Association between blood urea nitrogen and incidence of type 2 diabetes mellitus in a Chinese population: a cohort study

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Abstract. To examine the association between blood urea nitrogen (BUN) and risk of type 2 diabetes (T2DM) among Chinese adults, we performed an ongoing cohort study of 38578 Chinese adults (56.3% males; average age, 41.6 y) who underwent repeated health check-up examinations between 2009 and 2016 and without T2DM at baseline. During follow-up, incident T2DM cases were identified based on self-report, medication use, measurements of fasting plasma glucose, 2 h post oral glucose, or haemoglobinA1c. 2009 (5.2%) cases confirmed with incident T2DM were identified during median follow-up of 3.1 years. With increasing quartiles of BUN levels, the incidences of T2DM gradually increased with 0.69%, 1.11%, 1.53%, and 1.87% for quartile 1 to quartile 4 (p trend <0.001). Compared with quartile 1, the multivariate-adjusted hazard ratios (HRs) and its 95% confidence intervals (95% CIs) for T2DM risk were 1.16 (0.97–1.38) for quartile 2, 1.28 (1.07–1.51) for quartile 3, and 1.28 (1.08–1.52) for quartile 4 (p trend = 0.005). HR for per each standard deviation increase in BUN level was 1.10 (1.04–1.16) (p trend <0.001). This association tended to be more pronounced in those with a lower body mass index (p–interaction <0.001). Our results suggested that BUN levels were positively associated with incident T2DM risk among Chinese adults. Future prospective investigations in other populations are necessary to confirm our findings.

Key words: Type 2 of diabetes mellitus, Blood urea nitrogen, Chronic kidney disease, Cohort study

TYPE 2 DIABETES MELLITUS (T2DM) and its complications is recognized globally as one of the major public health challenges, ranking the ninth major cause of death [1]. In the past three decades, the prevalence of diabetes has been quadrupled [1]. In 2019, 463 million adults lived with diabetes worldwide, and more than 90% of whom had T2DM. This number is expected to increase up to 700 million in 2045 [2]. Asia has emerged as the major area with a rapidly developing T2DM epidemic and China is one of the top epicenters of the epidemic [1]. In China, the age-standardized prevalence of T2DM increased 11-fold from 1.0% in 1980s to 11.0% in 2017 [3]. Given its very large population size, development of effective strategies for T2DM prevention is of great public health importance in this region.

Kidney is an important organ in maintaining glucose homeostasis. Impaired insulin secretion and insulin resistance have been observed among chronic kidney disease (CKD) patients, mainly due to the retention of...
uremic metabolites including urea. Blood urea nitrogen (BUN), as a traditional marker for renal function for decades, recent attention has been given to the new role in urinary system, circulatory system, etc., which suggests clinical significance of urea [4]. Experimental evidence indicated that uremic mice displayed glucose intolerance, while urea infusion in normal animals elevated insulin resistance–associated adipokines [5, 6]. Cultured disease-specific concentrations 3T3-L1 with urea resulted in radical oxygen species (ROS) production and increased O-linked b-N-acetylglucosamine (O-GlcNAc) [5]. Elevated circulating levels of urea could directly impair pancreatic β-cell function through increasing islet protein O-GlcNAcylation and impairing glycolysis [6], thus leading to impaired glucose secretion and broken glucose homeostasis and the development of T2DM and the deterioration of renal function. In addition, plasma levels of amino acids related to urea cycle and their ratios of these amino-acids were associated with T2DM in Chinese adults [7]. Thus, BUN might play an important role in the development of T2DM.

Currently, few epidemiological studies have assessed the association between BUN and T2DM risk. Recently, a large cohort study using data from a national cohort of 1,337,452 United States Veterans with a median follow-up of 4.93 years indicated that, higher BUN was associated with increased T2DM risk [8]. However, average age of subjects included in this cohort were mainly old people (mean age: 65.5 years) and males (94.5%) [8].

Considering the age, gender, and even ethnical difference may affect the associations, more evidence is needed to confirm this association in other populations. Thus, we used an ongoing cohort with relatively large sample size to verify the association between BUN and T2DM risk among Chinese adults (56.4% males) at a younger age (mean age: 41.6 years).

