

Acute complications and drug-misuse are important causes of death for children and young adults with Type 1 diabetes: results from the Yorkshire Register of Diabetes in Children and Young People.

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ABSTRACT

Objective: To examine mortality rates and causes of death amongst subjects diagnosed with T1D aged 0-29 years.

Research Design And Methods: T1D subjects from a population-based Register in Yorkshire, UK diagnosed between 1978-2004 were linked to the UK National Health Service Central Register for death notifications. Deaths were coded using ICD-9 (1979-2000) and ICD-10 (2001-2005). Standardized mortality ratios (SMR) were calculated using expected numbers of deaths from UK mortality rates by cause of death and age at diagnosis.

Results: 4246 individuals were followed-up providing 50,471 person years of follow-up. Mean follow-up length was 12.8 years for 0-14 and 8.3 years for 15-29 year olds. Overall 108 patients died, of whom 77 (71%) were male. 74 (1.7/1000 pyrs) deaths occurred in the 0-14s and 34 (4.6/1000 pyrs) in the 15-29 year olds. The SMR was 4.7 (95% CI 3.8-5.6) overall, similar for males and females, but higher for 15-29s (6.2; 4.3-8.6) compared to 0-14s (4.2; 3.3-5.3). The SMR rose with increasing disease duration. 47/108 deaths (44%) occurred from diabetes complications: 32 acute and 15 chronic. 22% (n=24) of deaths were attributed to accidents or violence (SMR 2.1; 95% CI 1.4-3.2), including 6 suicides. 16% of all deaths were related to drug misuse (including insulin but excluding tobacco and alcohol): SMR=6.4 (3.7-10.2).

Conclusions: T1D subjects diagnosed under 30 years had a 4.7-fold excess mortality risk. Nearly half the deaths were due to acute or chronic complications of diabetes. Drug misuse-related deaths may be an emerging trend in this population warranting further investigation.

In recent years, there has been a trend towards more intensive insulin regimens using multiple daily injections and pump therapy for children and young adults with Type 1 diabetes (T1D) (1-3). This trend should improve long-term glucose control, avoid the chronic complications of diabetes and in theory reduce mortality rates in subjects with T1D.

The literature contains a number of studies focusing on mortality among those who have developed T1D in childhood (4-15), but few data exist on risk and causes of death in those diagnosed under 30 years of age. One UK analysis of 0-29 year olds (7) demonstrated an excess mortality risk ranging from 2-6 times that of the general population for individuals up to age 40. Older teenagers and young adults constitute a transitional group between children and adults and often fall out of healthcare provision. They have also been neglected in research studies and given differences in the delivery of care amongst 15-29 year olds, mortality risks may differ from 0-14 year olds.

Generation of robust mortality data relies on comprehensive and accurate information about subjects who have diabetes and their date and cause of death. In order to examine mortality trends, we were able to utilize a population-based diabetes Register in the north of England linked to the national population database and thereby obtained death notifications and details. The aim of the study was to obtain information on the causes of death in young people diagnosed under 30 years of age, thereby informing clinicians about how better to manage their patients prospectively.

RESEARCH DESIGN AND METHODS

Data Collection. Patient details were extracted from the Yorkshire Register of Diabetes in Children and Young People, a population-based database with ascertainment

rates exceeding 98% (16). The Register is unique in England by capturing clinical and demographic data on all 0-29 year olds in the geographical area of the former Yorkshire Regional Health Authority. The Yorkshire Region (Figure 1) covers an area of 12,000 km² and includes a total population of 3.5 million, 1.4 million aged 0-29 years.

Information was obtained on subjects who were newly diagnosed under 15 years of age between 1978-2004 in the whole of the Yorkshire Region and between 1991-2004 for cases diagnosed under 30 years of age in West Yorkshire only. The county of West Yorkshire comprises approximately 60% of the population of the Yorkshire Region. Diagnosis of T1D was based not only on insulin treatment from diagnosis but also using complete clinical information contained within the patient's medical records according to standard criteria (17). Patients whose diagnosis was uncertain were re-assessed by local clinical experts (HJB and Dr Fiona Campbell, Consultant Paediatrician, Leeds UK).

Death notifications and Coding. Each patient's vital status (alive/dead) was obtained by linking individuals from the Yorkshire Register to the National Health Service Central Register (NHSCR) using their NHS number. The NHSCR retains information on the current location of every individual in the UK, their vital status and whether they have emigrated. Notifications from the NHSCR were received up to September 2006 to ensure all patients were followed-up until 31st December 2005.

