Creatinine-to-body weight ratio is a predictor of incident diabetes: a population-based retrospective cohort study

Jiacheng He*

Abstract

Purpose: Creatinine to body weight (Cre/BW) ratio is considered the independent risk factor for incident type 2 diabetes mellitus (T2DM), but research on this relationship is limited. The relationship between the Cre/BW ratio and T2DM among Chinese individuals is still ambiguous. This study aimed to evaluate the correlation between the Cre/BW ratio and the risk of T2DM in the Chinese population.

Methods: This is a retrospective cohort study from a prospectively collected database. We included a total of 200,658 adults free of T2DM at baseline. The risk of incident T2DM according to Cre/BW ratio was estimated using multivariable Cox proportional hazards models, and a two-piece wise linear regression model was developed to find out the threshold effect.

Results: With a median follow-up of 3.13 ± 0.94 years, a total of 4001 (1.99%) participants developed T2DM. Overall, there was an L-shaped relation of Cre/BW ratio with the risk of incident T2DM (P for non-linearity < 0.001). When the Cre/BW ratio (× 100) was less than 0.86, the risk of T2DM decreased significantly as the Cre/BW ratio increased [0.01 (0.00, 0.10), P < 0.001]. When the Cre/BW ratio (× 100) was between 0.86 and 1.36, the reduction in the risk of developing T2DM was not as significant as before [0.22 (0.12, 0.38), P < 0.001]. In contrast, when the Cre/BW ratio (× 100) was greater than 1.36, the reduction in T2DM incidence became significantly flatter than before [0.73 (0.29,1.8), P = 0.49].

Conclusion: There was an L-shaped relation of Cre/BW ratio with incidence of T2DM in general Chinese adults. A negative curvilinear association between Cre/BW ratio and incident T2DM was present, with a saturation effect predicted at 0.86 and 1.36 of Cre/BW ratio (× 100).

Keywords: Type 2 diabetes, Creatinine, Body weight, Muscle mass, Insulin resistance, Skeletal muscle
(Cre) is the only metabolite of phosphate creatine in the body's skeletal muscles. Cre, although a marker of renal function, is affected by muscle size since the muscle mass produces Cre. Because the total skeletal muscle mass is generally stable, the Cre concentration is relatively stable [12]. Thus, Cre is also an inexpensive, quickly accessible alternative marker of muscle quality in individuals with normal renal functions [13]. Furthermore, in a recent study, the Cre-to-body weight (Cre/BW) ratio is closely related to the incidence of diabetes in Japanese participants [14]. However, the relationship between the Cre/BW ratio and T2DM has not been studied in Chinese participants. Our research goal was to evaluate the correlation between the Cre/BW ratio and the risk of developing incident T2DM using freely-downloaded data, in a secondary data analysis [15].

Methods

Data source
Data were freely downloaded from the DATADRYAD website (www.datadryad.org). In line with the Dryad Terms of Service, we obtained the Chen et al. [15] datasets on the association of body mass index (BMI) and age with incident diabetes in Chinese adults, from a prospectively collected database. The following variables were included in the dataset: sex, age, BMI, drinking status, smoking status, family history of diabetes, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), fasting plasma glucose (FPG), Cre, aspartate aminotransferase (AST), alanine aminotransferase (ALT), systolic blood pressure (SBP), diastolic blood pressure (DBP), incident diabetes at follow-up, and follow-up time. In the original paper [15], the authors declared that they had relinquished copyright and relevant ownership of the database. Thus, this database can be used for secondary analyses without violating the rights of the authors.

Study population
Data were obtained from a database provided by the Rich Healthcare Group in China. The present study enrolled 685,277 participants who received a health check-up, were at least 20 years old, and had records of at least two visits between 2010 and 2016 across 32 sites and 11 cities (Shanghai, Beijing, Nanjing, Suzhou, Shenzhen, Changzhou, Chengdu, Guangzhou, Hefei, Wuhan, Nantong) in China. The data we obtained were initially screened based on the following exclusion criteria: (1) no available information on weight, height, sex, and FPG at baseline; (2) extreme BMI values (< 15 or > 55 kg/m²); (3) participants with visit intervals less than two years; and (4) participants diagnosed with diabetes at baseline, and participants with undefined diabetes status at follow-up [15]. Finally, 211,833 participants were included in the analysis. The institutional ethics committee did not require any study approval or informed consent for the retrospective component of the research. Data of some participants were excluded from the cohort for further analysis as follows: those with missing Cre/BW ratios at baseline (n = 11,175). In total, 200,658 participants (110,431 men and 90,227 women) were included in the analysis (Fig. 1).

Measurement of the Cre/BW ratio and other covariates
The researchers retrieved the data included in our retrospective cohort study. The study design for the primary study was documented elsewhere [15]. A detailed questionnaire was used to obtain demographic characteristics, lifestyle, disease history, and medical history. Height measurement was accurate to 0.1 cm. Weight measurement was accurate to 0.1 kg, and the participants were required to wear lightweight clothes and no shoes. The BMI was calculated as weight/height squared (kg/m²). Cre/BW ratio was calculated as Cre (mg/dL) divided by the weight (kg) [16]. Fasting venous blood was drawn to estimate serum LDL-C, TG, TC, HDL-C, FPG, blood urea nitrogen (BUN), Cre, ALT, and AST levels using an automatic biochemical analyzer (Beckman 5800). Because this was a retrospective cohort study, observation bias was naturally reduced.

