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Associations of the fat-free mass index and the fat mass index with the risk of developing diabetes and prediabetes in US adults: a nationally representative cross-sectional study

Da Liu[1†], You-Lan Lei[2†], Li Zhang[3†], Wenyao Wang[4†], Chunli Shao[4], Qing Zhou[4], Haiping Liu[4], Jun Wen[4], Jingjia Wang[4], Chen Li[4], Yiming Luo[2], Jingxin Rao[2], Yukun Shi[2], Gang Liu[1*], Jie Yang[4*], Mingqi Zheng[1*] and Yi-Da Tang[1,4*]

Abstract

Background Obesity and overweight, as determined by the body mass index (BMI), are harmful to metabolic health. However, the BMI can not reflect body composition or fat distribution. The fat-free mass index (FFMI) and the fat mass index (FMI) can provide more information on body composition. The aim of the observational research was to determine whether the FMI and the FFMI are significantly associated with the risk of developing diabetes and prediabetes.

Methods The investigators included data for 10,085 National Health and Nutrition Examination Survey (2011–2018) participants aged over 20 years who underwent dual-energy X-ray absorptiometry (DXA). The FFMI and the FMI were determined based on total fat mass and lean mass measured by DXA. Diabetes and prediabetes status were determined by medical history and laboratory examination. Logistic regression analyses were performed to explore the correlations between the FMI/FFMI and the risk of developing diabetes/prediabetes. Restricted cubic spline analysis was used to explore underlying nonlinear associations.

Results In the present study, 1,135 patients were diagnosed with diabetes, 3,258 had prediabetes, and 5,692 were classified as control participants. The FFMI (odds ratio (OR) = 1.10, 95% confidence interval (CI) = 1.04–1.16) and the

[†]Da Liu, You-Lan Lei, Li Zhang and Wenyao Wang contributed equally to this work.

*Correspondence:
Gang Liu
cardio2004@hebmu.edu.cn
Jie Yang
yangjie3014529@163.com
Mingqi Zheng
mzheng2020@163.com
Yi-Da Tang
57303411@hebmu.edu.cn

Full list of author information is available at the end of the article

FMI (OR = 1.08, 95% CI = 1.04–1.12) were independently related to an increased risk of developing diabetes. Moreover, the FFMI (OR 1.08, 95% CI 1.02–1.16) and the FMI (OR 1.07, 95% CI 1.02–1.13) also independently correlated with a rising risk of developing prediabetes. The restricted cubic spline (RCS) outcomes suggested that the associations are approximately linear.

Conclusions Both the FMI and the FFMI significantly correlated with the danger of developing diabetes and prediabetes, and the correlations are approximately linear.

Keywords Fat-free mass index, Prediabetes, Fat mass index, Diabetes

Background

In the past 40 years, the number of people with diabetes worldwide has increased by more than 400% to 463 million [1]. Diabetes and its complications cause significant medical and economic burdens to society. It is estimated that $413 billion will be spent to treat people with diabetes in the United States in 2022, representing a 35% increase from 2012 [2]. Therefore, understanding the risk factors for diabetes is critical to effectively preventing its development. Obesity with insulin resistance represents the core conventional risk factor for developing type 2 diabetes, accounting for more than 90% of the diabetic population [3, 4]. The body mass index (BMI) is a good tool for diagnosing overweight or obesity, and relevant research have indicated that the BMI is significantly associated with the occurrence and development of diabetes [5, 6]. However, the BMI does not reflect body composition or fat distribution. The fat-free mass index (FFMI) and the fat mass index (FMI) can provide more information on body composition, which may be beneficial for evaluating diabetes risk more accurately [7–9]. Previous researches have indicated that the FMI correlates with the risk of developing diabetes and insulin resistance [10–12]. The associations between the FFMI and the risk of developing diabetes remain unclear, although previous studies have suggested that FFMI is associated with the risks of insulin resistance and metabolic syndrome [11, 13]. Moreover, few research have been implemented to investigate the impact of the FMI on the diabetes-adjusted FFMI via multivariable regression analysis. In the primary prevention and secondary prevention of diabetes, doctors and patients may pay more attention to the influence of body fat than to the influence of fat free weight. Therefore, the investigators carried out the present research to evaluate whether the FMI and the FFMI are significantly related to the risk of developing diabetes and prediabetes.

Methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional, nationwide survey aimed at evaluating the nutritional and health state of individuals in the U.S. The NHANES selects a representative sample of the U.S. population biennially. To enhance the reliability and precision of analyses, specific subgroups of public health interest are oversampled. Detailed introduction and information about the NHANES can be found at https://www.cdc.gov/nchs/nhanes/index.htm.

The present research pooled data from four independent NHANES cycles (2011–2012, 2013–2014, 2015–2016, and 2017–2018). Individuals aged over 20 years were included (n = 22,617), with approximately half providing the data necessary to calculate the FFMI and the FMI (n = 10,833). Participants needed to have at least one valid measurement of fasting blood glucose (FBG) concentrations, oral glucose tolerance test (OGTT) results, or glycated haemoglobin (HbA1c) values, along with the FFMI and the FMI values (n = 10,477). Those who self-reported as pregnant (n = 0) or as complicating malignant tumor (n = 392) were excluded. Ultimately, 10,085 adults were included in the present research (see Fig. 1). All subjects signed informed consent prior to their enrollment in the survey.

Definitions of outcomes

In this study, diabetes mellitus was determined by one or more of the following criteria: self-reported history of diabetes mellitus, use of insulin or oral hypoglycaemic drugs, FBG level ≥ 7.0 mmol/L (126 mg/dL), postprandial 2-hour blood glucose level ≥ 11.1 mmol/L (200 mg/dL) from OGTT, or HbA1c ≥ 6.5%. Prediabetes was defined by a self-reported history of prediabetes, a FBG level ≥ 5.6 mmol/L, a postprandial two-hour blood glucose concentration ≥ 7.8 mmol/L after an OGTT, or an HbA1c level ≥ 5.7%, and it was not classified as diabetes. The control group were subjects who did not conform to the criteria for either prediabetes or diabetes mellitus.

