



Temporal Trend in Young-Onset Type 2 Diabetes—Macrovascular and Mortality Risk: Study of U.K. Primary Care Electronic Medical Records

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Diabetes Care 2020;43:2208–2216 | <https://doi.org/10.2337/dc20-0417>

OBJECTIVE

To evaluate temporal prevalence trend, cardiometabolic risk factors, and the risk of atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality (ACM) in incident young- and usual-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS

From the U.K. primary care database, 370,854 people with a new diagnosis of type 2 diabetes from 2000 to 2017 were identified. Analyses were conducted by age-group (18–39, 40–49, 50–59, 60–69, 70–79 years) and high-/low-risk status without history of ASCVD at diagnosis, with subjects with two or more of current smoking, high systolic blood pressure, high LDL cholesterol (LDL-C), or chronic kidney disease classified as high risk.

RESULTS

The proportion of people aged <50 years at diagnosis increased during 2000–2010 and then stabilized. The incidence rates of ASCVD and ACM declined in people aged ≥50 years but did not decrease in people <50 years. Compared with people aged ≥50 years, those aged 18–39 years at diagnosis had a higher proportion of obesity (71% obese) and higher HbA_{1c} (8.6%), and 71% had high LDL-C, while only 18% were on cardioprotective therapy. Although 2% in this age-group had ASCVD at diagnosis, 23% were identified as high risk. In the 18–39-year age-group, the adjusted average years to ASCVD/ACM in high-risk individuals (9.1 years [95% CI 8.2–10.0]/9.3 years [8.1–10.4]) were similar to the years in those with low risk (10.0 years [9.5–10.5]/10.5 years [9.7–11.2]). However, individuals aged ≥50 years with high risk were likely to experience an ASCVD event 1.5–2 years earlier and death 1.1–1.5 years earlier compared with low-risk groups ($P < 0.01$).

CONCLUSIONS

Unlike usual-onset, young-onset type 2 diabetes has similar cardiovascular and mortality risk irrespective of cardiometabolic risk factor status at diagnosis. The guidelines on the management of young-onset type 2 diabetes for intensive risk factor management and cardioprotective therapies need to be urgently reevaluated through prospective studies.

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Received 1 March 2020 and accepted 21 May 2020

This article contains supplementary material online at <https://doi.org/10.2337/figshare.12357320>.

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Type 2 diabetes, once considered a disease of middle and old age, is frequently diagnosed in adolescents and young adults because of the rising prevalence of obesity and lifestyle changes (1,2). A previous U.S. study showed that the incidence of type 2 diabetes in young people increased significantly between 1980 and 2012 (3), and the problem is worse in minority ethnic groups (4). Although there is no clear definition for young-onset type 2 diabetes, some studies defined diagnosis of type 2 diabetes at <40 years of age as young onset (5).

The European Society of Cardiology-European Association for the Study of Diabetes guideline has categorized people who develop type 2 diabetes at age <50 years with diabetes duration <10 years as having moderate cardiovascular risk, without any evidence base (6). However, a Swedish study reported significantly higher BMI in people diagnosed with type 2 diabetes within the age range of 18–44 years, while the hemoglobin A_{1c} (HbA_{1c}) level was found to be similar at diagnosis across all age-groups (7,8). Yeung et al. (5), using data from 41,000 patients with type 2 diabetes from nine Asian countries, showed that those with young-onset type 2 diabetes had higher mean concentrations of HbA_{1c} and LDL cholesterol (LDL-C) and a higher prevalence of retinopathy compared with those with usual-onset diabetes. A recent study by Ke et al. (9) reported significantly higher mental health problems and hospitalization in people from Hong Kong with young-onset type 2 diabetes compared with usual-onset type 2 diabetes.

The presence of higher levels of cardiometabolic risk factors in patients with young-onset type 2 diabetes may lead to major cardiovascular complications, including mortality at an earlier age. Registry-based studies from Australia showed a positive association of age at diagnosis and diabetes duration with higher microvascular risk and cardiovascular mortality (10,11). However, these studies did not evaluate the cardiometabolic risk factor distributions. In a cohort of 7,844 patients with type 2 diabetes, Hillier and Pedula (12) showed that those diagnosed early (mean age 38 years) have a worse clinical and laboratory profile than those with usual-onset type 2 diabetes (mean age 60 years). In addition, this study showed that the risk of any macrovascular complication in early-onset type 2 diabetes

compared with control subjects without diabetes was twice as high as in usual-onset type 2 diabetes compared with control subjects without diabetes (hazard ratio [HR] 7.9 vs. 3.8). However, no study has holistically evaluated the pattern of young-onset type 2 diabetes, the comorbidities and cardiometabolic risk factor distribution at diagnosis, and the macrovascular diseases and all-cause mortality (ACM) risk by cardiometabolic risk stratification at diagnosis among those without a history of atherosclerotic cardiovascular disease (ASCVD) at diagnosis in a real-world setting. More importantly, while the guidelines identify patients with young-onset type 2 diabetes under moderate or minimum cardiovascular risk categories without any evidence (6), we are not aware of any study that has evaluated cardiometabolic risk distribution at the time of diagnosis of type 2 diabetes in different age-groups and its possible differentiated effects on the long-term cardiovascular and mortality risk in patients with young- and usual-onset type 2 diabetes. Using nationally representative U.K. primary care electronic medical records (EMRs) in patients diagnosed with type 2 diabetes between 2000 and 2017, the aims of the current study were to evaluate 1) the temporal patterns of young-onset type 2 diabetes diagnosis, 2) the comorbidities and cardiometabolic risk factor distribution at diagnosis by young- and usual-onset status, and 3) the dynamics of ASCVD and ACM risk by risk factor–driven categorizations in patients with young- and usual-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Source

The Health Improvement Network (THIN) database from the U.K. was used for this study. THIN is a comprehensive EMR derived from a network of >750 primary care providers across the U.K. with longitudinal data on ~17 million individuals registered in the primary care system. The accuracy, completeness, and the population-level representativeness of the U.K. primary care database in relation to chronic diseases have been previously validated (13,14).

