

All-Cause Mortality in the Canterbury (New Zealand) Insulin-Treated Diabetic Registry Population

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OBJECTIVE — To establish all-cause death rates and life expectancies of and risk factors for mortality in insulin-treated diabetic individuals living in Canterbury, New Zealand.

RESEARCH DESIGN AND METHODS — Insulin-treated diabetic subjects ($n = 1,008$) on the Canterbury Diabetes Registry were tracked over 9 years, and their vital status was determined. Death rates were standardized using direct and indirect methods. Cox proportional hazard regression was used to model the effects of demographic and clinical covariates on survival time.

RESULTS — At study entry, age ranged from 2.9 to 92.7 years, with mean 48.7 ± 20.4 years; age at diagnosis was 0.2–88.9 years, mean 34.5 ± 20.0 years; and duration of diabetes was 0.1–58.5 years, mean 14.0 ± 10.6 years. There were 303 deaths in 7,372 person-years of follow-up with a standardized mortality ratio (SMR) of 2.6 (95% CI 2.4–3.0). Relative mortality was greatest for those aged 30–39 years (SMR 9.2 [4.8–16.2]). The death rate for the diabetic cohort standardized against the Segi world standard population was 16.2 per 1,000. Attained age, sex, and clinical subtype were significant predictors of mortality. The SMR for subjects with type 1 diabetes and age at onset <30 years was 3.7 (CI 2.7–5.0), 2.2 (1.8–2.6) for those with onset ≥ 30 years, and 3.1 (2.5–3.7) for subjects suspected of having latent autoimmune diabetes in adulthood or insulin-treated type 2 diabetes. Life expectancy was reduced for both sexes at all ages.

CONCLUSIONS — Mortality rates for insulin-treated diabetic individuals remain high, resulting in shortened life spans relative to the general population. Marked differences in mortality exist between clinical groups of subjects. Further research is needed to improve diabetes classification and to clarify differences in health outcomes.

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Despite improvements in the prognosis of individuals with diabetes (1–6), mortality is still two to four times higher for this population compared with general populations (7–9), with life expectancy reduced by up to one-third (5,10). This research is a prospective cohort study examining mortality in the Canterbury Diabetes Registry insulin-treated population (11,12). Canterbury is a well-defined geo-

graphic and health services region of New Zealand. In 1991, Canterbury had a population of 357,183, 85% of which lived in Christchurch, the province's main urban center. Information on diabetes-related mortality in the Asia-Pacific region is very limited, particularly for type 1 diabetes. In a Western Australian study (13), determination of death rates for type 1 diabetic individuals was not feasible because of the small

number of events in this subject group. Diabetes was found to be a significant predictor of all-cause mortality and coronary heart disease in an elderly Australian community, but again, this study focused on type 2 diabetes (14). In New Zealand, Scragg (15) reported secular trends in mortality (1966–1985), but no distinction was made for type of diabetes, and cases were enumerated through death certificates, which is problematic (16). The Tasmanian (Australian) Diabetes Registry mortality study (9) is the only other research undertaken in the region that is directly comparable to that reported here.

The aims of this study were as follows: 1) to establish all-cause age-sex-specific death rates and life expectancies of insulin-treated diabetic individuals; 2) to compare these with those of the general Canterbury population; 3) to examine the importance of demographic and clinical risk factors as predictors of mortality (1,2,17); and 4) given the current debate over the heterogeneity of type 1 autoimmune diabetes (18–21), to determine whether differences in mortality exist between different clinical subgroups of insulin users.

RESEARCH DESIGN AND METHODS

Study population

Subjects were included on the Canterbury Diabetes Registry's 1984 prevalence database if they were using long-term insulin and Canterbury was their usual place of residence, i.e., they lived most of the year there and were not visiting the region. Procedures for case identification, data acquisition, and case ascertainment of the Registry have been described previously (11,12). Completeness of the registry was estimated to exceed 95%, with the primary case ascertainment method being community-based pharmacy surveys. Secondary identification included review of hospital admissions, attendance at specialist diabetes services, and contact with local general practitioners.

