BMJ Open Diabetes Research & Care

Comparative mortality and its determinants in community-based people with type 1 diabetes: the Fremantle Diabetes Study Phase I

Ruwani Rajapaksa,[1] Wendy A Davis,[2] Timothy M E Davis [1,2]

To cite: Rajapaksa R, Davis WA, Davis TME. Comparative mortality and its determinants in community-based people with type 1 diabetes: the Fremantle Diabetes Study Phase I. *BMJ Open Diab Res Care* 2023;**11**:e003501. doi:10.1136/bmjdrc-2023-003501

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2023-003501).

Received 3 May 2023
Accepted 13 July 2023

[1]Department of General Medicine, Fremantle Hospital and Health Service, Palmyra DC, Western Australia, Australia
[2]Medical School, University of Western Australia, Perth, Western Australia, Australia

Correspondence to
Dr Timothy M E Davis;
tim.davis@uwa.edu.au

ABSTRACT

Introduction The aim of this study was to compare mortality in community-based Australians with type 1 diabetes (T1D), without diabetes, or with type 2 diabetes (T2D).

Research design and methods The longitudinal observational Fremantle Diabetes Study Phase I (FDS1) T1D cohort, matched people without diabetes from the FDS1 catchment area, and matched FDS1 participants with T2D were followed up from entry (1993–1996) to death/end-2017. Mortality rates (MRs) and mortality rate ratios (MRRs) were calculated. Cox regression models identified independent determinants of death.

Results Of 121 participants with T1D and 484 age/sex/postcode-matched people without diabetes (pooled mean±SD age 43.1±15.3 years, 59.2% men), 55 (45.5%, MR 25.7 (95% CI 19.4 to 33.5)/1000 person-years) and 88 (18.2%, MR 8.5 (95% CI 6.8 to 10.4)/1000 person-years), respectively, died during 12 541 person-years of follow-up (MRR 3.04 (95% CI 2.13 to 4.31), p<0.001). Among participants with T1D, diagnosis at age 18–27 years and baseline HbA_{1c}, urinary albumin:creatinine ratio, and retinopathy were independent predictors of death (p≤0.011). Twenty-five FDS1 participants died from cardiovascular disease (MR 11.7 (95% CI 7.6 to 17.3)/1000 person-years) vs 28 residents without diabetes (MR 2.7 (95% CI 1.8 to 3.9)/1000 person-years; MRR (95% CI) 4.34 (2.43, 7.73) (p<0.001). There were 93 FDS1 participants with T1D who were age/sex matched with an FDS1 participant with T2D and 53 (57.0%) and 37 (39.8%), respectively, died (p=0.027). In pooled Cox regression analysis, T1D was not a determinant of mortality (HR 1.18 (95% CI 0.71 to 1.97), p=0.523).

Conclusions T1D substantially increases the risk of death, especially when diagnosed in late adolescence/young adulthood. Diabetes type does not influence mortality after adjustment for key confounding variables.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although type 1 diabetes (T1D) is associated with a shortened life span, there is a paucity of data examining the relationship between death and its determinants from long-duration studies of well-characterized community-based samples of individuals with T1D and matched people without diabetes or with type 2 diabetes.

WHAT THIS STUDY ADDS

⇒ T1D was associated with a mean 7 years loss of life, and this reduced longevity was associated with diagnosis at age 18–27 years, poor glycemic control, and microangiopathy. Type of diabetes did not influence the risk of death after adjustment for confounding variables.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The need for optimal multifactorial clinical management appears greatest in people diagnosed with T1D in late adolescence/young adulthood.

INTRODUCTION

Although there is evidence that there has been an improvement in life expectancy associated with type 1 diabetes (T1D) over recent decades,[1–5] studies published to date suggest a graded loss of 15 years of life in people diagnosed before the age of 10 years down to a 10-year loss if the diagnosis is made in people aged between 20 years and 30 years.[6 7] The epidemiology of T1D and its potential impact on mortality are, however, complex. There is an initial peak in incidence between 10 years and 14 years but a second peak at >50 years of age,[8] the latter observation questioning the validity of studies including only individuals diagnosed at younger ages.[1 2] Indeed, a significant proportion of people with T1D, probably even the majority, are diagnosed as adults.[9 10] In addition, there is significant variability in the incidence and clinical management across populations, and between racial and ethnic groups within the same community.[11]

A further issue in assessing prognosis in T1D is that many studies base the diagnosis on clinical grounds without supportive laboratory tests such as autoantibodies and serum C-peptide measurements.[1–3 11] Although the risk of death is increased in individuals with

T1D compared with matched people with type 2 diabetes (T2D),[12] T2D is increasingly found in younger individuals[13] whose associated mortality appears higher than that of individuals with T1D of similar age.[14] This latter difference may be even greater since, without confirmatory laboratory testing, misdiagnosis of T1D as T2D can be relatively common in young people.[15]

Notwithstanding the recent emergence of high-risk T2D in young people, the relatively high overall mortality in T1D[12] in the presence of a lower cardiovascular disease (CVD) risk factor burden in T1D versus T2D[16] has prompted the suggestion that there are features specific to T1D that contribute to premature mortality.[17] A valid examination of this hypothesis would require comparison of mortality rates (MRs) in closely matched groups of well-characterized individuals with confirmed T1D or T2D from the same community. Since risk of death associated with T2D has, in parallel with the situation in T1D,[1–5] declined in recent decades in low-income countries,[18 19] there is a need for contemporaneous comparative data.

Given these various considerations, the aim of the present study was to use data from the Fremantle Diabetes Study Phase I (FDS1) to (1) analyze deaths in participants with T1D and matched people without known diabetes from the same urban Australian population, (2) determine baseline variables associated with all-cause and cause-specific mortality in the participants with T1D, and (3) compare survival in the participants with T1D with that of age-matched and sex-matched FDS1 participants with T2D.

