The Association Between Age at Diagnosis of Type 2 Diabetes and Albuminuria in Chinese Adults

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Abstract

Background: Type 2 diabetes is increasingly diagnosed at a younger age worldwide and in China. Limited data are available regarding the association between age at diabetes diagnosis and risks of albuminuria, which is a common microvascular complication in diabetes patients. In addition, few studies on age at diagnosis and outcomes have fully accounted for the complex interplay between age at diagnosis and the actual age or diabetes duration, all of which are independently associated with vascular risks.

Methods: We used data from a nationwide multicenter study with 207,961 participants recruited from 25 communities across mainland China during 2010-2012. Age, sex, and study sites were matched for 31,366 screen-detected type 2 diabetes and 31,366 normal controls. Age, sex, study sites, and diabetes duration were matched for 7,490 self-reported type 2 diabetes and 7,490 normal controls. Risks of having albuminuria in matched type 2 diabetes vs. normal controls were examined using multivariable logistic regression analysis in strata of age at type 2 diabetes diagnosis (<50, 50-59, 60-69, or ≥70 years). Albuminuria was defined as urinary albumin-to-creatinine ratio ≥30 mg/g.

Results: Percentages of albuminuria were significantly higher among type 2 diabetes patients compared with normal controls in each stratum of age at diagnosis. Although the absolute rate of albuminuria is higher in older adults, the odds ratio of albuminuria in type 2 diabetes vs. matched controls decreased with increasing age at diagnosis. For participants with diabetes diagnosed at an age of <50, 50-59, 60-69, or ≥70 years, the multivariable adjusted risk of albuminuria increased by 81%, 60%, 45%, and 33% for screen-detected diabetes, and 135%, 121%, 90%, and 58% for self-reported diabetes compared with their normal controls, respectively.

Conclusions: A younger age at diagnosis of type 2 diabetes is associated with a more significantly elevated risk of albuminuria than an older age at diagnosis in Chinese adults.

Background

Although type 2 diabetes mellitus (T2DM) has been regarded as a condition that affects mostly elderly people, the number of younger people with diabetes is increasing. According to the International Diabetes Federation (IDF), 46% of deaths associated with diabetes among the 20–79 age group are in patients under age 60[1, 2]. Given the shifting age distribution of diabetes patients globally, the impact of age, age at diagnosis, and diabetes duration on vascular complications warrants investigation. Previous studies have established close associations of age[2] and diabetes duration[3, 4] with the risk of vascular complications in patients with diabetes. In addition, studies have suggested that a younger age at diagnosis was related to an increased risk of macrovascular and microvascular complications as well as death in diverse populations including Chinese patients[5–10]. However, few studies have fully accounted for the complex interplay between age at diagnosis and the actual age or diabetes duration, all of which are independently associated with vascular risks. Furthermore, most previous studies have compared

vascular risks in early-onset versus late-onset T2DM, rather than the effects of age at diagnosis across a wider age range.

Albuminuria is a biomarker of endothelial dysfunction and has been considered as the initial pathway to the progression of decline in renal function in patients with T2DM[11]. In addition, albuminuria has been regarded as a risk factor for cardiovascular diseases (CVD) and all-cause mortality in adults with or without diabetes[12, 13]. Currently, limited data are available investigating the association between age at diabetes diagnosis and urinary protein/albumin excretion. One study examined the risk of nephropathy defined by protein-to-creatinine ratio ≥ 0.5 g/g in participants with youth-onset diabetes compared with adult-onset diabetes in Pima Indians and the risk was not different[14]. Another study found significantly higher incidence of microalbuminuria in diabetes diagnosed at age 18–44 years compared with diabetes diagnosed at age ≥ 45 years[15].

Therefore, we used baseline data from a large nationwide cohort of Chinese adults and matched T2DM patients with normal controls on age, sex, and study sites. For diabetes not newly diagnosed, duration of diabetes was also matched. We examined the risk of albuminuria in T2DM patients compared with matched controls in each stratum of age at diagnosis to see whether the increased risk is similar for different age groups at diagnosis, therefore to examine the impact of age at diagnosis of T2DM on the risk of albuminuria in Chinese adults.

Methods

Study population

The Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study is a nationwide multicenter prospective cohort study[16,17], of which baseline data were used for the current analysis. During 2011-2012, a total of 259,657 adults aged ≥40 years were recruited from 25 communities across mainland China. Participants were examined comprehensively for their cardiometabolic health using a structured questionnaire, anthropometric measurements, and biochemical tests. Participants with other types of diabetes, diabetes diagnosed at an age <18 years, diabetes with a duration ≥10 years, diseases which may also cause albuminuria such as lymphoma and other renal diseases, and participants with missing data on diabetes status, age at diagnosis of diabetes, and urinary albumin to creatinine ratio (ACR) were excluded. Therefore, a total of 207,961 participants were used for matching (**Figure 1**).

The REACTION study was approved by the Ethical Review Committee of Ruijin Hospital. All study participants provided written informed consent.

Matching

Matching was conducted in 2 steps (**Figure 1**). In the 1st step, participants with T2DM were categorized into 4 groups according to their age at diagnosis (years): <50, 50-59, 60-69, or ≥70. Self-reported (i.e.

previously diagnosed) T2DM and screen-detected (i.e. newly-diagnosed) T2DM were separated because diabetes duration is an important confounding factor for self-reported T2DM but not for screen-detected T2DM. For patients with self-reported T2DM (n = 11,810), diabetes duration (±1 year) was matched between the 4 groups in a ratio of 2:4:3:1 based on the number of participants in each group[18]. In the 2nd step, controls were randomly selected from the general population without diabetes (n = 164,725) and were 1:1 pair matched with all T2DM patients in the 1st step for age (±1 year), sex, and study sites. After matching, 31,366 screen-detected T2DM and 31,366 matched controls, 7,490 self-reported T2DM and 7,490 matched controls were finally included in the current analysis.

Data collection

At each study site, trained staff collected data according to a standard protocol at local health stations or community clinics. Using a standard questionnaire, information on sociodemographic characteristics, lifestyle factors, and medical histories was collected through personal interviews. Participants were asked whether they were previously diagnosed as having diabetes by a physician. If the answer was 'yes', types of diabetes and time of diagnosis were reported.

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively with participants wearing light-weight clothes and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). Blood pressure (BP) was measured 3 times with 1-min intervals after at least 5-min sitting rest using an automated electronic device (Omron Model HEM-725 FUZZY; Omron Co, Dalian, China). Participants were advised to avoid alcohol, coffee, tea, smoking, and exercise at least 30 minutes before BP measurement. The average of three readings was used for analysis.

Blood samples were collected after an overnight fast for at least 10 hours. Participants without a known history of diabetes underwent the oral glucose tolerance test (OGTT) and 2h blood samples after the glucose load were also collected. Fasting and OGTT-2h plasma glucose levels were measured at local hospitals using the glucose oxidase or hexokinase method within 2 hours of blood sample collection. The first void urine samples were also collected from each participant in early morning. Serum and urine samples were aliquoted into 0.5-mL Eppendorf tubes within 2 hours after collection and were then frozen at -80 degrees at local hospitals. All samples were shipped in dry ice to the central laboratory at Shanghai Institute of Endocrine and Metabolic Diseases, accredited by the College of American Pathologists (CAP), where levels of serum creatinine (Cr), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were measured on an auto-analyzer (c16000 system, ARCHITECT ci16200 analyzer, Abbott Laboratories, Illinois, USA), and levels of glycosylated hemoglobin A_{1c} (HbA_{1c}) were measured using a high performance liquid chromatography method (VARIANT™ II System, BIO-RAD, Hercules, CA, USA). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation[19].

Urinary albumin concentrations were measured at the central laboratory by immunonephelometry using Siemens BNII nephelometers (Siemens Healthcare Diagnostics, Marburg, Germany). The lower limit of detection is 2.13 mg/l. The intra-assay and inter-assay coefficients of variation for urinary albumin were 2.1% and 2.3%, respectively. Urinary creatinine concentrations were measured at the central laboratory by an enzymatic method (ADVIA Chemistry XPT System; Siemens Healthcare, Erlangen, Germany). The intra-assay and inter-assay coefficients of variation for urinary creatinine were 1.1% and 1.3%, respectively.

Classification and Definition

Diabetes was defined according to the 2010 American Diabetes Association (ADA) criteria[20]. Self-reported T2DM was defined as a self-reported previous diagnosis of T2DM by physicians. Screen-detected T2DM was defined as a fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L), and/or an OGTT-2h post-load plasma glucose (PPG) ≥200 mg/dL (11.1 mmol/L), and/or HbA_{1c} ≥48 mmol/mol (6.5%) without prior known diabetes. Albuminuria was defined as an ACR ≥30 mg/g[21].

