Younger-onset compared with later-onset type 2 diabetes: an analysis of the UK Prospective Diabetes Study (UKPDS) with up to 30 years of follow-up (UKPDS 92)

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Summary

Background Younger-onset type 2 diabetes is associated with accelerated complications. We assessed whether complications and mortality rates differed for younger age compared with older age at diagnosis over 30 years of follow-up.

Methods In this study, we used data from the UKPDS, collected between 1977 and 2007, of participants aged 25–65 years with newly diagnosed type 2 diabetes with younger-onset (younger than 40 years) or later-onset (40 years or older), and without diabetes autoantibodies. We analysed standardised mortality ratios (SMR) using UK general population data, and incidence rates of prespecified outcomes by 10-year age intervals at diagnosis.

Findings Of 4550 participants testing negative to all measured autoantibodies, 429 (9·4%) had younger-onset type 2 diabetes. 2704 (59·4%) were male, and mean HbA_{1c} was 76 mmol/mol (SD 24·6). The median follow-up was 17·5 years (IQR 12·7–20·8). SMR for younger-onset type 2 diabetes was higher (3·72 [95% CI 2·98–4·64]) compared with later-onset type 2 diabetes (1·54 [1·47–1·61]). The incidence rate was higher for all outcomes in later-onset type 2 diabetes, except for microvascular disease (younger-onset 14·5 (11·9–17·7) *vs* later-onset 12·1 (11·3–13·0) per 1000 person-years). However, at any given age, the 5-year incidence of any diabetes-related endpoint, all-cause mortality, microvascular disease, and myocardial infarction was higher with younger age at diagnosis. Annual mean HbA_{1c} was higher in the first 20 years in younger-onset compared with later-onset type 2 diabetes. Among participants randomised to intensive versus conventional glycaemic control, we observed no interactions by subgroup of younger-onset versus later-onset type 2 diabetes for any outcome.

Interpretation The risk of dying relative to the general population is even greater for people diagnosed with type 2 diabetes at younger ages. The increased risk of complications and poorer glycaemic control in younger-onset type 2 diabetes calls for the development of services to identify and manage these individuals.

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Introduction

Over the past 30 years, the number of young adults diagnosed with type 2 diabetes has increased markedly worldwide.[1–3] Since 1990, the annual incidence has increased by over 50%,[4] and type 2 diabetes has overtaken type 1 diabetes as the predominant type of diabetes in adults aged 19–39 years in the UK.[3,5] Although traditionally considered a disease of people of middle and older age, younger-onset type 2 diabetes is now recognised as a distinct, non-autoimmune phenotype of diabetes.[6,7] There is growing concern that early lifetime exposure to hyperglycaemia in younger-onset type 2 diabetes increases the cumulative risk of complications and reduces life expectancy; however, these risks need to be better characterised.[3,6,8]

Several studies, including the landmark Treatment Options for Type 2 Diabetes in Adolescents and Youth trial and the Search for Diabetes in Youth trial, report accelerated diabetes-related complications and higher mortality compared with age-matched younger people with type 1 diabetes.[8–13] Evidence suggests that younger-onset type 2 diabetes is more aggressive than later-onset disease with faster deterioration in β-cell function,[14–17] and an even greater excess risk of complications such as cardiovascular disease and nephropathy.[18,19] For any given age, those diagnosed with type 2 diabetes when young also have higher excess all-cause and cardiovascular-related mortality compared with those diagnosed later.[20–23] There have been few prospective cohort studies specific to early-onset type 2 diabetes in adults, with most data derived from retrospective population audits or youth cohorts.[6] Although countries such as Australia have published dedicated guidelines for younger-onset type 2 diabetes, the evidence base is poor because younger-onset type 2 diabetes remains under-represented in clinical trials.[6,24]

The UK Prospective Diabetes Study (UKPDS) was a multicentre randomised trial of glucose-lowering

Research in context

Evidence before this study

To review the evidence surrounding the natural history of disease in people with younger-onset (<40 years) compared with later-onset (≥40 years) type 2 diabetes, we searched PubMed from database inception to May 1, 2024, using the following search terms: "young-onset" or "early-onset" or "young adult" AND "type 2 diabetes". Younger-onset type 2 diabetes is more aggressive than later-onset disease with β-cell function deteriorating faster, and is associated with more complications and reduced life expectancy. There have been few prospective cohort studies from time of diabetes diagnosis and specific to younger-onset type 2 diabetes in adults, with most data derived from retrospective audits or youth cohorts. To date, only one randomised controlled trial for adults with younger-onset type 2 diabetes has been published (DIADEM-I); and rarely do larger adult trials report on subgroup outcomes in their younger-onset cohort.

Added value of this study

The UK Prospective Diabetes Study (UKPDS) was a landmark randomised clinical trial with the longest follow-up ever evaluated in a trial of glycaemic control and diabetes complications. We report on the mortality and complication rates in younger-onset, compared with later-onset, type 2 diabetes from time of diagnosis to up to 30 years of follow-up in the UKPDS cohort. This included 429 participants with younger-onset type 2 diabetes with a median follow-up of almost 20 years, which is double that of other prospective studies. We only included participants who tested negative to autoantibodies, and thus excluded those with latent autoimmune diabetes in adults who have a different risk of complications than type 2 diabetes. We found higher rates of incident diabetes-related complications, higher standardised mortality ratios, and persistently poorer glycaemic control among adults diagnosed with type 2 diabetes at a younger age compared with those diagnosed later in life. In our post-hoc analysis of the UKPDS trial—ie, the interventional period of the study—we found no significant interaction between age of onset (younger *vs* later) and allocated glycaemic control strategy (intensive *vs* conventional).

Implications of all the available evidence

The increased risk of complications, excess mortality, and poorer glycaemic control in younger-onset type 2 diabetes supports a need to develop services that proactively identify and manage these individuals over their lifetimes. There remain significant opportunities for dedicated clinical trials in younger-onset type 2 diabetes, and an overdue need for data to inform a tailored pharmacological approach.

therapy in adults aged 25–65 years with newly diagnosed type 2 diabetes that ran from December, 1977, to September, 1997. Because trial participants were newly diagnosed, we have a clear measure of the duration of diabetes during follow-up with prospective data on complications and risk factors. Previously published data from the UKPDS showed that age at diagnosis had varying effects on different types of diabetic tissue damage during the first 6 years of type 2 diabetes.[25] In this extended analysis, we assess whether long-term complications and mortality rates differ between younger-onset compared with later-onset type 2 diabetes with up to 30 years of follow-up. We also explore the effect of randomised allocation within the UKPDS trial to intensive glycaemic control strategies compared with conventional strategies in adults with younger-onset versus later-onset type 2 diabetes.

