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Research: Complications

Young-onset type 2 diabetes and younger current age: increased susceptibility to retinopathy in contrast to other complications

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Abstract

Background Type 2 diabetes diagnosed during youth and early adulthood is aggressive and associated with a high burden of vascular complications. The increase in complications is often attributed to long disease duration and poor metabolic control. Whether people with young-onset type 2 diabetes are inherently more susceptible to long-term complications than those diagnosed in later adulthood is unclear.

Methods Prospective data from 3322 individuals, diagnosed between the age of 15 and 70 years and collected 10–25 years after diabetes diagnosis, were analysed. The cross-sectional associations between age at diagnosis and microvascular and macrovascular complications were analysed using logistic regression models, adjusted for duration of diabetes exposure and metabolic risk factors including blood pressure, cholesterol and updated mean HbA_{1c}.

Results The prevalence of retinopathy was highest in those with young-onset type 2 diabetes (diagnosed at age 15 to <40 years). After 10–15 years' diabetes duration, the adjusted odds ratio for retinopathy in this population was 2.8 (95% CI 1.9–4.1; reference group those diagnosed at 60 to <70 years of age). The odds of retinopathy remained higher in people with young-onset type 2 diabetes after longer durations of diabetes exposure; the odds decreased with increasing age at diagnosis. This pattern was not observed in models of other complications: after 10–15 years' diabetes exposure, the adjusted odds ratios for albuminuria, peripheral neuropathy and macrovascular disease in people with young-onset type 2 diabetes were 0.5 (95% CI 0.4–0.8), 0.7 (95% CI 0.5–1.1) and 0.2 (95% CI 0.1–0.3), respectively.

Conclusion After accounting for disease duration and other important confounders, people with type 2 diabetes diagnosed in youth and early adulthood (or with a younger current age) appeared to be inherently more susceptible to retinopathy. For other complications, adjusted risk appears highest in the oldest age of diagnosis group. These data have screening and treatment target implications.

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Introduction

The growing incidence and prevalence of young-onset type 2 diabetes [1–3] is concerning given the high complications burden and premature mortality associated with this aggressive subtype of diabetes [4–6]. New data from the RISE consortium suggest that the physiology underlying young-onset type 2 diabetes differs from older-onset type 2 diabetes [7]. A key question now is whether there are also underlying physiological differences in young-onset type 2 diabetes that might predispose to a greater susceptibility across the spectrum of diabetes complications. Poorer glycaemic control, a more rapid rate of pharmacotherapy failure and a greater duration of diabetes exposure are all factors suspected to contribute to the excess morbidity associated with young-onset type 2 diabetes [8–10]. Whether there is a residual long-term risk for young people after accounting for these and other factors is not clear across the spectrum of complications.

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What's new?

- Young-onset type 2 diabetes is an aggressive disease, associated with a higher burden of complications than that seen in older-onset diabetes.
- It is not known whether young people have an underlying increased susceptibility to complications or whether their long-term excess risk of complications can be explained by glycaemia and longer duration of disease exposure.
- Unlike other complications, risk of retinopathy in young-onset type 2 diabetes (or those with a younger current age) is twofold higher than in older-onset type 2 diabetes, after adjustment for duration of diabetes exposure, glycaemia and other known risk factors. This finding supports an underlying increased susceptibility to retinal complications for young people.
- This increased risk of retinopathy indicates a need for more frequent surveillance and aggressive management of known risk factors, and supports a reconsideration of the diabetic retinopathy guidelines for young people and those with a younger age at diagnosis.
- A search for as yet unidentified contributing factors for retinopathy risk in young people is warranted.

Given access to a large dataset, prospectively collected over 30 years, we explored the possibility of an inherent susceptibility to long-term complications. We compared the odds of microvascular and macrovascular complications in young-onset vs older-onset type 2 diabetes after extended durations of disease exposure. The increased granularity of our dataset allowed meaningful adjustments of important confounders and provided an opportunity to probe for an independent association between long-term complications and age at diabetes onset.

Methods

This cross-sectional study examined de-identified data from the Royal Prince Alfred Hospital Diabetes Centre Clinical Database. The centre provides multidisciplinary, secondary and tertiary level care to people with diabetes living in Sydney and a number of regional centres in New South Wales, Australia. Our clinical database contains prospectively collected clinical and complications data; the data analysed were collected between 1986 and 2016.