The THIN patient population is representative of the U.K. population by age, sex, medical conditions, and death rates adjusted for demographics and social deprivation. Notably, the database has

similar distribution of major chronic diseases, including diabetes, cardiovascular diseases, and mental illnesses, compared with U.K. national statistics (14,15) and has been extensively used by researchers and government bodies for clinical, epidemiological, and public health–related studies (16–18). The THIN database provides comprehensive patient-level longitudinal information on demographic, anthropometric, clinical, and laboratory measures; clinical diagnosis of diseases/events; and complete information on prescriptions for medications with dates. Clinically diagnosed diseases are recorded using Read codes (19) with event/diagnosis dates.

Study Population

From the THIN database, 370,854 people with a new diagnosis of type 2 diabetes from January 2000 were identified using a clinically guided algorithm on the basis of disease Read codes, additional health data codes, antidiabetic medications, and elevated glucose measures (17,20). Those with type 1 diabetes, gestational diabetes, or diabetes as a result of other causes, such as maturity-onset diabetes of the young, prediabetes, or metformin prescribed for polycystic ovary syndrome, were excluded. The study cohort comprised those with type 2 diabetes aged ≥18 and <80 years at diagnosis and with nonmissing sex and diagnosed from January 2000, with the date of diagnosis of type 2 diabetes at least 6 months after registration in the EMR to reduce bias in identifying patients with incident type 2 diabetes. The date of diagnosis was considered the index date (baseline).

Variables and Clinical Definitions

The presence of comorbidities before and after type 2 diabetes diagnosis was obtained by relevant disease identification codes (Read codes). People with ASCVD at type 2 diabetes diagnosis were identified as those having ischemic heart disease (myocardial infarction [MI], unstable angina, or coronary revascularization, excluding stable angina), cerebrovascular disease (ischemic/hemorrhagic stroke, transient ischemic attack, or carotid revascularization), or peripheral vascular disease. People with heart failure (HF) were identified as those with HF Read codes, including heart transplants. Cancer was defined as any malignancy except malignant neoplasm of the skin.

Baseline body weight, systolic blood pressure (SBP), and lipids were calculated as the average of available measures within a 3-month window of the index date. The closest measure within the 3-month window of the index date was taken for HbA_{1c}. For BMI, international classification was used as follows: normal weight (18.5–24.99 kg/m²), overweight (25–29.99 kg/m²), grade 1 obesity (30–34.99 kg/m²), and grade 2+ obesity (≥ 35 kg/m²). The Townsend deprivation score (TDS) was categorized as affluent (score 1–2), middle class (score 3), deprived (score 4–5), or missing.

Individuals who received antihypertensive medications were identified using prescription records for β -blockers, diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, other agents acting on the renin-angiotensin system, or other antihypertensive drugs. Similarly, lipid-lowering medications were identified using prescription records for statins, proprotein convertase subtilisin/kexin type 9 inhibitors, fibrates, bile acid sequestrates, nicotinic acid, and other lipid-lowering agents. Cardioprotective medications were identified if patients had a prescription record of antihypertensive or lipid-lowering therapies.

Individuals with high SBP and LDL-C were defined as having SBP ≥ 130 mmHg/LDL-C ≥ 1.8 mmol/L if with a history of ASCVD at type 2 diabetes diagnosis or SBP ≥ 140 mmHg/LDL-C ≥ 2.6 mmol/L if without a history of ASCVD at diagnosis (21,22). Chronic kidney disease (CKD) was identified using Read codes for CKD, estimated glomerular filtration rate < 60 mL/min/1.73 m² using the MDRD equation or urine albumin-to-creatinine ratio ≥ 3 mg/mmol. Among those without ASCVD at baseline, those with elevated levels of SBP and/or LDL-C, ex-/current smokers, or those who had CKD were classified as high risk.

To assess the cardiovascular risk in an individual on the basis of a population-level data-driven algorithm, the use of QRISK2 at the U.K. primary care level has been advocated over the past few years (23). As an additional exploratory exercise, we generalized the QRISK2 Cardiovascular Risk Score algorithm (23) to estimate the risk score at diagnosis of type 2 diabetes using the available data compared with our high-risk categorization. Given the missing data issues on

some clinical information, our generalized QRISK2 estimates will have some bias compared with the algorithm-driven estimates on complete data. Also, the QRISK2 was validated in the general U.K. primary care population aged 35–74 years. We used a $\geq 20\%$ estimated score for identification of high-risk category because QRISK2 overestimates cardiovascular disease risk in people with diabetes (24). The protocol for this study was approved by the scientific review committee of IQVIA Medical Research Data UK incorporating THIN (protocol number SRC_Protocol_15THIN031_v2_A1_07–11–2019).

Statistical Analyses

Baseline characteristics at type 2 diabetes diagnosis were summarized as number (%), mean (SD), or median (first quartile, third quartile), as appropriate, by age-groups. The temporal trend in the proportion of people at diagnosis in the age-groups 18–39, 40–49, 50–59, 60–69, and 70–79 years were evaluated from 2000 to 2017.

The patients were followed from index date until transfer out of practice, death, or end of follow-up on September 2017. The temporal trend of rates (95% CI) per 1,000 person-years (PY) for ASCVD and ACM were evaluated in those with/without ASCVD at index over calendar year of diagnosis, by age-groups at diagnosis. In a separate analysis, rates of ACM in those without ASCVD at baseline by age-group at type 2 diagnosis and BMI categories were reported.

Among people without a history of ASCVD at index, the time (95% CI) to ASCVD and ACM by high- and low-risk status (and by QRISK2 categories for additional exploratory analyses) were computed in different age-groups at type 2 diabetes diagnosis using propensity score-based (inverse probability of weights) survival analysis modeling (25,26) balanced on sex and TDS to account for the inherent heterogeneity in younger versus older patients at type 2 diabetes diagnosis and adjusting for age at diagnosis. Additional survival models incorporating BMI, blood pressure, HbA_{1c}, and lipids at diagnosis and the use of cardioprotective medications and antidiabetic medication were tested for possible additional information on the basis of a statistical information criterion.

