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Lower body mass index is not of more benefit for diabetic complications

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ABSTRACT

Aims/Introduction: To investigate the relationship between different body mass index (BMI) levels and vascular complications in type 2 diabetes mellitus patients.

Materials and Methods: Data were collected from 3,224 individuals with type 2 diabetes mellitus (male/female: 1,635/1,589; age 61.31 ± 11.45 years), using a retrospective case study design. The association of BMI quintiles and diabetes mellitus vascular complications was assessed using multiple logistic regression models adjusting for age, sex, diabetes duration, smoking status, drinking and other confounders, using those with the lowest quintile of BMI as the reference group.

Results: With increasing BMI, the detection rate of diabetic peripheral neuropathy and peripheral arterial disease initially decreased and then it increased, whereas the detection rate of diabetic kidney disease and carotid atherosclerotic plaques showed an upward trend; however, diabetic retinopathy was irregular. The odds ratios of diabetic peripheral neuropathy decreased as BMI increased from the 21st percentile to the 80th percentile initially, and increased when BMI was in >80th percentile. The same result was shown in peripheral arterial disease. BMI >80th percentile showed a 1.426-fold risk of diabetic kidney disease and a 1.336 -fold risk of carotid atherosclerotic plaque.

Conclusions: In patients with type 2 diabetes mellitus, the relationship between different BMIs and vascular complications varies. A U-shaped relationship was observed between BMI and diabetic peripheral neuropathy, as well as BMI and peripheral arterial disease. BMI is positively correlated with diabetic kidney disease and carotid atherosclerotic plaque; however, it is not correlated with diabetic retinopathy.

INTRODUCTION

Diet and lifestyle changes, in addition to increased incidences of overweight and obesity, are generally believed to be the main factors responsible for the global increase in the prevalence of type 2 diabetes mellitus[1]. The complications resulting from diabetes seriously affect patients' quality of life. In individuals with diabetes mellitus, atherosclerosis is the primary cause of impaired life expectancy, whereas diabetic kidney disease (DKD) and diabetic retinopathy (DR) are the largest contributors to end-stage renal disease and blindness, respectively[2]. Previous studies have shown that body mass index (BMI) is closely related to diabetes mellitus vascular complications[3,4]; however, there is still no consensus on the precise relationship between BMI and vascular complications.

Research has yielded many different and often conflicting conclusions about the exact relationship between BMI levels and vascular complications. Numerous studies have shown that obesity is a risk factor for diabetic peripheral neuropathy (DPN)[5,6]. Nevertheless, Xu *et al.*[7] have recently proposed the opposite concept; that is, that a low BMI might be a potential risk factor for DPN. Furthermore, most studies have suggested that a high BMI is a risk factor for DKD[8,9]; however, one study suggested that a low BMI is positively associated with the albumin-to-creatinine ratio[10]. Additionally, conflicting results have been reported about a possible relationship between a higher BMI and increased risk of DR[11]. An early study suggested that BMI is not associated with DR[12]. Nevertheless, one study showed a relationship between a higher BMI and increased risk of DR[13]. In addition, most of the studies that evaluated the

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association between BMI and peripheral arterial disease (PAD) used only elderly patients, and some of the studies have shown that a high BMI[5,14] and a low BMI[15] are associated with PAD. Other studies, however, have not reported such associations[16]. Compared with normal BMI, patients with high BMI have an increased risk of atherosclerosis[17,18].

These different conclusions might be explained in part by several different factors. In addition, there are few systematic investigations on the relationship between BMI and micro- and macrovascular complications. Therefore, the aim of the present study was to investigate the dynamic relationship between different BMI levels and diabetic vascular complications, and to assess the appropriate BMI range of patients with type 2 diabetes mellitus.

METHODS

Study participants

A total of 3,224 type 2 diabetes patients from the Endocrinology Department of the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China were enrolled in this study between 1 January 2011 and 30 December 2016. Type 2 diabetes mellitus was defined according to the American Diabetes Association classification[19]. Exclusion criteria were the following: type 1 diabetes, diabetic ketoacidosis, hyperosmolar non-ketotic comas, gangrene and amputation; other causes of renal disease, tumor, acute infection, patients in critical condition; and other causes of neuropathy[20,21], including familial[22], alcohol[23], nutrition[24], uremic, poisoning, drug addictions and so on (Appendix S1). Diseases or drugs that affect BMI, such as abnormal thyroid function, secondary obesity and use of weight-reducing tablets, were also excluded.

The ethics committee of the First Affiliated Hospital of Fujian Medical University approved this cross-sectional study, and written informed consent was obtained from all study participants.