Participants

Data from 3322 individuals with a clinical diagnosis of type 2 diabetes as determined by the treating clinician were considered. To ensure sufficient diabetes exposure time for complications to develop, the main study cohort was restricted to those individuals who had had at least one complication assessment performed between 10 and 25 years after their diabetes diagnosis. Age at diagnosis was categorized as: 15 to <40 years (young-onset type 2 diabetes); 40 to <50 years; 50 to <60 years; and 60 to <70 years.

Timing of complication assessments

In a shared care model, complications assessments were performed at the request of the referring primary care physician in a standardized way, as previously described [11]. To equate for disease duration, complications status was considered during three distinct diabetes exposure bands (10 to <15 years, 15 to <20 years and 20 to <25 years after diagnosis). Data from an individual's most recent complications assessment within each duration band were analysed. Given the long-standing nature of the database, an individual participant may have contributed data to more than one duration band. This consideration impacted on our analytical approach as described below. For those individuals who had undergone more than one complications assessment at the Diabetes Centre, the mean time between the first and second assessment was 2.5 years.

Complications

Microvascular outcomes

Diabetic retinopathy was diagnosed by direct ophthalmoscopy and/or retinal photography; grading was performed using a modified Early Treatment Diabetic Retinopathy Study (ETDRS) scale [12]. Retinopathy grading has been largely informed by direct ophthalmoscopy and in later years by retinal photography. Nevertheless, the majority of gradings were performed by a single trained clinician (D.K.Y.) who has published alignment of his retinopathy grading with a retinal specialist [13], or by clinicians with similar training.

Microalbuminuria was defined as a spot urinary albumin to creatinine ratio >2.5 mg/mmol (for men) and >3.5 mg/mmol (for women) or a urinary albumin concentration >30 mg/l. Chronic kidney disease was classified as an estimated GFR (Chronic Kidney Disease Epidemiology Collaboration formula) <60 ml/min/1.73 m^2. Peripheral neuropathy was defined as a ≥90th centile z-score for biothesiometry.

Macrovascular outcomes

A composite macrovascular disease endpoint of ischaemic heart disease, cerebrovascular disease and peripheral vascular disease was considered. Macrovascular outcomes were evidenced by self-report, medical records or documentation provided by the primary care physician. Ischaemic heart disease was defined as myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. Cerebrovascular disease was defined as stroke or transient ischaemic attack. Peripheral vascular disease was defined by confirmatory lower limb imaging studies and/or self-report of lower limb angioplasty or bypass surgery.

Variables

Demographic and clinical variables (BMI, blood pressure, lipids, smoking status and medications) were taken from an individual's most recent complication assessment within each duration band. In addition, updated mean HbA_{1c} was calculated from all available HbA_{1c} measurements associated with complication assessments. Updated mean HbA_{1c} is a measure of average glycaemic exposure that takes into account the number of, and time between HbA_{1c} assessments [14]. The updated mean HbA_{1c} was calculated according to the formula:

$$\frac{\sum_{i=1}^{n-1} 0.5 \times [HbA1c(i) + HbA1c(i+1)] \times [Time\ between\ HbA1c(i)\ and\ HbA1c(i+1)]}{[Time\ between\ HbA1c(n)\ and\ HbA1c(1)]}$$

Statistical analysis

Data from descriptive analyses are reported as mean (± SD) or median (interquartile range) values. Comparisons between groups were made using ANOVA for continuous variables and Pearson's chi-squared tests for categorical variables.

Logistic regression analyses were performed to determine differences between distinct age of diagnosis groups for each duration of diabetes exposure band in the log-odds of having a micro- or macrovascular complication of interest. For this study three retinopathy models were considered. Retinopathy model 1 considered all retinopathy grades, from minimal non-proliferative to proliferative diabetic retinopathy inclusive. Retinopathy model 2 considered only moderate non-proliferative, severe non-proliferative and proliferative diabetic retinopathy. Retinopathy model 3 considered severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and maculopathy.

