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Associations of age at diagnosis and disease duration with risk of vascular complications in type 2 diabetic patients: a cohort study in China

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Abstract

Background: The age-specific associations between type 2 diabetes (T2DM) and vascular complications (VCs) are not fully understood. We aim to explore the associations of early-onset T2DM and diabetic duration with risk of VCs.

Methods: A total of 88 803 T2DM patients from the Yinzhou Health Information System (YHIS) were included and followed until December 31, 2022. Data on age at diagnosis, T2DM duration, and VCs (including cardiovascular disease [CVD] and microvascular disease [MVD]) were also derived from the YHIS. Cox regression models were used to assess the associations between early-onset T2DM, disease duration, and VCs, with effect modification by age at diagnosis further explored.

Results: In stage 1, 37 242 and 36 751 participants were included for CVD and MVD analyses, with 4 136 CVD and 5 029 MVD cases, and median follow-up periods of 8.63 and 8.56 years, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs)for CVD and MVD in the early-onset group were 1.26 (1.08, 1.47) and 1.73 (1.54, 1.95), respectively. In stage 2, 82 370 and 84 792 participants were included, with 15 677 CVD and 10 949 MVD cases over 8.51 and 8.16 years. Age at diagnosis modified the association between diabetic duration and VCs, with stronger associations in the early-onset group (CVD: HR=1.56, 95% CI: 1.40, 1.73; MVD: HR=1.56, 95% CI: 1.50, 1.68).

Conclusions: Early-onset type 2 diabetes is associated with a significantly higher risk of VCs, with a higher lifetime risk that is not solely attributable to longer disease duration but is further amplified by the early onset age itself.

Introduction

Type 2 diabetes mellitus (T2DM), a global public health concern, caused all-age 75 million (95 % UI: 63-90) disability-adjusted life-years (DALYs) in 2021[1]. Although traditionally considered a disease of middle-aged and older adults, T2DM has been seen a significant rise in incidence among young adults, adolescents, and even children in recent years due to the increasing prevalence of sedentary lifestyles, unhealthy diets, and obesity[2]. Early-onset T2DM, defined as diabetes diagnosed before 40 years of age, represented a more heterogeneous and clinically aggressive disease phenotype[3]. Compared with late-onset T2DM patients, those with early-onset disease exhibited significantly higher rates of obesity at diagnosis, more rapid β-cell function deterioration, and poorer glycemic control post-diagnosis[4–6].

Vascular complications (VCs), including macrovascular disease (ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) and microvascular disease (diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy)[7], were the most common type of complications in T2DM, with lifelong risks of cardiovascular and kidney diseases exceeding 80% in T2DM patients[8]. Compared to late-onset T2DM patients, early-onset patients had a higher lifetime risk of VCs[9–11]. However, it was still unclear whether this was entirely due to longer disease duration in early-onset T2DM patients or inherent risks associated with early-onset T2DM. A meta-analysis showed that after adjusting for baseline age, each 1-year increase in age at diagnosis of T2DM was associated with 3% and 5% decrease in the risks of large vessel and microvascular diseases, respectively[12]. After adjusting for disease duration, each 1-year increase in age at diagnosis was associated with a 6% and 5% decrease in the risk of large vessel and microvascular diseases, respectively[12]. Another study conducted in Australia showed that during the early 10-15 years after the diagnosis of diabetes, the risk of end-stage renal disease was higher in patients with late-onset type 2 diabetes. However, after a longer follow-up period, the cumulative incidence risk of the early-onset patients surpassed that of the late-onset patients[13]. These studies suggested a complex interaction between age at diagnosis, disease duration, and age attainment regarding the risk of VCs.

The calculation of age attainment (sum of diagnostic age and disease duration) introduced analytical challenges due to the inherent interaction between these variables, necessitating specialized approaches to isolate the effect of diagnostic

age. A study from Hong Kong addressed this issue by comparing the risk of chronic kidney disease across different age groups while controlling for disease duration [14]. The results showed that among patients diagnosed at the age of 20-29 years, each 5-year increase in diabetic duration was associated with a 37% elevated risk of chronic kidney disease (hazard ratio [HR] = 1.37; 95% confidence interval [CI]: 1.13-1.65), whereas no association was observed in patients at the diagnostic age of ≥70 years (HR=1.01; 95% CI: 0.87-1.18)[14]. Furthermore, existing evidence indicated that early-onset T2DM patients may maintain or exacerbate their poor metabolic profiles and unhealthy lifestyles post-diagnosis[15]. Based on these findings, we hypothesized that, beyond the disease duration, early-onset had an additional impact on the risk of vascular complications in patients with type 2 diabetes. To test this hypothesis, we conducted a two-stage analysis using data from a Chinese retrospective cohort to examine the relationships of early-onset T2DM and disease duration with risk of VC.

Methods

Type 2 diabetes mellitus (T2DM), a global public health concern, caused all-age 75 million (95 % UI: 63-90) disability-adjusted life-years (DALYs) in 2021[1]. Although traditionally considered a disease of middle-aged and older adults, T2DM has been seen a significant rise in incidence among young adults, adolescents, and even children in recent years due to the increasing prevalence of sedentary lifestyles, unhealthy diets, and obesity[2]. Early-onset T2DM, defined as diabetes diagnosed before 40 years of age, represented a more heterogeneous and clinically aggressive disease phenotype[3]. Compared with late-onset T2DM patients, those with early-onset disease exhibited significantly higher rates of obesity at diagnosis, more rapid β-cell function deterioration, and poorer glycemic control post-diagnosis[4–6].

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data from a Chinese retrospective cohort to examine the relationships of early-onset T2DM and disease duration with risk of VC.