Statistical analysis

Variables were checked for the distributional assumption of normality using normal plots. Subject characteristics which conformed to a normal distribution were presented as means ± standard deviations (SDs), otherwise as medians (interquartile ranges). All categorical variables were presented as the numbers (proportions). The distributions of diabetes duration, TG, and urinary ACR were skewed. Analyses were done separately for self-reported and screen-detected T2DM. General characteristics of individuals with T2DM according to their age at diagnosis and matched controls were described. Covariate balances were evaluated by standardized differences, which contrasted the group means of covariates in units of the pooled SDs of the comparison groups. A standardized difference of less than 0.1 was considered well balanced[22,23]. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of albuminuria in T2DM patients *vs.* matched controls in each groups of age at diagnosis, either unadjusted or adjusted for covariates including education (high school education or above), current smoking (yes/no), current drinking (yes/no), history of CVD (yes/no), use of an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) (yes/no), BMI, systolic BP, LDL-c, TG, and eGFR. All the tests were two-tailed, with a p value <0.05 considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.6.3 (R Project for Statistical Computing, http://www.r-project.org).

Results

General characteristics of the study population are shown in Table 1 for screen-detected T2DM and matched controls and in Table 2 for self-reported T2DM and matched controls. Patients with T2DM were well matched with normal controls for age, sex, and study sites (all standardized differences < 0.001). In addition, median duration of diabetes was 2.7–2.8 years and was well-balanced between groups of age at diagnosis for self-reported T2DM. Compared with matched controls, participants with screen-detected

T2DM had higher levels of BMI, systolic BP, diastolic BP, FPG, HbA_{1c}, TG, TC, LDL-c and lower levels of HDL-c, while participants with self-reported T2DM had increased proportions of current drinkers, history of CVD and use of an ACEI or ARB, and higher levels of BMI, systolic BP, FPG, HbA_{1c}, TG and lower levels of HDL-c (all standardized differences ≥ 0.1). Furthermore, current smoking, current drinking, FPG, HbA_{1c}, and TG decreased significantly across the groups of age at diagnosis for both screen-detected T2DM and self-reported T2DM (all *p* values for trend < 0.001).

Table 1

Characteristics of participants with screen-detected T2DM and normal controls after matching

Characteristics	Screen-detected T2DM by age at diagnosis (years)					Normal controls[†]	Standardized Difference[‡]
	< 50	50–59	60–69	≥ 70	Total		
Participants (n)	4630	11431	10688	4617	31366	31366	
Age (years)	46.1 ± 2.7	55.7 ± 2.7	64.5 ± 2.8	74.5 ± 3.8	60.0 ± 9.1	60.0 ± 9.1	< 0.001
Men, n (%)	1938 (41.9)	3888 (34.0)	3935 (36.8)	1899 (41.1)	11,660 (37.2)	11,660 (37.2)	< 0.001
High school education or above, n (%)	1871 (40.4)	3809 (33.3)	2785 (26.1)	1182 (25.6)	9647 (30.8)	10,001 (31.9)	0.028
Current smokers, n (%)	871 (19.8)	1707 (15.7)	1265 (12.5)	393 (8.8)	4236 (14.2)	4363 (14.6)	0.013
Current drinkers, n (%)	693 (15.8)	1292 (11.9)	994 (9.9)	351 (7.9)	3330 (11.2)	3083 (10.3)	0.027
Previous CVD, n (%)	68 (1.5)	491 (4.3)	1018 (9.5)	776 (16.8)	2353 (7.5)	1934 (6.2)	0.053
Use of ACEI/ARB, n (%)	74 (1.6)	264 (2.3)	384 (3.6)	186 (4.0)	908 (2.9)	569 (1.8)	0.071
BMI (kg/m^2)	26.1 ± 3.9	25.7 ± 3.7	25.7 ± 3.6	25.1 ± 3.8	25.7 ± 3.7	24.4 ± 3.5	0.356
SBP (mmHg)	131.2 ± 18.9	136.0 ± 20.2	141.2 ± 20.3	144.8 ± 20.9	138.4 ± 20.6	132.6 ± 20.3	0.283
DBP (mmHg)	82.2 ± 11.8	81.7 ± 11.0	80.2 ± 10.7	76.5 ± 10.4	80.5 ± 11.1	77.9 ± 10.9	0.234

Data were presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, or numbers (proportions) for categorical variables.

[†] Control group included participants without diabetes and matched for age, sex, and study sites for each participant with screen-detected T2DM.

[‡] The standardized difference was < 0.001 for study sites after matching.

Abbreviations: T2DM, type 2 diabetes mellitus; NA, not applicable; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Characteristics	Screen-detected T2DM by age at diagnosis (years)					Normal controls[†]	Standardized Difference[‡]
	< 50	50–59	60–69	≥ 70	Total		
FPG (mg/dL)	134.6 ± 45.1	129.8 ± 40.2	126.1 ± 34.9	121.8 ± 32.1	128.1 ± 38.3	98.6 ± 9.9	1.054
HbA_{1c} (%)	6.8 ± 1.5	6.8 ± 1.4	6.8 ± 1.2	6.7 ± 1.1	6.8 ± 1.3	5.7 ± 0.4	1.101
TG (mg/dL)	147.8 (99.1, 227.4)	145.1 (100.9, 213.3)	139.8 (99.1, 200)	133.6 (95.6, 184.1)	141.6 (99.1, 206.2)	111.5 (80.5, 159.3)	0.351
TC (mg/dL)	192.8 ± 46.9	199.2 ± 46.4	197.3 ± 45.4	195.7 ± 46.8	197.1 ± 46.2	189.4 ± 42.9	0.173
LDL-c (mg/dL)	110.5 ± 34.1	115.8 ± 35.2	115.2 ± 34.6	114.5 ± 35.6	114.6 ± 35.0	109.6 ± 33.0	0.147
HDL-c (mg/dL)	47.9 ± 13.2	49.5 ± 13.6	49.4 ± 13.6	49.2 ± 13.7	49.2 ± 13.6	51.7 ± 13.9	0.182
eGFR (ml/min/1.73 m^2)	102.5 ± 11.4	94.5 ± 11.0	86.6 ± 12.2	77.8 ± 13.6	90.5 ± 14	91.6 ± 13.3	0.076

Data were presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, or numbers (proportions) for categorical variables.

[†] Control group included participants without diabetes and matched for age, sex, and study sites for each participant with screen-detected T2DM.

[‡] The standardized difference was < 0.001 for study sites after matching.

Abbreviations: T2DM, type 2 diabetes mellitus; NA, not applicable; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 2

Characteristics of participants with self-reported T2DM and normal controls after matching

Characteristics	Self-reported T2DM by age at diagnosis (years)†					Normal controls‡	Standardized Difference¶
	< 50	50–59	60–69	≥ 70	Total		
Participants (n)	1498	2996	2247	749	7490	7490	
Age (years)	48.2 ± 3.9	58.3 ± 3.5	67.4 ± 3.5	76.9 ± 3.7	60.9 ± 9.3	60.9 ± 9.3	< 0.001
Age at diagnosis (years)	45.1 ± 3.6	55.2 ± 2.8	64.2 ± 2.8	73.8 ± 3.3	57.8 (9.1)	NA	NA
Duration of diabetes (years)	2.7 (1.4, 4.4)	2.7 (1.4, 4.4)	2.7 (1.3, 4.4)	2.8 (1.4, 4.4)	2.7 (1.4, 4.4)	NA	NA
Men, n (%)	712 (47.5)	1190 (39.7)	844 (37.6)	320 (42.7)	3066 (40.9)	3066 (40.9)	< 0.001
High school education or above, n (%)	678 (45.3)	947 (31.6)	722 (32.1)	245 (32.7)	2592 (34.6)	2490 (33.2)	0.071
Current smokers, n (%)	340 (23.2)	436 (15.0)	227 (10.4)	48 (6.5)	1051 (14.4)	1207 (16.7)	0.063
Current drinkers, n (%)	171 (11.7)	279 (9.6)	146 (6.7)	36 (4.9)	632 (8.7)	851 (11.8)	0.103
Previous CVD, n (%)	54 (3.6)	313 (10.4)	384 (17.1)	187 (25.0)	938 (12.5)	551 (7.4)	0.173
Use of ACEI/ARB, n (%)	63 (4.2)	194 (6.5)	178 (7.9)	64 (8.5)	499 (6.7)	199 (2.7)	0.191

Data were presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, or numbers (proportions) for categorical variables.

† Self-reported T2DM was matched for duration of diabetes among the 4 groups of age at diagnosis.

‡ Control group included participants without diabetes and matched for age, sex, and study sites for each participant with self-reported T2DM.

¶ The standardized difference was < 0.001 for study sites after matching.