MATERIALS AND METHODS

Study site, participants, and approvals

The FDS1 is an observational, longitudinal cohort study of known diabetes conducted in a postcode-defined geographical area surrounding the port city of Fremantle in the state of Western Australia (WA).[20] Recruitment was between 1993 and 1996, with follow-up to death or end-2017. Participants were identified from hospital, clinic and primary care patient lists, widespread advertising through local media, pharmacies, optometrists, and networks of healthcare professionals. Details of recruitment and sample characteristics including classification of diabetes type and non-recruited patients have been published.[20 21]

In FDS1, 2258 people with diabetes were identified from a population of approximately 120 000, and 1426 (63%) were recruited. Of these, 125 (9.6%) had T1D based on age at diagnosis, history of insulin treatment, adiposity, islet autoantibody status, and plasma C-peptide concentrations if available.[20 21] Four age-matched, sex-matched, and postcode-matched residents without any prior documentation of diabetes were randomly selected from the study catchment area for each FDS1 participant at the time of their enrollment using the WA Electoral Roll of all adult residents in the FDS catchment area. Five of these residents died just before their matched FDS1 participant was enrolled and were therefore excluded. Matches could not be made for five young and four elderly FDS1 participants who were also excluded, leaving 121 participants with T1D (96.8%) matched with 484 residents without diabetes. There were 93 FDS1 participants with T2D who could be matched on age and sex with an FDS1 participant with T1D.

Baseline and annual assessments

Assessment at entry and at annual reviews included a comprehensive questionnaire, physical examination, and fasting biochemical tests performed in a single nationally accredited laboratory.[20] Details of all medical conditions/treatments and demographic, socioeconomic, and lifestyle data were recorded. In addition to body mass index (BMI), A Body Shape Index (ABSI) was calculated as $m^{11/6}/kg^{2/3}$.[22] Complications were identified using standard definitions.[23] Albuminuria was assessed by early morning spot urine albumin:creatinine ratio (uACR) measurement and renal impairment from the estimated glomerular filtration rate.[24] Peripheral sensory neuropathy (PSN) was defined using the clinical portion of the Michigan Neuropathy Screening Instrument.[25] Retinopathy was defined as one microaneurysm in either eye or worse and/or evidence of previous laser treatment on direct/indirect ophthalmoscopy and/or ophthalmologist assessment. Patients were classified as having prevalent ischemic heart disease (IHD) if there was a history of myocardial infarction (MI), angina, coronary artery bypass grafting or angioplasty, and as having prevalent cerebrovascular disease if there was a history of stroke and/or transient ischemic attack. Peripheral arterial disease (PAD) was defined as an ankle brachial index of ≤0.90 or the presence of a diabetes-related lower-extremity amputation.

Ascertainment of all-cause and cardiovascular mortality

The WA Registry for Births, Deaths and Marriages contains information on all deaths in WA.[26] Causes of death on the death certificate or coroner's report were reviewed independently by two study physicians and classified under the system used in the UK Prospective Diabetes Study.[27] In the case of discrepant coding, case notes were consulted and a consensus was obtained. Death from CVD was defined as death from IHD, cerebrovascular disease, or sudden death.

Ascertainment of comorbidities

The Hospital Morbidity Data Collection (HMDC) contains information regarding all public/private hospitalizations in WA since 1970. The HMDC and FDS1 were linked to supplement data obtained through FDS assessments relating to prevalent/prior disease during the 5 years prior to study entry as well as providing the same information for the matched residents without diabetes. These data were used to calculate the Charlson Comorbidity Index (CCI), which includes a history of MI, heart

failure, PAD, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, hemiparesis or paraparesis, renal disease, liver disease, and cancer.[28] For the purposes of the present study, we excluded those conditions coded as diabetes-specific complications (International Classification of Disease (ICD)-9-Clinical Modification (CM) 250 and ICD-10-Australian Modification (AM) E10-14 codes) in FDS1 participants.

Statistical analysis

The computer packages IBM SPSS Statistics V.25 and StataSE V.15 were used for statistical analysis. Data are presented as proportions, mean±SD, geometric mean (SD range), or, in the case of variables which did not conform to a normal or log-normal distribution, median and IQR. Two-sample comparisons were by Fisher's exact test for proportions, Student's t-test for normally distributed variables, and Mann-Whitney U test for other variables. Three-sample comparisons were by Fisher's exact test for proportions, one-way analysis of variance for normally distributed variables, and Kruskal-Wallis test for other variables. Bonferroni corrections were applied to multiple pairwise comparisons.

Kaplan-Meier curves were constructed for FDS1 participants with T1D and matched people without diabetes and compared using the log-rank test. MRs for all-cause and CVD mortality were derived separately for those with T1D and their matched counterparts without diabetes. Mortality rate ratios (MRRs) were then calculated for those with T1D versus those without diabetes, both overall and for 10-year age groups. Mortality rate differences were also calculated. To allow for differences in age, sex, and comorbidities, we adjusted for (1) age as the timeline in a Cox model of time to first event for each outcome using people without diabetes as reference and (2) in addition, sex, and CCI. For CVD death, competing risk modelling was performed similarly to allow for the competing risk of death from other causes.

For the T1D cohort alone, exploratory analyses were undertaken to identify which baseline variables determined all-cause and CVD mortality. Bivariable analyses of plausible clinical, biochemical, and sociodemographic variables measured at baseline were undertaken. Variables with bivariable p<0.10 were considered for entry into Cox and (for CVD death) competing risk models of time to death with age as the timeline. Backward conditional selection of variables was used with entry p<0.05 and removal p≥0.05.

Kaplan-Meier curves were constructed for FDS1 participants with T1D and matched FDS1 participants with T2D and compared using the log-rank test. Cox proportional hazards modelling was performed as described previously to identify independent determinants of mortality in the pooled sample after which type of diabetes was entered.

The proportional hazards assumption was checked using time-varying covariates but was not violated in any of the models tested in the present study.