RESULTS

Patient Characteristics at Diagnosis of Type 2 Diabetes

In the cohort of 370,854 patients diagnosed with type 2 diabetes between 2000 and 2017, with diagnosis at least 6 months after their first activity date in the database, 8% and 15% were in the 18–39- and 40–49-year age-groups with a mean age of 33 and 45 years, respectively (Table 1). Those diagnosed in the age-groups 18–39 and 40–49 years had higher mean levels of HbA_{1c}, higher BMI, and higher LDL-C and triglycerides compared with those diagnosed at older ages (Table 1). While 44% in the overall cohort had an HbA_{1c} $\geq 7.5\%$ at diagnosis, 58% and 55% had an HbA_{1c} $\geq 7.5\%$ at diagnosis in the 18–39- and 40–49-year age-groups, respectively. The proportions with obesity in these age-groups (71% and 70%) were significantly higher compared with 56% and 44% observed in the 60–69- and 70–79-year age-groups, respectively ($P < 0.01$).

While 18% in the overall cohort had a history of ASCVD at diagnosis, only 2% and 6% had ASCVD in the 18–39- and 40–49-year age-groups, respectively (Table 1). Among those without the history of ASCVD at diagnosis, 23% and 37% were at high risk in these age-groups, respectively. The proportions with microvascular diseases were similar across all age-groups.

Although 27% and 71% had high SBP and LDL-C in the 18–39-year age-group, only 16% and 4% were on antihypertensive and lipid-lowering therapies, respectively, at baseline. In the 40–49-year age-group, 41% and 75% had high SBP and LDL-C, while 33% and 13% were receiving antihypertensive and lipid-lowering therapies, respectively. In the 70–79-year age-group, 64% and 65% had high SBP and LDL-C, while 69% and 43% were receiving antihypertensive and lipid-lowering therapies, respectively.

Temporal Patterns in the Proportion of People Diagnosed With Type 2 Diabetes by Age-Group

The temporal pattern of diagnosis of type 2 diabetes over years of type 2 diabetes diagnosis by age-group are presented in Fig. 1A, suggesting significant differences in between age-group trend (trend $P < 0.001$). With marginal increasing trend in the proportion of patients diagnosed with type 2 diabetes