In our models, the dependent variable was the binary outcome variable related to the complication of interest and the primary independent variables were age-at-diagnosis group and duration-of-diabetes-exposure group. To further examine the specific odds in relation to particular disease durations, an interaction term of age-at-diagnosis group and duration-of-diabetes-exposure group was included. The inclusion of other independent variables was determined by the availability of clinical data and limited to those factors suspected to be of importance to the outcome of interest or those factors which were found to be statistically significant on univariable analysis. These variables included gender, ethnicity, smoking status (current, former, never), BMI category (<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2), updated mean HbA_{1c} [<42 mmol/mol (<6%), 42–63 mmol/mol (6.0–7.9%), ≥64 mmol/mol (≥8%)], systolic blood pressure (<115 mmHg, 115–129 mmHg, 130–144 mmHg, 145–159 mmHg, ≥160 mmHg) and total cholesterol (<4 mmol/l, 4 to <6 mmol/l, ≥6 mmol/l).

Due to the issue of collinearity, age at diagnosis and current age were not included as separate independent variables in our individual models. Our primary focus related to understanding the associations between age at diagnosis and complications of diabetes; the current age variable was not included in our modelling.

As noted, some study participants contributed data to more than one duration band. To address the issue of within-participant correlation, logistic regression analyses were performed within the framework of generalized estimating equations. This framework allows within-participant correlations to be taken into account. Adjusted odds ratios with their corresponding 95% CIs were calculated. For age-at-diagnosis group comparisons, the group with an age of onset of 60 to <70 years was used as the reference.

To allow sufficient time for the development of complications, our primary model specifically excluded those individuals who had undergone a complications assessment prior to 10 years of diabetes exposure; this exclusion may have predisposed our data to a selection bias. Consequently, a sensitivity analysis was undertaken in which complication assessment data from individuals with 0 to <10 years of diabetes exposure as well as 10 to <25 years of diabetes exposure were analysed in an expanded retinopathy model. Expanded retinopathy model 1 also included an adjustment for year of complications assessment (to exclude a potential cohort effect) and adjustments for use of renin angiotensin system blockade and 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase inhibitors (in lieu of blood pressure and cholesterol), which may have impacted on retinopathy prevalence.

Statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA). All statistical tests were two-tailed with the significance level set at 0.05.

Ethics

The collection of data from patients and its storage in our electronic database is approved by the Hospital Database Committee and the Human Ethics Committee of the Sydney Local Health District. The study protocol was approved by the Sydney Local Health District Ethics Review Committee and conforms to the STROBE guidelines.

Results

Data from 3322 people with type 2 diabetes were available for analysis. Clinical characteristics and complications prevalence, stratified by age-at-diabetes-diagnosis categories, are shown in Table 1 for those with 10 to <15 years' of diabetes duration and in Tables S1a and S1b (15 to <20 years and 20 to <25 years duration bands). Fully adjusted odds ratios for each complication, stratified by age-at-diagnosis group and duration band, are presented in Table 2 and Fig. 1. The complete univariable and simple adjusted models are presented in Tables S2a–g.

Overall, 56.2% of the study population were male. Follow-up times were similar for each of the age-at-diagnosis

Table 1 Characteristics of the cohort with 10 to <15 years of diabetes exposure, stratified by age of diabetes diagnosis

	Age at diagnosis				
	15 to <40 years	40 to <50 years	50 to <60 years	60 to <70 years	*P*
Number of study participants	348	588	796	460	-
Age at consultation, years	48.0 (44.0–50.6)	58.6 (56.0–60.9)	67.3 (65.4–69.8)	77.0 (74.7–79.6)	-
Duration, years	12.8 (11.4–14.1)	13.2 (11.7–14.1)	13.1 (11.4–14.2)	12.4 (11.0–13.9)	-
Male, *n* (%)	188 (54)	354 (60)	423 (53)	257 (56)	0.06
Current smoker*, *n* (%)	64 (22)	103 (21)	80 (11)	20 (5)	<0.001
Ex-smoker*, *n* (%)	71 (25)	158 (31)	269 (38)	165 (40)	<0.001
BMI, kg/m^2	30.0 (26.1–35.6)	30.8 (27.1–35.5)	30.2 (26.6–34.0)	28.4 (25.4–31.5)	<0.001
Mean ± SD updated HbA_{1c},					<0.001
mmol/mol	68 ± 23	65 ± 22	63 ± 21	60 ± 18	
%	8.4 ± 2.1	8.2 ± 1.8	7.9 ± 1.9	7.6 ± 1.6	
Systolic blood pressure, mmHg	125 (116–138)	130 (120–140)	131 (120–146)	132 (120–145)	<0.001
Estimated GFR, mL/min/1.73m^2	99 (84–106)	84 (70–96)	76 (61–89)	62 (46–77)	<0.001
Total cholesterol, mmol/l	4.7 (4.0–5.4)	4.4 (3.7–5.2)	4.3 (3.7–4.9)	4.2 (3.6–4.9)	<0.001
HDL cholesterol, mmol/l	1.1 (1.0–1.4)	1.1 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	0.003
Triglycerides, mmol/l	1.8 (1.2–2.8)	1.6 (1.1–2.4)	1.6 (1.1–2.2)	1.5 (1.1–2.0)	<0.001
LDL cholesterol, mmol/l	2.5 (1.9–3.1)	2.3 (1.7–2.9)	2.2 (1.7–2.8)	2.1 (1.6–2.7)	<0.001
Retinopathy, *n* (%)	125 (36)	192 (33)	189 (24)	79 (17)	<0.001
Albuminuria†, *n* (%)	110 (37)	195 (36)	249 (34)	170 (43)	0.03
CKD n (%)	12 (4)	73 (13)	179 (24)	197 (45)	<0.001
Biothesiometry z-score‡ (>90th centile), *n* (%)	235 (72)	441 (78)	538 (70)	328 (76)	0.01
Macrovascular disease§, *n* (%)	38 (11)	143 (25)	232 (29)	186 (41)	<0.001