Ascertainment of diabetes diagnosis
Diabetes diagnosis was defined according to FPG ≥ 7.00 mmol/L or self-reported diabetes diagnosis. Ascertainment of diabetes was dependent on the participants’ date of diagnosis or the last visit.

Statistical analysis
The missing values of the other variables were first imputed before the statistical analysis. The missing values for continuous variables (such as height, FPG, TC, TG, HDL-C, LDL, ALT, AST, BUN, SBP, and DBP) were imputed using the mean or median. Missing data on categorical variables (such as smoking and drinking status) were treated as a set of categorical variables [17]. Normally distributed continuous variables are presented as means with standard deviations (SDs), while those with skewed distribution are expressed as medians with interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages. We used the chi-square test, one-way analysis of variance, or Kruskal–Wallis test to examine the statistical differences between groups stratified by Cre/BW ratio quartiles. We employed univariate and multivariate Cox proportional hazard models to assess
the relationship between the Cre/BW ratio and the risk of T2DM. Three models were constructed: model 1 (univariate), the crude model; model 2, adjusted for age and sex; and model 3, adjusted for age, sex, height, FPG, TC, TG, LDL, HDL-C, BUN, AST, ALT, SBP, DBP, drinking status, smoking status, and family history of diabetes. In the models, we used the median value of each quartile of the Cre/BW ratio to perform the linear trend tests: quartile 1 (Q1), quartile 2 (Q2), quartile 3 (Q3), and quartile 4 (Q4). In addition, restricted cubic spline Cox regression analysis with 7 knots (2.5th, 18.33rd, 34.17th, 50.00th, 65.83rd, 81.67th, and 97.50th percentiles of Cre/BW ratio) was performed to test for linearity and explore the shape of the dose–response relationship of Cre/BW ratio and incident T2DM. The threshold level of Cre/BW ratio was determined using a recurrence method, including the selection of the turning point along a predefined interval and the selection of the turning point that yielded the maximum likelihood model. Meanwhile, to better reflect the changes in the curve and the dose–response effect, we set two additional turning points for the line inflection analysis. A log-likelihood ratio test was used to compare the three-piecewise linear regression model with the one-line linear model separately. To identify modifications and interactions, we used a stratified Cox regression model and likelihood ratio test for the different subgroups according to sex, age (<40, 40–60, and ≥60 years), smoking status (never, ever, current, or not recorded), drinking status (never, ever, current, or not recorded), family history of diabetes, and BUN (≤7.1 or >7.1). We used R statistical software (R
Foundation, Vienna, Austria) to analyze the data. Statistical differences were considered significant when the calculated P-value was less than 0.05.

Results
Baseline characteristics of the patients
Baseline characteristics of the selected participants according to the quartiles of Cre/BW ratio are presented in Table 1. A total of 206,658 participants (55.03% men and 44.97% women; mean age, 42.24 years) were included in this study. After an average follow-up of 3.13 ± 0.94 years, 4001 (1.99%) participants developed T2DM. Participants in the highest group of Cre/BW ratio (Q4) had lower weight, BMI, SBP, DBP, TC, TG, FPG, LDL-C, ALT, and AST, and consisted of more males and drinkers than for the other groups (Q1-3). The Q4 participants had higher Cre, Cre/BW ratio, HDL-C, BUN, and0.001.