**Material and Methods**

**Study population**

The participants were recruited from an ongoing cohort study conducted in Xiaotangshan hospital, Beijing, China. This cohort included adults who underwent a comprehensive annual or biennial health check-up examination at the clinics of the hospital. The majority of participants (90%) were civil servants of the government who have free annual or biennial health check-up benefits. Whereas the remaining participants voluntarily purchased screening exams at the health exam center. The design of the study has been previously described in detail [9-11].

The survey time in this study span 8-year period from January 1, 2009, through December 31, 2016. A total of 52,402 Beijing native individuals participated in the health examination during this period. We firstly excluded those less than two follow-up (n = 6,843) and those with history of stroke, cancer, coronary heart disease and myocardial infarction disease at baseline (n = 1,974), then removed missing data for diagnosis of T2DM and excluded those with T2DM at baseline through the same diagnostic criteria as the outcome (n = 3,513). We further excluded those with younger than 20 years old (n = 79), those with missing data for BUN (n = 319) and outliers for some important index which under 0.1% or/and over 99.9% at baseline (n = 1,096). Finally, 38,578 (21,757 males and 16,821 females) participants were included in the present analysis. The flow chart of research subject selection is shown in Fig. 1.

**Data collection**

Health examinations were conducted at clinics of the Xiaotangshan hospital in Beijing, China. A structured questionnaire was designed to collect information about demographic characteristics (e.g., age, gender, and marital status), lifestyle habits (e.g., smoking and alcohol drinking status), history of chronic diseases, and medical histories. The questionnaire was completed through a face-to-face interview by trained nurses at each visit. Height, weight, and blood pressure were measured after interview and BMI was calculated as weight in kilograms divided by height in meters squared. BMI was categorized into three groups on basis of the optimal cutoff points of body mass index (BMI) for Chinese adults recommended by the Working Group on Obesity in China (WGOC) [12]: 24.0 kg/m² and 28.0 kg/m² were set as the cutoff points for overweight and obesity, respectively. Hypertension was defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥130/85 mmHg or on antihypertensive drug treatment in patients with a history of hypertension [13].

Blood samples were obtained from each subject after at least overnight fasting. Serum fasting plasma glucose (FPG) concentration was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany). Serum lipids (total cholesterol (TC) and triglycerides (TG)) were measured with an enzymatic colorimetric assay (Type 7600; Hitachi Ltd., Tokyo, Japan). Determination of blood urea nitrogen (BUN) concentration by biochemical analyzer (OlympusAU640) according to manufacturer’s instructions [14]. The estimated glomerular filtration rate (eGFR) was calculated based on the MDRD 2006 equation (Re-expressed MDRD equation) [15, 16] and was classified into 2 categories: eGFR >60 mL/min per 1.73 m² and eGFR ≤60 mL/min per 1.73 m², due to smaller participants with eGFR <30 mL/min per 1.73 m² (n = 8).
Outcome

All subjects should be examined at least two follow-up surveys. At each survey, participants were invited to provide their medical records (e.g., diagnoses and hospital admissions), report major health events (e.g., diagnosed T2DM), or ever/currently using antidiabetic drugs. Incident T2DM was defined as follows: self-reported diagnosis of diabetes mellitus, use of antidiabetic medications, diagnosis of diabetes mellitus by a doctor, fasting glucose ≥126 mg/dL (7.0 mmol/L), 2-hour post oral glucose tolerance test glucose ≥200 mg/dL (11.1 mmol/L), or haemoglobin A1c (HbA1c) ≥48 mmol/mol (6.5%) [17].

Statistical analysis

Statistical analysis was performed by using R-3.5.2 (R Development Core Team, Vienna, Austria). Two-sided \( p < 0.05 \) was considered as statistical significance. Descriptive statistics were used to express characteristics of baseline data. Mean ± standard deviation (SD) was used to describe the continuous variables and number and percentage was used to present categorical variables. Analysis of variance was used for continuous variables and \( \chi^2 \) statistics for categorical statistics to compare the characteristics according to BUN quartiles (quartile 1 (Q1): <3.9 mmol/L, quartile 2 (Q2): 3.9–4.7 mmol/L, quartile 3 (Q3): 4.7–5.6 mmol/L, and quartile 4 (Q4): ≥5.6 mmol/L).

Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and their 95% confidence intervals (CIs) for the association between the BUN and incident T2DM. Three models were used: model 1 included age (continuous, years) and gender (male, female); model 2: covariates in model 1 + BMI (continuous, kg/m\(^2\)), marital status (married vs. not married), alcohol drinking status (never, past, vs. current-drinker), smoking status (never, past, vs. current-smoker), TC (continuous, mmol/L), TG (continuous, mmol/L), eGFR (continuous, mL/min per 1.73 m\(^2\)), and hypertension (yes vs. no); model 3: covariates in model 2 + fasting serum glucose (Glu) (continuous, mmol/L). \( p \) trend across increasing quartiles was estimated by assigning quartiles as continuous variables in the regression. HRs (95%CI) of T2DM per each SD increase of the
BUN was also estimated in Cox regression models.

We also explored the shape of the association between baseline BUN and incident T2DM risk by R smooth HR package [18], adjusting for the covariates as shown in model 3. The optimal degree of smoothing was obtained by minimizing any of the following criteria: Akaike’s Information Criterion (AIC), corrected version of AIC (AICc), or Bayesian Information Criterion (BIC). P-value for nonlinearity was calculated using a likelihood ratio test.

Subgroups analyses were conducted by age (<45; 45–64.9 vs. ≥65 years), gender (male vs. female), eGFR (<60 vs. ≥60 mL/min per 1.73 m<sup>2</sup>), BMI (<24, 24–27.9, vs. ≥28), alcohol drinking status (never, past, current drinker), smoking status (never, past, current smoker) using model 3. Interaction terms were added to estimate the interactions between the concentration of BUN and these factors.

In order to assess the potential reverse causality, we also performed sensitivity analyses based on model 3 to examine the robustness of the results by excluding participants with less than one or two years of follow-up.

**Results**

Characteristics of the included participants at baseline are shown in Table 1. The mean ages of all participants were 41.6 years (SD: 12.6 years) and 56.4% of them were males. In addition to the decrease of eGFR level with the increase of BUN level, other factors such as BMI, SBP, DBP, TC, TG, Glu, 2h postprandial blood glucose (Glu2h), HbA1c, and proportion of hypertension increased across BUN quartiles (all <0.05).

A median follow-up of 3.1 (interquartile range (IQR), 1.86–5.14) years from the 2009–2016 yielded a total of 2009 T2DM cases, resulting in an incidence of 5.20%. For BUN Q1–4, the number of incident T2DM cases were 267, 429, 591, and 722, corresponding to the