Data are median (interquartile range), unless otherwise stated.
*Smoking data available for 83–92% of study participants in this exposure cohort.
†Albuminuria data available for 85–92% of study participants in this exposure cohort.
‡Biothesiometry data available for 93–97% of study participants in this exposure cohort.
§Macrovascular disease status available for >97% of study participants in this exposure cohort.

groups within each duration band. Within the duration band 10 to <15 years, people with young-onset type 2 diabetes had significantly higher updated mean HbA_{1c}, LDL cholesterol and triglyceride levels, significantly higher BMI and smoking rates, but lower blood pressure and HDL cholesterol than their counterparts diagnosed at older ages. Similar patterns were seen for the duration bands 15 to <20 years and 20 to <25 years.

Microvascular complications

Retinopathy

Retinopathy data were available for >95% of the study population, with no substantial imbalances in missing data across the age-at-diagnosis groups (Table S3). For each diabetes duration band, the prevalence of diabetic retinopathy was highest in the young-onset type 2 diabetes subgroup, increasing from 36% after 10 to <15 years of diabetes to 58% after 20 to <25 years of diabetes exposure, with lower corresponding prevalence rates in the age-at-diagnosis group 60 to <70 years of 17% and 26%. Differences in the prevalence of diabetic retinopathy were observed across the age-at-diagnosis spectrum for each duration band ($P \leq 0.001$ for all).

For the outcome of any grade of retinopathy (model 1) the highest odds of retinopathy were seen in the young-onset type 2 diabetes group, irrespective of duration of diabetes exposure (Table 2 and Fig. 1). The adjusted odds ratios for diabetic retinopathy in young-onset type 2 diabetes in model 1 were 2.8 (95% CI 1.9–4.1), 2.2 (95% CI 1.4–3.5) and 5.6 (95% CI 1.8–16) for the 10 to <15 years, 15 to <20 years and 20 to <25 years of diabetes exposure bands, respectively. When retinopathy outcomes were restricted to more severe grades (models 2 and 3), a similar pattern of adjusted odds ratios was observed (Table 2). Higher odds of retinopathy were seen in the younger age-at-onset group in each of the models.

Expanded retinopathy model 1 (Table S4a,b and Fig. S1) contained data relating to 7945 complications assessments from 5177 individuals who were seen from 0 to 25 years post-diagnosis. Adjustments for calendar year of complications assessment, renin angiotensin system blockade and HMG CoA reductase inhibitor use (Tables S5a–c) did not alter the pattern of retinopathy findings. There were no significant differences in the odds of retinopathy across the age-at-diagnosis spectrum for the 0 to <5 years exposure band, but the pattern of increased risk of retinopathy in the young-onset group appeared to be emerging after 5 to <10 years of diabetes exposure.

Albuminuria and chronic kidney disease

Within each diabetes duration band, the prevalence of albuminuria was highest in the subgroup of people diagnosed at 60 to <70 years of age, and significant differences were noted among the different age-at-diagnosis groups (P=0.03).

