	<5	*	2.69 (0.07-15)	<5	*	0.00 (0.00-2.76)	<5	*	0.59 (0.01-3.26)
Cerebrovascular disease	<5	*	4.42 (0.53-16)	25	19.43	1.29 (0.83-1.90)	27	19.88	1.36 (0.90-1.98)
Ischemic Heart Disease	<5	*	0.00 (0.00-2.86)	42	35.63	1.18 (0.85-1.59)	42	36.92	1.14 (0.82-1.54)
Accident, Suicide and Violence	7	2.67	2.62 (1.05-5.40)†	<5	*	0.90 (0.24-2.30)	11	7.13	1.54 (0.77-2.76)

SMR, Standardized mortality ratio; CI, Confidence Interval; Obs, Observed deaths; Exp, Expected deaths; N, Number of participants

* In order to minimize the risk of disclosure of the identity of individual study participants, we have adhered to the rule of thumb suggested by the Office for National Statistics of suppressing all cell frequencies where the observed cell frequency is less than 5 (“Review of the Dissemination of Health Statistics: Confidentiality Guidance: National Statistics; HMSO 2006”).
† $P<0.05$

Table 3: Overall standardised mortality ratios by time since diagnosis

	Age at diagnosis								
	< 15 years (N= 284)			≥ 15 years (N= 318)			Total population (N= 602)		
Time since diagnosis	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
first yr.	<5	*	0.00 (0.00, 9.39)	11	2.27	4.85 (2.42, 8.68)†	11	2.66	4.14 (2.06, 7.40)†
1-4 yrs.	<5	*	0.00 (0.00, 2.87)	27	10.74	2.51 (1.66, 3.66)†	27	12.03	2.24 (1.48, 3.27)†
5-9 yrs.	<5	*	11.22 (3.06, 29.00) †	26	17.5	1.49 (0.97, 2.18)	30	17.86	1.68 (1.13, 2.40)†
10-14 yrs.	<5	*	2.18 (0.06, 12.00)	29	18.57	1.56 (1.05, 2.24)†	30	19.03	1.58 (1.06, 2.25)†
15-24 yrs.	<5	*	1.31 (0.16, 4.73)	50	37.93	1.32 (0.98, 1.74)	52	39.45	1.32 (0.98, 1.72)
25+ yrs.	25	11.18	2.24 (1.45, 3.30) †	62	64.01	0.97 (0.74, 1.24)	87	75.19	1.16 (0.93, 1.43)

SMR, Standardised mortality ratio; CI, Confidence Interval; Obs, Observed deaths; Exp, Expected deaths; N, Number of participants; yr.(s), years

* In order to minimize the risk of disclosure of the identity of individual study participants, we have adhered to the rule of thumb suggested by the Office for National Statistics of suppressing all cell frequencies where the observed cell frequency is less than 5 ("Review of the Dissemination of Health Statistics: Confidentiality Guidance: National Statistics; HMSO 2006").

† $P<0.05$

Table 4: Cause-specific standardised mortality ratios by time since diagnosis

	Age at diagnosis						Total population		
	<15 years (N= 284)			≥15 years (N= 318)					
Period after diagnosis	Obs	Exp	SMR (95%CI)	Obs	Exp	SMR (95%CI)	Obs	Exp	SMR (95%CI)
All malignancy									
< 15 years	<5	*	0.00 (0.00-23)	34	13.47	2.53 (1.75-3.53) †	34	13.62	2.50 (1.73-3.49) †
≥15 years	8	3.58	2.23 (0.96-4.40)	16	28.11	0.57 (0.33-0.92)†	24	31.69	0.76 (0.49-1.13)
Digestive cancer									
< 15 years	<5	*	0.00 (0.00-780)	12	3.62	3.31 (1.71-5.79) †	12	3.63	3.31 (1.71-5.78) †
≥15 years	<5	*	0.00 (0.00-4.56)	<5	*	0.56 (0.15-1.42)	<5	*	0.50 (0.14-1.28)
Lymphatic and haematopoietic tissue malignancies									
< 15 years	<5	*	0.00 (0.00 -66)	10	0.77	13.04 (6.25-24) †	10	0.82	12.15 (5.83-22) †
≥15 years	<5	*	9.44 (1.95-28) †	<5	*	1.53 (0.32-4.48)	6	2.28	2.64 (0.97-5.74)
Cerebrovascular disease									
< 15 years	<5	*	0.00 (0.00-260)	8	6.20	1.29 (0.56-2.54)	8	6.21	1.29 (0.56-2.54)

≥15 years	<5	*	4.56 (0.55-16)	17	13.23	1.29 (0.75-2.06)	19	13.67	1.39 (0.84-2.17)
Ischemic heart disease									
< 15 years	<5	*	0.00 (0.00-3200)	13	14.18	0.92 (0.49-1.57)	13	14.18	0.92 (0.49-1.57)
≥15 years	<5	*	0.00 (0.00-2.86)	29	21.45	1.25 (0.91-1.94)	29	22.74	1.28 (0.85-1.83)
Accident, Suicide and Violence									
< 15 years	<5	*	4.89 (1.01-14) †	<5	*	0.58 (0.01-3.22)	<5	*	1.71 (0.47-4.37)
≥15 years	<5	*	1.95 (0.53-4.98)	<5	*	1.10 (0.23-3.21)	7	4.79	1.46 (0.59-3.01)

