Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

The Burden of Multiple Metabolic Diseases and Their Impact on Cardiovascular and Kidney Complications in Type 2 Diabetes: A 10-Year Real-World Study

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Purpose: Although metabolic diseases (MDs) in type 2 diabetes mellitus (T2DM) have been discussed, few studies have comprehensively investigated the prevalence, clinical features, and impact of multiple MDs in T2DM. We aimed to analyze the prevalence and clinical characteristics of multiple MDs including hypertension (HTN), obesity (OB), hyperlipidaemia (HLP), hyperuricaemia (HUA), atherosclerosis (AS), and metabolic dysfunction-associated fatty liver disease (MAFLD) in T2DM patients, and to evaluate the impact of multiple MDs on cardiovascular and kidney complications.

Patients and Methods: This large real-world study involving 9453 T2DM patients was conducted from 2003 to 2012. The clinical features were compared between those with and without MDs. The impact of MDs on cardio-cerebrovascular events (CCBVEs) and chronic kidney disease (CKD) was investigated.

Results: The overall prevalence of MDs was 92.6% in T2DM patients, which remained consistently high from 2003 to 2012 and increased with age and diabetes duration (DD) except for MAFLD. HLP had the highest prevalence in both males and females, while HUA had the lowest. Among T2DM patients, the prevalences of CCBVEs and CKD were significantly higher in those with MDs than in those without (all $P<0.001$), and increased progressively with the number of MDs (all $P<0.001$).

Conclusion: The prevalence of comorbid MDs in T2DM patients was consistently high from 2003 to 2012. The presence of MDs in T2DM patients significantly increased the risk and severity of cardiovascular and kidney complications. Therefore, early screening and intervention for MDs may help to reduce the risk of macrovascular and microvascular complications in T2DM.

Keywords: type 2 diabetes, metabolic diseases, cardiovascular complications, chronic kidney disease

Introduction

Metabolic diseases (MDs) encompass a broad range of chronic conditions characterized by metabolic dysfunction, such as diabetes, hypertension (HTN), obesity (OB), hyperlipidemia (HLP), hyperuricaemia (HUA), atherosclerosis (AS) and metabolic dysfunction-associated fatty liver disease (MAFLD). Diabetes, one of the most prevalent MDs, currently affects approximately 536.6 million people globally.[1] Moreover, chronic complications are widely recognized as the leading cause of disability and mortality in patients with diabetes.[2] In an observational study of 1867 Chinese patients with type 2 diabetes mellitus (T2DM), 62.1% participants suffered from at least one chronic complication, in which the prevalence of cardiovascular and renal complications was 29.6% and 33.5%, respectively.[3]

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T2DM and other MDs share common mechanisms associated with metabolic dysfunction, such as insulin resistance, chronic low-grade inflammation, and oxidative stress.[4] Therefore, individuals with T2DM often coexist with other MDs, which are more prevalent than in the general population. Cusi et al found that the prevalence of non-alcoholic fatty liver disease (NAFLD) in T2DM was approximately 70%, significantly higher than the 19% to 46% reported in general population.[5] Additionally, a Chinese study revealed a 27.22% prevalence of carotid AS in individuals with multiple general health checks aged 30 to 79 years,[6] which is markedly lower than the prevalence of 46.5% to 50.9% reported in T2DM patients.[7,8]

It is well known that cardiovascular events substantially increase the risk of mortality in T2DM population. Einarson et al aggregated data from more than four million people and demonstrated that the prevalence of cardiovascular events was approximately 32.2% in T2DM.[9] However, the prevalence and clinical features of comorbid MDs in T2DM, as well as their impact on cardiovascular events have not been extensively explored to date. In addition, HTN, OB, HLP and HUA significantly contribute to the occurrence of cardiovascular events. Our previous studies also revealed that both abdominal OB and AS remarkably increased the risk of macrovascular lesions in T2DM.[10,11]

Chronic kidney disease (CKD) is a common microvascular complication of diabetes and a major contributor to kidney failure, with T2DM being the leading cause of end-stage kidney disease (ESKD).[12] Additionally, a three-year follow-up study showed that diabetic patients with MAFLD experienced a progression in CKD severity and a significantly increased risk of developing ESRD.[13] However, there is limited study on the impact of coexisting multiple MDs on CKD in T2DM population.

Evidence remains limited regarding the impact of comorbid MDs in T2DM on cardiovascular and kidney complications, and comprehensive data on the prevalence and clinical characteristics of multiple MDs in T2DM are scarce. We therefore aimed to investigate the prevalence and clinical features of MDs, and to explore their impact on CCBVEs and CKD in Chinese patients with T2DM.

Methods

Study Population and Design

This large, cross-sectional, real-world study obtained written informed consent from all subjects, and was approved by the Ethics Committee of the Shanghai Sixth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine (approval number: 2018-KY-018(K)), in accordance with the Declaration of Helsinki.

We consecutively enrolled patients with T2DM who were hospitalized in our department between January 2003 and December 2012, yielding a total of 11,978 participants. Exclusion criteria included: (1) age below 18 years old; (2) incomplete clinical data due to lack of laboratory tests, and abdominal and carotid ultrasound examination; (3) patients with acute diabetic complications such as diabetic ketoacidosis; (4) liver damage caused by drugs, viral hepatitis, and other reasons except for alcohol consumption; and (5) severe systemic or infectious diseases. Ultimately, 9453 T2DM patients were included in the final analysis.