Measurements

The patients' health records and history of neuropathy symptoms, such as numbness, prickling, burning or stabbing pain, were obtained. All patients underwent a routine physical examination, including height, weight and blood pressure (BP) measurements. For the bodyweight and height measurements, patients wore light clothing and no shoes. The BMI (kg/m^2) was calculated by dividing the weight by the squared height (kg/m^2). BP was measured after a 15-min rest, and the mean of three measurements was used. The neurological examination included the following: pinprick, temperature and vibration (using a 128-Hz tuning fork) perceptions; 10-g monofilament pressure sensation at the distal halluces; and ankle reflexes[25]. Neuropathy caused by other diseases, but not diabetes, was excluded by analyzing the patient's family and medication history, and by carrying out relevant investigations (e.g. albumin, complete blood count, creatinine, alanine aminotransferase, gamma-glutamyl transferase, postgastroplasty)[20]. DPN screening was carried out by an experienced endocrinologist in a quiet and secluded room. We referral to a neurologist in situations where the clinical features were atypical, and the diagnosis was unclear. A professional ophthalmologist carried out the fundus examination after mydriasis.

Blood samples were collected after overnight fasting (approximately 10 h). Consequently, blood urea nitrogen, serum creatinine, uric acid, albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol and fasting plasma glucose were measured. Glycated hemoglobin A1c was determined by high-performance liquid chromatography (VARIANTTM II; BIO-RAD, Hercules, CA, USA). The urinary albumin-to-creatinine ratio (mg/g) was calculated by dividing the urine albumin content by the urine creatinine content, after a morning urine collection. The estimated glomerular filtration rate ($mL/min/1.73\ m^2$) was calculated as $186 \times \text{serum creatinine (mmol/L)}^{-1.154} \times \text{age}^{-0.203}$ ($\times 0.742$ if female)[26].

An ultrasound examination of the carotid artery was carried out by expert sonographers with the Doppler ultrasonic diagnostic apparatus (Prosound α-10; ALOKA Company, Tokyo, Japan), using a probe frequency of 7.5–10 MHz. The examination included the measurement of both carotid arteries and bilateral subclavian artery intima-media thickness (IMT), and whether a plaque was attached. Ankle brachial index (ABI) was measured by a specialist using an 8-mHz hand-held Doppler device (Summit Doppler Systems, Trumbull, CT, USA). The systolic BP (SBP) from both brachial arteries, posterior tibial and dorsalis pedis arteries was measured with the patient in the supine position and post-exercise. The procedure required an initial measurement of the ABI at rest[27]. The patient was then asked to walk in the hallway for 3.2 km/h until claudication pain occurred (or a maximum of 5 min), after which, the ankle pressure was measured once again[28]. The ABI was calculated for each leg by taking the higher pressure of the two arteries (posterior tibial and dorsalis pedis) at the ankle, divided by the higher of the two arm brachial arterial systolic pressures[27].

Definitions of complications

DPN was defined as a combination of typical symptomatology and distal sensory loss with absent reflexes or, if symptoms were absent, the presence of signs in people with diabetes after the exclusion of non-diabetic causes[25]. DKD was identified and monitored by assessing kidney function (using estimated glomerular filtration rate $<60\ mL/min/1.73\ m^2$) and kidney damage (using urinary albumin-to-creatinine ratio >30 mg/g[29]. DR was defined by typical retinal changes, including microaneurysms, vitrectomy, hemorrhages and exudates on fundoscopy[30]. Hypertension was defined as SBP ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg and/or treatment with antihypertensive drugs[31]. Carotid atherosclerotic plaque was defined as the presence of at least one focal lesion >1.3 mm in any segment of either carotid artery[32]. Finally, it was reasonable to consider an ABI ≤0.9 or a post-exercise ABI decrease of >20% as a diagnostic criterion for PAD (Appendix S2)[27].

Statistical analysis

The Kolmogorov–Smirnov test was used to test whether a variable conformed to a normal distribution. Statistical results are presented as mean ± standard deviation, median (interquartile range) or proportions. The patients were divided into quintiles according to current BMI. Differences in the baseline characteristics among the BMI categories were analyzed by ANOVA test and post-hoc least significant difference *t*-test, Kruskal–Wallis test and Nemenyi post-hoc test, and the χ^2-test and partitions of the χ^2-test post-hoc test. Multivariate logistic regression model was used to investigate the associations between BMI categories with microvascular (DPN, DKD and DR) and macrovascular complications (carotid atherosclerotic plaque and PAD), using the $P_{\leq 20}$ group as the reference, and expressed as odds ratios (OR) with a 95% confidence interval (CI). $P < 0.05$ was considered statistically significant. All analyses were carried out using IBM SPSS software version 18.0 (IBM, Armonk, NY, USA).

