Association of a novel electrolyte index, SUSPPUP, based on the measurement of fasting serum and spot urinary sodium and potassium, with prediabetes and diabetes in Chinese population

Miaomiao Sang [1*], Yu Liu [1*], Tongzhi Wu [2], Xiaoying Zhou [1], Duolao Wang [3], Zilin Sun [1#], Shanhu Qiu [4#]

[1] Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China

[2] Adelaide Medical School and Centre of Research Excellence (CRE) in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, Australia

[3] Liverpool School of Tropical Medicine, Liverpool, United Kingdom

[4] Department of General Practice, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China

*Contributed equally

[#]Corresponding authors:

Zilin Sun, M.D., Ph.D., Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, No.87 Dingjiaqiao Street, Nanjing 210009, China. E-mail: sunzilin1963@126.com; Tel: +86-025-83262813, Fax: +86-025-83262609.

or Shanhu Qiu, MD, Department of General Practice, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, No.87 Dingjiaqiao Street, Nanjing 210009, China. E-mail: tigershanhu@126.com.

ABSTRACT

Background: SUSPPUP, calculated as serum sodium [Na^+] to urinary Na^+ divided by (serum potassium [K^+]) ^{2} to urinary K^+, is a composite electrolyte index that reflects renal Na^+ retention and K^+ excretion. It remains unclear whether SUSPPUP and its components including serum or urinary Na^+ or K^+, are associated with glucose metabolism. This study aimed to address their associations.

Methods: We conducted a cross-sectional study enrolling 5,581 Chinese adults (1,269 with prediabetes, 1,044 with diabetes, and 3,268 with normoglycemia). Fasting serum and morning spot urine were used to measure electrolytes that included Na^+ and K^+.

Results: SUSPPUP was higher in prediabetes and diabetes than normoglycemia. The odds of prediabetes and diabetes were increased by 21% and 39% for every 1-standard deviation increment of SUSPPUP after multivariable-adjustment. Multiple linear regression analysis showed that SUSPPUP correlated positively with fasting plasma glucose, 2h plasma glucose after OGTT, and glycated hemoglobin A1c. Higher spot urinary Na^+ was associated with lower odds of prediabetes and diabetes, while spot urinary K^+ showed the opposite.

Conclusion: Increases in Na^+ retention and K^+ excretion in the kidney, as reflected by an elevated SUSPPUP, are associated with increased prevalence of prediabetes and diabetes in Chinese community-dwellers.

Key Words

SUSPPUP; Serum Electrolytes; Urinary Electrolytes; Glucose Metabolism

1. Introduction

The homeostasis of electrolytes, including sodium (Na^+) and potassium (K^+), is critical to the maintenance of muscle function and regulation of osmotic pressure and acid base balance [1, 2]. There is increasing evidence suggesting that variations in the metabolism of electrolytes are linked to the development of metabolic disorders [3-5]. For example, low serum K^+ (even in the normal range) was shown to be related to increased risk of incident diabetes in young adults [6-9], while high serum Na^+ was associated with hypertension and dyslipidemia [10, 11]. In a cross-sectional study that enrolled patients with diabetes, serum Na^+ but not K^+ was found to correlate negatively with glycemic indices including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), and hemoglobin A1c (HbA1c) [12]. In addition, a prospective study conducted in Finland showed that 24-hour urinary Na^+ was positively associated with the risk of diabetes, but 24-hour urinary K^+ was not [13]. While analyses from these studies, which focused on an individual electrolyte, are robust, their conclusions remain debatable given the evidence that changes in a certain electrolyte often coincide with changes in another electrolyte, either in serum or in urine.

SUSPPUP, calculated as serum Na^+ to urinary Na^+ divided by (serum K^+) ^{2} to urinary K^+, is a composite electrolyte index that accounts for the mutual influence arising from the balance of Na^+ and K^+, and is considered a reliable measure to reflect renal function of Na^+ retention and K^+ excretion [14]. In recent years, SUSPPUP has been increasingly recognized as a convenient and effective screening tool for primary

aldosteronism [14-16], which is associated with increased risk of future diabetes [17, 18]. However, to the best of our knowledge, no studies have evaluated the association of SUSPPUP with prediabetes or diabetes.

Therefore, the primary aim of this study was to assess the associations of SUSPPUP with prediabetes and diabetes in Chinese community-dwellers. The secondary aim was to examine the association of spot urinary electrolytes with prediabetes and diabetes, since the measurement of 24-hour urinary electrolytes is time-consuming and inconvenient in clinical practice.

2. Materials and methods

2.1. Participants

This was a cross-sectional and population-based study conducted in 8 provinces (Guangxi, Fujian, Jilin, Yunnan, Jiangxi, Hebei, Xinjiang and Jiangsu provinces) in China between April 2020 and January 2021 in community-dwellers (aged >18 years). The study protocol was approved by the Human Research Ethics Committee of Zhongda Hospital, Southeast University, Nanjing, China. Written consent was obtained from each participant prior to enrollment.

Of the 6,310 participants enrolled in our study, 394 were excluded due to missing information on laboratory parameters (serum Na^+ or K^+, FPG, HbA1c, total cholesterol [TC], triglyceride [TG], high density lipoprotein [HDL], low-density lipoprotein [LDL] , serum creatinine [Cr], urinary Na^+ or K^+, urinary glucose) or anthropometric data (systolic blood pressure [SBP], diastolic blood pressure [DBP], height, weight,

waist circumference [WC], hip circumference [HC]), 111 due to concurrent use of diuretics, and 37 due to heart failure or severe liver disease or renal insufficiency (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2) . We also excluded 187 participants without information on glucose metabolism, leaving a total of 5,581 participants included in the final analysis (Figure 1).

2.2. Measurements

Information on medical history, medication use, family history of diabetes, physical activity and smoking status were collected using a pre-designed structured questionnaire by well-trained interviewers; height, weight, WC, HC, SBP, DBP were measured with standardized protocols [19]. Venous blood samples were collected after an overnight fast for at least 8 hours, and were used to measure FPG, HbA1c, TC, TG, HDL, LDL, Na^+, K^+, and Cr. 2hPG was measured after a 75-g oral glucose load among subjects without history of diabetes. Morning fasting spot urine was collected for the measurement of urinary Na^+, K^+, and glucose, as well as for the assessment of albumin-to-creatinine ratio (UACR). Measurements below the limits of detection (LOD) were imputed using the LOD. For serum and urinary Na^+, the intra-assay, inter-assay, and inter-institutional CVs were <1.0%, 1.5% and 2.0%, respectively; and for serum and urinary K^+, the corresponding CVs were <1.5%, 2.0% and 3.0%. eGFR was calculated based on the Modification of Diet in Renal Disease (MDRD) formula for Chinese population:175 × (serum Cr) ^ (−1.234) × age^ (−0.179) × (0.79 for women)) [20].