All subjects provided information on duration of diabetes (DD), medication use including lipid-lowering drugs (LLDs), antihypertensive drugs (AHAs), Antiplatelet agents (APAs), insulin or insulin analogues (IIAs), and metformin. Moreover, subjects were also interviewed to obtain smoking and alcohol histories. Smoking was defined as current or former smokers, and alcohol consumption was defined in the same.[14]

Physical Examination and Laboratory Measurements

Physical examination included weight, height, waist and hip circumference, and blood pressure. In addition, we collected overnight fasting and 2-hour post-breakfast venous blood samples as well as 24-hour urine to obtain laboratory data. The post-breakfast sample was drawn exactly 2 hours after the first bite of the standardized meal provided by our hospital. The analytes measured included fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2h PPG), fasting plasma peptide (FCP), and 2-hour postprandial plasma peptide (2h C-P), glycosylated haemoglobin A1c (HbA1c), Fasting insulin, 2h insulin, total triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-Cr), creatinine

(Cr), and C-reactive protein (CRP). Additionally, the detection and calculation methods for 24-hour urinary albumin excretion (UAE), estimated glomerular filtration rate (eGFR), and the homoeostasis model assessment for insulin resistance (HOMA-IR and HOMA2-IR) were described in our recent study.[15]

Diagnostic Criteria

All T2DM patients in our study were enrolled based on the WHO diagnostic criteria described in detail in our previous study.[16] In addition, smoking and alcohol consumption were defined as previously described by our team.[16] Meanwhile, according to the Asia-Pacific criteria established by the World Health Organization, a BMI ≥ 25 kg /m2 is classified as OB.[17] HTN, HLP, HUA, AS, and MAFLD were diagnosed according to the criteria in our previous studies.[16,18–20]

CVEs were defined as a history of myocardial infarction, angina pectoris, angioplasty, or coronary artery bypass surgery, while CBVEs were defined as evidence of transient ischemic attack, ischemic, or haemorrhagic stroke.[11] CCBVEs were defined by a history of CVEs and/or CBVEs, while CVEs + CBVEs referred to the coexistence of both conditions.[11] In addition, CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m2 and/or a urinary albumin excretion (UAE) ≥ 300mg/24h.[21]

Statistical Analysis

Quantitative data were presented as mean ± standard deviation (SD) or median (interquartile intervals). Qualitative variables were presented as percentages. For comparisons of normally distributed continuous variables, the one-way analysis of variance (ANOVA) with least significant difference (LSD) was conducted. For non-normally distributed continuous variables, the Kruskal–Wallis *H*-test or the Mann–Whitney *U*-test was performed. Prevalence data were analysed using the chi-square test. Binary logistic and general linear regression were applied to compare differences between groups before and after controlling for confounders, respectively.

All analyses were performed using SPSS software (version 15.0, SPSS Inc., Chicago, IL, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Subjects

The clinical characteristics of the subjects are reported in Table 1. All subjects were divided into two groups according to the presence or absence of comorbid MDs. There was a significant difference in age between the two groups. After correcting for age and gender, SBP, DBP, WC, WHR, BMI, TC, LDL, CIMT, FPG, 2h PPG, FCP, 2h

Table 1 Characteristics of Participants According to the Presence or Absence of MD

Variables	Without Coexisting MDs (n=698)	With Coexisting MDs (n=8755)	*P* Value	Adjusted *P* Value
Male (n, %)	428 (61.3%)	4738 (54.1%)	<0.001	0.183
Age (years)	53 ± 11	60 ± 12	<0.001	<0.001
*DD (months)	60 (12–120)	96 (36–156)	<0.001	0.11
HTN (n, %)	0 (0.0%)	5124 (58.5%)	<0.001	<0.001
Smoking (n, %)	237 (34.0%)	2555 (29.2%)	0.008	0.548
Drinking (n, %)	130 (18.7%)	1427 (16.4%)	0.121	0.529
AHAs (n, %)	8 (1.1%)	4709 (53.8%)	<0.001	<0.001
LLDs (n, %)	0 (0.0%)	3664 (41.9%)	<0.001	<0.001
APAs (n, %)	186 (26.6%)	4612 (52.7%)	<0.001	<0.001
IIAs (n, %)	498 (71.3%)	6094 (69.6%)	0.335	0.230
Metformin (n, %)	305 (43.7%)	5274 (60.2%)	<0.001	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Without Coexisting MDs (n=698)	With Coexisting MDs (n=8755)	*P* Value	Adjusted *P* Value
SBP (mmHg)	120 ± 13	134 ± 17	<0.001	<0.001
DBP (mmHg)	76 ± 8	81 ± 10	<0.001	<0.001
WC (cm)	79.9 ± 7.96	90.7 ± 10.1	<0.001	<0.001
WHR	0.88 ± 0.06	0.92 ± 0.06	<0.001	<0.001
BMI (kg/m^2)	21.5 ± 2.14	25.2 ± 3.40	<0.001	<0.001
TC (mmol/l)	4.06 ± 0.66	4.87 ± 1.18	<0.001	<0.001
HDL-C (mmol/l)	1.25 ± 0.32	1.12 ± 0.31	<0.001	<0.001
LDL-C (mmol/l)	2.54 ± 0.63	3.09 ± 0.95	<0.001	<0.001
CIMT (mm)	0.71 ± 0.16	0.82 ± 0.20	<0.001	<0.001
*FPG (mmol/l)	7.4 (5.9–9.7)	7.9 (6.4–10.0)	<0.001	<0.001
*2h PPG (mmol/l)	12.3 (9.2–16.3)	13.7 (10.5–17.0)	<0.001	<0.001
HbA1c (%)	9.30 ± 2.50	8.99 ± 2.24	<0.001	0.203
*FCP (ng/mL)	1.21 (0.71–1.72)	1.86 (1.20–2.67)	<0.001	<0.001
*2h C-P (ng/mL)	2.69 (1.35–4.55)	4.09 (2.40–6.12)	<0.001	<0.001
*HOMA2-IR	1.02 (0.61–1.46)	1.61 (1.03–2.33)	<0.001	<0.001
*HOMAIR	2.97 (1.74–4.94)	4.61 (2.75–7.92)	<0.001	<0.001
*Fasting insulin (mU/l)	8.91 (5.58–13.5)	13.0 (8.33–20.6)	<0.001	<0.001
*2h insulin (mU/l)	38.0 (23.4–56.6)	51.9 (33.7–79.2)	<0.001	<0.001
*ALT (U/l)	16 (12–23)	20 (14–31)	<0.001	<0.001
*γGT(U/l)	17 (13–25)	25 (17–39)	<0.001	<0.001
*TG (mmol/l)	0.85 (0.65–1.10)	1.52 (1.06–2.23)	<0.001	<0.001
*Cr (μmol/l)	63 (52–74)	66 (55–80)	<0.001	<0.001
*eGFR (mL/min/1.73 m^2)	122 (103–143)	109 (89–132)	<0.001	<0.001
*SUA (μmol/l)	261 (214–303)	316 (263–378)	<0.001	<0.001
*UAE (mg/24h)	8.08 (5.70–14.6)	12.4 (7.13–35.5)	<0.001	<0.001
*CRP (mg/l)	0.52 (0.24–1.47)	1.22 (0.54–3.00)	<0.001	<0.001

