Relationship between onset age of type 2 diabetes mellitus and vascular complications based on propensity score matching analysis

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ABSTRACT

Aims/Introduction: To assess the relationship between type 2 diabetes mellitus onset age and vascular complications in China.

Materials and Methods: A retrospective review of 3,568 patients with type 2 diabetes mellitus using a propensity score-matched (PSM) cohort analysis was carried out in two different age of onset groups (age 40 and 60 years). These groups were then subdivided into two groups, early-onset diabetes (EOD40 and EOD60; the onset age before 40 and 60 years, respectively) and late-onset diabetes (LOD40 and LOD60: the onset age after 40 and 60 years, respectively). Macrovascular and microvascular complications were analyzed before and after PSM.

Results: Patients categorized in both the early-onset disease (EOD) groups had a higher risk of developing macro- and microvascular complications before PSM. After PSM, no differences existed between the EOD and late-onset disease groups in the risk of macrovascular complications. Compared with the late-onset disease group, the odds ratio of having a microvascular complication of diabetic retinopathy, chronic kidney disease and diabetic peripheral neuropathy in the 40-year-old EOD group increased to 2.906, 1.967 and 1.672 ($P < 0.05$), respectively. The odds ratio of diabetic retinopathy and diabetic peripheral neuropathy in the 60-year-old EOD group was 1.763 and 1.675 ($P < 0.05$), respectively.

Conclusions: The earlier the onset of type 2 diabetes mellitus, the higher risk of microvascular, but not necessarily macrovascular, complications. It is not too late to prevent diabetes at any age. Pre-emptive microvascular treatment or preventative measures in EOD patients who do not yet show symptoms, might be beneficial.

INTRODUCTION

The quality of life of patients with type 2 diabetes mellitus is adversely affected by both macrovascular and microvascular complications. Atherosclerosis is a macrovascular complication that mostly develops in diabetes patients, and the life expectancy of diabetes patients is severely impaired[1–3]. The risk of myocardial infarction and stroke increases greatly in these patients as well[4,5]. Diabetic nephropathy and retinopathy (DR) are the leading causes of end-stage renal disease and blindness[1–3]. In previous decades, type 2 diabetes mellitus was a condition that usually developed in older people[6]. Currently, the incidence of early-onset type 2 diabetes mellitus (age ≤40 years) has increased globally as a result of the following factors: high-energy diets, reduced physical activity, and poor metabolic control of blood sugar, lipids and blood pressure[7]. Previous studies have reported that the risk of macrovascular events and mortality is higher in patients with type 2 diabetes

mellitus. These complications mostly develop in the following cases: old age, prolonged duration of diabetes and diagnosis at a younger age[8]. The risk of death is higher in patients with early-onset type 2 diabetes mellitus, and early cardiovascular disease (CVD) mortality is quite common in these patients[9]. The risk factors for diabetic microvascular complications and CVD are as follows: hyperglycemia, diabetes duration, dyslipidemia, hypertension and insulin resistance[10–13]. Compared with patients with late-onset diabetes (>40 years of age), metabolic control is poorer in patients with early-onset type 2 diabetes mellitus. In patients with early-onset type 2 diabetes mellitus, the protective effect of drugs is lesser and these patients have a higher risk of developing vascular complications[14]. Furthermore, this effect is also closely related to diabetes duration[15,16]. Previous studies only focused on single vascular complication events; the age- and sex-matching method of analysis was not used in these studies. In China, people aged ≥60 years are defined as the elderly. It is unknown whether the incidence of diabetes after the age of 60 years also brings a difference in complications. So, the aim of the present study was to determine if a clear difference between clinical features and vascular complications existed between EOD and LOD patients in two different age groups according to an onset age of 40 or 60 years.

MATERIALS AND METHODS
Study population and cohort
From March 2010 to July 2017, a total of 3,568 patients with type 2 diabetes mellitus were recruited at the Endocrinology Department of the First Affiliated Hospital of Fujian Medical University. The patients were divided into two groups according to an onset age of 40 or 60 years (EOD$_{40}$ and LOD$_{40}$ refer to the onset age before 40 years old and after 40 years, respectively; EOD$_{60}$ and LOD$_{60}$ refer to the onset age before 60 years and after 60 years, respectively). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex, yielding a total of 780 participants in the 40 years group: 520 participants in the LOD$_{40}$ group and 260 participants in the EOD$_{40}$ group. A total of 537 participants in the 60 years group: 358 participants in the LOD$_{60}$ group and 179 participants in the EOD$_{60}$ group (SAS Institute Inc., Cary, NC). The diagnostic criteria for type 2 diabetes mellitus were based on the 1999 World Health Organization's criteria[17]. The exclusion criteria were as follows: (i) type 1 diabetes, gestational diabetes or any other special types of diabetes, as such patients are prone to developing acute complications, such as diabetic ketoacidosis and heavy ketonuria; (ii) renal disease: this includes all kinds of acute or chronic glomerulonephritis, nephrotic syndrome, and acute and chronic renal failure; and (iii) neuropathy: this includes all kinds of neurotoxic effects: familial, alcoholic, nutritional, uremic, toxic and drug-induced. This study was approved by the Ethics Committee of Biomedical Research of the First Affiliated Hospital of Fujian Medical University, and all the participants provided signed informed consent.

Clinical measurements
By carrying out a detailed inquiry of patient history, the following information was obtained: sex, age, duration of diabetes, medical history, hypertension and Toronto Clinical Scoring System neurological symptoms (numbness in lower extremities, pain in lower extremities, pricking, fatigue, difficulty in walking and upper limb symptoms). Physical examination parameters were as follows: height, weight, waist circumference, hip circumference, blood pressure, neurological examination and ophthalmic examination. Body mass index (BMI; kg/m^2) = bodyweight (kg) / height^2 (m^2). Body surface area (BSA; m^2) = (men: $0.0067 \times$ height [m] + $0.0127 \times$ bodyweight [kg] − 0.0698; women: $0.00586 \times$ height [m] + $0.0126 \times$ bodyweight [kg] − 0.0461). Measurement of standardized systolic blood pressure and diastolic blood pressure was carried out after a rest of 15 min. Acupuncture was used to detect the severity of pain; 10 g of nylon silk was used for tactile sensation; a temperature sensation tester was used to determine temperature sensation; a standard 128-kHz tuning fork test was used for vibration sensation; and a tendon hammer was used to check iliac reflexes[18]. After the dilation of the pupils, the fundi of the eyes were examined by a professional ophthalmologist.

