An Inverse Relationship Between Age of Type 2 Diabetes Onset and Complication Risk and Mortality: The Impact of Youth-Onset Type 2 Diabetes

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OBJECTIVE

This study compared the prevalence of complications in 354 patients with T2DM diagnosed between 15 and 30 years of age ($T2DM_{15–30}$) with that in a duration-matched cohort of 1,062 patients diagnosed between 40 and 50 years ($T2DM_{40–50}$). It also examined standardized mortality ratios (SMRs) according to diabetes age of onset in 15,238 patients covering a wider age-of-onset range.

RESEARCH DESIGN AND METHODS

Complication status was assessed according to a standard protocol and extracted from our electronic database. Survival status was ascertained by data linkage with the Australian National Death Index. SMRs were calculated in comparison with the background Australian population and analyzed according to age of onset.

RESULTS

After matching for duration, despite their younger age, $T2DM_{15–30}$ had more severe albuminuria ($P = 0.004$) and neuropathy scores ($P = 0.003$). $T2DM_{15–30}$ were as commonly affected by metabolic syndrome factors as $T2DM_{40–50}$ but less frequently treated for hypertension and dyslipidemia ($P < 0.0001$). An inverse relationship between age of diabetes onset and SMR was seen, which was the highest for $T2DM_{15–30}$ (3.4 [95% CI 2.7–4.2]). SMR plots adjusting for duration show that for those with $T2DM_{15–30}$, SMR is the highest at any chronological age, with a peak SMR of more than 6 in early midlife. In contrast, mortality for older-onset groups approximates that of the background population.

CONCLUSIONS

The negative effect of diabetes on morbidity and mortality is greatest for those diagnosed at a young age compared with T2DM of usual onset. These results highlight the growing imperative to direct attention toward young-onset T2DM and for effective interventions to be applied before middle age.

Type 2 diabetes is well recognized to be a heterogeneous disorder, and its effect on morbidity and mortality may not be identical within this diagnosis. No longer just a disorder of mature age, there is now a well-recognized trend toward younger people presenting with this disease, particularly for some ethnic groups. Adolescents accounted for less than 4% of incident type 2 diabetes cases in the U.S. 15 years ago, but in a more

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recent report, 45% of new cases were in this category. The net result is a widening of the clinical spectrum, with age of diabetes onset increasingly recognized as an important factor in the heterogeneity of risk within this diagnosis.

The landmark Search for Diabetes in Youth (SEARCH) and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) studies, among others, have contributed to an understanding that type 2 diabetes presenting at a young age is of a particularly aggressive nature and have highlighted the challenges in the management of this patient group (1,2). Young people with type 2 diabetes are likely to be obese, with a clustering of unfavorable cardiometabolic risk factors all present at a very early age (3,4). In adolescents with type 2 diabetes, a 10–30% prevalence of hypertension and an 18–54% prevalence of dyslipidemia have been found, much greater than would be expected in a population of comparable age (4). In another study of patients with type 2 diabetes younger than 20 years of age, aortic pulse wave velocity was already higher than that of age-matched control subjects, indicating an increased degree of arterial stiffness (5). Most recently, results from the TODAY study have clearly documented the progression of cardiovascular disease (CVD) risk factors despite optimal within-trial interventions (6,7). These all portend a poor long-term prognosis, but there are still relatively limited data on long-term complication status and mortality risk in youth with type 2 diabetes.

Only a few studies have looked at the question of complications according to age of disease onset. More specifically, few data are available to assess whether the risk is truly in excess of that seen in diabetes presenting in the more usual middle age and beyond, after accounting for disease duration. Hillier and Pedula (8) reported a higher relative risk of macrovascular disease in those diagnosed with type 2 diabetes between 18 and 44 years of age than in those identified after 45 years of age, when each group was compared with an age-matched population without diabetes. Similarly, Song and Hardisty (9) showed that in cohorts with type 2 diabetes with disease onset before and after 40 years of age, by the sixth decade of life, a substantially higher risk of CVD is seen in those with the earlier onset of diabetes. Whether the excess risk seen in younger cohorts is simply the result of a longer diabetes duration at any attained age or whether there is an underlying enhanced susceptibility to complications is less clear.