SMR, Standardised mortality ratio; CI, Confidence Interval; Obs, Observed deaths; Exp, Expected deaths; N, Number of participants
* In order to minimize the risk of disclosure of the identity of individual study participants, we have adhered to the rule of thumb suggested by the Office for National Statistics of suppressing all cell frequencies where the observed cell frequency is less than 5 ("Review of the Dissemination of Health Statistics: Confidentiality Guidance: National Statistics; HMSO 2006").
† $P<0.05$

Table 5: Summary of key findings from all follow-up of the Lothian cohort

Study	No. patients	Follow-up Time	Statistical Measure	Key Findings and comments
Logan et al.[11]	653	Date of clinical diagnosis of CD to June 30, 1986 (8,823 person years at risk, 115 deaths)	Overall and cause-specific SMRs	• Mortality overall was 1.9-fold for CD patients than that of the general population. The SMR was similar in men and women. • 10 deaths were directly attributable to CD, compared to 44 from malignancies (corresponding SMR of 3.0 fold for malignancies). • Only 4 deaths occurred in cases diagnosed in childhood (aged<15 years, total sample size of 292). All these deaths were from external causes. • Overall, there was a gradual decline in SMR with increased time from diagnosis. For 15+ years, there was an SMR of 1.2; however, this was based on just 11.64 expected deaths and was not statistically significant.
Solaymani-Dodaran et al.[10]	*602	**Date of clinical diagnosis of CD or January 1, 1970 (whichever was later) to December 31, 2004 (14,926 person-years, 195 deaths)	Overall and cause-specific SMRs	• All analyses in this paper were presented separately for child (0-14 years) and adult (15+ years) diagnosed cases. The overall raised mortality risk was higher in childhood-diagnosed cases (SMR=2.6) than for adult-diagnosed cases (SMR=1.6) • Among childhood-diagnosed cases there were 21 deaths, of which 7 were due to external causes (SMR=2.9) and 5 due to neoplasms (SMR=3.6). Both these increases were statistically significant. • Due to the increased follow-up, the expected number of deaths 15+ years following diagnosis had increased to 68.71. In childhood-diagnosed cases there was a raised risk 25+ years after diagnosis (SMR=3.5). For adult-diagnosed cases, no corresponding risk was observed but the confidence interval was wide (SMR=1.26; 95% 0.86 to 1.77).
Current study	602	**Date of clinical diagnosis of CD or January 1, 1970	Overall and Cause-	• In the current study, the overall increase in mortality was 2.1-fold in childhood-diagnosed cases and 1.4-fold in adult-diagnosed cases. The

	(whichever was later) to October 20, 2016 (19,071 person years, 237 deaths)	specific SMRs	decrease in overall SMRs compared with the earlier reports reflects the decline in risk following increased time from diagnosis. • There were 32 deaths among childhood-diagnosed cases, of which the number of deaths from malignancy increased to 8 and the number from external causes remained at 7. However, the expected number of deaths from external causes only increased slightly compared with the previous report (2.67 vs. 2.39) as childhood-diagnosed participants are now at an age where deaths attributed to this cause are less common. • The expected number of deaths 15+ years following diagnosis has increased to 114.64. Among adult-diagnosed cases, the absence of an increased risk beyond 25 years reported previously remains but the confidence interval around this value has tightened considerably (SMR=0.97; (95% 0.74 to 1.24). The equivalent SMR for childhood-diagnosed cases was reduced in this updated follow-up (SMR=2.2) as the impact of deaths from external causes on this overall figure has been weakened. • There was a reduced risk of death from any malignancy more than 15 years after diagnosis in adult-diagnosed CD patients. Previously Grainge et al.[17] reported no change in malignancy incidence in this group compared with the general population 15 years after diagnosis. In the previous mortality report, cause-specific results only stratified time since diagnosis into <5 years and 5+ years.

CD, Coeliac disease; SMR, Standardised mortality ratio; CI, Confidence Interval

* The sample size reported in the paper was 625, however, the authors excluded 23 deaths (out of 218 deaths that had occurred in the 625 CD cases) that occurred before 1 Jan 1970 from the main analysis reported in the paper.

**The survival analysis commenced in 1970 in the analysis presented in this paper, to circumvent the problem of survival bias and because population mortality estimates by cause were more reliable from this date onwards.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix: Causes of death analysed and their corresponding ICD codes

Disease Group	ICD Code		
	ICD 8	ICD 9	ICD 10
Neoplasms			
All malignant neoplasms	140-209	140-209	C00-97
Malignant neoplasm of lymphoid, haematopoietic and related tissue	200-209	200-209	C81-96
Malignant neoplasm of breast	174	174-175	C50
§Malignant neoplasm of digestive organs	150-151, 153-155, 157-158	150-151, 153-155, 157-159	C15-16, C18, C19-22, C25
Diseases of the circulatory system			
Ischaemic heart disease	410-414	410-414	I20-25
Cerebrovascular disease	430-438	430-438	I60-69
External causes of morbidity and mortality			
‡Accident	E800-929, E940-946	E800-929	V01-X59, Y85, Y86
Intentional self-harm (suicide)	E950-959	E950-959	X60-84, Y87.0
Assault (violence)	E960-969	E960-969	X85-Y09, Y87.1
Event of undetermined intent	E980-989	E980-989	Y10-Y34, Y87.2

ICD, International Classification of Diseases
§Excludes malignant neoplasms of small intestine, gall bladder, other and ill-defined digestive organs
‡Includes transport accidents, falls and poisoning