The FFMI and the FMI

In the 2011–2018 NHANES study cycles, dual-energy X-ray absorptiometry (DXA) was performed to survey whole-body data, containing total fat mass and total lean mass. In this study, the FFMI and the FMI were calculated using the following formulas:

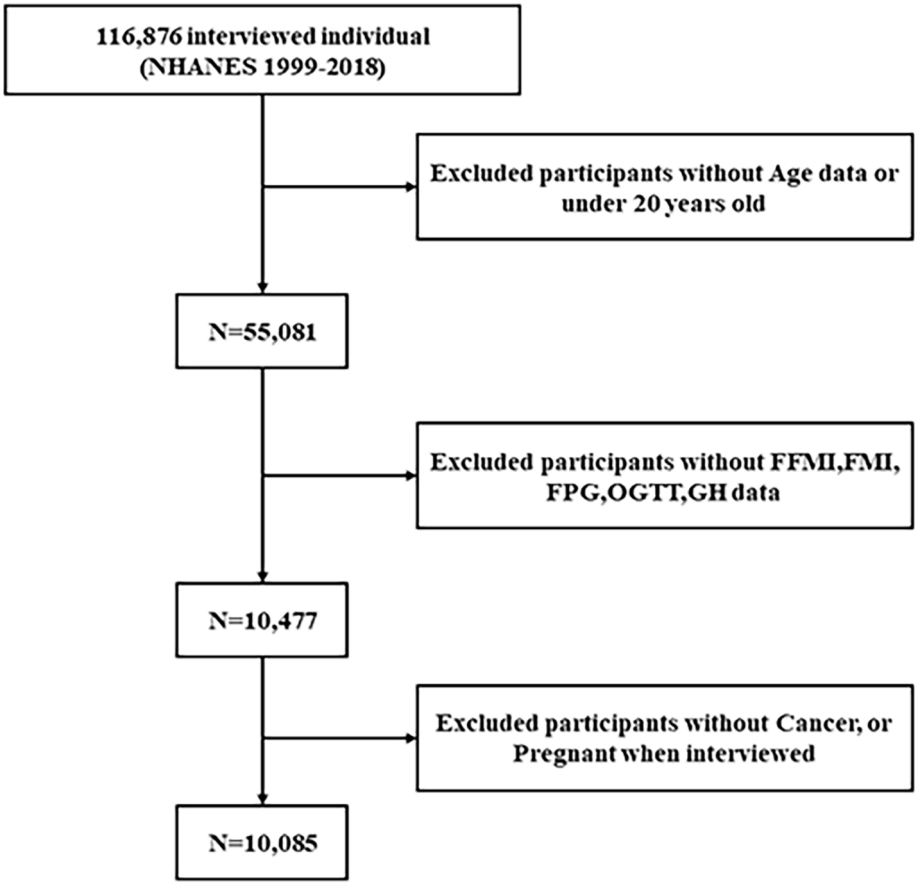

Fig. 1 Study population flow chart

$$FFMI\ \left(kg/m^2\right) = \frac{Total\ lean\ mass\ (kg)}{Height\ (m)^2}$$

$$FMI\ \left(kg/m^2\right) = \frac{Total\ fat\ mass\ (kg)}{Height\ (m)^2}$$

Covariate definitions

Information on age, gender, race, smoking state, alcohol use status, education level, sleep status, hypertension status, physical activity status, serum creatinine concentrations, C-reactive protein concentrations, triglyceride concentrations, low-density lipoprotein (LDL) concentrations, and high-density lipoprotein (HDL) concentrations were collected at enrolment.

Smoking state was classified into three groups: never smokers, ever smokers, and current smokers. Alcohol use status was classified as never drinker, ever drinker, mild drinker, moderate drinker, or heavy drinker. Sleep state was classified into three groups. The T1 group included individuals who usually had less than six hours of sleep per night. The T2 group consisted of individuals who usually had between six and eight hours of sleep per night. The T3 group included individuals who usually had more than eight hours of sleep per night.

Physical activity was classified into three groups: inactive, insufficiently active, and active. Inactive individuals reported no physical activity. Insufficiently active subjects engaged in moderate activity one to five times per week with a metabolic equivalent of task (MET) ranging from three to six or leisure-time vigorous activity one to three times per week with a MET greater than six. Active individuals reported more moderate or vigorous leisure-time activity than did insufficiently active individuals.

Statistical analysis

The baseline characteristics of the subjects were analyzed among the diabetes, prediabetes and control groups. The investigators used ANOVA to assess the differences in measurement data among the three groups. Logistic regression analyses were applied to calculate odds ratios. The possible nonlinear relationships of the FFMI and the FMI with the outcomes were further evaluated with restricted cubic spline (RCS) curves according to the multivariable logistic model. The FFMI and the FMI (as continuous variables) were also classified into tertiles

and then performed in multivariable logistic models with tertile 1 (T1) as the reference group. When investigating the associations of the FFMI and the FMI with the risk of developing diabetes, the investigators selected the 10,085 individuals included in the study as the study population. For the prediabetes analyses, 1,135 individuals with diabetes were excluded, and the remaining 8,950 individuals were included.