| Table 1 Baseline characteristics of study participants according to quartiles of Cre/BW ratio |
|-----------------------------------------------|
|                                               |
| Number (mmol/L) | Overall | Q1 (< 1.062) | Q2 (≥ 1.062 to < 1.219) | Q3 (≥ 1.219 to < 1.396) | Q4 (≥ 1.396) | P-value |
| Number (mmol/L) | 206,658 | 50,165 | 50,164 | 50,163 | 50,166 |  
| Age (years)     | 42.24 ± 12.73 | 42.37 ± 11.69 | 42.11 ± 12.04 | 41.98 ± 12.67 | 42.50 ± 14.35 | <0.001 |
| Height (cm)     | 166.50 ± 83.3 | 166.61 ± 8.88 | 166.63 ± 8.46 | 166.62 ± 8.23 | 166.13 ± 7.91 | <0.001 |
| Weight (kg)     | 64.75 ± 12.33 | 70.98 ± 13.54 | 65.75 ± 11.73 | 63.08 ± 10.72 | 59.18 ± 9.40 | <0.001 |
| BMI (kg/m²)     | 23.24 ± 3.34 | 25.43 ± 3.50 | 23.55 ± 2.95 | 22.62 ± 2.80 | 21.38 ± 2.66 | <0.001 |
| SBP (mmHg)      | 119.04 ± 16.4 | 121.38 ± 16.81 | 118.77 ± 16.25 | 118.03 ± 15.90 | 117.98 ± 16.41 | <0.001 |
| DBP (mmHg)      | 74.16 ± 10.81 | 75.65 ± 11.31 | 74.20 ± 10.83 | 73.68 ± 10.54 | 73.11 ± 10.36 | <0.001 |
| FPG (mmol/L)    | 4.91 ± 0.61 | 4.99 ± 0.62 | 4.91 ± 0.61 | 4.88 ± 0.61 | 4.87 ± 0.61 | <0.001 |
| TC (mmol/L)     | 4.72 ± 0.89 | 4.79 ± 0.91 | 4.73 ± 0.89 | 4.70 ± 0.89 | 4.64 ± 0.88 | <0.001 |
| TG (mmol/L)     | 1.34 ± 1.03 | 1.51 ± 1.22 | 1.37 ± 1.04 | 1.30 ± 0.95 | 1.20 ± 0.83 | <0.001 |
| Cre/BW ratio    | 1.24 ± 0.27 | 0.94 ± 0.10 | 1.14 ± 0.04 | 1.30 ± 0.05 | 1.59 ± 0.22 | <0.001 |
| LDL-C (mmol/L)  | 3.62 ± 0.33 | 3.62 ± 0.33 | 3.62 ± 0.33 | 3.62 ± 0.33 | 3.62 ± 0.33 | <0.001 |
| HDL-C (mmol/L)  | 1.37 ± 0.23 | 1.36 ± 0.23 | 1.37 ± 0.23 | 1.38 ± 0.24 | 1.38 ± 0.23 | <0.001 |
| ALT (U/L)       | 22.99 ± 21.98 | 27.78 ± 25.98 | 24.53 ± 22.77 | 22.96 ± 21.36 | 20.68 ± 16.03 | <0.001 |
| AST (U/L)       | 24.11 ± 7.95 | 24.53 ± 7.84 | 24.12 ± 8.34 | 23.96 ± 7.43 | 23.82 ± 8.15 | <0.001 |
| BUN (mmol/L)    | 4.66 ± 1.15 | 4.44 ± 1.10 | 4.58 ± 1.11 | 4.70 ± 1.12 | 4.92 ± 1.22 | <0.001 |
| Cre (mg/dl)     | 0.79 ± 0.18 | 0.66 ± 0.13 | 0.75 ± 0.14 | 0.82 ± 0.14 | 0.94 ± 0.18 | <0.001 |
| Develop T2DM    | <0.001 |
| No              | 196,657 (98.01) | 48,542 (96.76) | 49,175 (97.80) | 49,388 (98.07) | 49,552 (98.52) | 
| Yes             | 4001 (1.99) | 1623 (3.24) | 989 (1.97) | 775 (1.54) | 614 (1.22) | 
| Sex (%)         | <0.001 |
| Men             | 110,431 (55.03) | 20,467 (40.8) | 25,616 (51.06) | 29,599 (59.01) | 34,749 (69.27) | 
| Women           | 90,227 (44.97) | 29,067 (59.2) | 24,548 (48.94) | 20,564 (40.99) | 15,417 (30.73) | 
| Smoking status (%) | <0.001 |
| Current         | 11,373 (5.67) | 2421 (4.83) | 2817 (5.62) | 2964 (5.91) | 3171 (6.32) | 
| Ever            | 2473 (1.23) | 505 (1.01) | 596 (1.19) | 677 (1.35) | 695 (1.39) | 
| Never           | 43,816 (21.84) | 10,504 (20.94) | 10,942 (21.81) | 11,015 (21.96) | 11,355 (22.63) | 
| No recorded     | 142,996 (71.26) | 36,735 (73.23) | 35,809 (71.38) | 35,507 (70.78) | 34,945 (69.66) | 
| Drinking status (%) | <0.001 |
| Current         | 1284 (0.64) | 292 (0.58) | 344 (0.69) | 354 (0.71) | 294 (0.59) | 
| Ever            | 8649 (4.31) | 1764 (3.52) | 2110 (4.21) | 2363 (4.71) | 2412 (4.81) | 
| Never           | 47,729 (23.79) | 11,374 (22.67) | 11,901 (23.72) | 11,939 (23.8) | 12,515 (24.95) | 
| No recorded     | 142,996 (71.26) | 36,735 (73.23) | 35,809 (71.38) | 35,507 (70.78) | 34,945 (69.66) | 
| Family history of diabetes (%) | <0.001 |
| No              | 196,452 (97.90) | 48,785 (97.25) | 49,059 (97.80) | 49,193 (98.07) | 49,415 (98.5) | 
| Yes             | 4206 (2.10) | 1380 (2.75) | 1105 (2.2) | 970 (1.93) | 751 (1.5) | 

BMI body mass index, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein, FPG fasting plasma glucose, TC total cholesterol, TG triglyceride, SBP systolic blood pressure, DBP diastolic blood pressure, Cre/BW creatinine to body weight, Cre concentration of creatinine, AST aspartate aminotransferase, ALT alanine aminotransferase, BUN blood urea nitrogen, T2DM type 2 diabetes mellitus, CI confidence interval, HR hazard ratio
and more smokers and a family history of diabetes than those with in the Q1-Q3 groups.

**Univariate analysis for T2DM**

Table 2 presents the results of the univariate analysis of the association between risk factors and incident T2DM. Using the univariate Cox proportional hazard model, we identified age, height, weight, SBP, DBP, FPG, TC, TG, LDL, ALT, AST, BUN, Cre, and family history of diabetes as being positively related to future risk of diabetes. Moreover, never smoking and HDL-C levels were negatively correlated. Furthermore, compared to men, women showed a lower risk of diabetes. Ever smoking was not associated with T2DM compared to current smoking.

As shown in Fig. 2, the Kaplan–Meier curve revealed that the cumulative risk of incident diabetes was markedly different among the Cre/BW ratio quartiles (log-rank test, P < 0.001) and decreased gradually with an increase in Cre/BW ratio, resulting in a maximum risk of diabetes in the lowest quartile.