Notes: *The Mann–Whitney U–test was applied. *P*-value: The *P*-values were not adjusted for age and gender for the trend. Adjusted *P* value: The Adjusted *P* values were adjusted for age and gender for the trend.

Abbreviations: DD, diabetes duration; HTN, hypertension; AHAs, antihypertensive agent; LLDs, lipid-lowering drugs; APAs, Antiplatelet agents; IIAs, insulin or insulin analogues; SBP/DBP, systolic/diastolic blood pressure; BMI, body mass index; WHR, Waist-to-hip ratio; TC, total cholesterol; HDL-C/LDL-C, high-density/low-density lipoprotein cholesterol; CIMT, carotid intima-media thickness; FPG, fasting plasma glucose; 2hPPG, 2hpost-prandial plasma glucose; FCP, fasting C peptide; 2hC-P, 2hpost-prandial C-peptide; HbA1c, glycosylated haemoglobin A1c; HOMA2-IR and HOMA-IR, updated homoeostasis model assessment of insulin sensitivity/insulin resistance; ALT, alanine aminotransferase; γ-GT, γ-glutamyltransferase; TG, total triglycerides; Cr, creatinine; SUA, Serum uric acid; UAE, urinary albumin excretion; CRP, C-reactive protein.

C-P, HOMA2-IR, HOMAIR, fasting insulin, 2h insulin, ALT, γ-GT, TG, Cr, SUA, UAE, and CRP were significantly higher in T2DM patients with MDs compared to those without (all $P<0.001$). Additionally, T2DM patients with MDs had a significantly higher prevalence of HTN and were more likely to use AHAs, LLDs, APAs, and metformin (all $P<0.001$). In contrast, HDL and eGFR levels were significantly lower in patients with MDs (all $P<0.001$).

Prevalence and Characteristics of MDs

Figure 1 demonstrates the prevalence and characteristics of MDs in T2DM. The overall prevalence of MDs was 92.6% in T2DM subjects, without significant difference between genders (Figure 1A, 91.7% in men, 93.7% in women, $P=0.305$). In addition, the percentage of T2DM patients with different number of MDs showed an inverted U-shaped distribution in both genders (Figure 1B, $P<0.001$ for trend in men and women). When describing the prevalence of each MD separately, we observed that HUA had the lowest prevalence (Figure 1C 16.3% in men, 21.2% in women), while HLP had the highest prevalence in both genders (Figure 1C: 59.6% in men, 67.0% in women). Especially, the MDs prevalence

