Mortality and Causes of Death in Patients With Osteogenesis Imperfecta: A Register-Based Nationwide Cohort Study

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ABSTRACT

Osteogenesis imperfecta (OI) is a hereditary connective tissue disease that causes frequent fractures. Little is known about causes of death and length of survival in OI. The objective of this work was to calculate the risk and cause of death, and the median survival time in patients with OI. This study was a Danish nationwide, population-based and register-based cohort study. We used National Patient Register data from 1977 until 2013 with complete long-term follow-up. Participants comprised all patients registered with the diagnosis of OI from 1977 until 2013, and a reference population matched five to one to the OI cohort. We calculated hazard ratios for all-cause mortality and subhazard ratios for cause-specific mortality in a comparison of the OI cohort and the reference population. We also calculated all-cause mortality hazard ratios for males, females, and age groups (0 to 17.99 years, 18.00 to 34.99 years, 35.00 to 54.99 years, 55.00 to 74.99 years, and >75 years). We identified 687 cases of OI (379 women) and included 3435 reference persons (1895 women). A total of 112 patients with OI and 257 persons in the reference population died during the observation period. The all-cause mortality hazard ratio between the OI cohort and the reference population was 2.90. The median survival time for males with OI was 72.4 years, compared to 81.9 in the reference population. The median survival time for females with OI was 77.4 years, compared to 84.5 years in the reference population. Patients with OI had a higher risk of death from respiratory diseases, gastrointestinal diseases, and trauma. We were limited by the lack of clinical information about phenotype and genotype of the included patients. Patients with OI had a higher mortality rate throughout their life compared to the general population. © 2016 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOGENESIS IMPERFECTA; CAUSES OF DEATH; REGISTER-BASED RESEARCH; COLLAGEN DEFECTS; RARE BONE DISORDERS

Introduction

Osteogenesis imperfecta (OI) is a hereditary disorder of the connective tissue,1,2 with a heterogeneous clinical presentation.3,4 Inheritance is either autosomal dominant (OI type I to V), due to mutations in the COL1A1 or COL1A2 genes in OI type I to IV, and IFITM5/BRIL mutations in OI type V, or autosomal recessive, largely due to mutations in genes involved in the posttranslational processing of collagen type 1.1 Severe cases are often caused by de novo mutations.5 OI is grouped according to clinical severity and inheritance by the Sillence classification (originally 1979, updated 2014).3,4 The mildest phenotype, type I, accounts for 71% of cases in Denmark, and the most severe phenotype, type II, for 12% of cases.6 The prevalence of OI at birth is 21.8 per 100.000 and the population prevalence is 10.6 per 100,000.6

A hallmark of OI is frequent fractures.7,8 Although the skeletal consequences of OI are well described, less is known about other aspects of the disease. A British study on causes of death in patients with OI reported 79 deaths between 1980 and 1995 in a cohort of 1297 patients identified via a survey and clinically diagnosed with OI.9 The authors identified respiratory tract infection as the most frequent cause of death in OI, and found a mean age at death of 6.2 years in the severe phenotypes and 63.5 years in the milder phenotypes.10 It is feasible that OI causes diseases to other organ systems, because collagen type 1—the
affected collagen in OI—is the most abundant collagen in the human body.\(^{10,11}\)

For governance, Denmark has a long-standing tradition for registering individual-level information on among others; Danish births, deaths, migration, and all contacts to the healthcare system. Since 1977 this information has been available for research.\(^{12}\) The National Patient Register (NPR), housed under the National Board of Health, have registered referral diagnosis (from the primary healthcare system to the hospital case system, or between hospital wards) and discharge diagnosis for all in hospital stays since 1977, and for all outpatient clinic and emergency room visits since 1995 and onward, on an individual level.\(^{12}\) The data entered into the registers is done, as mandatory by Danish law, on a hospital level, based on administrative data on patient’s municipality, identification of hospital wards, date and time of activity, and clinical data based on a physicians evaluation of the patient. NPR has coverage above 99% for all hospital contacts in Denmark. Moreover, the Danish healthcare system is with few minor exceptions—uniform, tax-financed, and covers all residents. The Danish Cause of Death register covers all deaths in Denmark since 1977.\(^{13}\) The Civil Registration System contains a unique personal identifier that allows for record linkage through out the Danish health and civil registers.\(^{14}\) Everyone born, or having an address in Denmark, have since 1968 been allocated a unique personal identifier, a CPR number. The Civil Registration System includes references to parents and spouses, making it possible to establish the family unit.\(^{14}\)

