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# Relationship Between Creatinine and Body Weight Ratio and Diabetes Mellitus in a Chinese Cohort Study

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# Abstract

**Background:** Research on the relationship between Creatinine to Body Weight Ratios (Cre/BW ratios) and the prevalence of diabetes is still lacking. The aim of this study was to investigate the potential association between Cre/BW ratios and incident of diabetes in Chinese adults.

**Methods:** This retrospective study was conducted in 199,526 patients from Rich Healthcare Group in China from 2010 to 2016. The participants were divided into quartiles of the Cre/BW ratios. Multivariate multiple imputation and dummy variables were used to handle missing values. Cox proportional-hazards regression was used to investigate the association of Cre/BW and diabetes. Generalized additive models(GAM) were used to identify non-linear relationships.

**Results:** Of all participants,after handling missing values and adjustment for potential confounders, the multivariate Cox regression analysis results showed that Cre/BW ratios was inversely associated with diabetes risk( HR: 0.268; 95% CI:0.229 to 0.314, P < 0.00001).For men, the hazard ratios(HRs) of incident diabetes was 0.255(95%CI: 0.212-0.307);and for women HR= 0.297 (95%CI: 0.218-0.406).Moreover, sensitivity analysis confirmed the stability of the results. Furthermore, GAM revealed a saturation effect on the independent association between Cre/BW and incident of diabetes.

**Conclusions:** This study demonstrated that increased Cre/BW is negatively correlated with incident of diabetes in Chinese for the first time. And we found that the relationship between Cre/BW and incident of diabetes was non-linear.


# Introduction

Diabetes mellitus(DM) is a major health issue associated with considerable morbidity and mortality, which contributes to the global health burden. There are currently 351.7 million people of working age (20–64 years) with diagnosed or undiagnosed diabetes in 2019. This number is expected to increase to 417.3 million by 2030 and to 486.1 million by 2045. These data point to a significant increase in the diabetes population of the aging societies in the future, bringing greater public health and economic challenges[1, 2]. Not only has it been reported in adults, but there is also evidence that type 2 diabetes(T2DM) is increasing in children and adolescents, leading to early complications and serious adverse health consequences[3]. Therefore, it is essential to identify the occurrence of diabetes early in order to establish preventive strategies for this disease.

Skeletal muscle is one of the main target organs of insulin and plays an important role in maintaining glucose homeostasis[4, 5]. A reduction in the skeletal muscle mass leads to a decrease in systemic glucose uptake[6]. It contributes to insulin resistance both in non-obese and obese individuals[7, 8]. Skeletal muscle mass is associated with insulin resistance(IR), non-alcoholic fatty liver (NAFLD), DM, metabolic syndrome(MS), and cardiovascular disease(CVD)[9–11]. Insulin can enhance the synthesis of muscle protein and inhibit the breakdown of muscle protein. Both insulin resistance and insulin deficiency can cause a decrease in insulin signals in the skeletal muscle, affect the regulation of skeletal

muscle protein balance, and may cause a decline in skeletal muscle quality[10]. Abnormal muscle protein metabolisms and skeletal muscle atrophy have been observed in patients with T2DM[6, 12]. Therefore, decreased skeletal muscle mass is related to the occurrence and development of insulin resistance and diabetes.

Serum creatinine(Cre) is considered to be an inexpensive and easy to measure index instead of evaluating skeletal muscle quality[13]. Recently, studies have shown that Cre to body weight ratios(Cre/BW ratios), an interesting new indicator, is closely related to T2DM[14] and NAFLD[15, 16]. Hashimoto et al. proved Cre/BW ratios may predict future diabetes risks and is inversely related to incident diabetes in the Japanese population who underwent a medical health check-up program[14]. However, there is no report about Cre/BW ratios with diabetes to date in Chinese people, to address these issues, we conducted a study to investigate the relationship between Cre/BW ratios and incident of diabetes.

## Methods

# Study population and design

The present data were obtained from the public database 'DATADRYAD' (www.Datadryad.org), which was published by Chen et al[17]. The website permitted users to download freely, and the data providers have waived all copyright and related ownership of these data. The ethics committee has authorized the previous study, therefore the present study did not require any study approval or informed consent.

The database was provided by the Rich Healthcare Group in China, and the study recruited 685,277 participants who were at least 20 years old and received at least two health checks between 2010 and 2016. In the previous study[17], the data have been screened according to the following exclusion criteria, as follows:(1) a deficiency of available information about weight, height, gender, fasting plasma glucose(FPG) value at baseline, (2) participants with extreme BMI values (< 15 kg/$m^2$ or > 55kg/$m^2$), (3) individuals with visit intervals less than 2 years, (4) diabetes at baseline or undefined diabetes status at follow-up. Finally, they enrolled 211,833 participants in the analysis. The specific details of the inclusion/exclusion criteria and results have been presented in the retrospective cohort study[17]. For our further research, Cre/BW ratios was calculated as Cre divided by body weight, and we excluded missing values (n = 11,175)11175 and excluded outliers of Cre/BW ratios (< means minus 3 standard deviation (SD) or > means plus 3SD) (n = 1,132)[18]. Ultimately, this retrospective study was conducted in 199,526 participants (109,590 male and 89,936 female).