RESULTS

Participant characteristics

The baseline characteristics of the 3,224 type 2 diabetes mellitus patients categorized according to their BMI are shown in Table 1. The mean age was 61.31 ± 11.45 years, and the mean BMI was 24.56 ± 3.65 kg/m^2. The SBP, albumin, triglycerides, uric acid and detection rate of hypertension were positively correlated with increase in BMI ($P < 0.001$ for all). Significant changes were observed in the age, smoking, drinking, DBP, HbA1c, total cholesterol, HDL, creatinine, estimated glomerular filtration rate, albumin-to-creatinine ratio, left ABI and right ABI. However, no significant differences were observed between groups for the following characteristics: the duration of diabetes mellitus, sex, fasting plasma glucose, low-density lipoprotein cholesterol, blood urea nitrogen, left IMT and right IMT. In addition, significant differences were found between the five groups based on medication use (both $P < 0.05$), with the exception of oral hypoglycemic agents and β-blockers. Detection rates of vascular complications are shown in Figure 1.

Multiple logistic regression analysis for diabetic vascular complications according to BMI quintiles

This relationship between BMI and risk for vascular complications is shown in multivariable analyses after adjustment for age, sex, diabetes duration, smoking status, drinking, SBP, DBP, HbA1c level, and uric acid, total cholesterol, HDL, triglycerides level, albumin and treatment (angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, angiotensin receptor blocker, beta-blocker, calcium channel blocker and statins; Figure 2). Compared with individuals with BMI in the lowest quintile, those in the second, third and fourth quintiles had adjusted ORs of 0.764 (95% CI 0.598–0.976, $P = 0.031$), 0.698 (95% CI 0.543–0.897, $P = 0.005$) and 0.706 (95% CI 0.546–0.911, $P = 0.008$) for DPN, respectively. However, no significant differences in the rate of DPN were observed between the lowest quintile group and the highest quintile group (OR 0.914, 95% CI 0.705–1.185, $P = 0.496$; Figure 2a). In addition, individuals with a BMI of 21.62–27.33 kg/m^2 had a lower risk of DPN compared with individuals with a BMI <21.62 kg/m^2, but this was not true for individuals with a BMI >27.33 kg/m^2.

In a similar multiple logistic regression analysis carried out for the risk for DKD, a higher BMI was positively correlated with DKD. Compared with individuals with BMI in the lowest quintile, those in the highest quintile had an adjusted OR of 1.426 (95% CI 1.005–2.023) for DKD. In addition, there were no significant differences in the middle quintile group and the lowest quintile group. The highest risk for DKD was noted in individuals with a BMI >27.33 kg/m^2 (Figure 2b). Compared with the lowest quintile group, the other groups did not show any significant differences in the risk of DR ($P > 0.05$ for all; Figure 2c).

In a similar multiple logistic regression analysis carried out for the risk for carotid atherosclerotic plaque, a higher BMI was positively correlated with carotid atherosclerotic plaque. Patients with the highest quintile of BMI had a 33.6% increase in the odds of having carotid atherosclerotic plaque (OR 1.336; 95% CI 1.014–1.762; $P = 0.040$), as compared with those with the lowest quintile of BMI. No other significant changes in carotid atherosclerotic plaque were observed (Figure 2d).

Finally, compared with individuals with BMI in the lowest quintile, those in the second, third and fourth quintiles had adjusted ORs of 0.632 (95% CI 0.408–0.978, $P = 0.039$), 0.549 (95% CI 0.349–0.863, $P = 0.009$) and 0.525 (95% CI 0.334–0.827, $P = 0.005$) for PAD, respectively. Yet, no significant differences in the rate of PAD were observed between the lowest quintile group and the highest quintile group, as shown in Figure 2e. Compared with individuals with a BMI <21.62 kg/m^2, individuals with a BMI between 21.62 and 27.33 kg/m^2 had a lower risk of PAD, but this was not so for individuals with a BMI >27.33 kg/m^2.

DISCUSSION

To the best of our knowledge, the present study is the first to assess the possible associations between BMI and vascular complications in Chinese patients with type 2 diabetes. We showed that there are different relationships between different BMI levels and vascular complications. A U-shaped relationship was observed between BMI and DPN, as well as between BMI and PAD. Individuals with a BMI of 23.51–25.16 kg/m^2 had the lowest risk of DPN and PAD. In addition, a higher BMI was positively correlated with DKD and carotid atherosclerosis plaque. However, it was not possible to confirm the link between BMI and DR in the present study.