Table 1—Characteristics of patients at diagnosis of type 2 diabetes by age-group

	Age at type 2 diabetes diagnosis (years)					Total
	18–39	40–49	50–59	60–69	70–79	
Patients, <i>n</i> (%)	29,678 (8)	56,798 (15)	93,698 (25)	107,261 (29)	83,419 (23)	370,854
Age (years), mean (SD)	33 (5)	45 (3)	55 (3)	64 (3)	74 (3)	59 (13)
Male sex, <i>n</i> (%)	14,895 (50)	34,836 (61)	56,158 (60)	61,466 (57)	41,624 (50)	208,979 (56)
Smoking status, <i>n</i> (%)						
Current smoker	9,302 (31)	19,102 (34)	31,786 (34)	34,391 (32)	22,710 (27)	117,291 (32)
Ex-smoker	4,340 (15)	10,864 (19)	22,416 (24)	32,145 (30)	26,647 (32)	96,412 (26)
Never smoked	9,245 (31)	16,637 (29)	25,300 (27)	26,319 (25)	21,548 (26)	99,049 (27)
Unknown	6,791 (23)	10,195 (18)	14,196 (15)	14,406 (13)	12,514 (15)	58,102 (16)
TDS, <i>n</i> (%)						
Deprived	9,291 (36)	17,810 (36)	28,839 (36)	33,388 (36)	25,540 (36)	114,868 (36)
Middle	5,532 (22)	10,695 (22)	17,797 (22)	19,935 (22)	15,734 (22)	69,693 (22)
Affluent	10,673 (42)	20,512 (42)	34,060 (42)	38,752 (42)	30,507 (43)	134,504 (42)
HbA _{1c} , <i>n</i> (%) nonmissing)	14,204 (48)	33,841 (60)	57,817 (62)	67,096 (63)	50,972 (61)	223,930 (60)
HbA _{1c} (%), mean (SD)*	8.6 (2.4)	8.4 (2.3)	8.1 (2.2)	7.8 (2.1)	7.6 (2.0)	8.0 (2.2)
HbA _{1c} ≥7.5%, <i>n</i> (%)*	8,231 (58)	18,581 (55)	27,393 (47)	26,332 (39)	17,094 (34)	97,631 (44)
BMI, <i>n</i> (%) nonmissing)	17,516 (59)	37,866 (67)	63,763 (68)	73,699 (69)	54,358 (65)	247,202 (67)
BMI (kg/m ²), mean (SD)*	35 (8)	34 (8)	33 (7)	32 (6)	30 (5)	32 (7)
BMI category, <i>n</i> (%)						
Normal	1,711 (10)	2,672 (7)	4,723 (7)	7,563 (10)	9,229 (17)	25,898 (10)
Overweight	3,417 (20)	8,537 (23)	17,157 (27)	24,455 (33)	21,237 (39)	74,803 (30)
Grade 1	4,317 (25)	10,975 (29)	20,482 (32)	23,765 (32)	15,737 (29)	75,276 (30)
Grade 2+	8,071 (46)	15,682 (41)	21,401 (34)	17,916 (24)	8,155 (15)	71,225 (29)
SBP, <i>n</i> (%) nonmissing)	18,926 (64)	42,192 (74)	73,721 (79)	88,037 (82)	68,343 (82)	291,219 (78)
SBP (mmHg), mean (SD)*	130 (16)	136 (16)	140 (16)	141 (17)	142 (17)	140 (17)
SBP ≥140 mmHg, <i>n</i> (%)*	5,049 (27)	16,771 (40)	36,194 (49)	47,567 (54)	38,038 (56)	143,619 (49)
High SBP, <i>n</i> (%)	5,130 (27)	17,407 (41)	38,691 (52)	53,030 (60)	43,872 (64)	158,130 (54)
LDL-C, <i>n</i> (%) nonmissing)	8,837 (30)	24,450 (43)	44,822 (48)	53,445 (50)	39,530 (47)	171,084 (46)
LDL-C (mmol/L), mean (SD)*	3.2 (1.0)	3.2 (1.0)	3.2 (1.0)	3.0 (1.0)	2.8 (1.0)	3.0 (1.0)
High LDL-C, <i>n</i> (%)*	6,250 (71)	18,274 (75)	33,156 (74)	36,792 (69)	25,524 (65)	119,996 (70)
HDL-C, <i>n</i> (%) nonmissing)	11,769 (40)	31,810 (56)	56,247 (60)	65,898 (61)	48,375 (58)	214,099 (58)
HDL-C (mmol/L), mean (SD)	1.0 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)
Triglycerides, <i>n</i> (%) nonmissing)	11,841 (40)	31,503 (55)	55,704 (60)	64,912 (60)	47,394 (57)	211,354 (57)
Triglycerides (mmol/L), median (Q1, Q3)*	2.1 (1.5, 3.3)	2.2 (1.5, 3.2)	2.0 (1.5, 3.0)	1.9 (1.4, 2.6)	1.7 (1.3, 2.3)	1.9 (1.4, 2.7)
Comorbidities, <i>n</i> (%)						
ASCVD	522 (2)	3,180 (6)	11,837 (13)	24,557 (23)	27,290 (33)	67,386 (18)
Myocardial infarction	180 (1)	1,303 (2)	4,428 (5)	8,018 (7)	8,397 (10)	22,326 (6)
Heart failure	90 (0)	340 (1)	1,150 (1)	3,072 (3)	4,871 (6)	9,523 (3)
Stroke	128 (0)	603 (1)	2,104 (2)	4,509 (4)	5,851 (7)	13,195 (4)
Peripheral vascular disease	32 (0)	225 (0)	1,246 (1)	3,163 (3)	3,641 (4)	8,307 (2)
CKD	1,290 (4)	4,438 (8)	11,867 (13)	24,470 (23)	31,469 (38)	73,534 (20)
Microvascular disease	453 (2)	1,220 (2)	2,525 (3)	3,542 (3)	3,106 (4)	10,846 (3)
Cancer	383 (1)	1,209 (2)	3,851 (4)	8,174 (8)	9,899 (12)	23,516 (6)
High risk, <i>n</i> (%)	6,681 (23)	19,822 (37)	37,160 (45)	41,668 (50)	29,493 (53)	134,824 (44)
QRISK2 score, median (Q1, Q3)	—	13.6 (8.9, 20.5)	21.7 (16.0, 28.6)	30.9 (24.9, 38.0)	42.5 (36.2, 50.1)	—
QRISK2 score ≥10%, <i>n</i> (%)	—	36,316 (68)	77,757 (95)	82,665 (100)	56,129 (100)	—
QRISK2 score ≥20%, <i>n</i> (%)	—	13,659 (25)	45,102 (55)	74,270 (90)	56,091 (100)	—
Medications, <i>n</i> (%)						
Cardioprotective therapies	5,395 (18)	20,581 (36)	49,346 (53)	70,521 (66)	60,637 (73)	206,480 (56)
Antihypertensive therapies	4,835 (16)	18,463 (33)	45,082 (48)	65,550 (61)	57,689 (69)	191,619 (52)
Lipid-lowering therapies	1,265 (4)	7,401 (13)	23,387 (25)	40,555 (38)	35,855 (43)	108,463 (29)
Medications in those with history of ASCVD, <i>n</i> (%)						
Cardioprotective therapies	256 (49)	2,241 (70)	9,343 (79)	20,618 (84)	23,158 (85)	55,616 (83)
Antihypertensive therapies	238 (46)	2,101 (66)	8,827 (75)	19,672 (80)	22,349 (82)	53,187 (79)
Lipid-lowering therapies	149 (29)	1,859 (58)	7,960 (67)	17,501 (71)	18,749 (69)	46,218 (69)

QRISK2 score is calculated in patients aged ≥40 years without ASCVD at baseline. High LDL-C was defined as ≥1.8 and ≥2.6 mmol/L in those with and without ASCVD, respectively. High risk was defined as at least two of the following: current smoker, high SBP, high LDL, or CKD in those without ASCVD at type 2 diabetes diagnosis. High SBP was defined as ≥130 and ≥140 mmHg in those with and without ASCVD, respectively. Q, quartile. **P* < 0.001 for comparison between age-groups on the basis of ANOVA test or χ^2 test.

age <50 years from 2000 to 2010, the trend remained stable between 2011 and 2017. While an increasing trend after 2010 was observed in the 50–59-year age-group, the temporal trend was decreasing in those diagnosed at 70–79 years between 2000 and 2010 and stabilized after 2010.

Incidence Rates and Risk of ASCVD and ACM

With a total 2,581,322 PY of follow-up, the median follow-up ranged between 6.5 and 6.7 years within the 18–69-year age-group, while those aged ≥ 70 years had 5.8 years of median follow-up. The number of events and the rates/1,000 PY for ASCVD and ACM are presented in Table 2. The overall rates of ASCVD in people without a history of ASCVD and who were low risk at diagnosis in the age-groups 18–39 years ($n = 22,475$; rate 5.3 [95% CI 4.9, 5.7]) and 40–49 years ($n = 33,796$; 10.3 [9.9, 10.7]) were similar to

the estimates for the overall cohort of people without ASCVD (18–39-year age-group: $n = 29,156$ [95% CI of rate 5.6, 6.2]; 40–49-year age-group: $n = 53,618$ [10.7, 11.3]). People with a history of ASCVD at type 2 diabetes diagnosis had higher rates of mortality compared with those without ASCVD (37.8 vs. 16.6/1,000 PY).