Biochemical measurements
Fasting blood glucose, serum creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol and glycated hemoglobin (HbA1c) were analyzed. The HbA1c assay was determined by high-performance liquid chromatography (Variant TM II; Bio-Rad, Hercules, CA, USA). Urinary albumin-to-creatinine ratio was calculated by dividing the urine albumin by urine creatinine during mid-morning urine collection (mg/g). The estimated glomerular filtration rate (eGFR) was calculated by the dietary modification formula for kidney disease: eGFR = $186 \times$ (creatinine [μmol/L] / 88.41) − $1.154 \times$ age − 0.203 ($\times 0.742$, female)[19].

Ultrasonic measurements
Carotid intima-media thickness, bilateral common carotid arteries, the bifurcation between both the common carotid arteries and bilateral subclavian intima-media thickness were measured with a Prosound α-10 color Doppler ultrasound system (ALOKA). To determine whether there is plaque adhesion between the bilateral common carotid artery, internal carotid artery, external carotid artery and subclavian artery, the transverse and longitudinal sections of ALOKA were scanned. The frequency of the probe was 5–13 MHz. The ankle-brachial index (ABI) was carried out using Vista AVS, which is a peripheral vascular diagnostic system (U.S. summit company, White Plains, NY, USA). To measure systolic pressure of the bilateral brachial and radial artery, the patient was asked to lie down for 15 min and then exercise, respectively. The frequency of the probe was 8 MHz. These steps follow the AHA statement[20]. The formula for determining the ABI is as follows: ABI = ankle artery systolic pressure (mmHg) / brachial artery systolic pressure (mmHg). Echocardiographic measurements were as follows: left ventricular diastolic diameter (LVDd),

interventricular septal thickness (IVST) and left ventricular posterior wall end-diastolic thickness (LVPWT) were measured with two-dimensional Doppler echocardiography with Vivid 7 digital ultrasound system (GE-Vingmed Ultrasound, Horten, Norway). Early diastolic velocity (E), early diastolic annual velocities (e) and lateral e were determined in the apical four chamber view of these systems. The average "e" is the average of septal e and lateral e. Left ventricular mass (LVM) was calculated using the Devereux formula: LVM (g) = 0.8 × {1.04 × [(LVDd + IVST + LVPWT) 3 − LVDd3]} + 0.6 × LVMI (g/m^2)) = LVM / BSA. The relative thickness of left ventricular wall = (LVPWT + IVST)/LVDd[21].

Metabolic index
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or taking antihypertensive drugs[22]. Proteinuria: albumin : creatinine ratio (ACR) ≥30 mg/g[23]. Targets of metabolic control: HbA1c concentration <7%, low-density lipoprotein cholesterol <2.6 mmol/L and BMI <24 kg/m^2[24].

Microvascular complications
In the year 2014, the American Diabetes Association and the National Kidney Foundation defined the criteria for chronic kidney disease (CKD) for patients with type 2 diabetes mellitus and albuminuria (ACR >30 mg/g at least twice in 3–6 months and/or eGFR <60 mL/min/1.73 m^2); they excluded the possibility of another injured kidney[24,25]. To determine DR, physicians examined the fundus of the eye after the dilation of the pupil; some of the typical retinal changes are as follows: microhemangioma, hemorrhaging, exudate and vitrectomy[25,26]. The diagnosis criteria for diabetic peripheral neuropathy (DPN) are as follows[27]: (i) clear history of diabetes; (ii) diagnosis of peripheral neuropathy during or after diabetes; (iii) clinical symptoms and signs that coincide with the performance of DPN; and (iv) patients with clinical symptoms, such as pain, numbness and paresthesia. These patients were examined by any one of the following five processes: acupuncture analgesia, touch–pressure sensation, temperature sensation, vibration sensation or tendon reflexes. There were patients that did not show any clinical symptoms (other causes of diabetic neuropathy were excluded).

Macrovascular complications
Carotid atherosclerosis (CAS), while carrying out vascular longitudinal and cross-sectional scans, was defined as follows: an echogenic structure that protrudes into the lumen, a blood flow defect that protrudes into the lumen and a local intima-media thickness ≥1.3 mm[28]. Lower extremity atherosclerosis was defined as follows: resting ABI ≤0.9 or ABI after exercise ≥15% in either side of the lower extremities[20]. Cardiovascular structural lesions: left ventricular remodeling: left ventricular mass index >115 g/m^2 (in men), 95 g/m^2 (in women) or relative thickness of the left ventricular wall >0.42[29]. Left ventricular diastolic dysfunction: E/e > 15 or the average e < 0.09 m/s

(when E/e = 8–15)[30]. The 10-year risk score for coronary heart disease (Framingham risk score) was derived from the Framingham Heart Study, which calculated the risk of developing a coronary heart attack in the next 10 years based on the following factors: age, total cholesterol, history of smoking, high-density lipoprotein cholesterol and systolic blood pressure.

Statistical analysis
All statistical analyses were carried out using Statistical Analysis System (SAS; SAS Institute, Cary, NC, USA) and SPSS version 18 software (SPSS, Chicago, IL, USA). The median (interquartile range) was used to describe non-normal distribution data; the mean ± standard deviation (SD) was used to describe the data of normal distribution, and count variables data were described by percentages. Normal distribution of continuous variables was tested with a Student's t-test. Non-normal distribution of continuous variables was determined by analysis of a rank-sum test. The Pearson χ^2-test was used for classifying variables. To determine the correlation between EOD and LOD patients, diabetic vascular complications were analyzed by a two-classification logistic regression model. Statistical significance was determined by $P < 0.05$.

RESULTS
Population characteristics
Baseline characteristics after propensity score matching
A total of 3,568 patients with type 2 diabetes mellitus were recruited (Table 1). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex, yielding a total of 780 participants in the 40 years group: 520 participants in the LOD$_{40}$ group and 260 participants in the EOD$_{40}$ group. A total of 537 participants in the 60 years group: 358 participants in the LOD$_{60}$ group and 179 participants in the EOD$_{60}$ group. The results are shown in Table 1. In addition, compared with LOD$_{40}$ patients, EOD$_{40}$ patients had higher Toronto Clinical Scoring System and ACR scores. However, eGFR values of EOD$_{40}$ patients were lower than those of LOD$_{40}$ patients. Meanwhile, the prevalence of DR, CKD and DPN was higher in EOD$_{40}$ patients ($P < 0.05$). The same trend was seen in EOD$_{60}$ patients.

