# Fasting Serum Fructose Levels Are Associated With Risk of Incident Type 2 Diabetes in Middle-Aged and Older Chinese Population

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## OBJECTIVE

**We investigated the relationship between fasting serum fructose levels and the risk of incident type 2 diabetes in a prospective Chinese cohort.**

## RESEARCH DESIGN AND METHODS

**Among 949 community-based participants aged ≥40 years without diabetes at baseline, fasting serum fructose levels were measured using liquid chromatography–tandem mass spectrometry. The participants were followed up for the occurrence of diabetes. Cox regression models were performed to analyze the effect of fasting serum fructose levels on risk of incident diabetes.**

## RESULTS

**During a median of 3.5 years' follow-up, 179 of 949 (18.9%) participants developed type 2 diabetes. Elevated fasting serum fructose levels were associated with an increased risk of incident diabetes in a dose-response manner. After adjustment for age, sex, BMI, lipid profiles, blood pressure, liver function, smoking and drinking status, baseline glucose level, and sugar-sweetened beverage consumption, a 1-SD increased fasting fructose level was associated with a 35% (95% CI 1.08–1.67) increased risk of developing diabetes. After further adjustment for serum uric acid and estimated glomerular filtration rate, the association was partially attenuated (hazard ratio 1.33 [95% CI 1.07–1.65]). The association was similar by age, prediabetes status, BMI, and family history of diabetes but attenuated in women ($P$ for heterogeneity = 0.037).**

## CONCLUSIONS

**Elevated fasting serum fructose levels were independently associated with increased risk of incident type 2 diabetes in a middle-aged and older Chinese population. Our data suggest that higher fasting serum fructose levels might serve as a biomarker and/or a contributor to incident diabetes.**


Type 2 diabetes is globally epidemic (1) and associated with an increase in cardiovascular diseases and mortality (2,3), which pose a heavy public burden. In Asia, type 2 diabetes has become prevalent over the past few decades, and the number of people with type 2 diabetes continues to rise (4). Therefore, identifying risk factors and/or early markers for future diabetes is of major importance. Dietary factors have been well acknowledged to play a key role in triggering diabetes (5). Accumulating evidence demonstrates that dietary fructose consumption primarily from sugar-sweetened

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beverages (SSBs) and fruit juice is associated with an increase in diabetes incidence and poor glycemic control in patients with diabetes (6,7).

Fructose, a six-carbon monosaccharide with similar chemical structure and the same caloric value as glucose, is one of the major ingredients of SSBs and fruit juice. While the majority of metabolized fructose is derived from dietary sources of sugar, animals and humans are capable of synthesizing fructose endogenously. Fructose is produced endogenously through activation of the aldose reductase-sorbitol dehydrogenase pathway. This is the only known mechanism whereby humans and most mammals generate fructose. Although fructose can be metabolized by hexokinase similarly to glucose (8), the relative affinity for fructose is substantially less. Furthermore, under most conditions, fructose is metabolized by fructokinase (ketohexokinase [KHK]), an enzyme that is specific for fructose. KHK phosphorylates fructose to fructose-1-phosphate, resulting in ATP depletion and further generation of uric acid, oxidants, and inflammatory proteins (9). Moreover, Lanaspa et al. (10) found that with fructose-free diet intake, endogenous fructose in liver could induce insulin resistance and fatty liver through KHK, and the effect is independent of energy intake.

In micromolar concentrations, serum fructose is much more reactive in vivo and plays a pivotal role in mediating the pathology process. Therefore, quantification of serum fructose levels is of clinical importance to investigate the effect of fructose on metabolic disease in human. There is evidence that fructose levels are elevated in patients with diabetic nephropathy, retinopathy, and neuropathy (11–13). However, serum fructose has rarely been explored in individuals with and without diabetes, and the results are controversial (14,15). Despite compelling data in vitro and in animal studies, to our knowledge, the association of fasting serum fructose with incident diabetes has not been investigated. In the current study, we examined the association between fasting serum fructose concentrations and the risk of incident diabetes in a prospective cohort.

## RESEARCH DESIGN AND METHODS

### Participants and Study Design

We designed and performed a prospective cohort study, which was approved by the Ethical Committee of Zhongshan Hospital Fudan University. Each participant provided written informed consent.

The prospective cohort study was conducted in the Shanghai Chongming District, where 9,930 subjects participated in the baseline survey from 2011 to 2012 and 7,707 participants completed the follow-up survey in 2014 (16). One thousand individuals who were free of diabetes at baseline were randomly selected for fasting serum fructose measurement. Fasting serum fructose concentration was finally measured in 949 individuals who remained after exclusion of participants with missing blood samples at baseline ($n = 3$), missing blood glucose values at follow-up ($n = 1$), or extreme serum fructose values ($<0.43$ μg/mL or $>1.17$ μg/mL) ($n = 47$).