Results

Descriptive results

This study included 88 803 participants, with 43 329 females (48.79%). The mean ages at baseline and T2DM diagnosis were 60.27 ± 11.83 years and 57.46 ± 11.87 years, respectively. Participants had a median T2DM duration of 1.66 years (IQR 0.16-4.02), with 80.50%exhibiting 5 years or less (**Supplementary Figure 2**). Among the participants, 6 433 (7.24%) had a history of CVD, and 4 011 (4.52%) reported previous MVD.

Participants were stratified by age at T2DM diagnosis into early-onset (n=5 517, 6.21%) and late-onset (n=83 286, 93.79%) groups (**Table 1**). Compared with the late-onset group, the early-onset group exhibited longer T2DM duration, higher educational attainment, FBG, BMI, proportion of MVD history, but lower proportion of hypertension and CVD history, being more likely to be males, smokers, and non-drinkers. They also demonstrated lower utilization rates of antihypertensive and lipid-lowering drugs but slightly higher usage of glucose-lowering agents (**Table 1**). In the second analytical stage, focusing on participants aged 40-59 years (n=38 583), the early-onset group accounted for 5.39% (n=2 083). Similar results were observed between the groups, but differences in alcohol consumption, BMI, and glucose-lowering medication usage were not statistically significant (**Supplementary Table 3**).

When stratified by T2DM duration, the cohort was divided into three groups: short-duration group (<5 years; n=71 489, 80.50%), intermediate-duration group (5–<10 years; n=12 181, 13.72%), and long-duration group (≥10 years; n=5 133, 5.78%) (**Table 1**). Compared with the short-duration group, patients in the long-duration group were older at baseline but younger at diagnosis, with a higher proportion of early-onset T2DM and pre-existing MVD, having elevated FBG and decreased BMI levels. Additionally, individuals in the long-duration group were more likely to be females, non-smokers, non-drinkers, without pre-existing hypertension and dyslipidemia, and without using antihypertensive, lipid-lowering, and glucose-lowering medications.

Age at T2DM diagnosis and vascular complications

In stage 1, 37 242 participants, including 2 028 (5.45%) with early-onset T2DM, were analyzed for CVD outcomes over 278 145 person-years (median [IQR]: 8.63 [5.76-10.35] years), identifying 4 316 incident cases. When adjusting for baseline age, we observed a higher incidence density of CVD in the early-onset group as compared with the late-onset group (16.99 vs. 13.64 per 1000 person-years). As **Table 2** presented, early-onset patients had significantly higher risks of CVD (HR=1.26, 95% CI: 1.08-1.47), MACE (HR=1.18, 95% CI: 1.00-1.39), and UAP and HF (HR=1.80, 95% CI: 1.15-2.80) than the late-onset group. Furthermore, each 5-year decrease in diagnostic age was associated with increased risks of CVD (HR=1.12, 95% CI: 1.07-1.17), MACE (HR=1.10, 95% CI: 1.05-1.16), and UAP and HF (HR=1.30, 95% CI: 1.14-1.49). The cumulative incidence curves demonstrated that when both groups reached 60 years of age, the subsequent 10-year CVD risk remained consistently higher in the early-onset group, though the absolute difference was modest (**Supplementary Figure 3**).

The analysis of MVD outcomes included 36 751 participants, comprising 1 869 cases (5.09%) with early-onset T2DM. Over a follow-up period of 268 946 person-years (median [IQR] follow-up duration: 8.56 [5.74-10.28] years), 5 029 incident cases of MVD were documented. Individuals in the early-onset group exhibited a higher incidence density of MVD (30.43 vs. 17.57 per 1 000 person-years), after adjustment for baseline age. As presented in **Table 2**, early-onset T2DM was associated with significantly elevated risks of MVD (HR=1.73, 95% CI: 1.54-1.95), diabetic nephropathy (HR=1.64, 95% CI: 1.38-1.95), diabetic retinopathy (HR=2.10, 95% CI: 1.80-2.44), and diabetic neuropathy (HR=1.78, 95% CI: 1.48-2.16) compared to late-onset T2DM, respectively. Furthermore, each 5-year decrement in age at T2DM diagnosis was

associated with higher risks of MVD (HR=1.50, 95% CI: 1.44-1.56), diabetic nephropathy (HR=1.52, 95% CI: 1.43-1.62), diabetic retinopathy (HR=1.65, 95% CI: 1.57-1.73), and diabetic neuropathy (HR=1.48, 95% CI: 1.39-1.58), respectively. Cumulative incidence curves showed that by age 60, the early-onset group had consistently higher 10-year MVD risks than the late-onset group, with the absolute risk difference widening over time (**Supplementary Figure 4**).

The modification of T2DM diagnostic age on the association between duration and vascular complications

In stage 2, the analysis of CVD outcomes included 82 370 participants stratified by age at diagnosis into five groups: <40 (n=5 420), 40-49 (n=16 413), 50-59 (n=27 252), 60-69 (n=21 700), and ≥70 years (n=11 585). During a follow-up of 570 726 person-years (median [IQR] follow-up duration: 8.51 [5.45-10.32] years), 15 677 incident CVD cases were identified. Across all age-at-diagnosis subgroups, longer T2DM duration was consistently associated with elevated cardiovascular disease risk (**Figure 2**), with significant effect modification by diagnostic age ($P_{for\ interaction}$<0.001). Notably, in the early-onset subgroup (<40 years), each 5-year increment in diabetic duration was associated with a 56% increased risk of CVD (HR=1.56, 95% CI: 1.40-1.73). This excess risk demonstrated a progressive attenuation with elevating diagnostic age, diminishing to the HR of 1.16 (95% CI: 1.09-1.23) in the ≥70 years subgroup. Similar patterns were observed for MACE and UAP and HF.