To avoid potential overadjustment for covariates that could mediate the correlations of the FFMI and the FMI with the risk of developing diabetes, 5 models were performed (Table 1). In Model 1, demographic traits such as age, sex, and race were included as covariates. Hypertension status, sleep status, education degree, smoking state, alcohol use status and physical activity status were included for further adjustment. In Model 3, creatinine and C-reactive protein concentrations were added to adjust for the influence of biochemical characteristics. In Model 4, triglyceride, HDL, and LDL concentrations were added to adjust for blood lipid characteristics. In Model 5, the FFMI and the FMI were mutually adjusted. To mitigate potential collinearity between the FFMI and the FMI, the investigators calculated the variance inflation factor (VIF) values, where a VIF exceeding 5 suggests likely collinearity between the FFMI and the FMI. Sensitivity analyses of the associations between the FFMI or the FMI and patient outcomes were conducted. Considering the minimal impact of skeletal components on sugar metabolism, the researchers conducted a repeated analysis using total lean mass excluding bone mineral content to calculate the FFMI.

Results

Participant characteristics

Table 1 presents the comparison of main characteristics of the research subjects. Among the 10,085 participants included in this study, 1,135 were diagnosed with diabetes, 3,258 had prediabetes, and 5,692 were classified as control participants. The diabetes group had the highest FFMI and FMI of 21.05 and 12.33, respectively. The prediabetes group had the next highest FFMI and FMI of 19.79 and 10.49, and the control group had the lowest at 18.33 and 9.07, respectively. In addition, compared to those in the prediabetes and control groups, participants in the diabetes group were significantly older, had higher levels of creatinine, triglycerides, and C-reactive protein, and were more likely to be complicated with hypertension. However, individuals in the diabetes group reported lower frequency of physical exercise and were less likely to be moderate or heavy drinkers, with lower levels of HDL. Additionally, significant discrepancies were observed between the three groups regarding race, sex, education level, sleep patterns, and blood LDL levels. Detailed information is provided in Table 1.

Associations of the FFMI and the FMI with the risk of developing diabetes

As continuous variables, both the FFMI and the FMI were significantly associated with a greater risk of developing diabetes and prediabetes according to univariable logistic models. According to the multivariable logistic models, the FFMI and the FMI were consistently related to a rising risk of developing diabetes across all the models (Models 1–5). In Model 4, each 1.0 unit increase in the FFMI and the FMI corresponded to a 16% and 12% greater risk of developing diabetes, respectively. The outcome of the collinearity test suggested that collinearity between the FFMI and the FMI was not significant. Therefore, in Model 5, the investigators adjusted for the FMI when exploring the effect of the FFMI and adjusted for the FFMI when exploring the effect of the FMI; with mutual adjustments, each 1.0 unit increase in the FFMI and the FMI resulted in a 10% and 8% increased risk of developing diabetes, respectively, as illustrated in Fig. 2.

When considered categorical variables, univariable models indicated that compared to individuals in the T1 group, individuals in the T2 and T3 groups for both the FFMI and the FMI had a significantly greater risk of developing diabetes. According to the multivariable models (Models 1–3), the T2 and T3 groups for both the FFMI and the FMI continued to have a significantly greater risk of developing diabetes. However, after adjusting for blood lipid characteristics in Model 4, neither T2 FFMI status nor T2 FMI status was positively related to the risk of developing diabetes, whereas T3 status maintained a significant association. After mutual adjustments in Model 5, the results mirrored those of Model 4, with odds ratios for the FFMI and the FMI in the T3 group of 1.91 (1.22–2.98) and 2.30 (1.51–3.52), respectively. Detailed information is provided in Fig. 3.

The RCS analysis did not indicate a nonlinear relationship between the FFMI or the FMI and the risk of developing diabetes, with nonlinear P values of 0.343 and 0.652, respectively. Besides, the FFMI, as a continuous variable, was positively related to the risk of developing diabetes (P-overall = 0.011). Although the RCS plot did not show a significant relationship between the FMI and an increased risk of developing diabetes (P-overall = 0.185), the trend in the plot was consistent with the logistic regression results.

Associations of the FFMI and the FMI with the risk of developing prediabetes

The results for the risk of developing prediabetes mirrored those for the risk of developing diabetes mellitus when considering the FFMI and the FMI as continuous variables. According to both the univariable analysis and all the multivariable logistic models, the FFMI and the FMI were associated with a rising risk of developing