The risk factors of DPN include blood glucose control, diabetes duration, age, BMI and hyperlipidemia[33–35]. Recent studies have shown that obesity is a risk factor for DPN[5,6]; nevertheless, the way underweight or normal weight affects DPN remains unclear. A cross-sectional study has shown that significantly more women with a BMI <22.0 kg/m^2 have ulnar

Table 1 | Baseline characteristics of 3,224 patients with type 2 diabetes mellitus stratified by baseline body mass index

	BMI (kg/m^2)					All (n = 3,224)	P
	<21.62 (n = 644)	21.62–23.50 (n = 646)	23.51–25.16 (n = 645)	25.17–27.33 (n = 645)	>27.33 (n = 644)		
Age (years)	60.14 ± 11.63	61.19 ± 10.60	60.82 ± 10.67	62.03 ± 11.63†	62.34 ± 12.53†,§	61.31 ± 11.45	0.003
Male, n (%)	333 (51.7)	348 (53.9)	327 (50.7)	330 (51.2)	297 (46.1)	1,635 (50.7)	0.080
Diabetes duration (years)	7.58 ± 6.57	7.86 ± 6.51	7.88 ± 6.35	8.00 ± 6.83	8.13 ± 7.27	7.89 ± 6.71	0.669
Smoking, n (%)	133 (20.7)	127 (19.7)	128 (19.8)	95 (14.7)†,§	97 (15.1)†,‡,§	580 (18.0)	0.007
Drinking, n (%)	51 (7.9)	68 (10.5)	53 (8.2)	37 (5.7)‡	38 (5.9)‡	247 (7.7)	0.007
Hypertension, n (%)	320 (49.7)	387 (59.9)†	423 (65.6)†,‡	447 (69.3)†,‡	499 (77.5)†,‡,§,¶	2,076 (64.4)	<0.001
SBP (mmHg)	134.40 ± 20.80	137.32 ± 20.89†	138.43 ± 20.58†	139.34 ± 20.27†	142.22 ± 20.24†,‡,§,¶	138.34 ± 20.70	<0.001
DBP (mmHg)	77.05 ± 10.74	78.00 ± 10.74	79.58 ± 10.81†,‡	78.88 ± 11.17 †	79.83 ± 11.69†,‡	78.67 ± 11.08	<0.001
Left ABI	1.06 ± 0.13	1.08 ± 0.12†	1.08 ± 0.12†	1.08 ± 0.13†	1.07 ± 0.13	1.07 ± 0.13	0.047
Right ABI	1.07 ± 0.14	1.09 ± 0.14†	1.09 ± 0.12†	1.09 ± 0.12†	1.08 ± 0.12	1.08 ± 0.13	0.017
Left ABI (post-exercise)	1.05 ± 0.13	1.04 ± 0.12	1.07 ± 0.11	1.05 ± 0.11	1.04 ± 0.14	1.05 ± 0.12	0.358
Right ABI (post-exercise)	1.04 ± 0.13	1.04 ± 0.13	1.06 ± 0.13	1.08 ± 0.16	1.06 ± 0.14	1.05 ± 0.14	0.493
Left IMT (mm)	0.95 ± 0.52	1.04 ± 0.69	0.96 ± 0.37	1.00 ± 0.47	1.01 ± 0.60	0.99 ± 0.54	0.064
