BMJ Open

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058162
Article Type:	Original research
Date Submitted by the Author:	09-Oct-2021
Complete List of Authors:	Liu, Lu; Sichuan University West China Hospital, Department of Cardiology Jia, Shanshan; Sichuan University West China Hospital, Department of Cardiology Chen, Xiaoping; Sichuan University West China Hospital, Department of Cardiology He, Sen; Sichuan University West China Hospital, Department of Cardiology
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, INTERNAL MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Lu Liu Ph.D. [a], Shanshan Jia Ph.D. [a], Xiaoping Chen M.D. [a *], and Sen He M.D., Ph.D. [a *]

(Lu Liu and Shanshan Jia equally contribute to the article)

[a] Department of Cardiology, West China Hospital of Sichuan University, Chengdu, China

[*] **Corresponding author:** Xiaoping Chen and Sen He; Department of Cardiology, West China Hospital, Sichuan University No.37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China Tel: +86 028 85422343; Fax: +86 028 85422175; Email address: xiaopingchen0196@163.com (Xiaoping Chen), hesensubmit@163.com (Sen He).

ORCID IDs: 0000-0002-5274-4680 (for Lu Liu), 0000-0003-1824-3943 (for Xiaoping Chen), 0000-0002-9777-2650 (for Sen He)

Abstract

Objectives: With BMI failing to distinguish the mass of fat from lean, several novel predicted equations for predicted fat mass (FM), predicted lean mass (LM), and predicted percent fat (PF) were recently developed and validated. Our aim was to explore whether the three novel parameters could better predict DM than the commonly used obesity indicators, including BMI, waist circumference, hip circumference, and waist-hip ratio.

Design: A 15-year prospective cohort was used.

Setting: It was a prospective cohort, consisting of a general Chinese population from 1992 to 2007.

Participants: This cohort enrolled 711 people. People suffering from DM at baseline (n = 24) were excluded, and 687 non-diabetics with complete data were included to the analysis.

Primary outcome: New-onset DM.

Results: During the follow-up, 74 (48 men and 26 women) incidences of DM were documented. For men, the adjusted HRs were 1, 5.19 ($p = 0.003$), and 7.67 ($p < 0.001$) across predicted PF tertiles; 1, 2.86 ($p = 0.029$), and 5.60 ($p < 0.001$) across predicted FM tertiles; 1, 1.21 ($p = 0.646$), and 2.27 ($p = 0.025$) across predicted LM tertiles. Predicted FM performed better than other commonly used obesity indicators in discrimination with the highest Harrell's C-statistic among all the body composition parameters. Whereas, for women, none of the three novel parameters was the independent predictor.

Conclusion: Predicted PF, predicted LM, and predicted FM could independently predict the risk of DM for men, with predicted FM performing better than other commonly used obesity indicators in discrimination. For women, larger samples were further needed.

Key words: BMI, diabetes, fat mass, lean mass, obesity, percent fat

Strengths and limitations of this study

1. This study explored whether the three novel body composition parameters, including predicted FM, predicted LM, and predicted PF, could predict DM better than BMI and other commonly used obesity indicators.
2. Cox's regression analysis was used to estimate HRs for DM, and Harrell's C-statistic was used to assess and compare the discriminatory power of all the parameters in predicting new-onset DM.
3. The relatively small sample size might possibly lead to a statistical power decrease.

Introduction

Diabetes mellitus (DM) is a collection of chronic metabolic conditions, characterized by elevated blood glucose levels resulting from the body's inability to produce insulin or resistance to insulin action, or both(1). There are two primary forms of DM, insulin-dependent DM (type 1 diabetes mellitus, T1DM) and non-insulin-dependent DM (type 2 diabetes mellitus, T2DM). T2DM is the most common form, making up 90% - 95% of all diabetic patients(1). DM and its complications can result in disability and premature death(2), as well as enormous economic and social burdens(3). There is no cure for DM, thus, prevention is the best intervention.

Among the well-known modifiable risk factors, obesity, defined as an excess accumulation of body fat, is regarded as a major risk factor(4). Body mass index (BMI) has been mostly used as a simple and reasonable measure of general adiposity in clinical and public health settings. However, since it is defined as the result of weight in kilogram divided by height in meter squared, BMI is in poor discrimination of metabolically distinct components such as fat mass (FM) and lean mass (LM)(5). Direct measurement of FM and LM is impractical in large epidemiological studies for sophisticated and expensive technologies such as dual-energy X-ray absorptiometry (DXA) or imaging techniques (i.e. MRI and computerized tomography).

Recently, Lee et al developed anthropometric prediction equations for FM, LM, and percent fat (PF) from the large population samples of the noninstitutionalized civilians in the USA from National Health and Nutrition Examination Survey(6). In the original study, the validation tests showed robust and consistent results without evident substantial bias, and comparable abilities to predict obesity-related biomarkers with direct DXA measurements. Later, based on two large US prospective cohorts, predicted FM and predicted PF were both estimated to have a stronger association than BMI with

T2DM(7). However, body compositions differ across ethnic groups(8, 9). Healthy Chinese and South Asian individuals were measured to have a greater amount of visceral adipose tissue than Europeans with the same BMI or waist circumference(10). Therefore, we aimed to evaluate if these equations could better predict the risk of DM in comparison with BMI and other obesity indicators, including waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR), in a 15-year prospective cohort consisting of Chinese people.

Materials and methods

Patient and Public Involvement

In 2007, supported by the Mega-projects of Science Research for China's 11th five-year plan (Trends in the incidence of metabolic syndrome and integrated control in China), a group of 711 people, from an urban community situated in Chengdu, China, underwent a health examination. They also had a health examination in 1992 as part of the Chinese Multi-provincial Cohort Study approved by Beijing Institute of Heart, Lung, and Blood Vessel Disease that investigated cardiovascular risk factors across the country. Therefore, we picked up the data, and more details have been described elsewhere(11, 12). People suffering from DM at baseline (n = 24) were excluded. No one had missing data. Finally, the remaining 687 people with complete data were included in the analysis. All of them provided written informed consent. The study was approved by the Ministry of Health of China, as well as the Ethics Committee of West China Hospital of Sichuan University.

Evaluation

Definition

DM was defined by self-reported history or fasting plasma glucose (FPG) ≥ 7.0 mmol/L(13).

Hypertension was a conventional blood pressure of ≥ 140mm Hg systolic, ≥ 90mm Hg diastolic, or the use of antihypertensive drugs. DM family history was determined with a diagnosis of DM in the first-grade relatives. Smoking was defined as an average cigarette consumption of at least one per day. Frequent previous alcohol intake and present alcohol intake were both defined as alcohol consumption. Activity was defined as at least twice 20-minute moderately intensive physical activity per week.

Data collection

Baseline data in 1992 included medical history, physical examination, and biochemical tests. Questionnaires containing demographic information and cardiovascular disease risk factors were collected by well-trained investigators. WC was measured at the midpoint between the lower border of the rib cage and the iliac crest at the end of a normal exhalation. HC was measured at the maximum protrusion of the gluteal region. WHR was calculated by WC in cm divided by HC in cm. Height was measured without shoes. Weight was measured in light clothing. Blood pressure was measured in a sitting position after at least 15 min of rest, and the mean blood pressure of three measurements taken by a standardized mercury sphygmomanometer was used as a participant's blood pressure. Blood samples were drawn from participants in the morning after 12-h overnight fasting. FPG, total cholesterol (TC), and triglyceride (TG) levels were determined in an enzymatic method, and high-density lipoprotein cholesterol (HDL-C) was measured by the phosphotungstic acid/$MgCl_2$ precipitation method. Low-density lipoprotein cholesterol (LDL-C) was measured using a standard kit.

Equation profiles

Equations for predicted FM (kg)(6)

$$\text{For men} \quad = -18.592 - 0.009 \times \text{age (year)} - 0.080 \times \text{height (cm)} + 0.226 \times \text{weight (kg)}$$

$$+ 0.387 \times \text{WC (cm)} + 0.080 \times \text{Mexican} - 0.188 \times \text{Hispanic} - 0.483 \times \text{Black} + 1.050 \times$$

other ethnicity

For women $= 11.817 + 0.041 \times$ age (year) $-0.199 \times$ height (cm) $+0.610 \times$ weight (kg) $+0.044 \times$ WC (cm) $+0.388 \times$ Mexican $+ 0.073 \times$ Hispanic $- 1.187 \times$ Black $+ 0.325 \times$ other ethnicity

Equations for predicted LM (kg)(6)

For men $= 19.363 + 0.001 \times$ age (year) $+0.064 \times$ height (cm) $+0.756 \times$ weight (kg) $-0.366 \times$ WC (cm) $-0.066 \times$ Mexican $+ 0.231 \times$ Hispanic $+ 0.432 \times$ Black $- 1.007 \times$ other ethnicity

For women $= -10.683 - 0.039 \times$ age (years) $+0.186 \times$ height (cm) $+0.383 \times$ weight (kg) $-0.043 \times$ WC (cm) $-0.359 \times$ Mexican $- 0.059 \times$ Hispanic $+ 1.085 \times$ Black $- 0.34 \times$ other ethnicity

Equations for predicted PF (%)(6)

For men $= 0.02 + 0.00 \times$ age (year) $-0.07 \times$ height (cm) $-0.08 \times$ weight (kg) $+0.48 \times$ WC (cm) $+0.32 \times$ Mexican $+ 0.02 \times$ Hispanic $- 0.65 \times$ Black $+ 1.12 \times$ other ethnicity

For women $= 50.46 + 0.07 \times$ age (year) $-0.26 \times$ height (cm) $+0.27 \times$ weight (kg) $+0.10 \times$ WC (cm) $+0.89 \times$ Mexican $+ 0.49 \times$ Hispanic $- 1.57 \times$ Black $+ 0.43 \times$ other ethnicity

Statistical analyses

For descriptive results, variables were expressed as the mean ± standard deviation (SD), median and interquartile range, or counts and percentages as appropriate. Smoking, alcohol intake, activity, hypertension, and family history of DM were expressed as dummy variables (presence= 1, absence= 0). Differences in baseline characteristics between participants with and without new-onset DM were tested by independent t-test for normally distributed variables and by the non-parametric Mann-

Whitney U-test for skewed variables. Interactions between categorical variables were evaluated with the Pearson χ^2 test, Fisher's exact probabilities were used if necessary. Correlations between different variables were determined using Pearson's or Spearman's analysis.

We treated all the parameters as sex-specific tertiles. The cumulative incidences of DM across tertiles were graphically displayed according to the method of Kaplan-Meier, with comparisons among groups by the log-rank test. Cox proportional hazards regression models were used to assess the impact of the variables on the incidence rate of DM. Furthermore, restricted cubic spline analysis was used to visualize the relations between variables and incident DM. To quantify and compare the discriminative ability of different parameters, Harrell's c-index was calculated. A generally accepted approach suggests that the C-index of less than 0.60 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75, clearly useful discrimination(14).

All statistical tests were 2-sided, and p value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 3.6.3.

Results

Baseline characteristics

After excluding people suffering from DM at baseline (n = 24), the remaining 687 (399 men and 288 women) people free of DM at baseline with complete data were included in the analysis.

Those who had subsequent DM were associated with higher baseline levels of FPG, weight, BMI, WC, HC, predicted FM, predicted LM, and predicted PF for the males; associated with higher baseline levels of TC, TG, height, BMI, WC, HC, predicted FM, and predicted PF, and lower baseline level of HDL-C for the females. At baseline, age was not of significance between the group, but there was still

a trend that people suffering incident DM were older. Other details of baseline information were shown in Table 1.

As Table S1 showed, predicted FM was strongly correlated with WC (r_s = 0.98), followed by BMI (r_s = 0.88) and HC (r_s = 0.82) in men; strongly correlated with BMI (r_s = 0.94), followed by HC (r_s = 0.87) and WC (r_s = 0.83) in women. Predicted LM had a strong correlation with predicted FM (r_s = 0.83) in women and a relatively strong correlation with HC (r_s = 0.71) in men, but relatively weakly with WHR both in men (r_s = 0.15) and women (r_s = 0.29). Predicted PF was strongly correlated with WC (r_s = 0.97) in men and BMI (r_s = 0.95) in women, but relatively weakly with predicted LM both in men (r_s = 0.35) and women (r_s = 0.51).

Survival analysis

All the body composition parameters were divided into tertiles. Tertile 1 had the lowest estimated values while Tertile 3 had the highest. During the follow-up, 74 (48 men and 26 women) incidences of DM were documented (incidence rate: 0.17 per 100 person-years; 95% CI: 0.57-0.91). The cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (log-rank p = 0.001), predicted LM (log-rank p = 0.030), and predicted PF (log-rank p < 0.001) in men (Figure 1A-C), and people in the top tertile had the highest cumulative incidence of DM. For women, only predicted PF (log-rank p = 0.028) could help to distinguish the cumulative incidence across the tertiles (Figure 1D).

For other obesity indicators, the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of BMI (log-rank p < 0.001), WC (log-rank p = 0.001), HC (log-rank p = 0.006), and WHR (log-rank p = 0.001) in men; WC (log-rank p = 0.002) and WHR (log-rank p < 0.001) in women.

Relation to risk of DM

Univariate cox regression analysis was shown in Table S2. Predicted FM, predicted PF, BMI, WC, HC, and WHR were risk factors of DM for both men and women, and predicted LM was a risk factor for men only. Variables showing statistical significance or clinically relevance ($p < 0.1$) were entered into multivariate analysis.

In multivariate analysis, we adjusted potential confounders including hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG. As Table 2 showed, in the male group, predicted FM ($p < 0.001$), predicted LM ($p = 0.043$), and predicted PF ($p < 0.001$) were still significant predictors, with the top tertile associated with a higher risk of DM. Other commonly used parameters such as BMI ($p < 0.001$), WC ($p < 0.001$), HC ($p = 0.004$) and WHR ($p < 0.001$) were also significant predictors (Table S3). Higher predicted PF was more strongly associated with increased risk of DM, since it showed a positive association to the risk of DM with the adjusted HRs for Tertile 2 and Tertile 3 estimated as 5.19 ($p = 0.003$) and 7.67 ($p < 0.001$), respectively, in comparison with Tertile 1. There was a positive association across tertiles between predicted FM and the risk of DM as well (HR: 2.86, $p = 0.029$ for Tertile 2; HR: 5.60, $p < 0.001$ for Tertile 3, respectively). WC and WHR showed a positive association across tertiles (Table S3). However, there was no significant difference in risk of DM between Tertile 2 and Tertile 1 of predicted LM (HR: 1.21, 95% CI: 0.54-2.70, $p = 0.646$).

As for the female group, however, none of the three novel parameters was significantly independent (Table 2). Only WHR ($p < 0.001$) remained stable and significant (Table S3).

Furthermore, we treated the predicted FM, predicted LM, and predicted PF as continuous variables and used restricted cubic splines to flexibly models and visualize the relations with risk of

DM (Figure S1 for men and S2 for women). Confounders in Table 2 were adjusted. Consistently with the results above as categorical variables, predicted PF and predicted FM, but not predicted LM, showed a completely positive association in men with the medians as reference points (Figure S1); while in women, the relations were not completely significant (Table 2, Figure S2)

Discrimination

In the male group, predicted FM had the highest Harrell's c-index of 0.679 (95% CI: 0.606-0.752), followed by BMI of 0.675 (95% CI: 0.599-0.751), WC of 0.673 (95% CI: 0.600-0.746), predicted PF of 0.670 (95% CI: 0.598-0.742), WHR of 0.652 (95% CI: 0.578-0.726), HC of 0.636 (95% CI: 0.560-0.712), and predicted LM of 0.619 (95% CI: 0.537-0.701). All of these parameters could provide a possibly helpful discriminative power(14).

In the female group, since WHR was the only significantly independent risk factor of DM, we just estimated Harrell's c-index (0.768, 95% CI: 0.697-0.839) of WHR, and it showed a clearly useful discriminative power(14).

Discussion

In this study, we investigated the predictive abilities for the risk of DM of three novel body composition parameters including predicted FM, predicted LM, and predicted PF, and compared with other obesity indicators, in a Chinese prospective population during 15 years of follow-up. For men, our results showed predicted FM, predicted LM, and predicted PF could independently predict the new onset of DM; in all the parameters we studied, predicted FM had the best discriminative power, providing possibly helpful information. For women, none of the three novel parameters could be significantly independent in multivariate analysis; of all the parameters we estimated, WHR was the

only independent predictor, with Harrell's c-index of 0.768, which suggested a clearly useful discrimination.

To our knowledge, this was the first study in a Chinese prospective cohort to evaluate the associations of three novel body composition parameters with the incidence of DM. BMI has been preferred as a measure indicating overall obesity for a long time to identify people at increased risk of DM(15). However, BMI was not thought a good indicator of obesity.(5, 16). It fails to distinguish the mass of fat from lean, and had no gender distinction as well. For example, in common sense, athletes or someone liking exercise always had heavier weight for the mass of lean, they have greater BMI but they are not obese. Besides, aging is associated with an accumulation of visceral fat and a progressive loss of muscle mass(16). With the same BMI, an old man has more mass of fat but less mass of muscle than a younger man.

Recently, Lee et al. (6) developed equations predicting FM, LM, and PF to better reflect body composition. The predicted equations had a simple calculation and just require the information of gender, age, height, weight, WC, and ethnicity, which are easily measurable and accessible in clinical settings or even at home. Lee et al. later investigated the association between predicted FM and risk of DM in two large prospective cohorts of US men and women(7). They found predicted FM, as well as predicted PF, had a stronger association than BMI both in men and women. Similarly, in our study consisting of Chinese population, in the male group, both predicted PF and predicted FM could independently predict incident DM. Predicted FM had the highest Harrell's. Higher predicted PF was more strongly than other parameters associated with increased risk of DM.