Details of those patients who had died were obtained from the Office for National Statistics (ONS) General Registry Office, who provided us with copies of the death certificate. The underlying cause of death was coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) for those dying between 1979-2000

and the Tenth Revision (ICD-10) for those dying between 2001-2005 (18). Quality and consistency of mortality data are maintained by ONS through automation of the coding process, a procedure established in 1993 (19). Bridge coding (19) was used to align ICD-9 causes of death with ICD-10 causes of death. Full death certificate information was used to re-allocate cause of death for those where the underlying cause was reported as 'diabetes' but whose death was related to specified complications, e.g. chronic renal failure, cardiovascular complications. In instances where the cause of death was unknown/uncertain, the coroner would ask for an autopsy and hold an inquest, irrespective of age (20); findings from these investigations and any other available documentation were also used to assign the underlying cause of death.

A particular focus of the study examined the number of deaths caused by drug misuse, as we had noticed a number of certifications mentioning this. Drug-related deaths were defined according to the standard classification used by the ONS (20-21) based on the following codes: Mental and behavioural disorders due to drug use (excluding alcohol and tobacco), insulin poisoning, intentional self-poisoning/poisoning by drugs, and accidental poisoning by drugs (21). Careful scrutiny of the death certificate was made to ensure the cause was assigned correctly for each subject in conjunction with toxicology or coroner reports, since almost all drug-related deaths had an inquest.

Statistical analysis. A 'person years at risk' analysis was used to compare mortality in the cohort (by sex, current age, time since diagnosis and calendar period) with that in the background UK population (22). Cause-specific UK mortality rates were extracted by sex, five year calendar period and five year age-group. These were used to calculate numbers of deaths expected in the cohort

based on the accrued person-years within each sex/period/age group were it to have experienced UK mortality rates and standardized mortality ratios (SMRs) were obtained as the ratio of observed to expected numbers of deaths. Confidence intervals (CI) for SMRs were derived assuming a Poisson distribution (23).

RESULTS

3,349 and 897 patients diagnosed aged 0-14 years and 15-29 years respectively (Table 1) were included and provided 50,471 person years of follow-up. Mean length of follow-up was 12.8 years (range 0.9-27.9) for the younger and 8.3 years (0.3-14.9) for the older group at diagnosis. Only ten patients (0.2%) were untraceable.

Overall, 108 (2.5%) patients had died, of whom 77 (71%) were male. 74 (1.7 per 1000 person years) deaths occurred in the younger diagnosed group and 34 (4.6 per 1000 person years) in the older diagnosis group (Table 1). The SMR was 4.7 (95% CI 3.8-5.6) overall and non-significantly higher for 15-29 year olds (6.2; 4.3-8.6) compared to children (4.2; 3.3-5.3). Risk of death was similar for males and females diagnosed under 15 (Table 1) but non-significantly higher for females (7.5; 3.4-14.3) compared to males (5.8; 3.8-8.6) aged 15-29 at diagnosis.

Risk of death was significantly elevated in all attained age groups and every time point since diagnosis (Table 2), although no significant linear relationship was observed between increasing disease duration and mortality using Poisson regression. SMRs increased steadily by calendar period of diagnosis (Table 2), exhibiting a five-fold increased risk of death since 1995.

Cause-specific SMRs showed that risk of death was significantly higher for all causes compared to the background population, except cancer and stroke (Table 3). Almost half (44%, n=47) of all deaths were related to complications of diabetes (including heart

disease, stroke or renal disease). Mortality was high for deaths attributed to respiratory (SMR 5.6; 1.8-13.0) and mental disorders (7.5; 3.4-14.3). A further fifth of fatalities (n=24) were related to accidents or violence (2.1; 1.4-3.2), 6 of which were confirmed suicides (2.5; 0.9-5.4). The excess risk of death due to accidents and violence was non-significantly higher for females (3.4; 1.4-6.9) compared to males (1.9; 1.1-3.0). There were 19 deaths of 'other' (n=13) or 'unknown' (n=6) causes: SMR=3.3 (2.0-5.1).