**Relationship between Cre/BW ratio and incident T2DM in different models.**

We used Cox proportional hazard models to assess the independent effects of Cre/BW ratio (× 100) on the risk of incident T2DM (univariate and multivariate Cox proportional hazard models). Table 3 presents the effect sizes [hazard ratio (HR) and 95% confidence intervals (95% CI)]. According to the non-adjusted model, there was a negative relationship between the Cre/BW ratio (× 100) and incident T2DM, with an HR of 0.21 (0.18, 0.24). After adjusting for age, sex, height, FPG, SBP, DBP, TC, TG, LDL, HDL-c, BUN, AST, ALT, drinking status, smoking status, and family history of diabetes, the negative relationship between the Cre/BW ratio and incident T2DM did not change in the multivariate analysis [0.36 (0.31, 0.42)]. Participants who had a Cre/BW ratio in the highest quartile versus the lowest quartile had a half-decreased risk in the odds of the development of T2DM [0.52 (0.47, 0.58)] (P for trend <0.001).

**Dose–response association between Cre/BW ratio and incident T2DM**

We used the restricted cubic spline curves to evaluate the dose–response relationship between Cre/BW ratio (× 100) and incident T2DM. After adjusting for potential confounders, an L-shaped nonlinear relationship between the Cre/BW ratio (× 100) and T2DM was observed (Fig. 3). The risk of incident T2DM was negatively correlated with the Cre/BW ratio (× 100). The risk of developing T2DM decreased significantly with Cre/BW ratio (× 100) until it peaked at 0.86 [0.01 (0.00,0.10), P < 0.001]. When the Cre/BW ratio (× 100) was between 0.86 and 1.36, the risk ratio for developing T2DM was 0.22 (0.12,0.38), P <0.001. However, when the Cre/BW ratio (× 100) was > 1.36, the curve indicating the risk of developing T2DM became significantly flatter as the Cre/BW ratio (× 100) increased, with an HR of 0.73 (0.29,1.8), P = 0.49 (Table 4).

In Fig. 3, the solid line curve indicates the estimated risk of incident T2DM. The dotted lines represent point-wise 95% CIs adjusted for age, sex, height, FPG, SBP, DBP, TC, TG, LDL, HDL-C, BUN, AST, ALT, drinking status, smoking status, and family history of diabetes. As the Cre/BW ratio (× 100) increased, the slope of the

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**Table 2** Univariate analysis for type 2 diabetes mellitus

| Risk factor               | HR (95%CI) | P-value |
|---------------------------|------------|---------|
| Age (years)               | 1.07 (1.06,1.07) | <0.001 |
| Height (cm)               | 1.00 (1.00,1.01)  | 0.029   |
| Weight (kg)               | 1.05 (1.05,1.05)  | <0.001 |
| SBP (mmHg)                | 1.04 (1.04,1.04)  | <0.001 |
| DBP (mmHg)                | 1.05 (1.04,1.05)  | <0.001 |
| FPG (mmol/L)              | 10.43 (9.98,10.90) | <0.001 |
| TC (mmol/L)               | 1.43 (1.39,1.47)  | <0.001 |
| TG (mmol/L)               | 1.26 (1.25,1.28)  | <0.001 |
| HDL-C (mmol/L)            | 0.53 (0.47,0.61)  | <0.001 |
| LDL (mmol/L)              | 1.41 (1.34,1.49)  | <0.001 |
| ALT (U/L)                 | 1.00 (1.00,1.00)  | <0.001 |
| AST (U/L)                 | 1.01 (1.01,1.01)  | <0.001 |
| BUN (mmol/L)              | 1.24 (1.21,1.26)  | <0.001 |
| Cre (mg/dl)               | 1.67 (1.56,1.78)  | <0.001 |
| Sex (%)                   |             |         |
| Men                       | Ref         |         |
| Women                     | 0.48 (0.45,0.52) | <0.001 |
| Smoking status (%)        |             |         |
| Current                   | Ref         |         |
| Ever                      | 0.81 (0.64,1.04) | 0.097   |
| Never                     | 0.44 (0.38,0.49) | <0.001 |
| Not recorded              | 0.59 (0.53,0.65) | <0.001 |
| Drinking status (%)       |             |         |
| Current                   | Ref         |         |
| Ever                      | 0.46 (0.38,0.54) | <0.001 |
| Never                     | 0.42 (0.36,0.49) | <0.001 |
| Not recorded              | 0.49 (0.37,0.65) | <0.001 |
| Family history of diabetes (%) |       |         |
| No                        | Ref         |         |
| Yes                       | 1.7 (1.45,1.98)  | <0.001 |

Cre/BW = creatinine to body weight, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, LDL = low density lipoprotein, FPG = fasting plasma glucose, TC = total cholesterol, TG = triglyceride, SBP = systolic blood pressure, DBP = diastolic blood pressure, TyG = triglyceride-glucose, BUN = blood urea nitrogen, T2DM = type 2 diabetes mellitus, CI = confidence interval, HR = hazard ratio.
Fig. 2 Kaplan–Meier analysis of T2DM risk according to Cre/Bw ratio.

Table 3 Relationship between Cre/BW ratio and incident T2DM in different models

| Variable                  | Model 1          | Model 2          | Model 3          |
|---------------------------|------------------|------------------|------------------|
|                            | HR (95% CI)      | P value          | HR (95% CI)      | P value          | HR (95% CI)      | P value          |
| Cre/BW ratio (x 100)      | 0.21 (0.18~0.24) | <0.001           | 0.11 (0.1~0.13)  | <0.001           | 0.36 (0.31~0.42) | <0.001           |
| Cre/BW ratio quartiles    |                  |                  |                  |                  |                  |                  |
| Q1                        | Ref              |                  | Ref              |                  | Ref              |                  |
| Q2                        | 0.6 (0.56~0.65)  | <0.001           | 0.55 (0.51~0.59) | <0.001           | 0.72 (0.66~0.78) | <0.001           |
| Q3                        | 0.48 (0.44~0.52) | <0.001           | 0.39 (0.36~0.43) | <0.001           | 0.64 (0.58~0.7)  | <0.001           |
| Q4                        | 0.4 (0.36~0.44)  | <0.001           | 0.27 (0.24~0.29) | <0.001           | 0.52 (0.47~0.58) | <0.001           |
| P for trend               | <0.001           |                  | <0.001           |                  | <0.001           |                  |