Reflecting recent attempts at reclassification of diabetes (9,18,19), the study cohort was separated into three groups. In

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Abbreviations: SMR, standardized mortality ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Demographic characteristics of study subjects at entry to follow-up (1 January 1984)

Age-group (years)	Age			Age at diagnosis					
	Male	Female	Total	Male		Female		Total	
				n (%)	Insulin at onset	n (%)	Insulin at onset	n (%)	Insulin at onset
0–9	7 (1.4)	6 (1.2)	13 (1.3)	55 (11.0)	55	63 (12.5)	63	118 (11.8)	118
10–19	51 (10.2)	47 (9.3)	98 (9.7)	102 (20.4)	102	84 (16.7)	82	186 (18.5)	184
20–29	67 (13.4)	54 (10.6)	121 (12.0)	77 (15.4)	72	63 (12.5)	57	140 (13.9)	129
30–39	52 (10.4)	61 (12.0)	113 (11.2)	68 (13.6)	52	78 (15.5)	59	146 (14.5)	111
40–49	74 (14.8)	52 (10.3)	126 (12.5)	85 (17.0)	61	73 (14.5)	35	158 (15.7)	96
50–59	96 (19.2)	83 (16.3)	179 (17.8)	67 (13.4)	41	76 (15.1)	48	143 (14.2)	89
60–69	90 (18.0)	113 (22.3)	203 (20.1)	31 (6.2)	24	43 (8.5)	28	74 (7.4)	52
70–79	48 (9.6)	65 (12.8)	113 (11.2)	12 (2.4)	8	21 (4.2)	12	33 (3.3)	20
≥80	15 (3.0)	27 (5.3)	42 (4.2)	2 (0.4)	2	3 (0.6)	2	5 (0.5)	4
Total	500	508	1,008	499	417	504	386	1,003*	803

Data are n (%) or n. Insulin at onset indicates the number of subjects commencing insulin within 12 months of diagnosis. *Data are missing for five subjects.

the absence of adequate biomarker data on a sufficient number of subjects, categorization was based on age at onset of diabetes and commencement of insulin therapy. This approach was also used by Riley et al. (9). Group A comprised all subjects who had been diagnosed at age <30 years and who commenced insulin therapy within 12 months of diagnosis. It is assumed that this group has type 1 diabetes. Group B comprised patients defined by age at onset of diabetes of ≥30 years and commencement of insulin treatment within 12 months of diagnosis, indicating adult-onset type 1 diabetes. Group C subjects are those for whom insulin therapy commenced >12 months after diagnosis. While age at onset is not part of this categorization, virtually all of these subjects had maturity-onset diabetes. These subjects are assumed to have latent autoimmune diabetes or insulin-treated type 2 diabetes (22,23).

At commencement of follow-up on 1 January 1984, there were 1,008 subjects (500 male, 508 female). Age at entry to the study ranged from 2.9 to 92.7 years; 11% were <20 years and 15.4% were ≥70 years of age (Table 1). Female subjects were on average older than male subjects (mean ± SD 50.2 ± 20.7 vs. 47.3 ± 20.0, $P = 0.028$). Mean age at onset of diabetes was 34.5 ± 20.0 years (range 2.5 months to 88.9 years), and duration of diabetes was 14.0 ± 10.6 years (newly diagnosed to 58.5 years). Of the total cohort, 42.9% had been diagnosed with diabetes <10 years at time of entry to the study. Few subjects had diabetes of >30 years' duration (8.8%), with only four individuals having had diabetes for >50 years. Only 25 subjects were of

non-European background (16 Maori, 2 Pacific Islanders, and 7 Chinese), a number reflecting the lower incidence of type 1 diabetes in these ethnic groups (24). Of these, 16 subjects were classified as group B, 7 as group A, and only 2 as group C.

Data necessary to classify subjects into groups A, B, or C were missing for five individuals. Of the remaining 1,003 subjects, 431 were classified as group A, 372 as group B, and 200 as group C. Group A had relatively more male subjects (53.1% male), group B was sex-balanced (50.5% male), and group C had more female subjects (59.0% female) ($P = 0.017$). The mean age of subjects in group A at baseline was 31.9 ± 17.0; group B, 60.8 ± 12.6; and group C, 64.4 ± 10.9 years ($P < 0.001$). Mean age at diagnosis for group A was 16.4 ± 13.0; group B, 49.0 ± 12.6; and group C, 49.3 ± 12.5 years. Mean duration of diabetes for group A subjects at 15.5 ± 12.3 years was similar to that for those in group C (15.1 ± 7.6 years), but significantly greater than that for subjects in group B (11.8 ± 9.4 years; $P < 0.001$). Overall, male subjects were more likely than female subjects to start insulin at or within 12 months of diagnosis ($P = 0.006$), as were those in the younger than older decades ($P < 0.001$) (Table 1).