Right IMT (mm)	0.97 ± 0.64	1.02 ± 0.61	0.96 ± 0.38	1.04 ± 0.73	1.02 ± 0.68	1.00 ± 0.62	0.223
FPG (mmol/L)	8.68 ± 4.27	8.85 ± 3.97	8.74 ± 3.77	8.53 ± 3.36	8.54 ± 3.50	8.67 ± 3.79	0.544
HbA1c (%)	9.37 ± 2.69	9.35 ± 2.57	9.09 ± 2.35	8.93 ± 2.23†,‡	8.69 ± 2.24†,‡,§	9.09 ± 2.43	<0.001
ALB (g/L)	37.85 ± 5.12	38.90 ± 5.00†	39.27 ± 4.75†	39.49 ± 5.01†,‡	39.79 ± 4.92†,‡	39.06 ± 5.00	<0.001
TC (mmol/L)	4.57 ± 1.33	4.73 ± 1.47†	4.70 ± 1.27	4.78 ± 1.24†	4.81 ± 1.42†	4.72 ± 1.35	0.017
TG (mmol/L)	1.33 ± 0.99	1.69 ± 1.65†,‡	1.91 ± 1.70†,‡	1.98 ± 1.64†,‡	2.27 ± 2.22†,‡,§,¶	1.84 ± 1.71	<0.001
HDL (mmol/L)	1.25 ± 0.40	1.19 ± 0.38†,‡	1.11 ± 0.30†,‡	1.11 ± 0.33†,‡	1.10 ± 0.32†,‡	1.15 ± 0.35	<0.001
LDL (mmol/L)	2.80 ± 1.12	2.89 ± 1.17	2.87 ± 0.95	2.90 ± 1.04	2.88 ± 1.02	2.87 ± 1.06	0.482
BUN (mmol/L)	6.02 ± 3.50	5.92 ± 3.20	5.69 ± 2.27	6.20 ± 3.22	5.93 ± 2.74	5.95 ± 3.02	0.058
Cr (μmol/L)	57 (47–71.53)	60.2 (49.8–75)	60.85 (49.53–74)	63 (51.3–79.4)†,‡,§	62.55 (51.23–78.75)†	60.95 (49.7–76)	<0.001
eGFR (mL/min/1.73 m²)	116.7 (91.4–146.3)	110.89 (89.3–136.4)	111.4 (89.0–134.3)	105.29 (81.7–127.0)	103.85 (79.6–128.7)	109.7 (85.9–134.3)	<0.001
UA (μmol/L)	283.30 ± 96.76	302.94 ± 100.27†	309.38 ± 98.28†	342.90 ± 102.82†,‡,§	350.07 ± 107.63†,‡,§	317.74 ± 104.25	<0.001
UACR (mg/g)	14.82 (7.17–45.82)	11.31 (6.58–34.39)	12.73 (6.57–40.52)	14.56 (6.5–66.37)†,‡,§	16.21 (7.68–95.5)†,‡,§	13.61 (6.86–52.41)	0.016
Treatment							
Hypoglycemic agents, n (%)	489 (75.9)	516 (79.9)	521 (80.8)	494 (76.6)	518 (80.4)	2,538 (78.7)	0.091
Insulin therapy, n (%)	325 (50.5)	281 (43.5)†	323 (50.1)‡	303 (47.0)	284 (44.1)†,§	1,516 (47.0)	0.028
ACEI and/or ARBs, n (%)	59 (9.2)	74 (11.5)	83 (12.9)†	101 (15.7)†,‡	142 (22.0)†,‡,§,¶	459 (14.2)	<0.001
β-blockers, n (%)	24 (3.7)	32 (5.0)	39 (6.0)	44 (6.8)	44 (6.8)	183 (5.7)	0.073
CCB, n (%)	79 (12.3)	110 (17.0)†	149 (23.1)†	167 (25.9)†,‡	193 (30.0)†,‡,§	698 (21.7)	<0.001
Statins, n (%)	43 (6.7)	46 (7.1)	40 (6.2)‡	57 (8.8)	68 (10.6)†,‡,§	254 (7.9)	0.022