The analysis of MVD included 84 792 participants categorized into five diagnostic age groups: <40 (n=5 163), 40-49 (n=15 922), 50-59 (n=27 285), 60-69 (n=22 840), and ≥70 (n=13 582). During a follow-up period of 590 436 person-years (median [IQR] follow-up duration: 8.16 [5.00-10.16] years), 10 949 incident cases of MVD were identified. As illustrated in **Figure 3**, age at T2DM diagnosis significantly modified the association between disease duration and MVD risk ($P_{for\ interaction}$<0.001). A stronger association was observed in the early-onset subgroup (<40 years), where each 5-year increment in T2DM duration corresponded to a 56% increased risk of MVD (HR=1.56, 95% CI: 1.45-1.68), with this association progressively attenuating with increasing diagnostic age. Notably, in the ≥70 years subgroup, the association between T2DM duration and MVD risk attenuated to the null (HR=1.09, 95% CI: 0.98-1.22). Similar patterns of association were consistently observed in the analyses of specific MVDs, including diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.

Sensitivity analyses

Supplementary Table 4 presents the results of sensitivity analyses examining the association between early-onset T2DM (or age at diagnosis) and risks of VCs. When excluding participants who developed outcomes or died within the first year of follow-up, excluding participants with any missing covariates, or employing Fine-Gray competing risk models, the results remained consistent with the primary findings. The sensitivity analyses evaluating the effect modification by diagnostic age on the association between T2DM duration and VC risks demonstrated similar results to the main analysis (**Supplementary Table 5**).

Discussion

In this cohort study, when reaching the same baseline age, early-onset T2DM patients demonstrate significantly higher risks of both CVD and MVD compared to their late-onset counterparts. Furthermore, age at T2DM diagnosis significantly modified the association between disease duration and risks of CVD and MVD ($P_{for\ interaction}$<0.001). Stronger associations of T2DM duration with risk of VCs were observed in the early-onset subgroup, and this association exhibited a progressive attenuation with increasing diagnostic age.

Numerous previous studies have investigated the association between age at T2DM diagnosis and risk of VCs[22]. A large cross-sectional study involving 222 773 T2DM patients across 30 Chinese provinces demonstrated that after adjusting for baseline age and sex, early-onset T2DM patients had a 91% higher risk of non-fatal CVD compared to late-onset patients

(OR: 1.91, 95% CI: 1.81-2.02) [9]. Similarly, a prospective study from Hong Kong found that when reaching any given baseline age, early-onset T2DM patients consistently showed higher cumulative incidence for both CVD and chronic kidney disease during follow-up period compared to late-onset patients[10]. In the first stage of our current study, we employed a cohort design and expanded the outcomes to encompass all VCs, indicating that when reaching comparable baseline ages, early-onset patients exhibit significantly higher subsequent risks of developing CVD and its subtypes as well as MVD and its subtypes, thereby complementing previous findings. However, these findings alone could not determine whether the elevated VC risk in early-onset patients at comparable ages stemmed solely from longer disease duration or reflected inherent hazards of early-onset T2DM itself. To further control for duration effects, some studies have additionally adjusted for disease duration in their models, revealing that such adjustment either substantially attenuated the relative risks associated with early-onset status[9] or rendered them statistically non-significant [10]. From a methodological perspective, this adjustment approach is problematic because baseline age represents the sum of age at onset and disease duration, and adjusting simultaneously for both baseline age and duration mathematically fixes the age at diagnosis. Furthermore, an Australian study of over 1 million newly diagnosed T2DM patients showed that while older age at diagnosis initially predicted higher rates of kidney failure during the first two decades, this trend reversed with prolonged diabetic duration [11], highlighting the complex temporal dynamics between age at onset, disease duration, and complication risks.

The duration of T2DM represented a well-established risk factor for VCs, reflecting the cumulative impact of chronic hyperglycemia and associated metabolic disorders. Previous studies have consistently demonstrated that T2DM duration remained significantly associated with both macrovascular and microvascular disease risks, regardless of whether adjusting for age at baseline or at diagnosis [23,24]. For instance, an Australian cross-sectional study reported that each additional year of diabetic duration was associated with 5% and 7% increased risks of macrovascular and microvascular complications respectively after adjusting for age at diagnosis, whereas the corresponding excess risks of 2% and 7% were observed when adjusting for baseline age instead [23]. Several investigations have further examined potential effect modification by diagnostic age on the association between disease duration and risk of VCs. A post-hoc analysis of a randomized controlled trial involving 11 140 T2DM patients identified an interaction between diagnostic age and diabetic duration for MVD risk ($P_{for\ interaction}$=0.016), but not for macrovascular outcomes ($P_{for\ interaction}$=0.098) [24]. Nevertheless, this study did not conduct stratified analyses, which limited the ability to accurately determine differences in duration-related excess risks of VCs among various diagnostic age subgroups. Moreover, their study participants with either pre-existing VCs, diabetic duration ≥10 years, or cardiovascular risk factors might limit the generalizability of their results to community-based T2DM populations. A study based on registry system in Hong Kong revealed that younger diagnostic age substantially amplified the association between duration and chronic kidney disease risk - while each 5-year increment in duration conferred 37% increased risk in the 20-29 years diagnostic subgroup, the corresponding excess risk was merely 1% in patients at the diagnostic age of ≥70 years[14]. In the second stage of our study, we systematically evaluated associations between T2DM duration and VC risks across diagnostic age subgroups and formally tested for modified effects. Our findings demonstrated that VC risks increased with longer diabetic duration across all age subgroups, and their association was modified by diagnostic age, with stronger duration-associated excess risks observed in early-onset patients. These results could support our hypothesis that, beyond the influence of disease duration, early onset imposes an additional risk of vascular complications in patients with T2DM. The elevated risk of VCs observed in early-onset T2DM patients could originate from multiple interrelated factors. Primarily, these results may reflect inherent pathophysiological characteristics of early-onset diabetes. Substantial evidence indicated that early-onset T2DM patients experienced accelerated β-cell function decline at rates of 25-30% annually, compared to just 7% in late-onset counterparts [25–27]. Beyond β-cell dysfunction, these patients may also have severe insulin resistance [28]. The synergistic effects of rapid β-cell failure and pronounced insulin resistance rendered glycemic control particularly challenging in early-onset patients, leading to higher treatment failure rates and poor metabolic control. Secondly, as supported by existing literature [29], early-onset patients exhibited persistent and progressively worsening metabolic