Table 1 Baseline characteristics of the participants

	Overall	Control	pre_Diabetes	Diabetes	*p*
n	10,085	5692	3258	1135	
FFMI (mean (SD))	19.11 (3.46)	18.33 (3.20)	19.79 (3.40)	21.05 (3.71)	<0.001
FMI (mean (SD))	9.90 (4.43)	9.07 (4.04)	10.49 (4.48)	12.33 (4.96)	<0.001
Age (mean (SD))	39.10 (11.45)	35.66 (10.89)	42.27 (10.84)	47.24 (8.83)	<0.001
Sex = Female (%)	5040 (50.0)	3017 (53.0)	1465 (45.0)	558 (49.2)	<0.001
Race (%)					<0.001
Mexican American	1540 (15.3)	760 (13.4)	560 (17.2)	220 (19.4)	
Other Hispanic	1063 (10.5)	574 (10.1)	361 (11.1)	128 (11.3)	
Non-Hispanic White	3434 (34.1)	2238 (39.3)	912 (28.0)	284 (25.0)	
Non-Hispanic Black	2099 (20.8)	1036 (18.2)	773 (23.7)	290 (25.6)	
Other Race - Including Multi-Racial	1949 (19.3)	1084 (19.0)	652 (20.0)	213 (18.8)	
BMI (mean (SD))	28.88 (6.80)	27.27 (6.06)	30.16 (6.75)	33.31 (7.67)	<0.001
Physical activity (%)					<0.001
inactive	4506 (44.7)	2294 (40.3)	1570 (48.2)	642 (56.6)	
insufficiently active	2732 (27.1)	1563 (27.5)	888 (27.3)	281 (24.8)	
active	2846 (28.2)	1834 (32.2)	800 (24.6)	212 (18.7)	
Alcohol use (%)					<0.001
non-drinker	1234 (13.8)	663 (12.9)	399 (14.0)	172 (17.6)	
ever drinker	593 (6.6)	286 (5.6)	208 (7.3)	99 (10.1)	
mild drinker	3076 (34.3)	1679 (32.7)	1046 (36.6)	351 (35.9)	
moderate drinker	3591 (40.1)	2206 (43.0)	1069 (37.4)	316 (32.3)	
heavy drinker	468 (5.2)	293 (5.7)	134 (4.7)	41 (4.2)	
Education level (%)					<0.001
Less than 9th grade	645 (6.4)	264 (4.6)	259 (8.0)	122 (10.7)	
9-11th grade (Includes 12th grade with no diploma)	1202 (11.9)	601 (10.6)	433 (13.3)	168 (14.8)	
High school graduate/GED or equivalent	2215 (22.0)	1213 (21.3)	743 (22.8)	259 (22.8)	
Some college or AA degree	3279 (32.5)	1915 (33.6)	991 (30.4)	373 (32.9)	
College graduate or above	2742 (27.2)	1698 (29.8)	831 (25.5)	213 (18.8)	
Sleep time (%)					0.001
less than 6 h	3110 (30.9)	1677 (29.5)	1037 (31.9)	396 (35.1)	
6 to 8 h	5431 (54.0)	3104 (54.6)	1761 (54.2)	566 (50.1)	
more than 8 h	1520 (15.1)	901 (15.9)	452 (13.9)	167 (14.8)	
Hypertension (%)	2559 (25.4)	928 (16.3)	1024 (31.4)	607 (53.5)	<0.001
Creatinine (mg/dL) (mean (SD))	0.85 (0.37)	0.84 (0.29)	0.85 (0.24)	0.89 (0.79)	<0.001
Hb1Ac (%) (mean (SD))	5.63 (1.06)	5.22 (0.27)	5.65 (0.36)	7.63 (2.11)	<0.001
Fasting Glucose (mmol/L) (mean (SD))	5.90 (1.97)	5.10 (0.34)	5.76 (0.46)	9.18 (4.02)	<0.001
Two Hour Glucose(OGTT) (mmol/L) (mean (SD))	6.26 (2.78)	5.17 (1.13)	6.47 (1.80)	13.13 (5.66)	<0.001
Triglyceride (mg/dL) (mean (SD))	119.20 (120.00)	95.58 (66.22)	126.83 (111.69)	177.01 (225.59)	<0.001
LDL-cholesterol (mg/dL) (mean (SD))	113.67 (34.18)	106.44 (30.65)	120.47 (34.80)	116.73 (38.83)	<0.001
HDL-cholesterol (mg/dL) (mean (SD))	52.10 (15.31)	54.30 (15.73)	50.27 (14.33)	46.27 (13.55)	<0.001
C-reactive protein(mg/dL) (mean (SD))	3.77 (7.79)	2.79 (4.71)	4.13 (8.04)	7.10 (14.30)	<0.001
Take insulin (%)					<0.001
No	9898 (98.1)	5691 (100.0)	3258 (100.0)	949 (83.6)	
Yes	186 (1.8)	0 (0.0)	0 (0.0)	186 (16.4)	
Unknown	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	
Take diabetic pills (%)					<0.001
No	9545 (94.6)	5691 (100.0)	3258 (100.0)	596 (52.5)	
Yes	539 (5.3)	0 (0.0)	0 (0.0)	539 (47.5)	
Unknown	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	

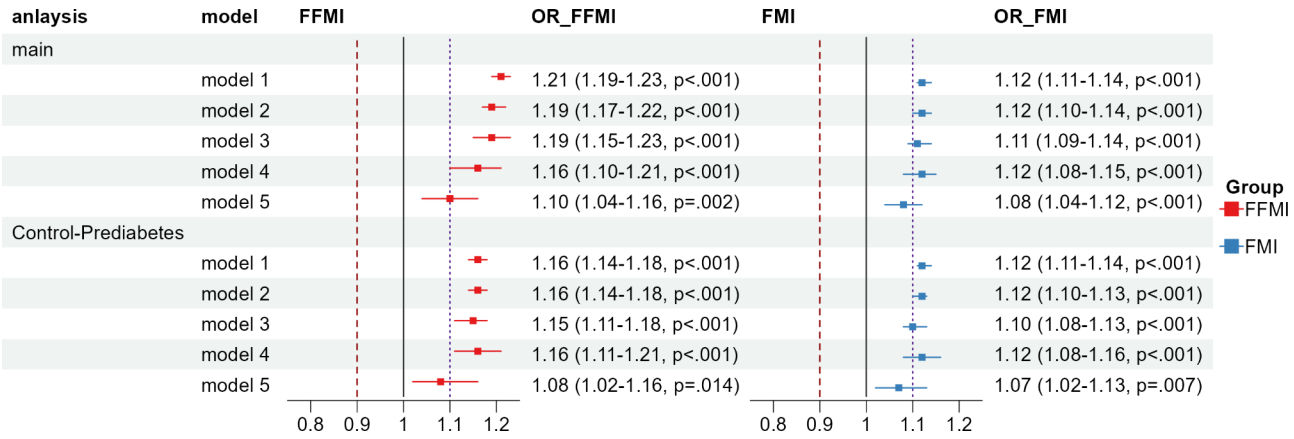

Fig. 2 Associations of the FFMI and the FMI as continuous variables with the outcomes across models