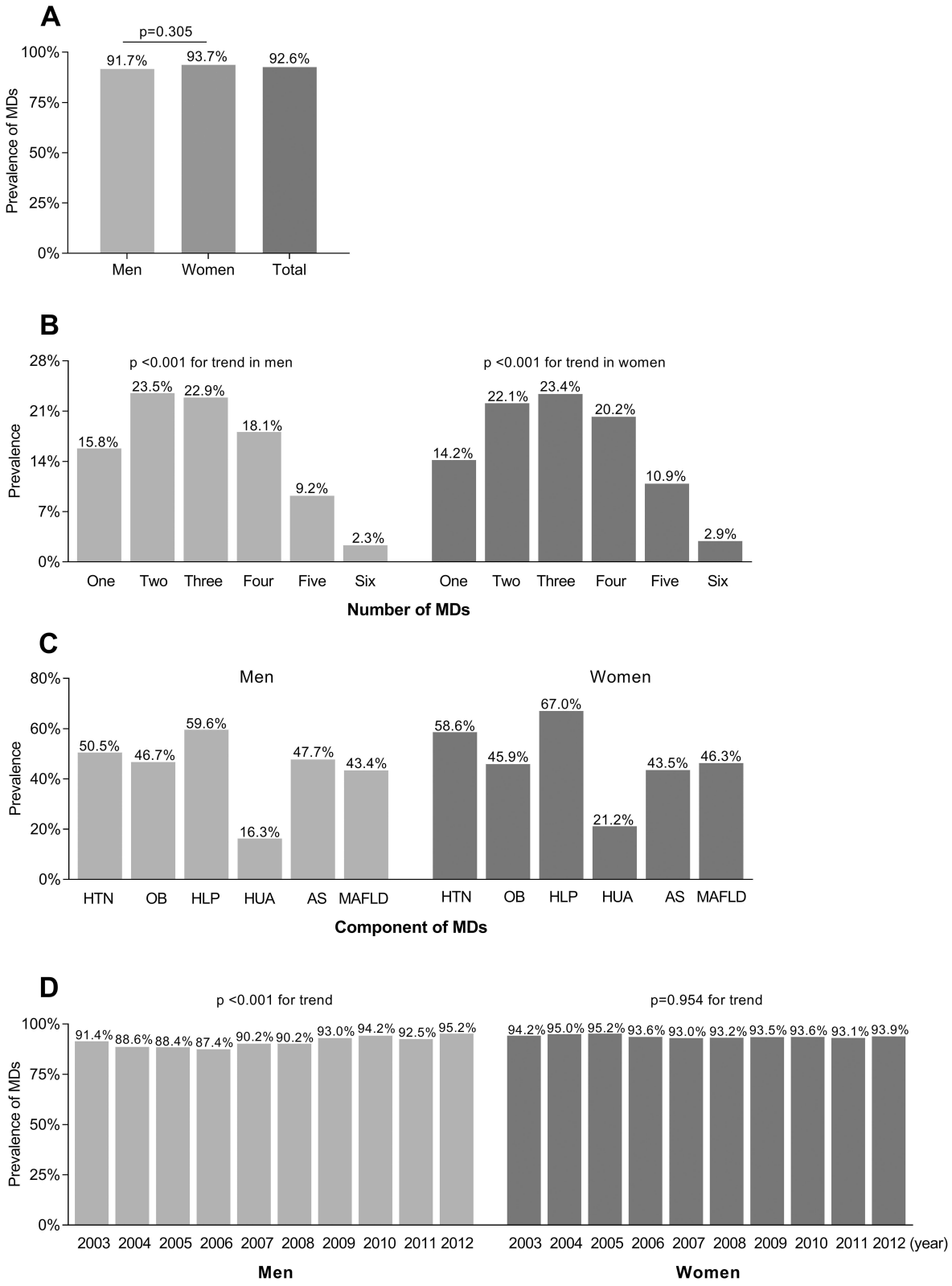

Figure 1 Prevalence and characteristics of MDs. (**A**) Comparison of the MDs prevalence between men and women with T2DM after adjusting for age and DD (*P*=0.305). (**B**) Comparison of prevalence of one to six types of MDs between men and women with T2DM after adjusting for age and DD (*P*<0.001 for trend in men, *P*<0.001 for trend in women). (**C**) Comparison of the prevalence of different types of MDs between men and women with T2DM after adjusting for age and DD. (**D**) Comparison of the MDs prevalence in different years of observation between men and women with T2DM after adjusting for age and DD (*P*<0.001 for trend in men, p=0.954 for trend in women).

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remained consistently high in both genders from 2003 to 2012, with the lowest prevalence recorded in 2006 in males (87.4%) and in 2007 in females (93.0%) (Figure 1D).

Comparison of the MDs Prevalence Stratified by Age

Figure S1 compares MDs prevalence stratified by age. The MDs prevalence in patients older than 65 years was significantly higher than in those younger than 65 years for both genders (Figure S1A, $P<0.001$ in both genders). In addition, the MDs prevalence showed a significant increasing trend with age in both genders (Figure S1B, $P<0.001$ for trend in both genders). Patients older than 65 years were more likely to have three or more MDs compared to those under 65 years (Figure S1C). Moreover, patients older than 65 years had a higher prevalence of HTN, HUA, and AS, while OB, HLP, and MAFLD were more prevalent in patients younger than 65 years (Figure S1D). In addition, the percentage of T2DM patients with four, five, or six MDs gradually increased with age (Figure S1E). Interestingly, the prevalence of HTN and AS increased with age, while the prevalence of OB and MAFLD showed a decreasing trend with age ($P<0.001$ for all trends) (Figure S1F).

Comparison of the MDs Prevalence Stratified by DD

Figure S2 compares MDs prevalence stratified by DD. Compared to those with a DD less than 120 months, patients with a DD greater than 120 months showed a higher MDs prevalence in both genders (Figure S2A, $P<0.001$ in both genders). Meanwhile, the MDs prevalence significantly increased with prolonged DD in T2DM patients (Figure S2B, $P<0.001$ for trend in both genders). Additionally, patients with a DD greater than 120 months were more likely to have two or more MDs (Figure S2C). Among the six types of MDs, patients with a longer DD had a higher prevalence of HTN, HUA, and AS, and a lower prevalence of OB, HLP, and MAFLD compared to those with a shorter DD (Figure S2D). When patients were stratified by DD, no remarkable difference was found in the prevalence of varying numbers of MDs among different DD groups (Figure S2E). Furthermore, the prevalence of HTN and AS increased with DD, while MAFLD showed a decreasing trend (Figure S2F).

The Risk Factors for MDs

Table 2 presents the risk factors for MDs in T2DM stratified by gender. Age was significantly and positively associated with MDs in both men (OR=1.05, 95% CI: 1.03–1.06) and women (OR=1.06, 95% CI: 1.04–1.08). After adjustment for multiple confounders, SBP (men: OR=1.03, 95% CI: 1.02–1.05; women: OR=1.04, 95% CI: 1.03–1.06), BMI (men: OR=1.32, 95% CI: 1.23–1.41; women: OR=1.33, 95% CI: 1.23–1.43), TC (men: OR=3.54, 95% CI: 2.23–5.63; women: OR=2.42, 95% CI: 1.91–3.08), TG (men: OR=1.87, 95% CI: 1.49–2.33; women: OR=2.34, 95% CI: 1.78–3.06), SUA (men: OR=1.41, 95% CI: 1.16–1.72; women: OR=1.70, 95% CI: 1.33–2.17), and CIMT (men: OR=5.04, 95% CI: 1.78–14.3; women: OR=4.24, 95% CI: 1.02–17.7) were positively associated with MDs in both genders.

Additionally, ALT (OR=1.29, 95% CI: 1.09–1.52), UAE (OR=1.26, 95% CI: 1.06–1.50), CRP (OR=1.17, 95% CI: 1.01–1.37), and 2h insulin levels (OR=1.22, 95% CI: 1.04–1.44) were positively associated with MDs only in men, whereas HDL showed an inverse association (OR=0.42, 95% CI: 0.20–0.89). In women, FCP was positively associated with MDs (OR=1.96, 95% CI: 1.24–3.09).