Besides in prediction of DM, predicted FM and predicted PF were also explored in the association with risk of heart failure and myocardial infarction in adults with T2DM(17). The results showed a

decline in predicted FM but not predicted LM, over 1 year was significantly associated with lower risk of overall heart failure (adjusted HR per 10% decrease in predicted FM: 0.80; 95% CI: 0.68-0.95); decline in predicted FM was significantly associated with lower risk of both heart failure subtypes (with preserved or reduced ejection fraction).

In a post hoc analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study(18), researchers modified the two parameters, fat mass index and lean BMI, calculated by predicted FM and predicted LM, respectively, in kilograms divided by the square of height in meters. They found that in patients with T2DM, fat mass index had a strong positive association with a higher risk of a major adverse cardiovascular event, while predicted lean BMI was not associated with major cardiovascular events ($p = 0.34$).

In a large prospective US cohort study of men(19), there was a strong positive association between predicted FM and mortality from all causes, cardiovascular disease, and cancer. Compared with those in the lowest fifth of predicted FM, men in the highest fifth had an HR of 1.35 (95% CI: 1.26-1.46) for all-cause mortality. In contrast, predicted LM showed a U-shaped association with all-cause mortality that men in the second to fourth fifths had 8-10% lower risk. The U-shaped associations were also found with deaths from cardiovascular disease and cancer. However, there was a strong inverse association between predicted LM and mortality from respiratory disease.

Lean body mass accounts for most of the human body mass, and it is essential not only in the stress response but also in metabolism(20). Muscle loss may have negative effects(20-22). Son et al. previously conducted a 2-yearly prospective assessment in middle-aged and older Korean adults, and reported that low muscle mass was associated with an increased risk of T2DM, independent of general obesity(23). In contrast, in our research, for the development of DM, the protective role of predicted

LM could not be concluded. Instead, the top tertile of predicted LM had an increased risk in the male group. Since there is a lack of randomized clinical trial studies that directly assess the role of increased muscle mass in the prevention of new on-set DM(24), the association between predicted LM and risk of DM needs further explorations. After all, increased LM was not always simply reported as the protective factor of diseases or mortality(17-19).

There are certainly some limitations in our study. Firstly, 687 was a relatively small sample size, possibly leading to a statistical power decrease, for example, the results for women. But we still observed that as a continuous variable, predicted PF could independently predict the risk of incident DM. Maybe in a larger population, the relations and comparisons would be more accurate. Secondly, due to the absence of oral glucose tolerance tests (OGTT) and hemoglobin A1c (HbA1c) data in our study, some people might not be adequately diagnosed. Thirdly, only one follow-up examination was carried out, so that there was no guarantee whether some "interval censoring" might have occurred.

In conclusion, in the general Chinese population, predicted PF, predicted LM, and predicted FM could independently predict the risk of DM for men, and predicted FM performed better than other commonly used obesity indicators including BMI, WC, HC, and WHR, in discrimination. For women, however, predicted PF, predicted LM, predicted FM, as well as other obesity indicators, but WHR, could not remain stable and independent in multivariate analysis, which might be attributed to the relatively small sample. Therefore, larger samples from different races are needed to explore the predictive strength of the novel equations reflecting body composition on incident DM and other diseases.

Acknowledgment

We thank all staff members for data collection, data entry and monitoring as part of this study.

Funding

This work was supported by the National Natural Science Foundation of China [Grant number: 81600299]; a project from China's eighth national 5-year research plan [Grant no: 85-915-01-02]; and the megaprojects of science research for China's 11th 5-year plan [Grant no: 2006BAI01A01].

Competing interests

None declared.

Contributors

LL and SSJ: Participated in the conception and design of the study, performed the data collection and the statistical analysis, and wrote the draft of the manuscript. SH and XPC: Participated in the design of the study, performed the statistical analysis, and revised subsequent drafts. All authors read and approved the final manuscript.

Data availability statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Reference

1. Wu Y, Ding Y, Tanaka Y, *et al.* Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185-200.

2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.

3. Zhao Y, Jiang Z, Guo C. New hope for type 2 diabetics: targeting insulin resistance through the immune modulation of stem cells. Autoimmun Rev. 2011;11(2):137-42.

4. Klein S, Sheard NF, Pi-Sunyer X, *et al.* Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Am J Clin Nutr. 2004;80(2):257-63.

5. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev. 2001;2(3):141-7.

6. Lee DH, Keum N, Hu FB, *et al.* Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Br J Nutr. 2017;118(10):858-66.

7. Lee DH, Keum N, Hu FB, *et al.* Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. Eur J Epidemiol. 2018;33(11):1113-23.

8. Lear SA, Humphries KH, Kohli S, *et al.* Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr. 2007;86(2):353-9.

9. Lear SA, Humphries KH, Kohli S, *et al.* The use of BMI and waist circumference as surrogates of

body fat differs by ethnicity. Obesity (Silver Spring). 2007;15(11):2817-24.

10. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. Jama. 2009;301(20):2129-40.

11. Ren J, Grundy SM, Liu J, *et al.* Long-term coronary heart disease risk associated with very-low-density lipoprotein cholesterol in Chinese: the results of a 15-Year Chinese Multi-Provincial Cohort Study (CMCS). Atherosclerosis. 2010;211(1):327-32.

12. Liu J, Hong Y, D'Agostino RB, Sr., *et al.* Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. Jama. 2004;291(21):2591-9.

13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.

14. Alba AC, Agoritsas T, Walsh M, *et al.* Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. Jama. 2017;318(14):1377-84.

15. Vazquez G, Duval S, Jacobs DR, Jr., *et al.* Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev. 2007;29:115-28.

16. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015;74(4):405-12.

17. Patel KV, Bahnson JL, Gaussoin SA, *et al.* Association of Baseline and Longitudinal Changes in Body Composition Measures With Risk of Heart Failure and Myocardial Infarction in Type 2 Diabetes: Findings From the Look AHEAD Trial. Circulation. 2020;142(25):2420-30.

18. Xing Z, Tang L, Chen J, *et al.* Association of predicted lean body mass and fat mass with

cardiovascular events in patients with type 2 diabetes mellitus. Cmaj. 2019;191(38):E1042-e8.

19. Lee DH, Keum N, Hu FB, *et al.* Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. Bmj. 2018;362:k2575.

20. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84(3):475-82.

21. Ruiz JR, Sui X, Lobelo F, *et al.* Association between muscular strength and mortality in men: prospective cohort study. Bmj. 2008;337(7661):a439.

22. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889-96.

23. Son JW, Lee SS, Kim SR, *et al.* Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. Diabetologia. 2017;60(5):865-72.

24. de Sousa MV, da Silva Soares DB, Caraça ER, *et al.* Dietary protein and exercise for preservation of lean mass and perspectives on type 2 diabetes prevention. Exp Biol Med (Maywood). 2019;244(12):992-1004.

Table 1. Basic characteristics of people with or without subsequent DM.

Variables	Men (n=399)			Women (n=288)		
	Subsequent DM (n=48)	Subsequent non-DM (n=351)	p-value	Subsequent DM (n=26)	Subsequent non-DM (n=262)	p-value
Age (years)	50.6 ± 5.0	49.0 (45.0-53.0)	0.079	48.4 ± 6.8	46.0 (42.0-52.0)	0.127
Smoking (%)	32 (66.7%)	213 (60.7%)	0.425	0	2 (0.8%)	1.000
Hypertension (%)	9 (18.8%)	50 (14.2%)	0.410	7 (26.9%)	38 (14.5%)	0.150
DM family history (%)	3 (6.3%)	9 (2.6%)	0.165	3 (11.5%)	18 (6.9%)	0.418
SBP (mm Hg)	118.1 ± 14.5	110.0 (105.0-120.0)	0.061	119.0 (103.0-132.5)	110.0 (102.0-120.0)	0.240
DBP (mm Hg)	74.0 (70.0-80.0)	72.0 (70.0-80.0)	0.292	76.4 ± 12.1	70.0 (71.0-80.0)	0.226
FPG (mmol/L)	4.6 ± 0.8	4.0 (3.8-4.7)	<0.001	4.6 ± 0.9	3.8 (4.0-4.7)	0.052
TC (mmol/l)	4.4 (4.1-4.8)	4.3 (3.9-4.8)	0.419	5.0 ± 0.7	4.4 (3.9-5.0)	0.006
TG (mmol/L)	1.9 (1.7-3.0)	1.9 (1.5-2.4)	0.104	1.9 (1.5-2.3)	1.8 (1.4-2.2)	<0.001
HDL-C (mmol/L)	1.2 (1.0-1.4)	1.2 (1.1-1.4)	0.193	1.2 ± 0.2	1.3 (1.1-1.5)	0.009
LDL-C (mmol/L)	2.2 ± 0.8	2.1 (1.7-2.7)	0.556	2.4 ± 1.0	2.3 (1.8-2.8)	0.460
Height (cm)	165.4 ± 5.9	165.3 ± 5.6	0.898	151.9 ± 4.4	151.0 (155.0-159.0)	0.006
Weight (cm)	68.5 (61.3-74.8)	62.9 ± 8.2	<0.001	58.6 ± 9.0	56.4 ± 7.5	0.168
BMI (kg/m^2)	24.8 (23.0-26.6)	23.0 (20.9-24.8)	<0.001	25.3 ± 3.3	23.4 ± 2.6	0.001
WC (cm)	83.6 ± 8.2	78.0 (72.0-83.0)	<0.001	79.9 ± 7.6	73.5 ± 7.1	<0.001
HC (cm)	95.0 (90.0-97.0)	91.0 (87.0-95.0)	<0.001	95.4 ± 7.4	92.6 ± 5.8	0.021
WHR	0.89 ± 0.05	0.85 ± 0.06	0.001	0.84 ± 0.04	0.79 ± 0.05	<0.001
FM (kg)	16.4 ± 5.2	13.3 (9.6-16.2)	<0.001	21.8 ± 5.4	19.6 ± 4.3	0.014
LM (kg)	50.2 ± 5.0	48.1 ± 4.5	0.004	34.3 ± 3.5	34.4 ± 3.4	0.894
PF (%)	24.0 ± 3.4	21.8 ± 3.1	<0.001	38.6 ± 2.9	36.4 ± 2.4	<0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Table 2 Multivariate Cox regression models for DM

	Case (%)	Multivariate hazards regression *	
		HR (95% CI)	p
For men			
FM			
per 1-SD increase		1.18 (1.11-1.25)	< 0.001
T1 (reference)	6 (4.54%)	1	-
T2	16 (12.21%)	2.86 (1.12-7.33)	0.029
T3	26 (19.12%)	5.60 (2.27-13.80)	< 0.001
p for trend			< 0.001
LM			
per 1-SD increase		1.10 (1.03-1.17)	0.003
T1 (reference)	11 (8.33%)	1	-
T2	13 (9.92%)	1.21 (0.54-2.70)	0.646
T3	24 (17.65%)	2.27 (1.11-4.63)	0.025
p for trend			0.043
PF			
per 1-SD increase		1.25 (1.14-1.36)	< 0.001
T1 (reference)	4 (3.03%)	1	-
T2	20 (15.27%)	5.19 (1.77-15.20)	0.003
T3	24 (17.65%)	7.67 (2.64-22.35)	< 0.001
p for trend			< 0.001
Women			
FM			
per 1-SD increase		1.00 (0.91-1.10)	0.145
T1 (reference)	5 (5.26%)	1	-

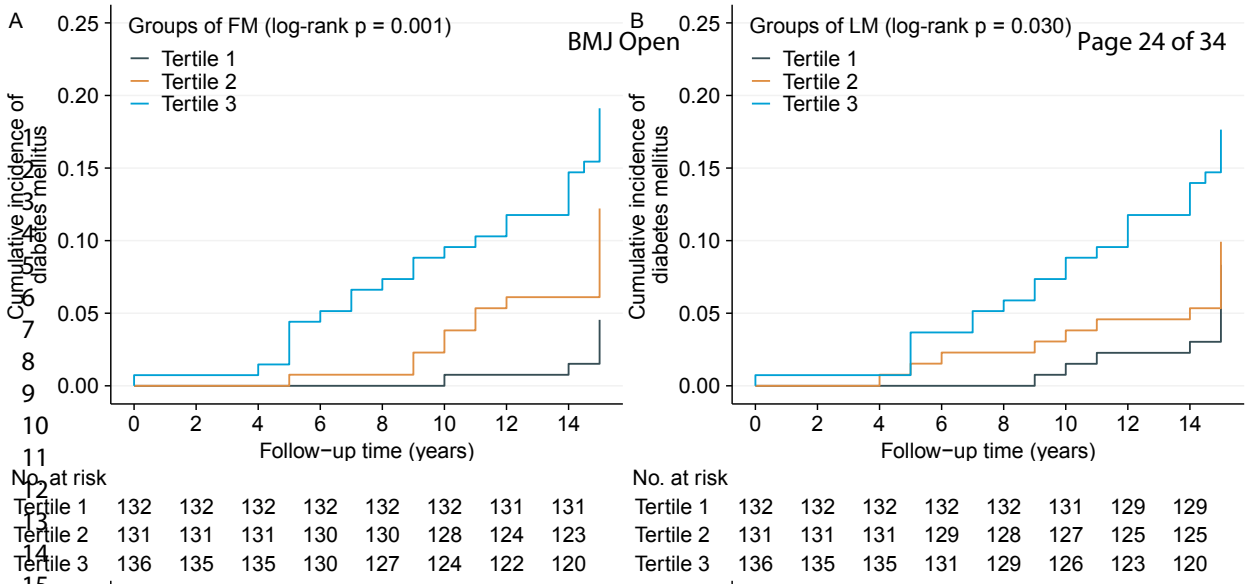
	T2	9 (9.47%)	1.00 (0.38-2.63)	0.625
	T3	12 (12.24%)	1.00 (0.36-2.77)	0.902
	p for trend			0.780
LM				
	per 1-SD increase		1.00 (0.89-1.13)	0.278
	T1 (reference)	6 (6.28%)	1	-
	T2	13 (13.54%)	1.00 (0.37-2.68)	0.126
	T3	7 (7.14%)	1.00 (0.37-2.70)	0.190
	p for trend			0.271
PF				
	per 1-SD increase		1.31 (1.11-1.53)	0.001
	T1 (reference)	3 (3.16%)	1	-
	T2	9 (9.47%)	1.00 (0.37-2.69)	0.763
	T3	14 (14.29%)	1.00 (0.35-2.86)	0.118
	p for trend			0.197

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG;
DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; PF, percent fat; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride

Figure legends

Figure 1 Cumulative incidence of DM across tertiles of three novel predicted body composition during follow-up.

Survival curves were presented as Kaplan-Meier curves, and the log-rank tests were used for comparison among tertiles. For men (n = 399), the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (A, log-rank p = 0.001), predicted LM (B, log-rank p = 0.030), and predicted PF (C, log-rank p < 0.001). For women (n = 288), the cumulative incidence of DM evaluated by Kaplan-Meier analysis was just significantly different across the tertiles of predicted PF (D, log-rank p = 0.028). People in the top tertile had the highest cumulative incidence of DM. DM = diabetes mellitus



Supplemental Digital Content

Figures

S1: Associations of three novel predicted body composition with risk of DM for men

S2: Associations of three novel predicted body composition with risk of DM for women

Tables

S1: Spearman correlations among different predicted body composition

S2: Univariate Cox regression analysis for DM

S3: Multivariate Cox regression analysis of commonly used obesity indicators for DM

Figure S1 Associations of three novel predicted body composition with risk of DM for men

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 13.61 kg), LM (B; 48.27 kg), and PF (C; 22.04%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.

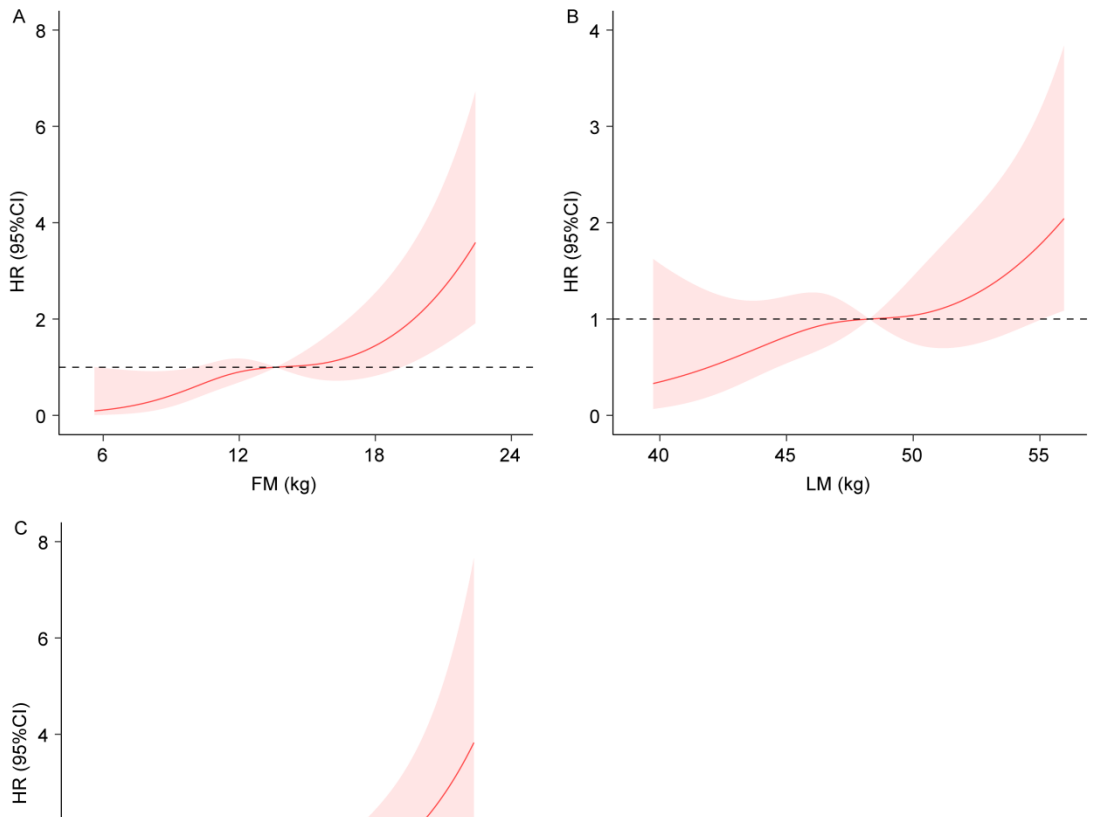


Figure S2 Associations of three novel predicted body composition with risk of DM for women

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 19.45 kg), LM (B; 34.38 kg), and PF (C; 36.39%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.