Abbreviations: T2DM, type 2 diabetes mellitus; NA, not applicable; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Characteristics	Self-reported T2DM by age at diagnosis (years)[†]					Normal controls[‡]	Standardized Difference[¶]
	< 50	50–59	60–69	≥ 70	Total		
BMI (kg/m^2)	25.7 ± 3.6	25.7 ± 3.5	25.6 ± 3.6	25.6 ± 3.4	25.7 ± 3.5	24.5 ± 3.5	0.325
SBP (mmHg)	130.2 ± 17.6	137.3 ± 20.3	142.0 ± 19.5	147.1 ± 20.6	138.3 ± 20.2	133.5 ± 20.5	0.239
DBP (mmHg)	80.9 ± 10.6	80.1 ± 10.6	77.2 ± 10.1	74.5 ± 10.0	78.8 ± 10.6	78.1 ± 10.9	0.064
FPG (mg/dL)	157.2 ± 52.5	146.5 ± 45.3	139.5 ± 41.7	134.6 ± 37.3	145.4 ± 45.6	98.3 ± 9.8	1.425
HbA_{1c} (%)	7.6 ± 1.8	7.4 ± 1.5	7.2 ± 1.5	7.1 ± 1.3	7.4 ± 1.6	5.7 ± 0.4	1.417
TG (mg/dL)	143.4 (97.3, 220.4)	140.3 (97.3, 209.7)	132.7 (95.6, 191.2)	132.7 (93.8, 179.6)	137.2 (96.5, 202.7)	114.2 (82.3, 162.8)	0.316
TC (mg/dL)	185.9 ± 43.6	191.5 ± 47.3	187.2 ± 45.8	189.7 ± 45.7	188.9 ± 46.0	189.5 ± 42.5	0.012
LDL-c (mg/dL)	105.9 ± 32.3	110.2 ± 34.7	108.2 ± 35	110.2 ± 34.4	108.7 ± 34.3	110.3 ± 32.6	0.047
HDL-c (mg/dL)	46.1 ± 12.1	47.0 ± 12.2	46.5 ± 12	46.6 ± 12.4	46.6 ± 12.1	50.9 ± 13.5	0.331
eGFR (ml/min/1.73 m^2)	101.3 ± 11.4	92.1 ± 12.3	83.4 ± 13.5	74.6 ± 14.3	89.6 ± 15.0	90.9 ± 13.2	0.093

Data were presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, or numbers (proportions) for categorical variables.

[†] Self-reported T2DM was matched for duration of diabetes among the 4 groups of age at diagnosis.

[‡] Control group included participants without diabetes and matched for age, sex, and study sites for each participant with self-reported T2DM.

[¶] The standardized difference was < 0.001 for study sites after matching.

Abbreviations: T2DM, type 2 diabetes mellitus; NA, not applicable; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

The distribution of age at T2DM diagnosis after matching is presented in Fig. 2. The mean age at diagnosis was 60.0 years in patients with screen-detected T2DM and 60.9 years in patients with self-reported T2DM. The range of age at diagnosis was 40.0-94.2 years in patients with screen-detected T2DM and 31.3–88.0 years in patients with self-reported T2DM.

Levels of urinary ACR in participants with screen-detected T2DM, self-reported type 2 T2DM, and matched controls in strata of age at T2DM diagnosis are depicted in Fig. 3. ACR levels significantly increased across groups of diagnosis age and were significantly higher in patients with self-reported T2DM or screen-detected T2DM compared with controls in each stratum of age at diagnosis (all *p* values for trend < 0.001).

Percentages of participants with albuminuria in T2DM and matched controls, and ORs (95% CIs) of albuminuria in participants with T2DM vs. control in strata of age at diagnosis are shown in Fig. 4. Percentages of albuminuria were significantly higher among T2DM patients compared with normal controls in each stratum of age at diagnosis. Logistic regression analysis revealed significantly increased risks of albuminuria in both screen-detected and self-reported T2DM patients compared with their normal controls, respectively in each stratum of age at diagnosis before and after adjustment. Furthermore, ORs of albuminuria in T2DM *vs.* normal controls decreased with increasing age at T2DM diagnosis. For participants with T2DM diagnosis at an age of < 50, 50–59, 60–69, or ≥ 70 years, the multivariable adjusted risk of albuminuria increased by 81%, 60%, 45%, and 33% for screen-detected T2DM, and 135%, 121%, 90%, and 58% for self-reported T2DM compared with their normal controls, respectively.

Discussion

Using baseline data from a nationwide multicenter community-based cohort, we showed that risks of albuminuria increased significantly in T2DM compared with normal controls matched by age, sex, and study sites. The relative risk of albuminuria in type 2 diabetes decreased with increasing age at diagnosis. It was the highest among patients with age at diagnosis < 50 years and the lowest among patients with age at diagnosis ≥ 70 years. Compared with matched controls, the risk of albuminuria was even more markedly elevated in those with T2DM diagnosed at a younger age. This pattern of association was observed for both screen-detected and self-reported T2DM, indicating that age at diagnosis of T2DM was independently associated with the risk of albuminuria.

Previous studies have reported a significant association between age at diagnosis of diabetes and risk of cardiovascular complications. Although the absolute rate of CVD is higher in older adults, young adults with early-onset T2DM have a much higher risk of CVD relative to age-matched control subjects in health maintenance organization and nationwide register studies[5, 15]. Recent studies also demonstrated a higher risk of microvascular complications such as progressive chronic kidney disease[6] and retinopathy[24] in individuals with early-onset T2DM. However, studies have suggested that patients with early-onset T2DM were at increased risk of cardio-renal complications mainly driven by longer diabetes duration[4, 7, 10, 25]. A recent study from Australia found that diabetes duration was the predominant

determinant of end-stage kidney disease (ESKD) and the incidence of ESKD was higher at a given duration in those diagnosed later, which may be partly related to the increased risk at an advancing age[10]. Because the actual age, age at diagnosis, and duration of diabetes are all important risk factors for diabetes complications such as chronic kidney disease and ESKD[20, 26], an appropriately designed study which takes into full consideration the confounding or impact from the actual age and diabetes duration is needed. The current study is one of the few studies which minimize the effect of these factors by matching on age and sex. Furthermore, for diabetes not newly diagnosed, duration of diabetes was also matched. Therefore, our data provide robust evidence regarding the association between age at diabetes diagnosis and albuminuria.

The potential mechanism for the increased risk at younger ages of T2DM diagnosis warrants investigation. In our study, young adults diagnosed with T2DM were more likely to have an unfavorable metabolic profile compared with normal controls, which has also been reported in previous studies[8, 27]. Compared with older patients, younger patients with T2DM were less likely to have a healthy lifestyle. A younger age of T2DM diagnosis was associated with poor self-management and medication adherence, increased stress, and depressive symptoms[28, 29]. In addition, genetic factors might play an important role in young-onset T2DM by affecting beta-cell development[30, 31].

Findings from the current study have important clinical implications. Current guidelines such as the ADA Standards of Medical Care in Diabetes[20] and the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm[32] recommend less aggressive risk management in individuals with diabetes aged < 40 years. However, because the risk of microvascular complications such as albuminuria was more significantly elevated in individuals with diabetes diagnosed at an earlier age, more intensive monitoring and control of glucose and other risk factors might be needed to prevent microvascular and macrovascular complications in younger people with T2DM[33].

Strengths of the current study included the large sample from a nationwide multicenter community-based cohort with a wide age range at T2DM diagnosis and the minimized confounding by matching on age, sex, study site, and diabetes duration. Limitations of the current study should also be acknowledged. First, for T2DM not newly diagnosed, age at diagnosis was self-reported. Recall bias in self-reported T2DM cannot be excluded and might be more prevalent in those with longer diabetes durations. Therefore, participants with a diabetes duration ≥ 10 years were excluded from the current analysis to minimize recall bias. Second, glucose measures and urinary ACR were tested only once, although centralized measurements were conducted in a CAP accredited laboratory with a standard methodology. Third, antibodies such as the glutamic acid decarboxylase antibody were not measured to define types of diabetes. Nevertheless, T2DM is the predominant type of diabetes in community adults and participants with diabetes diagnosed before age 18 were excluded. Forth, this is a cross-sectional study and prospective studies are needed to demonstrate the interrelationship between age at diagnosis of T2DM

and albuminuria. Finally, generalizability of the current findings to populations with other ethnicities is limited.

Conclusions

A younger age at diagnosis of T2DM is associated with a more significantly elevated risk of albuminuria than an older age at diagnosis in Chinese adults. Therefore, age at diagnosis of T2DM could serve as an important risk stratifying factor in the screening, prevention, and management of this chronic condition[34]. Evidence from intervention studies in T2DM patients diagnosed at different ages is warranted to minimize risks of microvascular and macrovascular complications.