In the youngest age-group (18–39 years) without a history of ASCVD at diagnosis ($n = 29,156$), the adjusted average time to ASCVD was similar between those with high risk (average time 9.1 years [95% CI 8.2, 10.0 years]) and low-risk (10.0 years [9.5, 10.5 years]) (Table 3 and Fig. 2A), with the average difference in time to ASCVD being only 0.9 years between these groups ($P > 0.05$). Overall, the average time to ASCVD was similar in all patients aged <50 years. Individuals aged ≥ 50 years with high risk at diagnosis of type 2 diabetes were likely to experience an event 1.5–2 years earlier compared with low-risk groups (all

$P < 0.01$) (Fig. 2A). The average time to ASCVD in the high- and low-risk groups was not different between males and females.

In the 18–39-year age-group, the adjusted average time to ACM was also similar for those with a high risk (average time 9.3 years [95% CI 8.1, 10.4 years]) and low risk (10.5 years [9.7, 11.2 years]) (Fig. 2B). Separately for the high- and low-risk status (all without history of ASCVD), the time to ACM was similar for all aged <70 years (Fig. 2B). Overall, overweight and obese patients with type 2 diabetes had lower ACM rates/1,000 PY compared with those of normal weight patients (Supplementary Table 1).

The rates of ASCVD and ACM for different age-groups by QRISK2 categories are presented in Supplementary Table 2. The patterns of difference in the average time to events by high and low QRISK2 score categories in the age-groups of 40–69 years were similar to those observed between the high- and low-risk categories

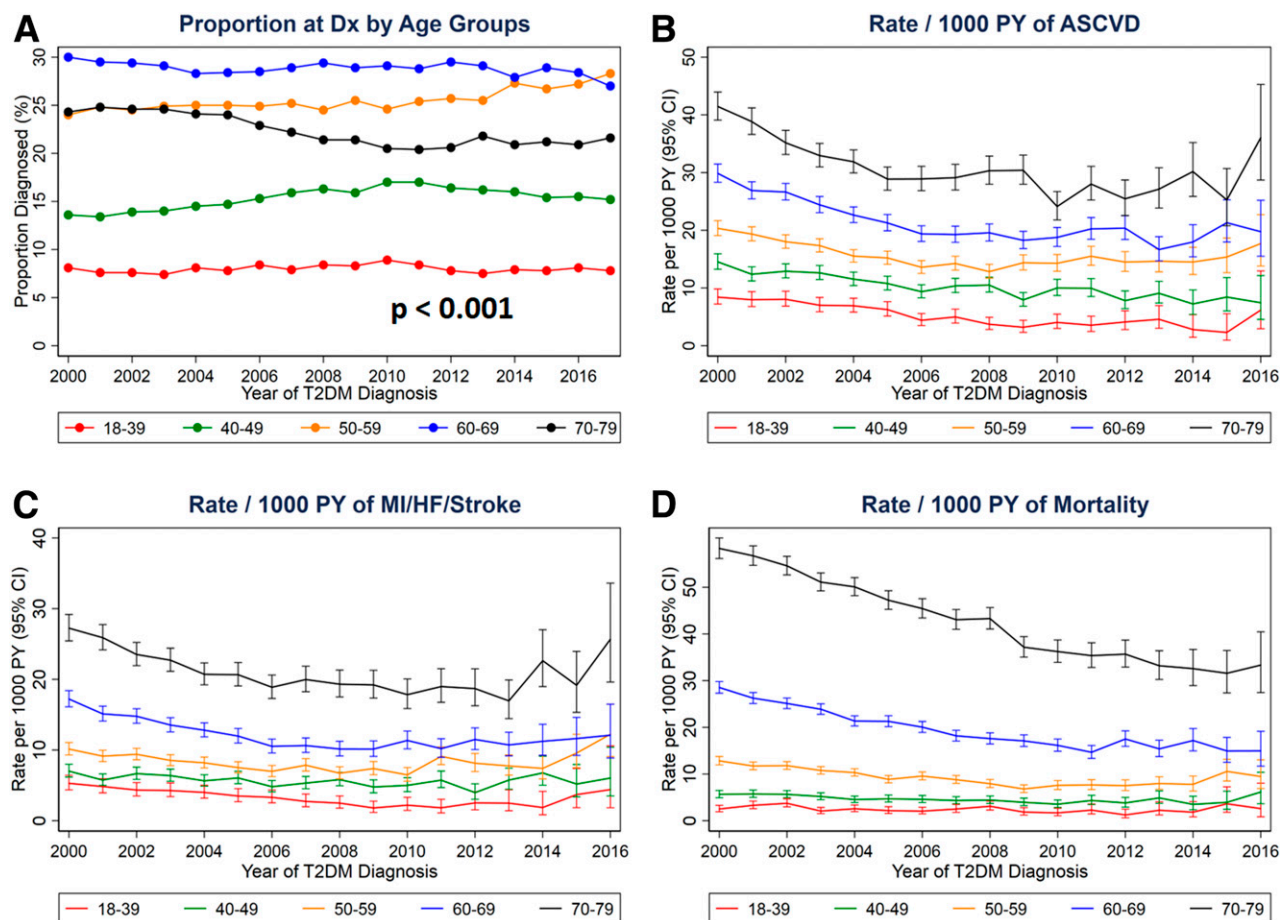


Figure 1—A: Temporal pattern of patients diagnosed with type 2 diabetes annually from 2000 by age-group. B: Rate/1,000 PY of ASCVD from 2000 by age-group among those without a history of ASCVD at diagnosis. C: Rate/1,000 PY of MI, HF, or stroke from 2000 by age-group among those without a history of ASCVD at diagnosis. D: Rate/1,000 PY of ACM from 2000 by age-group. Dx, diagnosis; T2DM, type 2 diabetes mellitus.