# Data Collection and Measurements

The researchers collected and measured the study cohort's information and described it in detail previously[17, 19]. Briefly, questionnaires were administered to collect information on demographics (age, sex), lifestyle (smoking, alcohol use), family history of disease and personal medical history in each visit. Body weight(BW) was measured, while subjects were minimally clothed without shoes and recorded to

the nearest 0.1 kg. Height was measured to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by square of height ($m^2$). Blood pressure (BP) was measured using a mercury sphygmomanometer. Smoking status was defined as: former smoker, current smoker and never smoker. Drinking status was defined as: former drinker, current drinker and never drinker. Venous Blood was drawn after at least a 10 hours fast at each visit and measured on autoanalyzers for fasting plasma glucose (FPG), Triglyceride(TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Serum creatinine (Cre). FPG of ≥ 7.00 mmol/L and/or self-reported diabetes during the follow-up period was defined as incident diabetes.

# Statistical analysis

Statistical analyses with the outcomes were run in the statistical software package R (http://www.R-project.org,The R Foundation) and Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). First, the patients were divided based on the quartiles of baseline Cre/BW ratios. Data are expressed as mean ± standard deviation for continuous variables (normally distributed) and median (interquartile range) for continuous variables (skewed distributed), and n (percentage) for categorical variables. The One-Way ANOVA (normal distribution), Kruskal Wallis H(skewed distribution) test and chi-square tests (categorical variables) were used to determine any statistical differences between the means and proportions of the groups.Subsequently, we checked the collinearity of variables by calculating the variance inflation factor using multiple linear regression analysis[20]. Cox proportional-hazards regression model was used to estimate the risk of Cre/BW ratios on diabetes by calculating the hazard ratio (HR) and 95% confidence interval (CI) adjusted for age, gender, SBP, DBP, FPG, TG, HDL-C, LDL-C, smoking status, drinking status and family history of diabetes. To quantify the strength of the association, the unadjusted and adjusted hazard ratio (HR) and 95% confidence intervals (CIs) were estimated and reported. We adjusted for variables that changed the matched hazard ratio by at least 10% when added to the model[21]. All of the models would be adjusted for none (model I), age, gender, SBP, DBP, smoking status, drinking status and family history of diabetes (model II), model2 + FPG, TG, HDL-C, LDL-C, (model III) according to the recommendation of the STROBE statement[22]. We converted the Cre/BW into a categorical variable and calculated the P for trend. The purpose was to verify the results of Cre/BW as the continuous variable and to observe the possibility of nonlinearity. Besides, we performed a weighted generalized additive model (GAM) model[23] to adjust for the covariates in GAM model, because the generalized linear model has limitations in dealing with nonlinearities.

In addition, to maximize statistical power and minimize bias, we dealt with missing values of covariates by the following analysis in the study. While the missing data was less than 20%, we used multivariate multiple imputation[24–26] with chained equations to impute missing values. Otherwise, dummy variables[27] were used to indicate missing continuous variables, and we treated the missing value of the categorical variable as a new group of the categorical variable[28]. We repeated baseline and Cox proportional-hazards regression analyses with the original data cohort for comparison as a sensitivity analysis.

Next, Generalized additive models was also used to observe the relationship between the Cre/BW and diabetes risk[29]. If the non-linear correlation was observed in the smoothing plot, a two-piecewise linear regression model was applied to investigate the threshold effect according to the smoothing plot. When the ratio between Cre/BW and diabetes risk appears obvious in the smoothed curve, the recursive method automatically calculates the inflection point, where the maximum model likelihood will be used. Additionally, Kaplan-Meier analysis and log-rank tests were performed to evaluate the difference between Cre/BW quartiles. Furthermore, considering the potential effects of sex in the Cre/BW ratios, we investigated the following/above statistical analyses in men and women separately.

Statistical significance was defined as $P < 0.05$ (two-sided).

## Results

Ultimately, a total of 199,526 participants (109 590 male and 89 936 female) were included in our analysis.The mean years of follow-up was 3.13 ± 0.94 years and the mean Cre/BW was 1.09 ± 0.22.The average age of the participants was 42.34 ± 12.87 years of men and 41.99 ± 12.38 years of women. The mean Cre in men and women were 79.67 ± 11.30 and 57.84 ± 8.98 umol/L, and the mean BMI were 24.22 ± 3.23 and 22.09 ± 3.08 kg/m2, respectively.2872 men and 1103 women were newly diagnosed with diabetes at the end.

# Baseline characteristics of the study participants

Baseline characteristics of original data were summarized in Table 1.We divide the participants into subgroups using Cre/BW quartiles,quartile 1 (Q1), Cre/BW < 0.94; quartile 2 (Q2), 0.94 ≤ Cre/BW < 1.08; quartile 3 (Q3), 1.08 ≤ Cre/BW < 1.23 and quartile4(Q4) Cre/BW > 1.23. In the lowest Cre/BW group, we found that participants generally had higher BMI, SBP, DBP, FPG, TC, LDL-C.and had lower creatinine. Moreover, Supplementary Table 1(Table S1) listed the baseline characteristics of males and females, respectively. There are significant differences in the smoking status and drinking status of different groups of men, however, no significant differences were found in women.