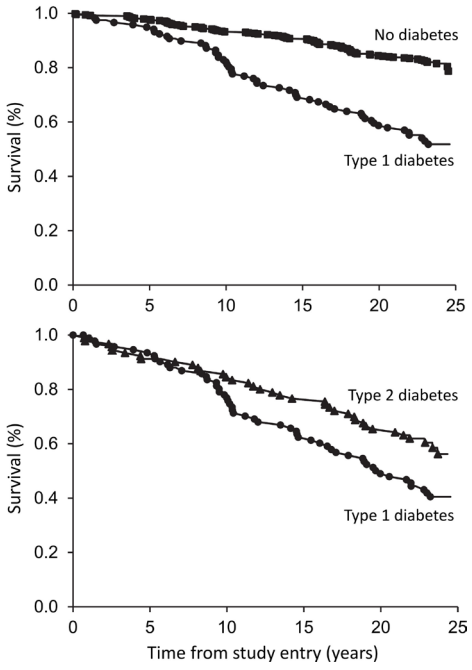

Figure 1 Kaplan-Meier curves showing survival in FDS1 participants with type 1 diabetes versus matched people without diabetes from the same population base (upper panel) and in matched groups of individuals with type 1 or type 2 diabetes from FDS1 (lower panel). FDS1, Fremantle Diabetes Study Phase I.

RESULTS

Sample characteristics

The 121 participants with T1D were matched with 484 people without diabetes at study entry. These groups combined had a mean±SD age of 43.1±15.3 years old at study entry and 59.2% were men. Those with T1D were diagnosed at age 29.5±11.6 years and had a median diabetes duration of 12.0 (3.2–21.0) years. Comorbidities defined by the CCI occurring in the 5 years before study entry were more common among those with T1D (0, 1 or 2, 3, or more comorbidities: 87.6% vs 96.1%, 9.9% vs 3.3%, 2.5% vs 0.6%, p=0.002).

All-cause mortality

During 2138 person-years (17.7±7.5 years) of follow-up from entry to death or end-2017, whichever came first, 55 (45.5%) FDS1 participants died (MR 25.7 (95% CI 19.4 to 33.5)/1000 person-years) vs 88 (18.2%) residents without diabetes during 10 403 person-years (21.5.1±4.9 years) (MR 8.5 (95% CI 6.8 to 10.4)/1000 person-years). The crude MRR for T1D versus no diabetes was 3.04 (95% CI 2.13 to 4.31) (p<0.001). The Kaplan-Meier curves for the two participant groups are shown in figure 1 (p<0.001 by log-rank test).

The 10-year age-specific MRRs are shown in table 1. In the age group of <35 years, there were no deaths in the T1D participants but three in the matched cohort. The age group of 35–44 years had the highest MRR (>20) with a declining trend to a non-significant twofold increased risk for those 75–94 years of age. The HR, adjusted for

Table 1 Ten-year age-specific MR, MRR, and MRD per 1000 person-years, of all-cause mortality and CVD mortality, for participants with T1D versus matched residents without diabetes

	Age group (years)	35–44	45–54	55–64	65–74	75–84	85–94	All
All-cause mortality								
T1D	No of deaths	5	7	10	18	12	3	55
	Person-years	464	456	446	268	137	17	2138
	MR (95% CI)	10.8 (3.5 to 25.2)	15.4 (6.2 to 31.6)	22.4 (10.8 to 41.2)	67.3 (39.9 to 106.3)	87.7 (45.3 to 153.2)	178.1 (36.7 to 520.5)	25.7 (19.4 to 33.5)
No diabetes	No of deaths	1	5	11	21	36	11	88
	Person-years	2081	2194	2099	1642	823	108	10 403
	MR (95% CI)	0.5 (0.01 to 2.7)	2.3 (0.7 to 5.3)	5.2 (2.6 to 9.4)	12.8 (7.9 to 19.6)	43.8 (30.6 to 60.6)	101.7 (50.8 to 182.0)	8.5 (6.8 to 10.4)
	MRR (95% CI)	22.4 (2.5 to 1061)	6.7 (1.8 to 26.9)	4.3 (1.6 to 11.1)	5.3 (2.6 to 10.4)	2.0 (0.95 to 3.9)	1.8 (0.3 to 6.6)	3.0 (2.1 to 4.35)
	MRD (95% CI)	10.3 (0.8 to 19.8)	13.1 (1.5 to 24.6)	17.2 (2.9 to 31.4)	54.5 (22.9 to 86.0)	44.0 (–7.7 to 95.6)	76.4 (–133.9 to 286.7)	17.3 (10.2 to 24.3)
CVD mortality								
T1D	No of deaths	0	3	7	10	5	0	25
	Person-years	464	456	446	268	137	17	2138
	MR (95% CI)	0	6.6 (1.4 to 19.2)	15.7 (6.3 to 32.3)	37.4 (17.9 to 68.7)	36.5 (11.9 to 85.3)	0	11.7 (7.6 to 17.3)
No diabetes	No of deaths	0	0	4	8	13	3	28
	Person-years	2081	2194	2099	1642	823	108	10 403
	MR (95% CI)	–	–	1.9 (0.5 to 4.9)	4.9 (2.1 to 9.6)	15.8 (8.4 to 27.0)	27.7 (5.7 to 81.1)	2.7 (1.8 to 3.9)
	MRR (95% CI)	–	–	8.2 (2.1 to 38.4)	7.7 (2.7 to 22.4)	2.3 (0.7 to 6.9)	0	4.3 (2.4 to 7.7)
	MRD (95% CI)	0	6.6 (–0.9 to 14.0)	13.8 (2.0 to 25.6)	32.5 (9.1 to 55.9)	20.7 (–12.4 to 53.9)	–27.7 (–59.1 to 3.7)	9.0 (4.3 to 13.7)

MR: per 1000 person-years, MRD: per 1000 person-years
CVD, cardiovascular disease; MR, mortality rate; MRD, mortality rate difference; MRR, mortality rate ratio; T1D, type 1 diabetes.

age as the timeline, for all-cause mortality in people with T1D versus no diabetes was 3.44 (95% CI 2.45 to 4.83) (p<0.001). Further adjustment for sex and comorbidities modestly attenuated the HR to 3.15 (95% CI 2.20 to 4.51) (p<0.001). The mean age at death was 6.6 (95% CI 2.0 to 11.2) years younger in those with T1D versus those without diabetes (p=0.006). The main cause of death was CVD with 25 (45.5%) deaths due to CVD in those with T1D and 28 (31.8%) in those without diabetes (p=0.112). In the T1D group, there were 5 deaths due to renal disease, 5 from cancer, 18 from a variety of other known causes (including infections, trauma, and suicide), and 2 in whom the cause was unknown. No deaths in the T1D group were sudden deaths, and none resulted directly from diabetic ketoacidosis (DKA) or severe hypoglycemia.