Follow-up

The study cohort was tracked over 9 years, with vital status determined as of 1 January 1993. Review of patient attendance on specialist diabetes and hospital services was the most productive and efficient tracking method because 1) every individual using New Zealand's nationwide public hospital

system is identified by a unique patient identification code under which all attendances and admissions are recorded irrespective of place of hospitalization, 2) public hospital inpatient and specialist diabetes outpatient clinical and educational services are provided through one centralized health service in Canterbury, and 3) >70% of Canterbury's insulin-treated diabetic population attend this service for annual review each year. The status of ~85% of subjects was determined using this method. The remaining patients were then tracked via search of electoral rolls, telephone books, and government death registries and through contacting the lay Diabetes Society, local community-based doctors, and patients' families. Overall, 4.1% of the total cohort were lost to follow-up through known emigration overseas or because they could not be traced over the entire study period. The mean age at study entry of the 19 migrants was 29.9 ± 19.4 years and that of the 22 untraced subjects was 34.3 ± 12.4 years.

Mortality data

Death certificate records registered at local branches and at the national office of the New Zealand Department of Justice Registrar of Births, Deaths and Marriages were reviewed for subjects identified as having died during the follow-up period. Demographic information was checked, and data on date, place, and cause(s) of death were obtained. Death notifications in local newspapers provided additional case identification and verification. Vital statistics and census data to derive age-sex-specific death rates for Canterbury's general

Mortality in Canterbury's type 1 diabetic population

Table 2—Mortality in Canterbury's insulin-treated diabetic population compared with the general population (1 January 1984–1 January 1993)

Age-group (years)	Follow-up (person-years)	Observed number of deaths	Death rate (per 1,000 person-years) (95% CI)	Death rate in the Canterbury population (per 1,000 person-years)	Expected number of deaths	SMR (95% CI)
0–29						
Female	674.5	2	3.0 (0.4–10.8)	0.67	0.5	4.43 (0.48–14.44)
Male	800.5	2	2.5 (0.3–9.0)	1.24	1.0	2.01 (0.24–7.22)
Total	1,475.0	4	2.7 (0.7–6.9)	0.98	1.5	2.67 (0.73–6.84)
30–39						
Female	557.4	5	9.0 (2.9–20.9)	0.96	0.5	10.00 (3.24–23.30)
Male	462.0	7	15.2 (6.1–31.2)	1.66	0.8	8.75 (3.51–18.03)
Total	1,019.4	12	11.7 (6.1–20.5)	1.31	1.3	9.23 (4.77–16.15)
40–49						
Female	478.0	4	8.4 (2.3–21.4)	1.76	0.8	5.00 (1.36–12.80)
Male	533.7	8	15.0 (6.5–29.5)	2.73	1.5	5.33 (2.30–10.50)
Total	1,011.7	12	11.9 (6.1–20.8)	2.24	2.3	5.22 (2.70–9.14)
50–59						
Female	487.4	13	26.7 (14.2–45.6)	4.73	2.3	5.65 (3.01–9.66)
Male	644.4	20	31.0 (19.0–47.8)	8.45	5.4	3.70 (2.26–5.70)
Total	1,131.8	33	29.2 (20.1–41.0)	6.59	7.7	4.29 (2.95–6.03)
60–69						
Female	818.1	37	45.2 (31.8–62.4)	12.31	10.1	3.66 (2.58–5.04)
Male	621.2	39	62.8 (44.6–85.7)	22.48	14.0	2.79 (1.98–3.81)
Total	1,439.2	76	52.8 (41.1–67.5)	16.86	24.0	3.17 (2.51–3.99)
70–79						
Female	598.7	45	75.2 (54.8–100.7)	33.96	20.3	2.22 (1.62–2.97)
Male	439.5	53	120.6 (90.4–158.5)	57.83	25.4	2.09 (1.57–2.75)
Total	1,038.2	98	94.4 (71.1–115.5)	43.78	45.8	2.14 (1.75–2.62)
≥80						
Female	165.9	41	247.1 (177.2–335.1)	113.33	18.8	2.18 (1.56–2.96)
Male	90.7	27	297.7 (196.2–434.6)	145.39	13.2	2.05 (1.35–2.99)
Total	256.6	68	265.0 (207.2–338.1)	123.15	32.0	2.13 (1.67–2.72)
Total						
Female	3,780	147	38.9 (33.0–45.9)	8.09	53.2	2.76 (2.34–3.26)
Male	3,592	156	43.4 (37.0–51.0)	8.88	61.4	2.54 (2.16–2.98)
Total	7,372	303	41.1 (36.7–46.1)	8.48	114.6	2.64 (2.36–2.96)