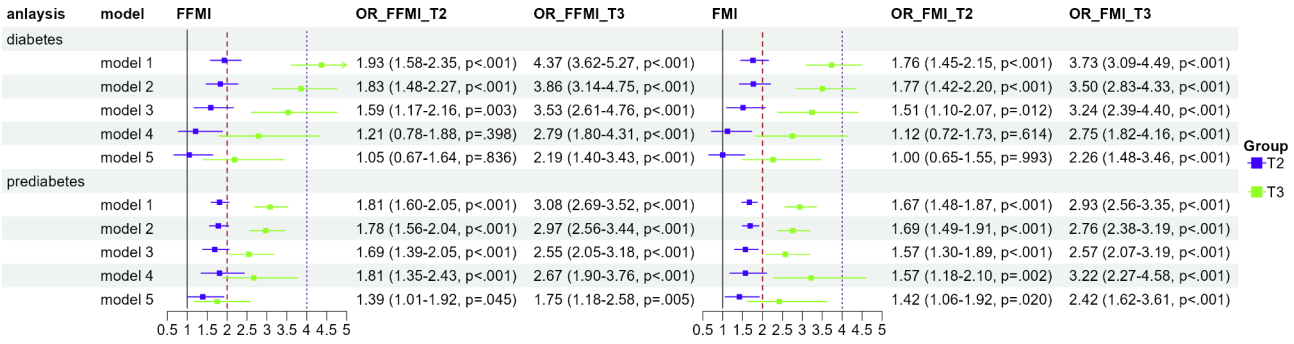

Fig. 3 Associations of the FFMI and the FMI as categorical variables with the outcomes across models

prediabetes. In Model 4, each 1.0 unit increase in the FFMI and the FMI was linked to a 16% and 12% greater risk of developing prediabetes, respectively. In Model 5, each 1.0 unit increase in the FFMI and the FMI corresponded to an 8% and 7% increased risk of developing prediabetes, respectively (Fig. 2).

When analysed as categorical variables, the FFMI and the FMI were related to a greater risk of developing prediabetes in both the univariate and multivariate logistic models. In Model 5, compared to the T1 group, the T2 group exhibited odds ratios for the risk of developing prediabetes of 1.45 (1.05–1.99) and 1.44 (1.07–1.94) for the FFMI and the FMI, respectively. The odds ratios of the T3 group for the risk of developing prediabetes were 1.70 (1.15–2.51) and 2.43 (1.63–3.65), respectively (Fig. 3).

Consistent with the results for diabetes, the RCS plot did not show nonlinear relationships of the FFMI and FMI with the risk of developing prediabetes (the *P*-nonlinear relationships for the FFMI and the FMI were 0.736 and 0.577, respectively). The trend in the plot aligned with the results from the logistic models (Fig. 4). In order to determine the predictive effect of BMI on diabetes and prediabetes, the researchers also conducted Cox regression analysis and drew a forest plot. The results showed that BMI was independently related to the risk of diabetes, but not to the risk of prediabetes (Supplementary Fig. 1). To determine the potential impact of age on the main outcomes, the investigators conducted a subgroup analysis based on age. The results indicated that the correlation between FFMI and diabetes remained consistent in the subgroups of individuals under 40 years old and those over 40 years old. However, the correlation between FMI and diabetes varied between the subgroups of individuals under 40 years old and those over 40 years old. (Supplementary Tables 1 and 2).

Sensitivity analysis

To eliminate any potential impact of skeletal components, which may have minimal effects on glucose metabolism, from the FFMI, the researchers performed multivariable logistic analysis and constructed a RCS plot after excluding the bone mineral content from the FFMI. The inclusion and exclusion criteria for participants in this analysis were identical to those used in the primary analysis. Ultimately, 10,281 participants were included, with variations in sample size attributed to the FFMI variable. The analysis produced results consistent with those of the primary analysis (Figs. 5, 6 and 7).

