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Temporal Trends in Comorbidities and Cardiometabolic Risk Factors at the Time of Diagnosis of Type 2 Diabetes in UK

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8 Short Title: Temporal Trends in Risk Factors in Incident Type 2 Diabetes
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ABSTRACT

Aims

To evaluate temporal patterns in comorbidities, cardiometabolic risk factors and high atherosclerotic cardiovascular disease (ASCVD) risk population at type 2 diabetes (T2DM) diagnosis by age groups and sex.

Materials and Methods

From the UK primary care database, 248,619 people with new diagnosis of T2DM over 2005-2016 were identified. Among people without ASCVD, high ASCVD risk was defined as \geq two of: current smokers, grade 2+ obesity, hypertension, dyslipidaemia, or microvascular disease. Cardiometabolic multimorbidity (CMM) was defined as \geq two of: cardiovascular disease, microvascular disease, hypertension, dyslipidaemia, grade 2+ obesity or cancer. Temporal patterns in the distribution of cardiometabolic risk factors were evaluated.

Results

While prevalence of ASCVD was stable over time (~18%), 50% were identified to have high ASCVD risk (26 /38% in 18-39 /40-49 years groups), with increasing trend in all age groups. Overall, 51% had CMM at diagnosis, increasing during 2005-2016 for 18-39 years: 14- 17%; 40-49 years: 27-33%; 50-59 years: 41-50%; 60-69 years: 56-65%; 70-79 years: 65-80%.

Young-onset T2DM had significantly higher HbA1c, BMI and lipids at diagnosis (all $p < 0.01$). Proportion with HbA1c $\geq 7.5\%$ in the 18-39 /40-49 years groups were 58 /54%, significantly and consistently higher over the last decade compared to those aged 50+ years, male having 15-26 / 10-18 percentage points higher proportion compared to female.

Conclusions

CMM and high ASCVD risk have been consistently increasing across all age groups and gender, particularly CMM in those < 50 years. Our findings indicate that the ESC-EASD

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3 recommendations need to change to consider the young-onset people with T2DM as a high-
4 risk group as recommended in the Primary Care Diabetes Europe Position Statement.
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10 **Keywords:** Atherosclerotic cardiovascular disease, Cardiometabolic Risk Factors, Electronic
11 Medical Records, Real-world Evidence, Type 2 Diabetes, Young-onset Diabetes.
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17 **Abbreviations:**

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ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CM	Cardiometabolic multimorbidity
CV	Cardiovascular
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
EMRs	Electronic medical records
SBP	Systolic blood pressure
THIN	The Health Improvement Network
UACR	Urine albumin creatinine ratio

INTRODUCTION

International guidelines and initiatives are promoting proactive screening for diabetes detection at a younger age ^{1,2}. Surprisingly, there is lack of epidemiological studies exploring whether population-level trends in cardiometabolic risk profiles at the time of type 2 diabetes diagnosis have changed over time. Large nationally representative electronic medical records (EMRs) have the ability to provide light on this much-needed information to support the clinical practice and health policy makers. However, most of EMR-based studies are focusing on post diagnosis cardiometabolic profiles, pharmacological effectiveness, and the risk of cardiovascular disease (CVD) and mortality ³⁻⁵. Furthermore, while it is well known that at the time type 2 diabetes diagnosis a great proportion of patients have already developed comorbidities ^{1,2}, and the temporal dynamics of comorbidity burden at the time of diagnosis have not been well explored, even though they largely affect diabetes treatment management and diabetes-related outcomes. To the best of our knowledge, only one small Chinese study (n=994) has evaluated time trends of cardiometabolic risk factors at time of diagnosis of type 2 diabetes in an inpatient setting from 2003-2012 ⁶.

The UK NICE guidelines recommend routine review of cardiovascular (CV) risk for those aged above 40 years; with the QRisk® calculator being promoted in the primary care setting to estimate cardiovascular risk ⁷. While recent evidence from epidemiological studies has shown an increase in the incidence of type 2 diabetes diagnosed at an earlier age ^{8,9}, the CV risk monitoring in these patients has not been well assessed. Growing prevalence of obesity partially explain the increasing young-onset type 2 diabetes prevalence, however recent evidence also suggests that it may be a more aggressive phenotype than usual-onset type 2 diabetes ^{10,11}. Currently, cardiometabolic risk differences beyond BMI are not well established in people with young-onset type 2 diabetes compared to usual-onset type 2 diabetes. To the best of our knowledge, the largest study reporting cardiometabolic risk differences at the

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3 time of diabetes diagnosis by age groups was conducted in 100,606 individuals from the
4 Swedish National Diabetes Register ¹⁰. Overall, most studies suggest that younger patients
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6 tend to have worse HbA1c, lipids, and BMI compared to usual-onset, with females have higher
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8 BMI and LDL than males ^{4,10,12-15}.

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12 The cardiometabolic risk factor burden, their longitudinal changes, and differences in young-
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14 (18-39 years), early- (40-49 years) and usual-onset (50+ years) type 2 diabetes are poorly
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16 understood at population level. Thus, using nationally representative primary care EMRs from
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18 United Kingdom (UK), the aims of this study were to evaluate the temporal patterns in
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20 comorbidities, cardiometabolic risk factors and high atherosclerotic cardiovascular disease
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22 (ASCVD) risk population at the time of type 2 diabetes diagnosis by age groups and gender.
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28 **MATERIALS AND METHODS**

29 **Data Source**

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32 This retrospective longitudinal cohort study used data obtained from The Health Improvement
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34 Network (THIN) database, a large, anonymised longitudinal dataset derived from a network of
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36 more than 700 primary care providers across the UK. Comprehensive patient-level longitudinal
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38 information on demographic, anthropometric, clinical and laboratory measures, clinical
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40 diagnosis of diseases and events, and prescriptions for medications were available in more than
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42 17 million individuals. The THIN database is demographically representative of the UK
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44 population, has been extensively used for academic research ¹⁶⁻²⁰, and widely validated with
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46 similar distribution of major chronic diseases when compared to UK national statistics ^{21,22}.
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53 **Study Cohort Identification**