Model 1 was not adjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, height, FPG, SBP, DBP, TC, TG, LDL, HDL-C, BUN, AST, ALT, drinking status, smoking status and family history of diabetes. Cre/BW creatinine to body weight.
curve showed a decreasing L-shaped trend. In addition, we found that the Cre/BW ratio remained non-linearly and negatively correlated with T2DM after removed the upper and the lower 0.25% of the data to fit the curves. (Additional file 1: Fig. S1).

Subgroup analyses

The participants were divided into subgroups according to age, sex, BMI, BUN, smoking status, drinking status, and family history of diabetes. Stratified analyses were performed to further explore the potential modification effect of the association between Cre/BW ratio (×100) (<0.86, 0.86–1.36 and ≥1.36) and the risk of incident T2DM by the various subgroups. (Table 5). The results showed that the association between Cre/BW ratio (×100) and incident T2DM was stable in the different subgroups. A stronger inverse association between Cre/BW ratio (×100) and the risk of incident T2DM was found in men (men vs. women, P interaction = 0.026); younger people [<40 (tertile 1) vs. 40– < 60 vs. ≥ 60 years old, P interaction < 0.001]; those with lower BUN (≤7.1 vs. >7.1 mmol/L, P interaction = 0.009); people who smoked more frequently [current (quartile 1) vs. ever vs. never vs. not-recorded, P interaction = 0.048]; and people who drank more frequently [current (quartile 1) vs. ever vs. never vs. not-recorded, P interaction = 0.049] (Table 5). Family history of diabetes (no vs. yes) did not significantly modify the association between Cre/BW ratio (×100) and the risk of incident T2DM (Table 5) (Additional file 2: Fig. S2, Additional file 3: Table S1).

Discussion

In this population-based retrospective cohort study, Cre/BW ratio was found to be negatively associated with the incidence of T2DM, independent of age, sex, height, FPG, SBP, DBP, TC, TG, LDL-C, BUN, AST, ALT, drinking status, smoking status, and family history of diabetes. We further revealed an L-shaped nonlinear relationship between the Cre/BW ratio and the risk of T2DM. The relationship was characterized as follows: the risk of developing T2DM decreased significantly with Cre/BW ratio (×100) until it peaked at 0.86 [0.00,0.10], P < 0.001. When the Cre/BW ratio (×100) was between 0.86 and 1.36, the risk ratio for developing T2DM was 0.22 (0.12,0.38), P < 0.001. However, when the Cre/BW ratio (×100) was >1.36, the curve showing the risk of developing T2DM became significantly flatter.

The skeletal muscle, which accounts for approximately 40% of the body weight, is the most significant metabolic organ and plays a vital role in the homeostasis regulation of glycometabolism and lipid metabolism throughout the body [18, 19]. Skeletal muscles can store about 60–80% of postprandial glucose [18]. During hyperinsulinemia-euglycemia episodes, the skeletal muscles account for 80–90% of the blood glucose [20]. Lower muscle mass may reduce the blood glucose intake [21]. In addition, muscle mass is negatively associated with IR and prediabetes, and IR is a critical pathogenic mechanism of diabetes [22]. Therefore, muscle quality is closely related to the occurrence of diabetes. It is well known that height-adjusted SMI, defined as appendicular skeletal muscle mass/height squared, is an important marker for sarcopenia [23]. However, an increase in both muscle mass and fat mass could lead to weight gain [24]. Thus, the proportion of muscle mass per body weight is essential. Multiple studies have reported that weight-adjusted appendicular skeletal

### Table 4 Threshold effect analysis of Cre/BW ratio on incident T2DM

| Outcome                          | HR (95% CI)       | P value |
|----------------------------------|------------------|---------|
| One-line linear regression model | 0.36 (0.31 ~ 0.42) | <0.001  |
| Three-piecewise linear regression model Cre/BW ratio < 0.86 | 0.01 (0.00,0.10) | <0.001  |
| Cre/BW ratio 0.86–1.36 | 0.22 (0.12,0.38) | <0.001  |
| Cre/BW ratio ≥ 1.36 | 0.73 (0.29,1.8) | 0.49     |
| Log-likelihood ratio test        | <0.001           |         |

