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Association of body mass index with risk of prediabetes in Chinese adults: A population-based cohort study

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ABSTRACT

Aims/Introduction: Overweight and obesity in adults are strongly associated with an increased risk of prediabetes, and this study set out to gain a better understanding of the optimal body mass index (BMI) range for assessing the risk of prediabetes in the Chinese population.

Materials and Methods: The cohort study included 100,309 Chinese adults who underwent health screening. Participants were divided into six groups based on the cut-off point for BMI recommended by the World Health Organization (underweight: <18.5 kg/m^2, normal-weight: 18.5–24.9 kg/m^2, pre-obese: 25.0–29.9 kg/m^2, obese class I: 30.0–34.9 kg/m^2, obese class II: 35.0–39.9 kg/m^2, and obese class III ≥40 kg/m^2). The association of BMI with prediabetes and the shape of the correlation were modeled using multivariate Cox regression and restricted cubic spline regression, respectively.

Results: In the multivariate Cox regression model, with normal weight as the control group, underweight people had a lower risk of developing prediabetes, whereas obese and pre-obese people had a higher risk of prediabetes. Additionally, in the restricted cubic spline model, we found that the association of BMI with prediabetes follows a positive dose–response relationship, but does not conform to the pattern of obesity paradox. Among the general population in China, a BMI of 23.03 kg/m^2 might be a potential intervention threshold for prediabetes.

Conclusions: The national cohort study found that the association of BMI with prediabetes follows a positive dose–response relationship, rather than a pattern of obesity paradox. For Chinese people with normal weight, more attention should be paid to glucose metabolism when BMI exceeds 23.03 kg/m^2.

INTRODUCTION

Prediabetes is a state of hyperglycemia in which blood glucose is above the normal level, but below the diabetes threshold. It is estimated that 5–10% of prediabetes patients develop diabetes each year, and this hyperglycemic state significantly increases the risk of cardiovascular disease, autonomic neuropathy, chronic kidney disease and retinopathy[1,2]. At present, China has the highest prevalence rate of prediabetes. According to a recent national cross-sectional survey, the prevalence of prediabetes defined according to the standards of the American Diabetes Association among Chinese adults has reached 35.7%[3]. With the prevalence of overweight and obesity, the incidence of prediabetes continues to increase, which will bring an enormous disease burden to the social and health system[3,4].

Body mass index (BMI) is a simple anthropometric measure most commonly used to measure general adiposity[5]. Previous studies have provided evidence that obesity assessed by BMI is an important risk factor for increased morbidity and mortality of many chronic diseases[6–8]. Conversely, a growing body of research has found that being underweight is also associated with a wide range of cardiovascular diseases and adverse clinical outcomes[8–10]. There are multiple types of J-shaped and U-

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shaped associations between BMI and mortality, a pattern known as the obesity paradox[6,8,9,11]. However, it is not clear whether the association of BMI with prediabetes also follows the pattern of the obesity paradox and the optimal range of BMI used to assess the risk of prediabetes. In the present study, we analyzed the national epidemiological data of China Rich Healthcare Group to evaluate the optimal BMI range used to predict the risk of prediabetes.

MATERIALS AND METHODS

Study design and participants

The present study used medical data of adult participants who underwent physical screening at China Rich Healthcare Group from 2010 to 2016. Participants came from 11 major cities in China and underwent at least two health screenings during the survey. The research dataset and related copyright have been shared and transferred to the Dryad Database by Li *et al* (https://datadryad.org)[12]. According to the Dryad Database terms of service, this dataset can be used for post-hoc analysis based on new research assumptions to make better use of the data. In their previous data analysis, Li *et al.*[13] screened the study population based on the original dataset, and participants with the following characteristics were excluded: (i) extreme BMI values (BMI >55 kg/m^2 or <15 kg/m^2); (ii) incomplete baseline information on height, fasting plasma glucose (FPG), weight and sex; (iii) diabetes was confirmed at the baseline visit; (iv) follow up was <2 years; and (v) diabetes status could not be determined during follow up. In the end, they enrolled 211,833 participants, and assessed the relationship between age, BMI and diabetes, and found that higher BMI was an independent risk factor for diabetes in young people. The present study was a post-hoc analysis of a previous study by Li *et al.*,[14] to further evaluate whether the association of BMI with prediabetes followed the pattern of the obesity paradox and the optimal BMI range used to predict prediabetes risk. According to the diagnostic criteria of prediabetes defined by American Diabetes Association, this study added the following items to the exclusion criteria of the previous study: (i) incomplete baseline lipid parameters; (ii) baseline FPG ≥5.6 mmol/L; and (iii) FPG >6.9 mmol/L or self-reported diagnosis of diabetes during follow up. Ultimately, 100,309 participants were included in the present study (Figure 1). Given that the current study was a post-hoc analysis in which the personally identifiable information of the participants had been anonymized, informed consent of the participants was waived. In addition, the Ethics Committee of Jiangxi Provincial People's Hospital examined and approved the design of this study (local identifier: 2021067). All procedures conformed to standards set forth in the Declaration of Helsinki.