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55 Using an extended clinically guided machine learning approach described earlier ^{19,23}, a cohort
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57 of patients with type 2 diabetes was identified. The learning process included relevant Read
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3 codes and other associated codes, at least one prescription for an anti-diabetic drug or two
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5 elevated glucose measures within a year.
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10 Patients were included in the study cohort if they were i) diagnosed from 1 January 2005 to 31
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12 December 2016, ii) known sex, iii) aged 18 to 79 at diagnosis, and iv) date of diagnosis of type
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14 2 diabetes is at least 12 months after the registration into the EMRs to reduce the bias in
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16 identifying incident type 2 diabetes patients. The index date was based on clinical diagnosis of
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18 type 2 diabetes or the date of first diabetes related health record . Those with type 1 diabetes,
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20 gestational diabetes, diabetes due to other causes, prediabetes only or individuals prescribed
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22 metformin for polycystic ovarian syndrome were excluded.
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28 **Study Variables**

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30 Demographic and laboratory data extracted at the time of type 2 diabetes diagnosis included:
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32 age, sex, smoking status, Townsend deprivation score (TDS, a socioeconomic status measure
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34 based on residential address), body weight, body mass index (BMI), glycated haemoglobin
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36 (HbA1c), systolic blood pressure (SBP), low density lipoproteins (LDL-C), high density
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38 lipoproteins (HDL-C), triglycerides, total cholesterol, non-HDL-C cholesterol, estimated
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40 glomerular filtration rate (eGFR) and urine albumin creatinine ratio (UACR). BMI categories
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42 at diagnosis of type 2 diabetes were defined as normal weight (18.5–24.99 kg/m²), overweight
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44 (25–29.99 kg/m²), grade 1 obese (30–34.99 kg/m²), and grade 2+ obese (≥ 35 kg/m²). All
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46 available measures on or within 3 months prior to the index date were considered as the baseline
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48 (index) measures, and the mean measure was used when multiple measurements existed; except
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50 for HbA1c, where the closest measure was taken. Records of disease / events (comorbidities)
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52 occurring on or prior to type 2 diabetes diagnosis were identified, and diagnostic cut-offs of
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54 laboratory measures with definitions provided in Supplementary Table 1. Microvascular
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3 disease was defined by a clinical recorded (and coded) diagnosis of neuropathy, retinopathy,
4 or chronic kidney disease (CKD). CKD definition included diagnostic codes (CKD stages 1-5,
5 end stage renal disease, dialysis, transplant, nephropathy, proteinuria, albuminuria, nephrotic
6 syndrome, and nephritis; excluding non-acute events and pyelonephritis) or estimated
7 glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73m}^2$ or urine albumin-creatinine ratio
8 (UACR) $\geq 30 \text{ mg/mmol}$. People with ASCVD at diagnosis were defined as those having:
9 ischaemic heart disease (myocardial infarction or unstable angina or coronary revascularization
10 or transient ischaemic attack) or cerebrovascular disease (ischaemic/haemorrhagic stroke or
11 carotid revascularisation) or peripheral vascular disease. Individuals with high SBP, LDL-C
12 and non-HDL-C were defined as: having SBP $\geq 130 \text{ mmHg}$ / LDL-C $\geq 1.8 \text{ mmol/L}$ / non-HDL-
13 C $\geq 2.6 \text{ mmol/L}$ if diagnosed with ASCVD prior to type 2 diabetes diagnosis, or SBP ≥ 140
14 mmHg / LDL-C $\geq 2.6 \text{ mmol/L}$ / non-HDL-C $\geq 3.4 \text{ mmol/L}$ in people without history of ASCVD
15 at type 2 diabetes diagnosis. Hypertension and dyslipidaemia were defined using the presence
16 of respective clinical codes or on antihypertensive / lipid lowering therapy. Cardio-protective
17 medications including anti-hypertensives and lipid-lowering therapies at baseline were
18 additionally extracted (Supplementary Table 1) .

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42 Among people without established ASCVD at baseline, a “high risk” category of patients was
43 created if they had at least two of the risk factors: current smokers, grade 2+ obesity,
44 hypertension, dyslipidaemia, or microvascular disease at baseline. Cardiometabolic
45 multimorbidity (CMM) was defined as having two or more conditions of any CVD,
46 microvascular disease, hypertension, dyslipidaemia, grade 2+ obesity or cancer.
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56 The protocol for this study was approved by the Independent Scientific Review Committee for
57 the THIN database (15THIN031-A1) and the Institutional Review Board of the Royal
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Melbourne Institute of Technology. This study has been conducted following The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines.

Statistical Methods

The summary statistics for study variables at index were summarised using number (%), mean (SD) or median (first quartile, third quartile), as appropriate, by age groups at diagnosis of type 2 diabetes (18-39, 40-49, 50-59, 60-69, 70-79 years). The TDS was categorised into most affluent (score 1-2), middle class (score 3) and least affluent (score 4-5) classes, while missing data category was captured.

The temporal patterns of the prevalence of ASCVD, CKD, hypertension, dyslipidaemia, CMM, and the high ASCVD risk population among those without established ASCVD were presented graphically using standard statistics by age groups and sex over the years of type 2 diabetes diagnosis from 2005 till 2016. Joinpoint regression analysis using permutation test to select the final model was used to estimate annual percentage change (APC) with 95% CI of the prevalence estimates over years of type 2 diabetes diagnosis^{24,25}. The temporal patterns of the distribution (mean or median and 95% CI) of BMI, SBP, HbA1c, LDL-C, non-HDL-C and triglyceride were also graphically explored by age groups over years of type 2 diabetes diagnosis.

RESULTS

From about 17 million research-ready individuals in the THIN, a total of 248,619 patients aged 18-79 with incident type 2 diabetes were identified between 2005 and 2016 (Figure 1). The mean follow-up time post type 2 diabetes diagnosis was similar between the age groups, with an overall mean follow-up of 5.4 years (Table 1). More than half in each age group were male

(50-62%), the distribution of TDS based social classification was similar in all age groups (p=0.87).