SUSPPUP was calculated as serum Na^+ to urinary Na^+ divided by (serum K^+)^2 to urinary K^+ [15]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Insulin resistance were assessed using the parameters such as triglyceride and glucose index (TyG), Chinese visceral adiposity index (CVAI), and lipid accumulation product (LAP) [21- 23]:

TyG = Ln [TG (mg/dL) × FPG (mg/dL)/2];

CVAI (males) = −267.93 + 0.68 × age (Y) + 0.03×BMI (kg/m^2) + 4.00 × WC (cm) + 22.00 × Lg TG (mmol/L) − 16.32 × HDL (mmol/L);

CVAI (females) = −187.32 + 1.71 × age (Y) + 4.32 ×BMI (kg/m^2) + 1.12 × WC (cm) + 39.76 × Lg TG (mmol/L) − 11.66 × HDL (mmol/L);

LAP (males) = [WC (cm) − 65] × TG (mmol/L);

LAP (females) = [WC (cm) − 58] × TG (mmol/L).

2.3. Definitions

According to the WHO 1999 diagnostic criteria, diabetes was defined as FPG ≥ 7.0 mmol/L, 2hPG ≥ 11.1mmol/L, the use of hypoglycemic drugs, and/or based on self-reported history. Prediabetes was defined as impaired fasting glucose (6.1mmol/L ≤ FPG < 7.0mmol/L and 2hPG < 7.8mmol/L) and/or impaired glucose tolerance (FPG < 7.0mmol/L and 7.8mmol/L ≤ 2hPG < 11.1mmol/L. Normoglycemia was defined as FPG < 6.1mmol/L and 2hPG < 7.8mmol/L. Hypertension was defined as SBP ≥ 140mmHg, DBP ≥ 90mmHg, the use of antihypertensive drugs, or based on self-

reported history. In this study, we considered participants with vascular complications if they had albuminuria (UACR ≥ 30 mg/g) or reported the history of coronary heart disease or stroke.

2.4. Statistical analysis

Continuous variables were presented as means ± standard deviations (SDs) or medians (25^{th} percentile, 75^{th} percentile), and categorical variables as numbers (percentages). Differences in parameters across groups were compared using one-way analysis of variance, non-parametric Kruskal–Wallis test, or Chi-squared test, when appropriate. Multinomial logistic regression analyses were performed to explore the associations of SUSPPUP and its components (expressed in quartiles and continuous scales) with the presence of prediabetes and diabetes with or without adjustment for age, gender, BMI, ethnicity (Han and others), current smoking, WHR, SBP, DBP, TG, HDL, LDL and eGFR. Subgroup analyses based on gender (male or female), age (≥ 65 or < 65 years), ethnicity (Han or others), hypertension (with or without), weight status (BMI < 24, 24-27.9, or 28 kg/m^2), current smoking (yes or no), regular exercise (yes or no), family history of diabetes (with or without), and the presence of vascular complications (with or without) were also conducted. Multiple linear regression analysis was used to assess the associations of SUSPPUP with glycemic indices (including FPG, 2hPG, HbA1c, urine glucose), cardiometabolic biomarkers (BMI, WHR, SBP, TC, TG, HDL, LDL) and insulin resistance-related markers (TyG, CVAI, LAP) with or without adjustment for the aforementioned covariates. Since antihypertensive and hypoglycemic agents

might affect the urine excretion of Na^+ and K^+, sensitivity analyses upon the exclusion of participants taking these agents were performed to assess their influence on the study outcomes. Moreover, we also conducted additional analyses to evaluate whether SUSPPUP showed any association with the presence of newly- or previously-diagnosed diabetes. All statistical analyses were conducted using SPSS version 25.0. A two-sided *P* value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of enrolled participants

The characteristics of included 5,581 participants (n = 3,268 with normoglycemia, n = 1,269 with prediabetes, and n = 1,044 with diabetes) are shown in Table 1. Among the participants with diabetes, 354 were newly diagnosed. About 65.5% of the included participants were females, and 87% were of Han ethnicity. The mean ages of the participants with normoglycemia, prediabetes, and diabetes were 53.4, 57.2, and 59.0 years, respectively.

Glycemic indices (including FPG, 2hPG, HbA1c and urinary glucose), insulin resistance-related markers (including TyG, CVAI and LAP), and cardiometabolic biomarkers (including BMI, WC, WHR, SBP, DBP, TC, TG, LDL) were all significantly higher in participants with prediabetes and diabetes than those with normoglycemia (all $P < 0.001$). SUSPPUP was higher in participants with prediabetes or diabetes vs. normoglycemia (both $P < 0.001$). However, relative to participants with

normoglycemia, spot urinary Na^+ was lower in participants with diabetes ($P < 0.001$), while spot urinary K^+ was higher in participants with prediabetes and diabetes (both $P < 0.01$), a lower ratio of urinary Na^+ and K^+ was also observed in participants with prediabetes and diabetes (both $P < 0.01$). While serum Na^+ was higher in participants with prediabetes than those with normoglycemia but not diabetes, serum K^+ did not differ between the three groups. Moreover, the proportion of family history of diabetes was higher in participants with diabetes, while the percentages of vascular complications and hypertension were higher in both diabetes and prediabetes group (Table 1).

3.2. SUSPPUP and its components with prediabetes

Table 2 shows the odds ratios (ORs) and 95% confidence intervals (CIs) for prediabetes in relation to SUSPPUP. Compared with the 1st quartile of SUSPPUP, the OR for prediabetes was 1.05 (95% CI: 0.87, 1.26) for the 2nd quartile, 1.06 (95% CI: 0.88, 1.28) for the 3rd quartile, and 1.39 (95% CI: 1.16, 1.67) for the 4th quartile in the crude model, respectively. These associations remained significant after multivariable adjustment (P for trend < 0.001). The OR for prediabetes per 1 SD increment of SUSPPUP was 1.21 (95% CI: 1.13, 1.29). Subgroup analyses did not reveal any significant interaction effects from gender, age, ethnicity, the presence of hypertension, weight status, current smoking, regular exercise, family history of diabetes, or the presence of vascular complications (Figure 2A).