Measurement of baseline characteristics

Trained investigators obtained baseline information from participants through standard questionnaires, including medical history (diabetes), demographic characteristics (age and sex), blood pressure measurement parameters, lifestyle (smoking and drinking) and family history (family history of diabetes). Among them, blood pressure was measured by trained personnel through a standard mercury sphygmomanometer, and smoking and drinking status were divided into four categories according to the baseline visit time: no, past, current and unrecorded.

BMI and its categories

BMI was calculated as weight (kg) divided by height (m) squared. Participants were asked to take off their shoes and wear only lightweight clothes when measuring height and weight, and the measurements were accurate to 0.1 cm and 0.1 kg. In addition, in the present study, BMI according to the standard of the World Health Organization was divided into six groups: underweight: <18.5 kg/m^2; normal-weight: 18.5–24.9 kg/m^2; pre-obese: 25.0–29.9 kg/m^2; obese class I: 30.0–34.9 kg/m^2; obese class II: 35.0–39.9 kg/m^2; and obese class III ≥ 40 kg/m^2[15].

Biochemical measurement

Venous blood samples were taken by professional medical staff after fasting for at least 10 h, and total cholesterol (TC), blood urea nitrogen, FPG, aspartate aminotransferase, high-density lipoprotein cholesterol, creatinine , alanine aminotransferase, triglyceride, aspartate aminotransferase and low-density lipoprotein cholesterol were measured on a automatic biochemical analyzer (Beckman Coulter AU5800, Brea, CA, USA).

Definition of prediabetes

According to the American Diabetes Association 2018 standard, prediabetes was defined as participants who did not progress to diabetes during follow up, but had an FPG level between 5.6 and 6.9 mmol/L[14].

Statistical analysis

In the present study, the characteristics of participants are expressed as means (standard deviations) or frequencies (%), unless stated otherwise. All statistical analyses and regression models were created in R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) and Empower(R) version 2.20 (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). The statistical significance was set at $P < 0.05$ (bilateral).

To analyze the association of BMI with prediabetes, multivariate Cox regression analysis was used to calculate hazard ratios (HR) and 95% confidence intervals (CI), and the Kaplan–Meier method was used to draw the cumulative incidence curve of different BMI groups. To systematically account for potential confounders, three covariate models were evaluated following the STROBE guidelines[16], in which two collinear covariates – bodyweight and TC – were excluded from the model (Table S1)[17]. In our first model, only sex, age and family history of diabetes were adjusted (model 1), and this model was regarded as the most basic adjustment model. To consider