Methods

Study design and participants

We did an observational analysis of UKPDS data with up to 30 years of follow-up (median 17·5 years; range 0·31–30·0). The UKPDS protocol has been previously reported.[26] Briefly, 5102 adults aged 25–65 years with newly-diagnosed type 2 diabetes were recruited between Dec 8, 1977, and March 27, 1991.[26,27] The original UKPDS trial aimed to assess whether an intensive blood-glucose control strategy, compared with a conventional strategy, would reduce the risk of microvascular and macrovascular clinical complications, and to examine the relative merits of available glucose-lowering therapies. The current analyses reflects the up-to-20 year interventional period, and the 10-year period following close-out of the trial on Sept 30, 1997, when all surviving participants entered a post-trial monitoring study until Sept 30, 2007.[27] Participants were included if they were aged 25–65 years, were newly diagnosed with diabetes, and had fasting plasma glucose of more than 6 mmol/L on two mornings 1–3 weeks apart. The main exclusion criteria at recruitment of the trial cohort were: severe vascular disease (myocardial infarction in the past year, current angina, or heart failure); accelerated hypertension; proliferative or preproliferative retinopathy; renal failure with plasma creatinine of more than 175 µmol/L; other life-threatening disease such as cancer; an illness requiring systemic corticosteroids; an occupation precluding insulin treatment; unfamiliarity with English; and ketonuria greater than 3 mmol/L suggestive of type 1 diabetes.

After a 3–4-month dietary run-in period, participants with a fasting plasma glucose (FPG) level between 6·0 mmol/L and 15·0 mmol/L were randomly assigned to either a conventional glycaemic control strategy (primarily with diet) or an intensive glycaemic control strategy (sulfonylurea or insulin or, if >120% of ideal bodyweight, metformin). Participants with a FPG of more than 15·0 mmol/L were allocated to intensive therapy and not eligible for randomisation. Those with a FPG less than 6·0 mmol/L were allocated to diet, but could be

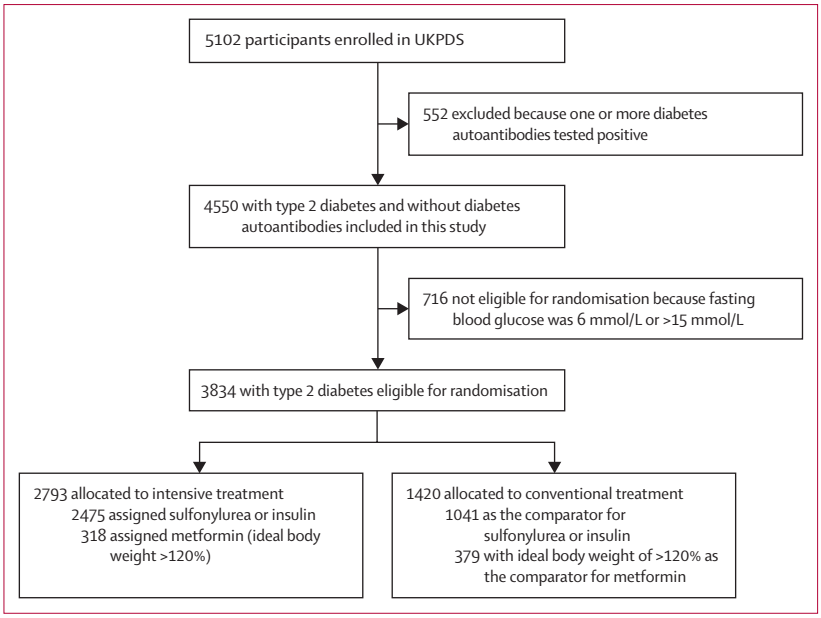

Figure 1: **Trial profile**
All participants allocated to conventional treatment (n=1041) were used as the comparator for the sulfonylurea or insulin treatment group. A subset of the participants allocated to conventional treatment who had an ideal body weight of more than 120% (n=379) were also used as the comparator group for the metformin intensive treatment group.

randomised if their FPG subsequently became 6·0 mmol/L or higher. All UKPDS participants (including those who were not randomly assigned) were followed quarterly in UKPDS clinics. FPG and anthropometrics were measured at baseline, every 3 months until 1990, and then every 4 months to trial end in 1997. HbA_{1c} and biochemical measurements were collected at baseline then annually to trial end. All items were then collected annually until 2002.

Autoantibodies associated with diabetes (islet cell autoantigen, glutamic acid decarboxylase, or protein tyrosine phosphatase isoforms IA-2) were measured in 5096 (99·9%) of 5102 UKPDS participants.[28] To restrict this study to those with type 2 diabetes, we included only participants who tested negative for all measured autoantibodies (n=4550). Younger-onset and later-onset type 2 diabetes were defined as those diagnosed at an age younger than 40 years and 40 years or older, respectively.[3] The UKPDS study protocol was approved by the ethics committee of all 23 UKPDS clinical centres. All patients provided written informed consent to participate.

Outcomes

The study administrator obtained full documentation for all putative outcomes from hospitals and general practitioners, whether reported at clinic visits or by means of questionnaires. The vital status of all participants still living in the UK was obtained from the Office of National Statistics. UKPDS Endpoint Committee members adjudicated all outcomes using medical records masked to treatment allocation. We analysed the seven prespecified UKPDS aggregate outcomes: any diabetes-related endpoint (ie, sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, fatal or non-fatal stroke, renal failure, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction), diabetes-related death (ie, sudden death or death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia, or hypoglycaemia), death from any cause, myocardial infarction (ie, sudden death or fatal or non-fatal myocardial infarction), stroke (ie, fatal or non-fatal stroke), peripheral vascular disease (ie, amputation of at least one digit or death from peripheral vascular disease), and microvascular disease (ie, vitreous haemorrhage, retinal photocoagulation, or renal failure). Additionally, we analysed major adverse cardiovascular events, defined as unknown or sudden death, fatal or non-fatal myocardial infarction, or fatal or nonfatal stroke.

In this study, we estimated the absolute and adjusted incidence risk of each aggregate outcome over follow-up in the younger-onset and older-onset type 2 diabetes groups. Incidence rates were also plotted over time by 10-year age intervals at diagnosis. Furthermore, we assessed the standardised mortality ratios for participants by younger-onset and later-onset type 2 diabetes, and by 10-year age intervals at diagnosis. We also examined the mean annual values of key clinical and biochemical values over time (HbA_{1c}, FPG, BMI, estimated insulin resistance [HOMA2-IR], and estimated percentage β-cell function [HOMA2-%B] using the Homeostasis Model Assessment version 2). Finally, we assessed whether there was an interaction between age of type 2 diabetes onset and the effect of randomisation to intensive or conventional glycemic control strategies.