Similarly, few data are available on the survival of individuals with young-onset type 2 diabetes, and this lack of robust clinical data has prompted the use of a Markov modeling approach by investigators. Extrapolating from the UK Prospective Diabetes Study cohort, Rhodes et al. (10) project a shortening of life expectancy by 15 years for type 2 diabetes in adolescents. Narayan et al. (11) used the same modeling approach to examine data from the National Health Interview Survey in the U.S. They similarly found that non-Hispanic white individuals diagnosed with diabetes at the age of 20 years would lose 15.3 years of life expectancy (11). We have found that for individuals with young-onset type 2 diabetes, survival is worse than for type 1 diabetes of similar age of onset (3,12). Given that young patients with type 2 diabetes are still a relatively new clinical cohort, a comparative perspective on long-term mortality has hitherto been lacking.

In this two-part study, we examined the effect of age of onset on *1*) diabetes complications after controlling for diabetes duration and *2*) the standardized mortality ratio (SMR). In the first part, prospectively collected clinical complications data from 354 patients with young-onset type 2 diabetes diagnosed between the ages of 15 and 30 years ($T2DM_{15–30}$) were compared with 1,062 subjects with type 2 diabetes onset between the ages of 40 and 50 years ($T2DM_{40–50}$), after matching for duration of known diabetes. Groups with older age were not used for direct comparison to minimize the additional confounding effect of chronological age on macrovascular complications. In the second part, we ascertained the mortality status of 15,238 patients with type 2 diabetes by linkage with the Australian National Death Index and related the findings to the age of diabetes onset. The effect of diabetes on mortality according to age of onset is difficult to compare directly given the confounder of intrinsically higher mortality rates related to age itself. Thus, this study standardized mortality rates to the general Australian population and stratified by age of onset of diabetes. In this way, the relative effect of diabetes beginning at different life stages can be more clearly compared.

RESEARCH DESIGN AND METHODS

Diabetes Database and Collection of Clinical Information

The Royal Prince Alfred Hospital Diabetes electronic database contains demographic and clinical information from patients who have attended the Royal Prince Alfred Diabetes Centre in Sydney Australia since 1986. Diabetes was defined by World Health Organization criteria (13). The diagnosis of type 2 diabetes was made on clinical grounds by the treating physician. Age-of-onset data are available for all patients in this study. The age of onset was taken from the primary care correspondence or from the date of the defining laboratory test. If neither was available, patient recall was relied on. If only the year of diagnosis was known, the default date of 1 January was used to calculate age of onset. All patients reported in this complications component of the study had a clinical and complications assessment via a standardized protocol and data entered in a purpose built database (14). Data quality is linked to the model of care; data were frequently reviewed as the clinical correspondence is linked to data entry and previously described and evaluated (14,15).

In brief, retinopathy was assessed by direct funduscopy with pupils dilated or by digital retinal photography in recent years. Albuminuria was determined by collection of spot urine samples and considered abnormal if the albumin concentration was greater than 30 mg/L or if the urine albumin-to-creatinine ratio was greater than 3.5 and 2.5 mg/mmol for females and males, respectively. Neuropathy assessment was by examination of ankle reflexes and testing of vibration perception threshold (volts) with a biothesiometer adjusted for age by expressing data as a Z score. Macrovascular disease and risk factors were assessed by clinical history of events or relevant symptoms and measurements of sitting blood pressure and lipid profiles. The degree of hyperglycemia was assessed by measurement of HbA_{1c} using the high-performance liquid chromatography method, and long-term glycemic control was documented by the calculation of updated HbA_{1c}, adjusting for the time between visits and the number of measurements (16).

Complications

To examine the differential effect of age of onset on clinical parameters and diabetes, the complication status of 354 patients with $T2DM_{15–30}$ was identified from the database and compared with a 1:3 matched sample of 1,062 patients with $T2DM_{40–50}$ with the same duration of known diabetes. Unadjusted mortality rates and cause of death are also presented for this cohort.