Standard questionnaires were used to obtain information about demographic characteristics, lifestyle, history of diseases, and medication by face-to-face interviews conducted by trained investigators. Body weight and height were obtained in light clothing and bare feet to the nearest 0.1 kg and 0.1 cm, respectively. BMI was derived from weight in kilograms divided by the square of height in meters. Blood pressure was measured in the nondominant arm with the subject in a seated position three consecutive times with a 1-min interval and at least a 10-min rest using an automated electronic sphygmomanometer. The average value of three readings was used. Smokers were defined as participants regularly consuming cigarettes (duration >6 months) right before the survey. Drinkers were defined as participants regularly consuming alcohol (duration >6 months) right before the survey. Fasting venous blood samples were collected after at least a 10-h fast. Plasma glucose levels were measured by glucose oxidase method. Serum insulin was measured using an electrochemiluminescence assay. The index of HOMA of insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L) / 22.5. The index HOMA of insulin sensitivity (HOMA-IS) was calculated as 1 / (fasting glucose × fasting insulin). Serum triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), ALT, AST, and serum creatinine were measured on the Auto-Analyzer. Estimated glomerular filtration rate (eGFR) was calculated by the following equations (Chronic Kidney Disease Epidemiology Collaboration): *1*) for females, creatinine (Cr) ≤0.7 mg/dL, $eGFR = 144 \times (Cr / 0.7)^{-0.329} \times (0.993)^{age}$ and Cr >0.7 mg/dL, $eGFR = 144 \times (Cr / 0.7)^{-1.209} \times (0.993)^{age}$; *2*) for males, Cr ≤0.9 mg/dL, $eGFR = 141 \times (Cr / 0.7)^{-0.411} \times (0.993)^{age}$ and Cr >0.9 mg/dL, $eGFR = 141 \times (Cr / 0.7)^{-1.209} \times (0.993)^{age}$ (17).

Diet information was assessed using a food frequency questionnaire at baseline, which was designed to assess usual diet over the previous year. Participants were asked how often they consumed each food item included in the questionnaire. The frequency response ranged from times per day to times per week, month, or year. In addition to frequency of consumption, participants were asked to estimate the usual quantity of SSB consumed as a standard bottle (250 mL). A typical serving of SSB was defined as 12 oz (360 mL) (18).

### Definition of Incident Diabetes

A 75-g oral glucose tolerance test was conducted, and blood samples were collected at 0 and 2 h postload. Glycated hemoglobin ($HbA_{1c}$) was measured by high-performance liquid chromatography. According to American Diabetes Association 2010 criteria, diabetes was defined as *1*) self-reported diabetes by health care professionals, and/or *2*) fasting plasma glucose ≥7.0 mmol/L, and/or *3*) 2-h oral glucose tolerance test plasma glucose ≥11.1 mmol/L, and/or *4*) $HbA_{1c}$ concentration ≥6.5% (48 mmol/mol). Incident diabetes was evaluated at the date of first diagnosis or the latest assessed date of follow-up, whichever occurred first. The duration of follow-up was calculated from the date of baseline blood draw to the date of assessment.

### Quantitation of Serum Fructose Concentrations

Peripheral venous blood samples were collected after at least a 10-h overnight fast and stored at −80°C until assay. Serum fructose concentration was measured by a validated liquid chromatography–tandem mass spectrometry method as described previously with some modifications (19).

Briefly, 50-μL serum samples were mixed with 10 μL internal standard (D-fructose-$^{13}C_6$) and 150 μL methanol, vortexed for 10 s, and centrifuged. Fifty microliters of supernatant were transferred

to a tube and mixed with 100 μL of 75% aqueous methanol containing 1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride (200 mmol/L) (Sigma-Aldrich) and 3-nitropheylhydrazine hydrochloride (150 mmol/L) (Sigma-Aldrich). The mixtures were reacted at 50°C for 60 min. After reaction, 350 μL water was added, and the solutions were stored at −15°C until assay.

The samples were analyzed by negative-ion ultraperformance liquid chromatography–electrospray ionization–mass spectrometry in a multiple reaction monitor mode performed on an UltiMate 3000 RSLC System (Thermo Fisher Scientific, Sunnyvale, CA) coupled to an API 4000 mass spectrometer (SCIEX, Concord, ON, Canada). Chromatographic separations were performed on a Waters ACQUITY UPLC HSS PFP (2.1 × 150 mm, 1.7 μm) column using water:formic acid (100:0.1 v/v; solvent A) and acetonitrile:formic acid (100:0.1 v/v; solvent B) as the mobile phase for gradient elution at a flow rate of 0.2 mL/min. The mass transitions were charge/mass ratio 314.1→236.0 for fructose and 320.1→240.0 for D-fructose-$^{13}C_6$, respectively. All the data were acquired and processed using Analyst 1.6 software (SCIEX). Coefficients of variation of the assay were assessed by repeatedly analyzing quality control samples. Interassay coefficients of variation were 2.1% for fructose measurements.