Statistical analysis

We compared the younger-onset with the later-onset type 2 diabetes groups using the *t* test for continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables, and χ^2 test for categorical variables.

We calculated absolute risk for each aggregate outcome as incidence rates per 1000 person-years over the total follow-up period in the younger-onset and later-onset type 2 diabetes groups. We calculated follow-up as from the time of diagnosis to the occurrence of the endpoint of interest, or among people who did not have the endpoint, to censoring defined as death (for non-fatal endpoints), date of last contact, or Sept 30, 2007. We created Kaplan–Meier plots for each aggregate outcome. Missing data were not imputed. We used Poisson regression to calculate the incidence rates adjusted for sex, ethnicity, HbA_{1c}, BMI, systolic blood pressure, low-density lipoprotein cholesterol, and smoking, all measured at baseline. We did not adjust for age because the main exposure, age of type 2 diabetes diagnosis, was also age dependent. We modelled competing risks for

each outcome by fitting flexible parametric survival models to create stacked cumulative incidence graphs.[29] To assess the effect of age at diagnosis further, we divided participants by age at diagnosis into 10-year age groups (25–35, 36–45, 46–55, and 56–65 years). In each of these groups, we calculated the incidence of diabetes-related complications and mortality in successive 5-year intervals over the 30-year follow-up period.

We calculated standardised mortality ratios (SMRs) for younger-onset and later-onset type 2 diabetes, and by 10-year age intervals at diagnosis. Follow-up data were split into 1-year intervals, recording attained age, sex, and calendar year. For each interval, we merged corresponding annual UK general population mortality rates (matched by age, sex, and calendar year) to compute the expected number of deaths. UK population mortality rates were derived from the Office of National Statistics census data.[30,31] We calculated the SMRs by dividing observed deaths in UKPDS participants by expected deaths in the UK population. We then used Poisson regression models to examine SMRs by age group of diagnosis.

We calculated the annual mean values of key clinical and biochemical variables including HbA_{1c}, FPG, BMI, and homoeostasis model assessment-estimated insulin resistance and β-cell function (HOMA2-IR and HOMA2-%B)[32] separately by age at diagnosis (10-year age groups: 25–35, 36–45, 46–55, and 56–65 years). We present the trajectory of HbA_{1c}, fasting blood glucose, HOMA2-IR, HOMA2-%B, and BMI across the 30-year follow-up period.

We tested whether the magnitude of the effect of the intensive compared with the conventional glycaemic control strategy differed significantly between younger-onset and later-onset type 2 diabetes among 3834 UKPDS participants testing negative to all diabetes autoantibodies, and who were randomised in the glucose control trial. We used Cox proportional hazards modelling to evaluate the effect of previous randomisation to an intensive or a conventional policy for glycaemic control on all outcomes within the younger-onset and later-onset type 2 diabetes subgroups. We tested for interaction using the χ^2 test for heterogeneity in the association between randomisation and outcomes by young-onset and later-onset subgroup. Analyses were done with STATA version 17.0 (StataCorp, College Station, TX, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 5102 participants enrolled in the UKPDS trial, we included 4550 participants with type 2 diabetes and without diabetes autoantibodies, and who participated in a 3-month dietary run-in and follow-up (figure 1). Overall, 429 (9·4%) of 4550 had younger-onset type 2 diabetes diagnosed at a mean age of 35·1 years (SD 3·5), and 4121 (90·6%) had later-onset type 2 diabetes diagnosed at a mean age of 53·8 years (6·7; table 1). At the time of diagnosis of type 2 diabetes, participants with younger-onset type 2 diabetes were more frequently of Asian or Indian ethnicity (100 [23·3%] of 429 participants with younger-onset type 2 diabetes *vs* 373 [9·1%] of 4121 with older-onset type 2 diabetes; p<0·001); younger-onset type 2 diabetes had a higher mean BMI (30·6 kg/m² *vs* 29·0 kg/m²; p<0·001) and a higher proportion of participants with obesity (50·8% *vs* 35·2%; p<0·001), a lower mean HbA_{1c}

	Total (n=4550)	Younger-onset type 2 diabetes (n=429)	Later-onset type 2 diabetes (n=4121)	p value
Demographics				
Age, years	52·0 (8·5)	35·1 (3·5)	53·8 (6·7)	..
Sex				
Male	2704 (59·4%)	270 (62·9%)	2434 (59·1%)	0·12
Female	1846 (40·6%)	159 (37·1%)	1687 (40·9%)	
Ethnicity	..	..	..	<0·001
White	3662 (80·5%)	303 (70·6%)	3359 (81·5%)	..
Black	376 (8·3%)	23 (5·4%)	353 (8·6%)	..
Asian Indian	473 (10·4%)	100 (23·3%)	373 (9·1%)	..
Other	39 (0·9%)	3 (0·7%)	36 (0·9%)	..
Socioeconomic status	..	..	..	0·03
Professional	186 (4·1%)	15 (3·5%)	171 (4·1%)	..
Managerial	911 (20·0%)	90 (21·0%)	821 (19·9%)	..
Skilled	1883 (41·4%)	177 (41·3%)	1706 (41·4%)	..
Partially skilled	1077 (23·7%)	106 (24·7%)	971 (23·6%)	..
Unskilled	327 (7·2%)	17 (4·0%)	310 (7·5%)	..
Data missing	166 (3·6%)	24 (5·6%)	142 (3·4%)	..
Clinical				
BMI, kg/m²	29·1 (5·5)	30·6 (6·6)	29·0 (5·4)	<0·001
Underweight, <18·5	17 (0·4%)	6 (1·4%)	11 (0·3%)	..
Normal, ≥18·5 to <25	983 (21·6%)	85 (19·8%)	890 (21·8%)	..
Overweight, ≥25 to <30	1883 (41·4%)	120 (28·0%)	1763 (42·8%)	..
Obesity, ≥30	1667 (36·6%)	218 (50·8%)	1449 (35·2%)	..
Waist-to-hip ratio	0·91 (0·08)	0·92 (0·08)	0·91 (0·07)	0·006
Systolic blood pressure, mm Hg*	136·0 (19·5)	126·8 (16·1)	136·9 (19·6)	<0·001
Smoking	..	..	..	<0·001
Never	1618 (35·6%)	185 (43·1%)	1433 (34·8%)	..
Former	1546 (34·0%)	88 (20·5%)	1458 (35·4%)	..
Current	1384 (30·4%)	156 (36·4%)	1228 (29·8%)	..
Data missing	..	..	2 (<1·0%)	..
Alcohol	..	..	..	0·71
None	1106 (24·3%)	113 (26·3%)	993 (24·1%)	..
Social	2519 (55·4%)	218 (50·8%)	2301 (55·8%)	..
Regular	752 (16·5%)	79 (18·4%)	673 (16·3%)	..
Dependent	61 (1·3%)	6 (1·4%)	55 (1·3%)	
Data missing	..	..	1 (<1·0%)	..