| Table 1 | Baseline characteristics of the overall cohort according to BUN quartiles at baseline |
|---------|---------------------------------------------------------------------------------|
|         | Total (N = 38,578) | Quartiles of BUN levels | p value |
| Age, years | 41.6 ± 12.6 | 38.7 ± 11.4 | 40.7 ± 11.9 | 42.2 ± 12.2 | 44.8 ± 13.8 | <0.001 |
| Males, N (%) | 21,755 (56.4) | 2,955 (31.9) | 5,091 (52.1) | 6,569 (65.1) | 7,140 (75.5) | <0.001 |
| Married participants, N (%) | 31,059 (80.5) | 6,766 (85.3) | 7,729 (89.3) | 8,352 (92.6) | 8,212 (94.2) | <0.001 |
| BMI, kg/m<sup>2</sup> | 24.83 ± 3.55 | 23.86 ± 3.61 | 24.63 ± 3.56 | 25.21 ± 3.46 | 25.55 ± 3.33 | <0.001 |
| SBP, mmHg | 118.3 ± 15.9 | 115.2 ± 15.9 | 117.6 ± 16.0 | 119.3 ± 15.7 | 120.9 ± 15.4 | <0.001 |
| DBP, mmHg | 74.3 ± 10.5 | 71.8 ± 10.6 | 74.0 ± 10.7 | 75.2 ± 10.4 | 76.0 ± 9.8 | <0.001 |
| TC, mmol/L | 4.82 ± 0.92 | 4.60 ± 0.87 | 4.78 ± 0.91 | 4.90 ± 0.91 | 4.99 ± 0.94 | <0.001 |
| TG, mmol/L | 1.53 ± 1.24 | 1.34 ± 1.10 | 1.50 ± 1.14 | 1.60 ± 1.22 | 1.68 ± 1.46 | <0.001 |
| Glu, mmol/L | 5.21 ± 0.51 | 5.10 ± 0.48 | 5.18 ± 0.49 | 5.24 ± 0.51 | 5.33 ± 0.52 | <0.001 |
| Glu2h, mmol/L | 6.24 ± 1.37 | 6.08 ± 1.34 | 6.15 ± 1.33 | 6.23 ± 1.36 | 6.41 ± 1.42 | <0.001 |
| HbA1c, % | 5.43 ± 0.37 | 5.35 ± 0.36 | 5.41 ± 0.36 | 5.45 ± 0.37 | 5.50 ± 0.37 | <0.001 |
| eGFR, mL/min per 1.73 m<sup>2</sup> | 86.0 ± 17.3 | 92.1 ± 18.2 | 87.9 ± 16.9 | 84.4 ± 15.7 | 79.9 ± 15.9 | <0.001 |
| Hypertension, N (%) | 8,252 (21.4) | 1,294 (3.4) | 1,849 (4.8) | 2,323 (6.0) | 2,786 (7.2) | <0.001 |
| Smoking status, N (%) | <0.001 |
| Never | 25,601 (66.4) | 7,317 (19.0) | 6,753 (17.5) | 6,229 (16.1) | 5,302 (13.7) |
| Past | 6,223 (16.1) | 936 (2.4) | 1,402 (3.6) | 1,822 (4.7) | 2,063 (5.3) |
| Current | 6,754 (17.5) | 1,006 (2.6) | 1,624 (4.2) | 2,039 (5.3) | 2,085 (5.4) |
| Alcohol drinking status, N (%) | <0.001 |
| Never | 22,796 (59.1) | 6,750 (17.5) | 5,896 (15.3) | 5,432 (14.1) | 4,718 (12.2) |
| Past | 4,307 (11.2) | 803 (2.1) | 1,070 (2.8) | 1,234 (3.2) | 1,200 (3.1) |
| Current | 11,475 (29.7) | 1,706 (4.4) | 2,813 (7.3) | 3,424 (9.1) | 3,532 (9.2) |

Notes: Values with normal distribution were expressed as mean ± SD and categorical variables were expressed as number and its proportion. BUN levels were divided into quartiles: <3.9 mmol/L (Q1), 3.9–4.7 mmol/L (Q2), 4.7–5.6 mmol/L (Q3), and ≥5.6 mmol/L (Q4). Abbreviations: BUN, blood urea nitrogen; DBP, diastolic blood pressure; HbA1c, haemoglobinA1c; Glu, fasting serum glucose; Glu2h, 2h postprandial blood glucose; Q, quartile; SBP, systolic blood pressure.
T2DM incident rate of 0.69%, 1.11%, 1.53%, and 1.87%, respectively (Table 2).

With adjustment for age and gender, the BUN concentration, either as quartiles or as continuous variable, was significantly and positively associated with incident T2DM risk (both \( p \) trends <0.001) (Table 2). The risk persisted after further adjustment for BMI, marital status, alcohol drinking and smoking status, TC, TG, eGFR, and a history of hypertension (both \( p \) trends: <0.001). The associations attenuated but sustained after further adjustment for fasting serum glucose based on models 3 (\( p \) trend: 0.005 as quartiles and <0.001 as continuous variable). The adjusted hazard ratios (a-HRs) and its 95% CIs for incident T2DM across BUN Q2–4 (using Q1 as reference) were 1.16 (1.00, 1.33), 1.50 (1.20, 1.80), and 1.87 (1.39, 2.51), respectively (Table 2). Each SD increase in BUN was associated with an a-HR of 1.10 (95% CIs: 1.04 to 1.16).