For the components of SUSPPUP, higher serum Na^+ was significantly associated with increased odds of prediabetes in the unadjusted model, but this association was no longer evident after multivariable adjustment. In addition, higher spot urinary Na^+ and urinary Na^+/K^+ was associated with lower odds of prediabetes, but spot urinary K^+ showed the opposite (Table S1). However, there was no significant association between serum K and prediabetes.

3.3. SUSPPUP and its components with diabetes

Compared with the 1st quartile of SUSPPUP, the OR for diabetes was 1.21 (95% CI: 0.98, 1.49) for the 2nd quartile, 1.35 (95% CI: 1.09,1.66) for the 3rd quartile, and 2.07 (95% CI: 1.69, 2.53) for the 4th quartile, respectively, in the crude model (Table 3). These associations were not significantly changed after multivariable adjustment. Moreover, the OR for diabetes in relation to every 1 SD increment of SUSPPUP was 1.39 (95% CI: 1.29, 1.49). Subgroup analyses did not reveal any significant interaction effects from the variables listed in Figure 2B.

For the components of SUSPPUP, higher serum Na^+, spot urinary Na^+ and urinary Na^+/K^+, and lower spot urinary K^+ were associated with lower odds of prevalent diabetes (Table S1).

3.4. SUSPPUP with glycemic indices, cardiometabolic biomarkers, and insulin resistance-related markers

As shown in Table 3, SUSPPUP was positively associated with FPG ($P < 0.001$), 2hPG ($P < 0.001$), and HbA1c ($P = 0.003$) after multivariable adjustment, but not with urinary glucose. A negative correlation between SUSPPUP and BMI was found; however, the correlation was not statistically significant after adjustment. In addition, SUSPPUP was negatively associated with SBP ($P < 0.001$) and TC ($P = 0.04$) but positively associated with TG ($P = 0.003$) after multivariable adjustment. As for insulin resistance-related markers, SUSPPUP was positively correlated with TyG, whereas there was no correlation with CVAI and LAP.

3.5. Sensitivity analysis

Sensitivity analyses upon the exclusion of participants taking antihypertensive and hypoglycemic agents showed comparable results regarding the association of SUSPPUP odds of prediabetes or diabetes to that from the original analyzes (Table S2 and S3). Moreover, outcomes on the association of the components of SUSPPUP with the odds of prediabetes or diabetes were also unchanged. Furthermore, a positive association of SUSPPUP with newly- or previously-diagnosed diabetes was observed (Table S4), and the association of SUSPPUP with glycemic indices remained significant in newly- or previously-diagnosed diabetes (Table S5).

4. Discussion

Main findings

Our study showed that high SUSPPUP was associated with dysglycemia, including increased odds of prediabetes and diabetes in Chinese community-dwellers. However, mixed outcomes were observed for the components of SUSPPUP: spot urinary K^+ was positively associated with the presence of prediabetes and diabetes, while serum and spot urinary Na^+ acted in the opposite manner.

Interpretations and implications

SUSPPUP is regarded to be a reliable measure to reflect renal function of Na^+ retention and K^+ excretion [14], which has been recently proposed as a simple and convenient screening method for primary aldosteronism [14]. Extending this insight, our study showed that SUSPPUP could be linked to the risk of dysglycemia, since higher SUSPPUP was associated with bigger odds of prediabetes and diabetes and related to elevated glycemic indices. Moreover, our study also showed that the association of SUSPPUP with the odds of prediabetes or diabetes was unlikely to be affected by gender, ageing, obesity, hypertension, smoking, regular excise, family history of diabetes, and the presence of vascular complications, all of which are identified risk factors for diabetes [24] or might confound the measurement of SUSPPUP. However, the mechanism underlying the association of SUSPPUP with glycemia and odds of diabetes remains unclear. One possible explanation could be that high SUSPPUP might be indicative of an excessive aldosterone secretion [15, 25]; the latter may contribute to the development of insulin resistance and impaired glucose disposal by the skeletal muscle [17]. Indeed, there was a positive relationship of SUSPPUP with TG and TyG,

both of which are associated with increased risk of dysglycemia including diabetes.

Since SUSPPUP was derived from serum and urinary Na^+ and K^+, the association of its components with glucose metabolism were also analyzed in the present study. We observed that low spot urinary Na^+ and high spot urinary K^+ were associated positively with the odds of prediabetes and diabetes. Serum Na^+ was positively associated with the odds of prediabetes but this association disappeared after adjusting for multivariable; however, there was a negative association between serum Na^+ and the odds of diabetes, indicating that the results may be contradictory regarding the association of serum Na^+ with prediabetes and diabetes. Given that there was no significant association of serum K^+ with prediabetes and diabetes, it seems that investigation of the association between electrolytes and glucose metabolism might be inadequate if we only focused on an individual electrolyte due to the inconsistent results. SUSPPUP, which is a composite electrolyte index accounts for the mutual influence arising from the balance of Na^+ and K^+, would be a reliable measure to reflect renal function of Na^+ retention and K^+ excretion. The positive association of SUSPPUP with glucose metabolism in the present study indicates that increases in Na^+ retention and K^+ excretion in the kidney, are associated with increased prevalence of prediabetes and diabetes.

There is evidence that the expression of sodium glucose co-transporter 2 (SGLT-2) in renal tubules is upregulated in the context of hyperglycemia and/or insulin resistance [26, 27], which would enhance Na^+ reabsorption in the proximal tubules. In support of this concept, Pruijm et al. [28] observed that patients with impaired fasting glucose and

diabetes had increased reabsorption of Na^+ in the proximal segments of the nephron. Similarly, Zhao et al. [29] found that hyperglycemia was associated with a reduction in 24-hour urinary Na^+ excretion, and that urinary Na^+ excretion correlated negatively with FPG and HbA1c in patients with type 2 diabetes. Accordingly, the lower spot urinary Na^+ may have reflected an enhanced Na^+ reabsorption caused by hyperglycemia and hyperinsulinemia in the present study. Despite decreased urinary Na^+ excretion was observed in participants with diabetes in the present study, we only found that serum Na^+ was higher in participants with prediabetes than those with normoglycemia but not diabetes, which may be related to the hemodilution caused by elevated plasma osmotic pressure induced by hyperglycemia [30]. Until now, there was no similar report on the association between spot urinary Na^+ and glucose metabolism, further research is needed to verify our results.