(Table 1 continues on next page)

	Total (n=4550)	Younger-onset type 2 diabetes (n=429)	Later-onset type 2 diabetes (n=4121)	p value
(Continued from previous page)				
Biochemical				
Fasting plasma glucose, mmol/L†	11·8 (3·7)	11·2 (3·4)	11·9 (3·7)	<0·001
HbA_{1c}‡	9·1% (2·3)	8·7% (2·2)	9·2% (2·2)	<0·001
HbA_{1c}, mmol/mol‡	76 (24·6)	71·6 (24·4)	77·1 (24·6)	..
HOMA2-IR§	1·6 (1·1–2·2)	1·8 (1·2–2·6)	1·6 (1·1–2·2)	<0·001
HOMA2-%B§	49·9 (30·6–73·5)	55·9 (36·15–86·4)	49·3 (30·2–72·1)	<0·001
Fasting triglycerides, mmol/L¶	1·73 (1·25–2·48)	1·85 (1·24–2·81)	1·69 (1·22–2·40)	<0·001
Total cholesterol, mmol/L‖	5·6 (1·2)	5·4 (1·2)	5·6 (1·2)	0·003
Low-density lipoprotein cholesterol, mmol/L**	3·7 (1·1)	3·5 (1·0)	3·7 (1·1)	<0·001
High-density lipoprotein cholesterol, mmol/L††	1·0 (0·3)	1·0 (0·3)	1·1 (0·2)	<0·001
Estimated glomerular filtration rate, mL/min/1·73m²‡‡	81·3 (23·0)	94·0 (24·7)	80·0 (22·4)	<0·001
Urine albumin to creatinine ratio§§	1·27 (0·60–3·35)	1·08 (0·52–2·95)	1·30 (0·61–3·42)	0·14

Data are mean (SD), n (%), or median (IQR). *Data missing for 604 (13·3%) participants (71 [16·6%] with younger-onset type 2 diabetes; 533 [12·9%] with later-onset type 2 diabetes). †Data missing for 12 (0·3%) participants (one [0·2%] with younger-onset type 2 diabetes; 11 [0·3%] with later-onset type 2 diabetes). ‡Data missing for 435 (9·6%) participants (40 [9·3%] with younger-onset type 2 diabetes; 395 [9·6%] with later-onset type 2 diabetes). §Insulin resistance and B-cell function (reported as percentage of a normal reference population) estimated with the Homeostasis Model Assessment Calculator version 2; data missing for 629 (13·8%) participants (65 [15·2%] with younger-onset type 2 diabetes; 564 [13·7%] with later-onset type 2 diabetes). ¶Data missing for 340 (7·5%) participants (35 [8·2%] with younger-onset type 2 diabetes; 305 [7·4%] with later-onset type 2 diabetes). ‖Data missing for 292 (6·4%) participants (27 [6·3%] with younger-onset type 2 diabetes; 265 [6·4%] with later-onset type 2 diabetes). **Data missing for 431 (9·5%) participants (43 [10·0%] with younger-onset type 2 diabetes; 388 [9·4%] with later-onset type 2 diabetes). ††Data missing for 385 (8·5%) participants (39 [9·1%] with younger-onset type 2 diabetes; 346 [8·4%] with later-onset type 2 diabetes). ‡‡Data missing for 24 (0·5%) participants (5 [1·2%] with younger-onset type 2 diabetes; 19 [0·5%] with later-onset type 2 diabetes); estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration formula. §§Data missing for 737 (16·2%) participants (72 [16·8%] with younger-onset type 2 diabetes; 665 [16·1%] with later-onset type 2 diabetes).

Table 1: **Baseline characteristics of participants with type 2 diabetes**

(8·7% *vs* 9·2%; 71·6 *vs* 77·1 mmol/mol; p<0·001), a higher median HOMA2-IR (1·8 *vs* 1·6, p<0·001), higher HOMA2-%B (55·9% *vs* 49·3%, p<0·001), higher median fasting triglycerides (1·85 *vs* 1·69 mmol/L; p<0·001), and lower mean low-density lipoprotein cholesterol (3·5 *vs* 3·7 mmol/L; p<0·001) than those with later-onset type 2 diabetes.

Any diabetes-related endpoint occurred in 202 (47·1%) participants with younger-onset type 2 diabetes and in 3016 (73·2%) with later-onset type 2 diabetes over a median follow-up time of 18·0 years (IQR 13·9–21·0) and 17·4 years (IQR 12·6–20·8), respectively (table 2). The absolute and adjusted incidence rates were higher for all aggregate outcomes in those with later-onset type 2 diabetes, except for microvascular disease (adjusted risk 18·0 [95% CI 13·8–22·1] per 1000 person-years for younger-onset type 2 diabetes *vs* 11·7 [10·7–12·7] per 1000 person-years for later-onset type 2 diabetes); appendix p 2). However, at any given age during follow-up, the 5-year incidence of all aggregate clinical outcomes, particularly all-cause mortality, diabetes-related mortality, and microvascular disease, was higher with younger age at diagnosis (figure 2). Stacked cumulative incidence graphs show that the competing risks, namely deaths, are greatest in those with later-onset type 2 diabetes particularly for microvascular disease (appendix p 3).

A total of 2048 deaths occurred over 74 979 person-years of follow-up. The crude mortality rate was lower in participants with younger-onset type 2 diabetes (10·4 per 1000 person-years) than later-onset disease (29·2 per 1000 person-years) given their younger attained age (table 3). However, the excess mortality associated with type 2 diabetes compared with the general population was higher in younger-onset type 2 diabetes (SMR 3·72 [95% CI 2·98–4·64]) compared with later-onset type 2 diabetes (1·54 [1·47–1·61]). When we further stratified participants by 10-year cohorts of age at diagnosis, the SMR was highest (3·85 [2·62–5·66]) in the youngest group diagnosed with type 2 diabetes between ages 24–35 years and attenuated with increasing age at diagnosis (table 4).