Trend in Comorbidities at Diagnosis

The overall prevalence of cardiometabolic comorbidities at type 2 diabetes diagnosis is presented in the Table 2. With 18% of the cohort having ASCVD at diagnosis of type 2 diabetes, the temporal prevalence trend remained stable over the last decade (Figure 2A) in all age groups. Males had significantly higher prevalence of ASCVD compared to females consistently in the 40-59 years age groups, while there was no gender difference in the youngest group (Supplementary Figure 1A). Overall, 22% and 41% in the 18-39 years and 40-49 years groups respectively had hypertension at diagnosis, and the prevalence has consistently increased from 2009 to 2016 in the 18-39 years group (19% to 25%; APC: 3.0%) and from 2013 to 2016 in the 40-49 years group (41% to 45%; APC: 3.8%) (Figure 2D). The proportions on antihypertensive therapy at diagnosis with continuing it for at least 3 months in 18-39 / 40-49 years age groups increased from 16% / 32% in 2005 to 21% / 41% in 2016. With 39% having dyslipidaemia at diagnosis in the cohort, an increasing prevalence pattern was evident from 2005 to 2016 in the 60-69 years group (40% to 55%; APC: 6.1% between 2005–2009 and 1.3% between 2009- 2016) and in the 70-79 years group (44% to 69%; APC: 8.2% between 2005-2008, 3.2% between 2008-2013, 1.3% between 2013-2016), while the prevalence trend remained stable in people aged 18-39 years (8%), 40-49 years (20%) and 50-59 years (34%; Figure 2E). The temporal prevalence patterns of the CKD (21% in the overall population) was consistent over the last decade in all age groups (Table 1, Figure 2C).

Overall 51% had CMM at diagnosis, with the prevalence of CMM significantly increasing from 2005 to 2016 in all age groups - 18-39 years: 14 to 17%; 40-49 years: 27 to 33%; 50-59

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3 years: 41 to 50%; 60-69 years: 56 to 65%; 70-79 years: 65 to 80% (all $p < 0.05$; Figure 2F).
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5 Females had consistently significantly higher CMM compared to males aged 40+ years over
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7 the last decade (40-49 years: 35% vs 28%; 50-59 years: 50% vs 43%; 60-69 years: 65% vs
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9 60%; 70-79 years: 75% vs 72%), while there was no gender difference in CMM prevalence in
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11 people aged 18-39 years (15%; Supplementary Figure 1C).
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17 **Trend in High ASCVD Risk Population**

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19 Among those without ASCVD at type 2 diabetes diagnosis ($n = 205,09$), 50% were identified
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21 to have high ASCVD risk overall, 26% and 38% were in the age groups 18-39 years and 40-
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23 49 years respectively (Table 2). The prevalence of high ASCVD risk has shown an increasing
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25 trend in all age groups - 18-39 years: 23% to 28% (APC: 1.6%); 40-49 years: 34% to 43%
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27 (APC: 3.6% from 2005 to 2008, 0.3% from 2008 to 2013, 3.3% 2013 to 2016); 50-59 years:
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29 43% to 53% (APC: 4.1% from 2005 to 2008, 1.1% from 2008 to 2016); 60-69 years: 50% to
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31 62% (APC: 4.1% from 2005 to 2009, 0.8% from 2009 to 2016); 70-79 years: 54% to 74%
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33 (APC: 6.3% from 2005 to 2008, 1.6% from 2008 to 2016), (Figure 2B). Compared to males,
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35 females had significantly higher prevalence of high ASCVD risk at diagnosis by about by 3
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37 percentage points in the 18-39 years group and by 10 percentage points across all older age
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39 groups (all $p < 0.01$; Supplementary Figure 1B).
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47 **Trend in Obesity at Diagnosis**

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49 Patients in the youngest two age groups had significantly higher BMI (34.5-35.2 kg/m^2) at
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51 diagnosis compared to the older age groups (Table 1; all $p < 0.01$). Increasing trends in the body
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53 weight and BMI over the last decade was observed in all age groups while individuals aged 18-
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55 49 years having consistently 5-6 kg/m^2 higher BMI at type 2 diabetes diagnosis compared those
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57 aged 70-79 years at diagnosis (Figure 3A). The proportions of individuals with grade 2+ obesity
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3 in the 18-39 years and 40-49 years were 47% and 42% respectively, compared to an overall
4 cohort proportion of 31%. Females had significantly higher obesity compared to males across
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6 all age groups (all $p < 0.01$; Supplementary Figure 1D).
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10 11 12 **Temporal pattern of HbA1c distribution at diagnosis**

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14 The mean HbA1c / proportion with HbA1c $\geq 7.5\%$ in the age groups 18-39 and 40-49 were
15 8.6% / 58% and 8.4% / 54% respectively, significantly and consistently higher over the last
16 decade compared to those who were diagnosed at age 50+ years (Table 1 and Figure 3C). The
17 proportions with HbA1c $\geq 8\%$ at diagnosis were 50% and 46% in the 18-39 years and 40-49
18 years groups respectively. While a declining trend in the mean HbA1c level at diagnosis was
19 observed in the oldest two age groups till 2013, the temporal pattern of the HbA1c distribution
20 at diagnosis was consistently similar and significantly higher in the youngest two age groups
21 without any sign of decline.
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32 Males in the 18-39 / 40-49 years age groups had consistently significantly higher proportion
33 with HbA1c $\geq 7.5\%$ at diagnosis by about 15-26 / 10-18 percentage points compared to females,
34 while this gender difference was relatively smaller in the 50-59 years age group
35 (Supplementary Figure 1F).
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45 **Temporal patterns of blood pressure and lipids at diagnosis**

46 The mean SBP declined over the years from 141-144 mmHg in 2005 to 137 mmHg in 2016 for
47 the 50-79 years age groups, while mean SBP in youngest two age groups remained stable at ~
48 130 mmHg and 135 mmHg respectively (Table 1, Figure 3B). At diagnosis 22% and 41% were
49 identified to have hypertension (diagnosis code or antihypertensive therapy) in the 18-39 years
50 and 40-49 years age groups respectively (Table 1 and 2). Overall, 69% with high SBP were on
51 antihypertensive therapy at baseline. While males in general had higher SBP at diagnosis
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3 compared to females, in the youngest age group males had consistently significantly higher
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5 SBP by 11-18% compared to females over the last decade (Supplementary Figure 1E).
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8 People aged 18-59 years had consistently higher mean LDL-C / proportion with high LDL-C
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10 (3.1-3.2 mmol/L / 70-74%) compared to older people aged 60+ years (2.7-3.0 mmol/L / 61-
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12 68%) at diagnosis (Table 1, Figure 3D and 3E). While the temporal trend in the LDL-C level
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14 at diagnosis remained stable in people aged < 60 years, a marginal declining trend from 3.0 to
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16 2.7 mmol/L and from 2.8 to 2.4 mmol/L in the 60-69 years and 70-79 years groups respectively
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18 were observed (Figure 3D). With mean LDL-C between 2005 and 2016 ranging between 2.8-
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20 2.9 mmol/L and 3.0-3.2 mmol/L in males and females respectively, females aged 40+ had
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22 consistently higher LDL-C compared to males (71% vs 66%), but this proportion was similar
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24 between gender in the 18-39 years group (71%, Supplementary Figure 1G). Younger people
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26 had significantly and consistently higher triglyceride compared to older people (Figure 3F).
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34 **DISCUSSION**