32 deaths were due to acute and 15 attributed to chronic complications. Acute complications comprised 14 from diabetic ketoacidosis (DKA), 2 from hyperglycemia (where the death certificate did not mention DKA), 8 from hypoglycemia and 8 unspecified cases. Males constituted 25/32 (78%) deaths from acute complications. Deaths from acute complications occurred evenly throughout the cohort by attained age. Deaths associated with chronic complications included: 6 from ischemic heart disease, 1 stroke, and 8 renal (6 of which were in females).

16% of all deaths (17/108) were related to drug misuse, SMR=6.4 (3.7-10.2). In this group, females (n=5) had a non-significantly higher SMR (8.8; 2.9-20.6) compared to males (5.7; 2.9-10.0). The majority (71%) of these deaths occurred between the ages of 20-29. Six of these 17 deaths were associated with insulin overdose: 3 confirmed suicides and 3 possible suicides. The remaining 11 deaths were accounted for by abuse of prescription drugs (analgesics, n=3) and non-prescription drugs (n=8, mainly opiates).

DISCUSSION

The Yorkshire Register data has enabled an investigation of mortality rates on over 4200 subjects diagnosed continuously from 0-29 years of age, comprising one of the largest and most recent population-based series in this age range. The Register is 98% complete

in terms of ascertainment and subjects were linked to a National Health Service register to provide a virtually complete level (99.8%) of tracing, with only 10 individuals lost to follow-up. This produced notifications of 108 deaths and detailed information on the precise cause of death.

Since publication of the DCCT study in 1993 (24), tight glycaemic control has been an emphasis of the treatment for patients with T1D. This should lead to a decrease in the occurrence of chronic complications of diabetes and thereby, deaths from them. In addition, intensive insulin treatment and enhanced patient education, with frequent out-patient supervision and close contact with a diabetes specialist nurse should theoretically avoid or reduce the occurrence of the acute diabetic complications of ketoacidosis and severe hypoglycemia. Therefore, it is of interest to examine the causes and rates of death in a cohort of subjects diagnosed in childhood and young adult life. Previously, studies have focused on mortality of subjects diagnosed in childhood (4-15), but more recently those diagnosed in early adult life have been examined. For example, one study noted that young adults with T1D had a raised SMR, but this was even higher in those with type 2 diabetes (25).

Risk of death for children and young adults in Yorkshire with T1D was four- and six times that of the background population. Acute complications accounted for approximately one-third of all deaths and emphasizes that, despite modern intensive education and insulin treatment, such deaths continue to occur. Similarly, chronic complications including cardiac, renal and cerebrovascular causes continued to arise and subsequently prove fatal.

Previously published data from the UK (7) showed an SMR for females of 3.6-4.4, but a notably lower SMR for males (2.5-2.9) with a similar length of follow-up, whereas our present data showed a similar SMR for

both sexes. We previously found that males seemed to be more at risk than females of developing microvascular complications, such as renal failure and severe retinopathy (26). The risk of death was significantly elevated at every time period since diagnosis reaching seven times the background population for those living with diabetes for 15-19 years, but did not increase linearly with increasing duration of diabetes. SMRs increased by period of diagnosis, especially since 1990 when 15-29 year olds were first registered, UK data reported from 1999 for deaths occurring in under 20 year olds where diabetes was mentioned on the death certificate showed an SMR of 2.3 (6) where DKA was the cause of death in the majority of these cases (69/83)

Mortality data on Norwegian children found that deaths from acute complications and from violent causes constituted about a third each of the total (27). In our study, 22% of the deaths were due to violence or accidents in agreement with previous UK data (8), but they are a common cause of death in this age group in the general population. Seventeen individuals died as a result of drug misuse, with a higher SMR for females than males, and a peak in the number of such deaths occurring between the ages of 20-29. Our findings also revealed that 6 of these fatalities were due to insulin overdoses, although we were unable to establish whether these were accidental or not. The remaining eleven patients in this group died due to opiate, cocaine or analgesic misuse. In addition, one 29 year old male subject, whose cause of death was inconclusive, had toxicological evidence of recent amphetamine and 3,4-methylenedioxy-N-methylamphetamine (MDMA) use, but was not thought to have died of an overdose of these drugs. Another male, aged 33 years, whose cause of death was uncertain, had a history of psychotic illness, IV amphetamine abuse, repeated suicide attempts and erratic

insulin usage with recurrent hypoglycemia and ketoacidosis. Our findings were based on examination of full toxicology/coroner's reports to ensure misclassification of cause of death attributable to drug misuse was minimized. However, we acknowledge that this approach may be a conservative estimate as there were 19 deaths classified as "other/unknown" where no further information was available.