At 1-year after diagnosis, participants in all age groups showed a significant improvement in HbA_{1c}, FPG, BMI, and HOMA2-%B compared with baseline once they were on established treatment (p<0·01). Thereafter, annual mean HbA_{1c}, FPG, BMI, and HOMA2-IR were higher in the first 20 years of follow-up in those diagnosed with type 2 diabetes at younger compared with diagnosed at later ages (figure 3; appendix p 4). At 10 years' follow-up, HbA_{1c}, FPG, and BMI had increased more in participants diagnosed at a younger age ($P_{trend\ across\ age\ groups}$ <0·05). Although HOMA2-%B was higher at diagnosis in those with younger-onset type 2 diabetes, the decline in estimated β-cell function by 10 years after diagnosis was greater in those with younger age of type 2 diabetes diagnosis (P_{trend}<0·001).

322 (75·1%) participants with younger-onset type 2 diabetes and 3512 (85·2%) with later-onset type 2 diabetes were randomised to glycaemic control strategies (appendix p 7). We observed no significant interactions for all outcomes, that is, no difference in the magnitude of the treatment effect among participants with young-onset versus later-onset diabetes (p for interaction >0·05). Among participants allocated to sulfonylurea or insulin therapy as compared with those allocated to conventional therapy, significant reductions in risk of diabetes-related death, death from any cause, myocardial infarction, and microvascular disease were observed in the later-onset type 2 diabetes group, but no significant risk reductions or risk increases in the younger-onset type 2 diabetes group (appendix p 5). Similarly, in the metformin group as compared with the conventional-therapy group, significant reductions in any diabetes-related endpoint, diabetes-related death, death from any cause, myocardial infarction, and major adverse cardiovascular events were observed in participants with later-onset type 2 diabetes.

See Online for appendix

	Patients with clinical outcome		Absolute risk (incidence per 1000 person-years, 95% CI)		Adjusted risk* (incidence per 1000 person-years, 95% CI)	
	Younger-onset type 2 diabetes (n=429)	Later-onset type 2 diabetes (n=4121)	Younger-onset type 2 diabetes (n=429)	Later-onset type 2 diabetes (n=4121)	Younger-onset type 2 diabetes (n=429)	Later-onset type 2 diabetes (n=4121)
Any diabetes-related endpoint	202 (47·1%)	3016 (73·2%)	32·8 (28·6–37·7)	59·6 (57·5–61·8)	38·0 (31·9–44·1)	57·8 (55·5–60·1)
Diabetes-related death	46 (10·7%)	1079 (26·2%)	6·15 (4·61–8·21)	16·2 (15·3–17·2)	6·57 (4·20–8·94)	15·0 (13·9–16·0)
Death from any cause	78 (18·2%)	1970 (47·8%)	10·4 (8·29–12·9)	29·2 (27·9–30·5)	12·0 (8·8–15·1)	27·3 (25·9–28·7)
Myocardial infarction	65 (15·2%)	1121 (27·2%)	9·06 (7·10–11·6)	17·9 (16·9–19·0)	10·6 (7·59–13·5)	17·0 (15·8–18·1)
Stroke	10 (2·3%)	462 (11·2%)	1·36 (0·73–2·52)	7·23 (6·60–7·92)	1·27 (0·25–2·30)	6·51 (5·80–7·21)
Peripheral vascular disease	14 (3·3%)	138 (3·3%)	1·91 (1·13–3·22)	2·12 (1·80–2·51)	1·97 (0·67–3·27)	2·04 (1·66–2·43)
Microvascular disease	98 (22·8%)	729 (17·7%)	14·5 (11·9–17·7)	12·1 (11·3–13·0)	18·0 (13·8–22·1)	11·7 (10·7–12·7)
Major adverse cardiovascular event	75 (17·5%)	1485 (36·0%)	10·5 (8·37–13·2)	24·2 (23·0–25·5)	12·0 (8·81–15·2)	22·7 (21·4–24·1)

Data are n (%), unless stated otherwise. The median follow-up time for the younger-onset type 2 diabetes group was 18·0 years (IQR 13·9–21·0) and for the later-onset type 2 diabetes group was 17·4 years (IQR 12·6–20·8). *Adjusted for baseline HbA_{1c}, BMI, systolic blood pressure, low-density lipoprotein cholesterol, smoking status, sex and ethnicity.

Table 2: **Aggregate outcomes from UKPDS from up to 30 years follow-up data**

No significant risk reductions or risk increases were observed in those with younger-onset type 2 diabetes. We were unable to reject the (null) hypothesis of no treatment effect in the subgroup of younger-onset participants with type 2 diabetes. Participants randomised to intensive glucose control had lower HbA_{1c} compared with those on conventional therapy in both the younger-onset and later-onset type 2 diabetes subgroups (appendix p 6).

Discussion

In this large prospective 30-year follow-up of people with newly diagnosed type 2 diabetes in the UKPDS trial, we found that younger age at diagnosis was associated with a higher risk of incident diabetes-related complications, excess mortality, and persistently poorer glycaemic control. The lower crude mortality rates of participants diagnosed younger-onset versus later-onset reflects that the younger-onset group naturally remained younger during follow-up, and does not adjust for this attained age. Yet, participants with younger-onset type 2 diabetes had a higher SMR reflecting an almost four-fold relative increase in risk of death compared with the general UK population. At any given attained age during follow-up, up to the age 60 years for which we have data across all age groups, the 5-year incidence rate of all aggregate outcomes was higher in younger-onset type 2 diabetes compared with later-onset type 2 diabetes. In our post-hoc analysis of the UKPDS trial, that is, the interventional period of the study, we found no significant interaction between younger versus later age of onset and randomised glycaemic control strategy.