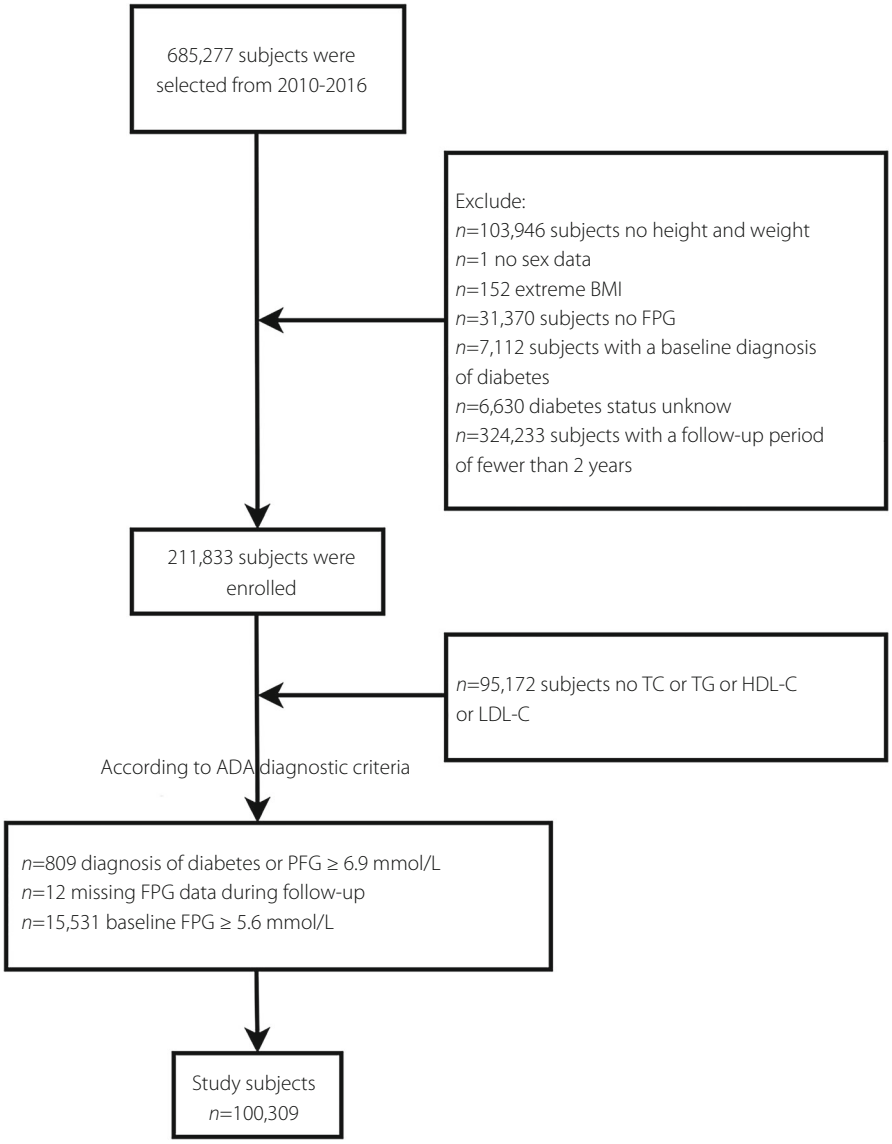

Figure 1 | Flowchart of the study selection process. ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

the influence of body size and blood pressure on BMI[18], we further adjusted the continuous variables height, systolic blood pressure and diastolic blood pressure in model 2. Finally, to further examine the independent association between BMI and prediabetes, we additionally adjusted blood urea nitrogen, creatinine, and related indexes of glucose and lipid metabolism on the basis of model 2 (model 3). Additionally, in the multivariate model, the trend *P* between BMI and prediabetes was estimated by using classified BMI as a continuous variable (median).

To detect any possible linear or non-linear dependence in the regression model, we also used the restricted cubic splines (RCS; based on model 3) with 5 knots at the 5th, 35th, 50th, 65th and 95th centiles to study the shape of the dose–response relationship between BMI and the risk of prediabetes. The model with the only linear term was compared with the model with linear and cubic spline terms by using the likelihood ratio test to test the potential non-linearity[19,20].

To further verify the robustness of the main results in the present study, we carried out several sensitivity analyses based on model 3, excluding participants with dyslipidemia (TC ≥5.2 mmol/L, triglyceride ≥1.7 mmol/L, low-density lipoprotein cholesterol ≥3.4 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L)[21], elevated blood pressure (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg)[22] and a family history of diabetes at the baseline visit.

RESULTS

General participant characteristics grouped according to BMI

The study included 100,309 Chinese people aged >20 years, with an average age and BMI of 42.91 years and 23.10 kg/m^2, respectively. A total of 51.97% of the participants were male. Table 1 shows the baseline characteristics of participants according to predefined BMI categories. With the increase of BMI, the proportion of male participants and non-smoking and drinking participants gradually increased, as well as the levels of blood pressure, alanine aminotransferase, weight, TC, height, low-density lipoprotein cholesterol, aspartate aminotransferase, FPG and triglyceride increased. It should be noted that alanine aminotransferase was significantly higher than the normal level in obese people. Additionally, the average values of age, blood urea nitrogen and creatinine reached the highest among people in the pre-obese state, and then decreased with the increase of BMI.

Association of BMI with the risk of prediabetes

During a median observation period of 3.1 years, we identified 12,352 (12.31%) participants with new-onset prediabetes. The incidence rate of prediabetes was 3,948.31 per 100,000 person-years in the entire population, 1,628.25 per 100,000 person-years in the underweight population, 3,303.82 per 100,000 person-years in the normal-weight population, 5,930.47 per 100,000 person-years in the pre-obese population, 7,284.43 per 100,000 person-years in the class I obese population, 9,901.49 per 100,000 person-years in the class II obese population and 14,142.10 per 100,000 person-years for the class III obese

Table 1 | Baseline characteristics of participants grouped according to body mass index categories