Table 2—Follow-up time postdiagnosis of type 2 diabetes and number of events and the rate of ASCVD and ACM (for all patients and separately for those with and without ASCVD at diagnosis) by age-group and for the whole study cohort

	Age at type 2 diabetes diagnosis (years)					Total
	18–39	40–49	50–59	60–69	70–79	
Patients, <i>n</i> (%)	29,678 (8)	56,798 (15)	93,698 (25)	107,261 (29)	83,419 (23)	370,854
Follow-up (years), median (Q1, Q3)	6.5 (3.2, 10.4)	6.6 (3.3, 10.6)	6.7 (3.3, 10.8)	6.5 (3.2, 10.4)	5.8 (2.8, 9.4)	6.4 (3.2, 10.3)
ASCVD						
All						
Events, <i>n</i>	1,432	5,747	15,530	25,691	24,601	73,001
Rate/1,000 PY (95% CI)	7.1 (6.8, 7.5)	15.3 (14.9, 15.7)	26.3 (25.8, 26.7)	41.7 (41.2, 42.2)	59.4 (58.7, 60.1)	33.2 (33.0, 33.4)
Without history of ASCVD						
Patients, <i>n</i>	29,156	53,618	81,861	82,704	56,129	303,468
Events, <i>n</i>	1,173	3,998	8,757	11,793	10,194	35,915
Rate/1,000 PY (95% CI)	5.9 (5.6, 6.2)	11.0 (10.7, 11.3)	16.1 (15.7, 16.4)	22.5 (22.1, 22.9)	31.9 (31.3, 32.5)	18.4 (18.2, 18.6)
Without history of ASCVD and high risk						
Patients, <i>n</i>	6,681	19,822	37,160	41,668	29,493	134,824
Events, <i>n</i>	340	1,514	3,916	5,643	4,878	16,291
Rate/1,000 PY (95% CI)	8.3 (7.5, 9.2)	12.4 (11.8, 13.0)	17.0 (16.5, 17.6)	22.5 (21.9, 23.0)	30.2 (29.4, 31.1)	20.2 (19.9, 20.5)
Without history of ASCVD and low risk						
Patients, <i>n</i>	22,475	33,796	44,701	41,036	26,636	168,644
Events, <i>n</i>	833	2,484	4,841	6,150	5,316	19,624
Rate/1,000 PY (95% CI)	5.3 (4.9, 5.7)	10.3 (9.9, 10.7)	15.4 (15.0, 15.8)	22.5 (21.9, 23.1)	33.6 (32.7, 34.6)	17.1 (16.9, 17.4)
With history of ASCVD						
Patients, <i>n</i>	522	3,180	11,837	24,557	27,290	67,386
Events, <i>n</i>	259	1,749	6,773	13,898	14,407	37,086
Rate/1,000 PY (95% CI)	113.5 (100.5, 128.2)	145.4 (138.7, 152.4)	145.0 (141.6, 148.5)	152.0 (149.4, 154.5)	152.2 (149.7, 154.7)	150.1 (148.5, 151.6)
ACM						
All						
Events, <i>n</i>	524	1,944	6,663	16,137	24,983	50,251
Rate/1,000 PY (95% CI)	2.5 (2.3, 2.7)	4.8 (4.6, 5.0)	9.8 (9.6, 10.0)	21.4 (21.0, 21.7)	47.1 (46.5, 47.7)	19.5 (19.3, 19.6)
Without history of ASCVD						
Events, <i>n</i>	494	1,728	5,237	10,784	15,029	33,272
Rate/1,000 PY (95% CI)	2.4 (2.2, 2.6)	4.5 (4.3, 4.7)	8.8 (8.6, 9.1)	18.4 (18.1, 18.8)	41.0 (40.4, 41.7)	15.6 (15.4, 15.8)
Without history of ASCVD and high risk						
Events, <i>n</i>	131	658	2,372	5,128	6,978	15,267
Rate/1,000 PY (95% CI)	3.1 (2.6, 3.6)	5.1 (4.7, 5.5)	9.5 (9.1, 9.9)	18.4 (17.9, 18.9)	38.1 (37.2, 39.0)	17.3 (17.0, 17.5)
Without history of ASCVD and low risk						
Events, <i>n</i>	363	1,070	2,865	5,656	8,051	18,005
Rate/1,000 PY (95% CI)	2.2 (2.0, 2.5)	4.2 (4.0, 4.5)	8.4 (8.1, 8.7)	18.5 (18.0, 19.0)	44.0 (43.0, 44.9)	14.4 (14.2, 14.6)
With history of ASCVD						
Events, <i>n</i>	30	216	1,426	5,353	9,954	16,979
Rate/1,000 PY (95% CI)	7.3 (5.1, 10.4)	9.6 (8.4, 10.9)	16.3 (15.5, 17.2)	31.4 (30.6, 32.2)	60.7 (59.5, 61.9)	37.8 (37.3, 38.4)

High risk was defined as at least two of the following: current smoker, high SBP, high LDL, or CKD in those without ASCVD at type 2 diabetes diagnosis.

described above (data not presented). However, the estimation of time to event by QRISK2 status did not converge for the 70–79-year age-group because of a very small number of events in the low QRISK2 category.

Temporal Trends in ASCVD and ACM Rates

The incidence rates of ASCVD and the composite of MI, HF, or stroke declined from 2000 to 2010 but remained stable from ~2010 onward (Fig. 1B and C). The ACM rates declined for all age-groups

≥60 years (by ~20% in the 60–69-year age-group and by ~30% in the 70–79-year age-group from 2000 to 2017) (Fig. 1D) but did not decline and remained similar for the 18–39- and 40–49-year age-groups from 2000 onward. The temporal trend of both ASCVD and ACM rates were significantly different between age-groups (trend $P < 0.001$).