disorders (such as obesity) beyond hyperglycemia, resulting in substantially greater cumulative exposure to pathogenic factors compared to late-onset patients with equivalent diabetic duration. Thirdly, behavioral patterns contributed significantly - early-onset patients typically maintained less favorable lifestyle habits (e.g., higher smoking rates) and showed poorer post-diagnosis lifestyles modification compared to late-onset patients[30–32]. Additionally, this population faced greater psychosocial challenges, including mental health burdens, inadequate diabetes self-management, and limited healthcare access [33,34]. Notably, even after comprehensive adjustment for established cardiovascular and microvascular risk factors in multivariable models, the persistent modifying effect of diagnostic age on the association between duration and complications suggested potential involvement of unidentified pathogenic mechanisms. Future investigations are needed to focus on elucidating the biological mechanisms underlying VCs in early-onset T2DM.

The findings of this study carried important implications for developing prevention strategies targeting VCs in early-onset T2DM patients. Within community-based management frameworks, early-onset T2DM patients could be categorized as either newly diagnosed or established cases. Although newly diagnosed early-onset T2DM patients generally exhibited reduced VC risks relative to late-onset cases owing to their younger diagnostic age (a key determinant of vascular outcomes), standard risk prediction models including the Pooled Cohort Equations[35], QRISK2[36], and China-PAR[37] frequently categorized them as low-risk in 10-year cardiovascular projections, which may postpone essential therapeutic interventions. However, over time, the effects of natural aging and T2DM duration may be amplified by early-onset, leading to premature CVD and MVD in early-onset patients. Furthermore, due to the unfavorable metabolic characteristics and lifestyles exhibited by patients with early-onset T2DM after diagnosis, achieving optimal glycemic control and intervention of vascular risk factors in the early stage may help reduce their lifelong risk of VCs. Ultimately, multifaceted approaches to prevent or delay T2DM onset could reduce both disease duration and complication burden across the lifespan, thereby generating more benefits.

Compared with previous studies, our study possessed several methodological strengths, including a substantially larger sample size (n>80 000), an extended follow-up period (>8 years), and a comprehensive assessment of vascular outcomes. Furthermore, our two-stage analytical approach enabled a systematic evaluation of the detrimental effects of early-onset on VCs in T2DM patients. However, several limitations in our study warranted consideration. Firstly, data on age at initial T2DM diagnosis were obtained through medical records or self-report, potentially compromising data accuracy, particularly among patients with longer disease duration due to recall bias. Secondly, outcome ascertainment relied on ICD-10 coded clinical diagnoses from the YHIS database, which may introduce misclassification bias. Thirdly, as an observational study, residual confounding remained a potential concern despite our rigorous adjustment for known covariates. Lastly, the study was conducted only in the Han population of a district in Ningbo, China, which limited the generalizability of our results. Further studies in different regions and among diverse racial groups are needed.

Conclusion

In this cohort study, at the same baseline age, early-onset T2DM was associated with a higher risk of CVD, MVD, and their subtypes. Further analysis revealed that in the population with early-onset T2DM, the higher lifetime risk of VCs was not solely driven by the prolonged disease duration. Age at T2DM diagnosis significantly modified the association between disease duration and VC risks, with early-onset amplifying the association. This suggests that implementing diabetes prevention measures at an earlier stage would yield greater clinical benefits.

Abbreviations

BMI body mass index

CVD cardiovascular disease

DALYs disability-adjusted life-years

FBG fasting blood glucose

HF heart failure

HR hazard ratio

ICD-10 International Classification of Diseases, 10th Revision

IQR interquartile range

MACE major adverse cardiovascular events

MVD microvascular disease

SD standard deviation

T2DM type 2 diabetes mellitus

UAP unstable angina pectoris

VC vascular complication

YHIS Yinzhou Health Information System

95% CI 95% confidence interval

Declarations

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Authors' contributions

Lisha Xu and Zongming Yang: Formal analysis, Methodology, Visualization, Writing- original draft**. Jiayun Zhang, Zihan Li, Ye Jiao, Yichao Dai, and Tian Ge:** Data curation, Writing-review &editing. **Yexiang Sun, Hongbo Lin, Liming Shui, Zhiqin Jiang, and Feng Tong:** Data curation, Investigation. **Chaochun Zou:** Supervision, Writing-review &editing. **Kun Chen, and Jianbing Wang:** Funding acquisition, Project administration, Supervision, Writing-review &editing.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Human ethics and consent to participate

This study strictly adhered to the ethical standards outlined in the Declaration of Helsinki and conducted with ethical clearance from Medical Ethics Committee of Zhejiang University School of Public Health (ZGL202205-2). Study procedures were approved by the Institutional Review Board, and all participants provided informed consent.

Competing interests

No potential conflicts of interest relevant to this article were reported.