A strength of this study is having data from diagnosis of diabetes, recognising that we do not have information on the duration of diabetes before diagnosis. However, because the UK has universal health care that is free at the point of delivery, we assume that symptomatic people sought care. In our cohort, people with younger-onset had a lower HbA_{1c} and higher HOMA2-%B (estimated β-cell function) than those with later-onset type 2 diabetes at diagnosis, suggesting a shorter or equal, but not longer, duration of pre-existing diabetes. This finding contrasts with observations from recent publications in which younger-onset cohorts have generally poorer glycaemic control at diagnosis.[6] It is possible that rising obesity rates since the start of the UKPDS trial have contributed to relatively higher HbA_{1c} levels at diagnosis. Another explanation could be that in most other studies, participants were not tested for pancreatic autoantibodies, and therefore might have included people with latent autoimmune diabetes in adults, who usually have higher HbA_{1c} at diagnosis than antibody-negative people.[33]

Our finding that the risk of excess all-cause mortality is substantial and highest with younger-onset of type 2 diabetes is largely consistent with previous reports.[22,34–36] This study offers evidence from a cohort of people with newly diagnosed diabetes, followed for a longer period than existing reports, and who have undergone antibody testing. The SMR of 3·85 in our participants diagnosed at ages 25–35 years was higher than those reported by databases from Australia (SMR 1·21 to 1·56) and Sweden (SMR 2·9).[34,35] This might, in part, be because the UKPDS trial began in the 1970s when therapeutics and glycaemic targets were less well established. The difference in SMRs across populations might also relate to different death rates in the general population.

Our cohort had a median follow-up time of almost 20 years, which is approximately double that of other studies from Australia, China, Hong Kong, Denmark, and Sweden.[19–22,34,35,37–39] In an observational study of primary care in the UK using the Clinical Practice Research Datalink, people with type 2 diabetes diagnosed between 2000 and 2020 were followed for a median duration of 9·5 years.[36] Thus, we might have captured more events in later decades of life for those diagnosed young, and been better placed to describe mortality with a longer follow-up time. Mortality risk has also been

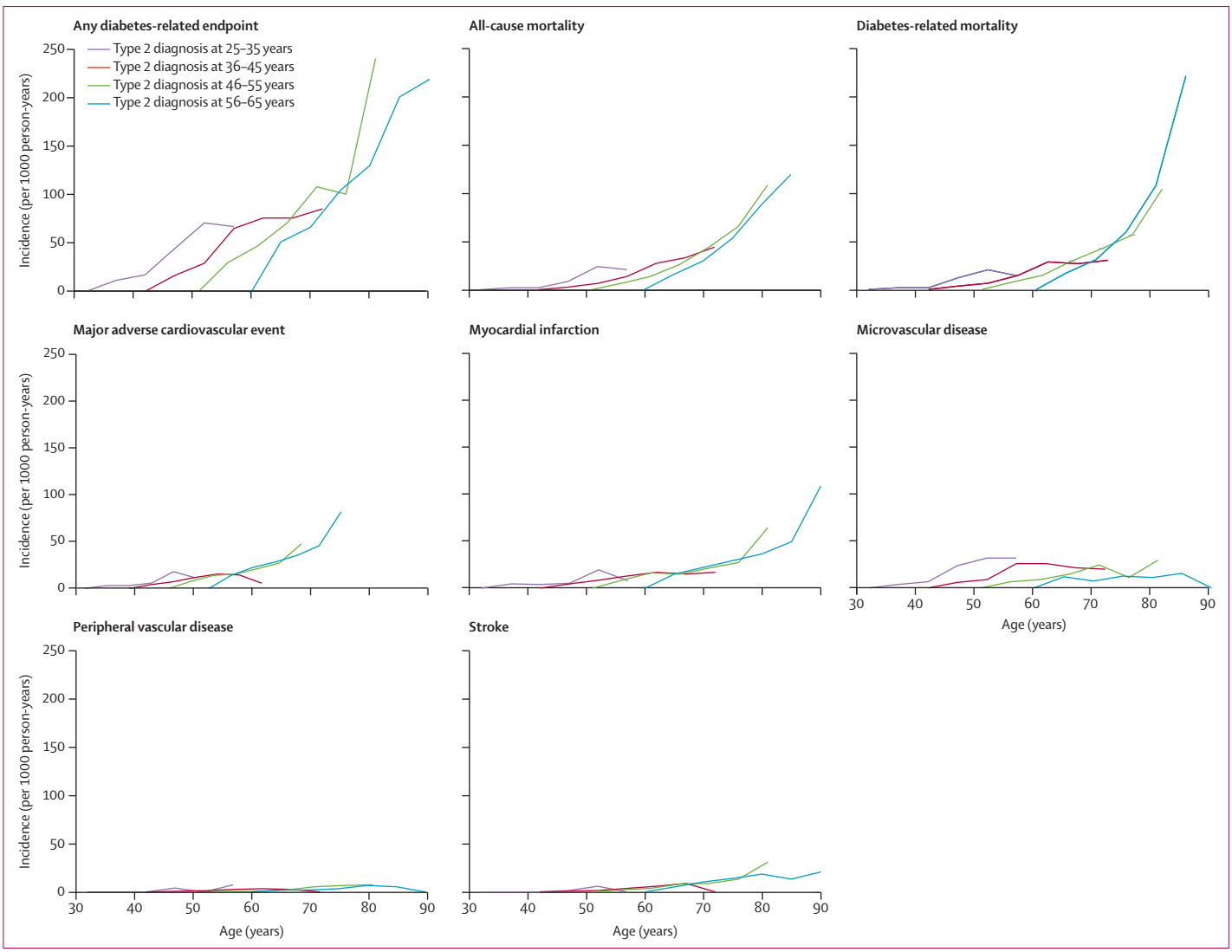

Figure 2: **Incidence rates of aggregate endpoints by 10-year age cohorts of age at diagnosis**
Incidence rates (per 1000 person-years) of aggregate endpoints in four consecutive 10-year age cohorts of UKPDS participants at diagnosis and successive 5-year intervals over 30-years of follow-up. Each curve begins at the median age at diagnosis for each group: 32 years for the 25–35 year age group, 42 years for the 36–45 year age group, 51 years for the 46–55 year age group, 60 years for the 56–65 year age group.

assessed by predictive modelling of life expectancy, where in a study using large-scale European and American population data, every decade earlier in diagnosis conferred another 3–4 years of life lost to type 2 diabetes.[40] Collectively, these data support a need to develop strategies that identify young adults with type 2 diabetes to prevent or delay complications including mortality. The implications of developing diabetes at a younger age include personal as well as potential societal consequences with effects on the workforce.