These are important new findings for clinicians treating young people with T1D, where we have identified a propensity for young adult subjects to misuse drugs or take insulin overdoses. A previous survey of young adult T1D found that street drug misuse was common (28). In their study of psychosocial and socioeconomic risk factors for premature death in young people, Laing and colleagues found an odds ratio of 4.6 for past drug misuse (29), but did not comment on drug misuse as a cause of death. A history of psychiatric disorder was noted in 10 of the 37 deaths in the childhood onset diabetes cohort in Israel (30). In our study, drug misuse was mentioned on the death certification and this factor was therefore actively involved as a cause of death. Furthermore, in most cases we were able to obtain information on the nature of the drugs involved following detailed scrutiny of coroners' reports. One may speculate whether some young diabetic adults are drawn into a drug culture because of their familiarity with injection techniques or as a result of a psychological maladaptation as a consequence of their diabetic condition. Alternatively, T1D with its prospect of long term complications may engender a fatalistic or reckless behavior pattern in this age group. There may therefore be an emerging trend for young people with T1D to misuse drugs which warrants further examination in future studies.

The cause of death was uncertain in 19 cases and we were interested to see if any of

these suggested the ‘dead in bed syndrome’ (31). This still appears to constitute a significant number of cases in some series (13). Only one case was found inexplicably dead in bed, following a full post-mortem examination and toxicology report. However, as that syndrome has been linked to hypoglycemia or autonomic neuropathy, some of our other unexplained cases may also have died from these causes. A proportion of the fatalities attributed to uncertain causes are likely to have been related to diabetes and accidents/violence, suggesting that we may have underestimated the true number in our diabetes population.

In conclusion, subjects diagnosed with T1D in childhood and early adult life showed significantly increased mortality from acute

and chronic diabetic complications, with death due to, or associated with, drug misuse or insulin overdose as an emerging feature.

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FIGURE 1. *Study area covered by the former Yorkshire Regional Health Authority in relation to the British Isles*