Post-hoc analysis: †compared with the body mass index (BMI) <21.62 group, $P < 0.05$; ‡compared with the BMI 21.62–23.50 group, $P < 0.05$; §compared with the BMI 23.51–25.16 group, $P < 0.05$; ¶compared with the BMI 25.17–27.33 group, $P < 0.05$. ABI, ankle brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, serum uric acid; UACR, urine albumin-to-creatinine ratio.

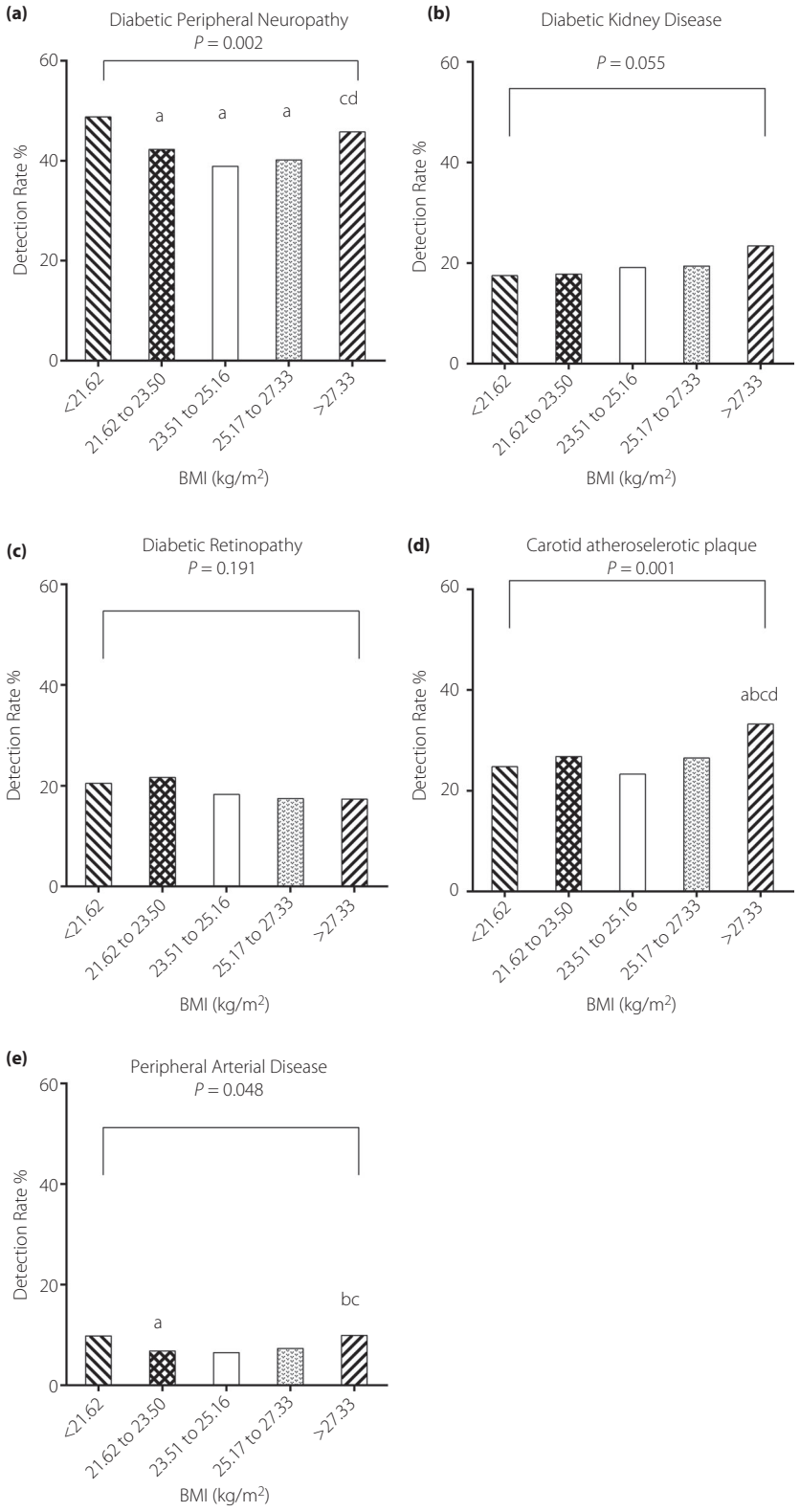

Figure 1 | Detection rate of vascular complications. Post-hoc analysis: a, Compared with the body mass index (BMI) <21.62 group, $P < 0.05$; b, compared with the BMI 21.62–23.50 group, $P < 0.05$; c, compared with the BMI 23.51–25.16 group, $P < 0.05$; d, compared with BMI 25.17-27.33 group $P < 0.05$.