CONCLUSIONS

This population-representative U.K. primary care study using routinely collected population-level data is unique and topical

in several aspects. While recent studies have reported divergent trends in the incidence of type 2 diabetes in different countries (27), detailed information on the temporal trend in young-onset type 2 diabetes, how young-onset diabetes is different from usual-onset diabetes in terms of cardiometabolic risk profiles, and the long-term risks are lacking. In >370,000 individuals with incident type 2 diabetes with ~7 years of median follow-up time, we observed that 1) the proportion of people diagnosed with type 2 diabetes at an early age remained

Table 3—Time (years) to ASCVD and ACM by age-group and separately by baseline risk status

	Age at type 2 diabetes diagnosis (years)				
	18–39	40–49	50–59	60–69	70–79
ASCVD					
Without history of ASCVD	9.8 (9.4, 10.2)	8.9 (8.7, 9.2)	8.2 (8.1, 8.4)	8.0 (7.9, 8.2)	7.1 (6.9, 7.3)
Without history of ASCVD and low risk	10.0 (9.5, 10.5)	9.4 (9.1, 9.7)	8.8 (8.6, 9.0)	8.8 (8.6, 9.0)	7.8 (7.5, 8.0)
Without history of ASCVD and high risk	9.1 (8.2, 10.0)	7.9 (7.4, 8.4)	7.5 (7.2, 7.8)	7.1 (6.9, 7.4)	6.4 (6.2, 6.6)
Without history of ASCVD and low QRISK2	—	9.3 (9.0, 9.6)	8.9 (8.6, 9.2)	8.9 (8.0, 9.7)	7.5 (4.7, 10.4)
Without history of ASCVD and high QRISK2	—	7.8 (7.3, 8.2)	7.8 (7.5, 8.0)	8.0 (7.9, 8.2)	7.2 (7.0, 7.3)
With history of ASCVD	4.1 (3.3, 4.9)	4.5 (4.0, 5.0)	4.7 (4.4, 4.9)	4.6 (4.4, 4.7)	4.2 (4.1, 4.3)
ACM					
Without history of ASCVD	10.1 (9.5, 10.8)	10.3 (10.0, 10.6)	10.1 (9.9, 10.3)	9.8 (9.7, 10.0)	9.0 (8.9, 9.1)
Without history of ASCVD and low risk	10.5 (9.7, 11.2)	10.7 (10.3, 11.1)	10.6 (10.3, 10.8)	10.5 (10.4, 10.7)	9.6 (9.5, 9.8)
Without history of ASCVD and high risk	9.3 (8.1, 10.4)	9.4 (8.8, 10.0)	9.5 (9.2, 9.8)	9.0 (8.8, 9.2)	8.1 (8.0, 8.3)
Without history of ASCVD and low QRISK2	—	10.6 (10.2, 11.0)	10.5 (10.2, 10.9)	9.6 (8.9, 10.3)	5.3 (1.9, 8.6)
Without history of ASCVD and high QRISK2	—	9.6 (8.9, 10.3)	9.9 (9.7, 10.2)	9.8 (9.7, 10.0)	9.0 (8.9, 9.1)
With history of ASCVD	10.8 (8.8, 12.8)	9.7 (8.7, 10.8)	10.2 (9.9, 10.6)	9.6 (9.4, 9.8)	8.0 (7.9, 8.2)

Data are mean (95% CI). High risk was defined as at least two of the following: current smoker, high SBP, high LDL, or CKD in those without ASCVD at type 2 diabetes diagnosis.

more or less similar in the U.K. during the past decade; 2) individuals with young-onset type 2 diabetes had significantly higher cardiometabolic risk factors, including adiposity, blood glucose levels, and lipids, compared with those who developed type 2 diabetes after the age of 50 years; 3) while more than one-quarter had high blood pressure and about three-quarters had high LDL-C levels at diagnosis within the ages of 18–39 years, only 16% and 4% were receiving an antihypertensive and lipid-lowering therapy, respectively; 4) the adjusted time to ASCVD and ACM was similar irrespective of baseline cardiometabolic risk factor level in people who developed type 2 diabetes at <40 years of age; and 5) while the ACM rate

had declined in people aged ≥ 50 years at the time of diagnosis of type 2 diabetes, it remained stable in those with young-onset type 2 diabetes.

One of the novelties of this study is the identification of high and low cardiometabolic risk levels in primary prevention people at diagnosis of type 2 diabetes by age groups using risk factor data and additionally generalizing the cardiovascular risk score estimation using QRISK2, and the evaluation of the long-term cardiovascular and mortality risk dynamics in the context of these measurable cardiometabolic risk levels in different age-groups at diagnosis. Among individuals with a diagnosis of type 2 diabetes within 18–49 years of age, although only 4.3% had a history of ASCVD at diagnosis,

~31% were identified as having high cardiometabolic risk and >70% were obese. In the setting of primary prevention, carefully adjusted average time to experiencing the first ASCVD event and average time to death in patients with young-onset type 2 diabetes were similar between high and low cardiometabolic risk at diagnosis, clearly suggesting the special need for proactive risk factor management through appropriate therapy initiation and intensification in young-onset type 2 diabetes, irrespective of the observed nonglycemic cardiometabolic risk levels at diagnosis.

Young-onset type 2 diabetes clearly represents a significantly adverse phenotype with a worse cardiometabolic profile, similarly observed in a study