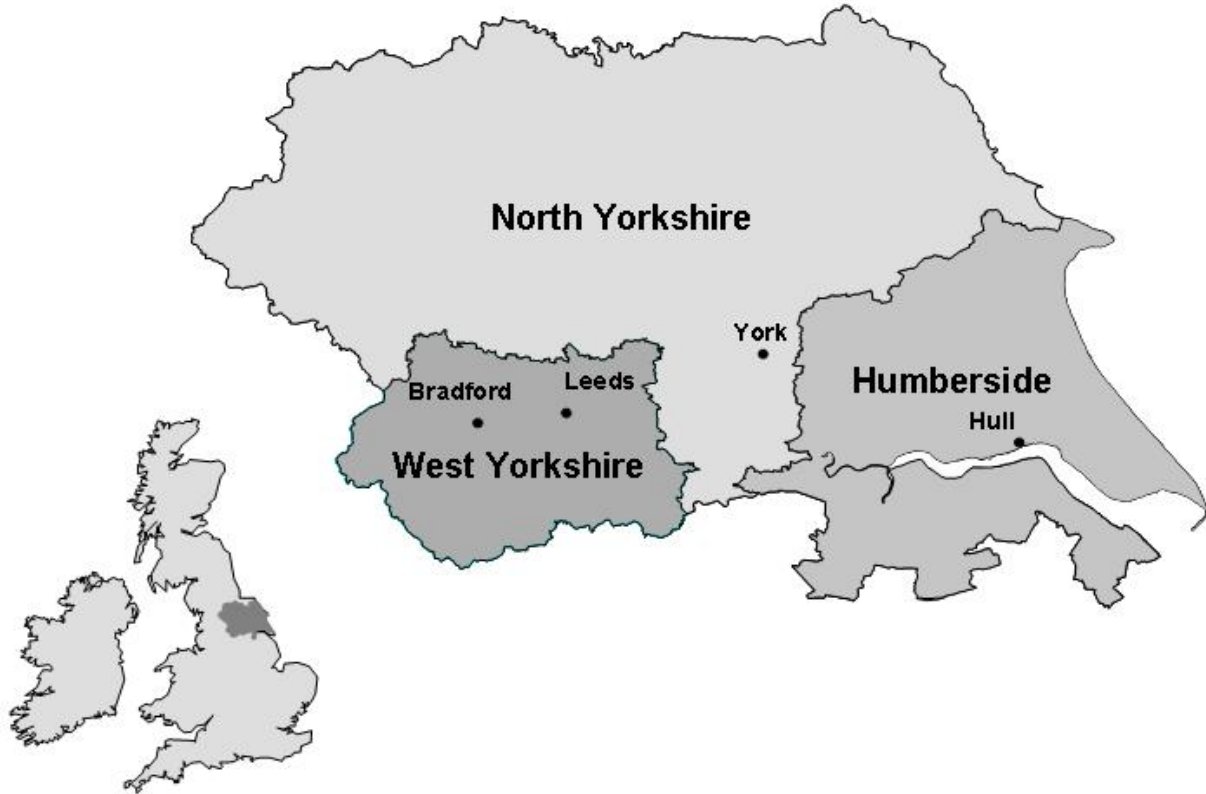


TABLE 1. Standardized mortality ratios by age at diagnosis and gender for patients diagnosed with Type 1 diabetes in Yorkshire 1978-2004

Age at diagnosis (years)	Gender	Number of patients	Observed (Expected)	Standardized Mortality Ratio (SMR)	SMR 95% CI
0-14 (Yorkshire)	Males	1742	52 (12.3)	4.2	3.2-5.5
	Females	1607	22 (5.3)	4.1	2.6-6.3
	Total	3349	74 (17.7)	4.2	3.3-5.3
15-29 (West Yorkshire)	Males	568	25 (4.3)	5.8	3.8-8.6
	Females	329	9 (1.2)	7.5	3.4-14.3
	Total	897	34 (5.5)	6.2	4.3-8.6

TABLE 2. Number of deaths and mortality risk by attained age, time since diagnosis (duration) and calendar period for patients diagnosed with Type 1 diabetes in Yorkshire 1978-2004

	Years	Observed (Expected)	Standardized Mortality Ratio (SMR)	SMR 95% CI
Total deaths		108 (23.2)	4.7	3.8-5.6
Attained age				
	0-4	3 (0.4)	6.8	1.4-19.9
	5-9	3 (0.8)	3.7	0.8-10.7
	10-14	5 (1.7)	2.9	0.9-6.7
	15-19	16 (5.0)	3.2	1.8-5.2
	20-24	22 (5.3)	4.2	2.6-6.3
	25-29	30 (4.6)	6.6	4.4-9.4
	30-34	19 (3.5)	5.4	3.2-8.4
	35-39	9 (1.5)	5.8	2.7-11.0
	40-44	1 (0.2)	4.1	0.1-22.8
Time since diagnosis				
	0-4	24 (6.4)	3.7	2.4-5.6
	5-9	30 (6.2)	4.8	3.3-6.9
	10-14	21 (4.9)	4.3	2.7-6.6
	15-19	22 (3.2)	6.8	4.3-10.4
	20+	11 (2.4)	4.5	2.3-8.1
Period of diagnosis				
	1978-1984	1 (0.7)	1.4	0.0-7.6
	1985-1989	3 (1.7)	1.8	0.4-5.1
	1990-1994	12 (3.3)	3.7	1.9-6.4
	1995-1999	32 (5.9)	5.4	3.7-7.7
	2000-2005	60 (11.5)	5.2	4.0-6.7

TABLE 3. Standardized mortality ratios by cause of death for patients diagnosed with Type 1 diabetes in Yorkshire 1978-2004

Cause of death	ICD10 code	Observed (Expected)	Standardized Mortality Ratio (SMR)	SMR 95% CI
Diabetes	E10-E14	32 (0.1)	356	243-502
Ischemic heart disease	I20-I25	6 (0.3)	9.6	7.2-42.7
Stroke	I60-I69	1 (0.4)	2.5	0.1-14.0
Renal disease	N00-N09	8 (0.0)	5481	2367-∞
Respiratory	J00-J98	5 (0.9)	5.6	1.8-13.0
Neoplasms	C00-C97, D00-D48	4 (3.3)	1.2	0.3-3.1
Mental disorder	F00-F99	9 (1.2)	7.5	3.4-14.3
Accidents and violence (including suicide)	S00-T98, V00-Y98	24 (11.2)	2.1	1.4-3.2
Suicide	X60-X84	6 (2.4)	2.5	0.9-5.4
	by subtraction	19 (5.8)	3.3	2.0-5.2
Other/unknown causes				
All causes		108 (23.2)	4.7	3.8-5.6