Furthermore, compared with LOD$_{40}$ patients, EOD$_{40}$ patients had higher systolic blood pressure; therefore, EOD$_{40}$ patients were more likely to use antihypertensive drugs and used a lipid-lowering strategy. Moreover, the prevalence of CAS was higher in EOD$_{40}$ patients.

Comparison in the prevalence of vascular complications for EOD and LOD groups after matching
Compared with LOD patients, EOD patients had a significantly higher prevalence of microvascular complications (DR, CKD and DPN; EOD$_{40}$ vs LOD$_{40}$: 39.2% vs 15.6%, $P < 0.001$; 57.3% vs 38.5%, $P < 0.001$; 34.2% vs 21.5%, $P < 0.001$; EOD$_{60}$ vs LOD$_{60}$: 26.8% vs 16.5%, $P = 0.005$; 42.9% vs 27.9%, $P = 0.001$; 40.8% vs 26%, $P < 0.001$). However, no statistical difference

Table 1 | Patient characteristics after propensity score matching

	Diabetes onset age by 40 years group			Diabetes onset age 60 years group		
	All (n = 780)	LOD$_{40}$ group (n = 520)	EOD$_{40}$ group (n = 260)	All (n = 537)	LOD$_{60}$ group (n = 358)	EOD$_{60}$ group (n = 179)
Male, n (%)	372 (47.7%)	247 (47.5%)	125 (48.1%)	268 (49.9%)	175 (48.9%)	93 (52%)
Age (years)	53.32 ± 6.18	53.44 ± 6.08	53.08 ± 6.37	75.26 ± 3.83	75.27 ± 3.81	75.24 ± 3.88
DM duration (years)	8 (3,13)	5 (1,8)	15 (10,20)*	10 (4,18)	6 (2,10)	20 (17,23)*
HT history, n (%)	339 (43.5%)	206 (39.6%)	133 (51.2%)*	382 (71.1%)	255 (71.2%)	127 (70.9%)
Biguanides, n (%)	433 (55.5%)	269 (51.7%)	164 (63.1%)*	280 (52.1%)	179 (50%)	101 (56.4%)
Insulin secretogue, n (%)	436 (55.9%)	285 (54.8%)	151 (58.1%)	328 (61.1%)	205 (57.3%)	123 (68.7%)*
Other oral hypoglycemic drugs, n (%)	139 (17.8%)	79 (15.2%)	60 (23.1%)*	258 (48%)	152 (42.5%)	106 (59.2%)*
Insulin, n (%)	329 (42.2%)	164 (31.5%)	165 (63.5%)*	202 (37.6%)	99 (27.7%)	103 (57.5%)*
Antihypertensive drugs, n (%)	215 (27.6%)	128 (24.6%)	87 (33.5%)*	231 (43%)	144 (40.2%)	87 (48.6%)
Lipid-lowering, n (%)	56 (7.2%)	28 (5.4%)	28 (10.8%)*	55 (10.2%)	32 (8.9%)	23 (12.8%)
SBP (mmHg)	135.01 ± 19.88	132.85 ± 18.3	139.32 ± 22.11*	142.88 ± 21.25	143.1 ± 19.64	142.42 ± 24.21
DBP (mmHg)	79.89 ± 10.69	79.77 ± 10.48	80.13 ± 11.13	75.28 ± 11.75	76.93 ± 10.16	71.97 ± 13.88*
BMI (kg/m^2)	24.25 ± 3.76	24.14 ± 3.67	24.46 ± 3.94	24.95 ± 3.63	25 ± 3.79	24.83 ± 3.3
HbA1c (%)	9.45 ± 2.56	9.49 ± 2.68	9.36 ± 2.3	9.15 ± 2.43	9.26 ± 2.57	8.93 ± 2.14
TCH (mmol/L)	4.85 ± 1.31	4.87 ± 1.26	4.82 ± 1.41	4.46 ± 1.25	4.56 ± 1.24	4.25 ± 1.25*
LDL (mmol/L)	3.02 ± 1.11	3.03 ± 1.06	3 ± 1.19	2.74 ± 1.06	2.82 ± 1.07	2.59 ± 1.03*
TG (mmol/L)	1.4 (1,2.11)	1.44 (1.05,2.07)	1.32 (0.89,2.25)	1.58 ± 1.26	1.69 ± 1.43	1.35 ± 0.81*
BP <140/90 mmHg, n (%)	466 (59.7%)	333 (64%)	133 (51.2%)*	215 (40.3%)	142 (39.8%)	73 (41.2%)
BMI <24 kg/m^2, n (%)	375 (50.3%)	262 (52.3%)	113 (46.3%)	199 (41.4%)	125 (38.6%)	74 (47.1%)
HbA1c <7%, n (%)	128 (16.8%)	90 (17.7%)	38 (15.1%)	108 (21.1%)	73 (21.5%)	35 (20.2%)
LDL <2.6 mmol/L, n (%)	291 (38.1%)	190 (37.5%)	101 (39.5%)	253 (48.7%)	157 (45.6%)	96 (54.5%)
Left ABI (at rest)	1.08 ± 0.1	1.09 ± 0.09	1.07 ± 0.12	1.03 ± 0.19	1.03 ± 0.19	1.01 ± 0.2
Right ABI (at rest)	1.09 ± 0.12	1.09 ± 0.12	1.09 ± 0.11	1.05 ± 0.24	1.06 ± 0.25	1.03 ± 0.2
Left ABI (after exercise)	1.06 ± 0.12	1.07 ± 0.13	1.03 ± 0.11	1.08 ± 0.13	1.11 ± 0.13	1.04 ± 0.11
Right ABI (after exercise)	1.07 ± 0.14	1.09 ± 0.14	1.04 ± 0.11*	1.06 ± 0.12	1.06 ± 0.13	1.06 ± 0.08
RWT	0.4 ± 0.06	0.39 ± 0.05	0.4 ± 0.06*	0.42 ± 0.06	0.42 ± 0.06	0.42 ± 0.06
LVM (g)	140 ± 38.23	138.59 ± 38.8	142.68 ± 37.07	157.08 ± 49.49	154.86 ± 41.53	161.37 ± 61.97
PVE/e	9.58 ± 3.55	9.2 ± 2.94	10.38 ± 4.47*	11.8 ± 4.4	11.5 ± 4.35	12.39 ± 4.46
Average e (m/s)	0.08 ± 0.02	0.08 ± 0.02	0.07 ± 0.02	0.07 ± 0.08	0.07 ± 0.07	0.07 ± 0.1
LVMI	145.72 ± 81.06	144.4 ± 80.78	148.35 ± 81.76	90.53 ± 27.5	88.71 ± 22.18	94.34 ± 36.16
Framingham score (%)	6.62 ± 7.04	6.44 ± 6.94	6.98 ± 7.24	19.65 ± 8.01	19.67 ± 7.87	19.61 ± 8.28
CAS, n (%)	134 (24.6%)	82 (22.1%)	52 (29.9%)*	141 (40.6%)	92 (40.2%)	49 (41.5%)
LEA, n (%)	107 (18.1%)	70 (17.9%)	37 (18.5%)	83 (21.9%)	54 (20.7%)	29 (24.6%)
LVDD, n (%)	201 (51.8%)	133 (50.6%)	68 (54.4%)	220 (90.5%)	146 (90.1%)	74 (91.4%)
LVR, n (%)	402 (67.2%)	263 (66.8%)	139 (68.1%)	136 (69.7%)	90 (67.7%)	46 (74.2%)
Cr (mmol/L)	58 (46.4,70.2)	56.5 (46,67.85)	60.15 (48,76.18)*	66.55 (53,87)	64.4 (52,83.6)	70.6 (58.6,91.9)*
ACR (mg/g)	14.23 (6.63,91.31)	11.82 (6.3,31.17)	27.82 (7.65,418.51)*	20.99 (9.28,112.3)	18.84 (9.15,47.25)	38.56 (9.35,517.71)*
eGFR (mL/min/1.73 m^2)	118.03 (94.68,143.08)	119.9 (97.52,143.9)	112.89 (90.14,137.91)*	92.23 (71.38,118.98)	96.09 (73.79,121.23)	84.57 (66.15,114.49)*
Albuminuria, n (%)	162 (33.1%)	82 (25.1%)	80 (49.4%)*	129 (40.3%)	69 (33.5%)	60 (52.6%)*
TCSS score	3.16 ± 3.78	2.73 ± 3.57	4 ± 4.04*	3.67 ± 3.9	3.18 ± 3.7	4.62 ± 4.1*