Abbreviations

ACEI: angiotensin converting enzyme inhibitor; ACR: albumin to creatinine ratio; ADA: American Diabetes Association; ARB: angiotensin II receptor blocke; BMI: body mass index; BP: blood pressure; CAP: College of American Pathologists; CIs: confidence intervals; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; Cr: creatinine; CVD: cardiovascular diseases; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; FPG: fasting plasma glucose; HbA_{1c}: glycosylated hemoglobin A_{1c}; HDL-c: high-density lipoprotein cholesterol; IDF: International Diabetes Federation; LDL-c: low-density lipoprotein cholesterol; OGTT: oral glucose tolerance test; ORs: odds ratios; PPG: post-load plasma glucose; REACTION: Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal; SDs: standard deviations; TC: total cholesterol; TG: triglycerides; T2DM: type 2 diabetes mellitus.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Committee of Ruijin Hospital. All study participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available because of data protection regulations.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Shujing Wu, Yufang Bi, Jieli Lu, Yu Xu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Shujing Wu and Shanshan Liu contributed to the work equally and should be regarded as co-first authors. Concept and design: Shujing Wu, Yufang Bi, Jieli Lu, Yu Xu, Weiqing Wang, Guang Ning. Acquisition, analysis, or interpretation of data: Xuefeng Yu, Xulei Tang, Ruying Hu, Zhen Ye, Lixin Shi, Qing Su, Li Yan, Guijun Qin, Qin Wan, Gang Chen, Zhengnan Gao,Guixia Wang, Feixia Shen, Zuojie Luo, Yingfen Qin, Li Chen, Yanan Huo, Qiang Li, Yinfei Zhang, Chao Liu, Youmin Wang, Shengli Wu, Tao Yang, Huacong Deng, Lulu Chen, Jiajun Zhao, Yiming Mu, Shujing Wu, Shanshan Liu, Min Xu, Yuhong Chen, Yufang Bi, Jieli Lu, Yu Xu, Weiqing Wang, Guang Ning. Statistical analysis: Shujing Wu, Shanshan Liu, Zhiyun Zhao, Mian Li, Tiange Wang. Participant recruitment: Xuefeng Yu, Xulei Tang, Ruying Hu, Zhen Ye, Lixin Shi, Qing Su, Li Yan, Guijun Qin, Qin Wan, Gang Chen, Zhengnan Gao,Guixia Wang, Feixia Shen, Zuojie Luo, Yingfen Qin, Li Chen, Yanan Huo, Qiang Li, Yinfei Zhang, Chao Liu, Youmin Wang, Shengli Wu, Tao Yang, Huacong Deng, Lulu Chen, Jiajun Zhao, Yiming Mu. Obtained funding: Yufang Bi, Jieli Lu, Yu Xu, Weiqing Wang, Guang Ning. Administrative, technical, or material support: Shuangyuan Wang, Meng Dai, Di Zhang, Xuefeng Yu, Xulei Tang, Ruying Hu, Zhen Ye, Lixin Shi, Qing Su, Li Yan, Guijun Qin, Qin Wan, Gang Chen, Zhengnan Gao,Guixia Wang, Feixia Shen, Zuojie Luo, Yingfen Qin, Li Chen, Yanan Huo, Qiang Li, Yinfei Zhang, Chao Liu, Youmin Wang, Shengli Wu, Tao Yang, Huacong Deng, Lulu Chen, Jiajun Zhao, Yiming Mu, Yiping Xu. Drafting the manuscript: Shujing Wu, Shanshan Liu, Yu Xu. Critical revision of the manuscript for important intellectual content: all co-authors. All authors have approved the final version of the manuscript.

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Figures

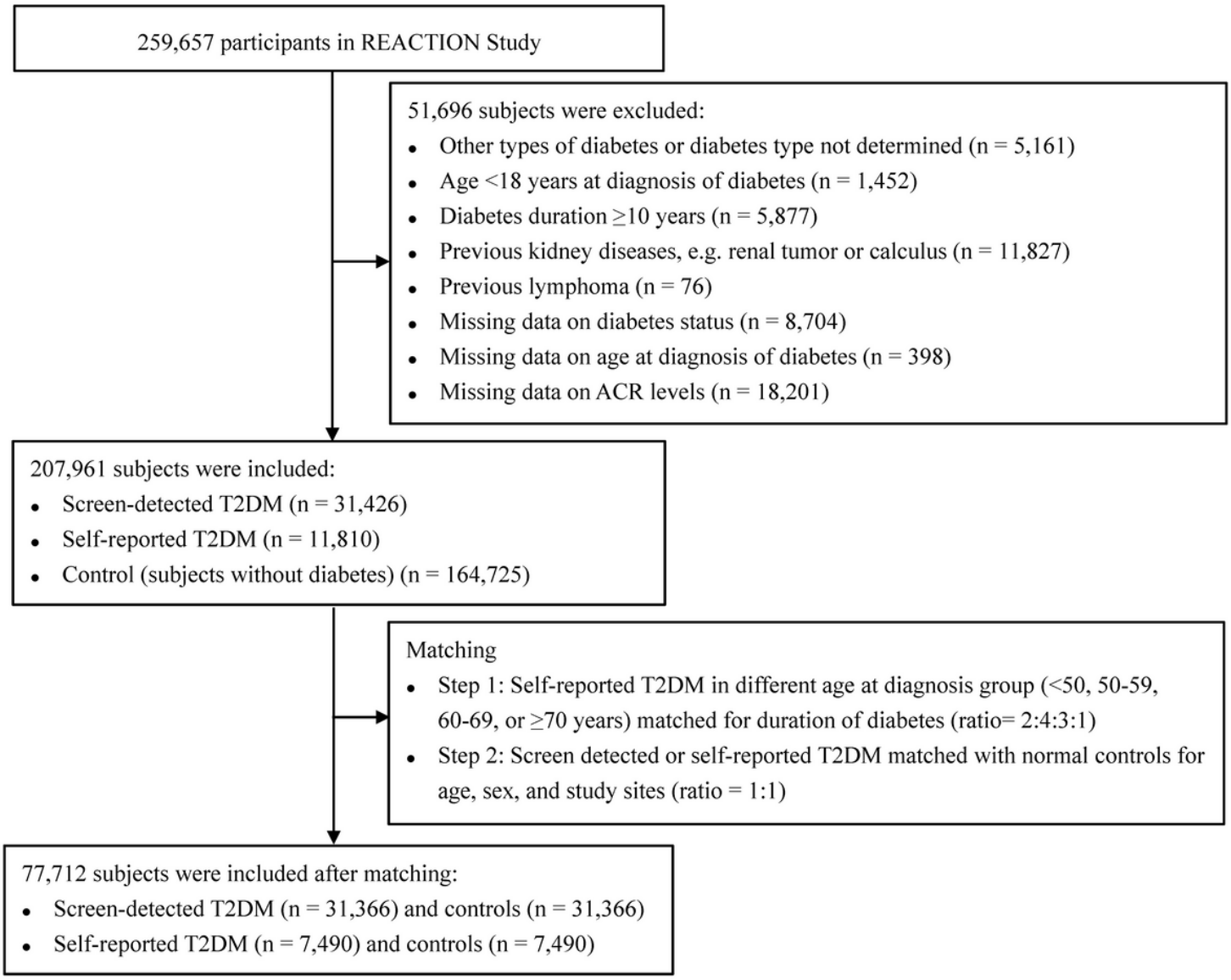
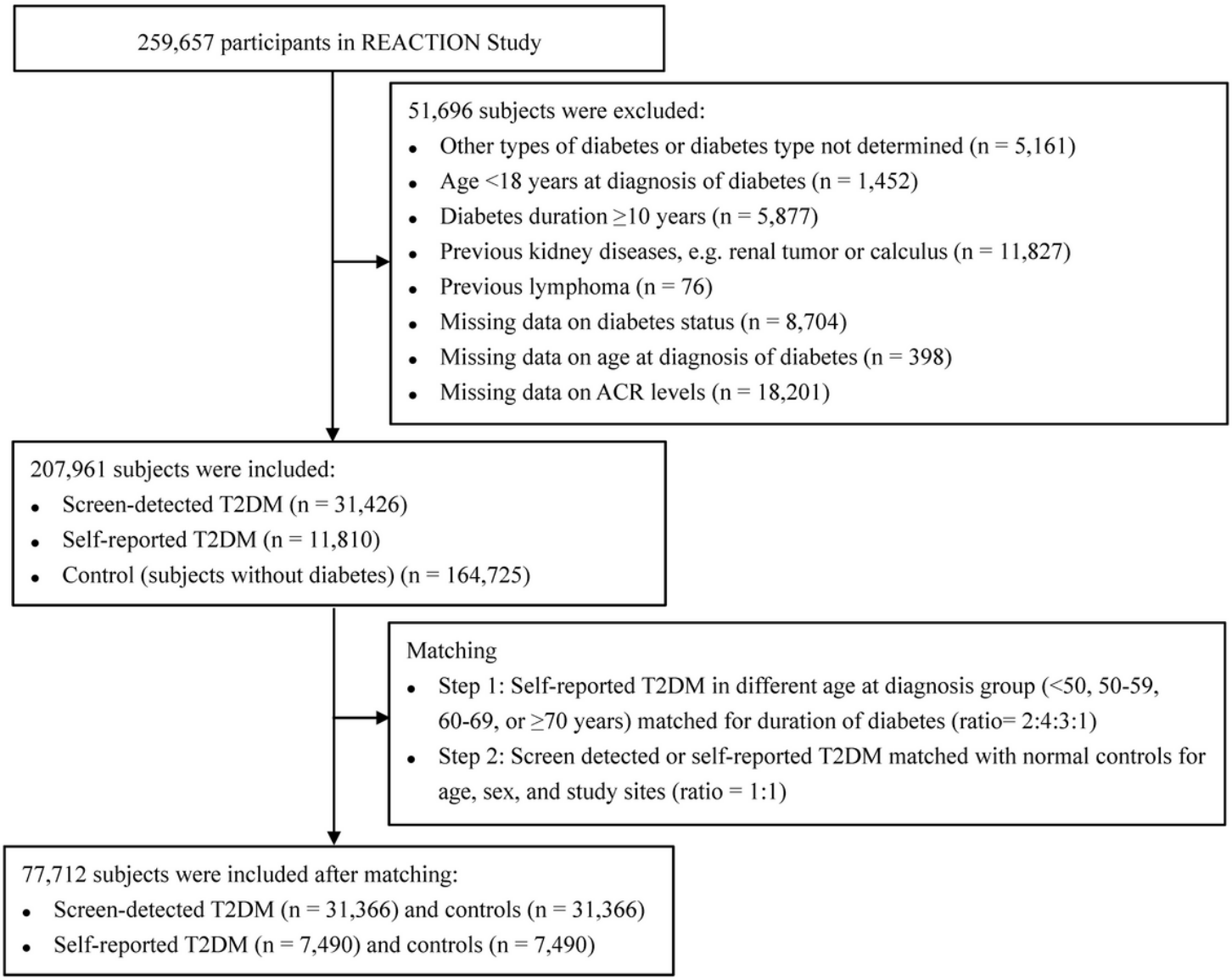