Mortality and SMR

A total of 24,415 names of patients, including 15,238 with type 2 diabetes from our database, were submitted to The National Death Index (NDI) of the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. An NDI standard linkage protocol was followed to match individuals from the two databases using the following fields: ID number, surname, first given name, second given name, third given name, sex, date of birth, date of last contact, and state of residency. When matching was ambiguous, mortality was confirmed by checking with the area-wide hospital database. This protocol has been validated in other populations and found to have a high sensitivity in determining survival (17). Because of a time lag in the updating of the NDI database, the primary cause of death was only available in 3,630 records, and data from these individuals were used to examine the specific cause of death. For deaths in and after 1997, all causes of death are available and are coded according to ICD-10. For deaths before 1996, the underlying cause of death was coded according

Table 1—Clinical profile and mortality of patients with T2DM (N = 1,416) grouped by age of diagnosis and matched for diabetes duration

	$T2DM_{15–30}$ n = 354	$T2DM_{40–50}$ n = 1,062	Test statistics P value
Age diagnosed (years)	25.6 ± 3.7	45.2 ± 2.9	<0.0001
Duration of diabetes at last visit (years)	11.6 (4.5–22.6)	11.4 (4.5–21.7)	Matched
Male (%)	50.6	50.6	Matched
Age at last visit (years)	40.4 ± 12.6	59.1 ± 10.7	<0.0001
Family history of diabetes (%)	80.9	67.1	<0.0001
Number of family members affected with diabetes	2.4 ± 2.0	2.0 ± 1.6	0.02
Updated HbA_{1c}			
Percentage (%)	8.1 ± 1.6	8.0 ± 1.7	0.3
IFCC (mmol/mol)	65.5 ± 17.7	64.3 ± 18.2	0.3
Diabetes treatment (%)			0.0002**
Diet	9.6	8.2	
Tablets	37.3	49.9	
Insulin	53.1	41.9	
BMI (kg/m^2)	32.2 ± 7.6	31.2 ± 7.4	0.04
Blood pressure (mmHg)			
Systolic	126 ± 17	132 ± 19	<0.0001
Diastolic	78 ± 10	77 ± 11	0.2
Blood pressure treatment (%)	49.3	68.1	<0.0001
Cholesterol (mmol/L)	5.2 ± 1.5	4.8 ± 1.2	<0.001
Triglyceride (mmol/L)	1.9 (1.3–3.0)	1.6 (1.2–2.5)	0.001
Statin treatment (%)	38.1	51.5	0.0001
Smoking (%)	41.3	45.3	0.2
Retinopathy (%)	37.0	35.4	0.5
Vibration perception threshold Z score*	2.3 ± 1.3	2.0 ± 1.2	0.003
Albuminuria (%)	47.4	41.1	0.07
Urine albumin concentration (mg/L)	19.1 (6.0–114.1)	14.5 (6.5–49.0)	0.004
Any macrovascular disease (%)	14.4	23.7	<0.0001
Peripheral arterial disease (%)	3.8	6.5	0.07
Ischemic heart disease (%)	12.6	17.5	0.02
Stroke (%)	4.3	7.0	0.1
Death, n (%)	39 (11.0)	204 (19.2)	<0.0001
Age at the time death (years)	52.9 ± 4.7	68.6 ± 12.4	<0.0001
Duration of diabetes at the time of death (years)	26.9 (18.1–36.0)	25.1 (15.3–32.0)	<0.0001
Cause of death (%)			0.7**
Vascular	50.0	42.8	
Cancer	7.1	10.1	
Other	42.9	47.1	

Results are presented as mean ± SD, as median (IQR), or as indicated. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine. *Vibration perception threshold is tested by biothesiometer adjusted for age by expressing data as a Z score. **P for differences in the distribution of the three categories between groups.

to ICD-9 and then aligned to ICD-10 for the purposes of this work. Cause of death was only examined for the matched cohort.

For the mortality analysis, individuals were monitored from 1986 or, if they presented later, from the time of the first clinic registration date, to the date of death or death censor on 6 January 2011. To establish the expected mortality rate of the diabetes population defined by age of diagnosis, the following procedure was undertaken. The age structure of each population with diabetes was established for each year of follow-up, and the expected mortality rates of the clinic population were calculated from the age- and sex-specific annual mortality rates of the general Australian population, published by the Australian Institute of Health and Welfare (18). SMRs were calculated by the ratio of the observed mortality rate of the clinic population/the calculated expected mortality. Thus an SMR of 1 indicates an equivalent mortality risk compared with an age-matched general Australian population.