Table 1
Baseline Characteristics of participants according to the quartiles of Cre/BW ratios

| Cre/BW | Q1(≤ 0.94) | Q2(0.94 to ≤ 1.08) | Q3(1.08 to ≤ 1.23) | Q4(> 1.23) | P-value |
|---|---|---|---|---|---|
| AGE(years) | 42.37 ± 11.69 | 42.12 ± 12.04 | 41.97 ± 12.65 | 42.27 ± 14.09 | < 0.001 |
| GENDER | | | | | < 0.001 |
| Male | 20330 (40.76%) | 25453 (51.02%) | 29326 (58.89%) | 34481 (69.01%) | |
| Female | 29548 (59.24%) | 24431 (48.98%) | 20475 (41.11%) | 15482 (30.99%) | |
| Height(cm) | 166.61 ± 8.68 | 166.63 ± 8.46 | 166.62 ± 8.23 | 166.21 ± 7.90 | < 0.001 |
| Weight(kg) | 71.00 ± 13.54 | 65.78 ± 11.74 | 63.11 ± 10.73 | 59.34 ± 9.40 | < 0.001 |
| BMI(kg/$m^2$) | 25.43 ± 3.50 | 23.56 ± 2.95 | 22.63 ± 2.80 | 21.42 ± 2.66 | < 0.001 |
| SBP(mmHg) | 121.38 ± 16.81 | 118.80 ± 16.26 | 118.02 ± 15.89 | 117.84 ± 16.27 | < 0.001 |
| DBP(mmHg) | 75.65 ± 11.32 | 74.20 ± 10.83 | 73.70 ± 10.55 | 73.08 ± 10.31 | < 0.001 |
| FPG(mmol/L) | 4.79 ± 0.92 | 4.73 ± 0.90 | 4.70 ± 0.89 | 4.64 ± 0.88 | < 0.001 |
| TC(mmol/L) | 4.99 ± 0.62 | 4.92 ± 0.61 | 4.88 ± 0.61 | 4.87 ± 0.61 | < 0.001 |
| TG(mmol/L) | 1.51 ± 1.23 | 1.37 ± 1.04 | 1.30 ± 0.96 | 1.19 ± 0.84 | < 0.001 |
| HDL-C(mmol/L) | 1.34 ± 0.31 | 1.37 ± 0.31 | 1.38 ± 0.31 | 1.39 ± 0.30 | < 0.001 |
| LDL-C(mmol/L) | 2.81 ± 0.70 | 2.77 ± 0.68 | 2.76 ± 0.68 | 2.73 ± 0.66 | < 0.001 |
| Cre(umol/L) | 58.59 ± 11.38 | 66.34 ± 11.94 | 72.49 ± 12.41 | 81.90 ± 13.44 | < 0.001 |
| Smoking status | | | | | < 0.001 |

Values are n(%) or mean ± SD

BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, fasting plasma glucose; TC, Total cholesterol; LDL-C, Low-density lipid cholesterol

| Cre/BW | Q1(≤ 0.94) | Q2(0.94 to ≤ 1.08) | Q3(1.08 to ≤ 1.23) | Q4(> 1.23) | P-value |
|---|---|---|---|---|---|
| Never smoker | 10453 (78.22%) | 10863 (76.18%) | 10942 (75.16%) | 11284 (74.59%) | |
| Ever smoker | 505 (3.78%) | 590 (4.14%) | 673 (4.62%) | 691 (4.57%) | |
| Current smoker | 2405 (18.00%) | 2807 (19.68%) | 2943 (20.22%) | 3154 (20.85%) | |
| Drinking status | | | | | < 0.001 |
| Never drinker | 11313 (84.66%) | 11826 (82.93%) | 11865 (81.50%) | 12412 (82.04%) | |
| Ever drinker | 1758 (13.16%) | 2094 (14.68%) | 2341 (16.08%) | 2420 (16.00%) | |
| Current drinker | 292 (2.19%) | 340 (2.38%) | 352 (2.42%) | 297 (1.96%) | |
| Family history of diabetes | | | | | < 0.001 |
| NO | 48504 (97.25%) | 48783 (97.79%) | 48842 (98.07%) | 49205 (98.48%) | |
| YES | 1374 (2.75%) | 1101 (2.21%) | 959 (1.93%) | 758 (1.52%) | |
| Values are n(%) or mean ± SD | | | | | |
| BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, fasting plasma glucose; TC, Total cholesterol; LDL-C, Low-density lipid cholesterol | | | | | |

# The processing of missing values

The dataset contained 20 missing values of SBP, 21 of DBP, 3102 of TG(accounting for 3.93% of the total data), 84 309 of HDL-C and LDL-C(43.3%, respectively),142,216 of smoking and drinking status(71.3%, respectively).(listed in Table S2). And then we compared the original and complete data with a sensitivity analysis(Table S3). There were significant differences between original and complete data($P < 0.05$).To evaluate the impact of the bias caused by not counting for the missing data, we performed the following analysis.We respectively treated missing data of smoking and drinking status as a categorical variable and used multiple imputation, based on 5 replications and a chained equation approach method for missing data of SBP, DBP, TG, HDL-C,LDL-C(Table S4). Interestingly, after repeated sensitivity analysis, there was still distinct difference in HDL-C and LDL-C between pre-imputation and post-imputation($P < 0.001$). Thus, after multiple imputation at SBP, DBP and TG, dummy variables were used to estimate the missing values of HDL-C and LDL-C.In addition, we treated the missing value of smoking and drinking status as a new group of the categorical variable, respectively.