The Relationship Between MDs and Macrovascular Events

Figure 2 analysis the association of MDs with macrovascular events. The prevalence of CVEs, CBVEs, CCBVEs, and combined CVEs and CBVEs in T2DM patients with comorbid MDs was 4.5%, 11.6%, 15.3%, and 0.8%, respectively, significantly higher compared to those without MDs (0.1%, 1.7%, 1.9%, and 0.0%, respectively) (Figure 2A, all $P<0.001$). Furthermore, the prevalence of CVEs (Figure 2B, 2.0%, 2.3%, 4.9%, 6.2%, 7.6%, 12.1% for one to six MDs, respectively, $p<0.001$ for trend), CBVEs (Figure 2C, 7.2%, 9.2%, 11.3%, 14.4%, 16.9%, 20.0% for one to six MDs, respectively, $P<0.001$ for trend), and CCBVEs (Figure 2D, 8.8%, 11.2%, 15.4%, 19.6%, 22.4%, 30.4% for one to six MDs, respectively, $P<0.001$ for trend) was all increased progressively with the increased number of MDs. Additionally, there was an upward trend in the prevalence of combined CVEs and CBVEs with the increasing number

Table 2 The Risk Factors for MDs Stratified by Gender

	B Statistic	OR	95% CI	*P* Value
Men				
Age	0.05	1.05	1.03–1.06	<0.001
SBP	0.03	1.03	1.02–1.05	<0.001
BMI	0.28	1.32	1.23–1.41	<0.001
ALT	0.25	1.29	1.09–1.52	0.003
TC	1.27	3.54	2.23–5.63	<0.001
HDL	−0.86	0.42	0.20–0.89	0.024
TG	0.62	1.87	1.49–2.33	<0.001
SUA	0.34	1.41	1.16–1.72	<0.001
UAE	0.23	1.26	1.06–1.50	0.007
CRP	0.16	1.17	1.01–1.37	0.037
CIMT	1.62	5.04	1.78–14.3	0.002
2h insulin	0.20	1.22	1.04–1.44	0.015
Women				
Age	0.06	1.06	1.04–1.08	<0.001
SBP	0.04	1.04	1.03–1.06	<0.001
BMI	0.28	1.33	1.23–1.43	<0.001
TC	0.88	2.42	1.91–3.08	<0.001
TG	0.85	2.34	1.78–3.06	<0.001
SUA	0.53	1.70	1.33–2.17	<0.001
CIMT	1.45	4.24	1.02–17.7	0.047
FCP	0.67	1.96	1.24–3.09	0.004

Notes: Men and Women: adjusted for age, diabetes duration, smoking, alcohol drinking, the use of IIAs and Metformin, SBP, DBP, WC, WHR, BMI, ALT, γ-GT, TC, HDL, LDL, TG, Cr, SUA, FPG, 2h PPG, UAE, CRP, HbA1c, CIMT, FCP, 2h C-P, fasting insulin, 2h insulin.

of MDs (Figure 2E: 0.4%, 0.3%, 0.8%, 1.1%, 2.2%, and 1.7% for one to six MDs, respectively; $P<0.001$ for trend), peaking in patients with five MDs.

The Relationship Between MDs and CKD

Figure 3 demonstrates the relationship between MDs and CKD. The CKD prevalence in T2DM patients with MDs was 10.9%, significantly higher than in those without MDs (1.7%) (Figure 3A, $P<0.001$). Furthermore, the CKD prevalence showed a significant upward trend with the increasing number of MDs (Figure 3B, 4.4%, 7.2%, 11.3%, 14.0%, 18.1%, 27.1% for one to six MDs, respectively, $P<0.001$ for trend). Similarly, UAE levels were significantly higher in those with MDs (Figure 3C, $P<0.001$), and showed a significant upward trend with the increasing number of MDs (Figure 3D, $P<0.001$ for trend). Conversely, eGFR levels were markedly lower in participants with MDs than in those without (Figure 3E, $P<0.001$). Moreover, eGFR levels significantly decreased as the number of MDs increased (Figure 3F, $P<0.001$ for trend).

Discussion

Our cross-sectional, real-world study revealed that the consistently high prevalence of comorbid MDs in T2DM from 2003 to 2012. More importantly, T2DM patients with comorbid MDs were at a significantly higher risk for cardiovascular and renal complications. Furthermore, this risk substantially increased with the increasing number of coexisting MDs. To the best of our knowledge, this is the first large-scale, cross-sectional study spanning over a decade to comprehensively investigate the clinical characteristics of comorbid MDs in T2DM and their impact on cardiovascular and kidney complications.