Table 2 Odds ratios for microvascular complications and macrovascular disease models according to age at diagnosis category

Duration of diabetes exposure strata	Age at diagnosis category	Retinopathy model 1* OR (95% CI)	Retinopathy model 2† OR (95% CI)	Retinopathy model 3‡ OR (95% CI)	Albuminuria model OR (95% CI)	CKD model OR (95% CI)	Peripheral neuropathy model OR (95% CI)	Macrovascular disease model OR (95% CI)
10 to <15 years	15 to <40 years	2.8 (1.9–4.1)§	3.2 (2.0–5.0)§	2.4 (1.2–4.6)¶	0.5 (0.4–0.8)§	0.04 (0.02–0.07)§	0.7 (0.5–1.1)	0.2 (0.1–0.3)§
	40 to <50 years	2.5 (1.8–3.6)§	2.8 (1.9–4.3)§	2.7 (1.5–4.9)§	0.6 (0.4–0.8)§	0.2 (0.1–0.3)§	1.0 (0.7–1.4)	0.4 (0.3–0.6)§
	50 to <60 years	1.6 (1.1–2.2)¶	1.7 (1.1–2.5)¶	1.9 (1.1–3.4)**	0.6 (0.5–0.8)§	0.4 (0.3–0.5)§	0.7 (0.5–0.9)¶	0.5 (0.4–0.7)§
	60 to <70 years	Reference	Reference	Reference	Reference	Reference	Reference	Reference
15 to <20 years	15 to <40 years	2.2 (1.4–3.5)§	3.1 (1.8–5.2)§	7.8 (2.8–22)§	0.5 (0.3–0.8)¶	0.07 (0.05–0.1)§	0.6 (0.3–1.1)	0.2 (0.1–0.3)§
	40 to <50 years	1.7 (1.1–2.6)**	1.8 (1.1–2.8)**	3.9 (1.4–11)¶	0.5 (0.3–0.7)§	0.2 (0.1–0.2)§	0.7 (0.4–1.1)	0.4 (0.3–0.6)§
	50 to <60 years	1.3 (0.9–2.1)	1.4 (0.9–2.3)	3.0 (1.1–8.4)**	0.6 (0.4–1.0)**	0.3 (0.2–0.4)§	0.5 (0.3–0.8)¶	0.7 (0.5–1.0)**
	60 to <70 years	Reference	Reference	Reference	Reference	Reference	Reference	Reference
20 to <25 years	15 to <40 years	5.6 (1.8–16)§	7.3 (2.2–24)§	3.0 (0.9–10)	0.6 (0.3–1.4)	0.2 (0.08–0.4)§	0.4 (0.1–2.0)	0.2 (0.1–0.4)§
	40 to <50 years	3.4 (1.2–9.3)**	4.5 (1.4–15)**	2.3 (0.7–7.7)	0.5 (0.2–1.1)	0.4 (0.2–0.8)¶	0.3 (0.1–1.4)	0.3 (0.1–0.7)¶
	50 to <60 years	2.4 (0.9–6.7)	3.5 (1.1–11)**	1.8 (0.5–5.9)	0.7 (0.3–1.5)	0.8 (0.4-1.6)	0.4 (0.1–1.9)	0.6 (0.3–1.2)
	60 to <70 years	Reference	Reference	Reference	Reference	Reference	Reference	Reference

CKD, chronic kidney disease; OR, odds ratio.
All models adjusted for sex, ethnicity, smoking status, BMI, mean updated HbA_{1c}, systolic blood pressure and cholesterol.
*Retinopathy considered positive if any degree of retinopathy was detected on fundoscopy and/or retinal photography.
†Retinopathy considered positive if moderate or severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy detected on fundoscopy and/or retinal photography.
‡Retinopathy considered positive if severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy or maculopathy detected on fundoscopy and/or retinal photography.
§$P \leq 0.005$.
¶$P \leq 0.01$.
**$P < 0.05$.