# The multivariate analysis of Cre/BW with DM risk

First, we conducted screening variables collinearity diagnostics, and the results and details are presented in Supplementary Table 2(Table S2). Secondly, the results of Cox proportional-hazards regression analysis after missing value processing were shown in Table 2.Cre/BW was negatively associated with incident diabetes(HR = 0.095, 95% confidence interval (CI):0.081 to 0.111, P < 0.00001) in crude model.In the adjusted model I (adjusted age, gender, family history of diabetes, smoking and drinking status), we could also detect the relationship (HR: 0.092, 95%CI: 0.078–0.108). After adjusting for model II, the result did not have obvious changes (adjusted age, gender, SBP, DBP, FPG, TG, HDL-C, LDL-C, smoking and drinking status, family history of diabetes), (HR: 0.268, 95%CI: 0.229–0.314). For the purpose of sensitivity analysis, we also handled Cre/BW as categorical variable (Quartile),the top quartile had 53.9% decline of diabetes risk when compared with the bottom quartile in the model II, and found that the trend across the quartiles was significant(P for trend < 0.00001). Then GAM was performed to insert the continuity covariate into the equation as a curve. It generally remained consistent with the GAM (HR: 0.314; 95% CI:0.226 to 0.369, P < 0.00001), which demonstrated the robustness of the results.Thirdly, we compared the risk relationship between Cre/BW and diabetes risk in different missing processing modes by multiple regression.The result retained a negative association between Cre/BW and incident diabetes in different modes. In addition, when the covariates are not adjusted, the HRs of incident diabetes in mode that multiple and dummy variables were used to estimate the missing values of continuous variable was same as the original datas'HRs.It seems that the result is more reliable.

Table 2
Relationship between Cre/BW and the incident of diabetes in different models

| Queue | | Crude model (HR,95%CI,P) | Model I (HR,95%CI,P) | Model II (HR,95%CI,P) | GAM (HR,95%CI,P) |
|---|---|---|---|---|---|
| Queue I | Cre/BW | 0.095 (0.081, 0.111) < 0.00001 | 0.092 (0.078, 0.108) < 0.00001 | 0.268 (0.229, 0.314) < 0.00001 | 0.314 (0.266, 0.369) < 0.00001 |
| | Cre/BW (quartile) | | | | |
| | Q1 | Ref | Ref | Ref | Ref |
| | Q2 | 0.565 (0.522, 0.612) < 0.00001 | 0.585 (0.540, 0.634) < 0.00001 | 0.711 (0.656, 0.770) < 0.00001 | 0.724 (0.668, 0.784) < 0.00001 |
| | Q3 | 0.413 (0.379, 0.451) < 0.00001 | 0.431 (0.395, 0.471) < 0.00001 | 0.622 (0.570, 0.680) < 0.00001 | 0.654 (0.598, 0.714) < 0.00001 |
| | Q4 | 0.317 (0.288, 0.348) < 0.00001 | 0.303 (0.275, 0.334) < 0.00001 | 0.506 (0.459, 0.558) < 0.00001 | 0.554 (0.502, 0.612) < 0.00001 |
| | P for trend | < 0.00001 | < 0.00001 | < 0.00001 | < 0.00001 |
| Queue II | Cre/BW | 0.095 (0.081, 0.111) < 0.00001 | 0.066 (0.049, 0.090) < 0.00001 | 0.182 (0.121, 0.273) < 0.00001 | 0.201 (0.134, 0.302) < 0.00001 |
| | Cre/BW (quartile) | | | | |
| | Q1 | Ref | Ref | Ref | Ref |
| | Q2 | 0.565 (0.522, 0.612) < 0.00001 | 0.589 (0.508, 0.682) < 0.00001 | 0.690 (0.571, 0.833) 0.00012 | 0.714 (0.590, 0.865) 0.00056 |
| | Q3 | 0.413 (0.379, 0.451) < 0.00001 | 0.376 (0.318, 0.444) < 0.00001 | 0.529(0.428, 0.655) < 0.00001 | 0.552(0.446, 0.685) < 0.00001 |
| | Q4 | 0.317 (0.288, 0.348) < 0.00001 | 0.249 (0.206, 0.300) < 0.00001 | 0.436 (0.340, 0.557) < 0.00001 | 0.461 (0.359, 0.592) < 0.00001 |
| | P for trend | < 0.00001 | < 0.00001 | < 0.00001 | < 0.00001 |
| Queue III | Cre/BW | 0.146 (0.124, 0.170) < 0.00001 | 0.092 (0.078, 0.109) < 0.00001 | 0.110 (0.094, 0.130) < 0.00001 | 0.143 (0.121, 0.169) < 0.00001 |
| | Cre/BW (quartile) | | | | |
| | Q1 | Ref | Ref | Ref | Ref |