	BMI categories (kg/m^2)					
	<18.5	18.5–24.9	25–29.9	30–34.9	35–39.9	≥40
No. participants	5,714	67,896	24,034	2,501	147	17
Sex						
Male	1,433 (25.08%)	31,259 (46.04%)	17,453 (72.62%)	1,870 (74.77%)	102 (69.39%)	13 (76.47%)
Female	4,281 (74.92%)	36,637 (53.96%)	6,581 (27.38%)	631 (25.23%)	45 (30.61%)	4 (23.53%)
Age (years)	36.56 ± 10.93	42.39 ± 12.21	45.83 ± 12.69	43.50 ± 12.80	39.90 ± 12.05	33.82 ± 5.27
Height (cm)	164.52 ± 7.31	165.66 ± 8.22	168.02 ± 8.32	168.60 ± 8.91	169.06 ± 10.24	167.91 ± 17.43
Weight (kg)	47.77 ± 4.68	60.41 ± 8.23	75.61 ± 8.38	89.61 ± 9.95	104.52 ± 12.15	119.15 ± 22.16
SBP (mmHg)	109.25 ± 13.42	115.91 ± 15.26	124.81 ± 15.87	131.25 ± 16.49	135.80 ± 15.98	133.53 ± 14.88
DBP (mmHg)	68.99 ± 9.08	72.26 ± 10.11	78.22 ± 10.99	81.81 ± 11.77	83.31 ± 13.25	80.88 ± 10.45
FPG (mmol/L)	4.66 ± 0.48	4.77 ± 0.47	4.86 ± 0.46	4.89 ± 0.46	4.89 ± 0.45	4.93 ± 0.41
TC (mmol/L)	4.47 ± 0.82	4.70 ± 0.87	4.93 ± 0.90	5.03 ± 0.88	4.95 ± 0.96	5.25 ± 0.96
TG (mmol/L)	0.81 ± 0.39	1.16 ± 0.78	1.76 ± 1.19	2.04 ± 1.33	2.08 ± 1.80	2.06 ± 1.18
HDL-C (mmol/L)	1.55 ± 0.32	1.41 ± 0.30	1.28 ± 0.27	1.24 ± 0.28	1.20 ± 0.26	1.30 ± 0.31
LDL-C (mmol/L)	2.51 ± 0.61	2.71 ± 0.66	2.87 ± 0.68	2.93 ± 0.68	2.89 ± 0.73	3.04 ± 0.75
ALT (U/L)	14.72 ± 12.48	20.12 ± 19.00	31.15 ± 24.07	43.13 ± 32.45	57.25 ± 61.95	51.45 ± 34.31
AST (U/L)	21.04 ± 12.28	22.74 ± 12.94	26.28 ± 11.33	30.05 ± 13.68	34.26 ± 19.49	28.55 ± 12.02
BUN (mmol/L)	4.34 ± 1.12	4.58 ± 1.15	4.83 ± 1.16	4.80 ± 1.12	4.71 ± 0.99	4.53 ± 1.10
Cr (μmol/L)	62.48 ± 12.96	68.43 ± 15.34	75.25 ± 15.81	75.24 ± 15.30	73.79 ± 15.36	69.12 ± 9.98
Family history of diabetes	106 (1.86%)	1,536 (2.26%)	504 (2.10%)	58 (2.32%)	4 (2.72%)	0 (0.00%)
No	5,608 (98.14%)	66,360 (97.74%)	23,530 (97.90%)	2,443 (97.68%)	143 (97.28%)	17 (100.00%)
Yes	106 (1.86%)	1,536 (2.26%)	504 (2.10%)	58 (2.32%)	4 (2.72%)	0 (0.00%)
Smoking status						
No	157 (2.75%)	3,063 (4.51%)	1,903 (7.92%)	211 (8.44%)	14 (9.52%)	1 (5.88%)
Past	19 (0.33%)	625 (0.92%)	396 (1.65%)	45 (1.80%)	4 (2.72%)	1 (5.88%)
Current	1,223 (21.40%)	14,540 (21.42%)	4,922 (20.48%)	480 (19.19%)	32 (21.77%)	2 (11.76%)
Unrecorded	4,315 (75.52%)	49,668 (73.15%)	16,813 (69.96%)	1,765 (70.57%)	97 (65.99%)	13 (76.47%)
Drinking status						
No	10 (0.18%)	346 (0.51%)	253 (1.05%)	27 (1.08%)	3 (2.04%)	0 (0.00%)
Past	112 (1.96%)	2,704 (3.98%)	1,551 (6.45%)	171 (6.84%)	9 (6.12%)	1 (5.88%)
Current	1,277 (22.35%)	15,178 (22.35%)	5,417 (22.54%)	538 (21.51%)	38 (25.85%)	3 (17.65%)
Unrecorded	4,315 (75.52%)	49,668 (73.15%)	16,813 (69.96%)	1,765 (70.57%)	97 (65.99%)	13 (76.47%)

Values were mean (standard deviation) or percentage (%) unless stated otherwise. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

people. The cumulative incidence of prediabetes increased with the increase of BMI (Figure 2; log-rank $P < 0.0001$).

Table 2 summarizes the associations between different BMI categories and the incidence of prediabetes. In the multivariate Cox regression model, with the normal weight as the control group, we always observed that underweight people had a lower risk of developing prediabetes, whereas obese and pre-obese people had a higher risk of prediabetes. In conclusion, increased BMI has a significant positive correlation with the risk of prediabetes (P for trend <0.0001).

Dose–response relationship between BMI and prediabetes

Figure 3 shows the spline curve between BMI and the risk of prediabetes in the form of a dose–response relationship. It can be seen that before BMI reached 23.03 kg/m^2, the risk of developing prediabetes in the general population was relatively small, and then began to increase rapidly, while in both sexes, the BMI critical point for assessing the risk of prediabetes was 24.24 kg/m^2 for men and 22.05 kg/m^2 for women. Additionally, we further evaluated the dose–response relationship between BMI and the risk of prediabetes in different ages (Figure 4). The results showed that the threshold point used to assess the risk of prediabetes was approximately 22.77 kg/m^2 in people aged ≤45 years, 23.09 kg/m^2 in people aged 46–59 years and 24.05 kg/m^2 in people aged ≥60 years. In conclusion, the relationship between BMI and the risk of prediabetes does not follow the pattern of the obesity paradox, and a potential prediabetes intervention plan should be started when BMI is approximately 23 kg/m^2 in the Chinese population.