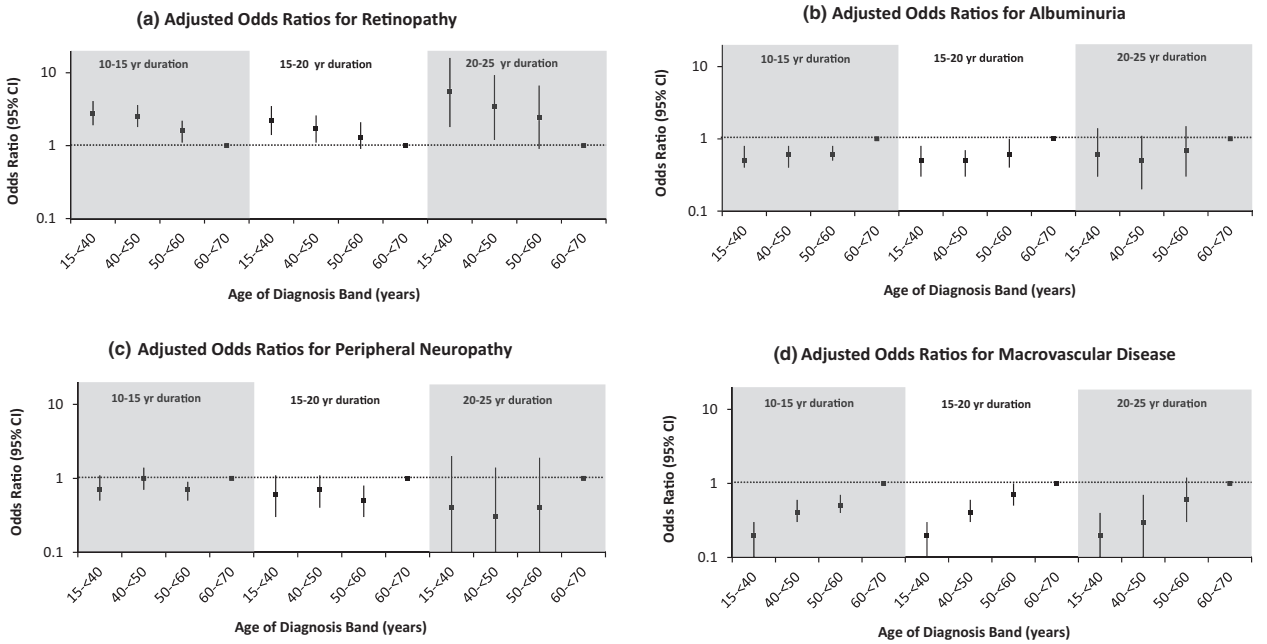

FIGURE 1 Adjusted odds ratios for microvascular and macrovascular complications for different age of diagnosis bands at different diabetes exposure times (10-15, 15-20, 20-25 years) [Correction added on 25 February 2020, after first online publication: elements missing in Fig. 1 (due to a typesetting error) have been corrected – the OR 1 line in panel (c) and the duration of diabetes exposure labels in panels (c) and (d).]

In adjusted modelling, after 10 to <15 years of diabetes exposure, the odds of albuminuria or chronic kidney disease were significantly lower in each of the younger age of diagnosis subgroups. However, after 20 to <25 years of diabetes exposure, no significant differences in albuminuria were observed across the age of diagnosis spectrum. The highest risk of chronic kidney disease was seen in those diagnosed at 60 to <70 years of age throughout the diabetes duration bands (Table 2 and Fig. 1).

Peripheral neuropathy

Peripheral neuropathy was the most common complication, and prevalence varied between 70% and 95% across the age-at-diagnosis spectrum for each of the duration of diabetes exposure bands. In adjusted modelling, age of diagnosis was not consistently associated with peripheral neuropathy across the duration of diabetes exposure bands.

Composite macrovascular complications

The lowest prevalence of macrovascular disease was observed in the young-onset type 2 diabetes cohort. After 10 to <15 years of diabetes exposure, the prevalence of macrovascular disease steadily increased from 11% in the young-onset group to 41% in the 60 to <70 year age of diagnosis group.

In our modelling, younger age at diagnosis was associated with lower odds of macrovascular disease, even after the effect of duration of diabetes exposure and other metabolic risk factors were taken into account (Table 2 and Fig. 1).

Discussion

The high prevalence of complications in young-onset type 2 diabetes is now well established in the literature, and a long duration of disease exposure and poor glycaemic control are undoubtedly important contributing factors. In the present study we sought to examine the possibility of a residual increased susceptibility to complications in young-onset type 2 diabetes as compared to later-onset disease. We found that, after 10 years of diabetes exposure, the odds of diabetic retinopathy in young-onset type 2 diabetes were more than double those observed in the age-at-onset reference group of 60 to <70 years. This difference was present after adjustments were made for glycaemia, blood pressure, cholesterol, year of assessment and other important confounders. Together, these results provide evidence of an excess susceptibility to diabetic retinopathy in young-onset type 2 diabetes. In contrast to diabetic retinopathy, adjusted models of albuminuria, peripheral neuropathy and macrovascular disease did not demonstrate an excess risk in those with young-onset type 2 diabetes.

