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Early deaths from ischaemic heart disease in childhood onset type 1 diabetes

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What is known about the topic?

- There is increased risk of death due to ischaemic heart disease (IHD) in the type 1 diabetes population
- Previous mortality studies have included no clinical validation of death certification data

What this study adds

- Results show that IHD deaths begin to emerge in young adulthood for individuals diagnosed with type 1 diabetes as children
- Death certification analysis without clinical validation can provide underestimation of IHD deaths

Abstract

Aims

The risk of ischaemic heart disease (IHD) death in early type 1 diabetes onset was assessed using death certification data.

Methods

The Yorkshire Register of type 1 Diabetes in Children and Young People (YRDCYP) was linked to clinically validated death certification data for those diagnosed under 15 years. Standardised mortality ratios (SMRs) were calculated using the England and Wales population and IHD death rates between 1978 to 2014 by 5-year age group and sex.

Results

The cohort included 4,382 individuals (83,097 person-years). Of 156 deaths, 9 were classed as IHD deaths before clinical validation. After clinical validation, 14 IHD deaths were classified, with an SMR of 13.8 (95% CI 8.2 – 23.3) and median age at death of 35.1 years (range 21.9 to 47.9 years).

Conclusions

There is an early emergence of death from IHD in early onset type 1 diabetes. Under-ascertainment of IHD deaths was present without clinical validation of death certification.

Keywords

Type 1 diabetes, mortality, ischaemic heart disease

Abbreviations

IHD - Ischaemic Heart Disease
NHS – National Health Service
ONS – Office for National Statistics
SMR – Standardised Mortality Ratio
YRDCYP – Yorkshire Register of Diabetes in Children and Young People

YRHA – Yorkshire Regional Health Authority

Introduction

In England and Wales, there were around 60,818 deaths due to ischaemic heart disease (IHD) registered in 2015. Most of these deaths (68%) occurred in older adults aged 75 years and over. In young adults, deaths due to IHD are rare with only 0.2% of all deaths attributable to IHD in under 25 year olds (1).

Although intensive insulin treatment has shown to reduce the development of cardiovascular disease, mortality risk from IHD is still increased within the type 1 diabetes mellitus population compared to the general population, where longer duration of diabetes is associated with increased risk of cardiovascular death (2). This would imply that children diagnosed with type 1 diabetes mellitus would have an increased risk of IHD death at younger ages due to exposure of longer diabetes duration.

The aim of this study was to examine the risk of IHD death in early type 1 diabetes onset compared with the general population and by time since type 1 diabetes diagnosis. Data from a population-based register linked with clinically validated death certification data were assessed.

Methods

Population-based register data

The Yorkshire Register of Diabetes in Children and Young People (YRDCYP) collected data from all secondary care units within the former Yorkshire Health Authority Region (YRHA), UK, for individuals diagnosed with type 1 diabetes at under 15 years of age (early onset) between 1978 and 2013. The YRDCYP also includes data from West Yorkshire (a metropolitan county within the YRHA and includes 57% of the total population within the YRHA) on individuals diagnosed with type 1 diabetes between 15 to 29 years of age (late onset) between 1991 and 2013. Due to limited follow-up time for the late onset group and differences in geographical coverage between the age groups, only individuals in the early onset group were included.

Death certification data

Each individual YRDCYP registration was linked to Office for National Statistics (ONS) death certification data up to 31st December 2015 via National Health Service (NHS) number (a personal identifier used for individuals in England and Wales), date of birth, gender and name. These data included text information from original death certificates, alongside the International Classification of Diseases (ICD) code for underlying cause of death. Underlying cause of death was defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" (3).

Death due to IHD within England and Wales was classified by ICD-9 codes 410 – 414 for deaths occurring between 1978 and 2000 and ICD-10 codes I20 – I25 from 2001. These codes were validated against the text information by a specialist clinician (HJB). If it was determined that type 1 diabetes initiated the IHD death, these deaths were identified as having an underlying cause of type 1 diabetes with IHD. Data on all other deaths were also clinically re-examined by HJB to identify any other deaths with an underlying cause of death of type 1 diabetes with IHD.