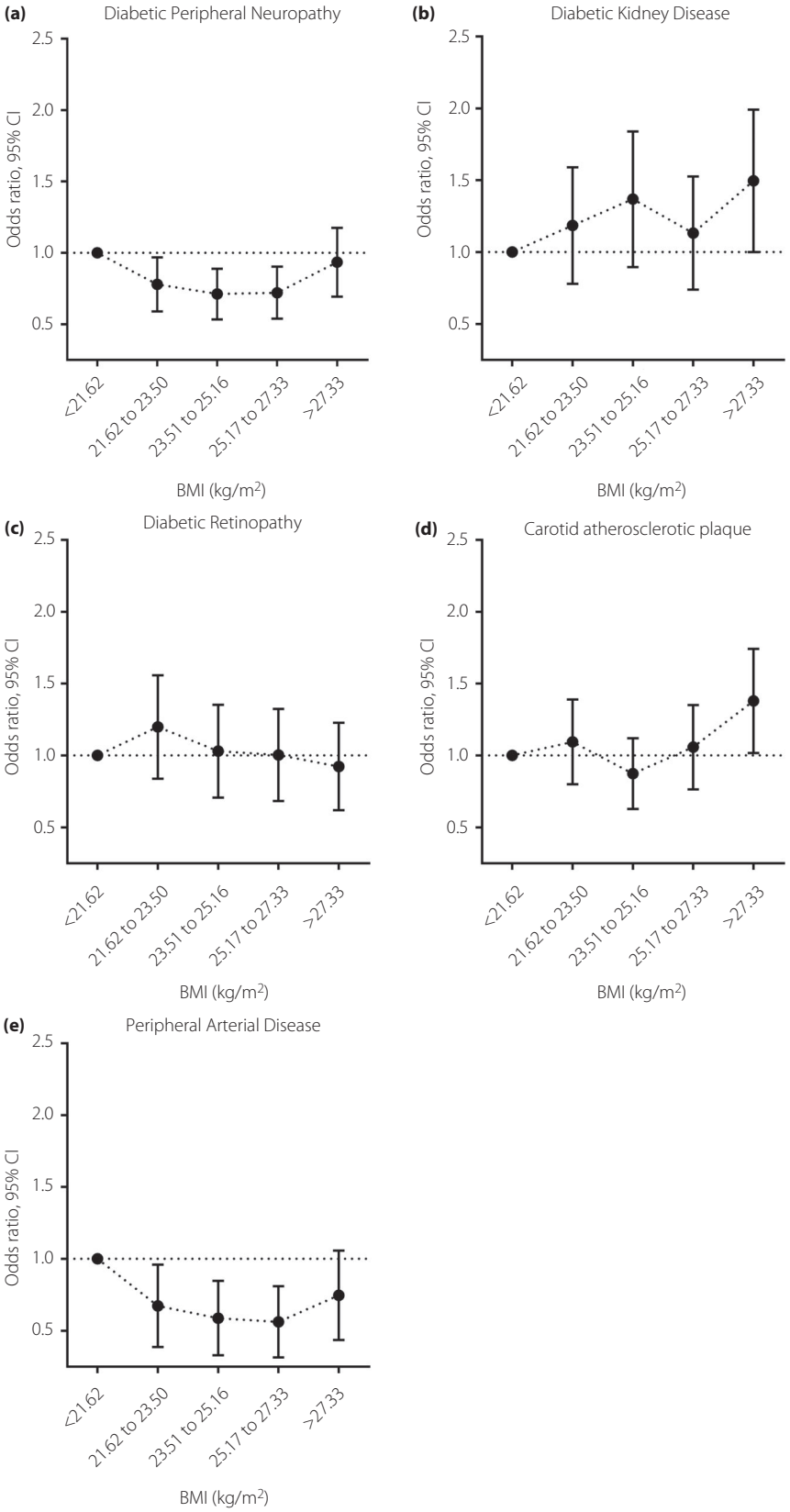

Figure 2 | Forest plots of body mass index (BMI) and vascular complications. 95% CI, 95% confidence interval.

mononeuropathy at the elbow compared with women with a BMI >22.0 kg/m^2, suggesting that thin women are at increased risk for ulnar mononeuropathy at the elbow[36]. Xu *et al.*[7] have suggested that a low BMI might be a potential risk factor for DPN. Their study was well controlled, and included 90 type 2 diabetes patients. However, the present study examined 3,224 patients, and showed that both lower BMI and higher BMI were risk factors for DPN. Lower BMI might imply a nutritional imbalance that could contribute to the neuropathy and hinder neuropathic rehabilitation[37]. In addition, patients with lower BMI might have a higher risk of metabolic and/or ischemic injury.

A previous study[38] has shown that BMI is a high independent risk factor for DKD, and another study has shown that past obesity, as well as present obesity, are risk factors for diabetic nephropathy[9]. Rossi *et al.*[8] have reported that increasing BMI is associated with a risk of albumin-to-creatinine ratio progression. A study with 3,749 participants (BMI 22.8–30.2 kg/m^2) from the Study of Health in Pomerania showed that low BMI is positively correlated with the urinary albumin-to-creatinine ratio[10]. Yet, in the present study, it was determined that a higher BMI was positively correlated with DKD. Potential reasons for these discrepancies include different study participants, BMI levels and measurements of kidney disease (e.g., often omitting albuminuria). It is obvious that through a variety of mechanisms, obesity produces negative effects, such as increased renal sinus fat, focal or segmental glomerulosclerosis, glomerular hypertrophy and increased glomerular permeability caused by glomerular filtration barrier injury[39].

Different people have proposed different views about the relationship between BMI and DR. An early study suggested that BMI is not associated with DR[12]. Recent studies, however, have shown that obesity or a high BMI is a risk factor for DR[40], whereas some studies have reported that a high BMI is a protective factor for DR[11,41]. The lack of consensus might be partially explained by methodological differences, inadequate clinical sample sizes and ethnic differences. Ethic differences, in particular, might have a role in the differing views, as a negative correlation between BMI and DR was observed in Asian populations[40]. This could be a result of type 2 diabetes developing in Asian patients at a lower mean BMI and a lower degree of obesity compared with those of European descent[42]. The present study found that compared with those with low BMI, a high BMI led to a higher risk of DR, nevertheless, this risk was not statistically significant. Individuals with high BMIs had a higher detection rate of DPN and DKD. Additionally, the presence of one microvascular complication might increase the risk of other microvascular complications in patients with type 2 diabetes mellitus[43]. Thus, the true relationship between BMI and DR might be somewhat unclear.

However, the link between lower BMI and DKD cannot be explained. Additional studies with more rigorous criteria and methodology are required to support the premise that low BMI is a risk factor for renal progression in patients with diabetes mellitus or as a parameter that reflects undernourishment[44]. Nevertheless, BMI conferred inconclusive results in DR patients. Evaluation of nutritional status of DR patients by BMI conferred ambiguous results[45]. Otherwise, it is well known that the risks associated with retinopathy include chronic hyperglycemia, nephropathy, hypertension and dyslipidemia[19]. In the present study, patients with lower BMI showed much poorer glycemic control, whereas high BMI showed poorer BP and serum lipid control. These could account for the fact that we did not observe that lower BMI contributed to DKD and DR.