It should be noted that, by controlling for duration, the effect of age of onset cannot be examined independently of current age. For example, after any given duration, those with an age at onset of 20 years will always be younger than those with an age at onset of 60 years. Thus, conceptually,

the effect of age at onset can also be considered to be an effect of current age in the present study. Although problematic from a statistical viewpoint, this issue does not detract from the clinical relevance of the finding that an earlier age at onset (or younger age) is associated with an excess residual risk of diabetic retinopathy.

Our retinopathy findings are supported by a number of previous studies. Both Dorf *et al.* [15] and Song and Hardisty [16] reported a greater prevalence of diabetic retinopathy in young-onset type 2 diabetes than in older-onset type 2 diabetes after >10 years of diabetes exposure. A Chinese study in >13 000 individuals reported a decreased risk of diabetic retinopathy with advancing age after adjustments for multiple risk factors [17]. Our data, with a standardized and more robust ascertainment of retinopathy status, extend the findings of Nanayakkara *et al.* [18], who reported decreased odds of any degree of retinopathy (odds ratio 0.98) for a 1-year increase in age at diagnosis (and a 1-year increase in current age) after adjustment for risk factors in an Australian benchmarking audit. Finally, our diabetic retinopathy results are in concordance with two smaller observational studies from India and the USA [19,20].

By contrast, others report a decreased hazard ratio for diabetic retinopathy in those diagnosed at an earlier age [21,22] or no effect of age of onset on retinopathy [23]. In these studies the mean duration of diabetes exposure was <10 years and the ways in which young onset was defined were different. As our sensitivity analysis demonstrated, significant differences in retinopathy risk were not observed when complications were assessed before 10 years of diabetes exposure. In essence the discordance of results are likely to be attributable to differences in diabetes exposure times, differences in stratification by age at diabetes diagnosis and inconsistency of adjustment for important risk factors across different studies, which make direct comparison difficult.

Understanding of the pathogenesis of diabetic retinopathy is evolving, and many factors, including vascular endothelial growth factor and growth hormone, have been implicated [24,25]. Conceivably, a more robust response to vascular endothelial growth factor during early adult life could accelerate pathogenesis of diabetic retinopathy in young-onset type 2 diabetes. Similarly, growth hormone and insulin-like growth factor 1 decrease with advancing age, and the highest levels of circulating growth hormone are seen during adolescence and early adult life. With this in mind, it is plausible that the diabetic milieu in youth could favour vascular proliferation and give rise to higher rates of retinopathy. Clearly, further work is required to elucidate the true underlying mechanisms.

Our findings on peripheral neuropathy indicate comparable adjusted risk across the age spectrum. There is a relative paucity of long-term data for peripheral neuropathy in young-onset type 2 diabetes in the literature, so the finding of elevated biothesiometry readings in >70% of our study cohort after 10 years of diabetes exposure is notable. The SEARCH study consortium recently reported an excess prevalence and risk of peripheral neuropathy in young-onset type 2 diabetes relative to type 1 diabetes [26]. Overall, the present study aids understanding of peripheral neuropathy in type 2 diabetes and suggests that the relative protection of youth is lost. The high prevalence of peripheral neuropathy probably heralds an increased lifetime risk of significant neuropathic sequelae including foot ulceration and amputation.

In contrast, the risks of albuminuria and macrovascular disease were significantly lower for the group with young-onset type 2 diabetes. This probably reflects the dominant influence of advanced age on macrovascular disease. In an analysis of data from the ADVANCE trial, a single standard deviation increase in age (or age at diagnosis) was found to have a much greater effect than a single standard deviation increase in duration of diabetes exposure on the outcomes of a macrovascular event and death [10].

An important strength of the present study stems from the availability of clinical data (including comprehensive information on complication status) for individuals with >10 years of diabetes exposure. Significantly, these data have been systematically collected for >30 years and have been drawn from a multi-ethnic population. Data were collected prospectively, reducing recall bias, and a standardized grading system for retinopathy was used. Available data enabled adjustments for known metabolic risk factors and therefore an insight into inherent susceptibility to complications could be achieved. While previous studies have focused on adolescents or adults in isolation, the present study sheds light on the experience of people with type 2 diabetes diagnosed during their early adult years. The emerging adult subgroup is increasing in number and an improved understanding of complication risk is essential for better management practices.