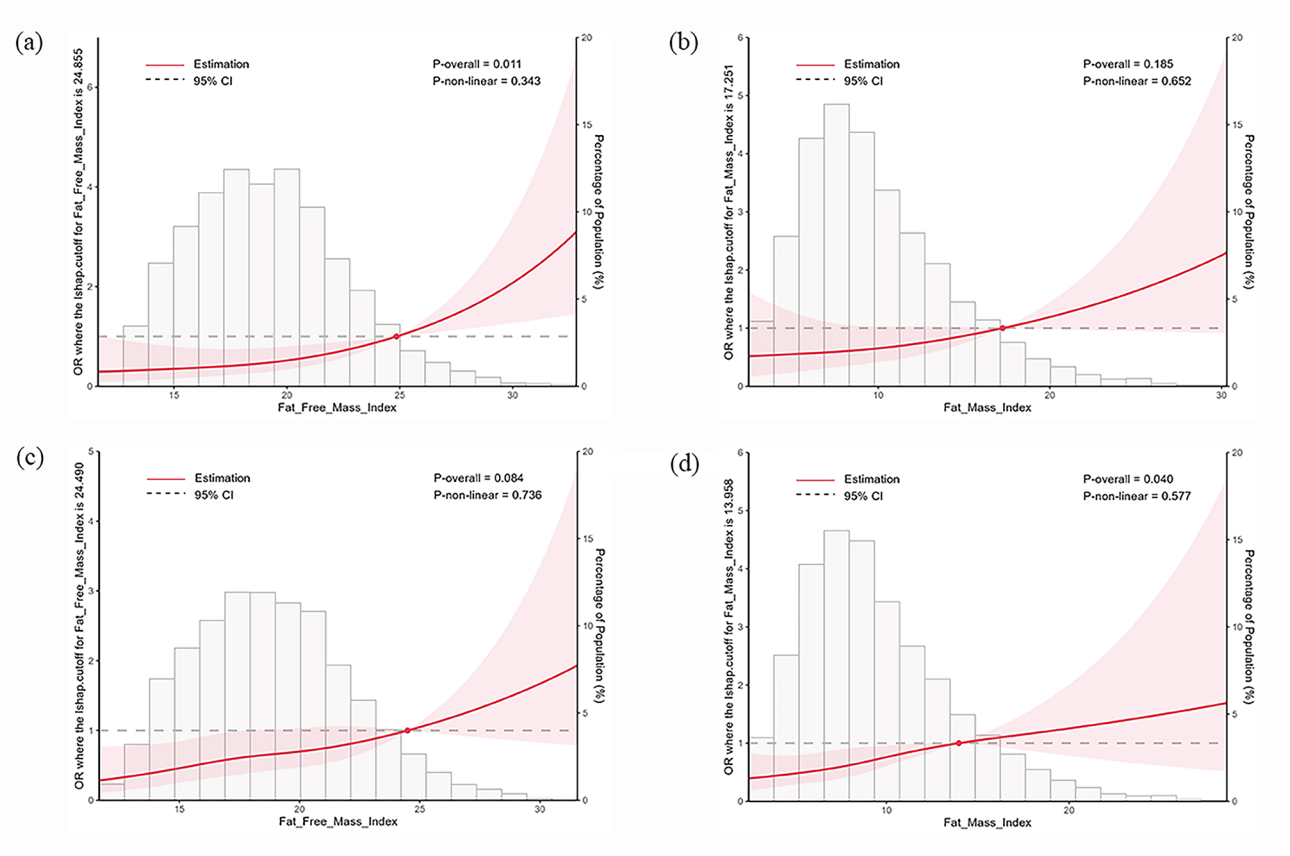

Fig. 4 RCS plots for the FFMI and the FMI. (**a**) The FFMI and the risk of developing diabetes. (**b**) The FMI and the risk of developing diabetes. (**c**) The FFMI and the risk of developing prediabetes. (**d**) The FMI and the risk of developing prediabetes

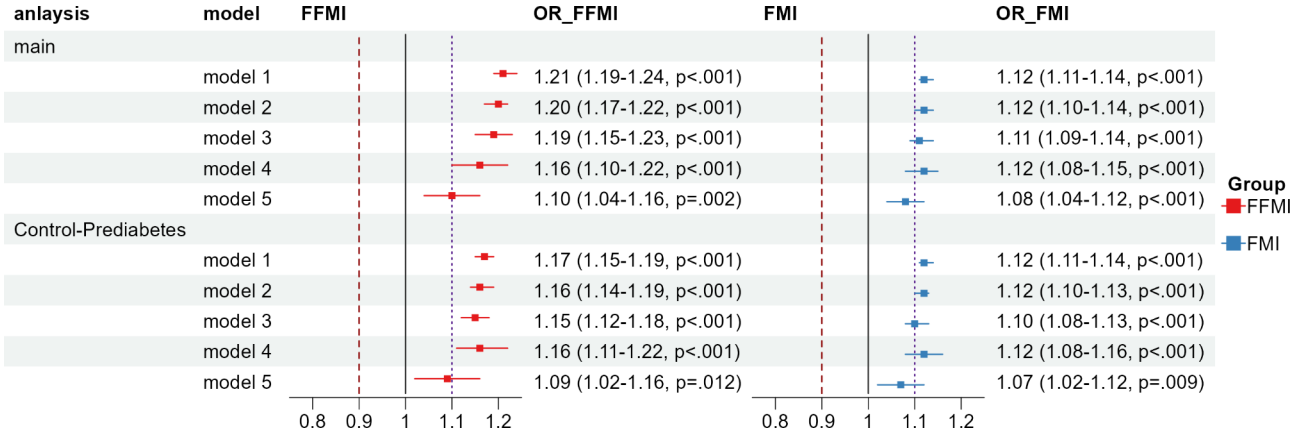

Fig. 5 Associations of FFMI and FMI as Continuous Variables with Outcomes in Sensitivity Analysis

Discussion

For this cross-sectional study, the investigators enrolled 10,085 NHANES subjects and evaluated the associations between the FMI/FFMI and the risk of developing diabetes/prediabetes, revealing the following two findings: (1) the FMI is independently associated with the risk of developing diabetes and prediabetes, and (2) the FFMI is also significantly related to diabetes and prediabetes.

Obesity is conventionally regarded as the excessive accumulation of body fat. In clinical practice and clinical trials, BMI is usually used to diagnose obesity and assess the degree of obesity. However, BMI does not reflect body composition or fat distribution. Given that the proportion and distribution of body fat determine the impact of obesity on metabolic and cardiovascular health [14, 15], BMI may not be suitable for precision medicine.

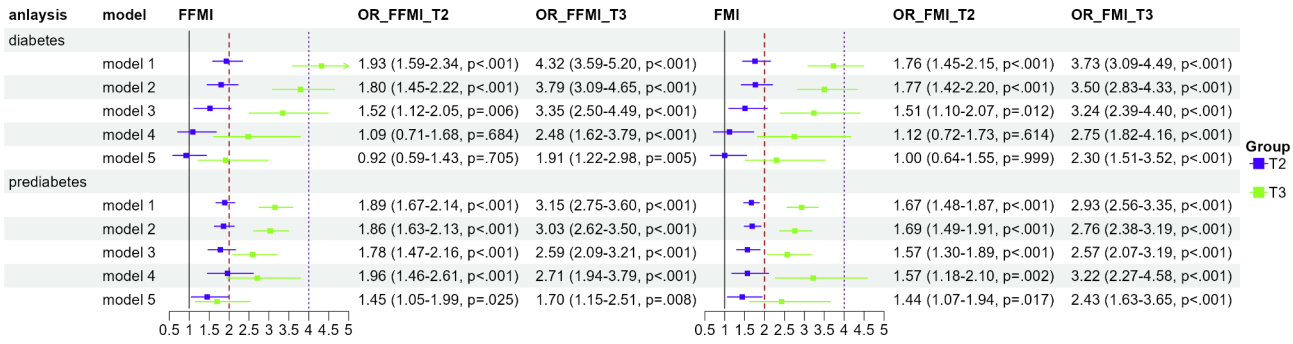

Fig. 6 Associations of FFMI and FMI as Categorical Variables with Outcomes in Sensitivity Analysis