In Fig. 2, we used non-linear fitting model and visualized the relation of predicted level of BUN and T2DM risk after adjusting potential confounders in model 3. The incident risk of T2DM gradually increased with rising concentration of BUN (\( p \) for non-linearity <0.001).

In stratified analyses, the association between BUN and risk of T2DM was similar for most strata (\( p \) for interaction: 0.143 to 0.864), with the exception for stratification by BMI (\( p \) for interaction <0.001) and eGFR (\( p \) for interaction = 0.051). The association between BUN and T2DM was more apparent among those with BMI

### Table 2  HR (95% CIs) for association between BUN levels and the risk of incident T2DM

| BUN quartiles | No. of incident T2DM | % of incident T2DM | Total person-years | Model 1 | Model 2 | Model 3 |
|---------------|----------------------|-------------------|--------------------|---------|---------|---------|
|               | HR (95% CI)          | \( p \) value     | \( p \) trend       | a-HR (95% CI) | \( p \) value | \( p \) trend | a-HR (95% CI) | \( p \) value | \( p \) trend |
| Q1            | 267                  | 0.69              | 29903              | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| Q2            | 429                  | 1.11              | 33893              | 1.20 (1.02, 1.39) | 1.23 (1.03, 1.47) | 1.16 (0.97, 1.38) |
| Q3            | 591                  | 1.53              | 36087              | 1.40 (1.20, 1.62) | 1.39 (1.17, 1.65) | 1.28 (1.07, 1.51) |
| Q4            | 722                  | 1.87              | 35883              | 1.50 (1.30, 1.74) | 1.50 (1.27, 1.78) | 1.28 (1.08, 1.52) |
| Per 1 SD increase | —                   | —                 | —                  | 1.16 (1.11, 1.22) | 1.16 (1.11, 1.22) | 1.16 (1.04, 1.16) |

Notes: BUN levels were divided into quartiles: <3.9 mmol/L (Q1), 3.9–4.7 mmol/L (Q2), 4.7–5.6 mmol/L (Q3), and ≥5.6 mmol/L (Q4). Three models were used. Model 1: age (continuous, years) and gender (male and female); Model 2: model 1 + BMI (continuous, kg/m\(^2\)), marital status (married vs. not married), alcohol drinking status (never, past vs. current), smoking status (never, past vs. current), TC (continuous, mmol/L), TG (continuous, mmol/L), eGFR (continuous, mL/min per 1.73 m\(^2\)), and hypertension (yes vs. no); Model 3: model 2 + fasting serum glucose (continuous, mmol/L).

Abbreviations: a-HR, adjusted hazard ratio; BUN, blood urea nitrogen; T2DM, type 2 diabetes mellitus; HR, hazard ratio; Q, quartile; 95% CI, 95% confidence interval.
Discussion

The results of the present cohort study among a Chinese health examination population suggest that the BUN concentration was positively associated with risk of incident T2DM. Subgroup analysis indicated that this association was more evident among those with lower BMI.

Comparisons with other studies

Limited evidence has explored the association of BUN levels with the risk of T2DM. A national cohort study conducted by Xie Y et al. [8], with 1,337,452 United States Veterans (mean age: 65.7 years; 94.5% males) that followed for 4.93 years with 172,913 incident diabetes cases developed, indicated that every 10-mg/dL increase in BUN concentration was associated with a 9% (8%–10%) increase in the risk of incident diabetes. Another cross-sectional study with 3,227 women and 610 prevalent T2DM cases also suggested a positive association [19]. In our study, we further confirmed that higher BUN concentration was associated with increased T2DM risk in younger adults.
In the study by Xie et al. [8], the association between BUN and T2DM risk was dependent on renal function. In addition, in joint risk models of eGFR and BUN, there was no association between eGFR and the risk of incident diabetes in those with a BUN ≤25 mg/dL, whereas the risk was significantly increased in those with a BUN >25 mg/dL at all eGFR levels, even in those with an eGFR of 60 mL/min/1.73 m² or more (HR: 1.27; CIs: 1.24–1.31) [8]. However, in our study, due to the small number of participants with BUN >25 mg/dL (n = 270), it was impossible to calculate the association between eGFR and T2DM at BUN >25 mg/dL (8.8 mmol/L). Nevertheless, we observed that participants with eGFR ≤60 mL/min per 1.73 m² had a higher risk than those with eGFR >60 mL/min per 1.73 m² (p interaction = 0.051).