Study objectives

Our aim was to calculate the risk of death, identify the main cause of death, and calculate the median survival time in patients with OI compared to the general population. We hypothesized that patients with OI have increased all-cause mortality and thus reduced median survival time. Furthermore, we hypothesized that patients with OI have increased risk of death from respiratory and cardiovascular diseases. Better knowledge about life expectancy and the primary causes of death in patients with OI, will give insight into diseases that need attention in the care for patients with OI.

Subjects and Methods

Study design

The present study is a national population-based and register-based cohort study, including all registered patients with OI in the Danish health registries and a reference population of randomly selected persons, matched on age and gender to each OI patient (5:1) from the Danish Personal Registration System (the CPR register).

Data sources

Statistics Denmark Division of Research Services supplied anonymized data (Project reference number: 704542). The Statistics Denmark Division of Research Services administers the different health registers used in this study. Statistics Denmark is a state institution under the Ministry of Social Affairs and the Interior.

Study participants

Patients

All patients registered in NPR with International Classification of Diseases, Eighth Revision (ICD-8) (756.59) or ICD 10th revision (ICD-10) (Q78.0) diagnosis of OI between January 1, 1977, and December 31, 2012, were included in the study.

Reference population

Five persons, randomly selected from the Danish Civil Registration system (CPR), were matched to each patient with OI by gender, birth year, and birth month. Reference individuals could not be first-degree or second-degree relatives to patients with OI, nor could they later acquire an OI diagnosis.

Outcome, variables, and data sources

Information on primary cause of death, time, and place of death was extracted from the Danish Cause of Death Register. ICD-8 diagnoses (1977 to 1993) were transformed into ICD-10 chapter codes (I to XXII). If fewer than three persons had died from diseases within an ICD-10 chapter, death was recoded as being from “other causes” to maintain patient confidentiality.

We extracted comorbidity data from the NPR for inpatient stays, outpatient visits, and emergency visits and included both primary and supplementary diagnoses. This information was used to calculate the maximum Charlson comorbidity index (CCI) for each participant, as described using data from the NPR.\(^{15}\) Data on migration were extracted from the Danish Civil Registration system.

Exposure

Because OI is a congenital disease, we defined all identified patients to have been at risk since birth, even if their diagnosis was nominally made at a later stage. Patients born prior to 1977 had to be alive until at least January 1, 1977, to be able to be featured in the registries, some patients will have suffered from OI, but died prior to the observations period. The observations time ended at death, December 31, 2013, or when a person emigrated from, without returning to, Denmark.

Confounders

We corrected for comorbidity as a confounder of all-cause mortality. We did not control for major fractures, because this is a pathognomonic feature of OI and would thus be correcting for the exposure. Patients with OI are often treated with bisphosphonates. Bisphosphonate treatment reduces mortality in osteoporotic women.\(^{16}\) We cannot correct for this possible confounder, because we have no information about cumulative dosages in the two cohorts.

Because data were available from the Cause of Death register until December 31, 2013 (1 year more than the NPR data), we cannot rule out that a reference person could have been diagnosed with OI in the last year of observation, but find this unlikely.

We corrected for gender and calendar year of birth as confounders of life expectancy and risk of death. We did not correct for place of birth or last known residence (rural or urban), as this is not possible through the given data sources.

Statistical analysis

Data are presented descriptively using Kaplan-Meier survival estimate curves to show survival for both the OI and reference cohort. We present hazard ratio (HR) and subhazard ratios (SHRs) with 95% confidence intervals (CI) between the OI and reference cohorts, and mean ± SD or median (range) as appropriate.
A p value <0.05 was considered statistically significant. HRs and SHRs were significant when the 95% CI did not include 1.00. All statistical analyses were done using Stata 14.1 (Stata Corporation, Inc., College Station, TX, USA), with a user-written program for the Laplace regression.\(^\text{[17]}\)

The all-cause mortality hazard was not proportional over time between the two cohorts. Therefore, we stratified the data into five age groups, and applied a parametric exponential piecewise regression model. The age groups were ages 0 to 17.99 years, 18.00 to 34.99 years, 35.00 to 54.99 years, 55.00 to 74.99 years, or >75.00 years. We calculated the gender-specific all-cause mortality HR using the same model, but including either men or women.