population were purchased from Statistics New Zealand for the census years 1986 and 1991.

Statistical methods

Age-sex-specific death rates for the diabetic population were calculated using person-years of follow-up accumulated by each age-sex group. Person-years for subjects lost to follow-up or who had moved overseas were calculated as the time to the last known date of contact. Mortality estimates were standardized using both indirect and direct methods (25,26). Age-sex-standardized mortality ratios (SMRs) were calculated to compare mortality in the study cohort to that of Canterbury's general population, with 95% CIs determined using methods outlined by Lilienfeld and Lilienfeld (26). To allow

international and future comparison, death rates age-standardized against the Segi standard world population (26,27) are also presented. Two forward stepwise Cox proportional hazards models (7,13,28–30), with *P* values for entry of covariates into the regression set at 0.05, were generated to investigate the combined effects of (attained) age, sex, age at onset of diabetes, duration of diabetes, and diabetes group on survival time. Stepwise regression objectively selects the variables according to their predictive power. The regression models were produced using StatView (31). Abridged actuarial life tables to derive life expectancies were constructed using the 10-year age-specific mortality rates (32,33). It was assumed that group B and C subjects experienced the same mortality rates as the general population up to age 30 years.

RESULTS — A total of 303 individuals died during the 9 years, with no difference in number by sex (51.5% male, 48.5% female). The mean age of those who died was 65.3 ± 14.3 years, and mean duration of diabetes was 16.5 ± 11.2 years at baseline, compared with 41.6 ± 18.5 years ($P < 0.001$) and 13.0 ± 10.1 years ($P < 0.001$), respectively, for survivors. Mean age at onset was also significantly different (48.6 ± 18.3 vs. 28.5 ± 17.5 years, $P < 0.001$). Age at death ranged from 18.2 to 96.7 years. Female subjects were older than male subjects (mean 71.2 ± 14.1 vs. 67.8 ± 13.8 years, $P = 0.037$). Only four deaths (1.3%) occurred in individuals <30 years of age, and most were in those aged ≥ 60 years (79.9%) (Table 2). Duration of diabetes at time of death ranged from 0.2 to 60.2 years (mean 20.8 ± 11.6).

Table 3—Rates of mortality by diabetes classification

Age-group (years)	Follow-up (person-years)	Observed number of deaths	Death rate (per 1,000 person-years) (95% CI)	SMR (95% CI)
Group A				
0–29	1,473.4	4	2.7 (0.7–6.9)	2.67 (0.73–6.84)
30–39	911.1	12	13.2 (6.8–23.1)	10.00 (5.17–17.50)
40–49	604.7	8	13.2 (5.7–26.0)	5.71 (2.46–11.25)
50–59	356.9	11	30.8 (15.4–55.1)	4.58 (2.29–8.20)
60–69	141.5	6	42.4 (15.6–92.4)	2.50 (0.68–8.40)
70–79	61.2	3	49.0 (10.1–143.1)	1.03 (0.21–3.10)
≥80	1.9	1	526.3 (13.3–2,931.5)	3.33 (0.08–18.50)
Total	3,550.7	45	12.7 (9.3–17.0)	3.72 (2.71–4.98)
Group B				
0–29	—	—	—	—
30–39	91.8	0	0.0	—
40–49	338.1	2	5.9 (0.7–21.3)	2.86 (0.35–10.32)
50–59	545.4	13	23.8 (12.7–40.7)	3.33 (1.77–5.69)
60–69	801.8	37	46.1 (32.5–63.6)	2.70 (1.9–3.72)
70–79	641.3	54	84.2 (63.4–110.3)	1.91 (1.44–2.50)
≥80	145.5	34	233.7 (162.0–327.0)	1.87 (1.3–2.54)
Total	2,563.9	140	54.6 (46.1–64.6)	2.16 (1.82–2.56)
Group C				
0–29	1.6	0	0.0	—
30–39	16.5	0	0.0	—
40–49	67.2	1	14.9 (0.4–83.0)	5.00 (0.13–27.85)
50–59	229.0	9	39.3 (18.0–74.7)	6.00 (2.75–11.40)
60–69	496.0	33	66.5 (45.8–93.8)	4.13 (2.84–5.81)
70–79	335.7	41	122.1 (89.4–166.1)	2.79 (2.00–3.78)
≥80	101.9	30	294.4 (198.7–421.0)	2.34 (1.58–3.35)
Total	1,247.9	114	91.4 (75.8–110.8)	3.06 (2.53–3.69)