In the present study, we also found that participants with prediabetes and diabetes had increased urinary K^+ excretion, which may be related to the hyperglycemia-induced osmotic diuresis [30]. Moreover, despite increased urinary K^+ excretion in participants with prediabetes and diabetes, serum K^+ did not differ between these three groups. This may be related to insulin resistance [30], as can be seen in our study, the insulin resistance-related markers were all higher in participants with prediabetes and diabetes; insulin resistance can reduce the entry of K^+ into cells, causing an increase in serum K^+, so that can balance the loss of urinary K^+. Lower serum K^+ (even in the normal range) has been reported to be related to increased risk of incident diabetes [6-9]. In the current

study, there was no significant association of serum K^+ with the presence of prediabetes, but a positive association of serum K^+ with the presence of diabetes in subjects without antihypertensive drugs was found, attesting to the insufficiency of an individual electrolyte for predicting the risk of dysglycemia.

Medications like antihypertensive (e.g., angiotensin-converting enzyme inhibitors) and hypoglycemic agents (e.g., insulin) affect the levels of electrolytes, and therefore may influence our results on the associations of SUSPPUP and its components with the odds of prediabetes or diabetes. However, our sensitivity analysis upon the exclusion of participants taking such medications suggested that they did not have significant impacts on our results.

Strength and Limitation

This is the first study with a large sample size to explore the association of SUSPPUP with glucose metabolism in Chinese community-dwellers. However, our study has some limitations. First, our study participants tended to be older and we included more females than males, although they had been used as covariables in the adjusted analyses. Second, due to the nature of cross-sectional design, the causality of the association of SUSPPUP with prediabetes and diabetes cannot be determined in the present study. Third, despite of the significant associations of SUSPPUP with prediabetes and diabetes, the diagnostic value of SUSPPUP for prediabetes and diabetes was inadequate (their area under the curves was slightly higher than 0.50), indicating that SUSPPUP might be not an ideal measure for screening for prediabetes or diabetes in general

population. Fourth, morning spot but not 24-hour urine collection was used in our study. However, there is evidence that electrolytes measured in morning spot urine showed good correlations with those in 24-hour urine samples [31]. Fifth, some Chinese herb (e.g., glycyrrhiza) may exert aldosterone action and could affect SUSPPUP ratio. However, such information was not collected in our study, which might potentially weaken the robustness of our findings. Finally, we did not collect data on dietary intake and urine volume, while they may influence the concentrations of Na^+ and K^+ in serum and urine. However, SUSPPUP is derived from serum Na^+ to urinary Na^+ divided by (serum K^+) ^{2} to urinary K^+, and therefore internally corrected for these variations.

Conclusions

Increases in Na^+ retention and K^+ excretion in the kidney, as reflected by an elevated SUSPPUP, are associated with increased prevalence of prediabetes and diabetes in Chinese community-dwelling population. Further studies are warranted to determine whether interventions that suppress renal Na^+ retention and K^+ excretion have the potential for reducing the risk of dysglycemia, and to explore whether SUSPPUP could be used as an effective indicator to construct lifestyle intervention programmes (e.g., diet modification and exercise) for diabetes prevention.

Appendices

Table S1: Odds of prediabetes and diabetes in relation to serum or urinary sodium and potassium;

Table S2: Odds of prediabetes and diabetes in subjects without antihypertensive drugs in relation to serum or urinary sodium and potassium and SUSPPUP ratio.

Table S3: Odds of prediabetes and diabetes in subjects without hypoglycemic drugs in relation to serum or urinary sodium and potassium and SUSPPUP ratio.

Table S4: Odds of newly- and previously-diagnosed diabetes in relation to SUSPPUP ratio.

Table S5: Association of SUSPPUP ratio with glycemic indices in participants with newly and previously diagnosed diabetes.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Human Research Ethics Committee of Zhongda Hospital, Southeast University (2016ZDSYLL092-P01).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Declarations of interest

None.

Credit authorship contribution statement

Miaomiao Sang: Conceptualization, Data curation, Formal analysis, Investigation,

Methodology, Roles/Writing - original draft; Yu Liu: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization; Tongzhi Wu: Data curation, Methodology,Validation, Visualization; Xiaoying Zhou: Data curation, Formal analysis, Investigation; Duolao Wang: Data curation, Formal analysis, Methodology, Software, Validation,Visualization; Zilin Sun: Conceptualization, Data curation,
Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review &editing; Shanhu Qiu: Conceptualization, Data curation, Formal analysis,Methodology, Validation, Visualization, Writing - review &editing.

Funding

This work was funded by the National Key R&D Program of China (grant No. 2016YFC1305700), the Postgraduate Research＆Practice Innovation Program of Jiangsu Province (grant No. SJCX21_0083). Shanhu Qiu has been supported by the "Best Young Scholars" Fellowship from Southeast University. The funders had no roles in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript.

Acknowledgments

None.

REFERENCE

1. Bohr DF. Electrolytes and smooth muscle contraction. Pharmacological reviews 1964; 16:85-127.

2. Lobo DN. Fluid, electrolytes and nutrition: physiological and clinical aspects. The Proceedings of the Nutrition Society 2004;63:453-66, https://doi.org/ 10.1079/pns2004376.

3. Cai X, Li X, Fan W, Yu W, Wang S, Li Z, et al. Potassium and Obesity/Metabolic Syndrome: A Systematic Review and Meta-Analysis of the Epidemiological Evidence. Nutrients 2016;8:183, https://doi.org/ 10.3390/nu8040183.

4. Soltani S, Kolahdouz Mohammadi R, Shab-Bidar S, Vafa M, Salehi-Abargouei A. Sodium status and the metabolic syndrome: A systematic review and meta-analysis of observational studies. Critical reviews in food science and nutrition 2019;59:196-206, https://doi.org/ 10.1080/10408398.2017.1363710.

5. Kolahdouz-Mohammadi R, Soltani S, Clayton ZS, Salehi-Abargouei A. Sodium status is associated with type 2 diabetes mellitus: a systematic review and meta-analysis of observational studies. European journal of nutrition 2021;60:3543-3565, https://doi.org/ 10.1007/s00394-021-02595-z.