Potential underlying mechanisms

There are some potential mechanisms to illustrate the observed BUN-T2DM association. It’s well-known that BUN is an important part of urea and urea is the chief culprit in chronic kidney disease. Some studies have found an increase in protein O-GlcNAcylation and oxidative stress with urea-exposed normal islets, which were associated with insulin secretion and insulin resistance [6]. Firstly, the experiment demonstrated that O-GlcNAcylation of proteins were increased in islets from urea-treated mice (+55% ± 1% vs. controls, n = 3–4, p < 0.05) [20] and O-GlcNAcylation played an important role in urea-induced insulin secretion disorders, mainly due to O-GlcNAcylation of glycolytic enzyme, which reduced glycolytic flux and attenuated insulin signal transduction [6, 21, 22]. Secondly, high concentration of urea increased reactive oxygen species (ROS) in mouse renal inner medullary (mIMCD3) cells in culture [23]. Andurea-induced ROS directly increased expression and secretion of the insulin resistance-associated adipokines RBP4 and resistin from 3T3-L1 adipocytes in a cell-autonomous manner, further resulting in adipocyte insulin resistance, which was closely related to development of T2DM [5]. In addition, some metabolites in the urea including arginine, citrulline and ornithine were associated with T2DM risk in Chinese adults and arginine was positively associated with T2DM while ornithine was negatively associated with T2DM [7]. Compared with control group, the ratios of arginine to ornithine, arginine to citrulline and citrulline to ornithine were significantly higher in T2DM [7].

BMI difference

After stratification of BMI, we found that the association between BUN and T2DM was significantly different among various BMI strata, with decreased risk observed among participants with higher BMI (p interaction <0.001). These results contradict the conventional view that the incidence of T2DM is on the rise as BMI increases. A cohort study by Xie et al. [8] found that, as kidney function deteriorated, the risk of diabetes increased in all BMI categories except for obese group (BMI ≥30 kg/m²) in joint risk models of BUN and BMI. A possible explanation of the associations is that, compared with the strong risk factor (obesity), the effect of a relatively less strong risk factor, such as elevated BUN level, on the increased risk of diabetes might be masked [24, 25]. Other explanation includes the “obesity paradox” existed in patients with T2DM [26]. Studies have indicated that, among patients with T2DM and cardiovascular co-morbidity, normal weight participants had a higher mortality compared to overweight or obese participants [26, 27]. Murphy et al. [27] found that “obesity paradox” was related to muscle size that played a 46% mediating role in the effect of normal weight on the risk of death. However, more evidence is needed to accurately examine the potential mechanism [24, 25].

Strength and limitations of this study

The strengths of the present study include a relatively large number of participants that allow sufficient power to estimate the strength of the association, adjustment for a variety of risk factors and several sensitivity analyses, which support the robustness of our findings. In addition, the diabetes was diagnosed based on one or more crite-
ria, which reduced prevalence-incidence bias.

However, some limitations of this study should be noted. Firstly, most of our included participants were civil servants of the government in Beijing, China, thus selection bias may exist in this study. Secondly, we only used BUN measured in baseline to assess its effect on incident T2DM risk and did not account for potential changes in BUN over time. Thirdly, use of medication regimen for T2DM during follow-up may affect the course of T2DM. If participants developed T2DM during the interval of follow-up and accepted treatment or intermittent treatment, the physiological indicators of the patients on the baseline may be affected by treatments such as drugs and the risk estimates of associations might be underestimated. For example, recent findings had indicated that pioglitazone and gliclazide could improve renal functions compromised by diabetes, thereby witnessing a drop of BUN [28-30]. Fourthly, although we have adjusted some factors that might affect the outcome and minimize bias, there were still some unknown confounding factors. Fifthly, those who participated in 2 or more physical examinations with blood glucose test during the follow-up of 8 years were eligible in the analysis, which means not every research subject was checked at each follow-up. The unequal distribution of individuals with unidentified diabetes may have affected the study results. Finally, this study is limited to the Chinese population, more evidence is needed to confirm the association in other population.