SMR was standardized against Canterbury's general population. †Group A includes subjects who were diagnosed at age <30 years and who commenced insulin therapy within 12 months of diagnosis. Group B comprises cases defined by age at onset of diabetes of ≥30 years and commencement of insulin treatment within 12 months of diagnosis. Group C subjects are those in whom insulin therapy commenced >12 months after diagnosis.

Female subjects provided 3,780 person-years of follow-up and male subjects 3,592 person-years, giving nonsignificantly different crude death rates of 38.9 deaths per 1,000 person-years (95% CI 33.0–45.9) for female subjects and 43.4 deaths per 1,000 person-years (37.0–51.0) for male subjects. The age-specific death rates increased significantly over the age structure of the population, reaching 265 deaths per 1,000 person-years in those aged ≥80 years. Applying these age-specific death rates to the Segi standard world population gives age-adjusted death rates of 16.2 per 1,000 for the diabetic cohort and 5.3 for Canterbury's general population.

With both age and sex standardization, mortality in the diabetic cohort was 2.64 (SMR, 95% CI 2.36–2.96) times higher than that for Canterbury's population in general (Table 2). Excess mortality applied for both male and female subjects

and was documented for diabetic subjects in all age-groups (SMR >2.00) except for those aged 0–29 years. Excess mortality peaked in the 30–39 years age-group, with an SMR of 9.23 (4.77–16.15).

Within the three clinical subgroups, 45 (10.4%) group A, 140 (37.6%) group B, and 114 (57.0%) group C patients had died by the end of follow-up ($P < 0.001$). Four deaths, all of female subjects, could not be attributed to a clinical group. These subjects were excluded from subsequent analyses. Age-specific death rates and SMRs for the three groups are given in Table 3. There were no sex differences in the age-specific death rates. The crude death rates were heavily influenced by the different age structures of the three groups. Standardization against the Segi standard world population gives age-adjusted rates of 17.2, 11.5, and 28.6 deaths per 1,000 person-years for groups A, B, and C, respectively (assigning Canter-

bury's death rate of 0.98 per 1,000 to the 0–29 years age-group for groups B and C).

Standardized for age and sex against the Canterbury population, group A subjects had an SMR of 3.72 (2.71–4.98), which was higher than that of the two other groups (Table 3). SMR was lowest in group B, although mortality was still double that of the general population (2.16 [1.82–2.46]). As indicated in Table 3, the high excess mortality noted for the 30–49 years age-group is largely attributable to group A subjects, whereas increased risk in older subjects is more reflective of the high relative mortality of group C subjects.

Results for duration of diabetes (not presented in detail here) are inconclusive, but suggest that there may be a difference in standardized mortality (relative to Canterbury's general population) between subjects with diabetes duration <20 years and ≥20 years, with SMRs of 2.44 (2.08–2.86) and 2.93 (2.48–3.47), respectively. Those most at risk of high relative mortality were subjects with duration of diabetes ≥20 years aged 30–39 years (SMR 18.60 [8.02–36.64]) and 40–49 years (SMR 7.14 [2.86–14.71]). However, these SMRs are based on small numbers of observed deaths and statistically are difficult to distinguish from those recorded for age-matched subjects with duration of diabetes <20 years (SMR 4.44 [1.21–11.37] and 3.13 [0.85–8.01], respectively).