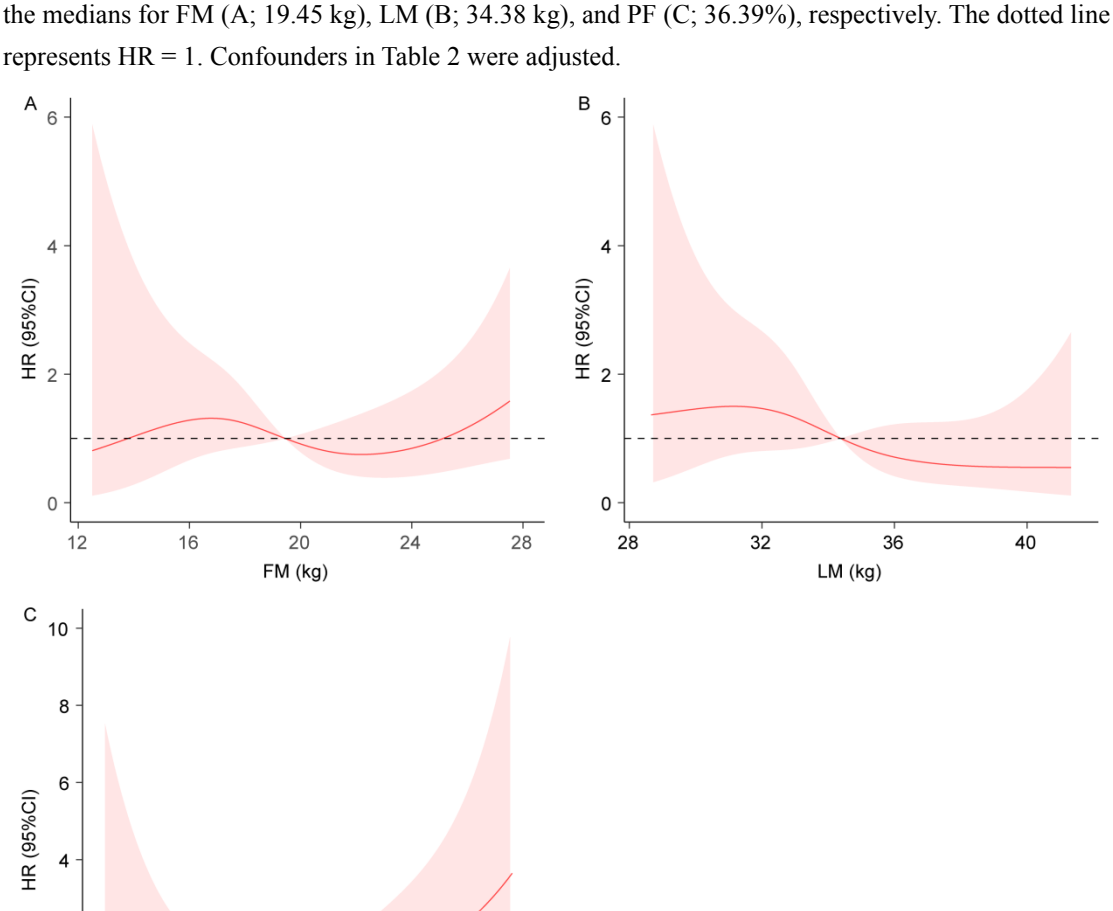


Table S1 Spearman correlations among different predicted body composition

	WC	HC	WHR	BMI	FM	LM	PF
Men							
WC	1.00	0.77	0.80	0.79	0.98	0.52	0.97
HC		1.00	0.28	0.76	0.82	0.71	0.69
WHR			1.00	0.51	0.72	0.15	0.84
BMI				1.00	0.88	0.69	0.75
FM					1.00	0.66	0.92
LM						1.00	0.35
PF							1.00
Women							
WC	1.00	0.83	0.74	0.76	0.83	0.62	0.84
HC		1.00	0.28	0.79	0.87	0.74	0.78
WHR			1.00	0.39	0.42	0.29	0.53
BMI				1.00	0.94	0.63	0.95
FM					1.00	0.83	0.89
LM						1.00	0.51
PF							1.00

BMI, body mass index; FM, fat mass; HC, hip circumference; LM, lean mass; PF: percent fat; WC, waist circumference; WHR, waist-hip ratio

All correlations were significant with $p < 0.05$.

Table S2 Univariate Cox regression analysis for DM

Variable	Change	HR	95% CI	p
Men				
Age (years)	1-SD increment	1.05	0.996-1.10	0.072
Smoking (%)	Yes vs no	0.79	0.44-1.45	0.448
Hypertension (%)	Yes vs no	1.36	0.66-2.81	0.406
DM family history (%)	Yes vs no	0.44	0.14-1.40	0.163
SBP (mm Hg)	1-SD increment	1.02	0.998-1.036	0.076
DBP (mm Hg)	1-SD increment	1.02	0.998-1.052	0.234
FPG (mmol/L)	1-SD increment	1.78	1.26-2.52	0.001
TC (mmol/l)	1-SD increment	1.15	0.79-1.66	0.476
TG (mmol/L)	1-SD increment	1.16	0.91-1.47	0.248
HDL-C (mmol/L)	1-SD increment	0.57	1.16-2.00	0.376
LDL-C (mmol/L)	1-SD increment	1.04	0.73-1.48	0.818
Height (cm)	1-SD increment	1.01	0.96-1.06	0.834
Weight (cm)	1-SD increment	1.07	1.04-1.11	< 0.001
BMI (kg/m^2)	1-SD increment	1.23	1.13-1.33	< 0.001
WC (cm)	1-SD increment	1.09	1.05-1.13	< 0.001
HC (cm)	1-SD increment	1.09	1.05-1.14	< 0.001
WHR	0.01-SD increment	1.09	1.04-1.15	< 0.001
FM (kg)	1-SD increment	1.16	1.09-1.22	< 0.001
LM (kg)	1-SD increment	1.10	1.04-1.17	0.002
PF (%)	1-SD increment	1.23	1.13-1.34	< 0.001
Women				
Age (years)	1-SD increment	1.04	0.98-1.11	0.161
Smoking (%)	Yes vs no	20.306	--	0.771

Hypertension (%)	Yes vs no	2.00	0.84-4.76	0.116
DM family history (%)	Yes vs no	0.57	0.17-1.88	0.353
SBP (mm Hg)	1-SD increment	1.02	0.999-1.04	0.062
DBP (mm Hg)	1-SD increment	1.03	0.99-1.07	0.111
FPG (mmol/L)	1-SD increment	1.86	1.14-3.03	0.013
TC (mmol/l)	1-SD increment	1.67	1.12-2.50	0.012
TG (mmol/L)	1-SD increment	1.46	1.26-1.69	< 0.001
HDL-C (mmol/L)	1-SD increment	0.081	0.01-0.54	0.009
LDL-C (mmol/L)	1-SD increment	1.05	0.67-1.65	0.824
Height (cm)	1-SD increment	0.91	0.84-0.98	0.009
Weight (cm)	1-SD increment	1.04	0.986-1.09	0.156
BMI (kg/m^2)	1-SD increment	1.27	1.10-1.46	0.001
WC (cm)	1-SD increment	1.11	1.06-1.17	< 0.001
HC (cm)	1-SD increment	1.08	1.01-1.16	0.019
WHR	1-SD increment	1.17	1.09-1.25	< 0.001
FM (kg)	1-SD increment	1.11	1.02-1.21	0.013
LM (kg)	1-SD increment	0.99	0.89-1.12	0.912
PF (%)	1-SD increment	1.38	1.19-1.60	< 0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Table S3 Multivariate Cox regression analysis of commonly used obesity indicators for DM

	Case (%)	Multivariate hazards regression *	
		HR (95% CI)	p
For men			
BMI			
per 1-SD increase		1.27 (1.16-1.380	< 0.001
T1 (reference)	9 (6.87%)	1	-
T2	10 (7.75%)	1.09 (0.44-2.69)	0.856
T3	29 (20.86%)	3.90 (1.81-8.37)	< 0.001
p for trend			< 0.001
WC			
per 1-SD increase		1.10 (1.07-1.14)	< 0.001
T1 (reference)	5 (4.03%)	1	-
T2	17 (12.78%)	3.24 (1.19-8.78)	0.021
T3	26 (18.31%)	5.97 (2.27-15.71)	< 0.001
p for trend			< 0.001
HC			
per 1-SD increase		1.11 (1.06-1.16)	< 0.001
T1 (reference)	9 (7.03%)	1	-
T2	11 (9.40%)	1.19 (0.49-2.88)	0.701
T3	28 (18.18%)	2.87 (1.35-6.08)	0.006
p for trend			0.004
WHR			
per 0.01-SD increase		1.09 (1.04-1.15)	< 0.001
T1 (reference)	5 (3.82%)	1	-
T2	18 (13.85%)	3.65 (1.35-9.83)	0.011

T3	25 (18.12%)	5.42 (2.07-14.18)	0.001
p for trend			< 0.001
Women			
BMI			
per 1-SD increase		1.19 (1.03-1.38)	0.016
T1 (reference)	4 (4.40%)	1	-
T2	8 (8.33%)	1.00 (0.38-2.61)	0.838
T3	14 (13.86%)	1.00 (0.38-2.73)	0.414
p for trend			0.512
WC			
per 1-SD increase		1.10 (1.04-1.16)	0.001
T1 (reference)	4 (4.26%)	1	-
T2	4 (4.60%)	0.81 (0.20-3.31)	0.766
T3	18 (16.82%)	2.51 (0.81-7.73)	0.110
p for trend			0.051
HC			
per 1-SD increase		1.00 (0.93-1.07)	0.080
T1 (reference)	4 (5.06%)	1	-
T2	8 (8.33%)	1.00 (0.37-2.73)	0.827
T3	14 (12.39%)	1.00 (0.37-2.71)	0.398
p for trend			0.648
WHR			
per 0.01-SD increase		1.16 (1.07-1.25)	< 0.001
T1 (reference)	1 (1.06%)	1	-
T2	5 (5.21%)	3.95 (0.468-34.15)	0.212
T3	20 (20.41%)	13.48 (1.56-103.38)	0.012

p for trend	< 0.001

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6, 7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6, 7*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, 9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	9, 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058162.R1
Article Type:	Original research
Date Submitted by the Author:	21-Mar-2022
Complete List of Authors:	Liu, Lu; Sichuan University West China Hospital, Department of Cardiology Ban, Chao; Sichuan University West China Hospital, Department of Equipment Jia, Shanshan; Sichuan University West China Hospital, Department of Cardiology Chen, Xiaoping; Sichuan University West China Hospital, Department of Cardiology He, Sen; Sichuan University West China Hospital, Department of Cardiology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Public health
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, INTERNAL MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Lu Liu Ph.D. [a], Chao Ban M.D. [b], Shanshan Jia Ph.D. [a], Xiaoping Chen M.D. [a *], and Sen He M.D., Ph.D. [a *]

(Lu Liu, Chao Ban, and Shanshan Jia equally contribute to the article)

[a] Department of Cardiology, West China Hospital of Sichuan University, Chengdu, China

[b] Department of Equipment, West China Hospital of Sichuan University, Chengdu, China

[*] **Corresponding author:** Xiaoping Chen and Sen He; Department of Cardiology, West China Hospital, Sichuan University No.37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China Tel: +86 028 85422343; Fax: +86 028 85422175; Email address: xiaopingchen0196@163.com (Xiaoping Chen), hesensubmit@163.com (Sen He).

ORCID IDs: 0000-0002-5274-4680 (for Lu Liu), 0000-0003-1824-3943 (for Xiaoping Chen), 0000-0002-9777-2650 (for Sen He)

Word count: 3136

ABSTRACT

Objectives: With body mass index (BMI) failing to distinguish the mass of fat from lean, several novel predicted equations for predicted fat mass (FM), predicted lean mass (LM), and predicted percent fat (PF) were recently developed and validated. Our aim was to explore whether the three novel parameters could better predict diabetes mellitus (DM) than the commonly used obesity indicators, including BMI, waist circumference, hip circumference, and waist-hip ratio.

Design: A 15-year prospective cohort was used.

Setting: It was a prospective cohort, consisting of a general Chinese population from 1992 to 2007.

Participants: This cohort enrolled 711 people. People suffering from DM at baseline (n = 24) were excluded, and 687 non-diabetics with complete data were included to the analysis.

Primary outcome: New-onset DM.

Results: After the follow-up, 74 (48 men and 26 women) incidences of DM were documented. For men, the adjusted hazard ratios (HR) were 1, 5.19 ($p = 0.003$), and 7.67 ($p < 0.001$) across predicted PF tertiles; 1, 2.86 ($p = 0.029$), and 5.60 ($p < 0.001$) across predicted FM tertiles; 1, 1.21 ($p = 0.646$), and 2.27 ($p = 0.025$) across predicted LM tertiles. Predicted FM performed better than other commonly used obesity indicators in discrimination with the highest Harrell's C-statistic among all the body composition parameters. Whereas, for women, none of the three novel parameters was the independent predictor.

Conclusion: Predicted PF, predicted LM, and predicted FM could independently predict the risk of DM for men, with predicted FM performing better in discrimination than other commonly used obesity indicators. For women, larger samples were further needed.

Key words: BMI, diabetes, fat mass, lean mass, obesity, percent fat

Strengths and limitations of this study

1. This study explored whether the three novel body composition parameters, including predicted FM, predicted LM, and predicted PF, could predict DM better than BMI and other commonly used obesity indicators.

2. Cox's regression analysis was used to estimate HRs for DM, and Harrell's C-statistic was used to assess and compare the discriminatory ability of all the parameters in predicting new-onset DM.

3. The relatively small sample size might possibly lead to a statistical power decrease.

INTRODUCTION

Diabetes mellitus (DM) is a collection of chronic metabolic conditions, characterized by elevated blood glucose levels resulting from the body's inability to produce insulin or resistance to insulin action, or both[1]. There are two primary forms of DM, insulin-dependent DM (type 1 diabetes mellitus, T1DM) and non-insulin-dependent DM (type 2 diabetes mellitus, T2DM). T2DM is the most common form, making up 90% - 95% of all diabetic patients[1]. DM and its complications can result in disability and premature death[2], as well as enormous economic and social burdens[3]. There is no cure for DM, thus, prevention is the best intervention.

Among the well-known modifiable risk factors, obesity, defined as an excess accumulation of body fat, is regarded as a major risk factor[4]. Body mass index (BMI) has been mostly used as a simple and reasonable measure of general adiposity in clinical and public health settings. However, since it is defined as the result of weight in kilogram divided by height in meter squared, BMI is in poor discrimination of metabolically distinct components such as fat mass (FM) and lean mass (LM)[5]. Direct measurement of FM and LM is impractical in large epidemiological studies for sophisticated and expensive technologies such as dual-energy X-ray absorptiometry (DXA) or imaging techniques (i.e. MRI and computerized tomography).

Recently, Lee et al developed anthropometric prediction equations for FM, LM, and percent fat (PF) from the large population samples of the noninstitutionalized civilians in the USA from National Health and Nutrition Examination Survey[6]. In the original study, the validation tests showed robust and consistent results without evident substantial bias, and comparable abilities to predict obesity-related biomarkers with direct DXA measurements. Later, based on two large US prospective cohorts, predicted FM and predicted PF were both estimated to have a stronger association than BMI with

T2DM[7]. However, body compositions differ across ethnic groups[8, 9]. Healthy Chinese and South Asian individuals were measured to have a greater amount of visceral adipose tissue than Europeans with the same BMI or waist circumference[10]. Therefore, we aimed to evaluate if these equations could better predict the risk of DM in comparison with BMI and other obesity indicators, including waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR), in a 15-year prospective cohort consisting of Chinese people.

MATERIALS AND METHODS

Study population

In 2007, supported by the Mega-projects of Science Research for China's 11th five-year plan (Trends in the incidence of metabolic syndrome and integrated control in China), a group of 711 people, from an urban community situated in Chengdu, China, underwent a health examination. They also had a health examination in 1992 as part of the Chinese Multi-provincial Cohort Study approved by Beijing Institute of Heart, Lung, and Blood Vessel Disease that investigated cardiovascular risk factors across the country. Therefore, we picked up the data, and more details have been described elsewhere[11, 12]. People suffering from DM at baseline (n = 24) were excluded. No one had missing data. Finally, the remaining 687 people with complete data were included in the analysis. All of them provided written informed consent. The study was approved by the Ministry of Health of China, as well as the Ethics Committee of West China Hospital of Sichuan University.

Evaluation

Definition

DM was defined by self-reported history or fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L[13].

Hypertension was a conventional blood pressure of ≥ 140mm Hg systolic, ≥ 90mm Hg diastolic, or the use of antihypertensive drugs. DM family history was determined with a diagnosis of DM in the first-grade relatives. Smoking was defined as an average cigarette consumption of at least one per day. Frequent previous alcohol intake and present alcohol intake were both defined as alcohol consumption. Activity was defined as at least twice 20-minute moderately intensive physical activity per week.