Statistics

For the analysis of complications, data were analyzed using NCSS 2007 and ACCorD software (version 2.0.10; Boffin Software, Sydney, Australia). An NCSS data-matching procedure was used to match 1:3 $T2DM_{15–30}$ case subjects to $T2DM_{40–50}$ control subjects for the duration of diabetes. A propensity score was calculated for the matching procedure using logistic regression. Sum of rank distances, including the propensity score, was used to calculate the distance between the groups for matching. Continuous data are presented as medians or means. Categorical data are presented as percentage. Matched data were compared using paired analysis, generalized estimating equations (ACCorD). Significance was accepted as $P < 0.05$.

A Poisson regression model was used to calculate SMRs and the corresponding 95% CI. SMRs were analyzed with a Poisson regression model using log-expected deaths as the offset. The patient follow-up data were split into 1-year intervals, with each interval recording the current age and diabetes duration in years. For each interval, we merged the corresponding overall population mortality rates (18) (matched by age-group, sex, and calendar year) and computed the expected number of deaths. SMR was analyzed with current age (in years), duration of diabetes, and the interaction of age and diabetes duration as the independent variables. The mortality analysis was done using SAS 9.3 software.

RESULTS

Clinical Features and Complications

The clinical characteristics, complications, and mortality rates of $T2DM_{15–30}$ and $T2DM_{40–50}$ are reported in Table 1. The $T2DM_{15–30}$ group was more likely to have a positive family history of diabetes ($P < 0.0001$) and diabetes involving more members of the family ($P = 0.02$). After the same duration of diabetes, ~11 years, the $T2DM_{15–30}$ group were more likely to be treated with insulin but achieved a similar updated HbA_{1c}. The prevalence of retinopathy was similar, but the $T2DM_{15–30}$ group had higher urine albumin concentration and vibration perception thresholds ($P \leq 0.004$), despite their younger age. The $T2DM_{15–30}$ group was also more obese and had higher cholesterol and triglyceride but was less frequently treated with a statin or antihypertensive agent. Although macrovascular disease was less clinically evident in the younger-onset group ($P <$ 0.0001 for any vascular disease), vascular deaths nevertheless predominated and were equivalent in percentage terms to the older cohorts. The age of death was significantly lower in the $T2DM_{15–30}$ group by ~15 years.

Mortality

The number of observed and expected deaths and the SMR for the different age-of-onset groups are given in Table 2. There were 15,238 patients with type 2 diabetes, contributing 156,804 person-years of follow-up, equating to an average follow-up time of 10 years until death or date of censure. Males comprised 57% of the population. Among the 15,238 patients with type 2 diabetes studied, 4,169 deaths occurred in a 25-year period. The crude mortality rate for the entire cohort was 27.2 deaths (95% CI 26.4–28.1) per 1,000 patient-years and was lowest for the younger age-of-onset group, a consequence of their still relatively young achieved age.

As reported in Table 2, with the age structure of the population accounted for, the SMR is highest for the youngest-onset group with a threefold increase compared with the general population (3.4 [95% CI 2.7–4.2]). The SMR of the older-diabetes-onset groups falls progressively toward 1, trending toward a negligible effect on mortality above the general population (Fig. 1 and Table 2).

The SMR at each age, adjusted for duration, for each age-of-onset group is shown in Fig. 2 and for males and females in Supplementary Figs. 1 and 2. The peak SMR is the highest for the youngest-onset group; the highest SMR of more than 6 is seen in the fourth decade of life and is highest for females. The SMRs for these younger-onset groups still remain elevated above background until extreme old age. In contrast, the peak SMR for those diagnosed after 50 years of age is at most twofold increased and declines with aging compared to that of the background population.