Two stepwise proportional hazard models (Table 4) show the independent effects of age, sex, age at diagnosis, duration of diabetes, and diabetes group on time to death. Based on probability values, age was found to be the dominant predictor of risk (hazard ratio = 1.08 per 1-year increase in age) when all five variables were free to enter the model (model 1). Given this and the presence of collinearity, age was excluded from model 2 in an attempt to isolate the effects of age at onset and duration of diabetes on relative hazard (correlation coefficients between these three variables were significant at $P < 0.001$).

Sex was a significant factor in both models, with a 44% increase in hazard over the study period for male versus female subjects. Diabetes group (with group B, which has the lowest SMR, as the reference population) also exerts a significant independent effect on risk of death. There was a 46% increase in hazard for group C versus group B subjects after controlling for the other covariates. Both age at onset and duration of diabetes were significant factors

Table 4—Cox proportional hazards models of time to death

Covariate	Estimate of regression coefficient (β)	P	exp(β)	95% CI
Model 1				
Age	0.07	<0.0001	1.08	1.07–1.09
Sex (male)	0.37	0.0016	1.44	1.15–1.81
Group		0.0078		
A	0.29	0.1474	1.34	0.90–1.97
C	0.38	0.0024	1.47	1.15–1.88
Model 2				
Sex (male)	0.37	0.0016	1.45	1.15–1.82
Age at onset	0.07	<0.0001	1.08	1.06–1.09
Duration	0.08	<0.0001	1.08	1.06–1.09
Group		0.0109		
A	0.24	0.3120	1.27	0.80–2.03
C	0.38	0.0028	1.46	1.14–1.87

Exp(β) is the increase in relative hazard by a 1-year increase in age, age at onset, and duration of diabetes, or the change in hazard for male subjects relative to female subjects and group A and C relative to group B. For model 1, age at onset and duration of diabetes were not significant at $P = 0.05$ and therefore are not included in the regression. For model 2, age was excluded from the model.

when age is excluded (model 2). The regression coefficient for duration of diabetes of 0.08 indicates that a patient who had diabetes for 20 years had a 4.48-fold increase in risk of dying over the 9-year follow-up period relative to a newly diagnosed individual of the same sex, age at diagnosis, and type of diabetes. However, given the similarity in the regression coefficients in models 1 and 2, this may not be due to the impact of duration of diabetes but rather age, i.e., the subject being 20 years older.

Life expectancy was reduced for both sexes and for all age-groups in the diabetic cohort compared with Canterbury's general population. Life expectancy at birth was 79.5 years for Canterbury women and 72.6 years for men, but 61.8 years for diabetic women and 57.5 years for diabetic men. As for the general population, life expectancy for female diabetic patients was higher in all age-groups than for male diabetic patients. The differential in life expectancy between the diabetic and the general population diminished with age (Fig. 1). Nevertheless, at 70 years of age, the average remaining years of life for diabetic female and male subjects were 9.1 and 7.1 years, compared with 15.1 and 11.8 years for Canterbury's general population. In terms of the probability of surviving to this age, only one of three diabetic individuals would be expected to be alive at 70 years of age, compared with three of every four individuals in the general population.

Group A subjects had the lowest life expectancy at birth (59.7 years): 1.9 years

below that for group C, 7.1 years below group B, and 16.5 years below that of the general population (Fig. 1). After 50 years of age, there was no difference in life expectancy between group A and B subjects. Some 17% of group A subjects would not be expected to survive to age 40 years. Reduction in life expectancy between ages 40 and 69 years was most marked for group C patients. While group C subjects

have a 97% chance of surviving to 40 years of age, 41% of these patients would not be expected to survive to 70 years of age.

CONCLUSIONS — The Canterbury Diabetes Registry cohort includes all individuals using insulin in the community. Therefore, mortality across the full spectrum of type 1 diabetic individuals could be studied. The two main methodological problems in measuring diabetes-related mortality are the representativeness of the study population and appropriateness of statistical methods (2,7). This study overcomes these problems, the longitudinal population perspective used, and the avoidance of death certificates as the source of enumeration giving confidence that the findings accurately describe the mortality experience of this diabetic population.