| Queue | | Crude model (HR,95%CI,P) | Model I (HR,95%CI,P) | Model II (HR,95%CI,P) | GAM (HR,95%CI,P) |
|---|---|---|---|---|---|
| | Q2 | 0.613 (0.567,0.664) < 0.00001 | 0.585 (0.540,0.634) < 0.00001 | 0.611 (0.564, 0.662) < 0.00001 | 0.631 (0.582, 0.683) < 0.00001 |
| | Q3 | 0.476 (0.437, 0.518) < 0.00001 | 0.431 (0.395,0.471) < 0.00001 | 0.461 (0.422,0.503) < 0.00001 | 0.494 (0.452,0.539) < 0.00001 |
| | Q4 | 0.392 (0.357,0.431) < 0.00001 | 0.303 (0.275,0.334) < 0.00001 | 0.335 (0.303,0.369) < 0.00001 | 0.394 (0.357, 0.435) < 0.00001 |
| | P for trend | < 0.00001 | < 0.00001 | < 0.00001 | < 0.00001 |
| Queue I: we handled missing data of smoking and drinking status as a categorical variable,used multiple imputation at SBP,DBP and TG,and estimated HDL-C and LDL-C by dummy variables | | | | | |
| Queue II: No missing value processing | | | | | |
| Queue III:we handled missing data of smoking and drinking status as a categorical variable and used multiple imputation at SBP,DBP,TG,HDL-C,LDL-C | | | | | |
| Crude model:we did not adjust other covariants | | | | | |
| Model I: we adjust age,gender,SBP,DBP, smoking status,drinking status and family history of diabetes | | | | | |
| Model II: we adjust age,gender,SBP,DBP,FPG,TG,HDL-C,LDL-C,smoking and drinking status,family history of diabetes | | | | | |
| GAM: All covariates listed in model II were adjusted. However, continuous covariates were adjusted as nonlinearity. | | | | | |

# The results of the associtionbetween Cre/BW and incident of diabetes in men and women after missing value processing

Table 3 presented the results of Cox proportional-hazards regression analyses between Cre/BW and incident of diaberes in men and women.After adjusting age, gender,SBP, DBP, FPG, TG, HDL, smoking and drinking status, family history of diabetes, Cre/BW was inversely associated with diabetes risk HR = 0.255(95%CI: 0.212–0.307) in men and HR = 0.297 (95%CI: 0.218–0.406) in women. Furthermore, it also remained consistent with the GAM(HR: 0.295; 95% CI:0.245 to 0.356 in men and HR: 0.340; 95% CI:0.248 to 0.466 in women).In addition, when Cre / BW was used as a categorical variable for the quartiles, the trend between the quartiles was also significant (P for trend < 0.00001).

Table 3
Relationship between Cre/BW and the incident of diabetes in men and women

| Men | Crude model (HR,95%CI,P) | Model I (HR,95%CI,P) | Model II (HR,95%CI,P) | GAM (HR,95%CI,P) |
|---|---|---|---|---|
| Cre/BW | 0.097 (0.081, 0.117) < 0.00001 | 0.089 (0.074, 0.108) < 0.00001 | 0.255 (0.212, 0.307) < 0.00001 | 0.295 (0.245, 0.356) < 0.00001 |
| Cre/BW(quartile) | | | | |
| Q1 | Ref | Ref | Ref | Ref |
| Q2 | 0.572 (0.521, 0.629) < 0.00001 | 0.570 (0.519, 0.627) < 0.00001 | 0.698 (0.635, 0.768) < 0.00001 | 0.710 (0.645, 0.780) < 0.00001 |
| Q3 | 0.417 (0.377, 0.461) < 0.00001 | 0.420 (0.380, 0.465) < 0.00001 | 0.610 (0.550, 0.675) < 0.00001 | 0.639 (0.576, 0.708) < 0.00001 |
| Q4 | 0.295 (0.265, 0.329) < 0.00001 | 0.283 (0.254, 0.316) < 0.00001 | 0.472 (0.422, 0.528) < 0.00001 | 0.514 (0.459, 0.575) < 0.00001 |
| P for trend | < 0.00001 | < 0.00001 | < 0.00001 | < 0.00001 |
| **Women** | **Crude model (HR,95%CI,P)** | **Model I (HR,95%CI,P)** | **Model II (HR,95%CI,P)** | **GAM (HR,95%CI,P)** |
| Cre/BW | 0.088 (0.064, 0.121) < 0.00001 | 0.103 (0.075, 0.140) < 0.00001 | 0.297 (0.218, 0.406) < 0.00001 | 0.340 (0.248, 0.466) < 0.00001 |
| Cre/BW(quartile) | | | | |
| Q1 | Ref | Ref | Ref | Ref |
| Q2 | 0.541 (0.467, 0.627) < 0.00001 | 0.616 (0.531, 0.715) < 0.00001 | 0.724 (0.623, 0.841) 0.00003 | 0.752 (0.647, 0.875) 0.00023 |
| Q3 | 0.394 (0.330, 0.470) < 0.00001 | 0.451 (0.378, 0.539) < 0.00001 | 0.650 (0.542, 0.779) < 0.00001 | 0.685 (0.570, 0.822) 0.00005 |
| Q4 | 0.431 (0.355, 0.523) < 0.00001 | 0.393 (0.322, 0.479) < 0.00001 | 0.616 (0.503, 0.755) < 0.00001 | 0.652 (0.529, 0.804) 0.00006 |
| P for trend | < 0.00001 | < 0.00001 | < 0.00001 | < 0.00001 |

Crude model:we did not adjust other covariants

Model I:we adjust age,gender,SBP,DBP, smoking status,drinking status and family history of diabetes

Model II: we adjust age,gender,SBP,DBP,FPG,TG,HDL-C,LDL-C,smoking and drinking status,family history of diabetes

GAM: All covariates listed in model II were adjusted. However, continuous covariates were adjusted as nonlinearity.