Figure 1

Flowchart of the study population. Abbreviations: T2DM, type 2 diabetes mellitus; ACR, albumin to creatinine ratio.



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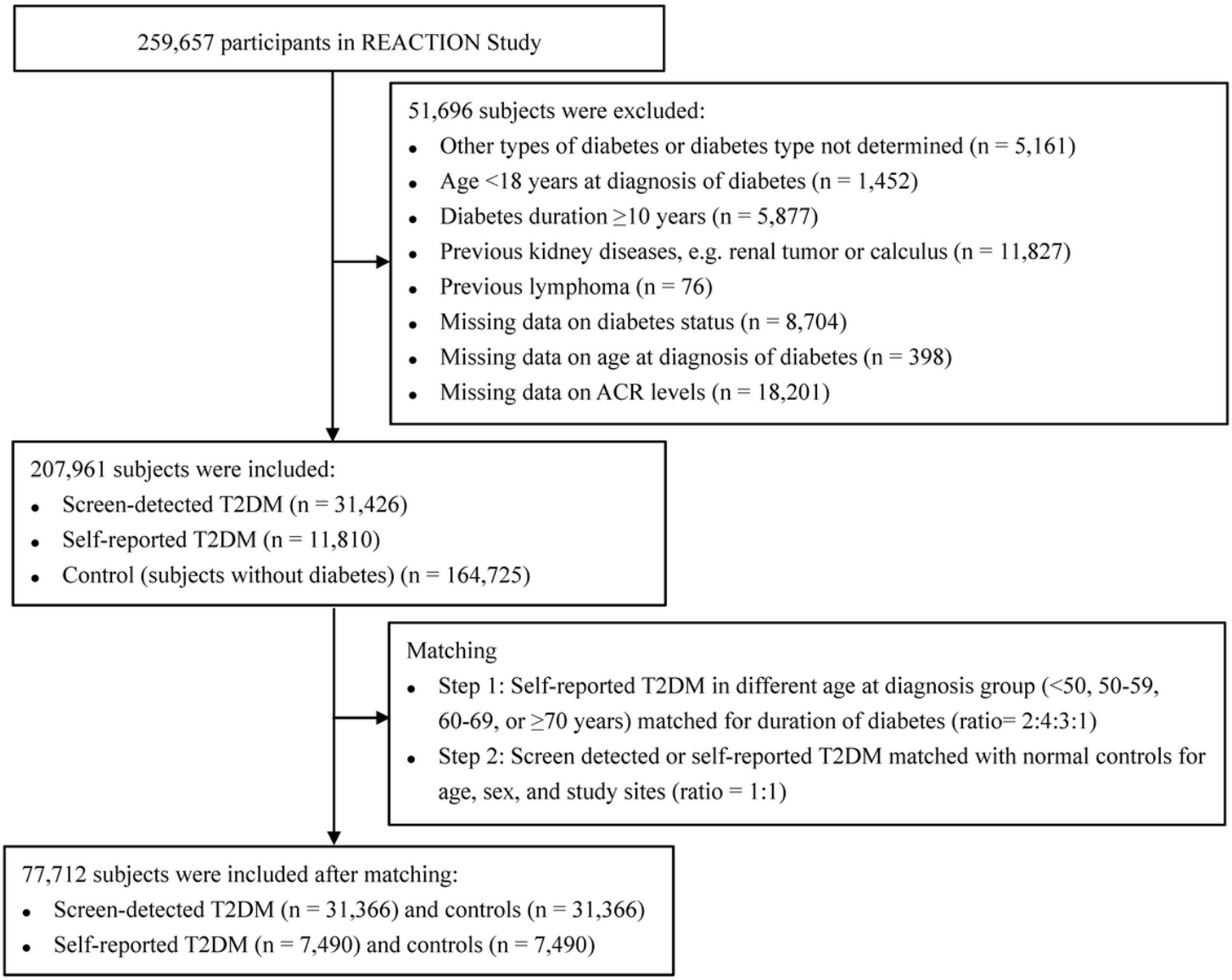