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36 This nationally representative, extensive epidemiological study provides unique information
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38 on the temporal patterns in the prevalence of comorbidities and cardiometabolic risk factor
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40 distributions in young- and usual-onset type 2 diabetes, with detailed exploration of the
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42 possible contrasting gender differences at population level. To our knowledge this study is
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44 the first to provide such detailed population-level profile exploration under one study design
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46 in an incident type 2 diabetes cohort.
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50 While the ASCVD prevalence trends remained similar in different age groups, we have
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52 observed significantly increasing trend in the prevalence of high ASCVD risk from
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54 diagnosis across all age groups. While among the younger people aged < 50 years a 5-10%
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56 increase in the high ASCVD risk prevalence was observed during the last decade, this
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58 prevalence increased by about 12-20% in the older age groups at diagnosis of diabetes. The
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3 primary prevention population aged 18-39 years at type 2 diabetes diagnosis with a quarter
4 being at high risk (38% in 40-49 years group), also have significantly higher adiposity,
5 HbA1c and lipids at diagnosis. With 59% of the cohort with a history of ASCVD or having
6 high ASCVD risk at diagnosis (27% / 42% / 55% / 67% / 76% in the 18-39 / 40-49 / 50-59
7 / 60-69 / 70-79 years groups), the multiplicity of higher risk factor burden puts the people
8 with young-onset type 2 diabetes at a significantly higher long-term lifetime risk, compared
9 to people with usual-onset type 2 diabetes ^{4,26,27}. While there is increasing concern about
10 multimorbidity in people with chronic diseases at population level ²⁸, the evidence of the
11 temporal patterns in CMM at the time of type 2 diabetes diagnosis is very limited. A recent
12 study reported increasing trend in the CMM prevalence in White Caucasians and African
13 Americans with incident type 2 diabetes in US ⁴. While a recent UK Biobank based study
14 evaluated the association of multimorbidity with mortality risk in people with prevalent type
15 2 diabetes ²⁹, we are not aware of any study reporting temporal trends in CMM in young-
16 and usual-onset type 2 diabetes. We have observed increasing trend in the prevalence of
17 CMM across all age groups, while also showing that CMM prevalence has been significantly
18 and consistently higher in females aged 40 years and older compared to males and no
19 difference in the 18-39 years group.

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45 The HbA1c remained consistently above 7.5% in over half the cohort aged <50 years at
46 diagnosis consistently over time. Results were driven by males (54-70%) while females had
47 lower percentages (42-52%) with HbA1c $\geq 7.5\%$ from 2005 to 2016. We recognise the
48 changes in the diagnostic criteria with HbA1c over time in this context. In the absence of
49 any comparative UK based data in incident type 2 diabetes, direct comparison of our results is
50 not possible. Using data from UK, Dennis and colleagues reported that regardless of HbA1c at
51 diabetes diagnosis, there was no change in mean HbA1c at 1st (8.6-8.8%), 2nd (8.7-9.1%), 3rd
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3 (8.8-9.3%) and 4th (9.1-9.6%) line therapy from 2010 to 2017 ³⁰. The National Diabetes audit
4 for England and Wales reports annually on the risk factor control among people with existing
5 diabetes. While our study was focused on newly diagnosed T2DM population, we observed
6 similar trend of improving BP control over time and stable trend for lipid control ³¹.
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14 The finding that youngest age groups have highest HbA1c, BMI, and lipids is consistent
15 with other reports ^{10,12,13}. In less comorbid population from Sweden (overall HbA1c: 6.7%,
16 BMI: 30.6 kg/m², LDL-C: 3.1 mmol/L), Steinarsson and colleagues reported that differences
17 in BMI, blood glucose and lipid levels remained with adjustment for potential confounders,
18 including marital status, education and country of birth ¹⁰.
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28 A Scottish registry database study reported that males develop type 2 diabetes at a lower BMI
29 level compared to females ³². We have observed that, in all age groups, males consistently had
30 higher HbA1c but lower adiposity levels compared to females at the time of diagnosis. Globally
31 more males are diagnosed with diabetes (57% in our cohort). In our study, the proportion of
32 females with type 2 diabetes was highest in the 18-39 years group (50%) and the sex-HbA1c
33 difference was highest in this group as well (Supplementary Figure 1F). Males aged <60 years
34 had significantly higher blood pressure compared to females, while this difference disappeared
35 in the older groups. Females aged 40 years or older had significantly higher LDL-C levels
36 compared to males, while the proportion of people with high LDL-C levels at type 2 diabetes
37 diagnosis was similar between males and females aged 18-39 years. This contrasting
38 cardiometabolic risk factor dynamics at type 2 diabetes diagnosis between males and females
39 needs to be addressed in future observational studies evaluating the long-term ASCVD and
40 mortality risk in people with incident type 2 diabetes ²⁶.
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3 The ESC-EASD guideline, mainly based on consensus, categorises people who develop
4 diabetes below the age of 50 with diabetes duration <10 years as having moderate
5 cardiovascular risk ³⁴. In our study, among those without existing ASCVD, 26% and 38% in
6 the 18-39 years and 40-49 years groups had high ASCVD risk, indicating that these people
7 already have at least 2 comorbidities at the time of type 2 diabetes and having higher
8 hyperglycaemia than usual-onset diabetes. Furthermore, we have seen that high ASCVD risk
9 was significantly higher among female compared to male (55% vs 45%, Supplementary Figure
10 1B). Our findings indicate that the ESC-EASD recommendations need to change to consider
11 the young onset people with type 2 diabetes as a high risk group as recommended in the Primary
12 Care Diabetes Europe Position Statement ³⁵.