To compare the all-cause mortality HR for the OI and reference cohorts by age group, we fitted a Cox proportional hazards regression model including only participants within each age group running the analysis for each age group alone.

We present the all-cause mortality HR for the total population and by age and gender, both unadjusted and adjusted for differences in CCI.

Between the OI cohort and the reference population SHRs for each primary cause of death were calculated using the Fine and Gray\(^\text{[18]}\) competing risk regression model for each ICD-10 chapter.

We estimated Schoenfeld residuals for the piecewise exponential regression models, and evaluated goodness of fit by visually estimating the Cox-Snell residuals after plotting the estimated cumulative hazard of the Cox-Snell residual to a Nelson-Aalen graph. The Cox proportional hazards models were tested using Stata’s built-in test of the proportional-hazards assumption (phtest). We tested the assumptions of the competing risk regression model by determining whether the covariates varied significantly over time.

We used Laplace-regression for censored data, as described by Bottai and Zhang,\(^\text{[17]}\) to determine the difference in median survival time between the OI and reference cohorts.

The CCI, place of death, and number of registered causes of death were summarized for the OI and reference cohorts, and the differences were tested using Pearson’s chi square test.

A sensitivity analysis was performed leaving all participants, only registered in the NPR with a referral diagnosis, and their matched counterparts in the reference population out of the analysis.

**Ethical considerations**

The study was approved by the Danish Data Protection Agency. All data were deidentified by the data provider. The study was not a clinical trial, and thus did not require ethics committee approval.

**Results**

We identified 687 patients (379 females, 55.2%) (25,615 person years at risk) with OI from the NPR. We identified 366 patients, born after 1977, of which 14 patients were only registered in the NPR with a referral diagnosis (ie, they had been referred from their general practitioner or from other hospitals (where the referral diagnosis [OI] had been registered in the NPR) without a discharge diagnosis being registered yet, in the NPR). In this period, the median annual incidence of OI was 15 (range, 5 to 24) per 100,000 births; 112 patients died during the observation period.

In the reference population, 3435 persons (1895 females) (132,131 person years at risk) were included in the study, and 1830 persons were born after 1977. During the observation period, 257 people died. There were significantly more non-European immigrants in the reference population (4.7%) than in the OI cohort (2%), \(p = 0.001\). Population characteristics are summarized in Table 1.

The two groups differed in the number of causes of death registered (\(p < 0.001\)), where 13.4% (\(n = 15\)) of the deceased in the OI cohort but 34.0% (\(n = 87\)) of the deceased in the reference population had only one cause of death registered, but not in the place of death. The overall CCI was significantly higher (\(p = 0.003\)) in the OI cohort, where more patients than controls had a CCI above 0. The age-specific comorbidity distributions are shown in Fig. 1.

Kaplan-Meier survival estimate curves for the total population from birth and for the subpopulation born after 1977 show a more rapid decline in survival in the OI cohort (Fig. 2). The median time of survival for males with OI was 72.4 years (95% CI, 68.8 to 77.7) versus 81.9 years (95% CI, 79.3 to 84.3) for men in the reference population (\(p < 0.001\)). The median survival time for females with OI was 77.4 years (95% CI, 74.6 to 79.8) versus 84.5 years (95% CI, 83.0 to 86.2) in the reference population (\(p < 0.001\)). Only truncated median survival time, with a maximum of 35 years, could be calculated for the subpopulation born after 1977. Only males with OI, born after 1977, showed attrition, with approximately 85% still alive at the end of the observation time.

The all-cause mortality HR in the OI and reference cohorts is summarized in Table 2. After correcting for differences in comorbidity and gender, we found an all-cause mortality HR of 2.9 (95% CI, 2.3 to 3.6) in patients with OI compared to the reference population. For women with OI, the HR was 2.4 (95% CI, 1.8 to 3.3) and for men with OI 3.7 (95% CI, 2.6 to 5.2), compared to the reference population. Unadjusted HR for all-cause mortality was 2.9 (95% CI, 2.3 to 3.6) for the total population, 2.5 (95% CI, 1.8 to 3.3) for women and 3.5 (95% CI, 2.5 to 5.0) for men.