CONCLUSIONS

The characteristics of young-onset type 2 diabetes have been the subject of a growing number of reports. The higher insulin use for similar glycemic indices seen in our cohort is in accordance with the results of the TODAY study, in which a rapid loss of glycemic

Table 2—SMR for each age-of-onset group

Age of onset (years)	*N*	Deaths (*n*)		SMR	95% CI
		Observed	Expected		
15–29	588	79	23	3.4	2.7–4.2
30–39	2,022	306	123	2.5	2.2–2.8
40–49	3,891	772	439	1.8	1.6–1.9
50–59	4,583	1,265	860	1.5	1.4–1.6
60–69	2,960	1,119	1,000	1.2	1.1–1.2
>69	1,194	628	633	1.0	0.9–1.1

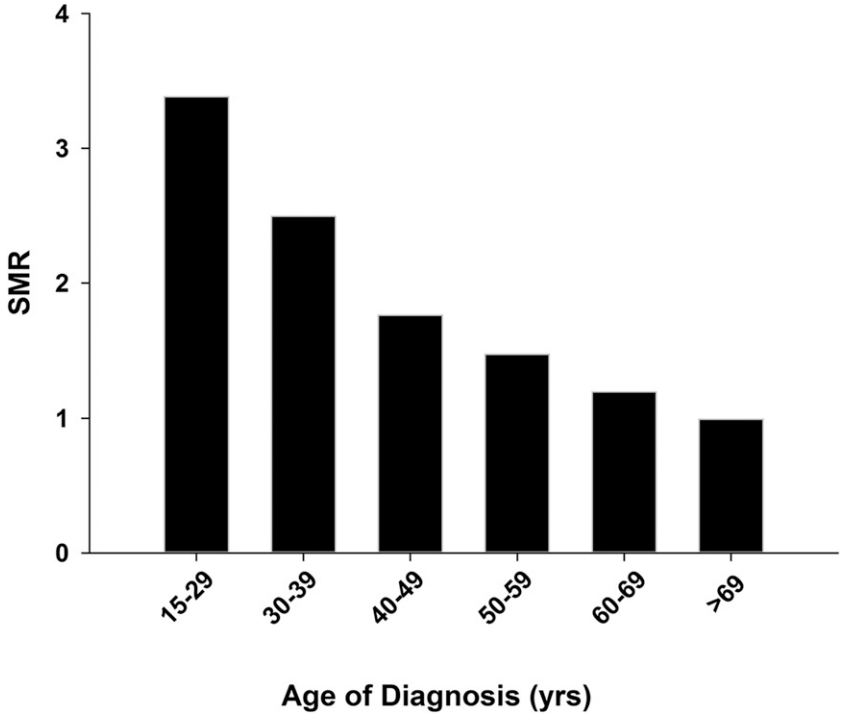

Figure 1—SMR for each age-of-onset cohort.

control and β-cell decline was observed (19). Our study also provides additional information on the relative effect of the age of diagnosis of diabetes on complications prevalence and the long-term mortality relative to the background population. Compared with type 2 diabetes of typical onset in middle age and older, younger-onset patients have a greater risk of renal and nerve complications and a higher standardized mortality. The greatest excess mortality is seen by the age of ~40. These perspectives on the effect of type 2 diabetes occurring at a young age are particularly important moving forward in considering how best to derive strategies for management of this high-risk patient group.

Duration of diabetes is one of the strongest determinants of complication risk, and our study is one of the few that minimizes the effect of duration by matching directly rather than using statistical adjustments for duration. In so doing, our data provide a more robust perspective of the underlying "inherent" morbidity of having type 2 diabetes at a younger age, particularly because differences in glycemic exposure were not evident in our cohorts. Once duration is equated, the younger-onset group has a higher prevalence of albuminuria and neuropathy scores than the later-onset group. There was less clinically evident macrovascular disease in the early-onset group, and taken together with the finding of an equivalent burden of cardiovascular deaths, introduces the possibility that subclinical/unrecognized CVD might be more prevalent in younger-onset groups and perhaps that the first manifestation of ischemic heart disease is more likely to be fatal. These