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Tables

Table 1. Baseline characteristics for patients with T2DM included in analyses

	Age at T2DM diagnosis (years)		*P* value[a]	T2DM duration (years)			*P* value[a]
	<40 (early-onset)	≥40 (late-onset)		<5	5-<10	≥10	
Number (n)	5 517	83 286		71 489	12 181	5 133	<0.001
Age at baseline (years, Mean ± SD)	38.02±6.02	61.75±10.57	<0.001	59.59±11.89	62.17±11.22	65.18±10.67	<0.001
Age at T2DM diagnosis (years, Mean ± SD)	34.39±4.33	58.99±10.55	<0.001	58.19±11.93	55.30±11.21	52.43±10.63	<0.001
T2DM duration [years, Median(IQR)]	2.11(0.34, 5.11)	1.60(0.16, 4.00)	<0.001	0.99 (0.08, 2.40)	6.56 (5.58, 8.00)	12.00 (10.83, 14.04)	<0.001
T2DM duration [years, (n, %)]			<0.001	-	-	-	-
<5	4 028(73.01)	67 461(81.00)		-	-	-	
5-<10	889(16.11)	10 932(13.13)		-	-	-	
≥10	600(10.88)	4 893(5.87)		-	-	-	
Early-onset T2DM (n, %)	-	-	-	4 028(5.63)	919(7.54)	570(11.10)	<0.001
Female (n, %)	2 055(37.25)	41 274(49.56)	<0.001	34 670(48.50)	6 030(49.50)	2 629(51.22)	<0.001
Married (n, %)	5 008(90.77)	74 846(89.87)	0.032	64 379(90.05)	10 940(89.81)	4 535(88.35)	<0.001
Education[b]			<0.001				<0.001
Illiterate	67(1.24)	9 458(11.56)		7 587(10.80)	1 336(11.18)	602(12.02)	
Primary or middle school	2 516(46.74)	58 544(71.56)		49 805(70.92)	8 031(67.18)	3 224(64.35)	
High school or above	2 800(52.02)	13 811(16.88)		12 839(18.28)	2 588(21.65)	1 184(23.63)	
Tobacco smoking (n, %)[b]	1 186(27.20)	18 111(24.81)	<0.001	16 126(25.81)	2 363(22.33)	808(18.76)	<0.001
Alcohol consumption (n, %)[b]	941(21.81)	16 853(23.18)	0.041	14 664(23.58)	2 294(21.75)	836(19.49)	<0.001
Physical activity (n, %)[b]			<0.001				<0.001
Less than once/week	807(18.73)	15 836(21.81)		13 529(21.78)	2 197(20.87)	917(21.43)	

1-<4 times/week	1 058(24.55)	15 586(21.46)		13 637(21.95)	2 154(20.47)	853(19.93)	
≥4 times/week	2 444(56.72)	41 196(56.73)		34 957(56.27)	6 174(58.66)	2 509(58.64)	<0.001
FBG (mmol/L, Mean±SD)[b]	9.63±3.31	8.87±2.78	<0.001	8.86±2.78	8.98±2.82	9.47±3.27	<0.001
BMI (kg/m^2, Mean±SD)[b]	24.48±3.48	24.09±3.06	<0.001	24.17±3.10	23.97±3.03	23.66±3.08	<0.001
BMI [kg/m^2, (n, %)][b]			<0.001				<0.001
<18.5	74(1.35)	1 761(2.13)		1 386(1.95)	290(2.40)	159(3.12)	
18.5-23.9	2 661 (48.63)	41 195(49.79)		34 910(49.16)	6 192(51.19)	2 754(54.07)	
24-27.9	1 941(35.47)	31 567(38.15)		27 207(38.31)	4 508(37.27)	1 793(35.21)	
≥28	796(14.55)	8 213(9.93)		7 516(10.58)	1 106(9.14)	387(7.60)	
History of diseases							
Hypertension (n, %)	1 789(32.43)	49 561(59.51)	<0.001	41 712(58.35)	6 966(57.19)	2 672(52.06)	<0.001
Dyslipidemia (n, %)	1 325(24.02)	27 497(33.02)	<0.001	23 597(33.01)	3 932(32.28)	1 293(25.19)	<0.001
CVD (n, %)	97(1.76)	6 336(7.61)	<0.001	5 042(7.05)	1 012(8.31)	379(7.38)	<0.001
MVD (n, %)	354(6.42)	3 657(4.39)	<0.001	2 492(3.49)	938(7.70)	581(11.32)	<0.001
Medication usage							
Antihypertensive drugs (n, %)	1 142(20.70)	35 134(42.18)	<0.001	29 908(41.84)	4 624(37.96)	1 744(33.98)	<0.001
Lipid-lowering drugs (n, %)	695(12.60)	16 312(19.59)	<0.001	14 173(19.83)	2 112(17.34)	722(14.07)	<0.001
Hypoglycemic drugs (n, %)	3 278(59.42)	47 858(57.46)	0.005	42 120(58.92)	6 559(53.85)	2 457(47.87)	<0.001

Abbreviations: BMI=body mass index; CVD=cardiovascular disease; FBG=fasting blood glucose; IQR= interquartile range; MVD= microvascular disease; SD=standard deviation; T2DM=type 2 diabetes mellitus.

[a]*t* tests were used for continuous variables with normal distribution, Mann-Whitney U tests were used for continuous variables with skewed distribution, and χ^2 tests were used for categorical variables.

[b]Missing values for education (n=1 607), tobacco smoking (n=11 435), alcohol consumption (n=11 776), physical activity (n=11 876), FBG (n=1 602), BMI (n=595).