Adjusted for age, sex, height, FPG, SBP, DBP, TC, TG, LDL-C, BUN, AST, ALT, drinking status, smoking status and family history of diabetes.
| Subgroup | N1 (< 0.86) | N2 (≥ 0.86, < 1.36) | N3 (≥ 1.36) | Cre/BW ratio (× 100) | P for. interaction |
|----------|-------------|---------------------|-------------|----------------------|-------------------|
| Sex      |             |                     |             |                      | 0.026             |
| Women    | 1 (Ref)     | 0.61 (0.52~0.71)    | 0.48 (0.38~0.6) | 0.44 (0.34~0.58)     | < 0.001           |
| Men      | 1 (Ref)     | 0.57 (0.5~0.65)     | 0.4 (0.34~0.46) | 0.34 (0.29~0.4)      | < 0.001           |
| Age      |             |                     |             |                      | < 0.001           |
| < 40     | 1 (Ref)     | 0.48 (0.38~0.6)     | 0.22 (0.16~0.31) | 0.09 (0.06~0.13)     | < 0.001           |
| ≥ 40, < 60 | 1 (Ref)   | 0.73 (0.6~0.89)     | 0.43 (0.36~0.52) | 0.33 (0.27~0.41)     | < 0.001           |
| ≥ 60     | 1 (Ref)     | 0.84 (0.68~1.03)    | 0.63 (0.5~0.78) | 0.7 (0.57~0.87)      | 0.001             |
| BUN      |             |                     |             |                      | 0.009             |
| ≤ 7.1    | 1 (Ref)     | 0.6 (0.54~0.66)     | 0.43 (0.38~0.49) | 0.34 (0.3~0.4)       | < 0.001           |
| > 7.1    | 1 (Ref)     | 0.33 (0.19~0.56)    | 0.21 (0.12~0.38) | 0.54 (0.35~0.83)     | 0.005             |
| Smoking status | | | | | | 0.048 | |
| Current  | 1 (Ref)     | 0.37 (0.26~0.53)    | 0.2 (0.13~0.32) | 0.18 (0.1~0.3)       | < 0.001           |
| Ever     | 1 (Ref)     | 0.52 (0.2~1.35)     | 0.27 (0.08~0.87) | 0.11 (0.03~0.42)     | 0.002             |
| Never    | 1 (Ref)     | 0.5 (0.39~0.64)     | 0.38 (0.28~0.52) | 0.37 (0.26~0.53)     | < 0.001           |
| No recorded | 1 (Ref) | 0.81 (0.71~0.91)    | 0.69 (0.61~0.79) | 0.4 (0.34~0.47)      | < 0.001           |
| Drinking status | | | | | | 0.049 | |
| Current  | 1 (Ref)     | 0.30 (0.10~0.92)    | 0.27 (0.07~1.1) | 0.11 (0.02~0.67)     | 0.035             |
| Ever     | 1 (Ref)     | 0.34 (0.21~0.55)    | 0.20 (0.10~0.38) | 0.21 (0.09~0.46)     | < 0.001           |
| Never    | 1 (Ref)     | 0.50 (0.40~0.62)    | 0.34 (0.26~0.45) | 0.3 (0.22~0.41)      | < 0.001           |
| No recorded | 1 (Ref) | 0.63 (0.57~0.71)    | 0.46 (0.4~0.53)  | 0.4 (0.34~0.47)      | < 0.001           |
muscle mass, but not height-adjusted SMI, is associated with cardiometabolic risk factors and IR [22, 25–28]. Moreover, weight-adjusted appendicular skeletal muscle mass is associated with incident diabetes [12], metabolic syndrome [29], and non-alcoholic fatty liver disease (NAFLD) [30–32]. This is because low-weight-adjusted SMI is associated with an increase in visceral fat, which in turn is also associated with the occurrence of diabetes [33]. Cre is an alternative marker of skeletal muscle mass, and its levels are positively correlated with skeletal muscle mass [13, 34, 35]. Therefore, weight-adjusted SMI was positively associated with the Cre/BW ratio. In addition, in previous studies, Cre/BW ratios have been confirmed to be associated with an increased risk of NAFLD, which has been confirmed to be positively associated with diabetes [7, 36–38]. Based on these findings, the Cre/BW ratio is associated with the incidence of diabetes.

Recently, a study indicated that Cre/BW is associated with incident diabetes and proposed that it predicts future diabetes and NAFLD [14, 16]. A cohort study of 9,659 men and 7,417 women with a follow-up mean (SD) of 5.6 (3.5) and 5.4 (3.4) years, respectively, showed that, compared to participants in the highest quartile of Cre/BW, participants in the lowest quartile had a higher risk of diabetes (relative risk 0.42 (0.32–0.54, P < 0.001) in men and 0.55 (0.34–0.89, P = 0.014) in women), after adjusting for age, FPG, alcohol consumption, exercise, and smoking [14, 16]. Moreover, Hashimoto et al. found that Cre/BW was negatively associated with incident diabetes (adjusted HR 0.84, 95% CI 0.80–0.88, P < 0.001 for men and 0.88, 0.81–0.96, P = 0.003 for women) [14]. In addition, a cohort study of Chinese and Japanese found that Cre/BW was negatively correlated with the occurrence of NAFLD [16]. Based on the positive relationship between fatty liver and the onset of diabetes [36], these conclusions are consistent with our findings (Cre/BW as continuous variable: HR 0.44 [0.34, 0.58] for women; HR 0.34 [0.29, 0.4] for men; P for interaction = 0.026). Moreover, in our study, the relationship between Cre/BW and diabetes mellitus showed different HRs across different age groups. The HR and 95% CI for incident diabetes mellitus associated with Cre/BW were 0.09 (0.06,0.13) and 0.7 (0.57,0.87) for adults < 40 and > 60 years, respectively. In contrast, our study found a nonlinear relationship between serum Cre/BW and incident diabetes. As the Cre/BW ratio increased, the risk of developing T2DM decreased rapidly until the Cre/BW ratio (∗100) reached 0.86. When the Cre/BW ratio (∗100) was > 1.36, the curve indicating the risk of developing T2DM became significantly flatter. These results may be because fat is essential to the body, and the proportion of fat mass must be maintained in a stable state. However, at the same time, we also found that the risk of diabetes decreased with the ratio increased, the risk of diabetes did not decrease significantly when the Cre/BW ratio (∗100) was ≥ 1.36. These results suggest Cre/BW ratio as a potentially viable predictor in people who want to prevent diabetes through weight loss. Further, the results suggest that prevention of T2DM development by aggressive muscle mass gain and weight loss is only optimal when the Cre/BW ratio (∗100) is < 0.86 and is slightly less effective when the Cre/BW ratio (∗100) is > 1.36. However, when the Cre/BW ratio (∗100) is > 1.36, increasing muscle mass and reducing body weight may not be as effective in preventing the onset of T2DM. When the Cre/BW ratio (∗100) was increased by 1 unit, the incidence of T2DM decreased by 99%. However, when the Cre/BW ratio (∗100) exceeded 1.36, for every 1 unit increase in the Cre/BW ratio (∗100) the T2DM incidence only decreased by 27%; further research is needed to verify this.