Another strength of this study is that 99·9% of the UKPDS cohort had undergone testing for pancreatic autoantibodies, with 98·8% of these being within the first 2 years of diagnosis.[28] Positivity to pancreatic autoantibodies identifies participants with latent autoimmune diabetes in adults who have a different risk of complications compared with people with type 2 diabetes. Recognising, and in this study excluding, people with latent autoimmune diabetes in adults helps clarify the differences in the incidence rates of complications between younger-onset and later-onset type 2 diabetes.[41,42]

Among outcomes, microvascular disease showed the greatest excess risk for incident complications in younger-onset type 2 diabetes compared with later-onset type 2 diabetes. Microvascular disease was the only aggregate outcome in which the absolute risk was higher after 20 years' duration of diabetes despite participants being of lower attained age, which aligns with other studies examining retinopathy and nephropathy.[21,22,39] It is

unclear whether this was because of greater exposure to glycaemic burden, or an inherently more aggressive phenotype of young-onset type 2 diabetes for microvascular complications. By following patients prospectively from time of diagnosis, we were able to study incident complications with minimal survival bias, a key advantage of this study. Two Australian studies have found that younger age of diagnosis was an independent predictor of nephropathy and retinopathy, even after adjusting for diabetes duration.[22,38] We acknowledge that an inherent limitation in assessing complications by age groups is that competing risks, predominantly deaths, are more frequent in the later-onset type 2 diabetes age group compared with younger-onset type 2 diabetes. Because people with younger-onset type 2 diabetes are developing and living with microvascular complications, policy makers should consider implementing intensified screening protocols and follow-on treatment for eye and renal disease for patients with younger-onset type 2 diabetes.[3,6,24,39]

The reasons for differing rates of outcomes in younger-onset compared with later-onset type 2 diabetes are not completely understood and are likely multifactorial.[3,6] It is possible that residual confounding exists, meaning that people diagnosed at a younger age differ fundamentally in ways (either unmeasured or unknown), which themselves increase the risk of complications. These factors might include, for example, differences in social determinants or environmental exposures. Longer disease duration, and consequently prolonged exposure to hyperglycaemia, has been postulated as a key mechanism. In this study, disease duration was uniform over follow-up, as all participants were newly diagnosed. Glycaemic control, however, was worse with younger age at diagnosis over the first 20 years of follow-up. This mirrors the increase in excess-mortality risk seen with younger age, suggesting that hyperglycaemia might in part be responsible. In a prospective study of age-matched youth-onset people with type 1 diabetes and type 2 diabetes, adjusting for HbA_{1c} and metabolic risk factors mitigated the higher risk of cardiorenal complications seen in those with type 2 diabetes compared with type 1 diabetes.[37] We know that intensive early control of diabetes is crucial for long-term outcomes.[27] Despite younger and older participants being treated according to the same glucose-lowering protocol, the underlying reason for worse glycaemic control in our younger-onset type 2 diabetes cohort in the UKPDS trial compared with older patients could be related to compliance, faster decline in β-cell function as shown by the RISE consortium,[15] worsening obesity, or clinical progression of insulin resistance.[17]Alternatively, younger people might have poorer adherence than older people. Young adults have distinct psychosocial needs and face increasing challenges to self-management with little support even in our current health-care models.[6] These challenges could include balancing the demands of managing diabetes with developing a career, family responsibilities, and health-related stigma.

	Person-years	Deaths observed	Deaths expected	Crude mortality rate (per 1000 person-years)	SMR (95% CI)*
Younger-onset type 2 diabetes, n=429	7535	78	21·0	10·4	3·72 (2·98–4·64)
Later-onset type 2 diabetes, n=4121	67 444	1970	1280·4	29·2	1·54 (1·47–1·61)

p value for difference between SMRs is <0·001. SMR=standardised mortality ratio. *Standardised mortality ratios were calculated using standard UK population mortality rates derived from the Office of National Statistics census data.

Table 3: **Standardised mortality ratios in younger-onset and later-onset type 2 diabetes**

	Person-years	Deaths observed	Deaths expected	SMR (95% CI)*
25–35 years, n=192	3328	26	6·8	3·85 (2·62–5·66)
36–45 years, n=809	14 562	185	75·1	2·46 (2·13–2·84)
46–55 years, n=1744	30 257	699	401·9	1·74 (1·61–1·87)
56–65 years, n=1805	26 832	1138	817·6	1·39 (1·31–1·48)

p value for trend across age groups for SMR is 0·039. SMR=standardised mortality ratio. *SMRs were calculated using standard UK population mortality rates derived from the Office of National Statistics census data.

Table 4: **Standardised mortality ratios by 10-year age cohorts of type 2 diabetes diagnosis**

Our post-hoc subgroup analyses of randomised trial participants showed no interaction between treatment effect and age of type 2 diabetes diagnosis (younger-onset *vs* later-onset type 2 diabetes). Based on the uncertainty around the estimates of effectiveness, the results include the possibility of sizable benefits with sulfonylureas or insulin (95% CI 0·67 to 1·41) or with metformin (95% CI 0·46 to 1·85) for all-diabetes related endpoints (appendix p 5). Given this, one would continue to treat people with younger-onset diabetes with the same efforts and modalities as people with later-onset disease. Given our small sample size of young adults, we were unable to detect all but very large differences in outcomes. To date, there have been no long-term trials specific to young adult-onset type 2 diabetes showing effective treatment and durable glycaemic control; and rarely do larger adult trials report on subgroup outcomes in their younger-onset cohort.[6] Only one randomised controlled trial for adults with younger-onset type 2 diabetes has been published (DIADEM-I).[43] The study was done in Qatar and recruited 158 participants aged 18–50 years with recently diagnosed type 2 diabetes, and showed intensive lifestyle intervention compared with usual medical care (defined by American Diabetes Association diabetes guidelines) increased rates of diabetes remission and normoglycaemia at 12 months. The VERIFY trial has published subgroup results in