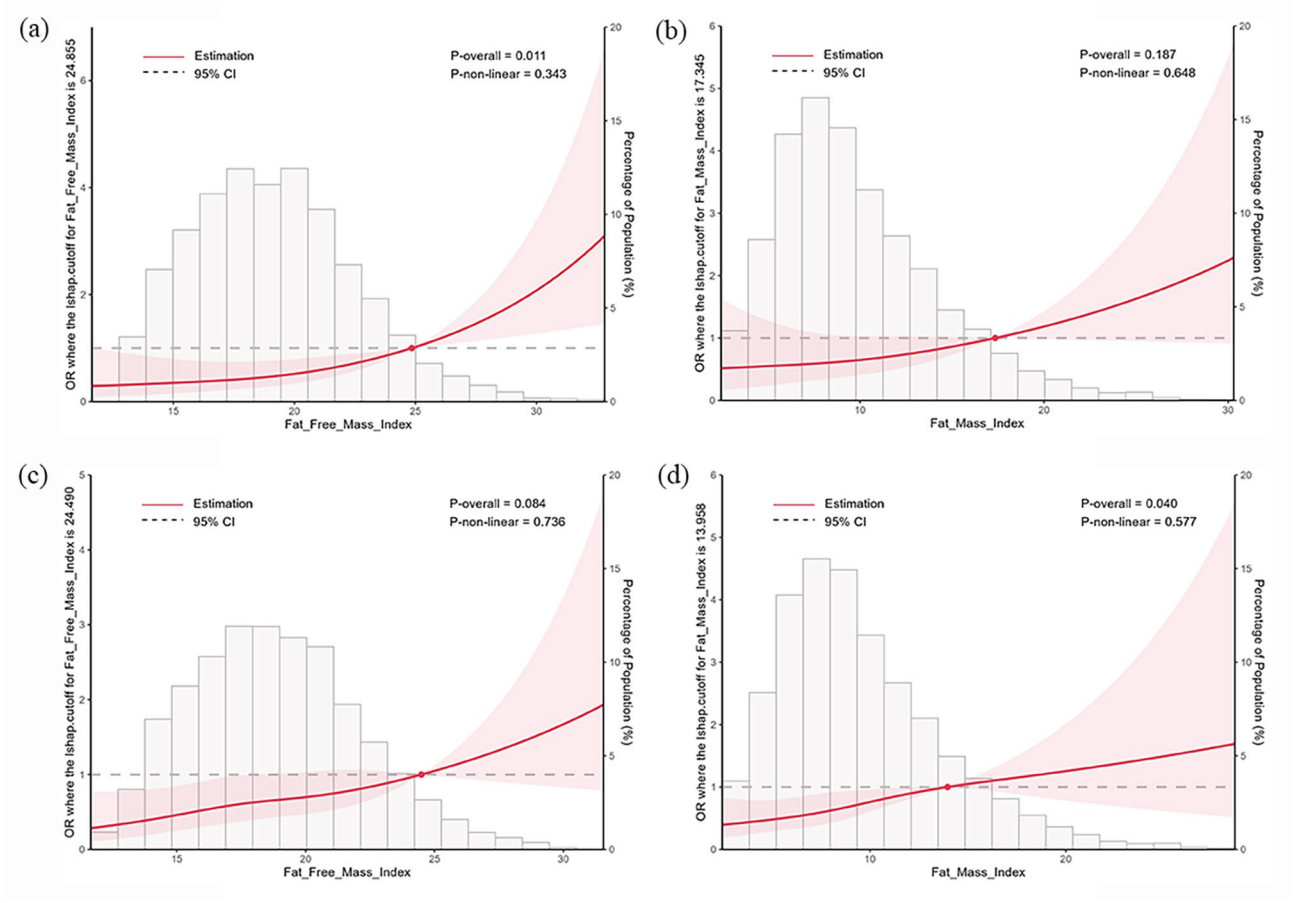

Fig. 7 RCS plots for the FFMI and the FMI in the sensitivity analysis. (**a**) The FFMI and the risk of developing diabetes. (**b**) The FMI and the risk of developing diabetes. (**c**) The FFMI and the risk of developing prediabetes. (d) The FMI and the risk of developing prediabetes

Excess fat accumulation, especially visceral fat accumulation, is a common characteristic of obesity and can lead to adipose tissue dysfunction. Adipose tissue dysfunction can induce the release of excessive free fatty acids (FFAs), reactive oxygen species (ROS) and proinflammatory cytokines, which trigger organ damage and cellular organelle dysregulation [16]. Mitochondrial biogenesis is impaired, mitochondrial fission increases, and ROS are produced uncontrollably in individuals with obesity [17–19]. In obese mice, excess lipids and misfolded proteins accumulate in the endoplasmic reticulum (ER), which can lead to ER stress and chronic inflammation of the liver and adipose tissue [20, 21]. Moreover, obesity can result in lysosomal dysfunction and autophagy defects by upregulating the S-nitrosylation of lysosomal proteins, exacerbating ER stress and impairing mitochondrial function [22, 23]. Due to cellular and organic dysfunction, as mentioned above, glucose homeostasis and insulin sensitivity are impaired, which promotes the occurrence and development of prediabetes and diabetes

[24]. Fat-free mass (FFM) was previously recognized as a protective factor for metabolic health by scientific and general community groups. Nevertheless, emerging evidence indicates that excess FFM may be harmful to metabolic health [25]. The underlying mechanism may include the following aspects. First, in general, more FFM is associated with a greater proportion of type II and type IIx muscle fibres, which can result in metabolic dysfunction by inducing a low capillary density and low oxidative capacity [26, 27]. Second, an excess of FFM can promote the capacity for ectopic fat accumulation, which can lead to muscle quality deterioration [27, 28]. Muscle quality is a more important predictive factor for metabolic health than FFM, namely, a high FFM without high muscle quality may not influence metabolic protection [29, 30]. Finally, a greater FFMI is associated with a greater level of interleukin 18, which induces chronic subclinical inflammation and impairs metabolic homeostasis [31].