**Table 1. Characteristics of Patients With Osteogenesis Imperfecta and the Reference Population, Total Person Time at Risk, and Median Survival Time From Kaplan-Meier Estimates**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osteogenesis imperfecta</th>
<th>Reference population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n)</td>
<td>687</td>
<td>3435</td>
</tr>
<tr>
<td>Females (n)</td>
<td>379</td>
<td>1895</td>
</tr>
<tr>
<td>Males (n)</td>
<td>308</td>
<td>1540</td>
</tr>
<tr>
<td>Total analysis time (years)</td>
<td>25615</td>
<td>132131</td>
</tr>
<tr>
<td>Person time at risk (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0–18</td>
<td>11464</td>
<td>58810</td>
</tr>
<tr>
<td>Age 18–35</td>
<td>7009</td>
<td>35783</td>
</tr>
<tr>
<td>Age 35–55</td>
<td>4863</td>
<td>24520</td>
</tr>
<tr>
<td>Age 55–75</td>
<td>2050</td>
<td>10985</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>229</td>
<td>2033</td>
</tr>
<tr>
<td>Median survival time (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>72.4 (95% CI, 68.8–77.7)</td>
<td>81.0 (95% CI, 79.3–84.3)</td>
</tr>
<tr>
<td>Females</td>
<td>77.4 (95% CI, 74.6–79.8)</td>
<td>84.5 (95% CI, 83.0–86.2)</td>
</tr>
</tbody>
</table>

\(p < 0.001\).
When comparing the two cohorts by age group, we found an increased all-cause mortality HR for the OI cohort using the comorbidity-adjusted and the unadjusted Cox proportional hazards model.

Age-specific all-cause mortality HR between the OI cohort and the reference population is summarized in Table 2. Primary causes of death are summarized in Table 3. OI (ICD-10 chapter 17) was reported as the primary cause of death in a total of 32 cases. The 15 patients with OI, who died before the age of 1 year, and the 19 who died before the age of 6 years, had OI as the primary cause of death. Cardiovascular diseases (ICD-10 chapter 9) and neoplasms (ICD-10 chapter 2) were the most frequently reported primary cause of death in both patients with OI and the reference population. SHRs were similar in the two groups, except that patients with OI had an increased SHR of 3.1 (95% CI, 1.4 to 6.9) for deaths caused by respiratory diseases (ICD-10 chapter 10, including pneumonia, influenza, and chronic obstructive pulmonary disease in acute exacerbation), an increased SHR of 4.2 (95% CI, 1.6 to 10.8) for deaths due to digestive illnesses (ICD-10 chapter 11, including gastrointestinal ulcerations and liver disease) and an increased SHR of 4.7 (95% CI, 1.4 to 16.3) for deaths due to external forces of morbidity and mortality (ICD-10 chapter 20, including death due to trauma and can be regarded as deaths associated with fractures).

**Discussion**

In this national register-based, cohort study we found the all-cause mortality among patients with OI was nearly three times that of an age- and gender-matched reference population. The median survival time in the OI cohort was 72.4 years for males (compared to 81.5 years in the reference population) and 77.4 for females (compared to 84.5 in the reference population). Apart from OI itself, the most frequently reported causes of death in both patients with OI and the reference population were cardiovascular disease and neoplasms. Patients with OI had an increased risk of death due to respiratory diseases, gastrointestinal diseases, and trauma compared to the reference population.

The relatively high median survival time, in our study, is influenced by the survival bias introduced into the data, because patients had to be alive at least until 1977, or born thereafter, to be featured in the registers. We found an increased risk of death during the early years of life for patients with OI and must assume that this risk was equally increased for participants born before 1977.

No previous studies have compared the risk of death for patients with OI and a reference population representative of the general population. We used the Danish NPR to identify cases of OI. There is no information about the specificity, sensitivity, positive predictive value, or negative predictive value of having an ICD-8 or ICD-10 diagnosis for OI in the register and actually having OI. The overall positive predictive value of any diagnosis in the NPR is above 95%. We cannot rule out misclassification of the patients, but the number of identified cases fits the estimated number of expected cases based on the population prevalence of 10.6 out of 100,000 persons, reported by Andersen and Hauge in 1989. The number of contacts with a given diagnosis in the NPR will increase the likelihood of a patient suffering from the given diagnosis. However the OI cohort was open, and participants entered (diagnosed at any point in life) and left (died or migrated) the cohort during the entire observation period, and therefore the number of registered contacts, with an OI diagnosis, in the NPR is not a good estimate of the likelihood of the diagnosis. When performing the sensitivity analysis, the HR did not change significantly. This further increases the likelihood that the participants in our study were indeed patients with OI.