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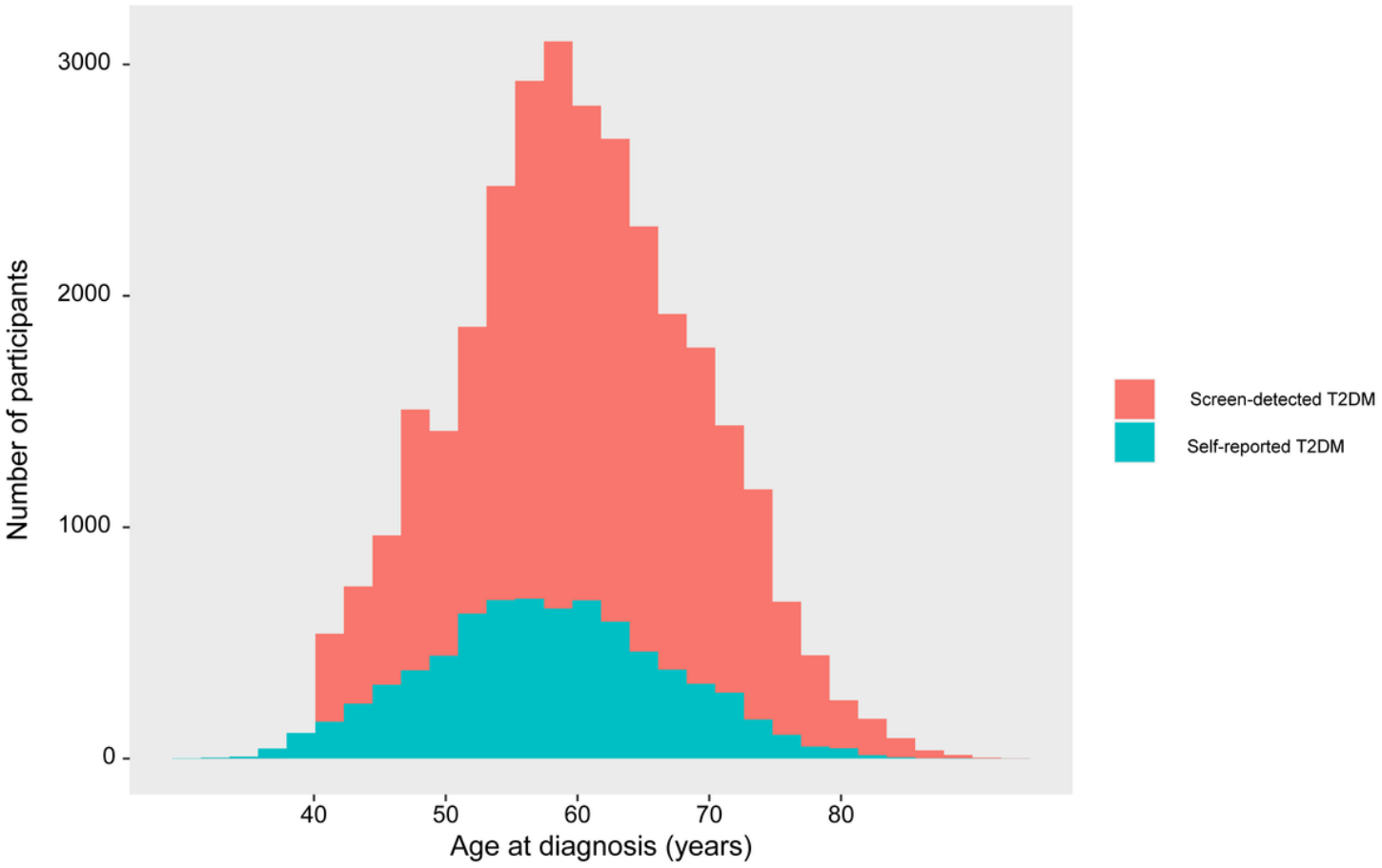
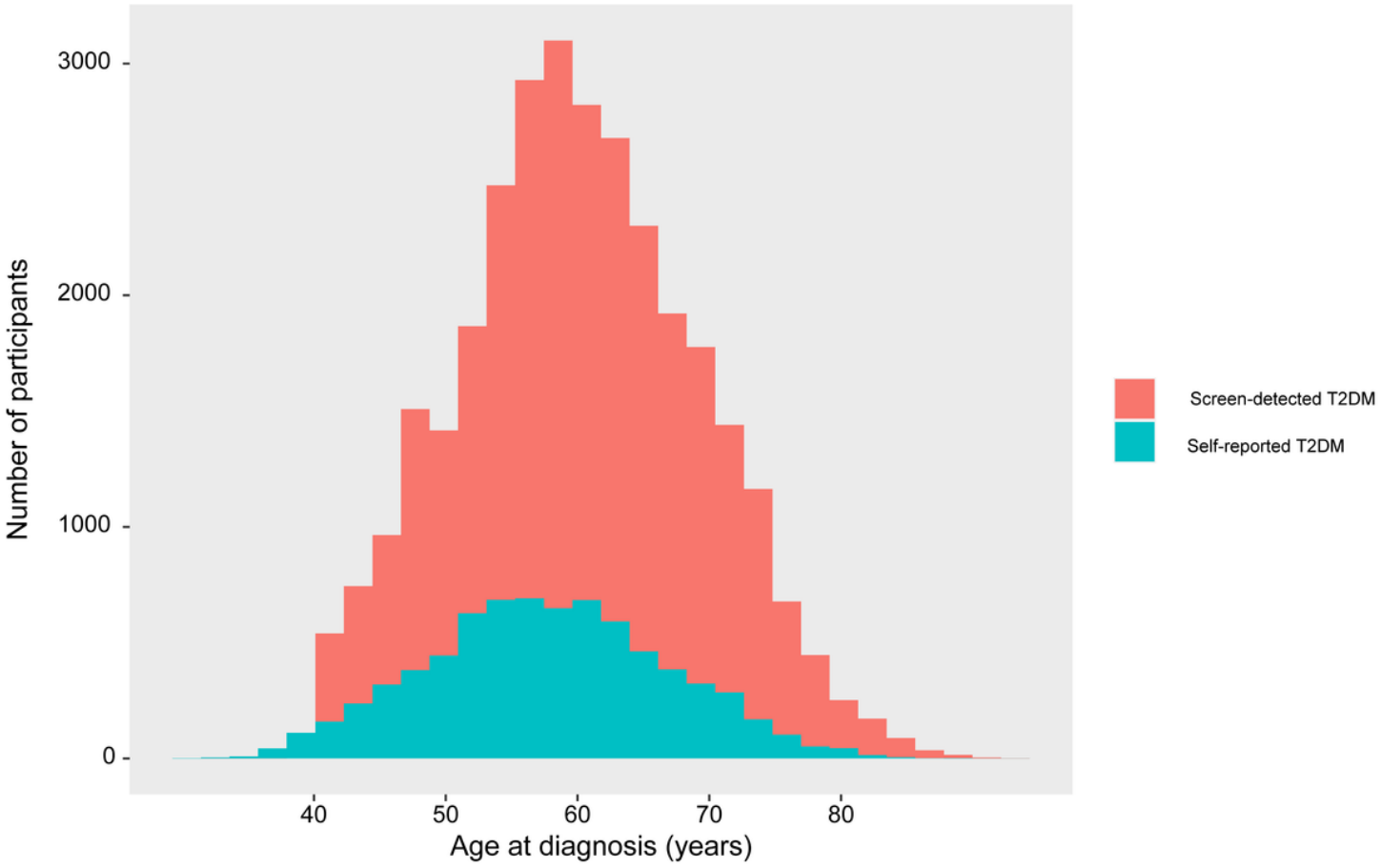


Figure 2

Histogram of age at diagnosis of type 2 diabetes after matching. Abbreviations: T2DM, type 2 diabetes mellitus.



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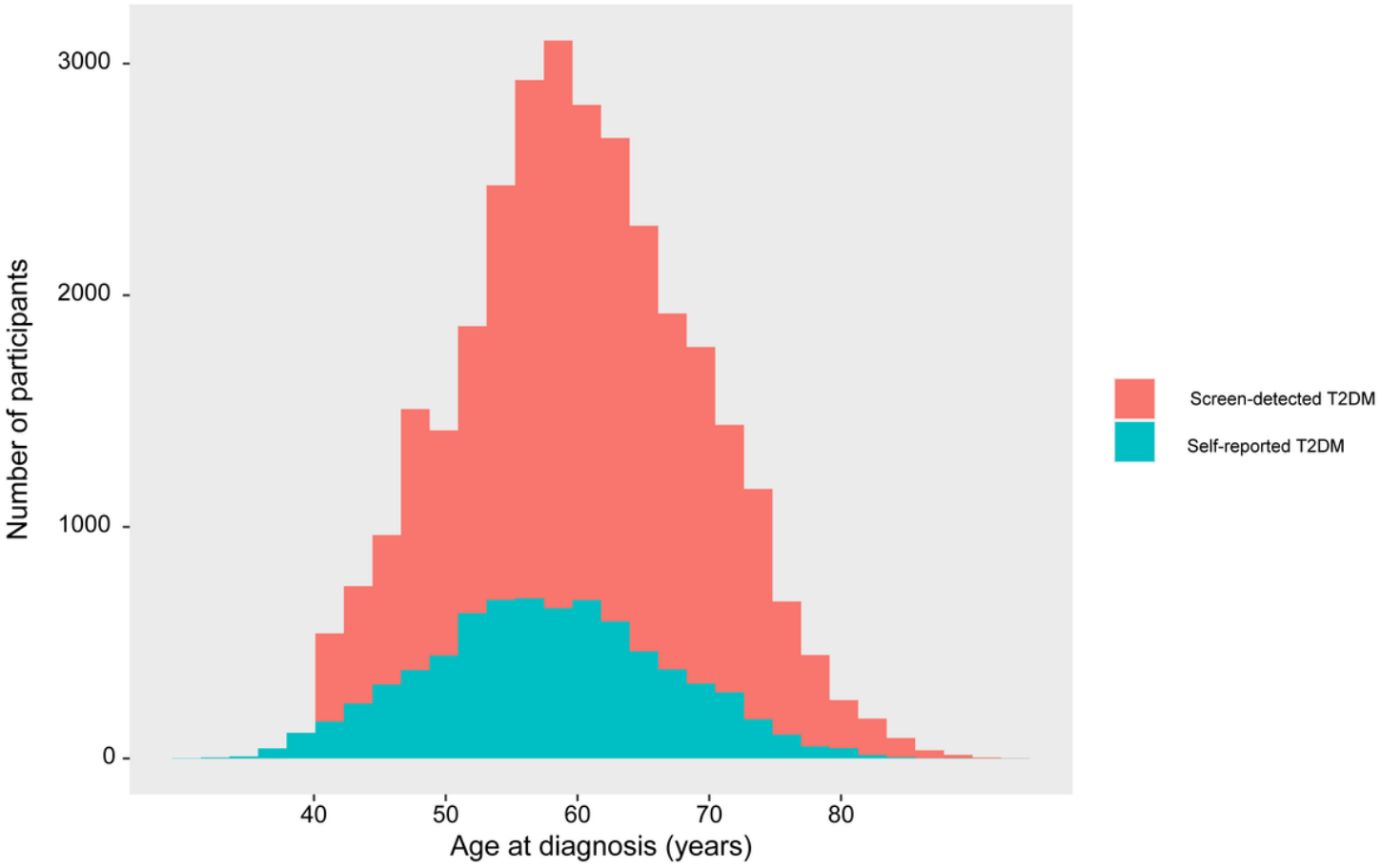