CI:confidence,Ref:reference

# The analyses of the non-linear relationship

A cubic spline smoothing technique was used to explore the non-linear relationship between Cre/BW and the incidence of diabetes. (Fig. 1),base on one replication of multiple imputation data. We found that the relationship between Cre/BW and incident of diabetes was also non-linear (after adjusting age, gender, SBP, DBP, FPG, TG, HDL-C, LDL-C, smoking and drinking status, family history of diabetes) in total(HR: 0.268; 95% CI:0.229 to 0.314) and in different sex group(HR = 0.255;95%CI: 0.212–0.307 in men and HR = 0.297;95%CI: 0.218–0.406 in women). Using a two-piecewise linear regression model, we calculated that the inflection point of Cre/BW was 1.06(Log-likelihood ratio test P < 0.001). On the left of the inflection point, we observed a positive relationship between Cre/BW and incident of diabetes(HR:0.13, 95%CI: 0.10–0.16,P < 0.0001). On the right side of the inflection point, however, their relationship tended to be saturated(HR:0.62, 95%CI:0.46–0.82,P = 0.0008). Furthermore,the inflection point of Cre/BW were 1.06(Log-likelihood ratio test P < 0.001) in males and 0.87(Log-likelihood ratio test P < 0.001) in females. And we also found the effect sizes on the left and right sides of the inflection point was not consistent in different sex.(Table 4)

Table 4
The result of two-piecewise linear regression model

| | Male (HR,95%CI, P) | Female (HR,95%CI, P) | Total (HR,95%CI, P) |
|---|---|---|---|
| Fitting model by standard linear regression | 0.26 (0.21, 0.31) < 0.0001 | 0.30 (0.22, 0.41) < 0.0001 | 0.27 (0.23, 0.31) < 0.0001 |
| Fitting model by two-piecewise linear regression | | | |
| Inflection point of TG/HDL-C | 1.06 | 0.87 | 1.06 |
| ≤ Inflection point | 0.11 (0.08, 0.16) < 0.0001 | 0.05 (0.02, 0.12) < 0.0001 | 0.13 (0.10, 0.16) < 0.0001 |
| > Inflection point | 0.55 (0.40, 0.75) 0.0002 | 0.59 (0.39, 0.89) 0.0126 | 0.62 (0.46, 0.82) 0.0008 |
| P for log likelihood ratio test | < 0.001 | < 0.001 | < 0.001 |
| CI: Confidence interval | | | |
| We adjusted age, gender, SBP, DBP, FPG, TG, HDL-C,LDL-C, smoking and drinking status, family history of diabetes in Total and adjust all variables in different sex except gender | | | |

# Kaplan–Meier analysis

Figure 2 showed the Kaplan-Meier curves of the cumulative hazards of diabetes incident risk stratified by Cre/BW quartiles. Diabetes incident risk between each of the four Cre/BW groups was significantly different (log-rank test, p < 0.0001). With increased Cre/BW, the cumulative diabetes incident risk gradually attenuated, rendering the lowest quartile group(Q1) has the strongest relationship with the risk of diabetes incident.Moreover,there was statistically significant difference among Cre tertiles in both men and women.

# Discussion

In the present study, we examined the relationship between Cre/BW on diabetes risk among participants in a Chinese cohort. We found that increased Cre/BW is negatively correlated with the incidence of diabetes after processing missing values. The association remained significantly independent of several confounders such as age, gender, SBP, DBP, FPG, TC, LDL, smoking and drinking status, family history of diabetes. The relationship between them did not change significantly in the original data, suggesting that their relationship is relatively stable. In addition, we also found that there was a nonlinear relationship between Cre/BW and incident diabetes.

A number of studies have reported an association between Cre/BW and NAFLD[15], and NAFLD is known to be associated with obesity and insulin resistance[30]. To our knowledge, studies investigating the association of Cre/BW and diabetes risks are sparse. Recently, a study conducted by Hashimoto et al.[14] suggested that an independent association of diabetes risks with Cre/BW ratios in The NAGALA Study in Japan. Our findings are similar to the result of Hashimoto and his colleagues.We observed that Cre/BW is negatively correlated with incident diabetes after handling missing value(HR: 0.268; 95% CI:0.229 to 0.314), and it also makes sense in different genders(HR = 0.255;95%CI: 0.212–0.307 in men and HR = 0.297;95%CI: 0.218–0.406 in women).Moreover, we found a nonlinear between Cre/BW and incident of diabetes using a cubic spline smoothing technique(after adjusting age,gender,SBP,DBP,FPG,TC,LDL,smoking and drinking status,family history of diabetes), and the effect sizes on the left and right sides of the inflection point was not consistent [left(HR: 0.13, 95%CI: 0.10–0.16,P < 0.0001);right(HR: 0.62, 95%CI: 0.46–0.82,P = 0.0008)]. This result suggested a saturation effect on the independent association between Cre/BW and incident of diabetes.