Table 1. *(Continued)*

	Diabetes onset age by 40 years group			Diabetes onset age 60 years group		
	All (n = 780)	LOD$_{40}$ group (n = 520)	EOD$_{40}$ group (n = 260)	All (n = 537)	LOD$_{60}$ group (n = 358)	EOD$_{60}$ group (n = 179)
DR, n (%)	183 (23.5%)	81 (15.6%)	102 (39.2%)*	107 (19.9%)	59 (16.5%)	48 (26.8%)*
CKD, n (%)	349 (44.7%)	200 (38.5%)	149 (57.3%)*	175 (32.6%)	100 (27.9%)	75 (41.9%)*
DPN, n (%)	201 (25.8%)	112 (21.5%)	89 (34.2%)*	166 (30.9%)	93 (26%)	73 (40.8%)*

ABI, ankle-brachial index; ACR, albumin : creatinine ratio; BMI, body mass index; BP, blood pressure; CAS, carotid atherosclerosis; CKD, chronic kidney disease; Cr, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; EOD$_{40}$, early-onset diabetes, onset age before 40 years-of-age; EOD$_{60}$, early-onset diabetes, onset age before 60 years-of-age; HbA1c, glycated hemoglobin; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; LEA, lower extremity atherosclerosis; LOD$_{40}$, late-onset diabetes, onset age after 40 years-of-age; LOD$_{60}$, late-onset diabetes, onset age after 60 years-of-age; LVDD, left ventricular diastolic dysfunction; LVM, left ventricular mass; LVMI, left ventricular mass index; LVR, left ventricular remodeling; PVE, peak mitral velocity E; RWT, relative thickness of left ventricular wall; SBP, systolic blood pressure; TCH, total cholesterol; TCSS, Toronto Clinical Scoring System; TG, triglycerides. *P < 0.05.

was observed in the prevalence of macrovascular complications, except for CAS. The prevalence of CAS was higher in EOD$_{40}$ patients (EOD$_{40}$ vs LOD$_{40}$: 29.9% vs 22.1%, P = 0.049; Table 1; Figure 1).

Correlation between onset age and vascular complications in diabetes patients

Binary regression analysis was carried out to determine the association between onset age and vascular complications in patients with diabetes (Figure 2). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex. Furthermore, adjustments for differences in the following parameters were made: HbA1c%, insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of hypertension. Compared with LOD$_{40}$ patients, the odds ratio for the prevalence of microvascular complications for DR, CKD and SN in EOD$_{40}$ patients was 2.906 (95% confidence interval [CI] 1.972–4.282), 1.967 (95% CI 1.387–2.791) and 1.672 (95% CI 1.152–2.429), respectively. Meanwhile, the odds ratio for the prevalence of DR and DPN in EOD$_{60}$ patients was 1.763 (95% CI 1.092–2.847) and 1.675 (95% CI 1.106–2.537), respectively. However, there were no statistically significant differences in macrovascular complications of EOD and LOD patients (Figure 2). A significant association between onset age and microvascular complications was found regardless of blood pressure, BMI or HbA1c value. The risks of vascular complications with onset age in different subgroups of patients with type 2 diabetes mellitus are shown (Figure 3).

DISCUSSION

The results of the present study show that early-onset age of type 2 diabetes mellitus increases the risk of microvascular complications later in life. Compared with late-onset type 2 diabetes mellitus, people with early-onset type 2 diabetes mellitus have a significantly higher risk of developing microvascular complications.

It was found in previous studies that patients with early-onset of type 2 diabetes mellitus had a higher risk of developing cardiovascular disease and a higher cardiac 10-year expected risk than patients with late-onset type 2 diabetes mellitus. Neither study was age or sex matched, nor were any other confounding variables considered[7,14–16].

Propensity score matching was carried out in the present study to adjust for differences in age and sex. It was found that there was no independent correlation between the onset age of type 2 diabetes mellitus and the following macrovascular complications: organic cardiopathy, carotid atherosclerosis or lower extremity atherosclerosis. This relationship can still be maintained after adjusting various related confounding factors.

Several epidemiological studies have reported that the risk of developing cardiovascular complications is higher in EOD patients. The occurrence and progression of vascular complications is also greater in EOD patients[7,9,14–16]. In EOD patients,

the risk of developing macrovascular events and death increases proportionally with decreases in age of diagnosis or duration of diabetes[8]. For example, a study carried out on white individuals presented the following results. Compared with LOD patients, the risk of developing myocardial infarction was 14-fold greater in EOD patients (≥45 years onset age)[7]. A data registry from Hong Kong also showed that EOD patients have a higher risk of developing CVD in all age groups[30].