CVD mortality

During 2138 person-years of follow-up from entry to death or end-2017, whichever came first, 25 (20.0%) FDS1 participants died from CVD (MR 11.7 (95% CI 7.6 to 17.3)/1000 person-years) vs 28 (5.8%) residents without diabetes during 10 403 person-years of follow-up (MR 2.7 (95% CI 1.8 to 3.9)/1000 person-years; crude MRR 4.34 (95% CI 2.43 to 7.73); p<0.001). The 10-year age-specific CVD MRRs are shown in table 1. There were no CVD deaths in those aged <45 years. In the age group of 45–54 years, there were three CVD deaths in the T1D participants but none in the matched cohort. The age group of 55–74 years had the highest CVD MRR (approximately 8) declining to a non-significant twofold increased risk for those 75–84 years and 0 in the age group of 85–94 years since there were no CVD deaths in those with T1D but three in those with no diabetes.

The cause-specific HR (csHR) for CVD mortality, adjusted for age as the timeline, in people with T1D versus no diabetes was 5.03 (95% CI 2.93 to 8.63) (p<0.001). Further adjustment for sex and comorbidities modestly attenuated the csHR to 4.64 (95% CI 2.64 to 8.16) (p<0.001). Further adjustment for the competing risk of non-CVD death resulted in a subdistribution HR of 4.10 (95% CI 2.30 to 7.33). The mean age at CVD death was 10.1 (95% CI 5.1 to 15.1) years younger in those with T1D versus those without diabetes (p<0.001).

Determinants of mortality in the FDS1 T1D cohort

Bivariable statistics for the associations between baseline characteristics and all-cause mortality for the complete FDS1 T1D cohort (n=125) are summarized in table 2. Compared with the survivors, the 55 participants who died during follow-up were significantly older at study entry and at onset of T1D; had longer diabetes duration; had higher BMI, ABSI, HbA_{1c}, blood pressure, and uACR; had worse lipid profiles and renal function; were more likely to have ever smoked; were centrally obese; and had more retinopathy, PSN, CVD, and comorbidities. The most parsimonious Cox model of baseline predictors of all-cause mortality with age as the timeline is shown in table 3. Participants diagnosed with diabetes between the ages of 17.6 years and 26.8 years (second quintile of the distribution) were more than three times more likely to die than those in the first quintile (1.6–<17.6 years) and in the higher quintiles (>26.8–75.2 years). An increase of 1% (11 mmol/mol) in HbA_{1c} was associated with a 37% increased risk of death. Higher uACR increased the risk of death, as did the presence of retinopathy.

Bivariable statistics for the associations between baseline characteristics by survival, CVD mortality, and death from other causes are shown in online supplemental table 1. Participants who died during follow-up had similar characteristics whatever the reason for death, except those who died from CVD had a significantly higher BMI and uACR than those who died from other causes. Compared with survivors, those who died from CVD, but not from other causes, had a higher BMI, were more likely to be centrally obese, to have ever smoked, to have a worse lipid profile and renal function, and to have CVD. By contrast, compared with survivors, those who died from non-CVD causes had significantly more comorbidities.

The most parsimonious Cox model of baseline predictors of CVD mortality with age as the timeline is shown in table 3. Participants diagnosed with diabetes between 17.6 years and 26.8 years of age (second quintile) were nearly seven times more likely to die from CVD than those in the first quintile (1.6–<17.6 years) and in the higher quintiles (>26.8–75.2 years). Increasing ABSI as a surrogate for visceral obesity significantly increased the risk of CVD death. An increase of 1% (11 mmol/mol) in HbA_{1c} was associated with a 43% increase in mortality. When the competing risk of death from non-CVD causes was allowed for in a Fine and Gray competing risk regression (table 3), uACR entered the model as did a prior history of IHD.

Mortality in type 1 versus type 2 diabetes

In the two matched FDS1 groups with T1D or T2D, 60.2% were men; the mean age at study entry was 48.6±12.8 years; the mean age at diabetes diagnosis was 38.4±12.8 years; and the median diabetes duration was 7.0 (1.7–16.0) years. The age at diabetes diagnosis was younger for the T1D participants (32.8±10.4 vs 44.0±12.6 years, p<0.001). Consequently, duration of diabetes at study entry was longer for the T1D participants (15.0 (6.5–23.0) vs 3.0 (0.7–7.0) years; p<0.001). The baseline HbA_{1c} was higher in those with T1D (8.8% (7.7–10.2) (73 (61–88) mmol/mol) vs 7.7% (6.5–8.9) (61 (48–74) mmol/mol), p<0.001) but not baseline urinary albumin:creatinine ratio (geometric mean (SD range) 2.9 (0.5–18.1) vs 2.4 (0.5–11.0) mg/mmol, p=0.052). The prevalence of retinopathy was greater in those with T1D (40.2% vs 11.2%, p<0.001) but not the prevalence of IHD (16.1% vs 21.5%, p=0.453) or the percentage with a CCI of ≥3 (3.2% vs 5.4%, p=0.721). There were 53 (57.0%) deaths in the participants with T1D and 37 (39.8%) in those with T2D (p=0.027). The Kaplan-Meier curves for

Table 2 Baseline characteristics of FDS1 participants with type 1 diabetes by all-cause mortality to end-2017