Our study had several strengths. (1) Compared to previous similar studies, our study had a relatively large sample size; (2) correlation between the Cre/BW ratio and T2DM was performed in China for the first

### Table 5 (continued)

| Subgroup | N1 (<0.86) | N2 (≥0.86, <1.36) | N3 (≥1.36) | Cre/BW ratio (∗100) | P for interaction |
|----------|------------|------------------|------------|---------------------|------------------|
| Family history of diabetes |            |                  |            |                     |                  |
| No       | <0.001     | <0.001           | <0.001     |                     | 0.997            |
| 1(Ref)   | 0.59 (0.53–0.66) | 0.42 (0.37–0.48) | 0.36 (0.31–0.42) |     |                  |
| Yes      | <0.001     | <0.001           | <0.001     |                     |                  |
| 1(Ref)   | 0.54 (0.34–0.85) | 0.37 (0.19–0.7) | 0.27 (0.12–0.59) |     |                  |
| 0.008    | 0.002      | 0.001            |           |                     |                  |

Cre/BW creatinine to body weight, BUN blood urea nitrogen, T2DM type 2 diabetes mellitus, CI confidence interval, HR hazard ratio
time; and (3) To reduce the contingency of the results and improve the robustness, we treated the Cre/BW ratio as continuous and classification variables with univariate and multivariate Cox proportional hazard models, and found saturation between the Cre/BW ratio and incidence of T2DM.

In the subgroup analysis, we used stratified linear regression models and likelihood ratio tests to identify modifications and interactions, to obtain stable results in the different subgroups. However, in adults aged < 40 years, we found that the risk of developing T2DM decreased more significantly with an increased Cre/BW ratio. Correspondingly, people > 60 years old did not have as high diabetes prevention effects through weight loss and controlling of the body fat rates as did people < 40 years old.

There are some limitations to our study. (1) The participants were all Chinese. Therefore, the universality and extrapolation of this study results are weak. However, one-quarter of the global population with diabetes live in China. Our data were obtained from multiple centers in China with a wide geographical region and age range, making the results widely applicable to the Chinese population and even the global Chinese people. Nevertheless, further research on the Cre/BW ratio in different populations needs to be evaluated, given the racial differences. (2) T2DM was not diagnosed using a two-hour oral glucose tolerance test, which may have resulted in an underestimation of the number of cases of diabetes. (3) Raw data were limited; hence, we could not adjust for waist circumference, education level, and the intensity and frequency of exercise, which may affect the relationship between Cre/BW ratio and incident T2DM. (4) The raw data did not include information on the types and amounts of foods and beverages (including all types of water) consumed during the 24 h before the examination, which may have affected the blood levels of TG and glucose. (5) Data were collected between 2004 and 2015, with a difference of almost ten years in between, for some individuals in this study. However, according to the median follow-up years used for the stratification, the association between the Cre/BW ratio and incident T2DM was stable. (6) In this study, we did not distinguish between type 1 and T2DM. However, since T2DM accounts for approximately 95% of all diabetes cases, our findings may represent the population with T2DM. (7) As the population in our study was mainly those with physical examination data, this might have resulted in an under-representation of the population with chronic kidney disease (CKD) and a population selection bias. Therefore, the relationship between the Cre/BW ratio and incident T2DM in the CKD population may not be well represented.

**Conclusions**

In conclusion, an increase in the Cre/BW ratio was independently associated with a lower incidence of T2DM in this retrospective study during a 3.1-year follow-up of Chinese participants. The Cre/BW ratio is a negative and independent risk factor for T2DM events in the Chinese population. An L-shaped negative curvilinear association between Cre/BW ratio and incident T2DM was present, with a saturation effect predicted at 0.86 and 1.36 of Cre/BW ratio (× 100). Further studies are required to evaluate the predictive value of the Cre/BW ratio for T2DM.

**Abbreviations**

T2DM: Type 2 diabetes mellitus; IR: Insulin resistance; Cre/BW: Creatinine to body weight; SMI: Skeletal muscle mass index; FPG: Fasting plasma glucose; BMI: Body mass index; HDL-c: High-density lipoprotein cholesterol; LDL: Low density lipoprotein; TC: Total cholesterol; TG: Triglycerides; Cre: Serum creatinine; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

**Supplementary Information**

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Authors’ contributions
The author designed the research, analyzed the data, and drafted the manuscript by himself. The author read and approved the final manuscript.

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Availability of data and materials
Data can be downloaded from the DRYAD database (http://www.Dryad.org).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable/all data used for the present study have been anonymized, and the submission does not include information that may identify individual persons.

Competing interests
The author declares no conflicts of interest in this work.

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References

1. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368(9548):1681–8.