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28 This study has several strengths, including the use of a nationally representative population
29 based data with mean 5 years of follow-up, pay for performance influenced recording of disease
30 events with dates of events, identification of people with type 2 diabetes using a robust
31 clinically guided machine learning approach – reducing the bias due to under-identification
32 and misclassification ¹⁹. The prevalence of T2DM estimated from the THIN database based on
33 End-of-year prevalence estimation approach ranged between 5.3 – 8.5% during 2012 – 2016
34 in UK, which is comparable to the UK Quality and Outcomes Framework data during that
35 period, given EMRs are less likely to contain data on healthy population. While the condition
36 of being registered in the database for at least 12 months prior to diabetes diagnosis introduces
37 some selection bias, such restriction reduces prevalent case inclusion in our study cohort ²⁶.
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51 For identifying patients with hypertension / dyslipidaemia we have adopted validated approach
52 combining disease identification codes and blood pressure / lipid lowering medication
53 information to reduce false negative cases ³⁶.
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3 The goal of this study was to report real-world population-level temporal trends by providing
4 unadjusted estimates at the time of T2DM diagnosis. While the overall Townsend deprivation
5 score distribution was similar across the age groups, only 45% of the cohort had ethnicity
6 recorded (Table 1). The pathophysiology of T2DM in South and East Asians was shown to
7 differ significantly from Caucasians, leading to earlier development of T2DM at lower BMI,
8 blood pressure and lipid levels ^{37,38}. Thus, the reported burden of CMM and high ASCVD risk
9 is likely to be different between ethnicities. Other studies using THIN database have compared
10 overall patterns of BMI at diagnosis of diabetes in a multi-ethnic population³⁹; prevalence of
11 complications at diagnosis of T2DM by BMI and ethnicity³⁸; and ethnicity-specific association
12 of BMI levels at diagnosis of type 2 diabetes with CVD and all-cause mortality risk⁴⁰.
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46 The limitations of this study include unavoidable indication bias that remains as a common
47 problem in any EMR based study, and lack of detailed data on lifestyle factors such as diet and
48 physical activity. Despite these limitations, we believe that nationally representative EMRs,
49 large cohort size, robust study design and advanced data mining methods applied, ensure
50 reliable epidemiological inferences and reflect real-world practice in general population over
51 time.
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Conclusion

47 At population level, the cardiometabolic multimorbidity and high cardiovascular risk level in
48 people type 2 diabetes without established ASCVD has been consistently increasing across all
49 age groups and gender, particularly cardiometabolic multimorbidity in younger people aged
50 below 50 years. Significant effort in proactive screening and management of risk factors needs
51 to be implemented to improve long term cardiovascular and mortality outcomes.
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Contributions

SKP conceptualized the study, S.K.P. and J.Z.J.L. were responsible for the primary design of the study. J.Z.J.L. extracted and analysed the data with input from O.M., D.K., LB and S.K.P. The first draft of the manuscript was developed by J.Z.J.L., S.K.P and O.M., and all authors contributed to the finalisation of the manuscript. S.K.P. and OM had full access to all the data in the study and is the guarantor, taking responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

S.K.P. has acted as a consultant and speaker for Novartis, Sanofi, GI Dynamics, Roche, AstraZeneca, Australian Red Cross Society and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator-initiated clinical studies from Novartis, Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals and Pfizer. 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-Aventis, Servier, has served on an advisory board for AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and has received grant in support of investigator and investigator initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier. O.M., D.K., J.L., and L.B. have no conflict to declare.

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Data availability

IQVIA Medical Research Data UK incorporating THIN, THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as a part of their routine primary care. Complete data is not available due to license agreement. Aggregated data may be provided upon request.

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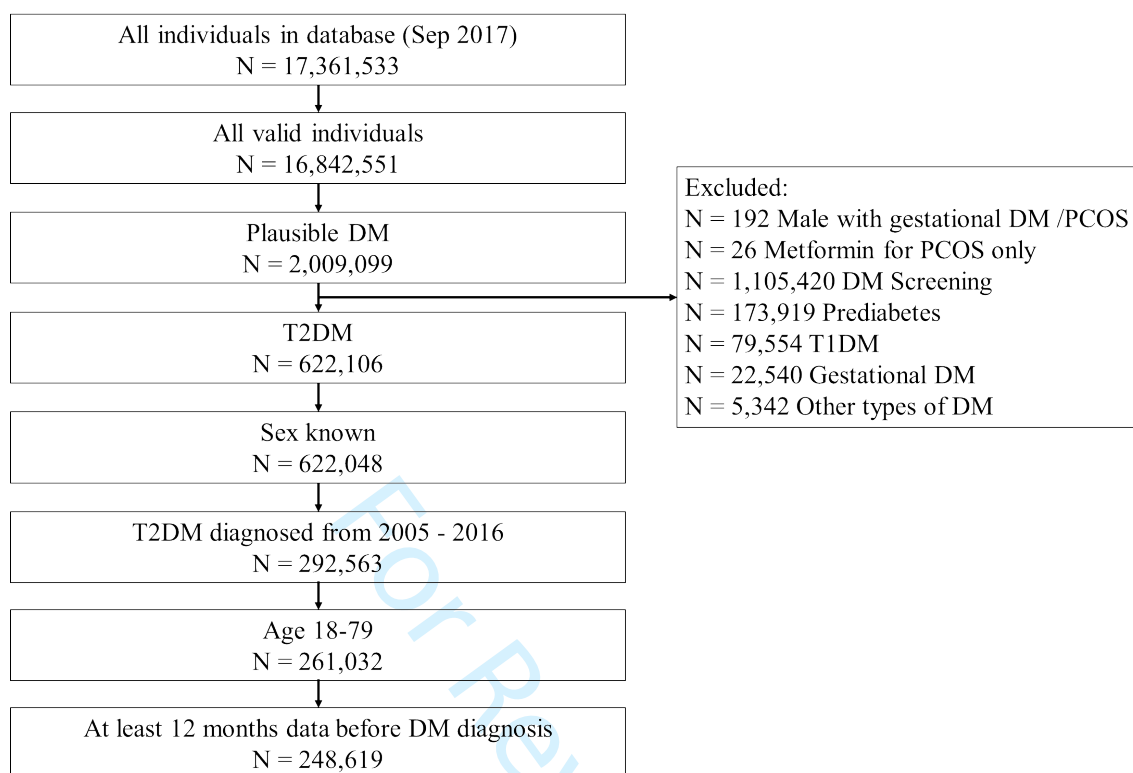
Figure 1 Study cohort selection flowchart

Table 1. Demographics and risk factors at diagnosis of type 2 diabetes by age group.