	Alive	Deceased	P value
n (%)	70 (56.0)	55 (44.0)	
Age (years)	33.1±12.5	53.5±12.3	<0.001
Male (%)	51.4	69.1	0.066
Education beyond primary (%)	89.2	83.3	0.423
Not fluent in English (%)	4.3	9.1	0.299
Overseas born (%)	26.1	38.2	0.175
Smoking status (%)			
Never	58.2	27.3	
Ex-smoker	20.9	43.6	0.002
Current	20.9	29.1	
Alcohol (standard drinks/day)	0.1 (0–1.1)	0 (0–0.5)	0.303
Any exercise in the past 2 weeks (%)	87.0	76.4	0.157
BMI (kg/m^2)	25.0±4.4	27.9±5.2	0.001
ABSI (m$^{11/6}$/kg$^{2/3}$)	0.075±0.006	0.081±0.005	<0.001
Abdominal obesity (% by waist circumference)	12.9	38.2	0.001
Age at diabetes diagnosis (years)	25.3±11.2	33.6±10.9	<0.001
Diabetes duration (years)	4.9 (0.7–12.7)	20.0 (1.0–29.0)	<0.001
Fasting serum glucose (mmol/L)	10.7 (6.7–16.7)	10.6 (8.5–14.6)	0.544
HbA$_{1c}$ (%)	8.0 (6.7–9.3)	9.5 (8.1–10.6)	<0.001
HbA$_{1c}$ (mmol/mol)	64 (50–78)	80 (65–92)	<0.001
Systolic blood pressure (mm Hg)	126±15	146±25	<0.001
Diastolic blood pressure (mm Hg)	73±9	81±12	<0.001
Antihypertensive medication (%)	8.6	45.5	<0.001
Total serum cholesterol (mmol/L)	4.9±1.0	5.6±1.7	0.019
Serum HDL cholesterol (mmol/L)	1.31±0.39	1.13±0.46	0.022
Serum triglycerides (mmol/L)	1.1 (0.6–2.0)	1.6 (0.7–3.6)	0.005
Lipid-modifying medication (%)	0	14.5	0.001
eGFR (Chronic Kidney Disease-Epidemiology Collaboration) category (%)			
≥90 mL/min/1.73m^2	59.4	37.0	
60–89 mL/min/1.73m^2	39.1	38.9	<0.001
45–59 mL/min/1.73m^2	1.4	16.7	
<45 mL/min/1.73m^2	0	7.4	
Urinary albumin:creatinine ratio (mg/mmol)	1.2 (0.4–3.4))	6.1 (0.9–41.6)	<0.001
Any retinopathy (%)	13.2	56.4	<0.001
Peripheral sensory neuropathy (%)	8.7	41.2	<0.001
Peripheral arterial disease (%)	17.1	27.8	0.190
Ischemic heart disease (%)	2.9	23.6	0.001
Cerebrovascular disease (%)	0	12.7	0.003
Charlson Comorbidity Index (%)			
0	95.7	78.2	
1 or 2	4.3	16.4	0.006
≥3	0	5.5	

ABSI, A Body Shape Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; FDS1, Fremantle Diabetes Study Phase I ; HDL, high-density lipoprotein.

Table 3 Most parsimonious Cox model of independent predictors of all-cause mortality (upper panel), and Cox and competing risk (Fine and Gray) models of independent predictors of death from CVD (lower panel) in FDS1 participants with type 1 diabetes with age as the timeline

Baseline variable	HR (95% CI)	P value	Subdistribution HR (95% CI)	P value
All-cause mortality				
Age at diabetes diagnosis quintiles*				
1st, 3rd–5th	1.00 (reference)			
2nd	3.57 (1.61 to 7.96)	0.002		
HbA_{1c} (increase of 1% (11 mmol/L))	1.37 (1.18 to 1.60)	<0.001		
Ln(urinary albumin:creatinine ratio (mg/mmol))†	1.21 (1.04 to 1.40)	0.011		
Any retinopathy	2.40 (1.31 to 4.39)	0.005		
CVD mortality				
Age at diabetes diagnosis quintiles*:				
1st, 3rd–5th	1.00 (reference)			
2nd	6.71 (2.08 to 21.67)	0.001		
ABSI‡ (increase of 0.001 $m11^{/6}/kg^{2/3}$)	1.14 (1.03 to 1.25)	0.008		
HbA_{1c} (increase of 1% (11 mmol/mol))	1.43 (1.11 to 1.86)	0.006		
Ln(urinary albumin:creatinine (mg/mmol))†			1.42 (1.19 to 1.71)	<0.001
History of ischemic heart disease			3.02 (1.32 to 6.90)	0.009

*Age at diabetes diagnosis (years) quintiles: first, 1.6–17.5; second,17.6–26.82; third, 26.83–32.1; fourth, 32.2–38.26; and fifth, 38.27–75.2.
†A 2.72-fold increase in urinary albumin:creatinine ratio corresponds to an increased risk of one in ln(urinary albumin:creatinine ratio).
‡ABSI=$m^{11/6}$ /$kg^{2/3}$.
ABSI, A Body Shape Index; CVD, cardiovascular disease.

the two participant groups are shown in figure 1 (p=0.019 by log-rank test). Of the deaths, 25 (26.9% of 93 or 47.2% of all deaths) were due to CVD in those with T1D and 37 (39.8% of 93 or 100% of all deaths) were CVD-related in those with T2D (p=0.087).

The baseline characteristics of the pooled T1D plus T2D cohort by mortality status at the end of follow-up are summarized in table 4. Independent predictors of death in the pooled cohort were assessed from Cox regression using time as the timeline since mean age at diagnosis was higher in this matched T1D plus T2D cohort than the whole T1D cohort and did not show a J-shaped relationship with mortality. Age (HR 1.06 (95% CI 1.04 to 1.08) for each year increase, p<0.001), HbA_{1c} (HR 1.29 (95% CI 1.14 to 1.46) for each 1% or 11 mmol/mol increase, p<0.001), ln(uACR) (HR 1.35 (95% CI 1.18 to 1.53), where a 2.72-fold increase in uACR in mg/mmol corresponds to an increased risk of 1 in ln(uACR), p<0.001), the presence of retinopathy, IHD, and a CCI of ≥3 were significant predictors of all-cause death, but T1D was not (HR 1.18 (95% CI 0.71 to 1.97), p=0.523 after adjustment). The relationship between baseline HbA_{1c} and mortality was similar for T1D and T2D (see figure 2). The 90 participants who died during follow-up were aged 67.7±13.7 (range 29.4–92.6) years at the time of death. There was no significant difference in age at death between those with T1D and T2D (66.9±13.8 vs 68.9±13.6 years, p=0.492).