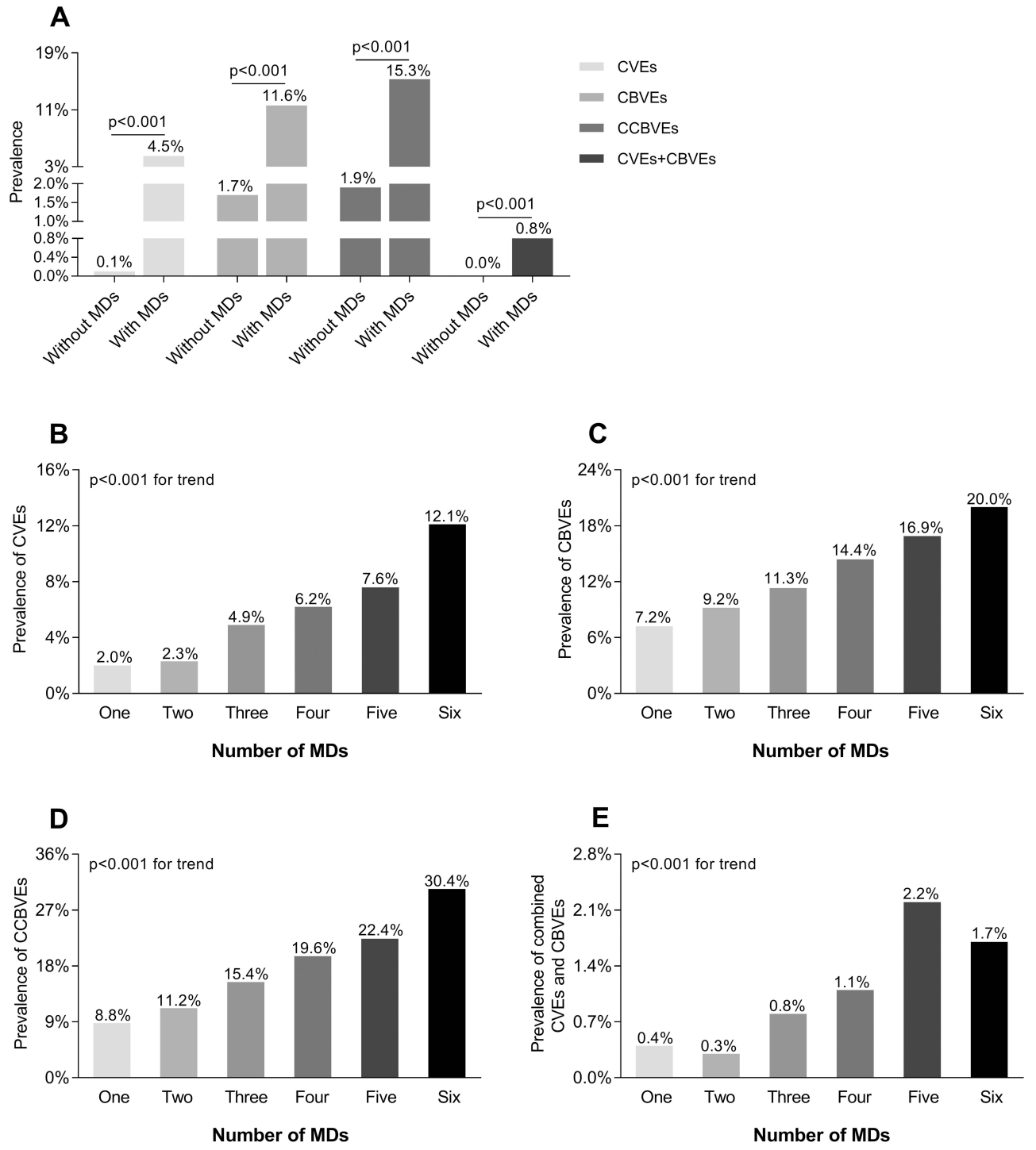

Figure 2 The relationship between MDs and macrovascular events. (**A**) Comparison of the prevalence of CVEs, CBVEs, CCBVEs and CVEs+ CBVEs in T2DM patients with and without MDs after adjusting age, gender and DD (*P*<0.001 for all). (**B**) Comparison of the prevalence of CVEs in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend). (**C**) Comparison of the prevalence of CBVEs in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend). (**D**) Comparison of the prevalence of CCBVEs in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend). (**E**) Comparison of the prevalence of CVEs+ in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend).

Similar to our findings, a study of 1633 T2DM patients reported that 98.5% of subjects had metabolic comorbidities including HTN, OB and HLP.[22] However, a large meta-analysis reported that the pooled prevalence of metabolic disorders in the general population ranged only from 12% to 24%,[23] which was significantly lower than the prevalence