6. Chatterjee R, Davenport CA, Svetkey LP, Batch BC, Lin PH, Ramachandran VS, et al. Serum potassium is a predictor of incident diabetes in African Americans with normal aldosterone: the Jackson Heart Study. Am J Clin Nutr 2017;105:442-9, https://doi.org/ 10.3945/ajcn.116.143255.

7. Chatterjee R, Yeh HC, Shafi T, Anderson C, Pankow JS, Miller ER, et al. Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2011;93:1087-91, https://doi.org/ 10.3945/ajcn.110.007286.

8. Doenyas-Barak K, Beberashvili I, Vinker S. Serum potassium is an age-dependent risk factor for pre-diabetes and diabetes in the Israeli population. Diabetes & vascular disease research 2014;11:103-9, https://doi.org/ 10.1177/1479164114521227.

9. Chatterjee R, Yeh HC, Shafi T, Selvin E, Anderson C, Pankow JS, et al. Serum and dietary potassium and risk of incident type 2 diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med 2010;170:1745-51, https://doi.org/ 10.1001/archinternmed.2010.362.

10. Gao S, Cui X, Wang X, Burg MB, Dmitrieva NI. Cross-Sectional Positive Association of Serum Lipids and Blood Pressure With Serum Sodium Within the Normal Reference Range of 135-145 mmol/L. Arteriosclerosis, thrombosis, and vascular biology 2017;37:598-606, https://doi.org/ 10.1161/ATVBAHA.116.308413.

11. Kuwabara M, Kanbay M, Niwa K, Ae R, Andres-Hernando A, Roncal-Jimenez CA, et al. Hyperosmolarity and Increased Serum Sodium Concentration Are Risks for Developing Hypertension Regardless of Salt Intake: A Five-Year Cohort Study in Japan. Nutrients 2020;12:1422, https://doi.org/ 10.3390/nu12051422.

12. Wang S, Hou X, Liu Y, Lu H, Wei L, Bao Y, et al. Serum electrolyte levels in relation to macrovascular complications in Chinese patients with diabetes mellitus. Cardiovasc

Diabetol 2013;12:146, https://doi.org/ 10.1186/1475-2840-12-146.

13. Hu G, Jousilahti P, Peltonen M, Lindström J, Tuomilehto J. Urinary sodium and potassium excretion and the risk of type 2 diabetes: a prospective study in Finland. Diabetologia 2005;48:1477-83, https://doi.org/ 10.1007/s00125-005-1824-1.

14. Willenberg HS, Kolentini C, Quinkler M, Cupisti K, Krausch M, Schott M, et al. The serum sodium to urinary sodium to (serum potassium)2 to urinary potassium (SUSPPUP) ratio in patients with primary aldosteronism. European journal of clinical investigation 2009;39:43-50, https://doi.org/ 10.1111/j.1365-2362.2008.02060.x.

15. Kanaan E, Haase M, Vonend O, Reincke M, Schott M, Willenberg HS. Aldosterone-Mediated Sodium Retention Is Reflected by the Serum Sodium to Urinary Sodium to (Serum Potassium)^2 to Urinary Potassium (SUSPPUP) Index. Diagnostics (Basel, Switzerland) 2020;10:545, https://doi.org/ 10.3390/diagnostics10080545.

16. Steichen O, Blanchard A, Plouin PF. Assessment of serum sodium to urinary sodium divided by (serum potassium)^2 to urinary potassium as a screening tool for primary aldosteronism. European journal of clinical investigation 2011;41:189-94, https://doi.org/ 10.1111/j.1365-2362.2010.02401.x.

17. Ronconi V, Turchi F, Appolloni G, di Tizio V, Boscaro M, Giacchetti G. Aldosterone, mineralocorticoid receptor and the metabolic syndrome: role of the mineralocorticoid receptor antagonists. Current vascular pharmacology 2012;10:238-46, https://doi.org/ 10.2174/157016112799304969.

18. Chen W, Li F, He C, Zhu Y, Tan W. Elevated prevalence of abnormal glucose

metabolism in patients with primary aldosteronism: a meta-analysis. Irish journal of medical science 2014;183:283-91, https://doi.org/ 10.1007/s11845-013-1007-x.

19. Qiu S, Du Z, Li W, Chen J, Wu H, Liu J, et al. Exploration and Validation of the Performance of Hemoglobin A1c in Detecting Diabetes in Community-Dwellers With Hypertension. Annals of laboratory medicine 2020;40:457-65, https://doi.org/ 10.3343/alm.2020.40.6.457.

20. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. Journal of the American Society of Nephrology: JASN 2006;17:2937-44, https://doi.org/ 10.1681/ASN.2006040368.

21. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metabolic syndrome and related disorders 2008;6:299-304, https://doi.org/ 10.1089/met.2008.0034.

22. Ahn N, Baumeister SE, Amann U, Rathmann W, Peters A, Huth C, et al. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. Sci Rep 2019;9:9693, https://doi.org/ 10.1038/s41598-019-46187-8.

23. Wan H, Wang Y, Xiang Q, Fang S, Chen Y, Chen C, et al. Associations between abdominal obesity indices and diabetic complications: Chinese visceral adiposity index and neck circumference. Cardiovasc Diabetol 2020;19:118, https://doi.org/

10.1186/s12933-020-01095-4.

24. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 2019;157:107843, https://doi.org/ 10.1016/j.diabres.2019.107843.

25. Balaş M, Zosin I, Maser-Gluth C, Hermsen D, Cupisti K, Schott M, et al. Indicators of mineralocorticoid excess in the evaluation of primary aldosteronism. Hypertension research : official journal of the Japanese Society of Hypertension 2010;33:850-6, https://doi.org/ 10.1038/hr.2010.76.

26. Vallon V. The proximal tubule in the pathophysiology of the diabetic kidney. American journal of physiology Regulatory, integrative and comparative physiology 2011;300:R1009-22, https://doi.org/ 10.1152/ajpregu.00809.2010.

27. Nakamura N, Matsui T, Ishibashi Y, Yamagishi S. Insulin stimulates SGLT2-mediated tubular glucose absorption via oxidative stress generation. Diabetology & metabolic syndrome 2015;7:48, https://doi.org/ 10.1186/s13098-015-0044-1.

28. Pruijm M, Wuerzner G, Maillard M, Bovet P, Renaud C, Bochud M, et al. Glomerular hyperfiltration and increased proximal sodium reabsorption in subjects with type 2 diabetes or impaired fasting glucose in a population of the African region. Nephrol Dial Transplant 2010;25:2225-31, https://doi.org/ 10.1093/ndt/gfq008.