Table 2. The association of early-onset T2DM and age at T2DM diagnosis with risk of CVD and MVD

	Age at T2DM diagnosis (years)		
	≥40(late-onset)	<40(early-onset)	Per 5 years decrease
Number(n)[#]	35 214	2 028	-
CVD			
Events/ person-years	4123/262 669	193/15 476	-
Incidence density /1000 person-years(95% CI)[a]	15.70(15.22, 16.18)	12.47(10.83, 14.36)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	13.64(13.14, 14.15)	16.99(14.69, 19.66)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.24(1.06, 1.45)	1.10(1.05, 1.15)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.26(1.08, 1.47)	1.12(1.06, 1.17)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.26(1.08, 1.47)	1.12(1.07, 1.17)
MACE			
Events/ person-years	3814/263 451	170/15 552	-
Incidence density /1000 person-years(95% CI)[a]	14.48(14.02, 14.94)	10.93(9.41, 12.70)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	12.66(12.18, 13.16)	14.70(12.59, 17.16)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.16(0.98, 1.37)	1.08(1.03, 1.14)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.17(1.00, 1.39)	1.10(1.04, 1.15)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.18(1.00, 1.39)	1.10(1.05, 1.16)
UAP and HF			
Events/ person-years	413/278 696	25/16 163	-
Incidence density /1000 person-years(95% CI)[a]	1.48(1.35, 1.63)	1.55(1.05, 2.29)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	1.21(1.07, 1.37)	2.29(1.52, 3.44)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.80(1.15, 2.80)	1.30(1.14, 1.48)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.80(1.15, 2.81)	1.30(1.13, 1.49)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.80(1.15, 2.80)	1.30(1.14, 1.49)
Number(n)[*]	3 4882	1869	-
MVD			
Event/ person years	4660/255 511	369/13 435	-
Incidence density /1000 person years(95% CI)[a]	18.24(17.72, 18.77)	27.47(24.8, 30.42)	-

	Age at T2DM diagnosis (years)		
	≥40(late-onset)	<40(early-onset)	Per 5 years decrease
Age-adjusted incidence density /1000 person years(95% CI)[b]	17.57(17.01, 18.15)	30.43(27.3, 33.91)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.72(1.53, 1.94)	1.50(1.44, 1.56)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.71(1.52, 1.93)	1.49(1.43, 1.55)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.73(1.54, 1.95)	1.50(1.44, 1.56)
Diabetic nephropathy			
Events/ person-years	1824/268 467	171/14 340	-
Incidence density /1000 person-years(95% CI)[a]	6.79(6.49, 7.11)	11.92(10.26, 13.85)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	6.86(6.53, 7.21)	11.59(9.87, 13.61)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.67(1.40, 1.99)	1.54(1.45, 1.63)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.63(1.37, 1.94)	1.51(1.42, 1.61)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.64(1.38, 1.95)	1.52(1.43, 1.62)
Diabetic retinopathy			
Events/ person-years	2679/264 034	231/14 028	-
Incidence density /1000 person-years(95% CI)[a]	10.15(9.77, 10.54)	16.47(14.47, 18.73)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	9.45(9.05, 9.87)	19.73(17.2, 22.64)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	2.08(1.79, 2.42)	1.64(1.56, 1.72)
Model 2, HR(95% CI)[d]	1.00(Ref)	2.07(1.78, 2.41)	1.63(1.55, 1.71)
Model 3, HR(95% CI)[e]	1.00(Ref)	2.10(1.80, 2.44)	1.65(1.57, 1.73)
Diabetic neuropathy			
Events/ person-years	1695/270 030	144/14 558	-
Incidence density /1000 person-years(95% CI)[a]	6.28(5.99, 6.58)	9.89(8.4, 11.65)	-
Age-adjusted incidence density /1000 person-years(95% CI)[b]	6.02(5.71, 6.35)	11.04(9.28, 13.14)	-
Model 1, HR(95% CI)[c]	1.00(Ref)	1.81(1.49, 2.18)	1.50(1.41, 1.60)
Model 2, HR(95% CI)[d]	1.00(Ref)	1.77(1.47, 2.14)	1.47(1.38, 1.57)
Model 3, HR(95% CI)[e]	1.00(Ref)	1.78(1.48, 2.16)	1.48(1.39, 1.58)

Abbreviations: CVD=cardiovascular disease; HF=heart failure; HR=hazard ratio; MACE=major adverse cardiovascular event; MVD=microvascular disease; Ref=reference; T2DM=type 2 diabetes mellitus; UAP=unstable angina pectoris; 95% CI=95% confidence interval.

[#] Number of participants for CVD analysis.

[*] Number of participants for MVD analysis.

[a] 95% CI of the rate estimated based on Poisson distribution.

[b] estimated based on Poisson regression, and with the baseline age of both the early-onset and late-onset groups set at 50 years for prediction.

[c] Model 1 adjusted for baseline age and gender.

[d] Model 2 further adjusted for marital status, education, BMI, FBG, smoking, drinking, physical activity, and history of diseases (hypertension and dyslipidemia) based on Model 1.

[e] Model 3 further adjusted for the usage of antihypertensive drugs, lipid-lowering drugs, and hypoglycemic drugs based on Model 2.