	18-39	40-49	50-59	60-69	70-79	Total
N (%)	20,181 (8)	39,731 (16)	63,329 (25)	71,692 (29)	53,686 (22)	(N= 248,619)
Duration of follow-up (years) [†]	5.4 (3.3)	5.6 (3.3)	5.6 (3.3)	5.5 (3.3)	5.1 (3.2)	5.4 (3.3)
Age at DM diagnosis [†]	33.0 (5.3)	45.1 (2.8)	54.7 (2.9)	64.4 (2.9)	74.1 (2.8)	58.4 (12.6)
Male [§]	10,087 (50)	24,435 (62)	37,901 (60)	41,551 (58)	27,126 (51)	141,100 (57)
<i>Ethnicity[§], N (% non-missing)</i>	10834 (54)	19803 (50)	29243 (46)	30955 (43)	21825 (41)	112660 (45)
Caucasian	6,871 (63)	14,126 (71)	23,363 (80)	27,146 (88)	19,617 (90)	91,123 (81)
African	726 (7)	1,430 (7)	1,342 (5)	807 (3)	593 (3)	4,898 (4)
South Asian	2,203 (20)	2,559 (13)	2,655 (9)	1,703 (6)	947 (4)	10,067 (9)
Others	1,034 (10)	1,688 (9)	1,883 (6)	1,299 (4)	668 (3)	6,572 (6)
Smoking status [§]						
Current smoker	6,349 (31)	13,542 (34)	21,544 (34)	23,017 (32)	14,730 (27)	79,182 (32)
Ex-smoker	3,520 (17)	8,707 (22)	17,054 (27)	24,618 (34)	19,901 (37)	73,800 (30)
Never smoked	6,966 (35)	12,613 (32)	18,337 (29)	17,933 (25)	14,049 (26)	69,898 (28)
Unknown	3,346 (17)	4,869 (12)	6,394 (10)	6,124 (9)	5,006 (9)	25,739 (10)
Townsend deprivation score [§]						
Most affluent	7,253 (36)	14,390 (36)	22,952 (36)	25,838 (36)	19,596 (37)	90,029 (36)
Middle class	3,759 (19)	7,482 (19)	12,006 (19)	13,310 (19)	10,102 (19)	46,659 (19)
Least affluent	6,378 (32)	12,508 (31)	19,609 (31)	22,412 (31)	16,452 (31)	77,359 (31)
Unknown	2,791 (14)	5,351 (13)	8,762 (14)	10,132 (14)	7,536 (14)	34,572 (14)
<i>HbA1c, N (% non-missing)</i>	10,915 (54)	26,406 (67)	43,762 (69)	50,286 (70)	37,144 (69)	168,513 (68)
HbA1c (%) [†]	8.6 (2.4)	8.4 (2.3)	8.1 (2.2)	7.7 (2.1)	7.5 (1.9)	7.9 (2.1)
HbA1c ≥7.5% [§]	6,288 (58)	14,219 (54)	20,006 (46)	18,431 (37)	11,232 (30)	70,176 (42)
HbA1c categorised [§]						
≤7	3,772 (35)	9,833 (37)	19,578 (45)	26,774 (53)	22,095 (59)	82,052 (49)
>7 - ≤7.5	1,081 (10)	2,944 (11)	5,250 (12)	6,280 (12)	4,660 (13)	20,215 (12)
>7.5 - ≤8	779 (7)	1,939 (7)	3,141 (7)	3,343 (7)	2,378 (6)	11,580 (7)
>8.0 - ≤9	1,230 (11)	2,917 (11)	4,163 (10)	4,030 (8)	2,588 (7)	14,928 (9)
>9 - ≤12	3,037 (28)	6,552 (25)	8,410 (19)	6,886 (14)	3,704 (10)	28,589 (17)
>12	1,016 (9)	2,221 (8)	3,220 (7)	2,973 (6)	1,719 (5)	11,149 (7)
<i>Weight, N (% non-missing)</i>	13,326 (66)	28,988 (73)	46,959 (74)	53,542 (75)	38,648 (72)	181,463 (73)
Weight (kg) [†]	102.2 (26.7)	100.9 (23.4)	96.4 (21.1)	90.7 (18.9)	83.3 (16.6)	93.1 (21.4)
<i>BMI, N (% non-missing)</i>	13,202 (65)	28,804 (73)	46,735 (74)	53,297 (74)	38,412 (72)	180,450 (73)
BMI (kg/m ²) [†]	35.2 (8.4)	34.5 (7.5)	33.4 (6.8)	31.9 (6.1)	30.0 (5.4)	32.6 (6.8)
BMI categorised [§]						
Normal	1,221 (9)	1,978 (7)	3,273 (7)	5,051 (9)	6,020 (16)	17,543 (10)
Overweight	2,609 (20)	6,344 (22)	12,129 (26)	16,861 (32)	14,607 (38)	52,550 (29)
Obesity Grade 1	3,216 (24)	8,273 (29)	14,920 (32)	17,444 (33)	11,484 (30)	55,337 (31)
Obesity Grade 2+	6,156 (47)	12,209 (42)	16,413 (35)	13,941 (26)	6,301 (16)	55,020 (30)
<i>SBP, N (% non-missing)</i>	13,934 (69)	31,611 (80)	53,004 (84)	62,335 (87)	46,969 (88)	207,853 (84)
SBP (mmHg) [†]	130 (15.1)	135 (15.6)	138 (15.8)	140 (15.6)	140 (15.9)	138 (15.9)
High SBP [§]	3,490 (25)	12,309 (39)	26,032 (49)	35,072 (56)	27,959 (60)	104,862 (50)
<i>LDL-C, N (% non-missing)</i>	7,413 (37)	20,583 (52)	36,454 (58)	43,077 (60)	31,335 (58)	138,862 (56)
LDL-C (mmol/L) [†]	3.1 (1.0)	3.2 (1.0)	3.1 (1.0)	2.9 (1.0)	2.7 (1.0)	3.0 (1.0)
High LDL-C [§]	5,222 (70)	15,260 (74)	26,507 (73)	28,630 (66)	19,211 (61)	94,830 (68)
<i>Triglyceride, N (% non-missing)</i>	9,377 (47)	25,185 (63)	42,929 (68)	49,420 (69)	35,476 (66)	162,387 (65)
Triglyceride (mmol/L) [‡]	2.1 (1.5,3.3)	2.1 (1.5,3.2)	2.0 (1.4,2.9)	1.9 (1.4,2.5)	1.7 (1.2,2.3)	1.9 (1.4,2.7)
<i>HDL-C, N (% non-missing)</i>	9,637 (48)	26,228 (66)	44,902 (71)	52,222 (73)	37,824 (71)	170,813 (69)
HDL-C (mmol/L) [†]	1.0 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)
<i>Non-HDL-C, N (% non-missing)</i>	9,625 (48)	26,215 (66)	44,882 (71)	52,202 (73)	37,803 (70)	170,727 (69)
Non-HDL-C (mmol/L) [†]	4.3 (1.3)	4.4 (1.2)	4.2 (1.2)	3.8 (1.1)	3.5 (1.1)	4.0 (1.2)
High non-HDL-C [§]	7,471 (78)	21,221 (81)	35,131 (78)	36,716 (70)	23,346 (62)	123,885 (73)