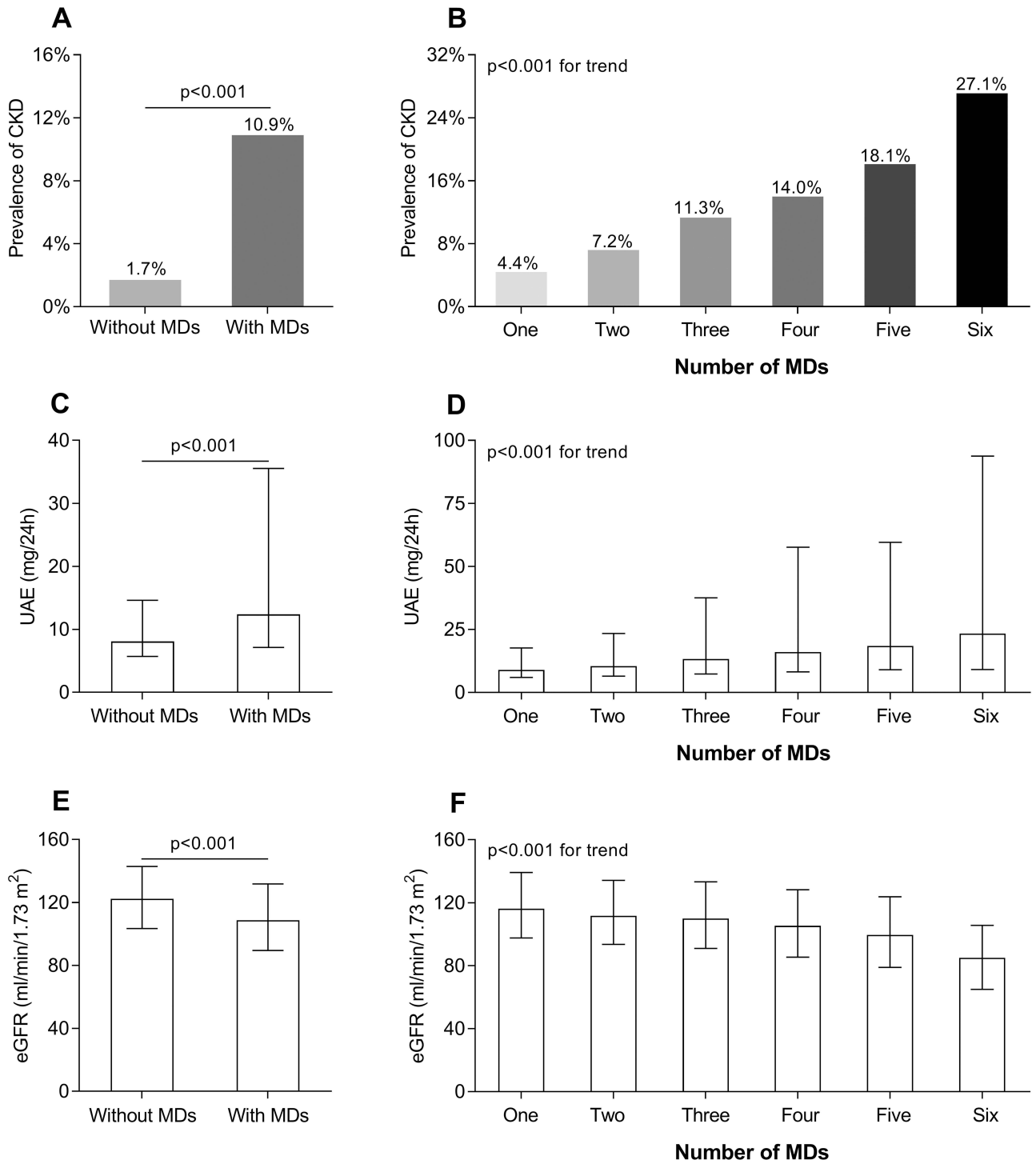

Figure 3 The relationship between MDs and CKD. (**A**) Comparison of the prevalence of CKD in T2DM patients with and without MDs after adjusting age, gender and DD (*P*<0.001). (**B**) Comparison of the prevalence of CKD in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend). (**C**) Comparison of UAE levels in T2DM patients with and without MD after adjusting age, gender and DD (*P*<0.001). (**D**) Comparison of UAE levels in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend). (**E**) Comparison of eGFR levels in T2DM patients with and without MD after adjusting age, gender and DD. (*P*<0.001). (**F**) Comparison of eGFR levels in T2DM patients coexisting with one to six MDs after adjusting age, gender and DD (*P*<0.001 for trend).

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of comorbid MDs in T2DM. Therefore, it is evident that T2DM patients are at considerable risk of developing MDs. More importantly, we observed a persistently elevated prevalence of coexisting MDs in T2DM patients from 2003 to 2012, without obvious decrease in either gender. It indicated that early screening and intervention for comorbid metabolic disorders in T2DM have not been adequately promoted in China. Therefore, greater emphasis is needed on monitoring metabolic dysfunction and ensuring early diagnosis and treatment of comorbidities in T2DM patients.

The present study also revealed the clinical characteristics of various MDs including HTN, OB, HLP, HUA, AS, and MAFLD in T2DM patients. Among these, HTN and AS showed the most pronounced increase in prevalence with advancing age and prolonging DD. Consistent with our findings, Janghorbani et al reported that the prevalence of HTN increases with age in T2DM patients of both genders.[24] Additionally, another investigation identified DD as a significant risk factor for increased carotid intima-media thickness (IMT) in T2DM patients.[25] However, unlike HTN and AS, we observed that the prevalence of MAFLD significantly decreased with advanced age and prolonged DD in T2DM patients. Our previous finding also observed a significant negative association of MAFLD with age and DD.[26] Similarly, Ajmera et al found that patients with NAFLD were more likely to be younger and had a shorter DD.[27] The inverse relationship observed between MAFLD and both age and DD may be partly explained by improvements in physical activity and dietary habits among older adults.[28] Moreover, a longer DD was associated with reduced fasting insulinemia and insulin resistance as measured by the HOMA-IR index, both of which are well-established triggers of MAFLD.[28] According to the WHO diagnostic criteria, the prevalence of OB among T2DM patients was approximately 50% in our study, which was significantly higher than the 32.3% reported among Chinese adults in 2010–2012.[29] Interestingly, the prevalence of OB declined with increasing age, and significantly decreased when the DD exceeds 120 months. Consistent with our findings, a study by Chandrasekaran et al also reported weight loss in T2DM population with increased age and prolonged DD.[30] Recent studies have reported a high prevalence of sarcopenia in T2DM patients and age-related anorexia in older adults, which may explain this association.[31,32] Both conditions can lead to unintentional weight loss. This pattern aligns with evidence of a high prevalence of sarcopenia and sarcopenic obesity in T2DM and anorexia of aging in older adults, conditions associated with unintentional weight loss. Therefore, managing OB in T2DM population is of significant clinical importance in reducing the incidence of multiple MDs.

Additionally, the prevalence of HLP was the highest among several MDs and remained consistently high, without significant differences observed across gender, age, and DD. Given that HLP is a major cardiovascular risk factor, controlling the occurrence and progression of HLP in T2DM is of significant clinical importance. On the contrary, although the prevalence of HUA was the lowest among the six MDs, with a 20% prevalence in T2DM patients, it still exceeded the prevalence of 14.8% observed in the general population.[33]

Given that macrovascular and microvascular complications are the leading causes of mortality and disability in T2DM patients, we also investigated the impact of comorbid MDs on cardiovascular and renal complications in these patients. The present study clearly demonstrated that the prevalence of CCBVEs was significantly higher in T2DM patients with coexisting MDs compared to those without, indicating that T2DM subjects combined with other MDs are at increased risk for cardiovascular complications. In consistent with our findings, it has been found that the incidence of cardiovascular disease increased by approximately 7% in T2DM patients with NAFLD compared to those without NAFLD.[34] Additionally, Fan et al found that the risk of total CCBVEs in T2DM with HLP was 1.68 times higher than in those without HLP, which may be due to the increased systemic inflammatory response caused by HLP.[35] Similarly, T2DM subjects combined with HUA, HTN, AS, and OB also face an increased cardiovascular risk. For example, a previous study by our group found that both carotid and lower limb AS significantly heightened the cardio-cerebrovascular risk in T2DM, and their concomitant presence further increased the prevalence of CCBVEs in T2DM.[36]