An Australian study[8] showed that the increased death risk of early-onset type 2 diabetes mellitus is closely related with CVD. Hyperglycemia, diabetes duration, dyslipidemia, hypertension and insulin resistance were risk factors for developing diabetic CVD[10–13]. Gunathilake et al.[31] found that EOD patients (average age of diagnosis was 34 years) already have a higher risk of developing cardiovascular complications (obesity, hyperlipidemia and hypertension). These complications are similar to those observed in older patients with type 2 diabetes mellitus (the average age of diagnosis is 67 years).

Several studies have reported that obesity, dyslipidemia, hypertension and microalbuminuria are common in young type 2 diabetes mellitus patients. These complications can worsen over a certain period of time[32,33]. The risk of developing macrovascular complications increases in EOD patients because of prolonged duration of diabetes and the fact that metabolic profiles of EOD patients worsen over time[14,15].

In the aforementioned studies, the effects of age and sex were reduced by the method of adjustment. For example, a large cross-sectional study was carried out by CNHSS (National
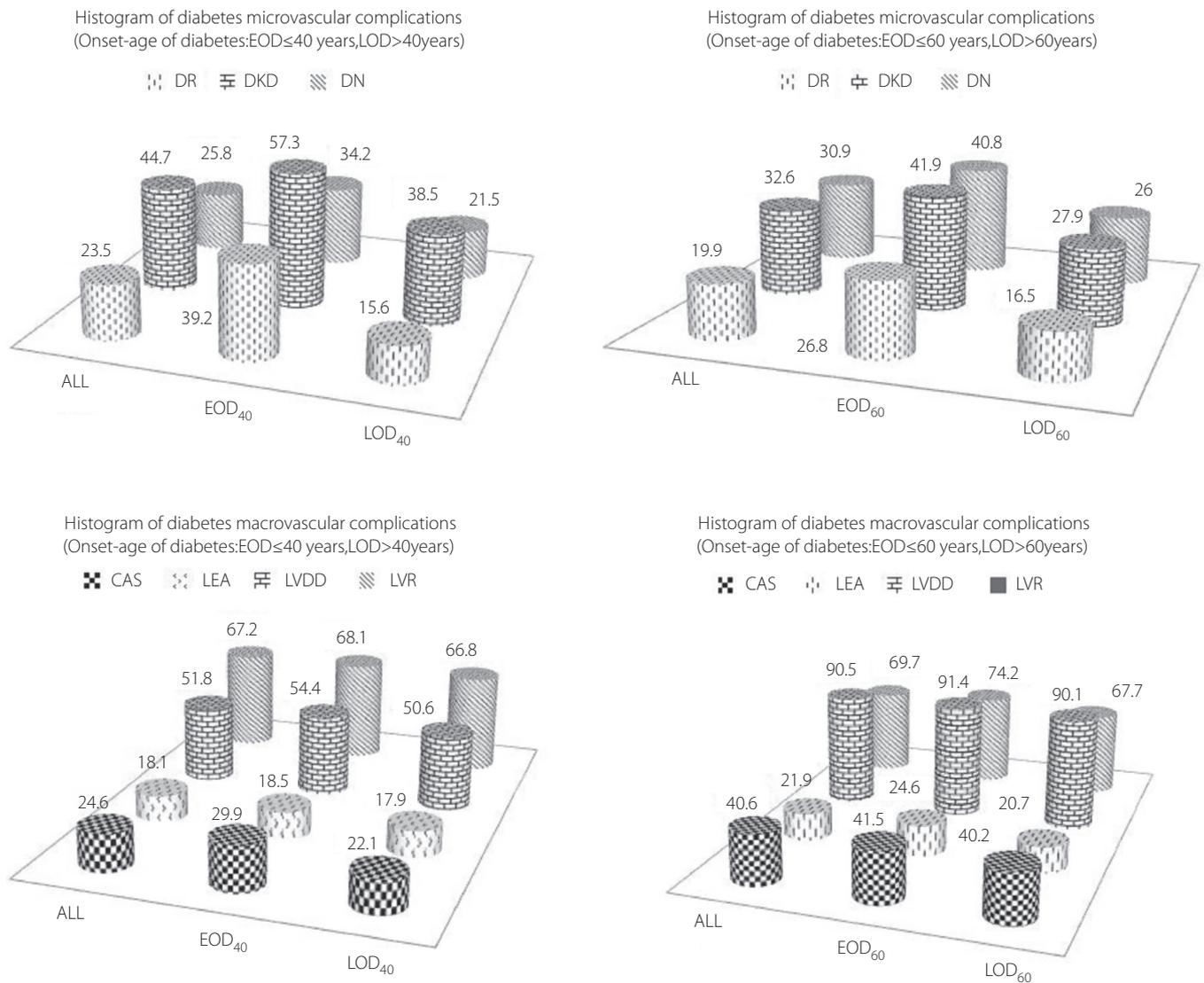

Figure 1 | Distribution of vascular complications in type 2 diabetes mellitus between the onset years of 40 and 60 years of in the early-onset diabetes (EOD) group and late-onset diabetes (LOD) group.

HbAlc% Surveillance System in China). The results showed that compared with EOD patients, the risk of developing cardiovascular complications was higher in LOD patients. Compared with LOD patients, EOD patients have a significantly higher risk of developing non-fatal cardiovascular events in all age groups; this is because EOD patients have to manage diabetes over a longer period of time and their body is exposed to damaging high-glucose conditions over a longer period of time. Subsequently, the metabolic conditions of EOD patients deteriorate over a period of time. Various factors that influence the condition of EOD patients have been taken into consideration[14].

In the present study, propensity score matching was used to eliminate the effects of age and sex. Patients who were categorized in the both age EOD groups had a significantly higher risk of developing macro- and microvascular complications before PSM. After PSM, it was found that the risk of developing macrovascular complications does not increase in EOD patients. Both young and elderly patients are at an equal risk of developing cardiovascular complications. In patients with type 2 diabetes mellitus, the risk of developing macrovascular

complications is not related to onset age of diabetes or diabetes duration. However, it was found that left ABI (after exercise), R relative thickness of the left ventricular wall WT, peak mitral velocity E (PVE/e) and other macrovascular indicators were higher in EOD patients. Compared with EOD patients, LOD patients have a greater risk of developing macrovascular diseases. Blood vessels tend to harden with age, so the probability of vascular events also increases with age[34]. Therefore, it is suggested that there is a close relationship between the risk of diabetic macrovascular complications and age.