The results confirm that diabetes is associated with high levels of mortality and shortened life spans. All-cause mortality in Canterbury's insulin-treated diabetic population was two and a half times higher than that in the general population, standardizing for age and sex. This level of relative mortality is consistent with that recorded in Tasmania (SMR 2.2 [2.0–2.4]), the Tasmanian Diabetes Registry cohort (9,34) being similar in demographic and clinical characteristics to the current study population. In Canterbury, relative mortality

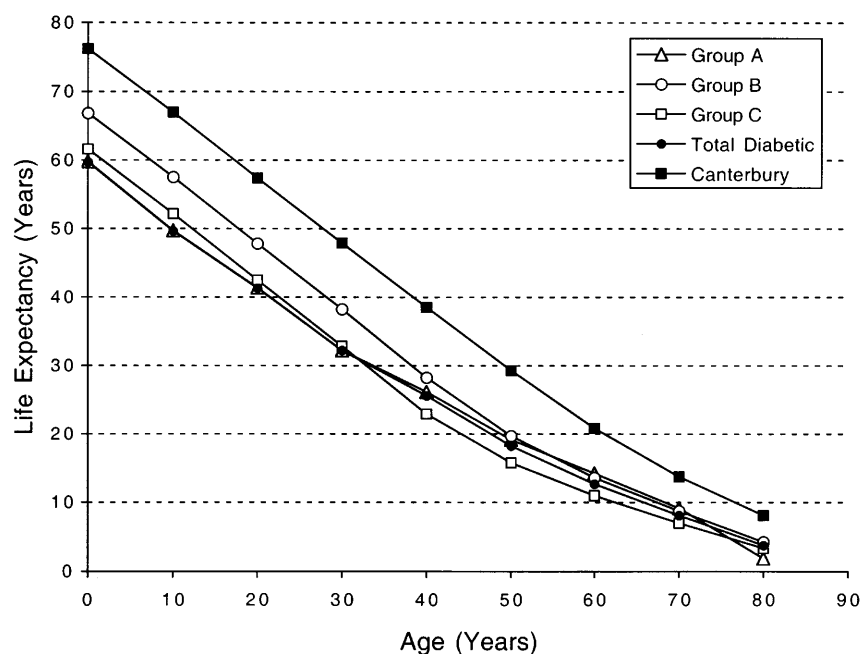


Figure 1—Age-specific life expectancies for Canterbury's insulin-treated diabetic cohort and by clinical subtype versus Canterbury's general population.

peaked in the 30–39 years age-group. High excess mortality has also been noted in Scandinavia for this age-group (1,2,7). This is postulated to reflect the cumulative impact of renal disease in juvenile-onset patients with long duration of diabetes.

The majority of studies indicate that there are no sex differences in mortality associated with type 1 diabetes (1–3,10,35,36). In the Canterbury cohort, the two Cox proportional hazard regression models, which describe the cumulative experience of the cohort over the study period, showed sex to be a significant predictor of death after controlling for age effects. Green and Hougaard (7) also used proportional hazard modeling to determine the effects of sex and age at onset of diabetes on mortality in type 1 diabetic individuals. Both studies show a 40% increase in hazard for male relative to female subjects over the respective follow-up periods. Female patients outlived male patients at all ages. Sex differentials in diabetes mortality thus appear to parallel those within the general population.

Few studies have measured the impact of diabetes on life expectancy. In type 1 diabetes, the generally held view is that of Panzram (6), who reported shortened life spans up to 70 years of age, after which there was little or no difference from those without diabetes. In contrast, this study shows marked reductions in life expectancy even in the very old. While it can be concluded that the calculated life expectancies of 62 years for female and 58 years for male subjects indicate a significant disease burden, these figures need to be interpreted within the context of their derivation. They assume that the mortality rates observed in the study cohort over the follow-up period would apply to an individual born today. However, >40% of the cohort were diagnosed before 1970. Calendar time periods, used as surrogates for different treatment eras, have been shown to be a predictor of survival (1–3). Although unable to differentiate between types of diabetes, Scragg (15) reported that diabetes-related death rates, based on death certificate data, declined in New Zealand over the period 1966–1985. Most of this decline occurred, however, in older age-groups, with no change in the 25–54 years age bracket. While life expectancies are likely to be higher in the future, the magnitude of the differences between the diabetic and general populations suggest that outcomes for diabetic individuals will remain poor, especially in young and middle-aged groups.