Data collection

Baseline data in 1992 included medical history, physical examination, and biochemical tests. Questionnaires containing demographic information and cardiovascular disease risk factors were collected by well-trained investigators. WC was measured at the midpoint between the lower border of the rib cage and the iliac crest at the end of a normal exhalation. HC was measured at the maximum protrusion of the gluteal region. WHR was calculated by WC in cm divided by HC in cm. Height was measured without shoes. Weight was measured in light clothing. Blood pressure was measured in a sitting position after at least 15 min of rest, and the mean blood pressure of three measurements taken by a standardized mercury sphygmomanometer was used as a participant's blood pressure. Blood samples were drawn from participants in the morning after 12-h overnight fasting. FPG, total cholesterol (TC), and triglyceride (TG) levels were determined in an enzymatic method, and high-density lipoprotein cholesterol (HDL-C) was measured by the phosphotungstic acid/$MgCl_2$ precipitation method. Low-density lipoprotein cholesterol (LDL-C) was measured using a standard kit.

Equation profiles

Equations for predicted FM (kg)[6]

For men $= -18.592 - 0.009 \times \text{age (year)} - 0.080 \times \text{height (cm)} + 0.226 \times \text{weight (kg)}$

$+ 0.387 \times \text{WC (cm)} + 0.080 \times \text{Mexican} - 0.188 \times \text{Hispanic} - 0.483 \times \text{Black} + 1.050 \times$

other ethnicity

For women $= 11.817 + 0.041 \times$ age (year) $-0.199 \times$ height (cm) $+0.610 \times$ weight (kg) $+0.044 \times$ WC (cm) $+0.388 \times$ Mexican $+ 0.073 \times$ Hispanic $- 1.187 \times$ Black $+ 0.325 \times$ other ethnicity

Equations for predicted LM (kg)[6]

For men $= 19.363 + 0.001 \times$ age (year) $+0.064 \times$ height (cm) $+0.756 \times$ weight (kg) $-0.366 \times$ WC (cm) $-0.066 \times$ Mexican $+ 0.231 \times$ Hispanic $+ 0.432 \times$ Black $- 1.007 \times$ other ethnicity

For women $= -10.683 - 0.039 \times$ age (years) $+0.186 \times$ height (cm) $+0.383 \times$ weight (kg) $-0.043 \times$ WC (cm) $-0.359 \times$ Mexican $- 0.059 \times$ Hispanic $+ 1.085 \times$ Black $- 0.34 \times$ other ethnicity

Equations for predicted PF (%)[6]

For men $= 0.02 + 0.00 \times$ age (year) $-0.07 \times$ height (cm) $-0.08 \times$ weight (kg) $+0.48 \times$ WC (cm) $+0.32 \times$ Mexican $+ 0.02 \times$ Hispanic $- 0.65 \times$ Black $+ 1.12 \times$ other ethnicity

For women $= 50.46 + 0.07 \times$ age (year) $-0.26 \times$ height (cm) $+0.27 \times$ weight (kg) $+0.10 \times$ WC (cm) $+0.89 \times$ Mexican $+ 0.49 \times$ Hispanic $- 1.57 \times$ Black $+ 0.43 \times$ other ethnicity

Statistical analyses

For descriptive results, variables were expressed as the mean ± standard deviation (SD), median and interquartile range, or counts and percentages as appropriate. Smoking, alcohol intake, activity, hypertension, and family history of DM were expressed as dummy variables (presence= 1, absence= 0). Differences in baseline characteristics between participants with and without new-onset DM were tested by independent t-test for normally distributed variables and by the non-parametric Mann-

Whitney U-test for skewed variables. Interactions between categorical variables were evaluated with the Pearson χ^2 test, Fisher's exact probabilities were used if necessary. Correlations between different variables were determined using Pearson's or Spearman's analysis.

We treated all the parameters as sex-specific tertiles. The cumulative incidences of DM across tertiles were graphically displayed according to the method of Kaplan-Meier, with comparisons among groups by the log-rank test. Cox proportional hazards regression models were used to assess the impact of the variables on the incidence rate of DM. Furthermore, restricted cubic spline analysis was used to visualize the relations between variables and incident DM. To quantify and compare the discriminative ability of different parameters, Harrell's c-index was calculated. A generally accepted approach suggests that the C-index of less than 0.60 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75, clearly useful discrimination[14].

All statistical tests were 2-sided, and p value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 3.6.3.

RESULTS

Baseline characteristics

After excluding people suffering from DM at baseline (n = 24), the remaining 687 (399 men and 288 women) people free of DM at baseline with complete data were included in the analysis.

Those who had subsequent DM were associated with higher baseline levels of FPG, weight, BMI, WC, HC, predicted FM, predicted LM, and predicted PF for the males; associated with higher baseline levels of TC, TG, height, BMI, WC, HC, predicted FM, and predicted PF, and lower baseline level of HDL-C for the females. At baseline, age was not of significance between the two groups both in men

and women, but there was still a trend that people suffering incident DM were older. Other details of baseline information are shown in Table 1.

As Online Supplemental Table S1 shows, predicted FM was strongly correlated with WC (r_s = 0.98), followed by BMI (r_s = 0.88) and HC (r_s = 0.82) in men; strongly correlated with BMI (r_s = 0.94), followed by HC (r_s = 0.87) and WC (r_s = 0.83) in women. Predicted LM had a strong correlation with predicted FM (r_s = 0.83) in women and a relatively strong correlation with HC (r_s = 0.71) in men, but relatively weakly with WHR both in men (r_s = 0.15) and women (r_s = 0.29). Predicted PF was strongly correlated with WC (r_s = 0.97) in men and BMI (r_s = 0.95) in women, but relatively weakly with predicted LM both in men (r_s = 0.35) and women (r_s = 0.51).

Survival analysis

All the body composition parameters were divided into tertiles. Tertile 1 had the lowest estimated values while Tertile 3 had the highest. After the follow-up, 74 (48 men and 26 women) incidences of DM were documented (incidence rate: 0.74 per 100 person-years; 95% CI: 0.57-0.91). As Figure 1A-C present, for men, the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (log-rank p = 0.001), predicted LM (log-rank p = 0.030), and predicted PF (log-rank p < 0.001), and people in Tertile 3 had the highest cumulative incidence of DM. For women, however, only predicted PF (log-rank p = 0.028) could help to distinguish the cumulative incidence across the tertiles (Figure 1D).

For other obesity indicators, the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of BMI (log-rank p < 0.001), WC (log-rank p = 0.001), HC (log-rank p = 0.006), and WHR (log-rank p = 0.001) in men; WC (log-rank p = 0.002) and WHR (log-rank p < 0.001) in women.

Relation to risk of DM

Univariate cox regression analysis is shown in Online Supplemental Table S2. Predicted FM, predicted PF, BMI, WC, HC, and WHR were risk factors of DM both for men and women, and predicted LM was a risk factor for men only. Variables showing statistical significance in univariate analysis or clinical relevance ($p < 0.1$) were entered into multivariate analysis.

In multivariate analysis, we adjusted potential confounders including hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women.

As Table 2 shows, in men, predicted FM ($p < 0.001$), predicted LM ($p = 0.043$), and predicted PF ($p < 0.001$) were all the significantly independent predictors with the top tertiles associated with the highest risk of DM. Compared with the other parameters we studied, predicted PF in higher level was more strongly associated with increased risk of DM, since it showed a positive association with the risk of DM with the adjusted hazard ratio (HR) for Tertile 2 and Tertile 3 estimated as 5.19 [95% confidence interval (CI): 1.77-15.20, $p = 0.003$] and 7.67 (95% CI: 2.64-22.35, $p < 0.001$), respectively. There was a positive association between predicted FM and the risk of DM (HR: 2.86, 95% CI: 1.12-7.33, $p = 0.029$ for Tertile 2; HR: 5.60, 95% CI: 2.27-13.80, $p < 0.001$ for Tertile 3, respectively) as well. Other commonly used parameters such as BMI ($p < 0.001$), WC ($p < 0.001$), HC ($p = 0.004$) and WHR ($p < 0.001$) were also significant predictors (Online Supplemental Table S3), and WC and WHR showed a positive association across tertiles.

As for the women, however, none of the three novel parameters was significantly independent after adjustment (Table 2), as well as other commonly used obesity indicators but WHR, which ($p <$

0.001) remained stable and significant (Online Supplemental Table S3).

Furthermore, as Table 2 shows, we treated the predicted FM, predicted LM, and predicted PF as continuous variables. In men, all of them were independent risk factors and it is true of the restricted cubic splines used to flexibly models and visualize the relations with risk of DM (Online Supplemental Figure S1). With the medians as reference points, all the three novel parameters showed an overall positive association with DM in men (Online Supplemental Figure S1); while in women, only predicted PF was independently associated with DM (Table 2, HR: 1.34 per 1-SD increase, 95% CI: 1.15-1.57, $p < 0.001$), and the restricted cubic spline shows the similar relationship, especially after the median (Online Supplemental Figure S2)

Discrimination

Table 3 shows discriminative abilities evaluated by Harrell's c-index of different body composition parameters. In the male group, predicted FM had the highest Harrell's c-index of 0.679 (95% CI: 0.606-0.752), and predicted LM had the lowest Harrell's c-index of 0.619 (95% CI: 0.537-0.701). All of the parameters we studied could provide possibly helpful discriminative information in the prediction of DM[14].

In the female group, since WHR was the only significantly independent risk factor of DM both as continuous variable and categorical variable, we just estimated Harrell's c-index of WHR (0.768, 95% CI: 0.697-0.839), and it showed a clearly useful discriminative ability in predicting DM[14].

DISCUSSION

In this study, we investigated the predictive abilities for the risk of DM of three novel body composition parameters including predicted FM, predicted LM, and predicted PF, and compared them

with other obesity indicators, in a Chinese prospective population during 15 years of follow-up. For men, our results showed predicted FM, predicted LM, and predicted PF could independently predict the new onset of DM; in all the parameters we studied, predicted FM had the best discriminative ability, providing possibly helpful information in the prediction of DM. For women, none of the three novel parameters could be significantly independent in multivariate analysis; of all the parameters we estimated, WHR was the only independent predictor, with Harrell's c-index of 0.768, which suggested a clearly useful discrimination.

To our knowledge, this was the first study in a Chinese prospective cohort to evaluate the associations of three novel body composition parameters with the incidence of DM. BMI has been preferred as a measure indicating overall obesity for a long time to identify people at increased risk of DM[15]. However, BMI was not thought as a good indicator of obesity recently.[5, 16]. It fails to distinguish the mass of fat from lean, and had no gender distinction as well. For example, in common sense, athletes or someone liking exercise always had heavier weight for the mass of lean, they have greater BMI but they are not obese. Besides, aging is associated with an accumulation of visceral fat and a progressive loss of muscle mass[16]. With the same BMI, an old man has more mass of fat with less mass of muscle than a younger man.

Recently, Lee et al. [6] developed equations predicting FM, LM, and PF in order to better reflect body composition. The predicted equations had a simple calculation and just require the information of gender, age, height, weight, WC, and ethnicity, which are easily measurable and accessible in clinical settings or even at home. Lee et al. later investigated the association between predicted FM and risk of DM in two large prospective cohorts of US men and women[7]. They found predicted FM, as well as predicted PF, had a stronger association with DM than BMI both in men and women. Similarly, in our

study consisting of Chinese population, in the male group, both predicted FM and predicted PF could independently predict incident DM and predicted FM had the highest Harrell's value. Higher predicted PF was more strongly associated with increased risk of DM than other parameters.

Besides in prediction of DM, predicted FM and predicted PF were also explored in the association with risk of heart failure and myocardial infarction in adults with T2DM[17]. The results showed a decline in predicted FM but not predicted LM, over 1 year was significantly associated with lower risk of overall heart failure (adjusted HR per 10% decrease in predicted FM: 0.80; 95% CI: 0.68-0.95); decline in predicted FM was significantly associated with lower risk of both heart failure subtypes (with preserved or reduced ejection fraction).

In a post hoc analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[18], researchers modified the two parameters, fat mass index and lean BMI, calculated by predicted FM and predicted LM, respectively, in kilograms divided by the square of height in meters. They found that in patients with T2DM, fat mass index had a strong positive association with a higher risk of a major adverse cardiovascular event, while predicted lean BMI was not associated with major cardiovascular events ($p = 0.34$).

In a large prospective US cohort study of men[19], there was a strong positive association between predicted FM and mortality from all causes, cardiovascular disease, and cancer. Compared with those in the lowest fifth of predicted FM, men in the highest fifth had an HR of 1.35 (95% CI: 1.26-1.46) for all-cause mortality. In contrast, predicted LM showed a U-shaped association with all-cause mortality that men in the second to fourth fifths had 8-10% lower risk. The U-shaped associations were also found with deaths from cardiovascular disease and cancer. However, there was a strong inverse association between predicted LM and mortality from respiratory disease.

Lean body mass accounts for most of the human body mass, and it is essential not only in the stress response but also in metabolism[20]. Muscle loss may have negative effects[20-22]. Son et al. previously conducted a 2-yearly prospective assessment in middle-aged and older Korean adults, and reported that low muscle mass was associated with an increased risk of T2DM, independent of general obesity[23]. In contrast, in our research, for the development of DM, the protective role of predicted LM could not be concluded. Instead, the top tertile of predicted LM had an increased risk in the male group. Since there is a lack of randomized clinical trial studies that directly assess the role of increased muscle mass in the prevention of new on-set DM[24], the association between predicted LM and risk of DM needs further explorations. After all, increased LM was not always simply reported as the protective factor of diseases or mortality[17-19].

There are certainly some limitations in our study. Firstly, 687 was a relatively small sample size, possibly leading to a statistical power decrease, for example, the results in women. Nevertheless, we still observed that as a continuous variable, predicted PF could independently predict the risk of incident DM in women. Maybe in a larger population, the relationships and comparisons would be more accurate. Secondly, due to the absence of oral glucose tolerance tests (OGTT) and hemoglobin A1c (HbA1c) data in our study, some people might not be adequately diagnosed. Thirdly, only one follow-up examination was carried out, so that there was no guarantee whether some "interval censoring" might have occurred.

In conclusion, in the general Chinese population, predicted FM, predicted LM, and predicted PF could independently predict the risk of DM in men, and predicted FM performed better in discrimination than other commonly used obesity indicators including BMI, WC, HC, and WHR. For women, however, predicted FM, predicted LM, predicted PF, as well as other obesity indicators, but

WHR, could not remain stable and independent in multivariate analysis, which might be attributed to the relatively small sample size with the corresponding few endpoints. Therefore, larger samples from different races are needed to explore the predictive abilities of the three novel equations reflecting body composition on incident DM and other diseases.

Acknowledgment

We thank all staff members for data collection, data entry and monitoring as part of this study.

Funding

This work was supported by the Key R&D Projects of Science and Technology Department of Sichuan Province, China (grant Number: 22ZDYF1527); the National Natural Science Foundation of China (Grant number: 81600299); a project from China's eighth national 5-year research plan (Grant no: 85-915-01-02); and the megaprojects of science research for China's 11th 5-year plan (Grant no: 2006BAI01A01).

Competing interests

None declared.

Contributors

LL and SSJ: Participated in the conception and design of the study, performed the data collection and the statistical analysis, and wrote the draft of the manuscript. BC: Participated in the conception and design of the study, performed the statistical analysis, and wrote the major revision. SH and XPC: The corresponding authors, participated in the design of the study, performed the statistical analysis, and revised subsequent drafts. All authors read and approved the final manuscript.

Data availability statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval statement

This study involved human patients and was approved by Ministry of Health of China and Ethics Committee of West China Hospital of Sichuan University.

REFERENCES

1. Wu Y, Ding Y, Tanaka Y. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci* 2014;11:1185-200.

2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018;14:88-98.

3. Zhao Y, Jiang Z, Guo C. New hope for type 2 diabetics: targeting insulin resistance through the immune modulation of stem cells. *Autoimmun Rev* 2011;11:137-42.

4. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr* 2004;80:257-63.

5. Prentice AM, Jebb SA. Beyond body mass index. *Obes Rev* 2001;2:141-7.

6. Lee DH, Keum N, Hu FB, et al. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999-2006. *Br J Nutr* 2017;118:858-66.

7. Lee DH, Keum N, Hu FB, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. *Eur J Epidemiol* 2018;33:1113-23.

8. Lear SA, Humphries KH, Kohli S, et al. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007;86:353-9.

9. Lear SA, Humphries KH, Kohli S, et al. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)* 2007;15:2817-24.

10. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *Jama* 2009;301:2129-40.

11. Ren J, Grundy SM, Liu J, et al. Long-term coronary heart disease risk associated with very-low-density lipoprotein cholesterol in Chinese: the results of a 15-Year Chinese Multi-Provincial Cohort Study (CMCS). *Atherosclerosis* 2010;211:327-32.

12. Liu J, Hong Y, D'Agostino RB, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *Jama* 2004;291:2591-9.

13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53.

14. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *Jama* 2017;318:1377-84.

15. Vazquez G, Duval S, Jacobs DR, Jr., et al. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007;29:115-28.

16. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proc Nutr Soc* 2015;74:405-12.

17. Patel KV, Bahnson JL, Gaussoin SA, et al. Association of Baseline and Longitudinal Changes in Body Composition Measures With Risk of Heart Failure and Myocardial Infarction in Type 2 Diabetes: Findings From the Look AHEAD Trial. *Circulation* 2020;142:2420-30.

18. Xing Z, Tang L, Chen J, et al. Association of predicted lean body mass and fat mass with cardiovascular events in patients with type 2 diabetes mellitus. *Cmaj* 2019;191:E1042-e8.

19. Lee DH, Keum N, Hu FB, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *Bmj* 2018;362:k2575.

20. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;84:475-82.

21. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *Bmj* 2008;337:a439.

22. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;50:889-96.

23. Son JW, Lee SS, Kim SR, et al. Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. *Diabetologia* 2017;60:865-72.

24. de Sousa MV, da Silva Soares DB, Caraça ER, et al. Dietary protein and exercise for preservation of lean mass and perspectives on type 2 diabetes prevention. *Exp Biol Med (Maywood)* 2019;244:992-1004.