There is also a lack of consensus about the relationship between PAD and BMI. Some studies have suggested that BMI is not associated with PAD[16,46], whereas other studies have shown that a high BMI[5,14] or low BMI[15,47] are associated with PAD. Tseng *et al.*[15,47] showed that a lower BMI (<23 kg/m^2) is a major risk factor for PAD. The present study showed that a lower BMI and a higher BMI are risk factors for PAD. The following reasons can account for the inconsistent results. First, compared with that study, our study participants had a lower smoking rate (18 vs 27.2%) and a lower mean age (61 vs 63 years). Second, our study participants with the lowest and the highest BMIs had higher detection rates of DPN, which is a risk factor for PAD[48]. Finally, poor health status, other chronic diseases, weight loss and PAD often coexist in patients, and complicate the relationship between BMI and PAD. Furthermore, a mechanism that can explain the relationship between a lower BMI and PAD has not yet been elucidated, which is likely because of the high metabolic rate, low oxidative capacity of skeletal muscle and increased inflammatory response in patients with low BMIs[49,50]. In addition, a low BMI is often accompanied by malnutrition, which might be related to the development of atherosclerosis[51]. Furthermore, insulin resistance/diabetes, inflammation, hypertension and hyperlipidemia could be consequences of obesity, and might lie on the causal pathway between obesity and PAD[52].

Body mass index is a risk factor for cardiovascular disease[53] and carotid artery atherosclerotic plaque[18], and is associated with increased IMT[54]. The present findings were consistent with most previous investigations. A higher BMI induces metabolic disturbances in lipids and blood glucose, which contribute to the development of atherosclerotic plaque[55].

The different relationships between BMI and carotid plaque and BMI and PAD might cause different risk factors. For example, the risk factors for PAD were HDL, blood urea nitrogen, SBP and diabetes duration, whereas the risk factors for carotid artery disease were BMI, DBP, age and endothelial dysfunction[56]. Pasterkamp *et al.*[57] have concluded that plaque area in the common carotid artery is not correlated to luminal stenosis in other peripheral arteries, which might be attributable to the phenomenon of de novo arterial remodeling. The same number of plaques might stimulate a different response to the vessel wall, such as arterial expansion or contraction. On average, plaque increase was compensated for more by enlargement

in the coronary, common carotid and renal arteries compared with the arteries obtained from the lower extremities[58].

Furthermore, some drugs might cause the progression of complications (e.g., β-blockers to DPN, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker to DKD, statins to PAD and carotid atherosclerotic plaque). Few studies have focused on the effects of β-blockers on diabetic peripheral neuropathy. Previous studies have reported that β-blockers leading to an increase in nitric oxide levels might be useful in the prevention of DPN[59]. Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker reduce the risk of new onset of kidney disease and the slowly progressive nature of DKD[60]. Several studies have shown that statin administration in patients with PAD results in a decreased progression[61], and even in growth regression of carotid atherosclerotic plaque[62]. However, this result was still robust after considering the drug's use.

In contrast, the present study suggested that patients with a higher BMI had lower HbA1c, whereas patients with lower BMI were more likely to drink alcohol and smoke cigarettes. These observations were similar to previous investigations[63]. The higher BMI and the lower HbA1c are not causal or reverse causal. Weight gain observed during optimized glycemic control might simply correspond to re-expression of patients' physiologically controlled bodyweight[64]. Otherwise, cigarette smoking is associated with decreased homeostasis model assessment of β-cell function, as manifested by the elevated HbA1c[65]. Alcohol might also induce hypoglycemia[66]. Tobacco and liquor consumption also indicate bad lifestyle behaviors, which lead to weight loss[67]. Previous research has shown that individuals might be lean because of the chronic accumulation of metabolic, inflammatory and pathological conditions caused by long-term exposure to smoking, drinking and unhealthy diets[68].

A limitation of the present study was that many patients only had one BMI measurement taken. Additionally, as this was a cross-sectional study, we could not allow causal inference of the associations between BMI and diabetic vascular complications. Furthermore, data on cardiovascular events were not available, such as atrial fibrillation, coronary heart disease and heart failure. Finally, the diagnosis of DPN was based on neurological symptoms and signs. It is often difficult to diagnose early DPN in clinical practice. A neurological conduction study is the most sensitive, accurate and reliable method for diagnosing DPN. However, because of the high cost and high time-consumption, these are not suitable as a routine examination for diabetes patients.

The major strength of the present study was the comprehensively discussed relationship between BMI and diabetic macrovascular and microvascular complications. We demonstrated that BMI showed a U-shaped association with DPN and PAD, whereas the results of the aforementioned studies showed a linear relationship[5,6,9,10,69]. The observed differences could result from methodological differences, differences in the definitions of vascular complications, inadequate clinical sample sizes and differences in study participants (e.g., some studies did not include the lean population, some studies only examined the elderly population). BMI has a U-shaped association with mortality[39], which is consistent with the present results. Otherwise, our findings confirmed that a higher BMI is positively correlated with DKD and carotid atherosclerotic plaque. Furthermore, the optimal BMI is important for randomized controlled trials, as it indicates when weight management interventions should start, in order to achieve the best clinical outcomes. In conclusion, lower BMI is of not of more benefit for diabetic complications. BMI can be managed through lifestyle interventions, which should be advocated to prevent vascular complications of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | The exclusion of non-diabetic causes.
Appendix S2 | Diagnostic criterion for peripheral arterial disease.