Under ideal conditions, creatinine is considered a good substitute for skeletal muscle[31]. When increased body weight is caused by decreased muscle mass and increased fat mass, especially visceral fat accumulation[32], the Cr/BW ratios are more reliable indicator of skeletal muscle mass than simple Cr levels[15, 33]. The relationship between weight-adjusted CR and metabolic parameters is better than height-adjusted CR[34], and it is closely related to metabolic syndrome[35] and NAFLD. The mechanism underlying the association between the reduction of skeletal muscle mass and the occurrence of diabetes has not been cleared, but it may be multiple mechanisms as follow. Skeletal muscle plays a vital role in glucose metabolism. It is one of the main parts of insulin-mediated glucose uptake, especially postprandial glucose[36]. Accompanied by decreased skeletal muscle mass, decreased insulin sensitivity, abnormal glucose, and fatty acid metabolism, the maintenance and increase of skeletal muscle mass may ameliorate insulin resistance[37, 38]. The mitochondrial network in muscle cells maintains the movement and metabolic functions of skeletal muscle. The decrease in skeletal muscle volume leads to the decline of mitochondria, which leads to the inability to metabolize fatty acids in skeletal muscle, which may increase insulin resistance by inhibiting insulin signaling, including inhibition of glucose transporter type 4 (GLUT4)[39–41]. The tissue-specific knockout of glucose transporter 4 (GLUT4) in muscle showed severely impaired glucose tolerance and hyperinsulinemia[42]. Besides, nuclear factor

secreted by skeletal muscle has been found to prevent insulin resistance[43, 44]. Therefore, insulin resistance may be a potential mechanism linking muscle mass and diabetes.

One of the key strengths of our study was a relatively large sample size and a Multi-center study. Furthermore, we found the nonlinear association between Cre/BW and diabetes risks in the present study and further explore this. Moreover, we handled missing values to maximize statistical power and minimize bias and sensitivity analysis to assess the potential effect of missing values. Meanwhile, we treat the target independent variable as both a continuous variable and a categorical variable. This method can reduce the contingency of data analysis and enhance the robustness of the results.

However, several limitations need to be mentioned in the present study. First, as the study population contains only Chinese participants, it may not be generalizable to other ethnic groups. Second, because the primary study was not designed to investigate the relation of Cre/BW and diabetes, there is inevitably a lack of data. However, we handled the missing data, and the sensitivity analysis indicated that the non-missing data was consistent with the processed data, the result was not be affected. Third, this study is based on a secondary analysis of published data, so some variables can not be obtained to analyze in the present study,for example exercise.

# Conclusion

This study demonstrated that Cre/BW was associated with the risk of diabetes in Chinese adults, and this relationship was nonlinear.

# Declarations

### Authors' contributions

Zhuangsen Chen,Yang zou and Fan Yang contributed to the study concept and design, researched and interpreted the data and drafted the manuscript. Xiaohan Ding and Changchun Cao oversaw the progress of the project, contributed to the discussion and reviewed the manuscript. Xinyu Wang and Haofei Hu are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final the manuscript.

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### Competing interests
The authors declare that they have no competing interests.

### Availability of data and materials
Data can be downloaded from the 'DATADRYAD' database (www.Datadryad.org).

### Consent for publication

Not applicable.

### Ethics approval and consent to participate

In the previously published article[17], Ying Chen et al. has clearly stated that: the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.