DISCUSSION

The present data show that community-based Australian adults with T1D were more than three times more likely to die compared with matched people without diabetes from the same population during an average of >20 years of follow-up. The age at death was approaching 7 years younger in the participants with T1D. CVD deaths were more frequent in the T1D group, accounting for approaching half of all-cause mortality versus one-third in the cohort without diabetes. Diagnosis of T1D in late adolescence/young adulthood in our participants carried a poor prognosis relative to other age groups, as did poor glycemic control and its consequences (albuminuria and retinopathy). In an analysis of age-matched and sex-matched groups of FDS1 participants with T1D or T2D, mortality was significantly greater in those with T1D driven primarily by their worse glycemic control and their higher retinopathy burden.

The mean 6.6 year loss of life expectancy in our participants with T1D is less than in previous reports (≥10 years)[6 7] and likely reflects the older age at diagnosis of the FDS1 cohort relative to other studies. Indeed, the MRR was not significantly increased in FDS1 participants aged ≥75 years at study entry compared with a substantially higher and significant MRR (>20) in those aged <45 years. The fact that individuals in the FDS1 diagnosed with T1D between the ages of 18 years and 27 years were at significantly increased risk of death compared with participants both younger and older at diagnosis

Table 4 Pooled baseline characteristics of 93 participants with T1D matched 1:1 on age and sex with 93 participants with type 2 diabetes from the Fremantle Diabetes Study Phase I by all-cause mortality

	Alive on 31 December 2017	Deceased by 31 December 2017	P value
Number (%)	96 (51.6)	90 (48.4)	
Age (years)	42.6±10.5	54.9±12.1	<0.001
Male (%)	53.1	67.8	0.051
Ethnic background (%)			0.566
Anglo-Celt	58.3	61.1	
Southern European	12.5	18.9	
Other European	9.4	6.7	
Asian	3.1	3.3	
Aboriginal	3.1	3.3	
Mixed/other	13.5	6.7	
Not fluent in English (%)	8.3	11.1	0.622
Educated beyond primary school level (%)	87.1	82.0	0.413
Married/de facto relationship (%)	65.6	68.9	0.643
Smoking status (%)			0.062
Never	46.2	30.0	
Ex-smoker	31.2	44.4	
Current	22.6	25.6	
Alcohol consumption (standard drinks/day)	0.1 (0–0.8)	0 (0–0.3)	0.273
Any exercise in past 2 weeks (%)	79.8	74.4	0.483
Body mass index (kg/m^2)	28.9±6.2	29.9±6.6	0.304
ABSI (m$^{11/6}$/kg$^{2/3}$)	0.078±0.006	0.082±0.005	<0.001
Overweight/obese by waist circumference (%)*	44.8	52.9	0.302
T1D (%)	41.7	58.9	0.027
Age at diagnosis (years)	36.5±11.2	40.5±14.1	0.033
Diabetes duration (years)	4.2 (0.8–9.0)	11.5 (4.9–22.0)	<0.001
Fasting serum glucose (mmol/L)	9.1 (6.6–14.1)	10.2 (7.9–14.1)	0.084
HbA_{1c} (%)	7.8 (6.5–8.6)	9.0 (7.7–10.2)	<0.001
HbA_{1c} (mmol/mol)	62 (48–70)	75 (61–88)	<0.001
Diabetes treatment (%)			<0.001
Diet	28.0	7.8	
OGLMs	29.0	26.7	
Insulin±OGLM	43.0	65.6	
Systolic blood pressure (mm Hg)	131±18	149±26	<0.001
Diastolic blood pressure (mm Hg)	79±10	82±12	0.027
On blood pressure-lowering medication (%)	18.8	44.4	<0.001
Heart rate (beats/min)	69±11	74±15	0.018
Total serum cholesterol (mmol/L)	5.3±0.9	5.5±1.8	0.281
Serum HDL cholesterol (mmol/L)	1.10±0.40	1.04±0.40	0.359
Serum triglycerides (mmol/L)	1.7 (0.8–3.4)	1.9 (0.8–4.2)	0.239
Lipid-lowering medication (%)	4.2	13.3	0.035
Aspirin use (%)	3.1	18.0	0.001
eGFR (CKD-EPI) category (%)			0.001
≥90 mL/min/1.73m^2	52.1	34.1	
60–89 mL/min/1.73m^2	44.7	46.6	

Continued

Table 4 Continued

	Alive on 31 December 2017	Deceased by 31 December 2017	P value
45–59 mL/min/1.73m^2	3.2	14.8	
<45 mL/min/1.73m^2	0	4.5	
Urinary albumin:creatinine ratio (mg/mmol)	1.3 (0.4–4.5)	5.4 (0.9–33.4)	<0.001
Any retinopathy (%)	12.8	40.2	<0.001
Ischemic heart disease (%)	7.3	31.1	<0.001
Heart failure (%)	0	8.9	0.003
Cerebrovascular disease (%)	2.1	13.3	0.004
Distal sensory polyneuropathy (8-point) (%)	10.4	40.0	<0.001
Peripheral arterial disease (%)	15.8	28.4	0.049
Charslon Comorbidity Index categories (%)			0.027
0	85.4	72.2	
1 or 2	13.5	20.0	
≥3	1.0	7.8	

*Waist circumference ≥94.0 cm (men), ≥80.0 cm (women).
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; OGLM, oral glucose-lowering medication; T1D, type 1 diabetes.

independently of other risk factors likely reflects the adverse impact of new-onset diabetes at a time of substantial life changes including reduced parental support and difficulties in transitioning to the adult healthcare system.[29 30]

Although interpretation is complicated by the low number of events, one in eight CVD deaths was in the FDS1 participants below the age of 55 years compared with none of the matched cohort without diabetes. In addition, late adolescence/early adulthood was an even stronger independent aetiological risk factor for CVD death compared with all-cause mortality in the Cox regression analysis. Clinical trial data supporting intensification of CVD risk factor management in young adults with T1D are lacking, but it is interesting that only around a quarter of the participants who died of CVD were taking lipid-lowering medication at baseline and that only half were on antihypertensive therapy. The latest American Diabetes Association guidelines recommend consideration of moderate-intensity statin therapy and a blood pressure target of <130/80 mm Hg in T1D,[31] the latter level well below the baseline mean in the FDS1 participants who died of CVD (148/81 mm Hg).