N (%)	18-39 20,181 (8)	40-49 39,731 (16)	50-59 63,329 (25)	60-69 71,692 (29)	70-79 53,686 (22)	Total (N= 248,619)
Total Cholesterol, N (% non-missing)	13,064 (65)	32,585 (82)	54,453 (86)	63,076 (88)	46,613 (87)	209,791 (84)
Total Cholesterol (mmol/L) †	5.3 (1.3)	5.4 (1.3)	5.3 (1.2)	5.0 (1.2)	4.8 (1.1)	5.1 (1.2)
High lipids §	7,812 (39)	22,086 (56)	36,731 (58)	38,842 (54)	25,341 (47)	130,812 (53)
eGFR, N (% non-missing)	12,643 (63)	30,657 (77)	51,702 (82)	60,582 (85)	45,759 (85)	201,343 (81)
eGFR (ml/min/1.73m ²)	86.9 (20.8)	81.6 (17.7)	77.6 (16.4)	72.5 (15.8)	66.1 (15.8)	74.6 (17.7)
eGFR categories §						
<30	13 (0)	47 (0)	97 (0)	238 (0)	444 (1)	839 (0)
30-<45	23 (0)	69 (0)	315 (1)	1,079 (2)	2,789 (6)	4,275 (2)
45-<60	149 (1)	741 (2)	2,640 (5)	7,250 (12)	10,609 (23)	21,389 (11)
≥60	12,458 (99)	29,800 (97)	48,650 (94)	52,015 (86)	31,917 (70)	174,840 (87)

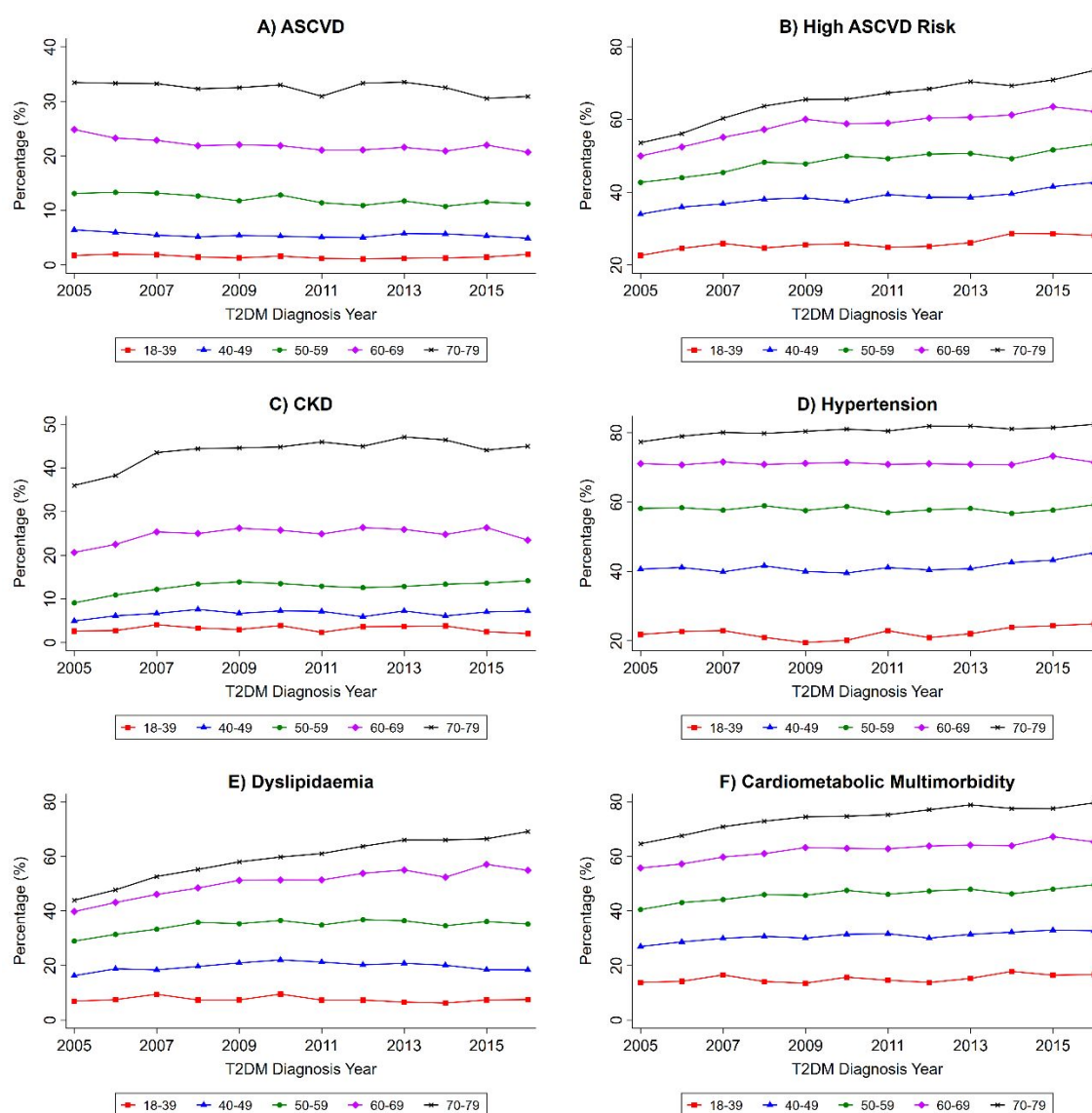
† mean (SD); ‡ median (Q1, Q3); § n (%); HbA1c: haemoglobin A1c; BMI: body mass index; ASCVD: atherosclerotic cardiovascular disease including ischaemic heart disease (myocardial infarction or unstable angina or coronary revascularization or transient ischaemic attack, excluding angina) or cerebrovascular disease (ischaemic/haemorrhagic stroke or carotid revascularisation) or peripheral vascular disease; SBP: systolic blood pressure; High SBP: SBP ≥140 mmHg if no ASCVD prior to type 2 diabetes diagnosis (non-ASCVD) or SBP ≥130 mmHg if ASCVD; LDL-C: low density lipoprotein cholesterol; High LDL-C: LDL-C ≥2.6 mmol/L if non-ASCVD or LDL-C ≥1.8 mmol/L if ASCVD; HDL-C: high density lipoprotein cholesterol; High non-HDL-C: non-HDL-C ≥3.4 mmol/L if non-ASCVD or non-HDL-C ≥2.6 mmol/L if ASCVD; High lipids: high LDL-C or high non-HDL-C