Table 1 Basic characteristics of people with or without subsequent DM.

Variables	Men (n=399)			Women (n=288)		
	Subsequent DM (n=48)	Subsequent non-DM (n=351)	p-value	Subsequent DM (n=26)	Subsequent non-DM (n=262)	p-value
Age (years)	50.6 ± 5.0	49.0 (45.0-53.0)	0.079	48.4 ± 6.8	46.0 (42.0-52.0)	0.127
Smoking (%)	32 (66.7%)	213 (60.7%)	0.425	0	2 (0.8%)	1.000
Hypertension (%)	9 (18.8%)	50 (14.2%)	0.410	7 (26.9%)	38 (14.5%)	0.150
DM family history (%)	3 (6.3%)	9 (2.6%)	0.165	3 (11.5%)	18 (6.9%)	0.418
SBP (mm Hg)	118.1 ± 14.5	110.0 (105.0-120.0)	0.061	119.0 (103.0-132.5)	110.0 (102.0-120.0)	0.240
DBP (mm Hg)	74.0 (70.0-80.0)	72.0 (70.0-80.0)	0.292	76.4 ± 12.1	70.0 (71.0-80.0)	0.226
FPG (mmol/L)	4.6 ± 0.8	4.0 (3.8-4.7)	<0.001	4.6 ± 0.9	3.8 (4.0-4.7)	0.052
TC (mmol/l)	4.4 (4.1-4.8)	4.3 (3.9-4.8)	0.419	5.0 ± 0.7	4.4 (3.9-5.0)	0.006
TG (mmol/L)	1.9 (1.7-3.0)	1.9 (1.5-2.4)	0.104	1.9 (1.5-2.3)	1.8 (1.4-2.2)	<0.001
HDL-C (mmol/L)	1.2 (1.0-1.4)	1.2 (1.1-1.4)	0.193	1.2 ± 0.2	1.3 (1.1-1.5)	0.009
LDL-C (mmol/L)	2.2 ± 0.8	2.1 (1.7-2.7)	0.556	2.4 ± 1.0	2.3 (1.8-2.8)	0.460
Height (cm)	165.4 ± 5.9	165.3 ± 5.6	0.898	151.9 ± 4.4	151.0 (155.0-159.0)	0.006
Weight (cm)	68.5 (61.3-74.8)	62.9 ± 8.2	<0.001	58.6 ± 9.0	56.4 ± 7.5	0.168
BMI (kg/m^2)	24.8 (23.0-26.6)	23.0 (20.9-24.8)	<0.001	25.3 ± 3.3	23.4 ± 2.6	0.001
WC (cm)	83.6 ± 8.2	78.0 (72.0-83.0)	<0.001	79.9 ± 7.6	73.5 ± 7.1	<0.001
HC (cm)	95.0 (90.0-97.0)	91.0 (87.0-95.0)	<0.001	95.4 ± 7.4	92.6 ± 5.8	0.021
WHR	0.89 ± 0.05	0.85 ± 0.06	0.001	0.84 ± 0.04	0.79 ± 0.05	<0.001
FM (kg)	16.4 ± 5.2	13.3 (9.6-16.2)	<0.001	21.8 ± 5.4	19.6 ± 4.3	0.014
LM (kg)	50.2 ± 5.0	48.1 ± 4.5	0.004	34.3 ± 3.5	34.4 ± 3.4	0.894
PF (%)	24.0 ± 3.4	21.8 ± 3.1	<0.001	38.6 ± 2.9	36.4 ± 2.4	<0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Table 2 Multivariate Cox regression models for DM

	Case (%)	Multivariate hazards regression *	
		HR (95% CI)	p
For men			
FM			
per 1-SD increase		1.18 (1.11-1.25)	< 0.001
T1 (reference)	6 (4.54%)	1	-
T2	16 (12.21%)	2.86 (1.12-7.33)	0.029
T3	26 (19.12%)	5.60 (2.27-13.80)	< 0.001
p for trend			< 0.001
LM			
per 1-SD increase		1.10 (1.03-1.17)	0.003
T1 (reference)	11 (8.33%)	1	-
T2	13 (9.92%)	1.21 (0.54-2.70)	0.646
T3	24 (17.65%)	2.27 (1.11-4.63)	0.025
p for trend			0.043
PF			
per 1-SD increase		1.25 (1.14-1.36)	< 0.001
T1 (reference)	4 (3.03%)	1	-
T2	20 (15.27%)	5.19 (1.77-15.20)	0.003
T3	24 (17.65%)	7.67 (2.64-22.35)	< 0.001
p for trend			< 0.001
Women			
FM			
per 1-SD increase		1.04 (0.95-1.15)	0.375
T1 (reference)	5 (5.26%)	1	-
T2	9 (9.47%)	1.38 (0.45-4.23)	0.571
T3	12 (12.24%)	1.08 (0.35-3.37)	0.900

p for trend			0.811
LM			
per 1-SD increase		0.92 (0.81-1.05)	0.205
T1 (reference)	6 (6.28%)	1	-
T2	13 (13.54%)	1.33 (0.49-3.61)	0.576
T3	7 (7.14%)	0.62 (0.19-2. 05)	0.432
p for trend			0.332
PF			
per 1-SD increase		1.34 (1.15-1.57)	< 0.001
T1 (reference)	3 (3.16%)	1	-
T2	9 (9.47%)	1.95 (0.49-7.66)	0.341
T3	14 (14.29%)	2.39 (0.63-9.10)	0.202
p for trend			0.442

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women.

CI: Confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; PF, percent fat; SBP, systolic blood pressure; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride

Table 3 Discriminative abilities evaluated by Harrell's c-index of different body composition parameters

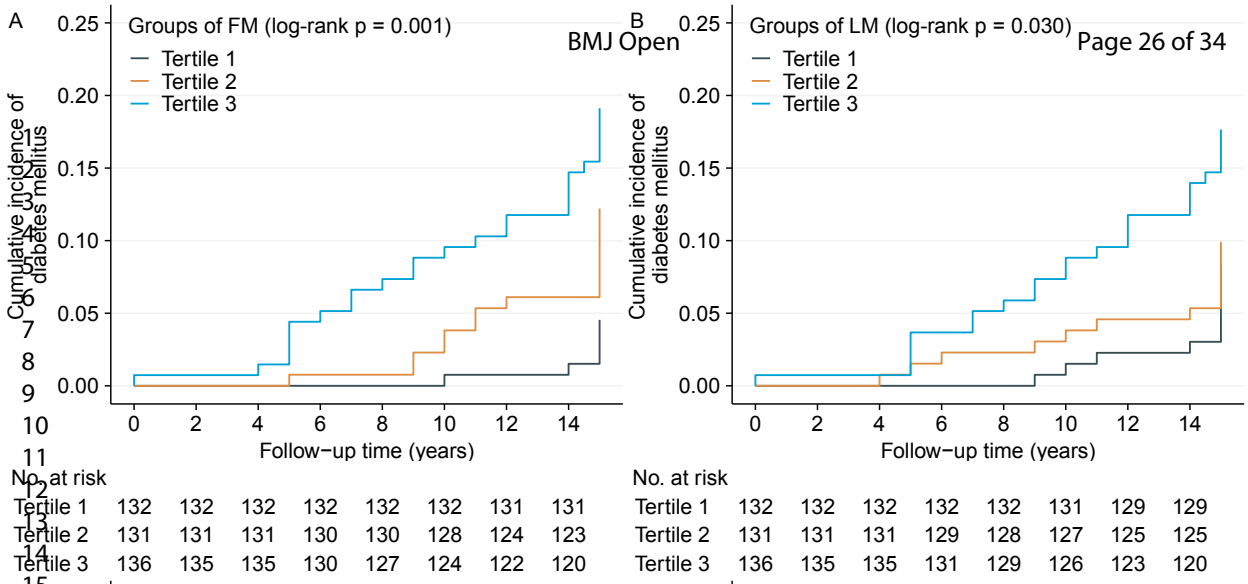
Variables	Men		Women	
	Harrell's c-index	95% CI	Harrell's c-index	95% CI
FM	0.679	0.606-0.752	-	-
LM	0.619	0.537-0.701	-	-
PF	0.670	0.598-0.742	-	-
BMI	0.675	0.599-0.751	-	-
WC	0.673	0.600-0.746	-	-
WHR	0.652	0.578-0.726	0.768	0.697-0.839
HC	0.636	0.560-0.712	-	-

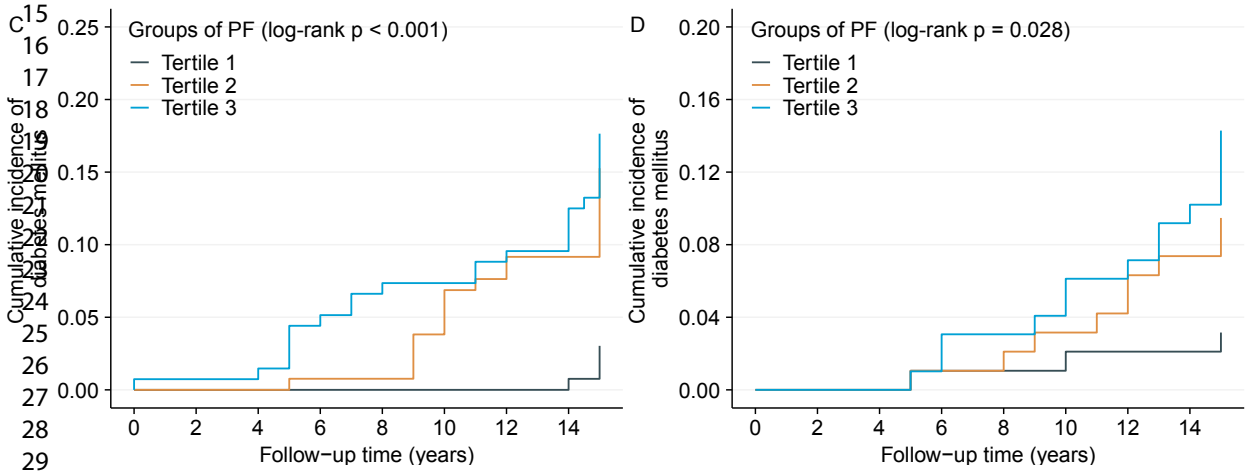
CI: Confidence interval; FM, fat mass; LM, lean mass; PF, percent fat; BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-hip ratio

Figure legends

Figure 1 Cumulative incidence of DM across tertiles of three novel predicted body composition during follow-up.

Survival curves were presented as Kaplan-Meier curves, and the log-rank tests were used for comparison among tertiles. For men (n = 399), the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (A, log-rank p = 0.001), predicted LM (B, log-rank p = 0.030), and predicted PF (C, log-rank p < 0.001). For women (n = 288), the cumulative incidence of DM evaluated by Kaplan-Meier analysis was just significantly different across the tertiles of predicted PF (D, log-rank p = 0.028). People in the top tertile had the highest cumulative incidence of DM. DM = diabetes mellitus





Supplemental Materials

Table S1: Spearman correlations among different predicted body composition

Table S2: Univariate Cox regression analysis for DM

Figure S1: Associations of three novel predicted body composition with risk of DM for men

Figure S2: Associations of three novel predicted body composition with risk of DM for women

Table S3: Multivariate Cox regression analysis of commonly used obesity indicators for DM

Table S1 Spearman correlations among different predicted body composition

	WC	HC	WHR	BMI	FM	LM	PF
Men							
WC	1.00	0.77	0.80	0.79	0.98	0.52	0.97
HC		1.00	0.28	0.76	0.82	0.71	0.69
WHR			1.00	0.51	0.72	0.15	0.84
BMI				1.00	0.88	0.69	0.75
FM					1.00	0.66	0.92
LM						1.00	0.35
PF							1.00
Women							
WC	1.00	0.83	0.74	0.76	0.83	0.62	0.84
HC		1.00	0.28	0.79	0.87	0.74	0.78
WHR			1.00	0.39	0.42	0.29	0.53
BMI				1.00	0.94	0.63	0.95
FM					1.00	0.83	0.89
LM						1.00	0.51
PF							1.00

BMI, body mass index; FM, fat mass; HC, hip circumference; LM, lean mass; PF: percent fat; WC, waist circumference; WHR, waist-hip ratio

All correlations were significant with $p < 0.05$.

Table S2 Univariate Cox regression analysis for DM

Variable	Change	HR	95% CI	p
Men				
Age (years)	1-SD increment	1.05	0.996-1.10	0.072
Smoking (%)	Yes vs no	0.79	0.44-1.45	0.448
Hypertension (%)	Yes vs no	1.36	0.66-2.81	0.406
DM family history (%)	Yes vs no	0.44	0.14-1.40	0.163
SBP (mm Hg)	1-SD increment	1.02	0.998-1.036	0.076
DBP (mm Hg)	1-SD increment	1.02	0.998-1.052	0.234
FPG (mmol/L)	1-SD increment	1.78	1.26-2.52	0.001
TC (mmol/l)	1-SD increment	1.15	0.79-1.66	0.476
TG (mmol/L)	1-SD increment	1.16	0.91-1.47	0.248
HDL-C (mmol/L)	1-SD increment	0.57	1.16-2.00	0.376
LDL-C (mmol/L)	1-SD increment	1.04	0.73-1.48	0.818
Height (cm)	1-SD increment	1.01	0.96-1.06	0.834
Weight (cm)	1-SD increment	1.07	1.04-1.11	< 0.001
BMI (kg/m^2)	1-SD increment	1.23	1.13-1.33	< 0.001
WC (cm)	1-SD increment	1.09	1.05-1.13	< 0.001
HC (cm)	1-SD increment	1.09	1.05-1.14	< 0.001
WHR	0.01-SD increment	1.09	1.04-1.15	< 0.001
FM (kg)	1-SD increment	1.16	1.09-1.22	< 0.001
LM (kg)	1-SD increment	1.10	1.04-1.17	0.002
PF (%)	1-SD increment	1.23	1.13-1.34	< 0.001
Women				
Age (years)	1-SD increment	1.04	0.98-1.11	0.161
Smoking (%)	Yes vs no	20.306	--	0.771

Hypertension (%)	Yes vs no	2.00	0.84-4.76	0.116
DM family history (%)	Yes vs no	0.57	0.17-1.88	0.353
SBP (mm Hg)	1-SD increment	1.02	0.999-1.04	0.062
DBP (mm Hg)	1-SD increment	1.03	0.99-1.07	0.111
FPG (mmol/L)	1-SD increment	1.86	1.14-3.03	0.013
TC (mmol/l)	1-SD increment	1.67	1.12-2.50	0.012
TG (mmol/L)	1-SD increment	1.46	1.26-1.69	< 0.001
HDL-C (mmol/L)	1-SD increment	0.081	0.01-0.54	0.009
LDL-C (mmol/L)	1-SD increment	1.05	0.67-1.65	0.824
Height (cm)	1-SD increment	0.91	0.84-0.98	0.009
Weight (cm)	1-SD increment	1.04	0.986-1.09	0.156
BMI (kg/m^2)	1-SD increment	1.27	1.10-1.46	0.001
WC (cm)	1-SD increment	1.11	1.06-1.17	< 0.001
HC (cm)	1-SD increment	1.08	1.01-1.16	0.019
WHR	0.01-SD increment	1.17	1.09-1.25	< 0.001
FM (kg)	1-SD increment	1.11	1.02-1.21	0.013
LM (kg)	1-SD increment	0.99	0.89-1.12	0.912
PF (%)	1-SD increment	1.38	1.19-1.60	< 0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Figure S1 Associations of three novel predicted body composition with risk of DM for men

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 13.61 kg), LM (B; 48.27 kg), and PF (C; 22.04%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.

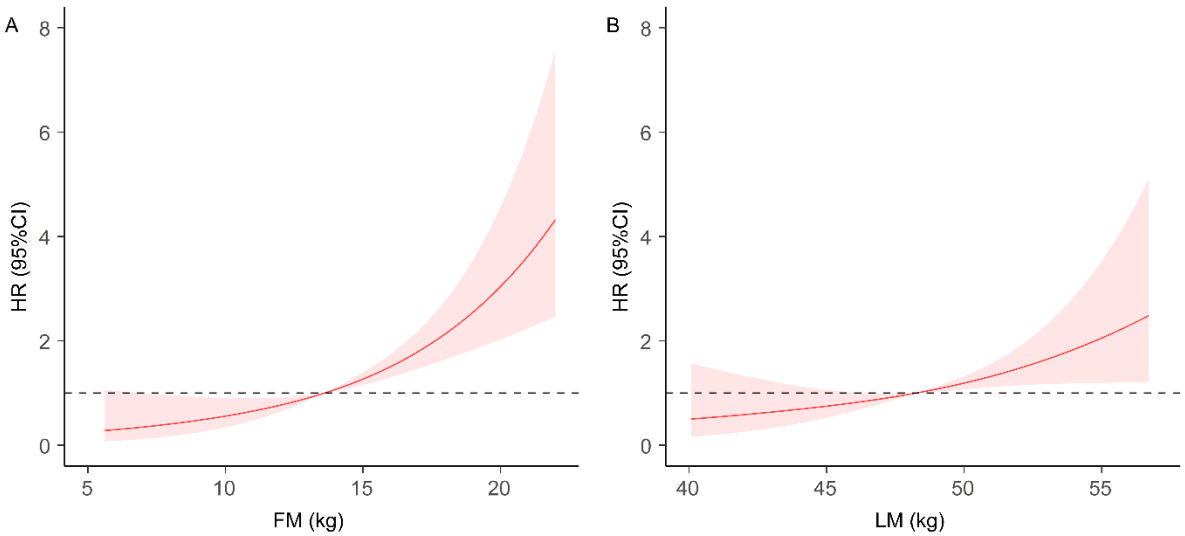


Figure S2 Associations of three novel predicted body composition with risk of DM for women

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 19.45 kg), LM (B; 34.38 kg), and PF (C; 36.39%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.