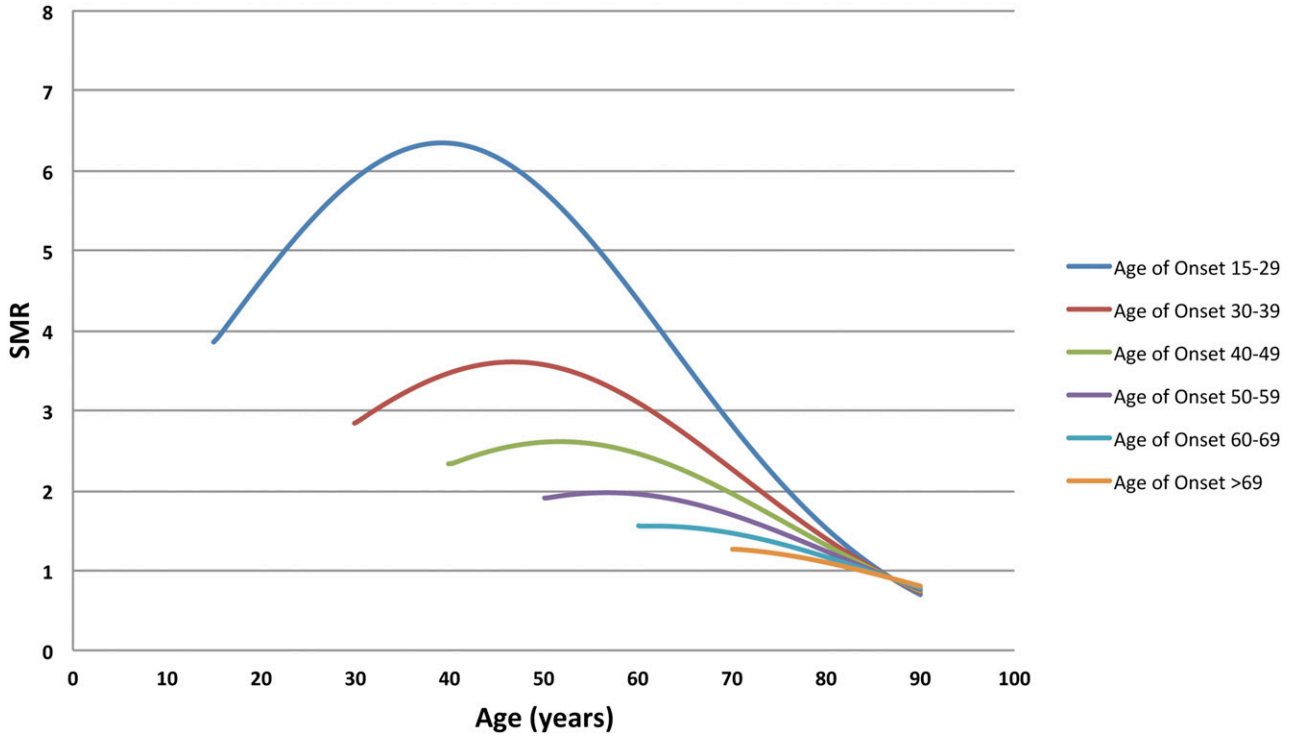

Figure 2—SMR plots for attained age for each age-of-onset cohort.

data imply that for youth with type 2 diabetes, their poorer complications outcomes, at least for renal complications and neuropathy, are not simply a result of a lead-time bias given their longer duration of disease. In contrast to neuropathy and albuminuria, we did not find differences in the prevalence of retinopathy between the age-of-onset groups. Data from Hillier and Pedula (8) showed a slight decrease in susceptibility to retinopathy in young adults with early-onset diabetes, and the TODAY study suggested that obesity might be a protective factor in the development of retinopathy. In both studies, however, diabetes duration was much shorter than here (20). We previously found an excess risk of retinopathy in younger-onset type 2 diabetes (aged <45 years) compared with older-onset groups with equivalent glycemic exposure, a finding that was not seen here. Our previous analysis did not specifically examine the groups with very young onset. It included much older age-of-onset cohorts monitored for a longer duration and had a wider range of glycemic exposure than in this study (21).