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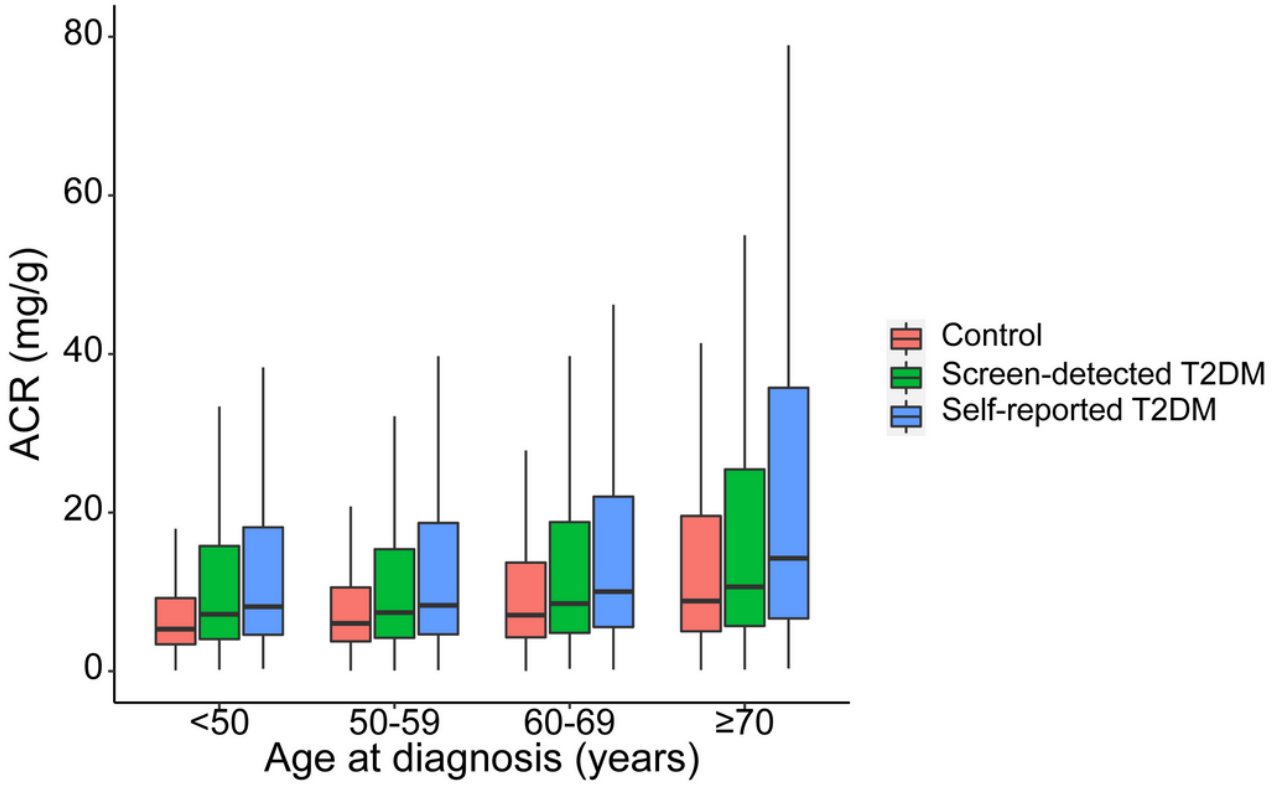
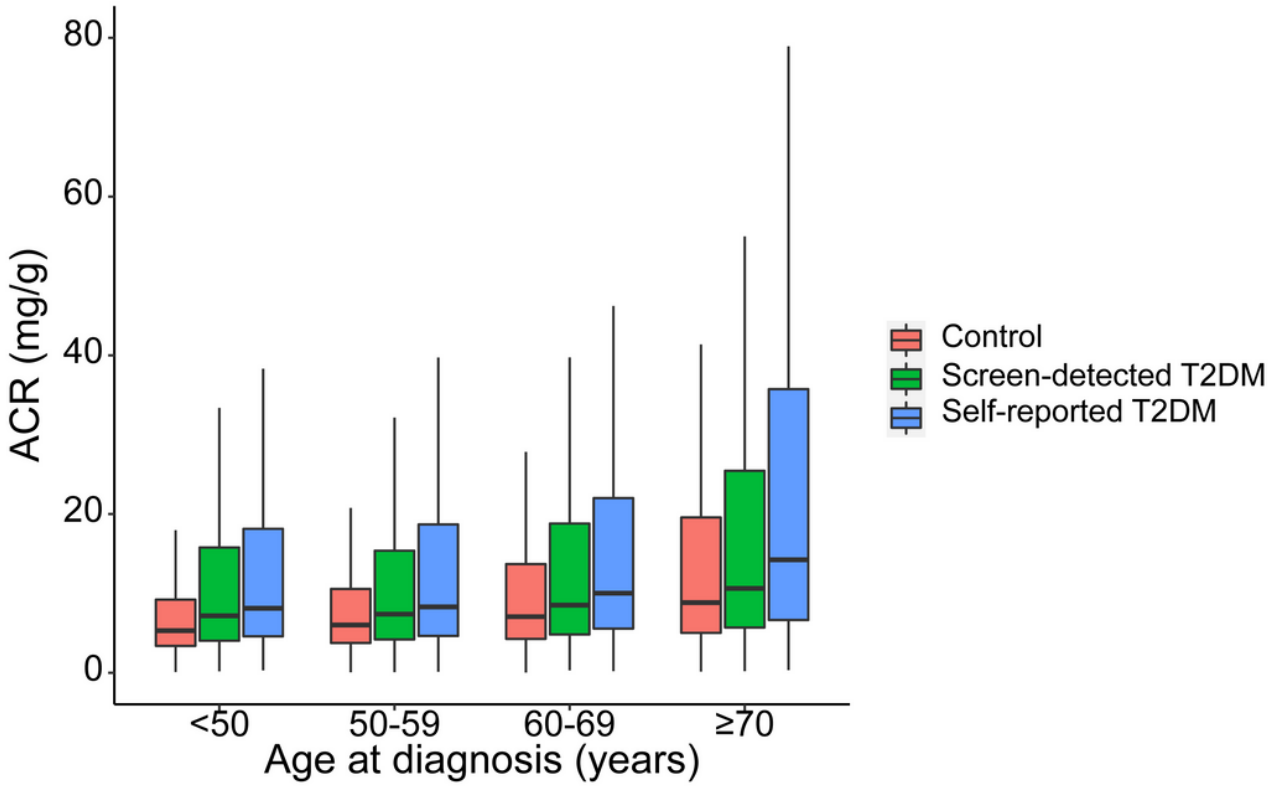


Group	ACR (mg/g) levels by age at diagnosis (years)			
	<50	50-59	60-69	≥70
Normal controls	5.31 (3.39, 9.22)	6.02 (3.76, 10.56)	7.07 (4.28, 13.70)	8.85 (5.03, 19.58)
Screen-detected T2DM	7.18 (4.04, 15.79)	7.39 (4.20, 15.39)	8.53 (4.83, 18.81)	10.63 (5.71, 25.45)
Self-reported T2DM	8.13 (4.60, 18.14)	8.30 (4.64, 18.70)	10.03 (5.57, 22.02)	14.24 (6.65, 35.75)

Figure 3

ACR levels in participants with T2DM and matched controls according to age at diagnosis. The boxes indicate the 25th to 75th percentiles, and horizontal lines within the box indicate the medians. The error bars indicate the lowest and highest value in the 25th percentile minus 1.5IQR and 75th percentile plus 1.5IQR regions, respectively. The outliers were excluded. Abbreviations: ACR, albumin to creatinine ratio; T2DM, type 2 diabetes mellitus; IQR, interquartile range.