More importantly, we observed a higher prevalence of CCBVEs as the number of comorbid MDs increased in T2DM patients. Similar to our findings, Cherney et al demonstrated that compared to the general T2DM population, individuals with multiple concurrent metabolic comorbidities, such as HTN and HLP, experienced a significantly increased risk of cardiovascular adverse outcomes and even all-cause mortality.[37] Thus, an increase in the number of metabolic disorders in T2DM further elevates the cardiovascular risk. Since cardiovascular disease is the leading cause of death in T2DM, early detection and intervention for the occurrence and progression of MDs in T2DM are crucial for controlling the risk of cardiovascular events and mortality.

Furthermore, our study revealed that the prevalence of CKD was nearly 10-fold higher in T2DM patients with combined MDs compared to those without comorbid MDs, and increased with the number of MD types. Consistent with our study, a matched case-control analysis showed that the risk of CKD is considerably higher in overweight T2DM patients across ethnic groups (95% CI of IRR: 1.5, 3.4).[38] Additionally, the risk of developing CKD and kidney dysfunction is also significantly increased in T2DM patients with other MDs such as HLP, HUA, AS and MAFLD.[19,39–41] For example, our previous study observed that both HUA and low urinary uric acid excretion are closely associated with an increased risk of CKD, and their coexistence further exacerbates CKD risk in T2DM.[19] Furthermore, Hu et al found that among obese patients with T2DM, the prevalence of CKD was significantly higher in those combined with HTN (OR=1.768, P=0.042) and HUA (OR=2.263, *P*=0.003).[42] Taken together, our findings and previous reports provide convergent evidence of a graded increase in CKD risk among T2DM patients with metabolic comorbidities, supporting risk stratification by the presence and number of MDs.

In addition, we observed that comorbid MDs significantly worsened the severity of CKD, as evidenced by a notably elevated UAE and decreased eGFR levels in subjects with comorbid MDs. Consistently, a previous study also suggested that T2DM patients with coexisting NAFLD had elevated albuminuria and microalbuminuria, along with reduced GFR levels.[43] Kidney complications and mortality due to end-stage renal disease (ESRD) impose substantial burdens on T2DM patients. Therefore, the early identification and management of concomitant MDs in T2DM patients are critically important for reducing the risk of CKD, mitigating its severity and associated mortality.

Notable differences in postprandial and fasting blood glucose were observed between two groups, indicating greater blood glucose fluctuation in T2DM patients with comorbid MDs. A previous study had uncovered a direct correlation between glycemic variability and the occurrence of cardiovascular complications and CKD in patients with diabetes mellitus.[44] Furthermore, our results demonstrated the increased insulin resistance, as indicated by higher HOMA2-IR values, in T2DM patients with comorbid MDs. Likewise, a review also demonstrated that IR is a key pathophysiological factor in the development and progression of CKD in different types of diabetes.[45] Therefore, greater blood glucose fluctuation and more severe IR might be factors contributing to the higher risk of cardiovascular and renal complications in T2DM patients with comorbid MDs.

Finally, we found that T2DM patients with comorbid MDs had more than double the CRP levels compared to those without. CRP has been well-established as an important clinical marker of chronic inflammation-related disease. Inflammatory responses and associated oxidative stress cause direct damage to vascular endothelium, which is closely linked to both macrovascular and microvascular complications in diabetes.[46] This may explain why T2DM patients with comorbid MDs exhibited a higher risk and severity of CCBVEs and CKD in the present study.

There are several limitations in the present study. Firstly, this was a single-center study conducted in T2DM patients, which may introduce selection bias and limit the generalizability of our findings to other populations. Future multicenter studies involving diverse clinical backgrounds are warranted to reduce this bias. Second, our study did not include other MDs, such as lower limb arteriosclerosis and polycystic ovary syndrome (PCOS). This incomplete classification of MDs may have led to misclassification bias, underscoring the need for future research to adopt a more comprehensive classification system. Additionally, our study used the least significant difference (LSD) procedure for post-hoc pairwise comparisons, which affords less stringent control of the family-wise type I error. Future studies should therefore adopt multiplicity-adjusted procedures. Finally, as a cross-sectional study, we are unable to determine whether managing comorbid MDs in T2DM reduces the risk of microvascular and macrovascular complications. Therefore, future prospective studies building on our findings would be valuable.

Conclusion

Over a ten-year period from 2003 to 2012, T2DM patients consistently exhibited a high prevalence of comorbid MDs, with an overall prevalence exceeding 90%. More importantly, the presence of comorbid MDs in T2DM patients significantly increased the risk and severity of cardiovascular and kidney complications. In clinical practice, early screening and intervention for MDs may help reduce the risk and severity of macrovascular and microvascular complications in T2DM. Future study should include multicenter prospective cohort studies to validate these

associations and determine whether targeted management of MDs can reduce the risk of cardiovascular and kidney complications.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study obtained written informed consent from all subjects, and was approved by the Ethics Committee of the Shanghai Sixth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine (approval number: 2018-KY-018(K)).

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Author Contributions

Lian-Xi Li and Yu-Ren Zhang: investigation, conceptualisation, resources, project administration, and supervision. Man-Rong Xu, and Ya-Wen Zhang: data curation, formal analysis, software, and visualization. Man-Rong Xu: writing – original draft. Lian-Xi Li: funding acquisition. Meng-Han Li, Jun-Xi Lu: methodology, validation, and writing– review & editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

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Disclosure

No potential conflict of interest relevant to this article was reported.

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