29. Zhao Y, Gao P, Sun F, Li Q, Chen J, Yu H, et al. Sodium Intake Regulates Glucose Homeostasis through the PPARδ/Adiponectin-Mediated SGLT2 Pathway. Cell

metabolism 2016;23:699-711, https://doi.org/ 10.1016/j.cmet.2016.02.019.

30. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. World J Clin Cases 2014;2:488-96, https://doi.org/ 10.12998/wjcc.v2.i10.488.

31. Lee SG, Lee W, Kwon OH, Kim JH. Association of urinary sodium/creatinine ratio and urinary sodium/specific gravity unit ratio with blood pressure and hypertension: KNHANES 2009-2010. Clinica chimica acta; international journal of clinical chemistry 2013;424:168-73, https://doi.org/ 10.1016/j.cca.2013.05.027.

Table 1. Characteristics of included participants with different glycemic condition.

Characteristics	Normoglycemia (N = 3268)	Prediabetes (N = 1269)	Diabetes (N = 1044)	*P*
Female (%)	2196 (67.2%)	846 (66.7%)	613 (58.7%) **	< 0.001
Age (y)	53.4 ± 10.0	57.2 ± 8.8**	59.0 ± 8.5**	< 0.001
Glycemic indices				
FPG (mmol/L)	5.2 ± 0.5	5.5 ± 0.6**	7.6 ± 2.4**	< 0.001
2hPG (mmol/L) [a]	6.1 ± 1.1	8.8 ± 1.2**	12.7 ± 2.9**	< 0.001
HbA1c (%)	5.5 ± 0.6	5.7 ± 0.6**	7.0 ± 1.6**	< 0.001
Urine Glucose (mmo/L)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6) **	0.6 (0.3, 1.3) **	< 0.001
Insulin resistance-related markers				
TyG	8.5 ± 0.5	8.8 ± 0.6**	9.2 ± 0.7**	< 0.001
CVAI	89.8 ± 39.5	107.5 ± 36.9**	116.2 ± 37.4**	< 0.001
LAP	26.2 (15.4, 43.6)	37.8 (23.2, 60.7) **	43.4 (26.6, 68.3) **	< 0.001
Cardiometabolic biomarkers				
BMI (kg/m^2)	24.9 ± 3.9	25.9 ± 4.0**	26.2 ± 3.8**	< 0.001
WC (cm)	83.6 ± 10.5	86.7 ± 10.4**	88.8 ± 10.2**	< 0.001
WHR	0.87 ± 0.07	0.89 ± 0.06**	0.91 ± 0.06**	< 0.001
SBP (mmHg)	132 ± 19	139 ± 19**	142 ± 20**	< 0.001
DBP (mmHg)	82 ± 12	86 ± 11**	85 ± 11**	< 0.001
TC (mmo/L)	4.7 ± 0.9	4.8 ± 0.9**	4.0 ± 1.1**	< 0.001
TG (mmo/L)	1.1 (0.8, 1.6)	1.5 (1.0, 2.1) **	1.6 (1.1, 2.2) **	< 0.001
HDL (mmo/L)	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	0.06
LDL (mmo/L)	2.6 ± 0.7	2.7 ± 0.7**	2.7 ± 0.8**	< 0.001
eGFR (mL/min/1.73 m^2)	133.9 ± 29.8	133.7 ± 29.9	136.7 ± 34.2	0.24
Electrolytes				
SUSPPUP (mmol/L)$^{-1}$	3.0 ± 1.9	3.4 ± 2.3**	3.7 ± 2.6**	< 0.001
Serum Na^+ (mmo/L)	143 ± 3	143 ± 3**	142 ± 3	< 0.001
Serum K^+ (mmo/L)	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.4	0.07
Urinary Na^+ (mmo/L)	153 ± 53	150 ± 54	137 ± 53**	< 0.001
Urinary K^+ (mmo/L)	47.2 ± 16.2	48.9 ± 16.1**	48.9 ± 16.4**	< 0.001
Urinary Na^+ / K^+	3.7 ± 1.9	3.5 ± 1.9**	3.2 ± 1.8**	< 0.001
Current smoking (%)	510 (15.6%)	189 (14.9%)	182 (17.4%)	0.23
Family history of diabetes (%) [b]	615 (19.3%)	232 (18.9%)	343 (34.3%) **	< 0.001
Regular exercise (%) [c]	825 (25.9%)	309 (25.0%)	264 (25.8%)	0.84
Vascular complications (%) [d]	646 (20.3%)	364 (29.5%) **	456 (44.7%) **	< 0.001
Hypertension (%)	1509 (46.2%)	798 (62.9%) **	764 (73.2%) **	< 0.001
Newly diagnosed diabetes (%)	NA	NA	354 (33.9%)	NA
Anti-hypertensive treatment (%)	713 (21.8%)	416 (32.8%) **	480 (46.0%) **	< 0.001
Hypoglycemic treatment (%)	NA	NA	405 (38.8%)	NA

FPG, fasting plasma glucose; 2hPG, 2h-postprandial plasma glucose; HbA1c, glycated

hemoglobin A1c; TyG, the product of triglyceride and glucose; CVAI, Chinese visceral adiposity index; LAP, lipid accumulation product; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; Na^+, sodium; K^+, potassium; SUSPPUP, serum sodium to urinary sodium to (serum potassium)^2 to urinary potassium.

[a]834 participants did not provide data on 2hPG; [b]174 participants did not provide information on family history of diabetes; [c]132 participants did not provide information on regular exercise (defined as >30 min of moderate-intensity exercise for at least 3 days per week); [d]148 participants did not provide information on vascular complications (defined as having albuminuria or reporting the history of coronary heart disease or stroke).

Data were presented as means ± SDs or medians (25th percentile, 75th percentile) or numbers (percentages).

* $P < 0.05$ and ** $P < 0.01$ compared with subjects with normoglycemia.

Table 2. Odds of prediabetes and diabetes in relation to SUSPPUP ratio.