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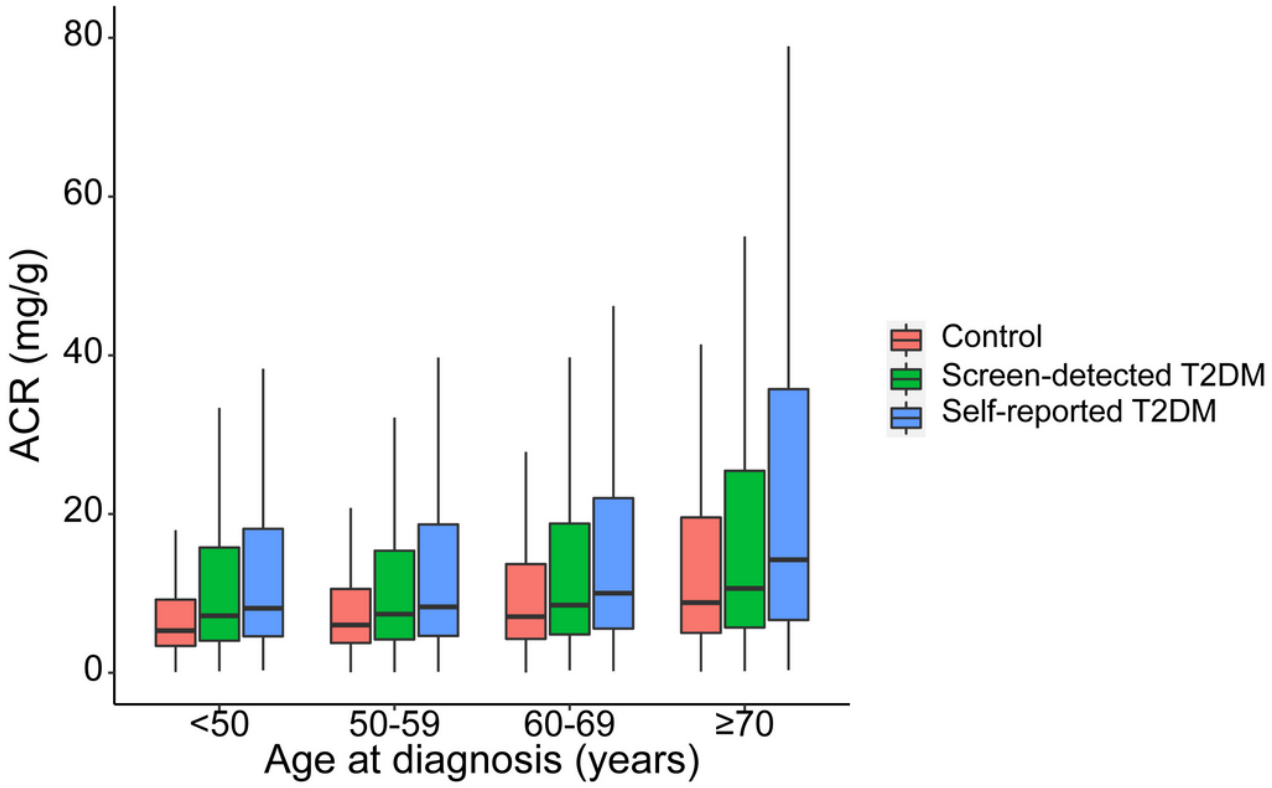

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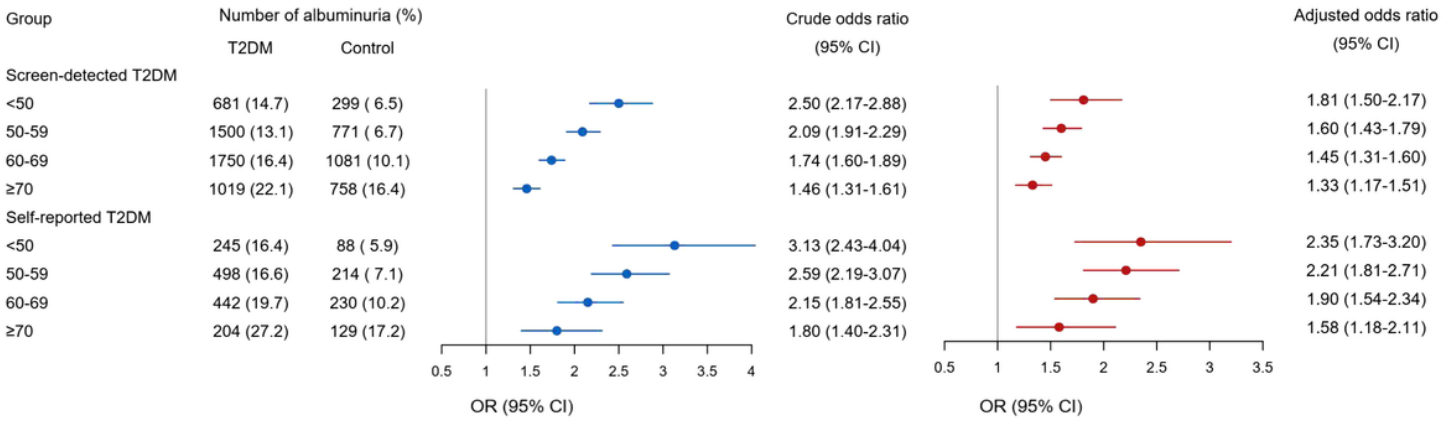
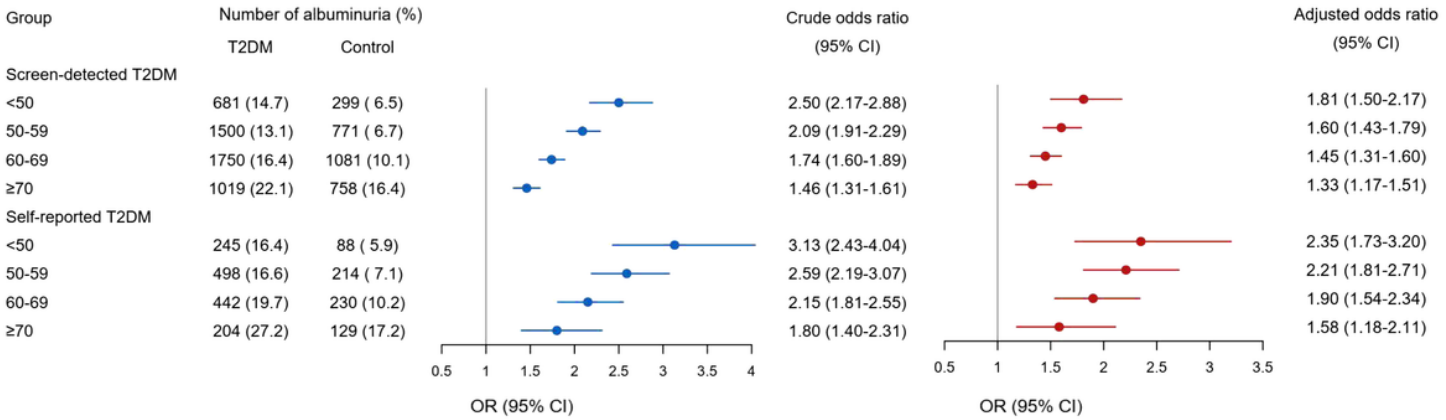


Figure 4

OR (95% CI) of albuminuria in T2DM vs. matched controls according to age at diagnosis. Adjustment was made for education, current smoking, current drinking, history of CVD, use of ACEI/ARB, systolic BP, BMI, LDL-c, TG, and eGFR. Abbreviations: T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate.



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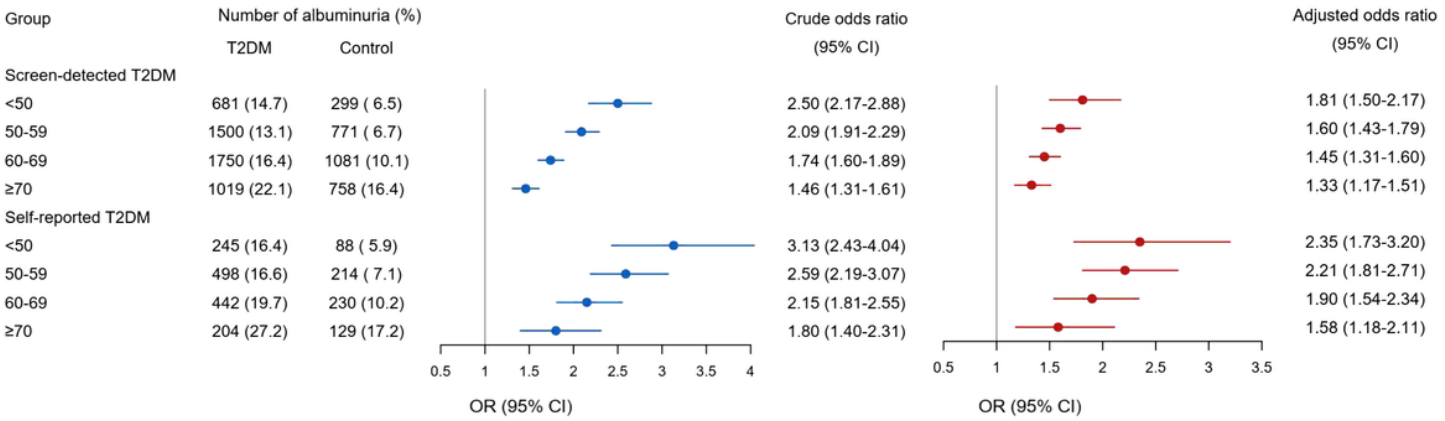

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