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# Figures

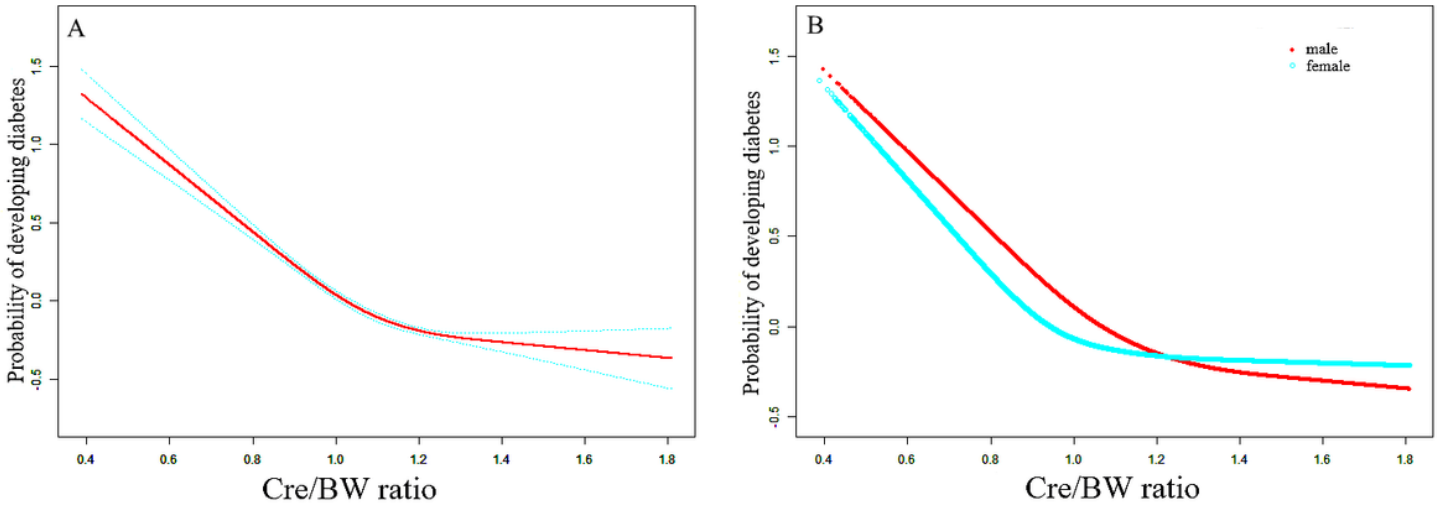
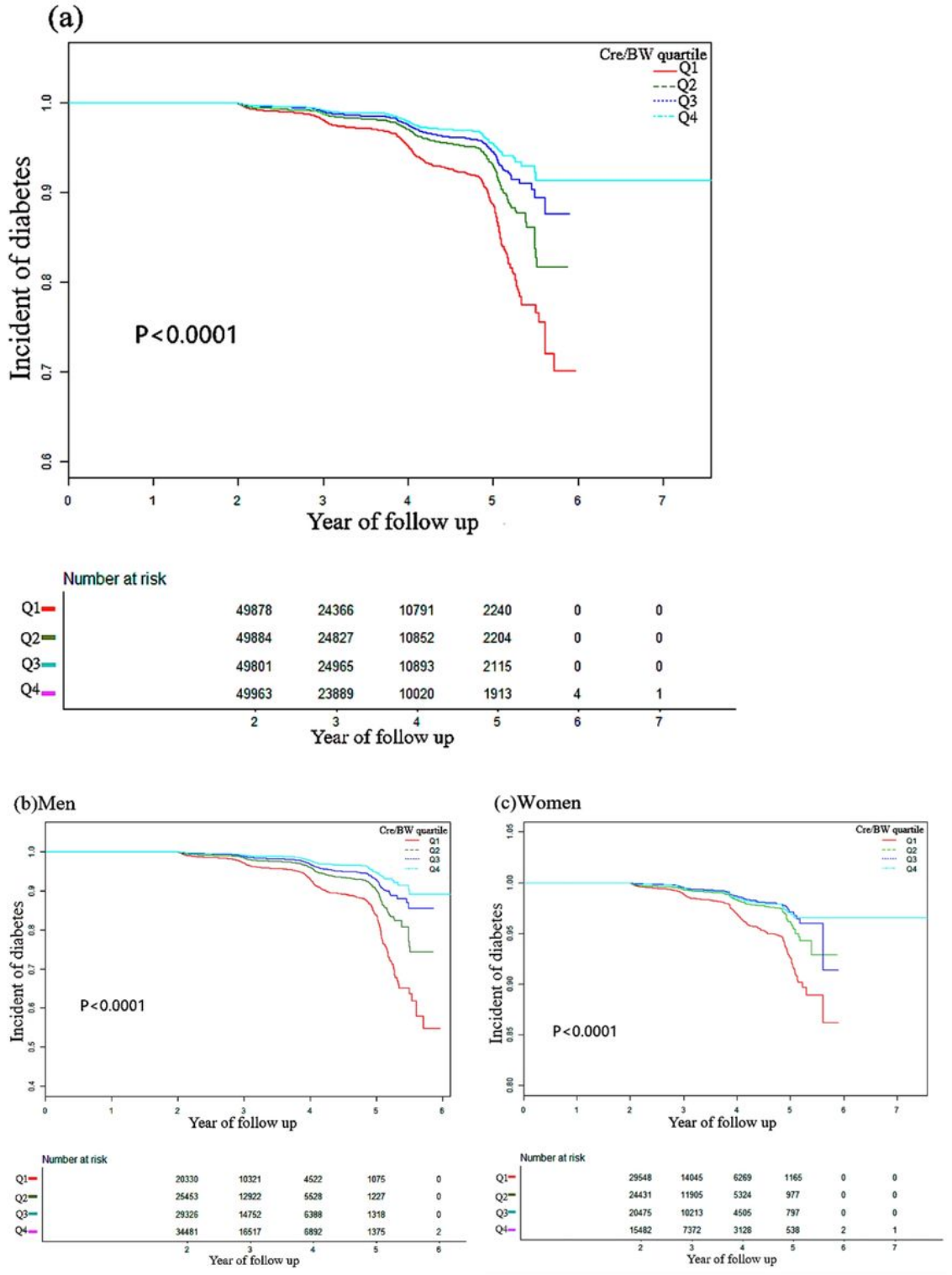



**Figure 1**

The non-linear relationship between Cre/BW and incident of diabetes(A), and a non-linear relationship between them in different sex(B).




## Figure 2

Kaplan–Meier event-free survival curve. (a)Kaplan–Meier analysis of incident of diabetes based on Cre/BW quartiles (logrank,P < 0.0001) in total.(b) Kaplan–Meier analysis of incident of diabetes in men. (c) Kaplan–Meier analysis of incident of diabetes in women.

# Supplementary Files

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