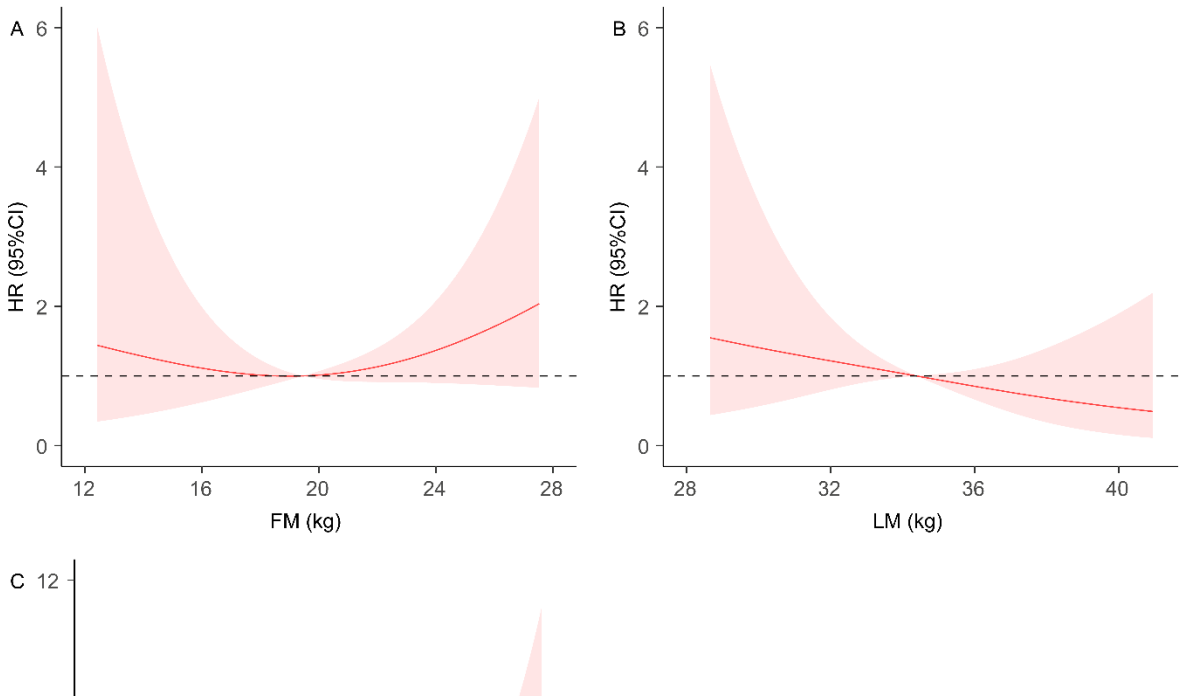


Table S3 Multivariate Cox regression models of commonly used obesity indicators for DM

	Case (%)	Multivariate hazards regression *	
		HR (95% CI)	p
For men			
BMI			
per 1-SD increase		1.27 (1.16-1.380	< 0.001
T1 (reference)	9 (6.87%)	1	-
T2	10 (7.75%)	1.09 (0.44-2.69)	0.856
T3	29 (20.86%)	3.90 (1.81-8.37)	< 0.001
p for trend			< 0.001
WC			
per 1-SD increase		1.10 (1.07-1.14)	< 0.001
T1 (reference)	5 (4.03%)	1	-
T2	17 (12.78%)	3.24 (1.19-8.78)	0.021
T3	26 (18.31%)	5.97 (2.27-15.71)	< 0.001
p for trend			< 0.001
HC			
per 1-SD increase		1.11 (1.06-1.16)	< 0.001
T1 (reference)	9 (7.03%)	1	-
T2	11 (9.40%)	1.19 (0.49-2.88)	0.701
T3	28 (18.18%)	2.87 (1.35-6.08)	0.006
p for trend			0.004
WHR			
per 0.01-SD increase		1.09 (1.04-1.15)	< 0.001
T1 (reference)	5 (3.82%)	1	-
T2	18 (13.85%)	3.65 (1.35-9.83)	0.011

T3	25 (18.12%)	5.42 (2.07-14.18)	0.001
p for trend			< 0.001
Women			
BMI			
per 1-SD increase		1.23 (1.07-1.42)	0.005
T1 (reference)	4 (4.40%)	1	-
T2	8 (8.33%)	1.50 (0.44-5.07)	0.515
T3	14 (13.86%)	1.64 (0.50-5.36)	0.413
p for trend			0.712
WC			
per 1-SD increase		1.10 (1.04-1.16)	0.001
T1 (reference)	4 (4.26%)	1	-
T2	4 (4.60%)	0.77 (0.18-3.18)	0.712
T3	18 (16.82%)	2.54 (0.83-7.78)	0.104
p for trend			0.051
HC			
per 1-SD increase		1.06 (0.99-1.14)	0.114
T1 (reference)	4 (5.06%)	1	-
T2	8 (8.33%)	1.26 (0.37-4.33)	0.718
T3	14 (12.39%)	1.52 (0.47-4.92)	0.481
p for trend			0.768
WHR			
per 0.01-SD increase		1.16 (1.07-1.25)	< 0.001
T1 (reference)	1 (1.06%)	1	-
T2	5 (5.21%)	4.54 (0.53-38.91)	0.168
T3	20 (20.41%)	15.91 (2.10-120.52)	0.007

p for trend	< 0.001

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women

BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio

BMJ Open

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058162.R2
Article Type:	Original research
Date Submitted by the Author:	05-May-2022
Complete List of Authors:	Liu, Lu; Sichuan University West China Hospital, Department of Cardiology Ban, Chao; Sichuan University West China Hospital, Department of Equipment Jia, Shanshan; Sichuan University West China Hospital, Department of Cardiology Chen, Xiaoping; Sichuan University West China Hospital, Department of Cardiology He, Sen; Sichuan University West China Hospital, Department of Cardiology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Public health
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, INTERNAL MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association of predicted fat mass, predicted lean mass, and predicted percent fat with diabetes mellitus in Chinese: a 15-year prospective cohort

Lu Liu Ph.D. [a], Chao Ban M.D. [b], Shanshan Jia Ph.D. [a], Xiaoping Chen M.D. [a *], and Sen He M.D., Ph.D. [a *]

(Lu Liu, Chao Ban, and Shanshan Jia equally contribute to the article)

[a] Department of Cardiology, West China Hospital of Sichuan University, Chengdu, China

[b] Department of Equipment, West China Hospital of Sichuan University, Chengdu, China

[*] **Corresponding author:** Xiaoping Chen and Sen He; Department of Cardiology, West China Hospital, Sichuan University No.37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China Tel: +86 028 85422343; Fax: +86 028 85422175; Email address: xiaopingchen0196@163.com (Xiaoping Chen), hesensubmit@163.com (Sen He).

ORCID IDs: 0000-0002-5274-4680 (for Lu Liu), 0000-0003-1824-3943 (for Xiaoping Chen), 0000-0002-9777-2650 (for Sen He)

Word count: 3204

ABSTRACT

Objectives: With body mass index (BMI) failing to distinguish the mass of fat from lean, several novel predicted equations for predicted fat mass (FM), predicted lean mass (LM), and predicted percent fat (PF) were recently developed and validated. Our aim was to explore whether the three novel parameters could better predict diabetes mellitus (DM) than the commonly used obesity indicators, including BMI, waist circumference, hip circumference, and waist-hip ratio.

Design: A 15-year prospective cohort was used.

Setting: It was a prospective cohort, consisting of a general Chinese population from 1992 to 2007.

Participants: This cohort enrolled 711 people. People suffering from DM at baseline (n = 24) were excluded, and 687 non-diabetics with complete data were included to the analysis.

Primary outcome: New-onset DM.

Results: After the follow-up, 74 (48 men and 26 women) incidences of DM were documented. For men, the adjusted hazard ratios (HR) were 1, 5.19 ($p = 0.003$), and 7.67 ($p < 0.001$) across predicted PF tertiles; 1, 2.86 ($p = 0.029$), and 5.60 ($p < 0.001$) across predicted FM tertiles; 1, 1.21 ($p = 0.646$), and 2.27 ($p = 0.025$) across predicted LM tertiles. Predicted FM performed better than other commonly used obesity indicators in discrimination with the highest Harrell's C-statistic among all the body composition parameters. Whereas, for women, none of the three novel parameters was the independent predictor.

Conclusion: Predicted PF, predicted LM, and predicted FM could independently predict the risk of DM for men, with predicted FM performing better in discrimination than other commonly used obesity indicators. For women, larger samples were further needed.

Key words: BMI, diabetes, fat mass, lean mass, obesity, percent fat

Strengths and limitations of this study

1. This study explored whether the three novel body composition parameters, including predicted FM, predicted LM, and predicted PF, could predict DM better than BMI and other commonly used obesity indicators.

2. Cox's regression analysis was used to estimate HRs for DM, and Harrell's C-statistic was used to assess and compare the discriminatory ability of all the parameters in predicting new-onset DM.

3. The relatively small sample size might possibly lead to a statistical power decrease.

INTRODUCTION

Diabetes mellitus (DM) is a collection of chronic metabolic conditions, characterized by elevated blood glucose levels resulting from the body's inability to produce insulin or resistance to insulin action, or both[1]. There are two primary forms of DM, insulin-dependent DM (type 1 diabetes mellitus, T1DM) and non-insulin-dependent DM (type 2 diabetes mellitus, T2DM). T2DM is the most common form, making up 90% - 95% of all diabetic patients[1]. DM and its complications can result in disability and premature death[2], as well as enormous economic and social burdens[3]. There is no cure for DM, thus, prevention is the best intervention.

Among the well-known modifiable risk factors, obesity, defined as an excess accumulation of body fat, is regarded as a major risk factor[4]. Body mass index (BMI) has been mostly used as a simple and reasonable measure of general adiposity in clinical and public health settings. However, since it is defined as the result of weight in kilogram divided by height in meter squared, BMI is in poor discrimination of metabolically distinct components such as fat mass (FM) and lean mass (LM)[5]. Direct measurement of FM and LM is impractical in large epidemiological studies for sophisticated and expensive technologies such as dual-energy X-ray absorptiometry (DXA) or imaging techniques (i.e. MRI and computerized tomography).

Recently, Lee et al developed anthropometric prediction equations for FM, LM, and percent fat (PF) from the large population samples of the noninstitutionalized civilians in the USA from National Health and Nutrition Examination Survey[6]. In the original study, the validation tests showed robust and consistent results without evident substantial bias, and comparable abilities to predict obesity-related biomarkers with direct DXA measurements. Later, based on two large US prospective cohorts, predicted FM and predicted PF were both estimated to have a stronger association than BMI with

T2DM[7]. However, body compositions differ across ethnic groups[8, 9]. Healthy Chinese and South Asian individuals were measured to have a greater amount of visceral adipose tissue than Europeans with the same BMI or waist circumference[10]. Therefore, we aimed to evaluate if these equations could better predict the risk of DM in comparison with BMI and other obesity indicators, including waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR), in a 15-year prospective cohort consisting of Chinese people.

MATERIALS AND METHODS

Study population

In 2007, supported by the Mega-projects of Science Research for China's 11th five-year plan (Trends in the incidence of metabolic syndrome and integrated control in China), a group of 711 people, from an urban community situated in Chengdu, China, underwent a health examination. They also had a health examination in 1992 as part of the Chinese Multi-provincial Cohort Study approved by Beijing Institute of Heart, Lung, and Blood Vessel Disease that investigated cardiovascular risk factors across the country. Therefore, we picked up the data, and more details have been described elsewhere[11, 12]. People suffering from DM at baseline (n = 24) were excluded. No one had missing data. Finally, the remaining 687 people with complete data were included in the analysis. All of them provided written informed consent. The study was approved by the Ministry of Health of China, as well as the Ethics Committee of West China Hospital of Sichuan University.

Evaluation

Definition

DM was defined by self-reported history or fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L[13].

Hypertension was a conventional blood pressure of ≥ 140mm Hg systolic, ≥ 90mm Hg diastolic, or the use of antihypertensive drugs. DM family history was determined with a diagnosis of DM in the first-grade relatives. Smoking was defined as an average cigarette consumption of at least one per day. Frequent previous alcohol intake and present alcohol intake were both defined as alcohol consumption. Activity was defined as at least twice 20-minute moderately intensive physical activity per week.

Data collection

Baseline data in 1992 included medical history, physical examination, and biochemical tests. Questionnaires containing demographic information and cardiovascular disease risk factors were collected by well-trained investigators. WC was measured at the midpoint between the lower border of the rib cage and the iliac crest at the end of a normal exhalation. HC was measured at the maximum protrusion of the gluteal region. WHR was calculated by WC in cm divided by HC in cm. Height was measured without shoes. Weight was measured in light clothing. Blood pressure was measured in a sitting position after at least 15 min of rest, and the mean blood pressure of three measurements taken by a standardized mercury sphygmomanometer was used as a participant's blood pressure. Blood samples were drawn from participants in the morning after 12-h overnight fasting. FPG, total cholesterol (TC), and triglyceride (TG) levels were determined in an enzymatic method, and high-density lipoprotein cholesterol (HDL-C) was measured by the phosphotungstic acid/$MgCl_2$ precipitation method. Low-density lipoprotein cholesterol (LDL-C) was measured using a standard kit.

Equation profiles

Equations for predicted FM (kg)[6]

For men $= -18.592 - 0.009 \times \text{age (year)} - 0.080 \times \text{height (cm)} + 0.226 \times \text{weight (kg)}$

$+ 0.387 \times \text{WC (cm)} + 0.080 \times \text{Mexican} - 0.188 \times \text{Hispanic} - 0.483 \times \text{Black} + 1.050 \times$

other ethnicity

For women $= 11.817 + 0.041 \times$ age (year) $-0.199 \times$ height (cm) $+0.610 \times$ weight (kg) $+0.044 \times$ WC (cm) $+0.388 \times$ Mexican $+ 0.073 \times$ Hispanic $- 1.187 \times$ Black $+ 0.325 \times$ other ethnicity

Equations for predicted LM (kg)[6]

For men $= 19.363 + 0.001 \times$ age (year) $+0.064 \times$ height (cm) $+0.756 \times$ weight (kg) $-0.366 \times$ WC (cm) $-0.066 \times$ Mexican $+ 0.231 \times$ Hispanic $+ 0.432 \times$ Black $- 1.007 \times$ other ethnicity

For women $= -10.683 - 0.039 \times$ age (years) $+0.186 \times$ height (cm) $+0.383 \times$ weight (kg) $-0.043 \times$ WC (cm) $-0.359 \times$ Mexican $- 0.059 \times$ Hispanic $+ 1.085 \times$ Black $- 0.34 \times$ other ethnicity

Equations for predicted PF (%)[6]

For men $= 0.02 + 0.00 \times$ age (year) $-0.07 \times$ height (cm) $-0.08 \times$ weight (kg) $+0.48 \times$ WC (cm) $+0.32 \times$ Mexican $+ 0.02 \times$ Hispanic $- 0.65 \times$ Black $+ 1.12 \times$ other ethnicity

For women $= 50.46 + 0.07 \times$ age (year) $-0.26 \times$ height (cm) $+0.27 \times$ weight (kg) $+0.10 \times$ WC (cm) $+0.89 \times$ Mexican $+ 0.49 \times$ Hispanic $- 1.57 \times$ Black $+ 0.43 \times$ other ethnicity

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analyses

For descriptive results, variables were expressed as the mean ± standard deviation (SD), median and interquartile range, or counts and percentages as appropriate. Smoking, alcohol intake, activity,

hypertension, and family history of DM were expressed as dummy variables (presence= 1, absence= 0). Differences in baseline characteristics between participants with and without new-onset DM were tested by independent t-test for normally distributed variables and by the non-parametric Mann-Whitney U-test for skewed variables. Interactions between categorical variables were evaluated with the Pearson χ^2 test, Fisher's exact probabilities were used if necessary. Correlations between different variables were determined using Pearson's or Spearman's analysis.

We treated all the parameters as sex-specific tertiles. The cumulative incidences of DM across tertiles were graphically displayed according to the method of Kaplan-Meier, with comparisons among groups by the log-rank test. Cox proportional hazards regression models were used to assess the impact of the variables on the incidence rate of DM. Furthermore, restricted cubic spline analysis was used to visualize the relations between variables and incident DM. To quantify and compare the discriminative ability of different parameters, Harrell's c-index was calculated. A generally accepted approach suggests that the C-index of less than 0.60 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75, clearly useful discrimination[14].

All statistical tests were 2-sided, and p value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 3.6.3.

RESULTS

Baseline characteristics

After excluding people suffering from DM at baseline (n = 24), the remaining 687 (399 men and 288 women) people free of DM at baseline with complete data were included in the analysis.

Those who had subsequent DM were associated with higher baseline levels of FPG, weight, BMI,

WC, HC, predicted FM, predicted LM, and predicted PF for the males; associated with higher baseline levels of TC, TG, height, BMI, WC, HC, predicted FM, and predicted PF, and lower baseline level of HDL-C for the females. At baseline, age was not of significance between the two groups both in men and women, but there was still a trend that people suffering incident DM were older. Other details of baseline information are shown in Table 1.

As Online Supplemental Table S1 shows, predicted FM was strongly correlated with WC (r_s = 0.98), followed by BMI (r_s = 0.88) and HC (r_s = 0.82) in men; strongly correlated with BMI (r_s = 0.94), followed by HC (r_s = 0.87) and WC (r_s = 0.83) in women. Predicted LM had a strong correlation with predicted FM (r_s = 0.83) in women and a relatively strong correlation with HC (r_s = 0.71) in men, but relatively weakly with WHR both in men (r_s = 0.15) and women (r_s = 0.29). Predicted PF was strongly correlated with WC (r_s = 0.97) in men and BMI (r_s = 0.95) in women, but relatively weakly with predicted LM both in men (r_s = 0.35) and women (r_s = 0.51).