All our data for both the patient cohort and the reference population were extracted from the same registers. Our patient cohort did have a higher risk of death due to respiratory diseases than the reference population, but only 10 of 112 (8.9% of total

![Fig. 1. Distribution of CCI by age in the reference population and in the patient cohort with OI. The distribution of CCI scores per decade of the participant’s maximum age at the end of the observational period. CCI = Charlson comorbidity index; OI = osteogenesis imperfecta.](image-url)
deaths) deaths were due to this cause. This differs from the 57% of patients who died from respiratory tract infections reported by McAllion and Paterson. One explanation could be that we only used information available in the Danish Cause of Death register that relies on death certificates, whereas McAllion and Paterson also included information from postmortem reports, relatives, and the OI patient organization. Their methods are likely to be more prone to recall bias than our register-based approach. Furthermore the McAllion and Paterson study was not population based, and included 38 out of 79 patients with type III OI, adding to 48% of the participants. The remaining patients were clinically diagnosed with type IV or type I OI. Thus, most of the patients had moderate to severe phenotypes. In contrast, we would expect that a total of 24% of our cohort had a moderate or severe phenotype. Thus, the differences in case mix between the present study and the McAllion and Paterson study were significant.

![Kaplan-Meier survival curves for males and females in the patient cohort with OI and the reference population, for total population (upper graphs) and for those born after 1977 (lower graphs). Patients with OI had higher risk of early mortality, especially for males. OI = osteogenesis imperfecta.](image)

**Table 2. All-Cause Mortality for Patients With OI and the Reference Population, Followed From Birth and Including All Individuals**

<table>
<thead>
<tr>
<th></th>
<th>Initial patients with OI (n)</th>
<th>Deaths in OI cohort n (%)</th>
<th>Reference population (n)</th>
<th>Deaths in reference population n (%)</th>
<th>HR 95% CI</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>687</td>
<td>112 (16.3)</td>
<td>3435</td>
<td>257 (7.5)</td>
<td>2.9</td>
<td><strong>2.3–3.6</strong></td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0–18 years</td>
<td>687</td>
<td>26 (3.9)</td>
<td>3435</td>
<td>3435</td>
<td>66.1</td>
<td><strong>15.7–278.7</strong></td>
</tr>
<tr>
<td>Age 18–35 years</td>
<td>486</td>
<td>6 (1.2)</td>
<td>2520</td>
<td>2520</td>
<td>15.3</td>
<td><strong>3.1–75.9</strong></td>
</tr>
<tr>
<td>Age 35–55 years</td>
<td>326</td>
<td>18 (5.0)</td>
<td>1628</td>
<td>1628</td>
<td>3.0</td>
<td><strong>1.7–5.5</strong></td>
</tr>
<tr>
<td>Age 55–75 years</td>
<td>163</td>
<td>39 (23.9)</td>
<td>837</td>
<td>837</td>
<td>2.4</td>
<td><strong>1.7–3.5</strong></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>38</td>
<td>23 (60.5)</td>
<td>135</td>
<td>135</td>
<td>2.4</td>
<td><strong>1.3–3.2</strong></td>
</tr>
<tr>
<td><strong>Total female population</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>379</td>
<td>61 (16.1)</td>
<td>1895</td>
<td>1895</td>
<td>2.5</td>
<td><strong>1.8–3.3</strong></td>
</tr>
<tr>
<td><strong>Total male population</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>308</td>
<td>51 (16.6)</td>
<td>1540</td>
<td>1540</td>
<td>3.5</td>
<td><strong>2.5–5.0</strong></td>
</tr>
</tbody>
</table>

Significant 95% CI values (not including 1.00) are indicated in bold.

OI = osteogenesis imperfecta; HR = hazard ratio; CCI = Charlson comorbidity index.

<sup>*HR was calculated using piecewise exponential regression for the total population, and for subgroups including only women or men.</sup>

<sup>**For each age group, the HR was calculated using a Cox proportional hazards regression model, including only the individuals within each age group.</sup>

<sup>***Not disclosed to maintain patient confidentiality due to low number of cases.</sup>
study(9) may explain the difference in the primary causes of death.