The present study has some limitations. The data analysed relate to a cohort referred to a hospital outpatient clinic. Consequently, referral bias could potentially reduce generalizability and, as with any cross-sectional study, causality cannot be inferred. Other limitations include the potential for survival bias and competing risk of death in the setting of diabetic complications. We cannot refute the assertion that those with an older age of onset and retinopathy would be less likely to survive, and this phenomenon is likely to be most relevant in the longest duration of diabetes exposure band. However, we do note that the pattern of excess risk of retinopathy persists if we compare the young-onset type 2 diabetes group with the group diagnosed during middle age after a modest (i.e. 10 to <15 years) duration of diabetes exposure. The effect of survival bias would be much less pronounced in this comparison. We also note that, although an adjustment was made for glycaemic exposure (i.e. updated mean HbA_{1c}), the time from diagnosis to the time of first complications assessment was not accounted for in our calculation. In addition, for some individuals, some of the HbA_{1c} measurements used in the calculation of updated

mean HbA_{1c} were made after complications had developed. This limits the ability of our updated mean HbA_{1c} measure to control for its influence on the development of complications. Finally, the effect of unmeasured confounders such as socio-economic status may play a role in the development of diabetic complications. In this setting, socio-economic status would be unlikely to be a confounder for the complication of retinopathy alone, and given the discrepancy observed between retinopathy and the other microvascular complications, it could be argued that an inherent physiological susceptibility is a more likely explanation for the retinopathy results.

In conclusion, the present study adds to the growing knowledge base of long-term complication risk in young-onset type 2 diabetes. Although duration and glycaemia contribute to the poorer outcomes seen in young-onset type 2 diabetes, the persistent increase in adjusted odds of diabetic retinopathy suggests a particular susceptibility for retinopathy in youth not seen for the other vascular complications. Our findings would be best confirmed by a prospective cohort study, however, there will be a considerable wait for confirmatory data given the delay between time of diagnosis and the development of complications. Until then, we believe that our results support the need for more frequent surveillance of diabetic retinopathy in young-onset type 2 diabetes and aggressive management of known risk factors, which could be reflected in clinical care guidelines.

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Competing interests

None declared.

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Prior presentation

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1a. Characteristics of the 15-<20 years of diabetes exposure cohort, stratified by age of diabetes diagnosis.
Table S1b. Characteristics of the 20-<25 years of diabetes exposure cohort, stratified by age of diabetes diagnosis.
Table S2a. Exponentiated marginal mean difference of log (odds) for retinopathy (any retinopathy).
Table S2b. Exponentiated marginal mean difference of log (odds) for retinopathy (moderate NPDR, severe NPDR & proliferative DR).
Table S2c. Exponentiated marginal mean difference of log (odds) for retinopathy (severe NPDR, proliferative DR & maculopathy).
Table S2d. Exponentiated marginal mean difference of log (odds) for albuminuria (UACR >2.5 mg/mmol male; >3.5 mg/mmol female).
Table S2e. Exponentiated marginal mean difference of log (odds) for CKD (eGFR <60 mL/min/1.73 m^2).
Table S2f. Exponentiated marginal mean difference of log (odds) for peripheral neuropathy.
Table S2g. Exponentiated marginal mean difference of log (odds) for macrovascular disease.
Table S3. Summary of missing retinopathy data (stratified by age of diagnosis group).
Table S4a. Expanded retinopathy model 1 (any retinopathy) incorporating: (1) individuals with 0-25 years duration of diabetes exposure; (2) adjustment for year of complication assessment; (3) adjustments for renin angiotensin system blockade and HMG CoA reductase inhibitor use.
Table S4b. OR (95% CI) expanded retinopathy model 1. According to age at diagnosis category. Stratified by duration of diabetes exposure strata.
Table S5a. Utilisation of renin angiotensin system blockade stratified by age of diagnosis.
Table S5b. Utilisation of HMG CoA reductase inhibition stratified by age of diagnosis.
Table S5c. Utilisation of fenofibrate stratified by age of diagnosis.
Figure S1. Adjusted odds ratios for expanded retinopathy model 1 for different age of diagnosis bands at different diabetes exposure times (0–5, 5–10, 10–15, 15–20, 20–25 years).