Survival analysis

All the body composition parameters were divided into tertiles. Tertile 1 had the lowest estimated values while Tertile 3 had the highest. The category boundaries of all the parameters were displayed by gender in Online Supplemental Table S2. After the follow-up of 15 years, 74 (48 men and 26 women) incidences of DM were documented (incidence rate: 0.74 per 100 person-years; 95% CI: 0.57-0.91). As Figure 1A-C present, for men, the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (log-rank p = 0.001), predicted LM (log-rank p = 0.030), and predicted PF (log-rank p < 0.001), and people in Tertile 3 had the highest cumulative incidence of DM. For women, however, only predicted PF (log-rank p = 0.028) could help to distinguish the cumulative incidence across the tertiles (Figure 1D).

For other obesity indicators, the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of BMI (log-rank $p < 0.001$), WC (log-rank $p = 0.001$), HC (log-rank $p = 0.006$), and WHR (log-rank $p = 0.001$) in men; WC (log-rank $p = 0.002$) and WHR (log-rank $p < 0.001$) in women.

Relation to risk of DM

Univariable cox regression analysis is shown in Online Supplemental Table S3. Predicted FM, predicted PF, BMI, WC, HC, and WHR were risk factors of DM both for men and women, and predicted LM was a risk factor for men only. Variables showing statistical significance in univariable analysis or clinical relevance ($p < 0.1$) were entered into multivariable analysis.

In multivariable analysis, we adjusted potential confounders including hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women.

As Table 2 shows, in men, predicted FM ($p < 0.001$), predicted LM ($p = 0.043$), and predicted PF ($p < 0.001$) were all the significantly independent predictors with the top tertiles associated with the highest risk of DM. Compared with the other parameters we studied, predicted PF in higher level was more strongly associated with increased risk of DM, since it showed a positive association with the risk of DM with the adjusted hazard ratio (HR) for Tertile 2 and Tertile 3 estimated as 5.19 [95% confidence interval (CI): 1.77-15.20, $p = 0.003$] and 7.67 (95% CI: 2.64-22.35, $p < 0.001$), respectively. There was a positive association between predicted FM and the risk of DM (HR: 2.86, 95% CI: 1.12-7.33, $p = 0.029$ for Tertile 2; HR: 5.60, 95% CI: 2.27-13.80, $p < 0.001$ for Tertile 3, respectively) as well. Other commonly used parameters such as BMI ($p < 0.001$), WC ($p < 0.001$), HC

($p = 0.004$) and WHR ($p < 0.001$) were also significant predictors (Online Supplemental Table S4), and WC and WHR showed a positive association across tertiles.

As for the women, however, none of the three novel parameters was significantly independent after adjustment (Table 2), as well as other commonly used obesity indicators but WHR, which ($p < 0.001$) remained stable and significant (Online Supplemental Table S4).

Furthermore, as Table 2 shows, we treated the predicted FM, predicted LM, and predicted PF as continuous variables. In men, all of them were independent risk factors and it is true of the restricted cubic splines used to flexibly models and visualize the relations with risk of DM (Online Supplemental Figure S1). With the medians as reference points, all the three novel parameters showed an overall positive association with DM in men (Online Supplemental Figure S1); while in women, only predicted PF was independently associated with DM (Table 2, HR: 1.34 per 1-SD increase, 95% CI: 1.15-1.57, $p < 0.001$), and the restricted cubic spline shows the similar relationship, especially after the median (Online Supplemental Figure S2)

Discrimination

Table 3 shows discriminative abilities evaluated by Harrell's c-index of different body composition parameters. In the male group, predicted FM had the highest Harrell's c-index of 0.679 (95% CI: 0.606-0.752), and predicted LM had the lowest Harrell's c-index of 0.619 (95% CI: 0.537-0.701). All of the parameters we studied could provide possibly helpful discriminative information in the prediction of DM[14].

In the female group, since WHR was the only significantly independent risk factor of DM both as continuous variable and categorical variable, we just estimated Harrell's c-index of WHR (0.768, 95% CI: 0.697-0.839), and it showed a clearly useful discriminative ability in predicting DM[14].

DISCUSSION

In this study, we investigated the predictive abilities for the risk of DM of three novel body composition parameters including predicted FM, predicted LM, and predicted PF, and compared them with other obesity indicators, in a Chinese prospective population during 15 years of follow-up. For men, our results showed predicted FM, predicted LM, and predicted PF could independently predict the new onset of DM; in all the parameters we studied, predicted FM had the best discriminative ability, providing possibly helpful information in the prediction of DM. For women, none of the three novel parameters could be significantly independent in multivariable analysis; of all the parameters we estimated, WHR was the only independent predictor, with Harrell's c-index of 0.768, which suggested a clearly useful discrimination.

To our knowledge, this was the first study in a Chinese prospective cohort to evaluate the associations of three novel body composition parameters with the incidence of DM. BMI has been preferred as a measure indicating overall obesity for a long time to identify people at increased risk of DM[15]. However, BMI was not thought as a good indicator of obesity recently.[5, 16]. It fails to distinguish the mass of fat from lean, and had no gender distinction as well. For example, in common sense, athletes or someone liking exercise always had heavier weight for the mass of lean, they have greater BMI but they are not obese. Besides, aging is associated with an accumulation of visceral fat and a progressive loss of muscle mass[16]. With the same BMI, an old man has more mass of fat with less mass of muscle than a younger man.

Recently, Lee et al. [6] developed equations predicting FM, LM, and PF in order to better reflect body composition. The predicted equations had a simple calculation and just require the information of

gender, age, height, weight, WC, and ethnicity, which are easily measurable and accessible in clinical settings or even at home. Lee et al. later investigated the association between predicted FM and risk of DM in two large prospective cohorts of US men and women[7]. They found predicted FM, as well as predicted PF, had a stronger association with DM than BMI both in men and women. Similarly, in our study consisting of Chinese population, in the male group, both predicted FM and predicted PF could independently predict incident DM and predicted FM had the highest Harrell's value. Higher predicted PF was more strongly associated with increased risk of DM than other parameters.

Besides in prediction of DM, predicted FM and predicted PF were also explored in the association with risk of heart failure and myocardial infarction in adults with T2DM[17]. The results showed a decline in predicted FM but not predicted LM, over 1 year was significantly associated with lower risk of overall heart failure (adjusted HR per 10% decrease in predicted FM: 0.80; 95% CI: 0.68-0.95); decline in predicted FM was significantly associated with lower risk of both heart failure subtypes (with preserved or reduced ejection fraction).

In a post hoc analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[18], researchers modified the two parameters, fat mass index and lean BMI, calculated by predicted FM and predicted LM, respectively, in kilograms divided by the square of height in meters. They found that in patients with T2DM, fat mass index had a strong positive association with a higher risk of a major adverse cardiovascular event, while predicted lean BMI was not associated with major cardiovascular events ($p = 0.34$).

In a large prospective US cohort study of men[19], there was a strong positive association between predicted FM and mortality from all causes, cardiovascular disease, and cancer. Compared with those in the lowest fifth of predicted FM, men in the highest fifth had an HR of 1.35 (95% CI: 1.26-1.46) for

all-cause mortality. In contrast, predicted LM showed a U-shaped association with all-cause mortality that men in the second to fourth fifths had 8-10% lower risk. The U-shaped associations were also found with deaths from cardiovascular disease and cancer. However, there was a strong inverse association between predicted LM and mortality from respiratory disease.

Lean body mass accounts for most of the human body mass, and it is essential not only in the stress response but also in metabolism[20]. Muscle loss may have negative effects[20-22]. Son et al. previously conducted a 2-yearly prospective assessment in middle-aged and older Korean adults, and reported that low muscle mass was associated with an increased risk of T2DM, independent of general obesity[23]. In contrast, in our research, for the development of DM, the protective role of predicted LM could not be concluded. Instead, the top tertile of predicted LM had an increased risk in the male group. Since there is a lack of randomized clinical trial studies that directly assess the role of increased muscle mass in the prevention of new on-set DM[24], the association between predicted LM and risk of DM needs further explorations. After all, increased LM was not always simply reported as the protective factor of diseases or mortality[17-19].

There are certainly some limitations in our study. Firstly, 687 was a relatively small sample size, possibly leading to a statistical power decrease, for example, the results in women. Nevertheless, we still observed that as a continuous variable, predicted PF could independently predict the risk of incident DM in women. Maybe in a larger population, the relationships and comparisons would be more accurate. Secondly, due to the absence of oral glucose tolerance tests (OGTT) and hemoglobin A1c (HbA1c) data in our study, some people might not be adequately diagnosed. Thirdly, only one follow-up examination was carried out, so that there was no guarantee whether some “interval censoring” might have occurred.

In conclusion, in the general Chinese population, predicted FM, predicted LM, and predicted PF could independently predict the risk of DM in men, and predicted FM performed better in discrimination than other commonly used obesity indicators including BMI, WC, HC, and WHR. For women, however, predicted FM, predicted LM, predicted PF, as well as other obesity indicators, but WHR, could not remain stable and independent in multivariable analysis, which might be attributed to the relatively small sample size with the corresponding few endpoints. Therefore, the conclusion of these findings should be extrapolated with caution, and larger samples from different races are needed to explore the predictive abilities of the three novel equations reflecting body composition on incident DM and other diseases.

Acknowledgment

We thank all staff members for data collection, data entry and monitoring as part of this study.

Funding

This work was supported by the Key R&D Projects of Science and Technology Department of Sichuan Province, China (grant Number: 22ZDYF1527); the National Natural Science Foundation of China (Grant number: 81600299); a project from China's eighth national 5-year research plan (Grant no: 85-915-01-02); and the megaprojects of science research for China's 11th 5-year plan (Grant no: 2006BAI01A01).

Competing interests

None declared.

Contributors

LL and SSJ: Participated in the conception and design of the study, performed the data collection and the statistical analysis, and wrote the draft of the manuscript. BC: Participated in the conception and design of the study, performed the statistical analysis, and wrote the revision version. SH and XPC: The corresponding authors, participated in the design of the study, performed the statistical analysis, and revised subsequent drafts. All authors read and approved the final manuscript.

Data availability statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval statement

This study involved human patients and was approved by Ministry of Health of China and Ethics Committee of West China Hospital of Sichuan University.

REFERENCES

1. Wu Y, Ding Y, Tanaka Y. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci* 2014;11:1185-200.

2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018;14:88-98.

3. Zhao Y, Jiang Z, Guo C. New hope for type 2 diabetics: targeting insulin resistance through the immune modulation of stem cells. *Autoimmun Rev* 2011;11:137-42.

4. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr* 2004;80:257-63.

5. Prentice AM, Jebb SA. Beyond body mass index. *Obes Rev* 2001;2:141-7.

6. Lee DH, Keum N, Hu FB, et al. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999-2006. *Br J Nutr* 2017;118:858-66.

7. Lee DH, Keum N, Hu FB, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. *Eur J Epidemiol* 2018;33:1113-23.

8. Lear SA, Humphries KH, Kohli S, et al. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007;86:353-9.

9. Lear SA, Humphries KH, Kohli S, et al. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)* 2007;15:2817-24.

10. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *Jama* 2009;301:2129-40.

11. Ren J, Grundy SM, Liu J, et al. Long-term coronary heart disease risk associated with very-low-density lipoprotein cholesterol in Chinese: the results of a 15-Year Chinese Multi-Provincial Cohort Study (CMCS). *Atherosclerosis* 2010;211:327-32.

12. Liu J, Hong Y, D'Agostino RB, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *Jama* 2004;291:2591-9.

13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53.

14. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *Jama* 2017;318:1377-84.

15. Vazquez G, Duval S, Jacobs DR, Jr., et al. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007;29:115-28.

16. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proc Nutr Soc* 2015;74:405-12.

17. Patel KV, Bahnson JL, Gaussoin SA, et al. Association of Baseline and Longitudinal Changes in Body Composition Measures With Risk of Heart Failure and Myocardial Infarction in Type 2 Diabetes: Findings From the Look AHEAD Trial. *Circulation* 2020;142:2420-30.

18. Xing Z, Tang L, Chen J, et al. Association of predicted lean body mass and fat mass with cardiovascular events in patients with type 2 diabetes mellitus. *Cmaj* 2019;191:E1042-e8.

19. Lee DH, Keum N, Hu FB, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *Bmj* 2018;362:k2575.

20. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;84:475-82.

21. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *Bmj* 2008;337:a439.

22. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;50:889-96.

23. Son JW, Lee SS, Kim SR, et al. Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. *Diabetologia* 2017;60:865-72.

24. de Sousa MV, da Silva Soares DB, Caraça ER, et al. Dietary protein and exercise for preservation of lean mass and perspectives on type 2 diabetes prevention. *Exp Biol Med (Maywood)* 2019;244:992-1004.

Table 1 Basic characteristics of people with or without subsequent DM.

Variables	Men (n=399)			Women (n=288)		
	Subsequent DM (n=48)	Subsequent non-DM (n=351)	p-value	Subsequent DM (n=26)	Subsequent non-DM (n=262)	p-value
Age (years)	50.6 ± 5.0	49.0 (45.0-53.0)	0.079	48.4 ± 6.8	46.0 (42.0-52.0)	0.127
Smoking (%)	32 (66.7%)	213 (60.7%)	0.425	0	2 (0.8%)	1.000
Hypertension (%)	9 (18.8%)	50 (14.2%)	0.410	7 (26.9%)	38 (14.5%)	0.150
DM family history (%)	3 (6.3%)	9 (2.6%)	0.165	3 (11.5%)	18 (6.9%)	0.418
SBP (mm Hg)	118.1 ± 14.5	110.0 (105.0-120.0)	0.061	119.0 (103.0-132.5)	110.0 (102.0-120.0)	0.240
DBP (mm Hg)	74.0 (70.0-80.0)	72.0 (70.0-80.0)	0.292	76.4 ± 12.1	70.0 (71.0-80.0)	0.226
FPG (mmol/L)	4.6 ± 0.8	4.0 (3.8-4.7)	<0.001	4.6 ± 0.9	3.8 (4.0-4.7)	0.052
TC (mmol/l)	4.4 (4.1-4.8)	4.3 (3.9-4.8)	0.419	5.0 ± 0.7	4.4 (3.9-5.0)	0.006
TG (mmol/L)	1.9 (1.7-3.0)	1.9 (1.5-2.4)	0.104	1.9 (1.5-2.3)	1.8 (1.4-2.2)	<0.001
HDL-C (mmol/L)	1.2 (1.0-1.4)	1.2 (1.1-1.4)	0.193	1.2 ± 0.2	1.3 (1.1-1.5)	0.009
LDL-C (mmol/L)	2.2 ± 0.8	2.1 (1.7-2.7)	0.556	2.4 ± 1.0	2.3 (1.8-2.8)	0.460
Height (cm)	165.4 ± 5.9	165.3 ± 5.6	0.898	151.9 ± 4.4	151.0 (155.0-159.0)	0.006
Weight (cm)	68.5 (61.3-74.8)	62.9 ± 8.2	<0.001	58.6 ± 9.0	56.4 ± 7.5	0.168
BMI (kg/m^2)	24.8 (23.0-26.6)	23.0 (20.9-24.8)	<0.001	25.3 ± 3.3	23.4 ± 2.6	0.001
WC (cm)	83.6 ± 8.2	78.0 (72.0-83.0)	<0.001	79.9 ± 7.6	73.5 ± 7.1	<0.001
HC (cm)	95.0 (90.0-97.0)	91.0 (87.0-95.0)	<0.001	95.4 ± 7.4	92.6 ± 5.8	0.021
WHR	0.89 ± 0.05	0.85 ± 0.06	0.001	0.84 ± 0.04	0.79 ± 0.05	<0.001
FM (kg)	16.4 ± 5.2	13.3 (9.6-16.2)	<0.001	21.8 ± 5.4	19.6 ± 4.3	0.014
LM (kg)	50.2 ± 5.0	48.1 ± 4.5	0.004	34.3 ± 3.5	34.4 ± 3.4	0.894
PF (%)	24.0 ± 3.4	21.8 ± 3.1	<0.001	38.6 ± 2.9	36.4 ± 2.4	<0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Table 2 Multivarible Cox regression models for DM

	Case (%)	Multivariable hazards regression *	
		HR (95% CI)	p
For men			
FM			
per 1-SD increase		1.18 (1.11-1.25)	< 0.001
T1 (reference)	6 (4.54%)	1	-
T2	16 (12.21%)	2.86 (1.12-7.33)	0.029
T3	26 (19.12%)	5.60 (2.27-13.80)	< 0.001
p for trend			< 0.001
LM			
per 1-SD increase		1.10 (1.03-1.17)	0.003
T1 (reference)	11 (8.33%)	1	-
T2	13 (9.92%)	1.21 (0.54-2.70)	0.646
T3	24 (17.65%)	2.27 (1.11-4.63)	0.025
p for trend			0.043
PF			
per 1-SD increase		1.25 (1.14-1.36)	< 0.001
T1 (reference)	4 (3.03%)	1	-
T2	20 (15.27%)	5.19 (1.77-15.20)	0.003
T3	24 (17.65%)	7.67 (2.64-22.35)	< 0.001
p for trend			< 0.001
Women			
FM			
per 1-SD increase		1.04 (0.95-1.15)	0.375
T1 (reference)	5 (5.26%)	1	-
T2	9 (9.47%)	1.38 (0.45-4.23)	0.571
T3	12 (12.24%)	1.08 (0.35-3.37)	0.900

p for trend			0.811
LM			
per 1-SD increase		0.92 (0.81-1.05)	0.205
T1 (reference)	6 (6.28%)	1	-
T2	13 (13.54%)	1.33 (0.49-3.61)	0.576
T3	7 (7.14%)	0.62 (0.19-2. 05)	0.432
p for trend			0.332
PF			
per 1-SD increase		1.34 (1.15-1.57)	< 0.001
T1 (reference)	3 (3.16%)	1	-
T2	9 (9.47%)	1.95 (0.49-7.66)	0.341
T3	14 (14.29%)	2.39 (0.63-9.10)	0.202
p for trend			0.442

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women.