Sensitivity analysis

In people with normal baseline blood pressure, normal blood lipids and no family history of diabetes, we found that the relationship of BMI with the risk of prediabetes was similar to the previous main analysis (Table S2). Although the present results remain robust in the sensitivity analysis, one thing was still worth noting: the association between BMI and prediabetes was significantly weakened in people with normal blood lipids.

DISCUSSION

The current analysis used a nationwide epidemiological dataset, which included physical data of >100,000 participants who

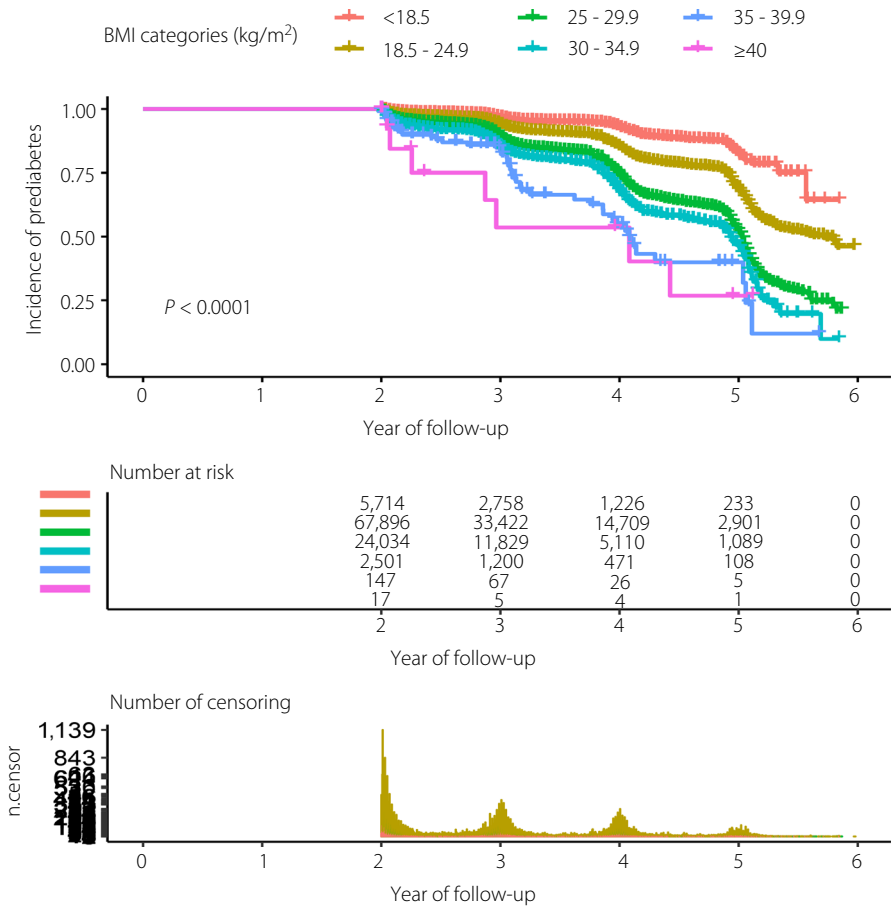

Figure 2 | Cumulative prediabetes incidence curve in different body mass index (BMI) groups.

Table 2 | Adjusted hazardous ratios and 95% confidence interval of the risk of prediabetes for the baseline body mass index groups

BMI categories (kg/m^2)	Participants (*n*)	Prediabetes events, *n* (%)	Per 100,000 person-years	Hazard ratio (95% CI)			
				Unadjusted model	Model 1	Model 2	Model 3
Total	100,309	12,352 (12.31%)	3,948.31	1.67 (1.63, 1.71)	1.48 (1.44, 1.52)	1.36 (1.32, 1.40)	1.26 (1.22, 1.30)
<18.5	5,714	288 (5.04%)	1,628.25	0.50 (0.44, 0.56)	0.64 (0.57, 0.72)	0.67 (0.59, 0.75)	0.72 (0.64, 0.82)
18.5–24.9	67,896	7,001 (10.31%)	3,303.82	Ref	Ref	Ref	Ref
25–29.9	24,034	4,450 (18.52%)	5,930.47	1.80 (1.73, 1.86)	1.50 (1.44, 1.56)	1.38 (1.33, 1.44)	1.25 (1.20, 1.31)
30–34.9	2,501	563 (22.51%)	7,284.43	2.28 (2.09, 2.48)	2.03 (1.86, 2.21)	1.71 (1.57, 1.87)	1.51 (1.38, 1.65)
35–39.9	147	43 (29.25%)	9,901.49	3.36 (2.49, 4.53)	3.07 (2.27, 4.14)	2.29 (1.69, 3.09)	2.15 (1.59, 2.91)
≥40	17	7 41.18%	14,142.10	4.11 (1.96, 8.63)	6.00 (2.86, 12.60)	5.00 (2.38, 10.49)	2.84 (1.27, 6.33)
P for trend				<0.0001	<0.0001	<0.0001	<0.0001