Several previous studies have shown that compared with LOD patients, EOD patients have a higher risk of developing microvascular complications, including diabetic nephropathy, DR and diabetic neuropathy[6,31,35]. Previous studies have reported that EOD patients suffer from this disease for a longer duration of time, because they develop severe metabolic disorders due to higher amounts of glucose and fat in their bloodstream. This causes oxidative stress, which activates the renin–angiotensin system. These events finally lead to the development of microvascular complications in EOD patients[35,36]. In the present study, no significant difference was
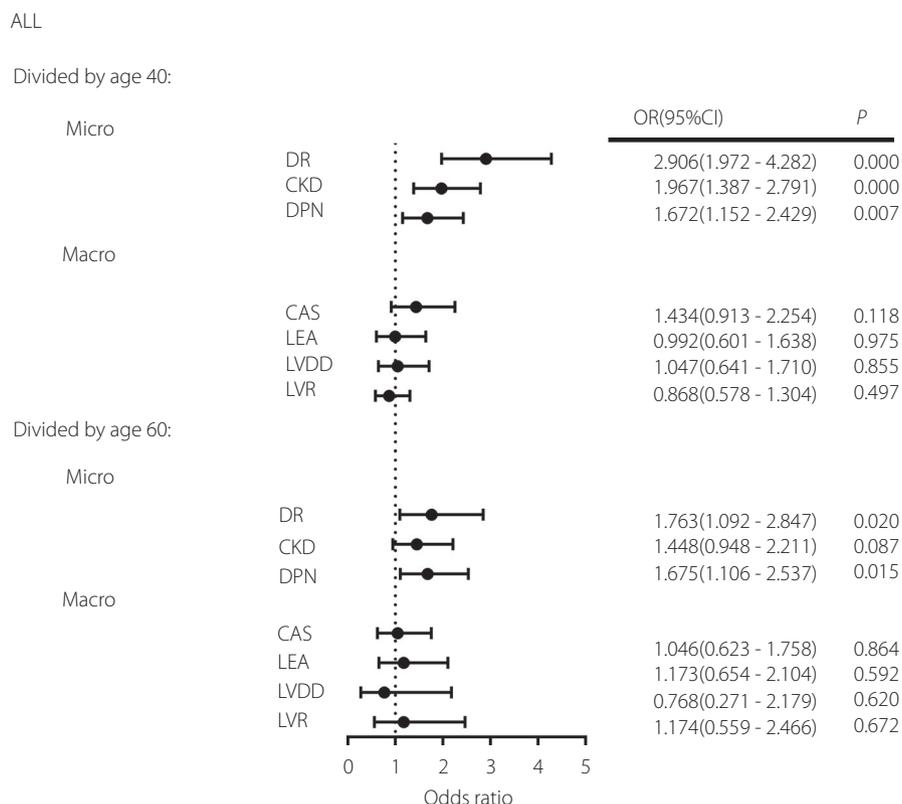
Figure 2 | Forest plot of the risk of vascular complications of type 2 diabetes mellitus between early-onset diabetes and late-onset diabetes patients. A fully adjusted model including the following parameters: percentage glycated hemoglobin (HbA1c%), insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of hypertension. CAS, carotid atherosclerosis; CI, confidence interval; CKD, chronic kidney disease; DPN, diabetic peripheral neuropathy; DR, include diabetic retinopathy; EOD, early-onset diabetes; LEA, lower extremity atherosclerosis; LOD, late-onset diabetes; LVDD, left ventricular diastolic dysfunction; LVR, left ventricular remodeling; OR, odds ratio.

(a) BP<140/90mmHg

Divided by age 40		OR(95%CI)	P
Micro	DR	2.516(1.461 - 4.334)	0.001
	CKD	2.156(1.345 - 3.456)	0.001
	DPN	1.452(0.852 - 2.477)	0.171
Macro			
	CAS	1.545(0.822 - 2.906)	0.117
	LEA	1.227(0.632 - 2.382)	0.546
	LVDD	0.914(0.476 - 1.756)	0.787
	LVR	0.744(0.438 - 1.263)	0.273
Divided by age 60			
Micro	DR	1.626(0.747 - 3.537)	0.220
	CKD	1.743(0.864 - 3.516)	0.121
	DPN	2.490(1.292 - 4.797)	0.006
Macro			
	CAS	1.369(0.596 - 3.143)	0.459
	LEA	0.895(0.321 - 2.494)	0.832
	LVDD	0.203(0.035 - 1.190)	0.077
	LVR	1.028(0.324 - 3.259)	0.962

Odds ratio

(b) BP≥140/90mmHg

Divided by age 40		OR(95%CI)	P
Micro	DR	3.348(1.889 - 5.933)	0.000
	CKD	1.559(0.900 - 2.700)	0.113
	DPN	1.849(1.077 - 3.172)	0.026
Macro			
	CAS	1.339(0.692 - 2.589)	0.386
	LEA	0.687(0.310 - 1.524)	0.356
	LVDD	1.449(0.640 - 3.280)	0.374
	LVR	1.105(0.572 - 2.135)	0.766
Divided by age 60			
Micro	DR	1.897(1.016 - 3.542)	0.044
	CKD	1.348(0.774 - 2.350)	0.292
	DPN	1.245(0.708 - 2.190)	0.466
Macro			
	CAS	0.880(0.437 - 1.773)	0.720
	LEA	1.272(0.604 - 2.677)	0.527
	LVDD	1.172(0.250 - 5.488)	0.841
	LVR	2.154(0.713 - 6.510)	0.174

Odds ratio

(c) BP<24kg/m²

Divided by age 40		OR(95%CI)	P
Micro	DR	2.777(1.627 - 4.740)	0.000
	CKD	2.029(1.222 - 3.369)	0.006
	DPN	1.638(0.955 - 2.808)	0.073
Macro			
	CAS	1.375(0.691 - 2.737)	0.364
	LEA	0.885(0.426 - 1.842)	0.745
	LVDD	1.184(0.587 - 2.389)	0.636
	LVR	1.060(0.598 - 1.880)	0.842
Divided by age 60			
Micro	DR	1.891(0.844 - 4.236)	0.122
	CKD	3.088(1.441 - 6.618)	0.004
	DPN	2.352(1.182 - 4.678)	0.015
Macro			
	CAS	1.297(0.578 - 2.912)	0.528
	LEA	2.402(0.847 - 6.814)	0.099
	LVDD	1.359(0.276 - 6.690)	0.706
	LVR	2.268(0.699 - 7.356)	0.173