The present research was not only the first in which the correlation between the FFMI and the risk of developing diabetes/prediabetes was revealed, but also provided new evidence for the correlation between the FMI and the risk of developing diabetes/prediabetes. In this population-based research, the investigators enrolled a total of 10,085 NHANES participants and revealed that not only the FMI but also the FFMI were significantly associated with the risk of developing diabetes/prediabetes. The RCS results suggested that the correlations were approximately linear, and the results of sensitivity analyses in which the bone mineral content was excluded from the FFMI illustrated the robustness of the main outcomes. Takase et al. [32] conducted a cross-sectional study of 12,922 Japanese individuals who were not treated for diabetes. In addition to data on body composition and HbA1c levels, researchers also collected data on smoking state and drinking state. They found that the FMI was independently related to HbA1c levels, and the FFMI was also significantly associated with HbA1c levels after excluding subjects who were diagnosed with diabetes. Another observational population-based study [33] enrolled 552 Asian subjects with obesity and survey the fat free mass based on bioelectrical impedance. The outcomes revealed that a higher FFMI was significantly related to metabolically abnormal obesity and metabolic syndrome in women. Rehunen et al. [34] conducted a cohort study including 704 subjects without diabetes at baseline. They measure the body composition via bioelectrical impedance. Besides, FBG, fasting plasma insulin, triglyceride and cholesterol level were also measured. The investigators followed up and recorded the glucose metabolism status of the subjects. The outcomes demonstrated that a high FMI and FFMI at baseline significantly increased the risk of developing type 2 diabetes. He et al. [35] explored the associations between different body composition indices and blood pressure.They enrolled 1,608 underage subjects in China, and measure the data on body composition and blood pressure. The results revealed that the association between blood pressure and the FFMI was stronger than that between the BMI and the FMI. Wang et al. [13] explored the correlations of free fat mass and fat mass with the risk of metabolic syndrome in Asian subjects. The investigators included 1,144 adult participants from multi-centers and the data on body composition was determined by DXA. The outcomes indicated that both free fat mass and fat mass were related to increased risk of metabolic syndrome. Ghachem et al. [36] conducted a cross-sectional study in which 703 subjects aged between 50 and 80 years were enrolled in the NHANES (2007–2008). They used Janmahasation's equations to estimate the FFMI and the FMI and found that both the FFMI and the FMI correlated with impaired fasting glucose concentrations, namely, a subtype of prediabetes. Although Ghachem's study suggested that both the FFMI and the FMI were associated with the risk of developing prediabetes, the FMI and the FFMI were not determined using gold standard measurements, and the sample size was relatively small, which may have resulted in inaccurate conclusions. The present research had an adequate sample size, and the FFMI and the FMI were determined using gold standard measurements, decreasing the possibility of false-positive outcomes. Moreover, the researchers investigated the impact of the FMI on the diabetes-adjusted FFMI via multivariable regression analysis.

Strengths and limitations

The present study included a large sample size, and the FMI and the FFMI were measured using the gold standard measurement (DXA results). The statistical analysis was rigorous, as the FFMI and the FMI were mutually adjusted in the multivariable logistic regression analysis. Moreover, further RCS analysis excluded the underlying nonlinearity associations. Finally, the results of sensitivity analyses in which bone mineral content was excluded from the FFMI illustrated the robustness of the main outcomes. The present research also had some limitations. First, the present research was a cross-sectional study; therefore, no causal relationships can be identified. Second, not all NHANES populations underwent OGTT, so the researchers could not determine the glucose metabolism status of all participants. Third, the researchers could not distinguish the type of diabetes from the data provided by the NHANES.

Conclusions

Both the FMI and the FFMI are significantly associated with the risk of developing diabetes and prediabetes, and the correlations are approximately linear. Therefore,

doctors and researchers should also focus on the impact of fat free mass in the primary prevention and secondary prevention of diabetes mellitus. More large-scale, multicentre, prospective studies need to be implemented to determine the correlation between the FFMI and the risk of developing diabetes/prediabetes.

Abbreviations

FFMI	Fat-free mass index
FMI	Fat mass index
VIF	Variance inflation factor
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
FPG	Fasting plasma glucose
OGTT	Oral glucose tolerance test
HbA1c	Glycated haemoglobin
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
MET	Metabolic equivalent of task
RCS	Restricted cubic spline
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Supplementary Information

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Supplementary Material 1

Supplementary Material 2: Supplementary Figure 1. Associations of the BMI with the outcomes across models.

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Author contributions
DL, JY, YDT and YLL conceived and designed the study, acquired the data and drafted the manuscript; ZL, CL, GL and MQZ analysed the data; CLS, WYW and QZ contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content; WYW, HPL, JW and JJW developed the software and provided technical support; YML, JXR and YKS had primary responsibility for the final content. All authors have read and approved the final manuscript. The authors report no conflicts of interest.

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Data availability
No datasets were generated or analysed during the current study.

Declarations
The protocol for the NHANES study received approval from the Ethics Review Board of the National Center for Health Statistics. Each participant provided written informed consent prior to their involvement in the survey. As this study constitutes a secondary analysis of the publicly available NHANES database, it does not necessitate additional ethical review by the hospital's ethics committee.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiology, the First Hospital of Hebei Medical University, No.89 Donggang Road, Shijiazhuang 050000, Hebei, China
[2]Peking University Health Science Center, Peking University, Beijing 100191, China
[3]Department of Cardiology, Beijing Longfu Hospital, Beijing Institute of Integrated Traditional Chinese and Western Medicine for Elderly Health, Beijing 100010, China
[4]Department of Cardiology, Institute of Vascular Medicine, State Key Laboratory of Vascular Homeostasis and Remodelling, NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Beijing Key Laboratory of Cardiovascular Receptors Research, Peking University Third Hospital, Peking University, Beijing 100191, China

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