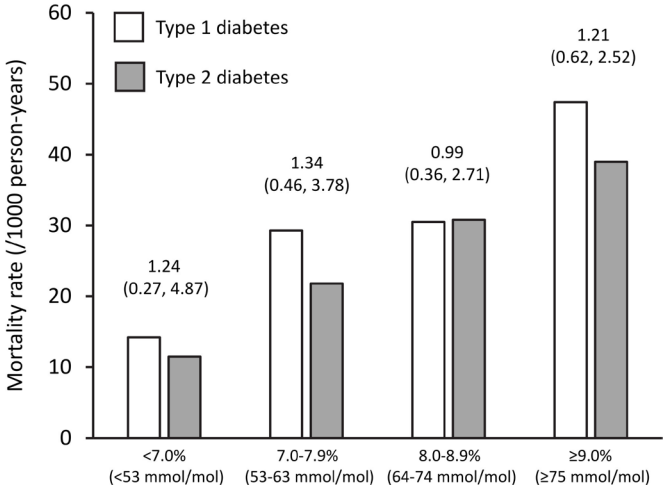

Figure 2 Histogram showing the mortality rates for participants with type 1 or type 2 diabetes by baseline HbA_{1c} category. Mortality rate ratios (and 95% CIs) are shown above the two columns for each HbA_{1c} category. None were statistically significant (p≥0.532).

Glycemic control at baseline in our participants with T1D in the form of HbA_{1c} was significantly associated with both all-cause and CVD death in Cox models. These real-world findings add weight to the need for continued good glycemic control in T1D as exemplified by the durable benefits for CVD outcomes in the Diabetes Control and Complications Trial.[32] Retinopathy and an increased uACR were also independent aetiological predictors of all-cause death, and uACR was prognostically significant in a competing risk model of CVD death in our T1D cohort. These observations are consistent with the well-recognized associations between both retinopathy[33] and albuminuria[34] and death in T1D. In addition, the association between ABSI (which, when elevated, indicates that the waist circumference is higher than expected for a given height and weight) and death in our cohort is consistent with findings from studies in the general population[22] and of obesity in T1D.[35]

We explored comparative mortality in T1D versus T2D in our cohort using age-matched and sex-matched samples, with three-quarters of the FDS1 cohort successfully matched with a participant with T2D. Consistent with other population-based studies,[12] our study showed that there was a higher risk of all-cause death in T1D. However, the detailed phenotypical data allowed an assessment of whether this was due to the type of diabetes

per se or other independent risk factors. Age, HbA_{1c}, uACR, retinopathy, IHD, and a CCI of ≥3 were independent predictors of all-cause mortality, but T1D was not. This questions whether, as has been postulated,[17] there are factors specific to T1D that contribute to premature mortality and adds further to the evidence supporting intensive management of conventional modifiable cardiorenal risk factors including glycemic control, regardless of diabetes type.[31]

The non-CVD-related deaths in the T1D cohort were spread across a range of causes, with renal disease and malignancy the main subgroups although with small numbers of cases. There were no recorded cases of deaths due to acute metabolic complications. This is consistent with a declining rate of acute presentations with DKA and severe hypoglycemia over recent decades,[19] but there is also evidence that such complications may be underreported on death certificates.[36]

The present study had limitations. Given the relative prevalence of T1D versus T2D, the FDS1 T1D sample was small compared with some other longitudinal studies, with a limited number of deaths especially in the subgroup where this was due to CVD. In light of population differences in the epidemiology and management of T1D,[11] the racial/ethnic backgrounds of our participants were considered for inclusion in multivariable models, but the majority (approximately 60%) were of Anglo-Celtic origin. We did not have data on interventions (such as statin initiation) during follow-up in either our participants with T1D or T2D that may have influenced the risk of death. We had relatively few paediatric participants but would likely have captured most people with T1D, given the peaks in incidence in adolescence and middle age.[8 11] The strengths of the study are its representative, community-based sample,[20] the availability of detailed phenotypical data including diabetes type, detailed death data which may be deficient in administrative database studies,[1 2 7 37] and the long duration of follow-up over several decades.

We conclude that poor glycemic control and its associated tissue damage have implications for premature all-cause and CVD mortality in T1D. People diagnosed in late adolescence/young adulthood need careful assessment and management of CVD risk. Visceral obesity is a potential modifiable risk factor for CVD death in T1D, while people with T1D and a history of IHD should also have their CVD risk factor management optimized. Although the risk of death was higher in T1D versus T2D in the FDS1 cohort, we found no evidence that type of diabetes was independently associated with mortality.

Acknowledgements We thank the Fremantle Diabetes Study Phase I staff and participants. The authors also wish to thank the staff from the Department of Health WA's Data Linkage Services, the Hospital Morbidity Data Collection and the Western Australian Registry of Births, Deaths and Marriages.

Contributors RR reviewed the relevant literature, contributed to data interpretation, and produced the first draft of the manuscript. WD supervised data collection, conducted the statistical analysis, contributed to Fremantle Diabetes Study Phase I interpretation and reviewed/edited the manuscript. TMED is principal investigator of Fremantle Diabetes Study Phase I, contributed to the data interpretation and produced the final version of the manuscript. TMED is the guarantor of this work and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The Fremantle Diabetes Study Phase I was supported by the Raine Foundation, University of Western Australia. TMED is supported by a Medical Research Future Fund Practitioner Fellowship (1154192). Neither of these funding bodies had a role in study design, collection or interpretation of data, writing of the manuscript, or in the decision to submit the final version for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the Fremantle Diabetes Study Phase I (FDS1) protocol was approved by Fremantle Hospital Human Rights Committee (which reviewed all hospital ethics applications in 1992). No reference number was provided. The participants gave informed consent to participate in the study before taking part. FDS1 has been linked through the WA Data Linkage System to the WA Registry for Deaths, as approved by the WA Department of Health Human Research Ethics Committee, to provide validated data on mortality to end-2017.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The matched data from people without diabetes in this study are available from the Western Australian Department of Health but restrictions apply to the availability of these data, which were used under strict conditions of confidentiality for the current study and so are not publicly available. These data are however available from the authors upon reasonable request and with permission of Western Australian Department of Health. Data from the FDS1 are also available on reasonable request.