	Prediabetes (n = 1269)			**Diabetes (n = 1044)**		
		Unadjusted model	Adjusted model[#]		Unadjusted model	Adjusted model[#]
Quartiles of variables	N(cases/non-case)	OR (95% CI)	OR (95% CI)	N (cases/non-case)	OR (95% CI)	OR (95% CI)
SUSPPUP $(mmol/L)^{-1}$						
< 1.9	304/871	1.00	1.00	202/871	1.00	1.00
1.9-2.7	313/855	1.05 (0.87, 1.26)	1.09 (0.91, 1.33)	240/855	1.21 (0.98, 1.49)	1.34 (1.07, 1.68)
2.7-3.8	306/827	1.06 (0.88, 1.28)	1.14 (0.94, 1.39)	259/827	1.35 (1.09, 1.66)	1.63 (1.30, 2.04)
≥ 3.8	346/715	1.39 (1.16, 1.67)	1.51 (1.24, 1.83)	343/715	2.07 (1.69, 2.53)	2.56 (2.05, 3.19)
P for trend		< 0.001	< 0.001		< 0.001	< 0.001
Per 1-SD increase		1.19 (1.11, 1.27)	1.21 (1.13, 1.29)		1.33 (1.25, 1.42)	1.39 (1.29, 1.49)

SUSPPUP, serum sodium to urinary sodium to $(\text{serum potassium})^2$ to urinary potassium

[#] Adjusted for age, gender, body mass index, ethnicity (Han and others), current smoking, waist hip ratio, systolic blood pressure, diastolic blood pressure, triglyceride, high-density lipoprotein, low-density lipoprotein and estimated glomerular filtration rate.

Table 3. Association of SUSPPUP ratio with glycemic indices, cardiometabolic biomarkers and insulin resistance-related markers.

	Unadjusted model			Adjusted model[#]		
Outcome variables	β (95% CI)	Std β	*P*	β (95% CI)	Std β	*P*
Glycemic indices						
FPG (mmol/L)	0.057 (0.039, 0.075)	0.082	< 0.001	0.063(0.046, 0.081)	0.092	< 0.001
2hPG (mmol/L) [a]	0.140 (0.108, 0.173)	0.121	< 0.001	0.134 (0.103, 0.165)	0.116	< 0.001
HbA1c (%)	0.016 (0.003, 0.028)	0.033	0.01	0.018 (0.006, 0.030)	0.038	0.003
Urinary Glucose (mmol/L)	0.141 (-0.133, 0.415)	0.014	0.32	0.223 (-0.050, 0.497)	0.021	0.11
Cardiometabolic biomarkers						
BMI (kg/m2)	-0.068 (-0.117, -0.020)	-0.037	0.006	-0.009(-0.054, 0.036)	-0.005	0.69
WHR	-0.001 (-0.001, 0.000)	-0.021	0.12	-0.000 (-0.001, 0.001)	-0.006	0.63
SBP (mmHg)	-0.655 (-0.903, -0.408)	-0.069	< 0.001	-0.382 (-0.543, -0.220)	-0.040	< 0.001
TC (mmo/L)	0.001 (-0.010, 0.013)	0.003	0.81	-0.003 (-0.007, -0.000)	-0.008	0.04
TG (mmo/L)	0.013 (-0.005, 0.031)	0.019	0.17	0.027 (0.009, 0.044)	0.039	0.003
HDL (mmo/L)	0.002 (-0.001, 0.006)	0.017	0.20	-0.002 (-0.005, 0.002)	-0.012	0.32
LDL (mmo/L)	-0.001 (-0.010, 0.007)	-0.004	0.79	0.001 (-0.006, 0.009)	0.005	0.71
Insulin resistance-related markers						
TyG	0.020 (0.012, 0.028)	0.067	< 0.001	0.017 (0.012, 0.021)	0.056	< 0.001
CVAI	-0.046 (-0.537, 0.444)	-0.002	0.85	-0.018 (-0.209, 0.172)	-0.001	0.85
LAP	0.060 (-0.482, 0.603)	0.003	0.83	-0.068 (-0.251, 0.115)	-0.003	0.47

SUSPPUP, serum sodium to urinary sodium to (serum potassium)^2 to urinary potassium; FPG, fasting plasma glucose; 2hPG, 2h-postprandial plasma glucose; HbA1c, glycated hemoglobin A1c; BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; TC, total

cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TyG, the product of triglyceride and glucose; CVAI, Chinese visceral adiposity index; LAP, lipid accumulation product.

[a] 834 participants without 2hPG data.

[#] Adjusted for age, gender, body mass index, ethnicity (Han and others), current smoking, waist hip ratio, systolic blood pressure, diastolic blood pressure, triglyceride, high-density lipoprotein, low-density lipoprotein and estimated glomerular filtration rate. To be noted, if the outcome is BMI (or WHR), WHR (or BMI) was not adjusted in the model.