Model 1 adjusted for sex, age and family history of diabetes; model 2 adjusted for sex, age, family history of diabetes, height, systolic blood pressure and diastolic blood pressure; model 3 adjusted for sex, age, family history of diabetes, height, systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen and creatinine. BMI, body mass index; CI, confidence interval.

underwent health screening, showed that an increase in BMI was associated with an increased risk of prediabetes, and these relationships followed a positive dose–response relationship rather than a pattern of the obesity paradox. To our knowledge, this is the first longitudinal study to investigate the dose–response relationship between BMI and the risk of prediabetes in Chinese adults.

Weight gain is a recognized risk factor for glycemic metabolic disorders[13,23], but it has always been a controversial topic at what level of BMI Asian people require weight intervention[24–26]. In 1993, the World Health Organization defined obesity as having a BMI of >30 kg/m^2[27]. However, subsequent evidence suggests that Asian people have a higher risk of metabolic diseases and death than white people at a lower BMI[15,25,28]. At present, the most widely accepted explanations for this obvious racial difference are as follows: (i) Asian people have more visceral fat than white people, which is more disadvantageous in metabolism, and can lead to lipotoxicity and insulin resistance at any given BMI[29,30]; (ii) compared with white people and African people, the insulin secretion capacity of Asian people seems to be more limited[31,32]; and (iii) genetic predisposition to insulin resistance might also be an important factor[33].

Several studies have been carried out in the Chinese population specifically to assess the optimal BMI range or cut-off value for predicting the risk of diabetes[33–36]. It is important to note that the analytical methods and conclusions used in these studies are not identical; in addition, similar to the findings of the present study, the association between BMI and diabetes does not follow the pattern of the obesity paradox. In an earlier study by Chiu *et al.*[33], they used the RCS with 4 knots to model the influence of BMI and diabetes incidence, and found that Chinese people living in Canada had the same diabetes incidence when BMI was approximately 25 kg/m^2, as local white people had a BMI of 30 kg/m^2. Ma *et al.*[34] used different research methods in a recent study. They calculated the BMI cut-off points for predicting diabetes risk by receiver operating characteristic curve analysis. The result suggested that the best cut-off points for predicting diabetes in young men and women in China were 25.5 kg/m^2 and 24.4 kg/m^2, whereas those in middle-aged men and women were 23.5 kg/m^2 and 23.0 kg/m^2. Additionally, two recent studies have specially assessed the optimal BMI range for predicting diabetes risk in the Chinese elderly population through the RCS with 3 knots and 5 knots, respectively[35,36]. In the study of Hu *et al.*[5], they found that when BMI was approximately 22 kg/m^2, the HR of diabetes risk of the elderly in China was approximately 1, while similar results were obtained in the study of Tang *et al.*[36], the cut-off value of BMI measured by them was approximately 22.4 kg/m^2. These studies point out that BMI is a powerful indicator for assessing the risk of diabetes and provide potential BMI intervention thresholds for different populations.

BMI not only can be used to better assess the risk of diabetes, but it also maintains a similar ability in assessing the risk of prediabetes[37,38]; however, the optimal range of BMI used to assess the risk of prediabetes has not been well described. In the present study, by the analysis of a large longitudinal cohort of >100,000 people, the shape of BMI and prediabetes was fitted with 5 knots of RCS, and it was measured that a BMI of 23.03 kg/m^2 might be the threshold point for assessing the risk of prediabetes in the Chinese population, whereas in men, women, and people aged ≤45 years, 46–59 years and ≥60 years, it is approximately 24.24 kg/m^2, 22.05 kg/m^2, 22.77 kg/m^2, 23.09 kg/m^2 and 24.05 kg/m^2, respectively. In addition, it is worth mentioning that in a recent study by Ding *et al.*[39], the cut-off value used to assess impaired fasting glucose was calculated by receiver operating characteristic analysis to be 23.4 kg/m^2 in men and 22.5 kg/m^2 in women; the finding of them is similar to the sex subgroup finding in the current study, but