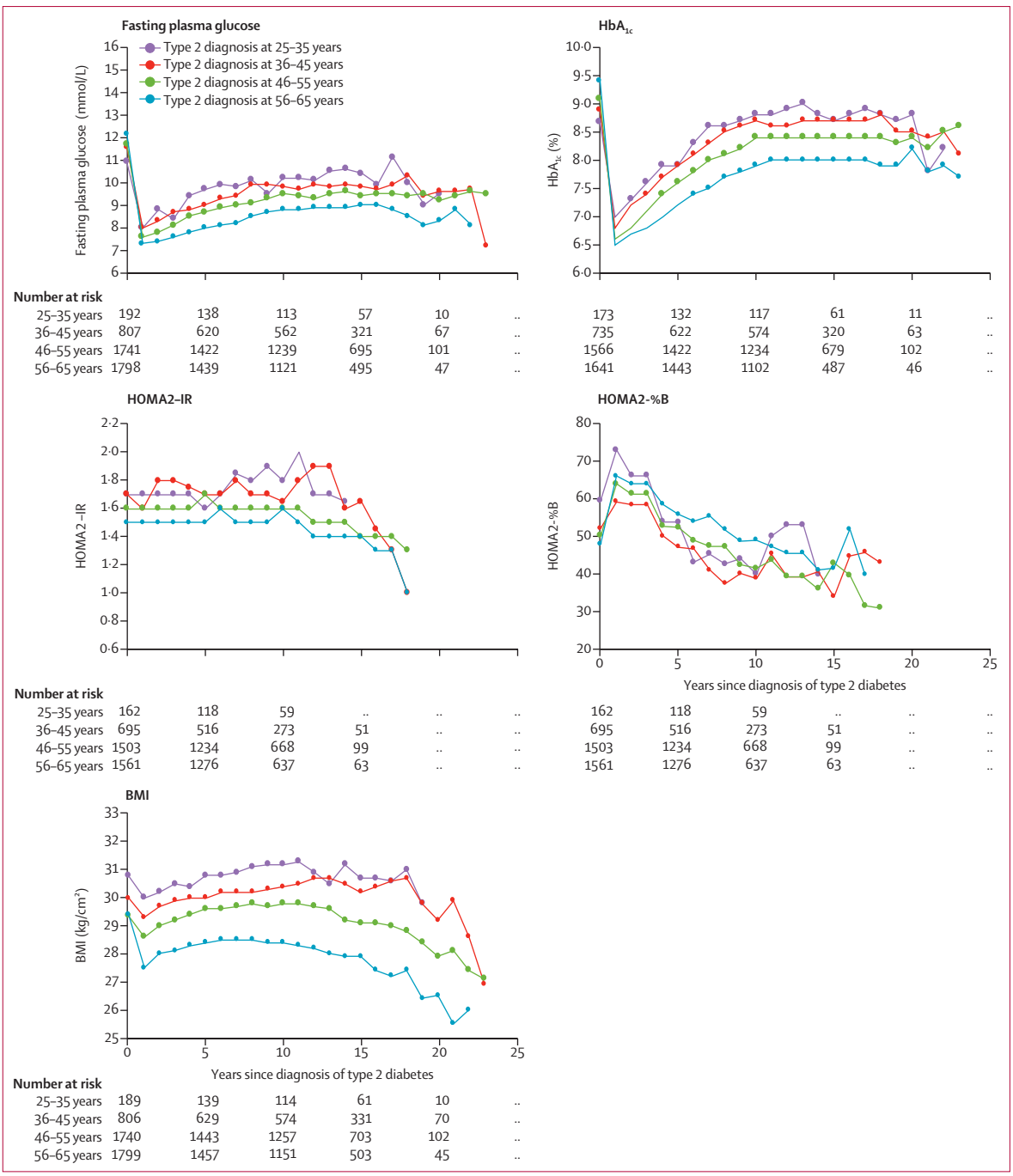

Figure 3: **Annual clinical and biochemical variables during follow-up from study entry of UKPDS participants by 10-year age cohorts of age at diagnosis**
Mean fasting plasma glucose, HbA1c, BMI, and median HOMA2-IR and HOMA2-%B at annual follow-up in approximately four consecutive 10-year age cohorts: 32 years for the 25–35 year age group, 42 years for the 36–45 year age group, 51 years for the 46–55 year age group, 60 years for the 56–65 year age group. Each curve starts at time of diagnosis and ends when number of data points are fewer than 10.

younger-onset type 2 diabetes that showed that early combination therapy with metformin and vildagliptin, compared with metformin plus placebo, improved glycaemic control, but, being placebo-controlled, did not address a clinically relevant question.[44] Management has otherwise been largely informed by generalising from adult studies that largely consist of individuals with later-onset disease, or paediatric trials. There remain significant opportunities for therapeutic clinical trials of sufficient duration and size in younger-onset type 2 diabetes, and an overdue need for data to inform a tailored pharmacological approach.

The key strength of this study is the prospective study design and long follow-up of participants from time of type 2 diabetes diagnosis with detailed longitudinal data on glycaemic control and metabolic risk. This enabled us to examine disease progression including incident complications and deaths with minimal survival bias. Furthermore, we were able to describe the natural history of β-cell function and insulin resistance in younger-onset compared with later-onset type 2 diabetes. However, our study has several limitations. Because of the inherent increase in mortality and complications associated with increasing age, and its collinearity with age at diagnosis and diabetes duration, we chose to analyse our data descriptively and were unable to interrogate the effect of age of type 2 diabetes onset independent of chronological age. We had a relatively smaller number of participants with younger-onset type 2 diabetes with few events for specific outcomes such as stroke. The 20-year interventional trial largely predates the use of therapies that modify cardiometabolic and mortality risk such as GLP-1 receptor agonists and SGLT2i. However, most evidence for their cardiovascular benefit is from trials of older individuals. Although our UK cohort was largely White, younger-onset type 2 diabetes disproportionately affected those of Asian and Indian ethnicity, which is consistent with the literature.[3] Further data in non-White ethnicities, and in low-income and middle-income countries, are needed. Lastly, in this study, we did not assess non-vascular complications of diabetes, such as liver disease and pregnancy-related morbidity.

In conclusion, in up to 30 years of UKPDS follow-up, we observed that people diagnosed with type 2 diabetes at a younger age showed a high risk of incident diabetes-related complications, excess age-standardised mortality, and poorer glycaemic control compared with people with later-onset disease. There remains a paucity of dedicated clinical trial data to inform the care of patients with this distinct and aggressive phenotype of younger-onset type 2 diabetes. Our findings support the need to develop interventions and services that identify and support the health-care needs of these individuals over their lifetimes.

Contributors

BL: conceptualisation, formal analysis, methodology, software, visualisation, writing–original draft, and writing–review & editing. RLC: data curation, methodology, software, resources, supervision, validation, and writing–review & editing. FB: methodology, supervision, and writing–review & editing. EM: methodology, supervision, and writing–review & editing. RRH: conceptualisation, funding acquisition, investigation, methodology, supervision, and writing–review & editing. AIA: conceptualisation, funding acquisition, investigation, methodology, project administration, resources, supervision, and writing–review & editing. BL drafted the manuscript, which was critically revised by all authors who approved the final version and agreed to be accountable for it. BL did the data analysis and RLC verified the data. AIA had the final responsibility for the decision to submit for publication.

Declaration of interests

EM has received grants from scientific societies supported by Lilly and AstraZeneca; support for attending scientific meetings from Abbott and Theras; and honoraria or consulting fees from Lilly, Medical Technology and Devices, Merck, Pikdare, AstraZeneca, NovoNordisk, and Abbott. RRH has received honoraria from Lilly and consulting fees from Anji Pharmaceuticals, Novartis, and AstraZeneca. All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request, provided any costs incurred are covered.

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