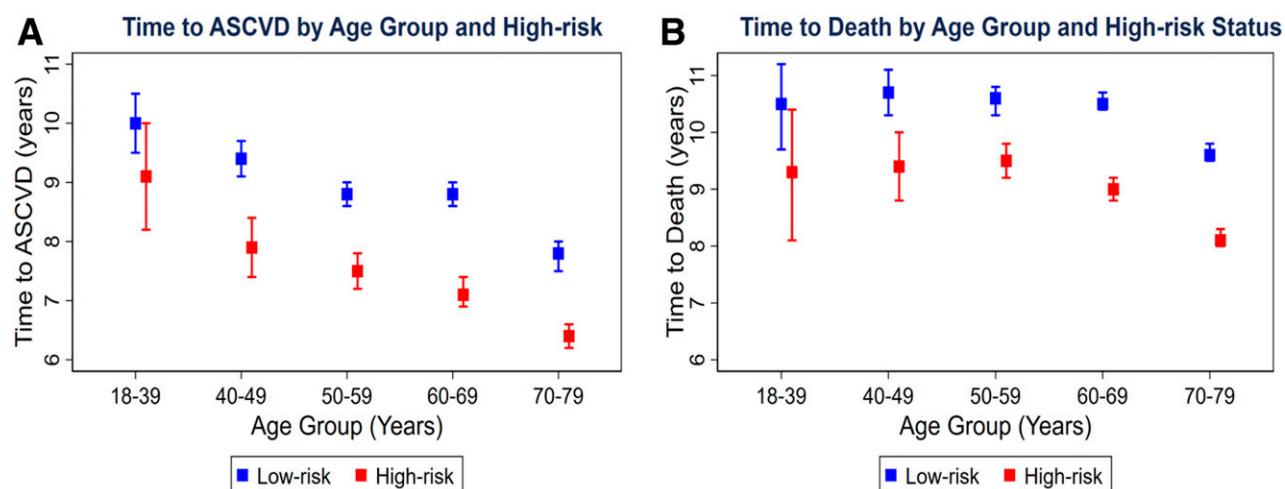


Figure 2—Adjusted average years (95% CI) to ASCVD (A) and ACM (B) by risk status and age-group at diagnosis of type 2 diabetes.

that was based on only 527 patients from two clinics in the U.K. (28). While the observational studies by Hillier and Pedula (12) and Sattar et al. (29) evaluated the cardiovascular and mortality risk in young people with type 2 diabetes compared with matched/unmatched control subjects without diabetes, we are not aware of any study that addressed the crucial issue of holistically differentiating the cardiometabolic risk levels at diagnosis in young- or usual-onset type 2 diabetes and evaluated the long-term cardiovascular and mortality risk dynamics in this context.

Our findings clearly challenge the European Society of Cardiology-European Association for the Study of Diabetes guideline (6) that categorized people who developed diabetes at age <50 years with diabetes duration <10 years as having moderate cardiovascular risk. While we are not aware of any population-level data on the cardiometabolic risk stratification at diagnosis of type 2 diabetes by age-groups, our study clearly provides strong evidence for the revision of international guidelines in the context of the proactive and holistic management of people with young-onset type 2 diabetes, irrespective of observed risk stratification at the time of diagnosis. While the longitudinal glycemic and cardiometabolic risk factor dynamics post-diagnosis of young- and normal-onset type 2 diabetes needs to be evaluated at the population level, the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, which was based on only 700 individuals (10–17 years old) with type 2 diabetes, reported worsening dyslipidemia and chronic inflammation over time, with inadequate therapeutic interventions in this patient population (30). The increasing incidence of young-onset type 2 diabetes and the observed high cardiometabolic risk profile in this population at the time of diagnosis clearly calls for the conduct of cardiovascular outcome studies in this population. There have recently been urgent calls for cardiovascular outcome trials in young-onset type 2 diabetes (31). Our data would support this because there are substantial gains to be made through improving life years lost in young people with type 2 diabetes.

The U.S. survey data from 1990 to 2010 (32) and the registry data-based

studies from Hong Kong (2000–2012) (33) and Australia (1997–2010) (34) reported overall declining trend in the rates of cardiovascular events (or diabetes-related complications) and ACM in people with type 2 diabetes, while the cohorts under consideration were not necessarily of incident type 2 diabetes. While we have observed a declining trend in the mortality rate over the past 10 years in people diagnosed with type 2 diabetes at age ≥ 50 years, these rates were similar and stable at the same level in people with young-onset type 2 diabetes (age 18–49 years) since 2000.

This study has several strengths, including the use of nationally representative population-based data with significant follow-up time; availability of reliable data on disease events with dates; identification of a type 2 diabetes cohort using a robust, clinically guided machine learning approach that reduced bias related to underidentification and misclassification; evaluation of the type 2 diabetes population from the time of diagnosis; and robust methodologies to address the inherent heterogeneities in the context of risk estimation in different age-groups. As is common with EMRs, a significant proportion of the study cohort did not have the clinical and biochemical measurements at the time of diagnosis of diabetes, which could be due to both random and nonrandom reasons (35). However, there was no significant differences in the rates of ASCVD and ACM in those with and without missing risk factor data. Cardiovascular mortality could not be evaluated because of nonavailability of cause-specific mortality data. Another limitation includes the selection biases and residual confounding issues inherent in any EMR-based outcome studies.

In conclusion, type 2 diabetes in young people is a high-risk phenotype with high cardiometabolic risk. Although there have been declines in rates of cardiovascular events and ACM over the past 15 years, these rates seem to have not changed in patients with young-onset type 2 diabetes. Among patients with young-onset type 2 diabetes without a history of ASCVD at diagnosis, the risk of ASCVD has been similar, irrespective of the cardiometabolic risk status at diagnosis. In view of substantial high risk and the life years lost in younger patients with type 2 diabetes, there is an urgent need for tight risk factor control and a need for further

research on best methods to manage this group. This includes models of care, multifactorial risk factor control, and cardiovascular outcome trials using novel therapies.

Acknowledgments. The authors are grateful to Emily Herrett and her group at the London School of Hygiene and Tropical Medicine for providing the Stata version of the QRISK2 algorithm and code lists.

Funding. The Melbourne EpiCentre gratefully acknowledges support from the National Health and Medical Research Council and the Australian Government's National Collaborative Research Infrastructure Strategy initiative through Therapeutic Innovation Australia.

Duality of Interest. K.K. has served as a consultant for and received speaker fees from Amgen, AstraZeneca, Bayer, Berlin-Chemie AG/Menarini Group, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NAPP, Novartis, Novo Nordisk, Roche, Sanofi, and Servier; has served on an advisory board for AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi; and has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, and Servier. S.K.P. has acted as a consultant and/or speaker for Novartis, Gl Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical, and Amylin Pharmaceuticals and has received grants in support of investigator and investigator-initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi, Aventis, and Pfizer. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.N.K., J.L., and S.K.P. were responsible for the primary design of the study and conducted the statistical analyses. D.N.K. and S.K.P. developed the first draft of the manuscript. J.L. conducted the data extraction. D.N.K., J.L., J.D., K.K., O.M., and S.K.P. contributed to the finalization of the manuscript. S.K.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16–20 September 2019.

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