Odds ratio

(d) BMI≥24kg/m²

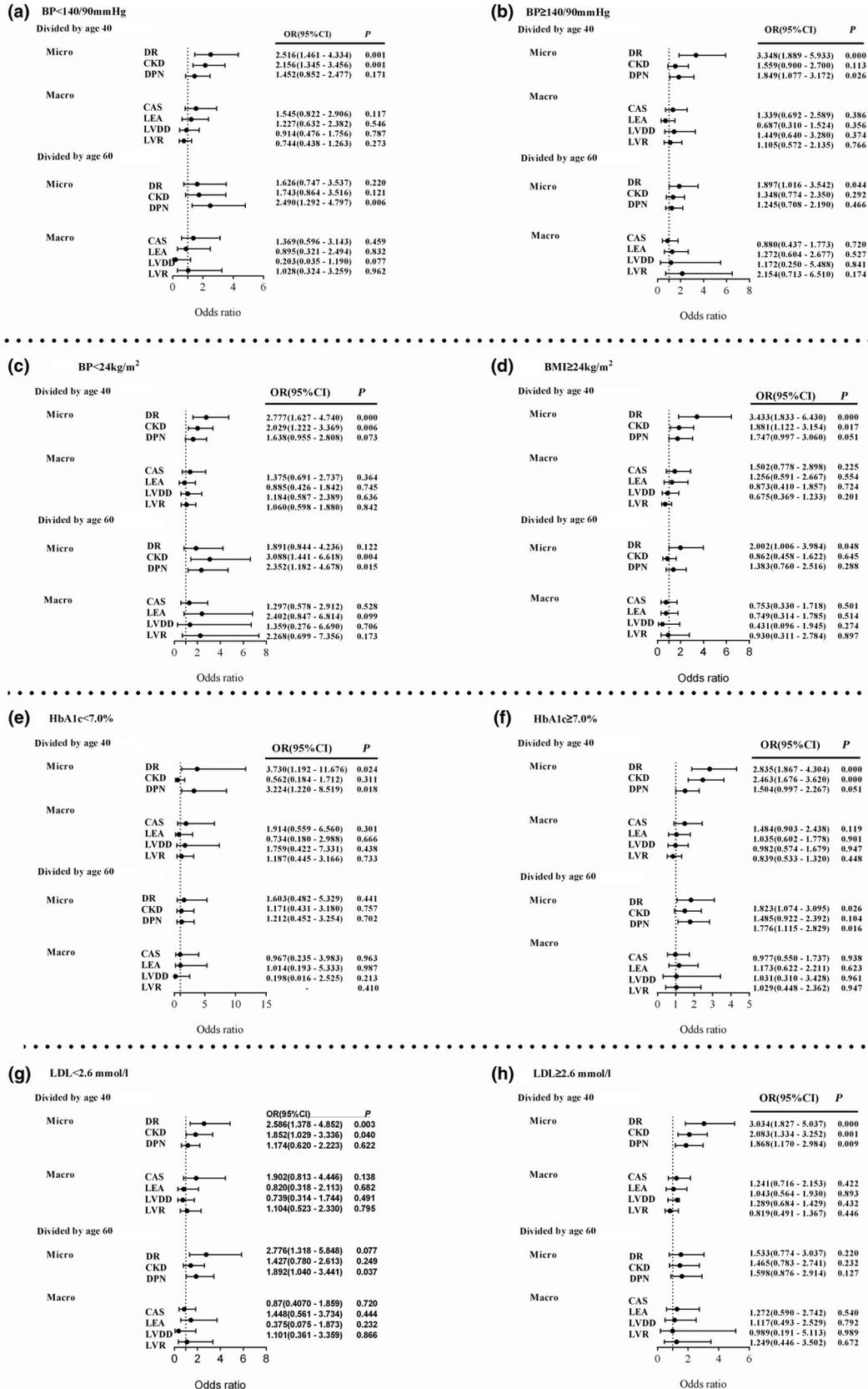| Divided by age 40		OR(95%CI)	P
Micro	DR	3.433(1.833 - 6.430)	0.000
	CKD	1.881(1.122 - 3.154)	0.017
	DPN	1.747(0.997 - 3.060)	0.051
Macro			
	CAS	1.502(0.778 - 2.898)	0.225
	LEA	1.256(0.591 - 2.667)	0.554
	LVDD	0.873(0.410 - 1.857)	0.724
	LVR	0.675(0.369 - 1.233)	0.201
Divided by age 60			
Micro	DR	2.002(1.006 - 3.984)	0.048
	CKD	0.862(0.458 - 1.622)	0.645
	DPN	1.383(0.760 - 2.516)	0.288
Macro			
	CAS	0.753(0.330 - 1.718)	0.501
	LEA	0.749(0.314 - 1.785)	0.514
	LVDD	0.431(0.096 - 1.945)	0.274
	LVR	0.930(0.311 - 2.784)	0.897

Odds ratio

(e) HbA1c<7.0%

Divided by age 40		OR(95%CI)	P
Micro	DR	3.730(1.192 - 11.676)	0.024
	CKD	0.562(0.184 - 1.712)	0.311
	DPN	3.224(1.220 - 8.519)	0.018
Macro			
	CAS	1.914(0.559 - 6.560)	0.301
	LEA	0.734(0.180 - 2.988)	0.666
	LVDD	1.759(0.422 - 7.331)	0.438
	LVR	1.187(0.445 - 3.166)	0.733
Divided by age 60			
Micro	DR	1.603(0.482 - 5.329)	0.441
	CKD	1.171(0.431 - 3.180)	0.757
	DPN	1.212(0.452 - 3.254)	0.702
Macro			
	CAS	0.967(0.235 - 3.983)	0.963
	LEA	1.014(0.193 - 5.333)	0.987
	LVDD	0.198(0.016 - 2.525)	0.213
	LVR	-	0.410

Odds ratio

(f) HbA1c≥7.0%

Divided by age 40		OR(95%CI)	P
Micro	DR	2.835(1.867 - 4.304)	0.000
	CKD	2.463(1.676 - 3.620)	0.000
	DPN	1.504(0.997 - 2.267)	0.051
Macro			
	CAS	1.484(0.903 - 2.438)	0.119
	LEA	1.035(0.602 - 1.778)	0.901
	LVDD	0.982(0.574 - 1.679)	0.947
	LVR	0.839(0.533 - 1.320)	0.448
Divided by age 60			
Micro	DR	1.823(1.074 - 3.095)	0.026
	CKD	1.485(0.922 - 2.392)	0.104
	DPN	1.776(1.115 - 2.829)	0.016
Macro			
	CAS	0.977(0.550 - 1.737)	0.938
	LEA	1.173(0.622 - 2.211)	0.623
	LVDD	1.031(0.310 - 3.428)	0.961
	LVR	1.029(0.448 - 2.362)	0.947