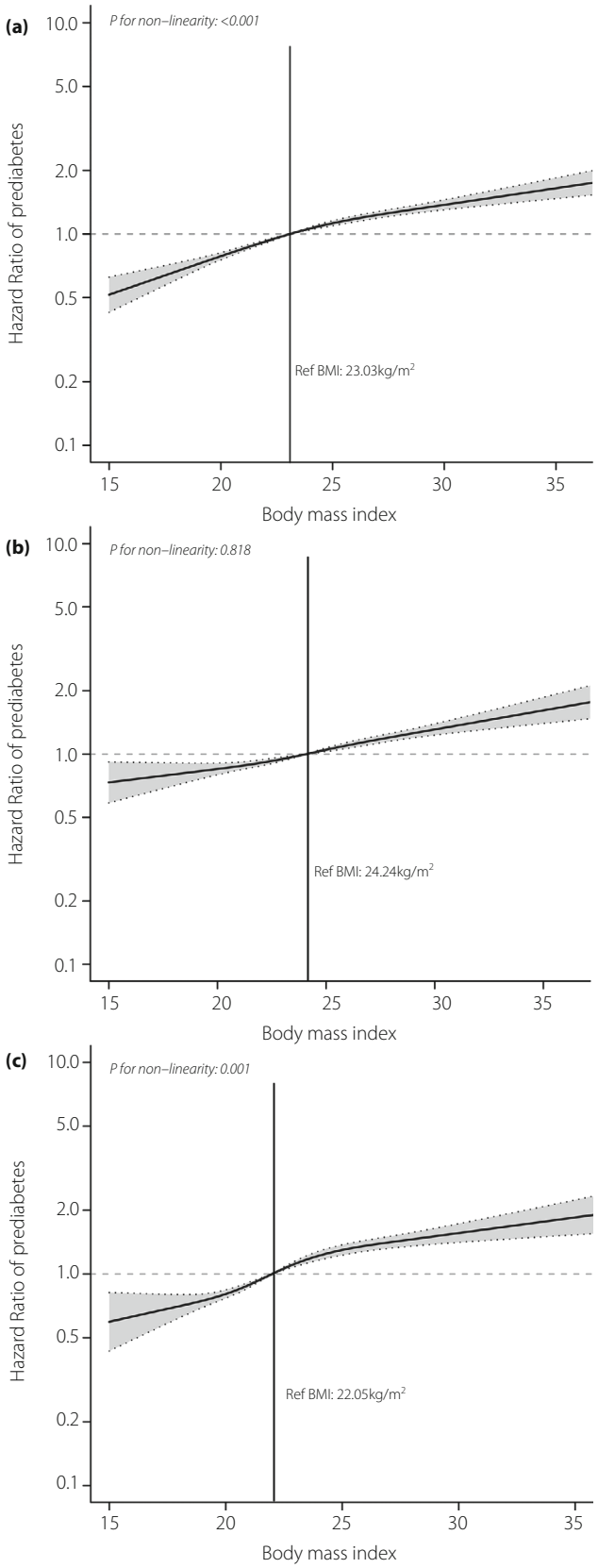

Figure 3 | Dose–response relationship between body mass index (BMI) and prediabetes. (a) Chinese population; (b) Chinese men; (c) Chinese women. Adjusted for age, family history of diabetes, height, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen and creatinine.

our study carried out a more detailed subgroup analysis based on a larger sample size and different research methods, which further verified and enriched the current research data.

After excluding participants with high baseline blood pressure, dyslipidemia and a family history of diabetes, we found that the association between BMI and prediabetes was similar to that of the main analysis. Robust sensitivity analysis results further support that the positive association between BMI and prediabetes does not follow the obesity paradox pattern. However, it is worth noting that in people with no family history of diabetes or normal blood lipids, the HR value of the association between BMI and prediabetes is lower than the results of the main analysis, especially in people with normal blood lipids. This finding suggests that active hypolipidemic treatment while taking intervention measures against BMI might be the key to reducing the risk of prediabetes. Diet intervention and lifestyle intervention have been proved to be effective methods for the prevention and treatment of prediabetes[1,40], whereas the use of lipid-lowering-related drugs is still controversial[40–42]. Further studies are required to confirm the benefits of lipid-lowering-related treatments in the general population.

There are several advantages worth mentioning in this study. First, in the obesity paradox theory, higher BMI means better outcomes. However, in the present study, the dose–response relationship between BMI and prediabetes was evaluated by RCS, and it was found that the relationship between BMI and prediabetes did not conform to the obesity paradox pattern, even in different populations. Second, BMI is a simple and powerful indicator for evaluating the risk of blood glucose metabolism. On the basis of previous studies, the present study further provides a reference BMI threshold for the prevention of prediabetes in different populations in China. Third, sensitivity analysis further suggested the robustness of the study and found that maintaining normal levels of blood lipids could better prevent the risk of prediabetes.