Statistical analysis

IHD mortality within the YRDCYP was compared with the population of England and Wales by calculating standardised mortality ratios (SMRs). SMRs determined the ratio between the observed and the expected number of IHD deaths in the YRDCYP. The expected numbers of deaths were calculated by applying England and Wales IHD mortality rates to the YRDCYP cohort using population and mortality data between 1978 and 2014 which were available by 5-year age group and sex. The Poisson distribution was used to calculate the SMRs' 95% confidence intervals.

All analyses were performed using STATA 13.

Results

The cohort included 4,382 individuals (51.9% male and 48.1% female), with 83,097 person-years of follow-up. Median follow-up time per individual was 17.7 years

(range 1.5 to 38 years). In total, there were 156 deaths. The median age of death was 28.2 years (range 6.5 to 48.9 years).

Prior to validation of death certificates, nine deaths were classed as IHD by ICD-9 codes 410 – 414 and ICD-10 codes I20 – I25. After validation of death certification data, there were 14 deaths classified with an underlying cause of death due to type 1 diabetes with IHD. The additional deaths were originally coded with diabetes-related ICD codes.

Deaths began to emerge noticeably in the 20 to 24 year age group, with the youngest death at 21.9 years. This individual had 12 years of type 1 diabetes duration. The median age at death was 35.1 years (range 21.9 to 47.9 years).

The SMR was 13.8 (95% CI 8.2 – 23.4) and was significantly higher than the general population. The SMRs for time since diagnosis were highest between 10 to 19 years at 116.1 (95% CI 48.3 – 278.9) (figure 1).

Discussion

This study showed a 13.8-fold excess in IHD deaths in individuals with early onset type 1 diabetes compared with the general population. Deaths began to emerge in the early 20s.

In addition, as there is no ICD code for underlying cause of death of type 1 diabetes with IHD, deaths were originally classified either under a diabetes or an IHD code. Without validation of underlying cause of death, almost half of IHD deaths within this cohort would not have been captured. This suggests that any future research into type 1 diabetes deaths with IHD needs objective and expert scrutiny of death certification data to avoid underestimation.

Early death observed in early onset could be due to longer duration of diabetes, allowing for risk factors of IHD death to develop at an earlier age. This study found deaths began to emerge significantly after 10 years duration. This was similar to results found in the Allegheny County (Pennsylvania, USA) cohort (2), suggesting

that risk factors for cardiovascular dysfunction may be appearing during adolescence and young adulthood. Margeirsdottir et al (4) found that in a cohort of paediatric patients in Norway (mean age of 13.1 years and mean diabetes duration time of 5.7 years), 86% had at least one cardiovascular risk factor. These risk factors included high HbA1c, blood pressure, body mass index, cholesterol levels (high LDL, low HDL), persistent microalbuminuria and smoking. Forty-five per cent had two or more risk factors, 15% had three or more and 2% had four or more. Unfortunately, no clinical data were available in this current study to assess the impact of additional risk factors on IHD mortality risk.

A major limitation to this study was the exclusion of individuals with late onset type 1 diabetes. Although the YRDCYP includes individuals with late onset type 1 diabetes, this group could not be included in this analysis due to data collection differences from the early onset group. This contributed to a small number of IHD deaths (fewer than five), where interpretation of results was not possible. Comparison with a late onset group would be useful in determining whether early IHD death was a specific characteristic in the early onset group. Higher IHD mortality in an early onset age group compared to late onset was observed by Harjutsalo et al (5), where the SMR calculated for the early onset group was five times the SMR for the late onset group for deaths occurring under the age of 40 years (26.9 (95% CI 19.8 – 35.8) vs. 4.6 (95% CI 2.8 – 7)). They also reported higher risk of death for women in the late onset group. Due to small numbers, comparisons between sexes could not be analysed in this study.

Despite the small number of deaths in this study, the excess of IHD deaths emerging in young adults from early type 1 diabetes onset is concerning. The increasing evidence for cardiovascular risk factors developing during adolescence suggests that a targeted approach in care for early type 1 diabetes onset is needed to reduce the risk of IHD death in young adulthood.

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Duality of interest
There are no conflicts of interest to declare by the authors.

Contribution Statement
T.C.E-C. analysed the data and wrote the manuscript. H.J.B. provided clinical validation of death certification data and reviewed the manuscript. R.G.F and R.C.P. contributed to the discussion and reviewed/edited the manuscript.

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