Figures

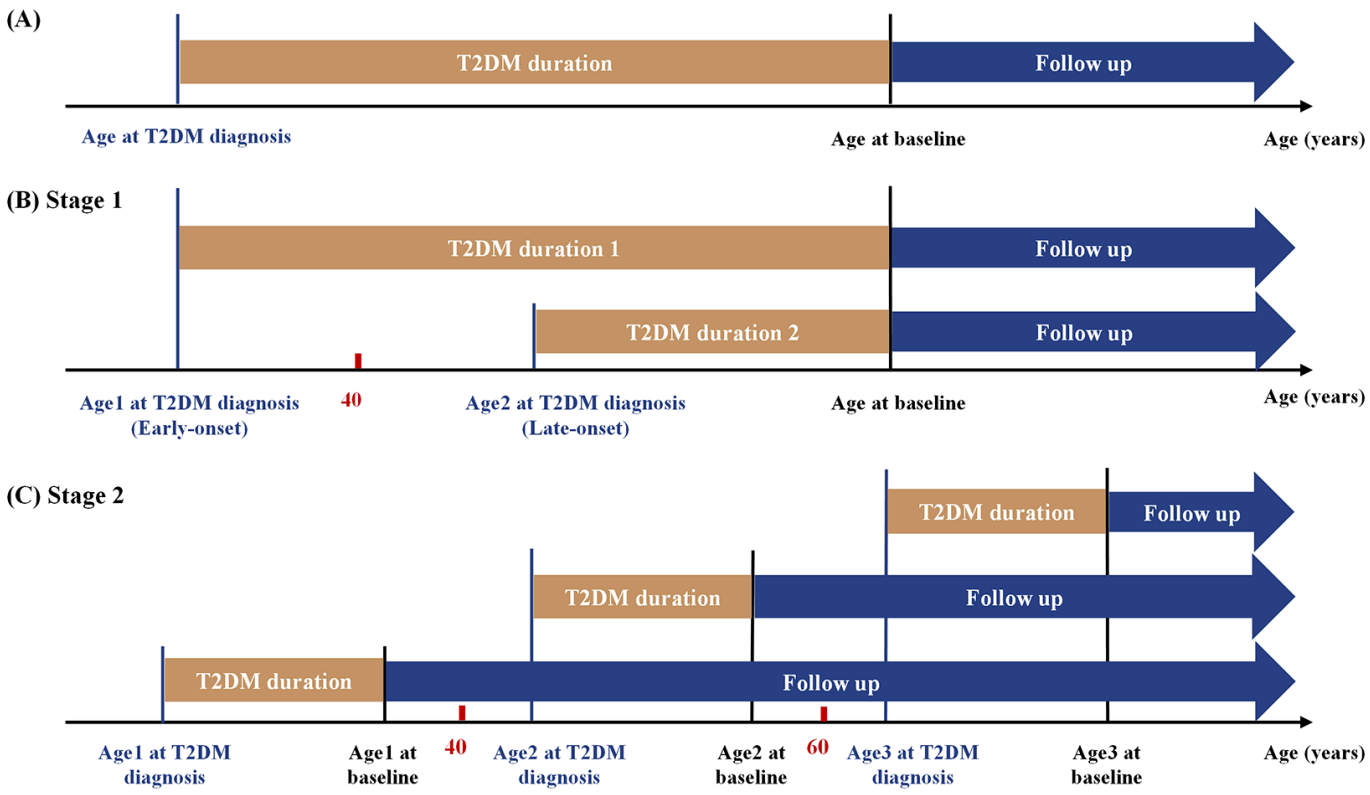


Figure 1

Study design and approach

Abbreviations: T2DM=type 2 diabetes mellitus.

T2DM duration was the difference between baseline age and diagnostic age (A). In stage 1, we explored the association between early-onset T2DM and risk of outcome when reaching the same baseline age (B). In stage 2, we explored the association between age at T2DM diagnosis and risk of outcome when using the same T2DM duration (C).

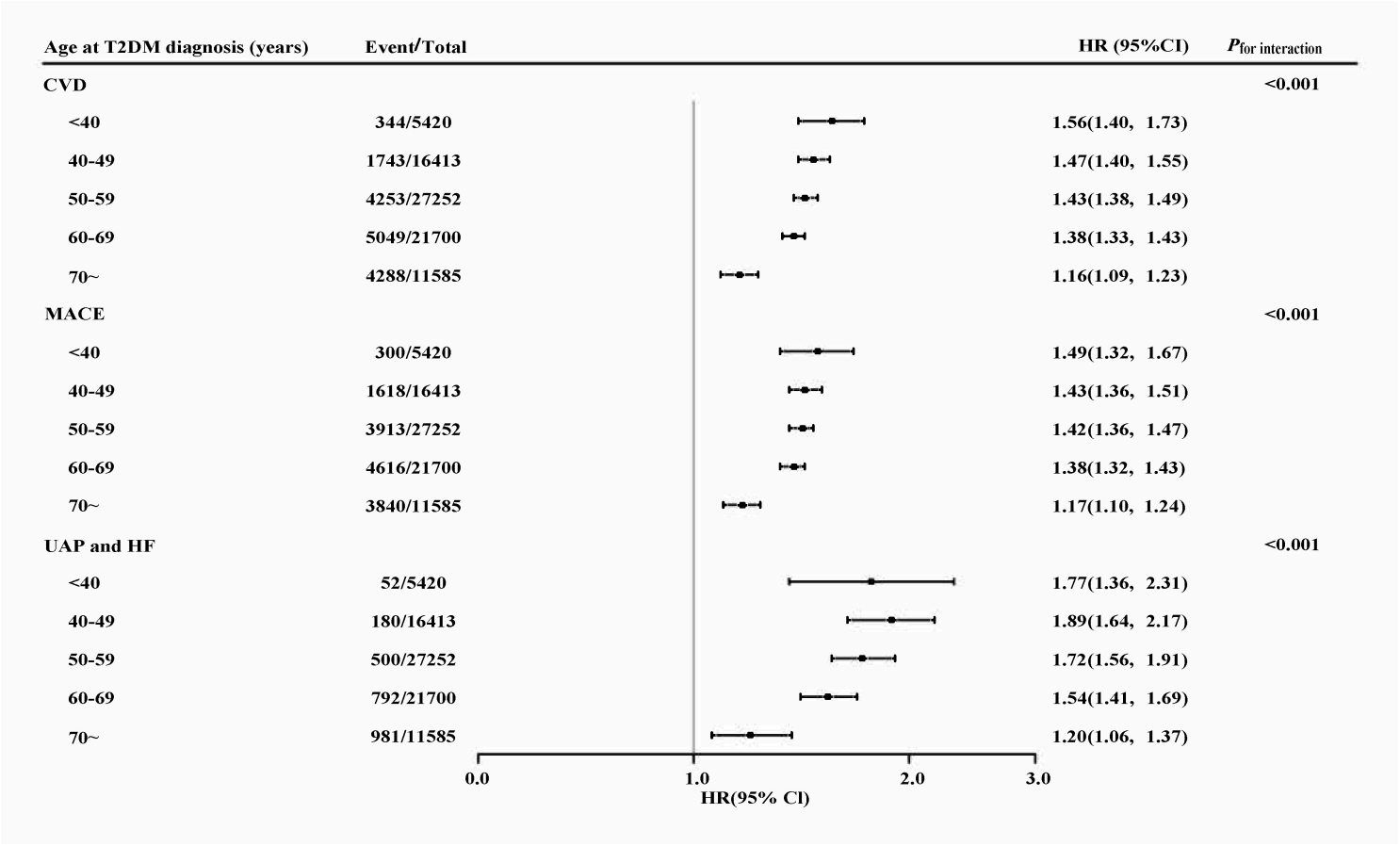


Figure 2

Association of T2DM duration with CVD and its subtypes in different T2DM diagnostic age subgroups