Odds ratio

(g) LDL<2.6 mmol/l

Divided by age 40		OR(95%CI)	P
Micro	DR	2.586(1.378 - 4.852)	0.003
	CKD	1.852(1.029 - 3.336)	0.040
	DPN	1.174(0.620 - 2.223)	0.622
Macro			
	CAS	1.902(0.813 - 4.446)	0.138
	LEA	0.820(0.318 - 2.113)	0.682
	LVDD	0.739(0.314 - 1.744)	0.491
	LVR	1.104(0.523 - 2.330)	0.795
Divided by age 60			
Micro	DR	2.776(1.318 - 5.848)	0.077
	CKD	1.427(0.780 - 2.613)	0.249
	DPN	1.892(1.040 - 3.441)	0.037
Macro			
	CAS	0.87(0.4070 - 1.859)	0.720
	LEA	1.448(0.561 - 3.734)	0.444
	LVDD	0.375(0.075 - 1.873)	0.232
	LVR	1.101(0.361 - 3.359)	0.866

Odds ratio

(h) LDL≥2.6 mmol/l

Divided by age 40		OR(95%CI)	P
Micro	DR	3.034(1.827 - 5.037)	0.000
	CKD	2.083(1.334 - 3.252)	0.001
	DPN	1.868(1.170 - 2.984)	0.009
Macro			
	CAS	1.241(0.716 - 2.153)	0.422
	LEA	1.043(0.564 - 1.930)	0.893
	LVDD	1.289(0.684 - 1.429)	0.432
	LVR	0.819(0.491 - 1.367)	0.446
Divided by age 60			
Micro	DR	1.533(0.774 - 3.037)	0.220
	CKD	1.465(0.783 - 2.741)	0.232
	DPN	1.598(0.876 - 2.914)	0.127
Macro			
	CAS	1.272(0.590 - 2.742)	0.540
	LEA	1.117(0.493 - 2.529)	0.792
	LVDD	0.989(0.191 - 5.113)	0.989
	LVR	1.249(0.446 - 3.502)	0.672

Odds ratio

Figure 3 | Forest plot of risk of vascular complications with onset age in different subgroups of patients with type 2 diabetes mellitus. A fully adjusted model including the following parameters: insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of hypertension. BMI, body mass index; BP, blood pressure; CI, confidence interval; CAS, carotid atherosclerosis; CKD, chronic kidney disease; DPN, diabetic peripheral neuropathy; DR, include diabetic retinopathy; EOD, early-onset diabetes; HbA1c, glycated hemoglobin; LEA, lower extremity atherosclerosis; LOD, late-onset diabetes; LVDD, left ventricular diastolic dysfunction; LVR, left ventricular remodeling; OR, odds ratio.

observed in the HbA1c and lipid profiles of EOD and LOD patients. Compared with LOD patients, EOD patients required greater doses of insulin and lipid-lowering drugs. This was probably related to benefits from drug use. Furthermore, EOD patients have relatively poor metabolic control (BP $\geq$140/90 mmHg, BMI $\geq$24 kg/m^2, HbAlc% $\geq$7.0%, and low-density lipoprotein cholesterol $\geq$2.6 mmol/L). In the elderly population, there was no significant risk of developing microvascular complications in EOD patients compared with LOD patients. This is because the elderly population is more susceptible to developing hypertension and using antihypertensive drugs. There was no correlation between the incidence of macrovascular complications in EOD and LOD patients. This confirms that there is no correlation between the onset age of type 2 diabetes mellitus and macrovascular complications – it is not affected by metabolic factors, such as blood pressure, BMI, blood glucose or blood lipids.

In the present study, age and sex factors were matched from large, non-matched groups by segregating type 2 diabetes mellitus patients into smaller, matched groups. The participants were not matched according to their age and sex in previous studies. Thus, one can accurately assess the relationship between the onset age of type 2 diabetes mellitus and vascular complications. Chronic complications were evaluated with objective medical instruments. These findings are more accurate and objective than a self-reported analysis, which was carried out in previous large-scale studies.

Many studies focused on the clinical risk factors to prevent the chronic complications of diabetes. The development of diabetes complications is strictly related to many factors, such as age, sex, metabolic control, diabetes duration, hypertension and use of antihypertensive drugs/antidiabetic agents/lipid-lowering drugs and so on. In the present study, propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex. Furthermore, adjustments for differences in the following parameters were made: HbA1c%, insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of HT. We adjusted the confounding factors to make the conclusion more credible. Of course, for patients with diabetes, the prevention of chronic complications, comprehensive management is very important.

Much emphasis has been laid on formulating a public health policy for the prevention of diabetes in China. In the past 30 years, the incidence of diabetes has been increasing steadily. Young people are being diagnosed with diabetes! In EOD patients, the risk of developing microvascular complications is higher than in LOD patients. Furthermore, EOD patients have a greater tendency of developing macrovascular complications. Therefore, it is proposed that adequate steps must be taken to prevent diabetes in young people. The diabetes duration has been thought to be an uncontrollable factor. The Da Qing Diabetes Prevention Study (DQDPS) showed that lifestyle intervention in people with IGT delayed the onset of type 2 diabetes, and reduced the incidence of cardiovascular events, microvascular complications, cardiovascular and all-cause mortality, and increased life expectancy[37].

The present study had some limitations. Maturity onset diabetes of the young or latent autoimmune diabetes in adults have been ruled out according to patient medical history and diabetes autoantibodies. It is a great pity that genetic testing has not been carried out. The age onset of type 2 diabetes mellitus was always underestimated due to a long asymptomatic stage. Patients were grouped according to their age at onset, but for asymptomatic patients, the age onset might be underestimated. This group failed to take the exact cardiovascular event as the end-point. The present study was carried out on non-severe hospitalized type 2 diabetes patients, so the hospital admission rate might also be biased. However, randomized, prospective, multicenter studies should be carried out to confirm this bias. Furthermore, this was a cross-sectional study that does not prove causality; it only suggests that there is a correlation between the two factors.

Compared with LOD patients, EOD patients have a greater tendency of developing microvascular complications; however, the risk of developing macrovascular complications is not significantly increased in EOD patients. It is suggested that there is a close relationship between the risk of diabetic macrovascular complications and age. Pre-emptive microvascular treatment or preventative measures in EOD patients who do not yet show symptoms might be beneficial.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent: Obtained from all patients included in the study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University, and the participants gave informed consent.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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