CI: Confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; PF, percent fat; SBP, systolic blood pressure; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride

Table 3 Discriminative abilities evaluated by Harrell's c-index of different body composition parameters

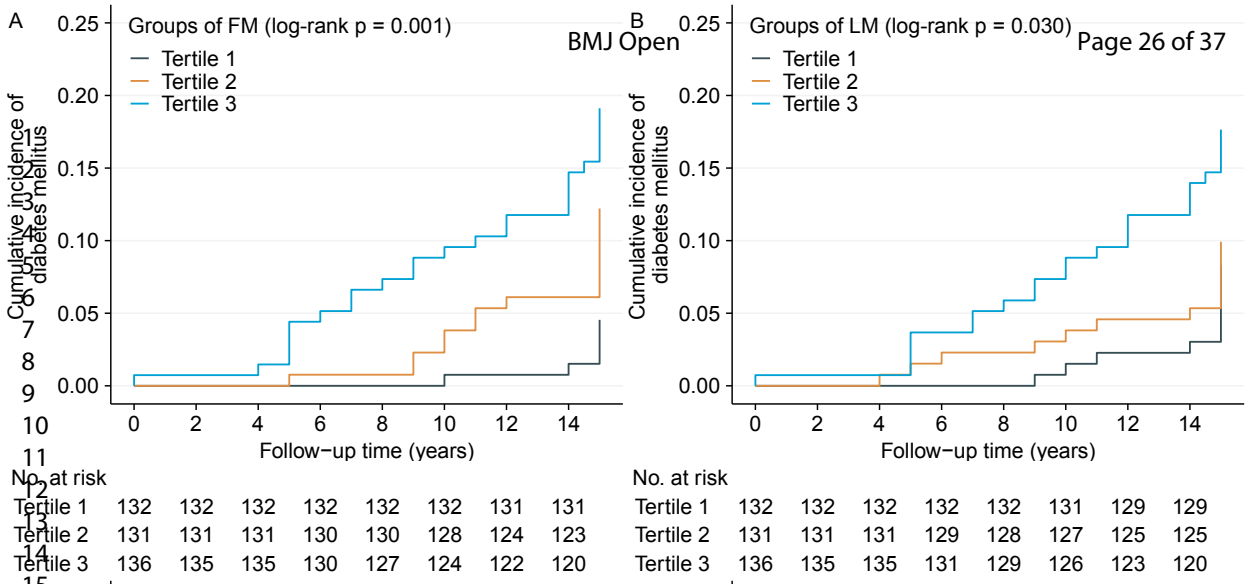
Variables	Men		Women	
	Harrell's c-index	95% CI	Harrell's c-index	95% CI
FM	0.679	0.606-0.752	-	-
LM	0.619	0.537-0.701	-	-
PF	0.670	0.598-0.742	-	-
BMI	0.675	0.599-0.751	-	-
WC	0.673	0.600-0.746	-	-
WHR	0.652	0.578-0.726	0.768	0.697-0.839
HC	0.636	0.560-0.712	-	-

CI: Confidence interval; FM, fat mass; LM, lean mass; PF, percent fat; BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-hip ratio

Figure legends

Figure 1 Cumulative incidence of DM across tertiles of three novel predicted body composition during follow-up.

Survival curves were presented as Kaplan-Meier curves, and the log-rank tests were used for comparison among tertiles. For men (n = 399), the cumulative incidences of DM evaluated by Kaplan-Meier analysis were significantly different across the tertiles of predicted FM (A, log-rank p = 0.001), predicted LM (B, log-rank p = 0.030), and predicted PF (C, log-rank p < 0.001). For women (n = 288), the cumulative incidence of DM evaluated by Kaplan-Meier analysis was just significantly different across the tertiles of predicted PF (D, log-rank p = 0.028). People in the top tertile had the highest cumulative incidence of DM. DM = diabetes mellitus



Supplemental Materials

Table S1 Spearman correlations among different predicted body composition parameters

	WC	HC	WHR	BMI	FM	LM	PF
Men							
WC	1.00	0.77	0.80	0.79	0.98	0.52	0.97
HC		1.00	0.28	0.76	0.82	0.71	0.69
WHR			1.00	0.51	0.72	0.15	0.84
BMI				1.00	0.88	0.69	0.75
FM					1.00	0.66	0.92
LM						1.00	0.35
PF							1.00
Women							
WC	1.00	0.83	0.74	0.76	0.83	0.62	0.84
HC		1.00	0.28	0.79	0.87	0.74	0.78
WHR			1.00	0.39	0.42	0.29	0.53
BMI				1.00	0.94	0.63	0.95
FM					1.00	0.83	0.89
LM						1.00	0.51
PF							1.00

BMI, body mass index; FM, fat mass; HC, hip circumference; LM, lean mass; PF: percent fat; WC, waist circumference; WHR, waist-hip ratio

All correlations were significant with $p < 0.05$.

Table S2 Category boundaries of all the body composition parameters

	Men (n = 399)			Women (n = 288)		
	Tertile 1 (n = 132)	Tertile 2 (n = 131)	Tertile 3 (n = 136)	Tertile 1 (n = 95)	Tertile 2 (n = 95)	Tertile 3 (n = 98)
FM (kg)	< 11.088	11.088 - 15.650	> 15.650	< 17.478	17.478 - 21.573	> 21.573
LM (kg)	< 46.377	46.377 - 50.377	> 50.377	< 32.867	32.867 - 35.735	> 35.735
PF (%)	< 20.622	20.622 - 23.304	> 23.304	< 35.402	35.402 - 37.630	> 37.630
BMI (kg/m^2)	< 21.800	21.800 - 24.500	> 24.500	<22.200	22.200 - 24.700	> 24.700
WC (cm)	< 75.000	75.000 - 82.000	> 82.000	< 71.000	71.000 -76.000	> 76.000
HC (cm)	< 90.000	90.000 - 94.000	> 94.000	< 90.000	90.000 - 95.000	> 95.000
WHR	< 0.841	0.841 - 0.879	> 0.879	< 0.773	0.773 - 0.814	> 0.814

BMI, body mass index; FM, fat mass; HC, hip circumference; LM, lean mass; PF: percent fat; WC, waist circumference; WHR, waist-hip ratio

Table S3 Univariable Cox regression analysis for DM

Variable	Change	HR	95% CI	p
Men				
Age (years)	1-SD increment	1.05	0.996-1.10	0.072
Smoking (%)	Yes vs no	0.79	0.44-1.45	0.448
Hypertension (%)	Yes vs no	1.36	0.66-2.81	0.406
DM family history (%)	Yes vs no	0.44	0.14-1.40	0.163
SBP (mm Hg)	1-SD increment	1.02	0.998-1.036	0.076
DBP (mm Hg)	1-SD increment	1.02	0.998-1.052	0.234
FPG (mmol/L)	1-SD increment	1.78	1.26-2.52	0.001
TC (mmol/l)	1-SD increment	1.15	0.79-1.66	0.476
TG (mmol/L)	1-SD increment	1.16	0.91-1.47	0.248
HDL-C (mmol/L)	1-SD increment	0.57	1.16-2.00	0.376
LDL-C (mmol/L)	1-SD increment	1.04	0.73-1.48	0.818
Height (cm)	1-SD increment	1.01	0.96-1.06	0.834
Weight (cm)	1-SD increment	1.07	1.04-1.11	< 0.001
BMI (kg/m^2)	1-SD increment	1.23	1.13-1.33	< 0.001
WC (cm)	1-SD increment	1.09	1.05-1.13	< 0.001
HC (cm)	1-SD increment	1.09	1.05-1.14	< 0.001
WHR	0.01-SD increment	1.09	1.04-1.15	< 0.001
FM (kg)	1-SD increment	1.16	1.09-1.22	< 0.001
LM (kg)	1-SD increment	1.10	1.04-1.17	0.002
PF (%)	1-SD increment	1.23	1.13-1.34	< 0.001
Women				
Age (years)	1-SD increment	1.04	0.98-1.11	0.161
Smoking (%)	Yes vs no	20.306	--	0.771

Hypertension (%)	Yes vs no	2.00	0.84-4.76	0.116
DM family history (%)	Yes vs no	0.57	0.17-1.88	0.353
SBP (mm Hg)	1-SD increment	1.02	0.999-1.04	0.062
DBP (mm Hg)	1-SD increment	1.03	0.99-1.07	0.111
FPG (mmol/L)	1-SD increment	1.86	1.14-3.03	0.013
TC (mmol/l)	1-SD increment	1.67	1.12-2.50	0.012
TG (mmol/L)	1-SD increment	1.46	1.26-1.69	< 0.001
HDL-C (mmol/L)	1-SD increment	0.081	0.01-0.54	0.009
LDL-C (mmol/L)	1-SD increment	1.05	0.67-1.65	0.824
Height (cm)	1-SD increment	0.91	0.84-0.98	0.009
Weight (cm)	1-SD increment	1.04	0.986-1.09	0.156
BMI (kg/m^2)	1-SD increment	1.27	1.10-1.46	0.001
WC (cm)	1-SD increment	1.11	1.06-1.17	< 0.001
HC (cm)	1-SD increment	1.08	1.01-1.16	0.019
WHR	0.01-SD increment	1.17	1.09-1.25	< 0.001
FM (kg)	1-SD increment	1.11	1.02-1.21	0.013
LM (kg)	1-SD increment	0.99	0.89-1.12	0.912
PF (%)	1-SD increment	1.38	1.19-1.60	< 0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; FM, fat mass; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LM, lean mass; SBP, systolic blood pressure; PF, percent fat; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

Table S4 Multivariable Cox regression models of commonly used obesity indicators for DM

	Case (%)	Multivariable hazards regression *	
		HR (95% CI)	p
For men			
BMI			
per 1-SD increase		1.27 (1.16-1.380	< 0.001
T1 (reference)	9 (6.87%)	1	-
T2	10 (7.75%)	1.09 (0.44-2.69)	0.856
T3	29 (20.86%)	3.90 (1.81-8.37)	< 0.001
p for trend			< 0.001
WC			
per 1-SD increase		1.10 (1.07-1.14)	< 0.001
T1 (reference)	5 (4.03%)	1	-
T2	17 (12.78%)	3.24 (1.19-8.78)	0.021
T3	26 (18.31%)	5.97 (2.27-15.71)	< 0.001
p for trend			< 0.001
HC			
per 1-SD increase		1.11 (1.06-1.16)	< 0.001
T1 (reference)	9 (7.03%)	1	-
T2	11 (9.40%)	1.19 (0.49-2.88)	0.701
T3	28 (18.18%)	2.87 (1.35-6.08)	0.006
p for trend			0.004
WHR			
per 0.01-SD increase		1.09 (1.04-1.15)	< 0.001
T1 (reference)	5 (3.82%)	1	-

T2	18 (13.85%)	3.65 (1.35-9.83)	0.011
T3	25 (18.12%)	5.42 (2.07-14.18)	0.001
p for trend			< 0.001
Women			
BMI			
per 1-SD increase		1.23 (1.07-1.42)	0.005
T1 (reference)	4 (4.40%)	1	-
T2	8 (8.33%)	1.50 (0.44-5.07)	0.515
T3	14 (13.86%)	1.64 (0.50-5.36)	0.413
p for trend			0.712
WC			
per 1-SD increase		1.10 (1.04-1.16)	0.001
T1 (reference)	4 (4.26%)	1	-
T2	4 (4.60%)	0.77 (0.18-3.18)	0.712
T3	18 (16.82%)	2.54 (0.83-7.78)	0.104
p for trend			0.051
HC			
per 1-SD increase		1.06 (0.99-1.14)	0.114
T1 (reference)	4 (5.06%)	1	-
T2	8 (8.33%)	1.26 (0.37-4.33)	0.718
T3	14 (12.39%)	1.52 (0.47-4.92)	0.481
p for trend			0.768
WHR			
per 0.01-SD increase		1.16 (1.07-1.25)	< 0.001
T1 (reference)	1 (1.06%)	1	-
T2	5 (5.21%)	4.54 (0.53-38.91)	0.168

T3	20 (20.41%)	15.91 (2.10-120.52)	0.007
p for trend			< 0.001

*, adjusted for hypertension (yes/no), DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), TG, TC, HDL-C, LDL-C, and FPG in men; DM family history (yes/no), smoking (yes/no), alcohol (yes/no), activity (yes/no), SBP, TG, TC, HDL-C, and FPG in women

BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio

Figure S1 Associations of three novel predicted body composition with risk of DM for men

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 13.61 kg), LM (B; 48.27 kg), and PF (C; 22.04%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.

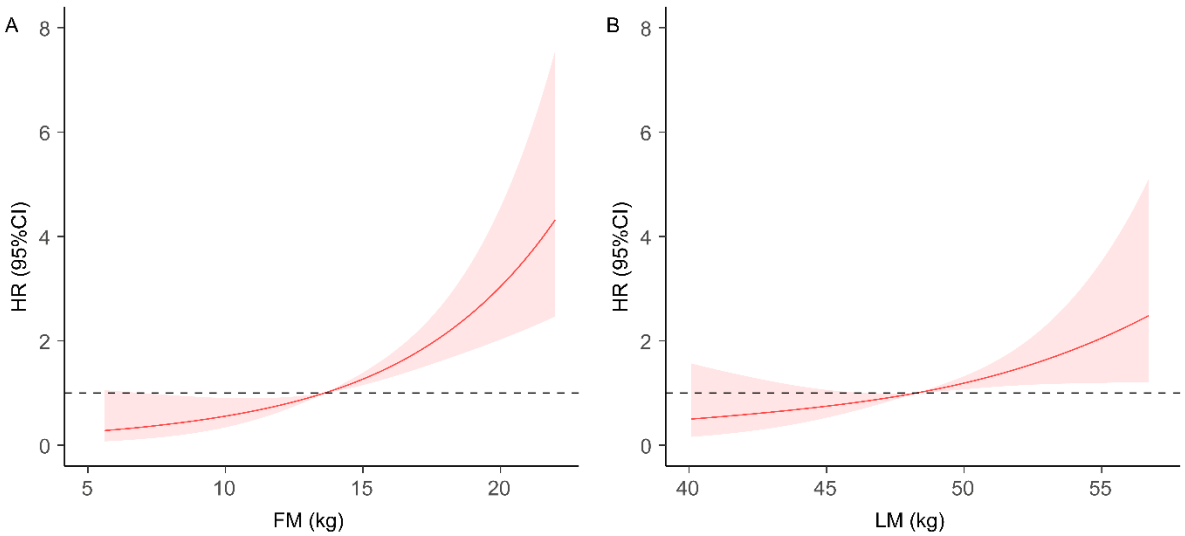
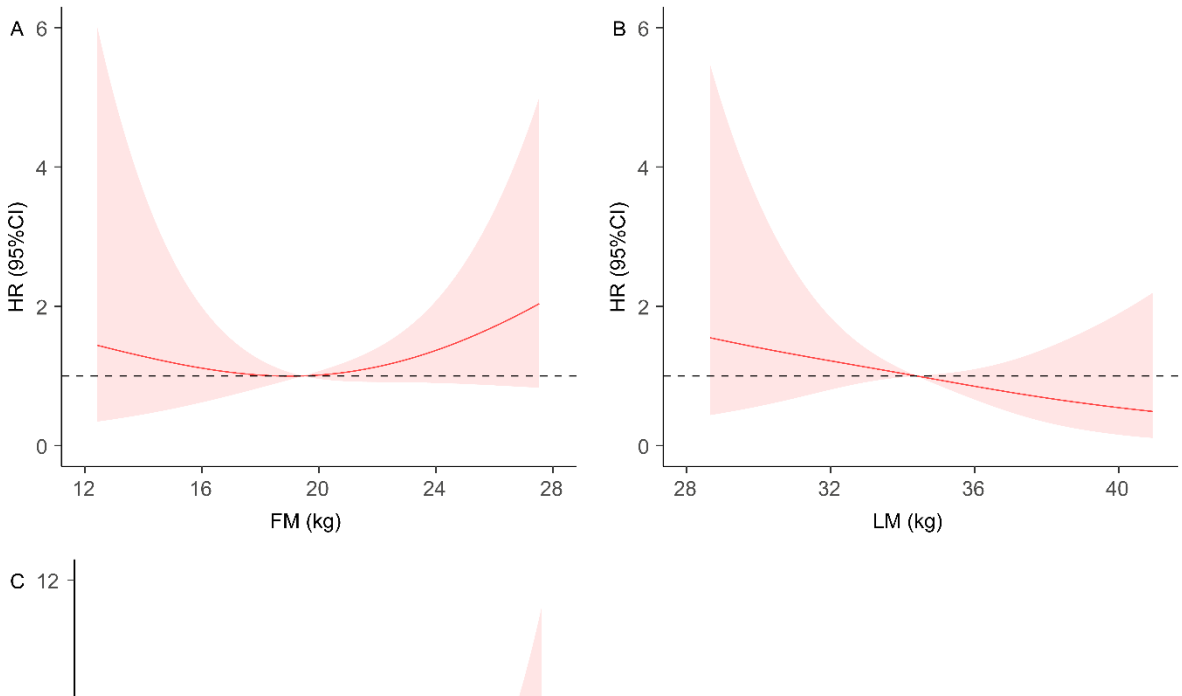


Figure S2 Associations of three novel predicted body composition with risk of DM for women

Restricted cubic splines were used to flexibly models and visualize the relations of different parameters with risk of DM. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference points were the medians for FM (A; 19.45 kg), LM (B; 34.38 kg), and PF (C; 36.39%), respectively. The dotted line represents HR = 1. Confounders in Table 2 were adjusted.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11 9 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.