Similarly, we also recognize that the current research has some limitations: (i) the population of this study is from 12 major cities in China, 10 of which are from southern China, so the promotion of the results of the present study in northern China should be more cautious; (ii) in this study, only the participants with impaired fasting glucose during follow up were diagnosed as prediabetes, which might lead to certain missed diagnosis[43]; (iii) although a relatively strict statistical adjustment strategy has been implemented in the current study, there are still some covariables in the study dataset that have not been recorded or measured, so the possibility of unmeasured or

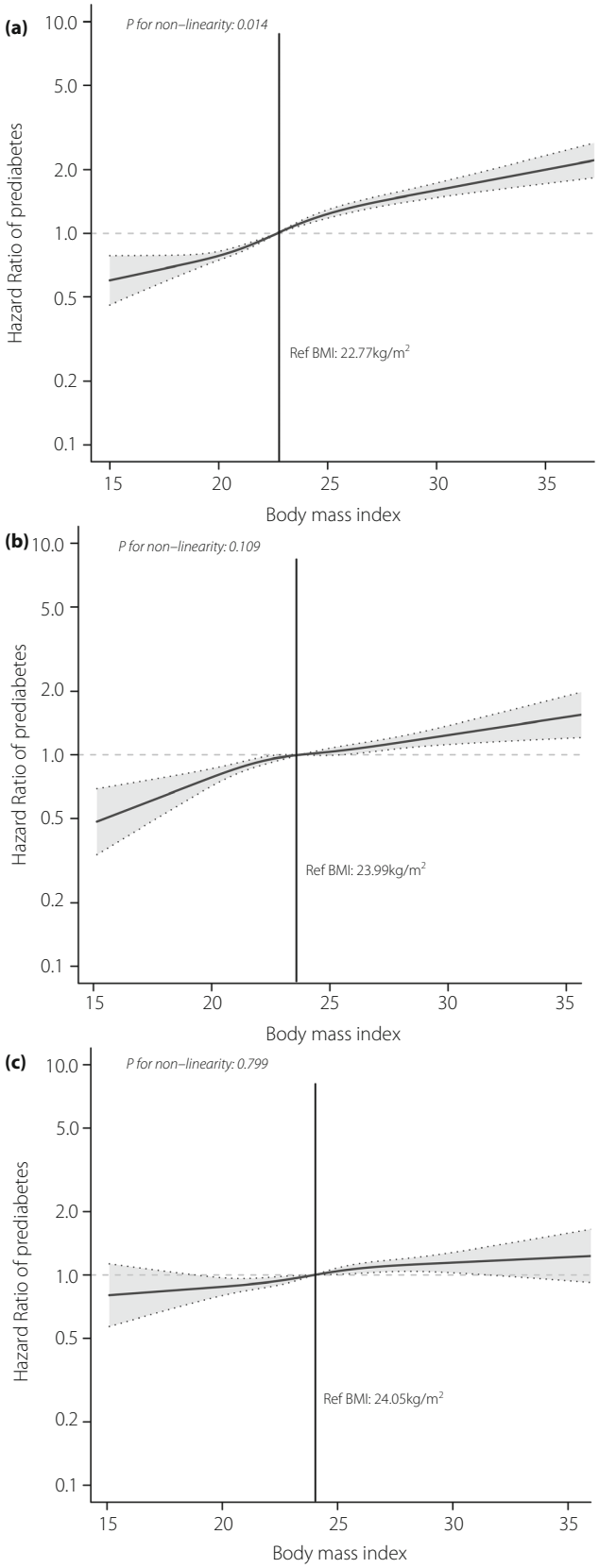

Figure 4 | Multivariable adjusted hazard ratios (95% confidence intervals) for the non-linear relationship between body mass index (BMI) and the risk of prediabetes in Chinese people of different ages. (a) Aged ≤45 years, (b) aged 46–59 years and (c) aged ≥60 years. Adjusted for sex, family history of diabetes, height, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen and creatinine.

unknown confounders cannot be completely excluded; (iv) the main purpose of this study was to analyze the optimal range of baseline initial BMI to predict the future risk of prediabetes, but the relationship between the rate of change of BMI and prediabetes is not clear, and repeated measurements of general simple data are required in further studies; and (v) visceral adiposity plays a more important role in developing insulin resistance and diabetes rather than overall adiposity[44,45]. However, waist circumference and area of visceral adipose tissue were not measured in the current study, so the association and interaction between visceral obesity and prediabetes could not be further evaluated, which requires further study.

In this large national cohort, we found that the increase in BMI was associated with an increased risk of prediabetes, even in people of 'normal weight'. In further dose–response relationship analysis, we found that when BMI is approximately 23.03 kg/m^2, it might be a potential intervention threshold for prediabetes in the Chinese population. Additionally, we also found that the risk of prediabetes corresponding to BMI was significantly reduced in people with normal blood lipids; this finding suggests that active hypolipidemic treatment while taking intervention measures against BMI might be the key to reducing the risk of prediabetes.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
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Animal studies: N/A.

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SUPPORTING INFORMATION

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

Table S1 | Collinearity diagnostics steps.

Table S2 | The adjusted hazard ratios and 95% confidence intervals of the risk of prediabetes for the baseline body mass index groups: sensitivity analysis.