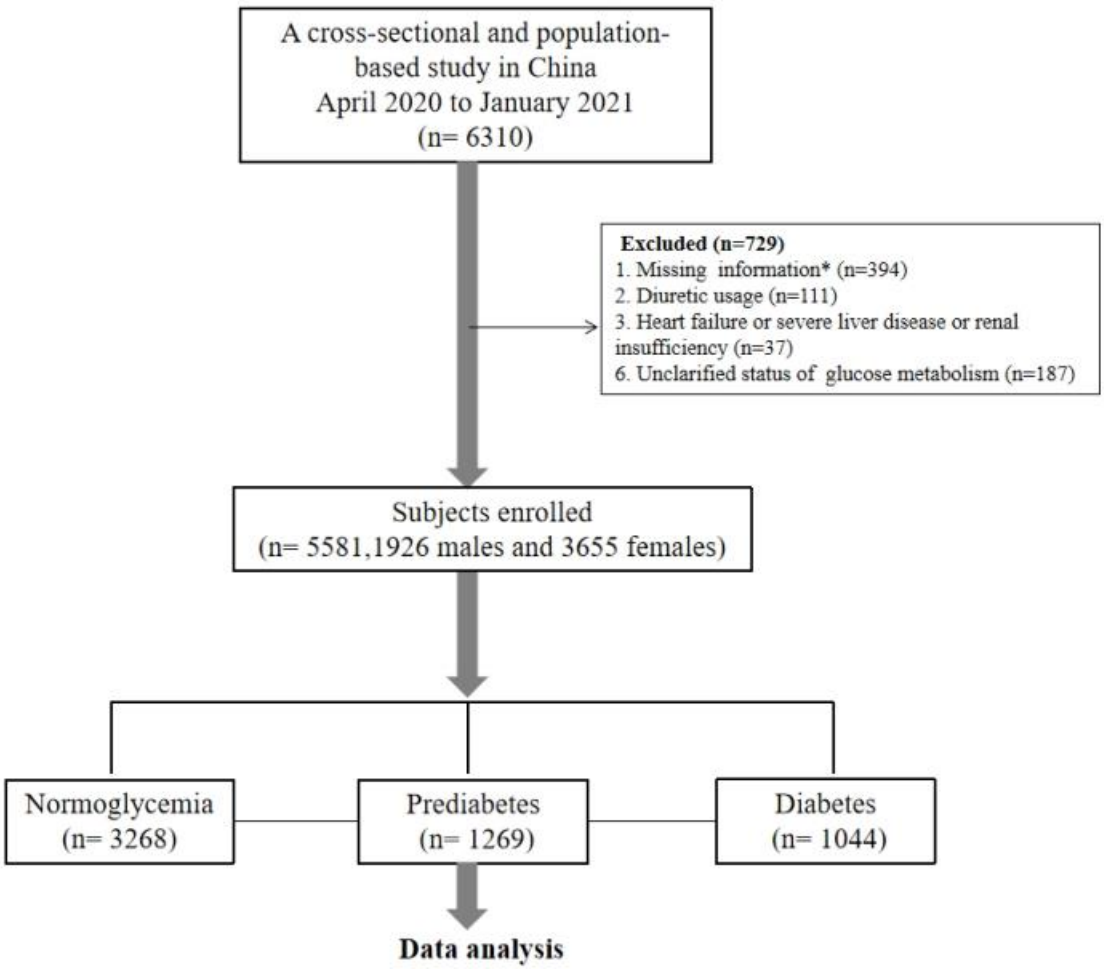
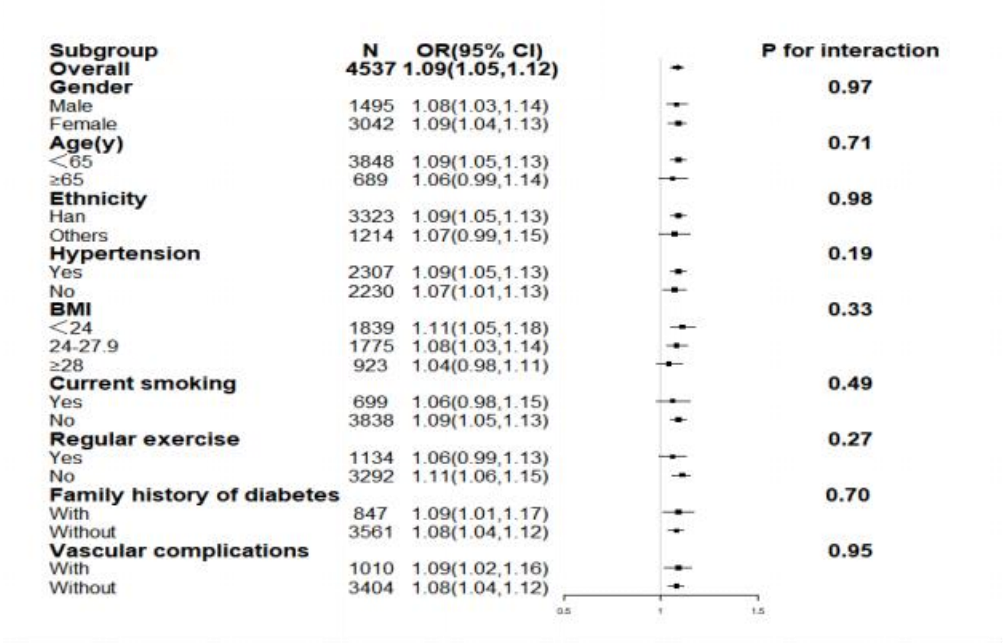


Figure 1. Flowchart of the study population

*indicates missing information on laboratory parameters (including serum Na^+ or K^+, fasting plasma glucose, glycated hemoglobin A1c, total cholesterol, triglyceride, high density lipoprotein, low-density lipoprotein, serum creatinine, urinary Na^+ or K^+, and urinary glucose) or anthropometric data (including systolic blood pressure, diastolic blood pressure, height, weight, waist circumference, hip circumference).

A



B

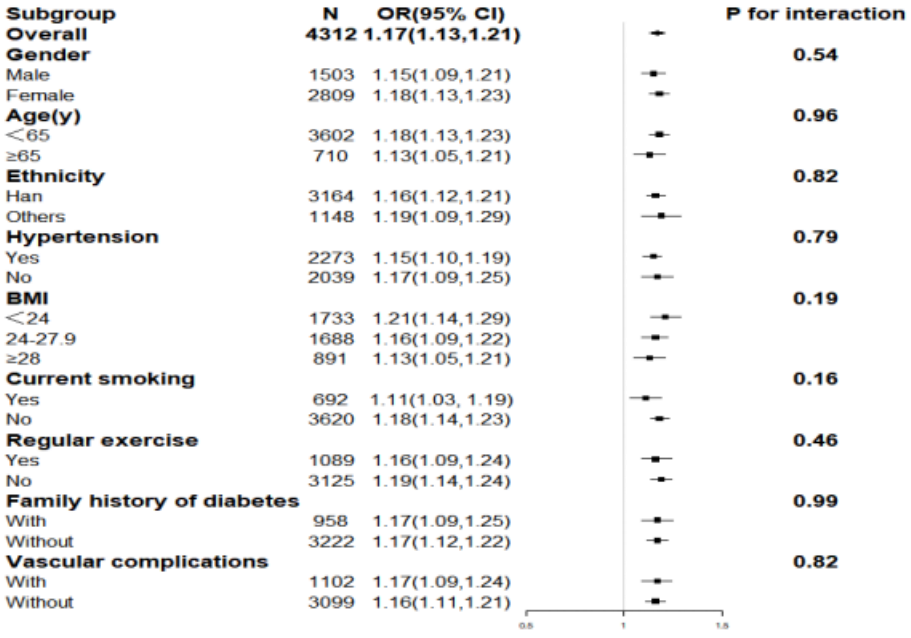


Figure 2. (A) Forest plots of the association between SUSPPUP and Prediabetes in various subgroups*; (B) Forest plots of the association between SUSPPUP and Diabetes in various subgroups*

*Adjusted for age, gender, body mass index, ethnicity (Han and others), current smoking, waist hip ratio, systolic blood pressure, diastolic blood pressure, triglyceride, high density lipoprotein, low-density lipoprotein, estimated glomerular filtration rate.