2. Lancet Diabet Endocrinol. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. 2014;28(6):634–47.

3. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. PharmacoEconomics. 2015;33(9):811–31.

4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):14–14.

5. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes in adults since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet (London, England). 2016;387(10027):1513–30.

6. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA. 2017;317(24):2515–23.

7. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. J Clin Biochem Nutr. 2017;61(2):118–22.

8. Mitsuhashi K, Hashimoto Y, Tanaka M, et al. Combined effect of body mass index and waist-height ratio on incident diabetes: a population-based cohort study. J Clin Biochem Nutr. 2017;61(2):118–22.

9. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102–7.

10. Lien AS, Hwang JS, Jiang YD. Diabetes related fatigue sarcopenia, frailty. J Diabetes Investig. 2018;9(1):13–4.

11. Moon SS. Low skeletal muscle mass is associated with insulin resistance, diabetes, and metabolic syndrome in the Korean population: the Korea National Health and Nutrition Examination Survey (KNHANES). 2009–2010. Endocr J. 2014;61(1):61–70.

12. 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.

13. Baumann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008;3(2):348–54.

14. Hashimoto Y, Okamura T, Hamaguchi M, Obora A, Kojima T, Fukui M. Creatinine to body weight ratio is associated with incident diabetes: a population-based cohort study. J Clin Med. 2020. https://doi.org/10.3390/jcm9010227.

15. Chen Y, Zhang XP, Yuan J, et al. Association of body mass index and age with incident diabetes in Chinese adults: a population-based cohort study. BMJ Open. 2018;8(9):e21768.

16. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Creatinine-to-bodyweight ratio is a predictor of incident non-alcoholic fatty liver disease: a population-based longitudinal study. Hepatol Res. 2020;50(1):57–66.

17. Inoue Y, Alonso A, Obila B, et al. Oral bisphosphonates are associated with increased risk of subtrochanteric and diaphyseal fractures in elderly women: a nested case-control study. BMJ Open. 2013. https://doi.org/10.1136/bmjopen-2012-002091.

18. Kats L, Glickman MG, Rappoport S, Ferrannini E, DeFronzo RA. Splanchnic and peripheral disposal of oral glucose in man. Diabetes. 1983;32(7):675–9.

19. Chen Q, Rong P, Xu D, et al. Radia deficiency in skeletal muscle causes hyperlipidemia and hepatosteatosis by impairing muscle lipid uptake and storage. Diabetes. 2017;66(9):2387–99.

20. Duncan BB, Schmidt ML, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes. 2003;52(7):799–805.

21. Someya Y, Tamura Y, Suzuki R, et al. Characteristics of glucose metabolism in overweight Japanese women. J Endocr Soc. 2018;2(3):279–89.

22. Lim S, Kim JH, Yoon JW, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care. 2010;33(7):1652–4.

23. Chen LK, Liu LX, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.

24. Hashimoto Y, Osaka T, Fukuda T, Tanaka M, Yamazaki M, Fukui M. The relationship between hepatic steatosis and skeletal muscle mass index in men with type 2 diabetes. Endocr J. 2016;63(10):877–84.

25. Kim TN, Park MS, Lee EJ, et al. Comparisons of three different methods for defining sarcopenia: an aspect of cardiometabolic risk. Sci Rep. 2017;7(1):6491.

26. Fujishima T, Miyachi M, Imitusu M, et al. Comparison between clinical significance of height-adjusted and weight-adjusted appendicular skeletal muscle mass. J Physiol Anthropol. 2017;36(11):14.

27. Takamura T, Kita Y, Nakagem M, et al. Weight-adjusted lean body mass and calf circumference are protective against obesity-associated insulin resistance and metabolic abnormalities. Heliyon. 2017;3(7):e0347.

28. Scott D, Park MS, Kim TN, et al. Associations of low muscle mass and the metabolic syndrome in Caucasian and Asian middle-aged and older adults. J Nutr Health Aging. 2016;20(3):248–55.

29. Park BS, Yoon JS. Relative skeletal muscle mass is associated with development of metabolic syndrome. Diabetes Metab J. 2013;37(6):458–64.

30. Osaka T, Hashimoto Y, Okamura T, et al. Reduction of fat to muscle mass ratio is associated with improvement of liver stiffness in diabetic patients with non-alcoholic fatty liver disease. J Clin Med. 2019. https://doi.org/10.3390/jcm8122175.

31. Shida T, Oshida N, Oh S, Okada K, Shoda J. Progressive reduction in skeletal muscle mass to visceral fat area ratio is associated with a worsening of the hepatic conditions of non-alcoholic fatty liver disease. Diabetes Metab Syndr Obes. 2019;12:495–503.

32. Mizuno N, Seko Y, Kataeki S, et al. Increase in the skeletal muscle mass to body fat mass ratio predicts the decline in transaminase in patients with nonalcoholic fatty liver disease. J Gastroenterol. 2019;54(2):160–70.

33. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007;56(4):1010–3.

34. Heymsfield SB, Atteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr. 1983;37(3):478–94.

35. Nishida K, Hashimoto Y, Kaji A, et al. Creatinine/(cystatin C x body weight) ratio is associated with skeletal muscle mass index. Endocr J. 2017;64(6):817–25.

36. Katz L, Glickman MG, Rappoport S, Ferrannini E, DeFronzo RA. Splanchnic and peripheral disposal of oral glucose in man. Diabetes. 1983;32(7):675–9.
37. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71(4):793–801.
38. Fukuda T, Hamaguchi M, Kojima T, et al. The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals. Liver Int. 2016;36(2):275–83.

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