Table 2. Comorbidities and medications at diagnosis of type 2 diabetes by age groups

N (%)	18-39 20,181 (8)	40-49 39,731 (16)	50-59 63,329 (25)	60-69 71,692 (29)	70-79 53,686 (22)	Total (N= 248,619)
Comorbidities						
ASCVD [‡]	310 (2)	2,183 (5)	7,688 (12)	15,861 (22)	17,518 (33)	43,560 (18)
No ASCVD [‡]	19,871 (98)	37,548 (95)	55,641 (88)	55,831 (78)	36,168 (67)	205,059 (82)
High ASCVD risk [§]	5,093 (26)	14,312 (38)	26,832 (48)	32,355 (58)	23,284 (64)	101,876 (50)
Myocardial Infarction [§]	97 (0)	906 (2)	2,853 (5)	4,983 (7)	5,167 (10)	14,006 (6)
Ischaemic stroke [§]	59 (0)	334 (1)	1,226 (2)	2,698 (4)	3,654 (7)	7,971 (3)
Peripheral vascular disease [§]	18 (0)	145 (0)	800 (1)	2,097 (3)	2,306 (4)	5,366 (2)
Transient ischaemic attack [§]	33 (0)	243 (1)	905 (1)	2,164 (3)	3,003 (6)	6,348 (3)
Heart failure [§]	50 (0)	264 (1)	764 (1)	1,993 (3)	2,912 (5)	5,983 (2)
Chronic kidney disease [§]	644 (3)	2,642 (7)	7,981 (13)	17,734 (25)	23,289 (43)	52,290 (21)
Microvascular disease [§]	936 (5)	3,397 (9)	9,455 (15)	19,541 (27)	24,438 (46)	57,767 (23)
Cancer excluding melanoma [§]	280 (1)	918 (2)	2,800 (4)	6,158 (9)	7,149 (13)	17,305 (7)
Hypertension [§]	4,436 (22)	16,319 (41)	36,713 (58)	51,040 (71)	43,133 (80)	151,641 (61)
Dyslipidaemia [§]	1,538 (8)	7,835 (20)	21,842 (34)	35,670 (50)	30,989 (58)	97,874 (39)
Cardiometabolic multimorbidity [§]	3,032 (15)	12,132 (31)	28,980 (46)	44,339 (62)	39,467 (74)	127,950 (51)
Medications						
Cardio-protective therapy [§]	3,914 (19)	15,383 (39)	35,204 (56)	49,825 (69)	41,482 (77)	145,808 (59)
Antihypertensive therapy [§]	3,458 (17)	13,622 (34)	31,789 (50)	45,813 (64)	39,129 (73)	133,811 (54)
Lipid-lowering therapy [§]	1,015 (5)	6,014 (15)	18,418 (29)	32,076 (45)	28,665 (53)	86,188 (35)

† mean (SD); ‡ median (Q1, Q3); § n (%); ASCVD: atherosclerotic cardiovascular disease including ischaemic heart disease (myocardial infarction or unstable angina or coronary revascularization or transient ischaemic attack, excluding angina) or cerebrovascular disease (ischaemic/haemorrhagic stroke or carotid revascularisation) or peripheral vascular disease; Chronic kidney disease (CKD): chronic kidney disease (including nephropathy) diagnosis or estimated glomerular filtration rate < 60 mL/min/1.73m² or urine albumin:creatinine ratio >30 mg/mmol; High ASCVD risk population: among those without ASCVD, at least two of the following – current smoker, grade 2+ obesity, hypertension, dyslipidaemia or microvascular disease (percentage denominator based on number without ASCVD at diabetes diagnosis); Microvascular disease: retinopathy or neuropathy or nephropathy (including CKD); Hypertension: hypertension diagnosis or antihypertensive therapy; Dyslipidaemia: dyslipidaemia diagnosis or lipid-lowering therapy; Cardiometabolic multimorbidity: two or more comorbidities of any cardiovascular disease, microvascular disease, hypertension, dyslipidaemia, grade 2+ obesity or cancer; Cardioprotective therapy includes all antihypertensive therapy, peripheral vasodilators and lipid-lowering therapy

Figure 2: Temporal trends of the proportion of patients with (A) ASCVD, (B) high ASCVD risk among those without ASCVD at diagnosis, (C) CKD, (D) hypertension, (E) dyslipidaemia, and (F) cardiometabolic multimorbidity by age groups at diagnosis of type 2 diabetes over years of diagnosis from 2005 to 2016.



ASCVD: atherosclerotic cardiovascular disease including ischaemic heart disease (myocardial infarction or unstable angina or coronary revascularization or transient ischaemic attack, excluding angina) or cerebrovascular disease (ischaemic/haemorrhagic stroke or carotid revascularisation) or peripheral vascular disease; High ASCVD risk population: among those without ASCVD, at least two of the following – current smoker, grade 2+ obesity, hypertension, dyslipidaemia, microvascular disease; Chronic kidney disease (CKD): chronic kidney disease (including nephropathy) diagnosis or estimated glomerular filtration rate < 60 mL/min/1.73m² or urine albumin:creatinine ratio >30 mg/mmol; Hypertension: hypertension diagnosis or antihypertensive therapy; Dyslipidaemia: dyslipidaemia diagnosis or lipid-lowering therapy; Cardiometabolic multimorbidity: two or more comorbidities of any cardiovascular disease, microvascular disease, hypertension, dyslipidaemia, grade 2+ obesity or cancer.

Figure 3: Mean or Median (95% CI) of the trajectory of (A) BMI, (B) systolic blood pressure, (C) HbA1c, (D) LDL-C, (E) Non-HDL-C and (F) Triglyceride by age groups at diagnosis of type 2 diabetes over years of diagnosis from 2005 to 2016.