Earlier studies have shown a tendency for common causes of death (eg, myocardial infarction) to be overdiagnosed, and rare causes (eg, cerebral hemorrhage and intestinal thrombosis) to be underdiagnosed in the Danish Cause of Death Register. Possible misclassification or discontinuity in the Danish Causes of Death Register of the registrations of underlying causes of death has no impact on the results of the all-cause mortality.(13)

Insufficient data in the national register prevented us from grouping patients according to the Sillence classification, and no information on patient genotype was available either. We found, however, that 24 of the OI patients followed from birth (born after 1977) had died. In 19 of these, OI was reported as the primary cause of death and 15 of the patients died shortly after birth. The mean age at death has been reported to be 15 of the patients died shortly after birth, in our study, was evenly distributed across the observation time (1977 to 2013). This suggests that early patient death may be due to a more severe phenotype, where the advances in pediatric and neonatal care did not alter the outcome. Due to the low number of yearly events, we cannot disclose the number of deaths per year for the patients who die prior to turning 10 years old and live past the first weeks after birth. But seven patients died from 1977 to 1994 and three patients died from 1995 to 2013, suggesting an effect of the institution of bisphosphonates and a multidisciplinary team approach in the treatment of the most severe nonlethal OI phenotypes.

We adjusted for between-group differences in CCI, because higher CCI is a predictor of worse outcome or earlier death.(21) However, the all-cause mortality HR, whether adjusted for comorbidity or not, was similar between the two populations, indicating that the diagnosed comorbidity in the patients with OI was not a strong predictor of death in the OI cohort. It is more likely for patients with OI to receive hospital care than for the general population, who may contact their general practitioner (GP) and thus not have their disease recorded in the NPR. The difference in CCI between the two groups could be a result of surveillance bias and Berkson’s bias in the OI cohort.

The OI patients had an increased risk of death due to gastrointestinal disease compared to the reference population. One explanation could be increased use of nonsteroid anti-inflammatory drugs in the patient cohort, as pain is a hallmark of OI. Mild analgesics (paracetamol and ibuprofen) are sold over the counter in Denmark and are thus not registered in prescription databases. Concerns have been raised regarding colon, gastric, and esophageal cancers in patients with OI, even though there have been reports of both higher and lower risks.(22) Available register data, however, do not allow us to look at any additional granulation in the gastrointestinal (GI) diseases that caused death. We did, however, not see any increased risk of death due to cancers in the OI cohort.

Mortality due to cardiovascular diseases was similar among OI patients and the reference population. We cannot rule out that a lack of power, due to relatively few events, caused a type II error, thus masking a higher risk of cardiovascular disease in patients with OI.

The lack of detailed information on genotype, phenotype, and on what basis the OI diagnosis was made in the national study. (9)
The study had coverage above 99% in a country with a uniform tax-financed healthcare system, and have complete long-term follow-up further strengthening the results.

We conclude that patients with OI have increased all-cause mortality rates, with a higher risk of death due to respiratory diseases, gastrointestinal diseases, and trauma (bone fractures). The shorter survival of patients with OI may be due to increased risk of neonatal death associated with more severe OI phenotypes, and to increased risk of death throughout life. Further studies should explore underlying causes of death and the association between genotype/phenotype and risk of death.

**Disclosures**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work; these forms are available online in the Supporting Information. LF received speaker fees from Genzyme, a Sanofi Company, and AstraZeneca; JH received speaker fee from Amgen; BL serves on advisory boards for Merck, Eli Lilly, Amgen, and UCB and has received research funding from Novo Nordisk, Eli Lilly, and Orkla. APH serves on advisory boards for Merck, Eli Lilly, Amgen, and Shire and she has received research funding from Eli Lilly, speaker fee from Eli Lilly, GSK, Genzyme, Amgen; BA reports grants from Novartis (current), personal fees from Nycomed/Takeda/past, within 36 mo), personal fees from Merck/past, within 36 mo), personal fees from Amgen/past, within 36 mo), grants from UCB/current), outside the submitted work; KB reports other from Merck, Sharpe, Dohme, other from Amgen, other from Novartis, other from NPS, outside the submitted work.

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**References**