Abbreviations: CVD=cardiovascular disease; HF=heart failure; HR=hazard ratio; MACE=major adverse cardiovascular event; T2DM=type 2 diabetes mellitus; UAP=unstable angina pectoris; 95% CI=95% confidence interval.

All estimates were given per 5-year increase in T2DM duration and adjusted for baseline age, gender, marital status, education, BMI, FBG, smoking, drinking, physical activity, history of diseases (hypertension and dyslipidemia), and the usage of antihypertensive drugs, lipid-lowering drugs, and hypoglycemic drugs.

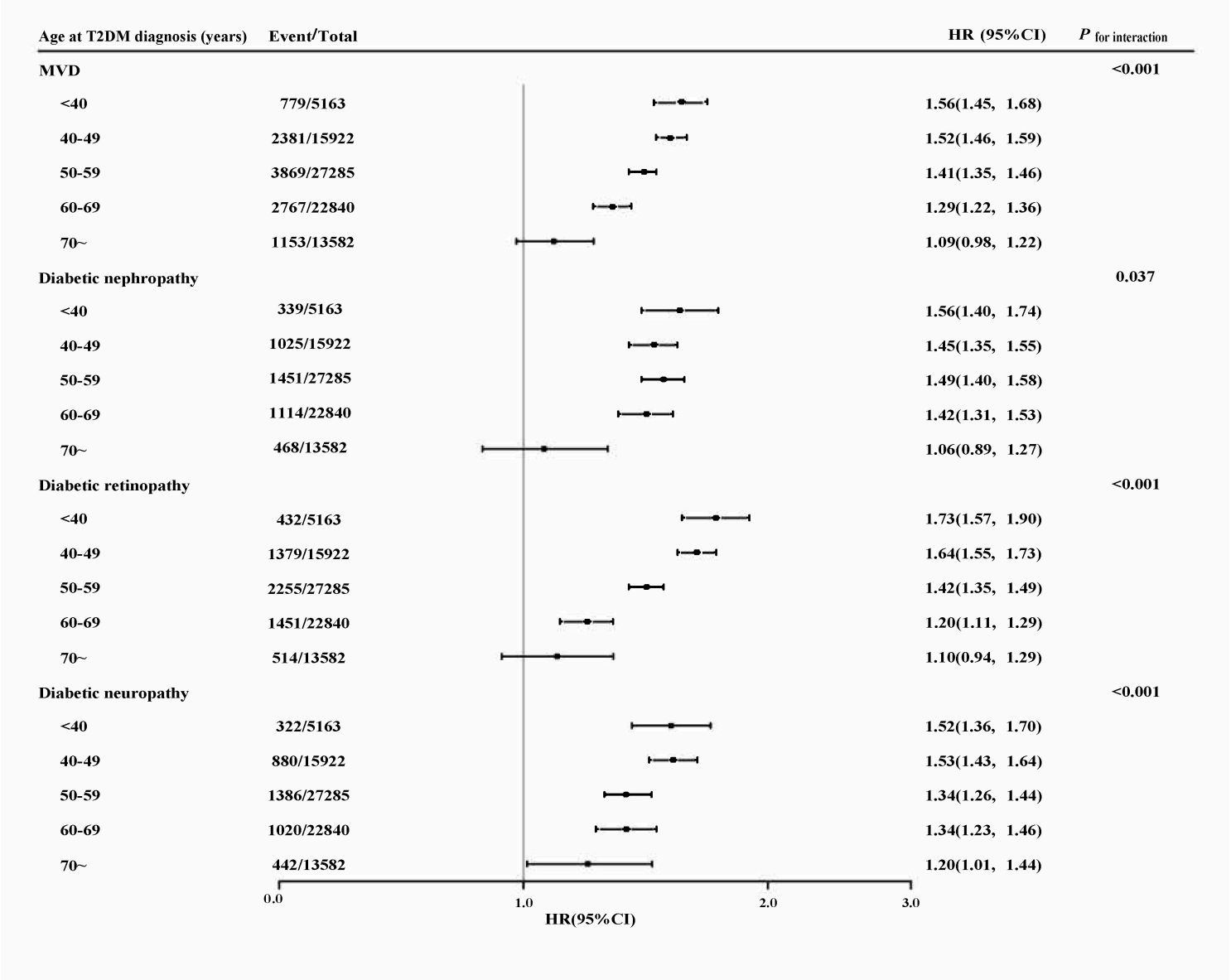


Figure 3

Association of T2DM duration with MVD and its subtypes in different T2DM diagnostic age subgroups

Abbreviations: HR=hazard ratio; MVD=microvascular disease; T2DM=type 2 diabetes mellitus; 95% CI=95% confidence interval.

All estimates were given per 5 years increase in T2DM duration and adjusted for baseline age, gender, marital status, education, BMI, FBG, smoking, drinking, physical activity, history of diseases (hypertension and dyslipidemia), and the usage of antihypertensive drugs, lipid-lowering drugs, and hypoglycemic drugs.

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