A shortened life expectancy associated with diabetes has been recognized for decades, but few previous studies have examined the relative effect of age of diagnosis in this regard. To generate a true perspective of the effect of age of diagnosis of diabetes, it is not possible to just examine mortality by using standard Kaplan-Meier survival analyses, because chronological age in itself is such a dominant factor in determining mortality. We thus used the calculation of SMR and also examined the SMR by attained age. Our data are in keeping with a U.S. study of diabetic versus nondiabetic mortality that found a more than threefold relative increase in mortality among individuals with diabetes between the ages of 25 and 44 (22). Our data highlight this phenomenon in a more general sense by showing the progressive and inverse relationship between age of onset and the SMR. Notably, an adverse effect is seen more with early-onset disease, where peak excess mortality at the attained age of 40 and thereabouts is approximately sixfold increased above that of the background population. In contrast in diabetes of onset at a later age, the total SMR and SMR at any attained age more closely approximates that of the general population.

A strength of our study on complications is the comprehensive documentation of individual demographic profile, glycemic control, cardiovascular risk factors, and the micro- and macrovascular complication status over a long period of time, using a set of standardized clinical criteria and an electronic database (14). The almost identical updated HbA_{1c} in the two cohorts was fortuitous but added strength to our conclusions. The ability to cross-reference our data with actual mortality recorded in a national database also provided a unique opportunity to link to outcomes. By taking a total SMR and the SMR by attained age approach, we have been able to assess not only the effect of the age of onset of disease on mortality but also the timing of any such adverse effect.

Some limitations of this study should be acknowledged. The study is from a single center, and the numbers of individuals with youth-onset type 2 diabetes are relatively low. There were no consistent measures of anti-GAD or other relevant antibody measurements to define better the types of diabetes, but the risk of misclassification is probably small because most patients with younger-onset diabetes were not treated with insulin in the first 5 years of diabetes.

Although the data were entered prospectively, they were not collected according to a prespecified time schedule. Many of the individuals did not present immediately after their diagnosis of diabetes, with the potential for "immortal time bias" to be favoring survival. In other words, patients would have had to survive long enough to reach our clinic. This bias, if present, would mean that our SMR calculations may have even underestimated the true mortality for our youth-onset groups. As for all such analyses, we recognize that the mortality data provided for the general population by the Australian Institute of Health and Welfare will also contain individuals with diabetes, and so the expected mortality rate calculations cannot be assumed to be from those completely disease free. The cohorts studied were not population based and therefore were susceptible to selection bias. Differential referral of more severe patients could potentially affect the mortality rates by age of diagnosis; however, the effects on the findings would depend on whether the bias was seen only in some age-of-onset groups. It is reassuring to note that the total SMRs in our study are of a similar magnitude to those seen in a recent mortality study of diabetes in Australia using data from national administration databases where selection bias would be less likely (23). Despite these limitations, the data obtained provide information that would otherwise take several decades to gather.

The clinical implications of our results are profound for the clinicians managing younger patients with type 2 diabetes. The observation that the relative morbidity and mortality risk in the younger-onset group is not only high but also early should prompt interventions to control glycemia and CVD risk factors before middle age. Existing absolute risk calculators used to aid treatment decisions are likely not to adequately capture the risk for our younger-onset patients. At the population level, enormous resources are presently directed toward the prevention and treatment of diabetes. In view of our findings, direction of these limited resources needs to be prioritized toward those at a younger age. The challenges identified by the landmark TODAY study showing the progression of adverse cardiovascular risk factors and glycemia, despite intensive interventions, will render this no easy task (24). Currently, we have no specific evidence of how to successfully prevent CVD in the young because trials of interventions, such as statin treatment and blood-pressure lowering, have not included young people with type 2 diabetes.

Furthermore, there is little specific evidence to guide how to prevent diabetes in the young. In the context of rising rates of obesity largely driving type 2 diabetes in younger age groups, research into effective and diverse strategies, including modifying in utero glycemic exposure, public health policy, addressing social disadvantage, and urban planning, are needed to tackle this. There is now some urgency to develop an evidence base in this regard and to determine the optimal timing of such interventions more closely. Our results highlight the growing imperative to prevent diabetes in youth and, if not possible, at least to delay

the development of diabetes to an older age.

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