This study shows that there are significant differences in the mortality of the three identifiable clinical subgroups of insulin users. The results confirm that relative mortality is highest in child and young adult-onset patients, with nearly a fourfold increase in mortality compared with the background population. This is similar to the finding from Tasmania. A lower SMR of 2.38 was reported in Leicestershire (3), but the oldest age at which a patient died in this study was only 51 years (3). In the Canterbury cohort, half of the deaths occurred at >50 years of age. Joner and Patrick (37) also report a lower SMR of 2.07 for Norway, but the attained age of all subjects was <30 years of age. This level of relative mortality is consistent with that found for the 0–29 years age-group. Similarly, Nystrom et al. (38) reported a SMR of 2.1 for young-onset (15–34 years) type 1 patients living in Sweden, although the duration of follow-up was short and there were only 18 recorded deaths in the study. It should be noted that while SMRs permit comparison of the direction of the ratios and basic consistency of findings, they do not give the underlying levels of mortality within these different populations. Without using a common standard population to control for varying age structures, the death rates cannot be compared directly (27).

Results in the literature are conflicting as to whether age at diagnosis is a significant predictor of mortality for type 1 diabetes. Some studies report no relationship between age at onset and chances of survival, especially when controlling for duration of diabetes (3,37), whereas others found relative mortality decreased with increasing age at onset and increased with duration of diabetes up to ~20 years' duration, after which it declined (1,2,7). However, the problem of colinearity between attained age, age at diagnosis, and duration of diabetes in proportional hazard regression modeling makes interpretation of results difficult (1,17). In Canterbury, attained age, sex, and diabetes group were the key predictors of diabetes mortality. Age at onset of diabetes became a significant factor only when age was excluded from the regression. However, the resultant coefficient is contrary to other findings, indicating increasing mortality with increasing age at onset while controlling for duration of diabetes and diabetes type. This most likely reflects a substitution rather than a real effect in the modeling, with age at diagnosis and duration of diabetes mirroring the risk associated with increasing age.

There are marked differences in the survival of the three diabetes groups, group B individuals having lower relative mortality rates and longer life expectancies. Young-onset patients must survive relatively high death rates in early to middle adult life to achieve life expectancies similar to subjects diagnosed in adulthood or in the general population. Group C individuals, indicative of those who have slowly progressed to insulin deficiency or who had insulin-treated type 2 diabetes, had three times the risk of death than age-sex-matched individuals in the general population. These results support Swedish and Tasmanian research showing significant excess mortality in this group of patients (9,38). The high rates of mortality in the >40 years age-group is largely attributable to group C subjects.

A major limitation of this study is the lack of immunologic, genetic, and clinical data for subjects, which would have allowed a more definitive classification of diabetes and subsequent analysis by diabetes type. The results for groups B and C may be affected by misclassification and heterogeneity. However, the degree of difference in mortality and life expectancy between the three groups, combined with the consistency of findings particularly with the Tasmanian study (9), suggest that very real differences do exist between clinical groups of insulin-treated subjects.

The merits of delaying the onset of type 1 diabetes in susceptible children have been debated widely in the literature. The findings of this research indicate that emphasis should also be given to the clinical application of autoimmune markers for the detection of latent type 1 diabetes. This may prevent incorrect diagnosis of type 2 diabetes and enable early treatment with insulin rather than oral agents (23,39–41). The effects of future treatment approaches of immune modulation and early commencement of insulin therapy on change in complication status and survival times need to be measured in both children and adults with type 1 diabetes. For those subjects with impending β -cell failure, earlier initiation of insulin therapy, lipid modification, and blood pressure control are possible approaches that could easily be implemented now as plausible strategies to improve the documented poor survival outcomes (42). Researching the causes of death will assist in the identification of appropriate early interventional treatment strategies.

This study provides a baseline from which trends in mortality can be established and improvements in health outcomes gauged. Research into cause-specific mortality is currently being undertaken. However, further investigation and refinement of the classification of diabetes is needed to confirm and clarify those mortality differentials between clinical subgroups indicated by this research.

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