Conclusions

In summary, we found that a higher BUN level was associated with increased T2DM risk, especially among individuals with lower BMI. These findings provide evidence that BUN might be considered as a clinical marker for the development of T2DM.

Disclosure

The authors declare that they have no competing interests. Fang-fang Zeng and Chang-yi Wang contributed to the study concept and design. Zhao Ping, Chang-yi Wang, Yan-mei Lou, Hong-en Chen, Xiao-lin Peng, Dan Zhao, Shan Xu, Li Wang, Jian-ping Ma contributed to the data collection. Fang-fang Zeng, Shu-na Li and Zeyan Luo wrote the first draft of the manuscript and conducted the data analysis. Fang-fang Zeng, Shu-na Li, Zeyan Luo, Xu-ping Gao and Min-qi Liao, Qing-shan Chen were involved in data review and interpretation. Yun-feng Cui made a great contribution to the revised work. All authors contributed to, critically revised and approved the final version of the manuscript.

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Ethical Approval

The study was approved by the Institutional Review Board of the Xiaotangshan hospital (No. 202006), which waived the requirement for informed consent as we used only de-identified data obtained as part of routine health-screening exams.

References

1. Zheng Y, Ley SH, Hu FB (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 14: 88–98.
2. IDF DIABETES ATLAS 9th edition (2019) International Diabetes Federation. http://www.diabetesatlas.org/ accessed 3 October 2020.
3. Global Health Data Exchange (2017) Institute for Health Metrics and Evaluation. USA. http://ghdx.healthdata.org/ accessed 1 October 2020.
4. Wang H, Ran J, Jiang T (2014) Urea. Subcell Biochem 73: 7–29.
5. D’Apolito M, Du X, Zong H, Catucci A, Maiuri L, et al. (2010) Urea-induced ROS generation causes insulin resistance in mice with chronic renal failure. J Clin Invest 120: 203–213.
6. Koppe L, Nyam E, Vivot K, Manning Fox JE, Dai XQ, et al. (2016) Urea impairs beta cell glycolysis and insulin secretion in chronic kidney disease. J Clin Invest 126: 3598–3612.
7. Cao YF, Li J, Zhang Z, Liu J, Sun XY, et al. (2019) Plasma Levels of Amino Acids Related to Urea Cycle and Risk of Type 2 Diabetes Mellitus in Chinese Adults. Front Endocrinol (Lausanne) 10: 50.
8. Xie Y, Bowe B, Li T, Xian H, Yan Y, et al. (2018) Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. Kidney Int 93: 741–752.
9. Qin P, Lou Y, Cao L, Shi J, Tian G, et al. (2020) Dose-response associations between serum creatinine and type 2 diabetes mellitus risk: a Chinese cohort study and meta-analysis of cohort studies. *J Diabetes* 12: 594–604.

10. Hu F, Lou Y, Shi J, Cao L, Wang C, et al. (2020) Baseline serum albumin and its dynamic change is associated with type 2 diabetes risk: a large cohort study in China. *Diabetes Metab Res Rev* 36: e3296.

11. Lou YM, Liao MQ, Wang CY, Chen HE, Peng XL, et al. (2013) Adjusted HR: an R package for pointwise nonparametric estimation of hazard ratio curves of continuous predictors. *Comput Math Methods Med* 2013: 745742.

12. Meira-Machado L, Cadarso-Suarez C, Gude F, Araujo A (2013) smoothHR: an R package for pointwise nonparametric estimation of hazard ratio curves of continuous predictors. *Comput Math Methods Med* 2013: 745742.

13. Li Q, Wang X, Ni Y, Hao H, Liu Z, et al. (2019) Epidemiological characteristics and risk factors of T2DM in Chinese premenopausal and postmenopausal women.