ORCID iD

Timothy M E Davis http://orcid.org/0000-0003-0749-7411

REFERENCES

1 Harding JL, Shaw JE, Peeters A, *et al*. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. *Diabetes Care* 2014;37:2579–86.
2 Harding JL, Shaw JE, Peeters A, *et al*. Age-specific trends from 2000–2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of more than one million people. *Diabetes Care* 2016;39:1018–26.
3 Rawshani A, Rawshani A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med* 2017;377:300–1.
4 Jørgensen ME, Almdal TP, Carstensen B. Time trends in mortality rates in type 1 diabetes from 2002 to 2011. *Diabetologia* 2013;56:2401–4.
5 Arffman M, Hakkarainen P, Keskimäki I, *et al*. Long-term and recent trends in survival and life expectancy for people with type 1 diabetes in Finland. *Diabetes Res Clin Pract* 2023;198:S0168-8227(23)00055-4.
6 Livingstone SJ, Levin D, Looker HC, *et al*. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. *JAMA* 2015;313:37–44.
7 Rawshani A, Sattar N, Franzén S, *et al*. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in

relation to age at Onset: a nationwide, register-based cohort study. *Lancet* 2018;392:477–86.
8 Thunander M, Petersson C, Jonzon K, *et al*. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Res Clin Pract* 2008;82:247–55.
9 Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. *Pediatr Clin North Am* 2005;52:1553–78.
10 Leslie RD, Evans-Molina C, Freund-Brown J, *et al*. Adult-onset type 1 diabetes: Current understanding and challenges. *Diabetes Care* 2021;44:2449–56.
11 Vanderniet JA, Jenkins AJ, Donaghue KC. Epidemiology of type 1 diabetes. *Curr Cardiol Rep* 2022;24:1455–65.
12 Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. *BMJ Open Diabetes Res Care* 2020;8:e001071.
13 Htike ZZ, Webb D, Khunti K, *et al*. Emerging epidemic and challenges of type 2 diabetes in young adults. *Diabetes Management* 2015;5:473–83.
14 Reynolds K, Saydah SH, Isom S, *et al*. Mortality in youth-onset type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. *J Diabetes Complications* 2018;32:545–9.
15 Mayer-Davis EJ, Bell RA, Dabelea D, *et al*. The many faces of diabetes in American youth: type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for diabetes in youth study. *Diabetes Care* 2009;32:S99–101.
16 Duca L, Sippl R, Snell-Bergeon JK. Is the risk and nature of CVD the same in type 1 and type 2 diabetes *Curr Diab Rep* 2013;13:350–61.
17 Mameli C, Mazzantini S, Ben Nasr M, *et al*. Explaining the increased mortality in type 1 diabetes. *World J Diabetes* 2015;6:889–95.
18 Davis WA, Gregg EW, Davis TME. Temporal trends in cardiovascular complications in people with or without type 2 diabetes: the Fremantle diabetes study. *J Clin Endocrinol Metab* 2020;105:dgaa215.
19 Harding JL, Pavkov ME, Magliano DJ, *et al*. Global trends in diabetes complications: a review of current evidence. *Diabetologia* 2019;62:3–16.
20 Davis TME, Bruce DG, Davis WA. Cohort profile: the Fremantle diabetes study. *Int J Epidemiol* 2013;42:412–21.
21 Davis TM, Zimmet P, Davis WA, *et al*. Autoantibodies to glutamic acid decarboxylase in diabetic patients from a multi-ethnic Australian community: the Fremantle diabetes study. *Diabet Med* 2000;17:667–74.
22 Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. *PLoS One* 2012;7:e39504.
23 Norman PE, Davis WA, Bruce DG, *et al*. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle diabetes study. *Diabetes Care* 2006;29:575–80.
24 Levey AS, Bosch JP, Lewis JB, *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. *Ann Intern Med* 1999;130:461–70.
25 Feldman EL, Stevens MJ, Thomas PK, *et al*. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994;17:1281–9.
26 Holman CDJ, Bass AJ, Rosman DL, *et al*. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. *Aust Health Rev* 2008;32:766–77.
27 United Kingdom prospective diabetes study group. intensive blood-glucose control with Sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet* 1998;352:837–53.
28 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying Prognostic Comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
29 Bryden KS, Dunger DB, Mayou RA, *et al*. Poor prognosis of young adults with type 1 diabetes: a longitudinal study. *Diabetes Care* 2003;26:1052–7.
30 Laing SP, Jones ME, Swerdlow AJ, *et al*. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care* 2005;28:1618–23.
31 ElSayed NA, Aleppo G, Aroda VR, *et al*. 10. cardiovascular disease and risk management: standards of care in Diabetes-2023. *Diabetes Care* 2023;46:S158–90.
32 Nathan DM, Cleary PA, Backlund J-YC, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–53.
33 van Hecke MV, Dekker JM, Stehouwer CDA, *et al*. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. *Diabetes Care* 2005;28:1383–9.
34 Groop P-H, Thomas MC, Moran JL, *et al*. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes* 2009;58:1651–8.
35 Edqvist J, Rawshani A, Adiels M, *et al*. BMI, mortality, and cardiovascular outcomes in type 1 diabetes: findings against an obesity paradox. *Diabetes Care* 2019;42:1297–304.
36 Mühlhauser I, Sawicki PT, Blank M, *et al*. Reliability of causes of death in persons with type I diabetes. *Diabetologia* 2002;45:1490–7.
37 Harriss LR, Ajani AE, Hunt D, *et al*. Accuracy of national mortality codes in identifying Adjudicated cardiovascular deaths. *Aust N Z J Public Health* 2011;35:466–76.