### Oral SSB Challenge Test

We enrolled 11 healthy men and women aged 18–35 years who had no chronic illness (including no known history of diabetes, heart, renal, pulmonary, or hematologic disease) or active infections and were not pregnant or lactating. Participants were instructed not to consume any SSB or fruit juice 7 days before the study. The fructose-containing beverage challenge was administered to all participants. For each participant, a baseline blood sample was obtained after at least a 10-h overnight fast. SSB (330 mL can of cola) was drunk by each participant within a 10-min period in the morning after the overnight fast. A can of SSB (330 mL) contains a total of 10.6 g sugar, of which 10.3 g is high-fructose corn syrup (55% fructose and 43% glucose) and 0.3 g sucrose. Participants refrained from eating and drinking until the final blood sample was collected. Serial venous blood samples were drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h. Blood was centrifuged at 3,000*g* for 10 min, and serum was collected and stored at −80°C until assay.

### Statistical Analysis

Normally distributed continuous variables are presented as means with SDs, whereas skewed distributed continuous variables are presented as geometrical median and interquartile range. Continuous variables were compared by Student *t* test and one-way ANOVA, whereas skewed distribution variables were compared by Mann-Whitney *U* and Kruskal-Wallis tests. Categorical variables were expressed as proportions and compared across groups using $\chi^2$ tests.

To minimize the potential confounding factors, covariates were selected on the basis of biologic interest, well-established risk factors for diabetes, or associated exposures and outcomes. Age- and sex-adjusted models and multivariable-adjusted models were used to explore the independent effect of fructose on risk of diabetes. Cox proportional hazards regressions were used to estimate hazard ratios (HRs) and 95% CIs of incident type 2 diabetes according to quartiles of serum fructose concentration, with the lowest quartile as the reference. In addition, the HR for per-SD increase of fructose levels was also tested. Potential effect modification was analyzed for age, sex, glucose tolerance status, obesity status, and family history of diabetes by assessing the significance of multiplicative interaction terms using Wald tests. Multivariable linear regression analysis was performed to build a composite predictor score for incident diabetes. Log-likelihood ratios (LHRs) were calculated to identify the predictive model fit, and the C-statistic was used to evaluate model discrimination.

Statistical analyses were performed on SAS 9.3 software (SAS Institute, Cary, NC). A two-sided $P < 0.05$ was considered statistically significant.

## RESULTS

### Baseline Characteristics of the Participants

In the prospective cohort, 949 individuals without diabetes were assessed. The mean age was 56 years (range 40–71 years), and 291 (30.7%) individuals were male. Fasting serum fructose concentrations were approximately normally distributed with a mean value of 0.85 ± 0.21 μg/mL (Fig. 1).

During a median of 3.5 years follow-up, 179 of 949 (18.9%) individuals developed diabetes. Individuals who developed diabetes tended to have higher age, BMI, fasting plasma glucose, 2-h postload glucose, $HbA_{1c}$, systolic blood pressure, diastolic blood pressure, TC, TG, ALT, and AST at baseline (Table 1). Fasting serum fructose concentrations were elevated in individuals who developed diabetes compared with those who did not (0.85 ± 0.15 vs. 0.82 ± 0.15 μg/mL, $P = 0.0053$) (Table 1).

### Serum Fructose Levels Were Associated With an Increased Risk of Incident Diabetes

The participants were categorized according to quartiles of fasting serum fructose concentrations (Table 2). Fasting plasma glucose, 2-h postload glucose, $HbA_{1c}$, HOMA-IR, serum TG, ALT, AST, and uric acid were increased by increasing serum fructose quartiles (all $P < 0.05$), whereas HOMA-IS decreased by increasing serum fructose quartiles ($P < 0.0001$). Pearson correlation analyses revealed that sex, current smoker status, current drinker status, fasting plasma glucose, 2-h postload glucose, $HbA_{1c}$, serum TG, ALT, AST, and uric acid levels were significantly correlated with fasting serum fructose concentrations (Supplementary Table 1).

A graded increase of incident diabetes rate was observed with an increase of fasting serum fructose quartiles. Furthermore, Cox regression models were performed to investigate the effect of fasting serum fructose concentrations on developing diabetes in a series of adjusted models (Table 3). In the age- and sex-adjusted model, compared with the lowest quartile, participants in the highest quartile had a 79% (HR 1.79 [95% CI 1.17–2.76]) higher risk of incident diabetes, and each SD increase in fasting serum fructose levels was associated with a 39% (1.39 [1.13–1.69], $P = 0.0015$) increased risk of incident diabetes. The association was slightly attenuated but still remained after additional adjustment for BMI, smoking and drinking status, family history of diabetes, systolic and diastolic blood pressure, serum TC, TG, LDL-C, HDL-C, ALT, AST, and baseline glucose level. In addition, we adjusted the potential mediators and factors influencing serum fructose, including SSB consumption, uric acid, and eGFR. In the final model, each SD increase in fasting fructose

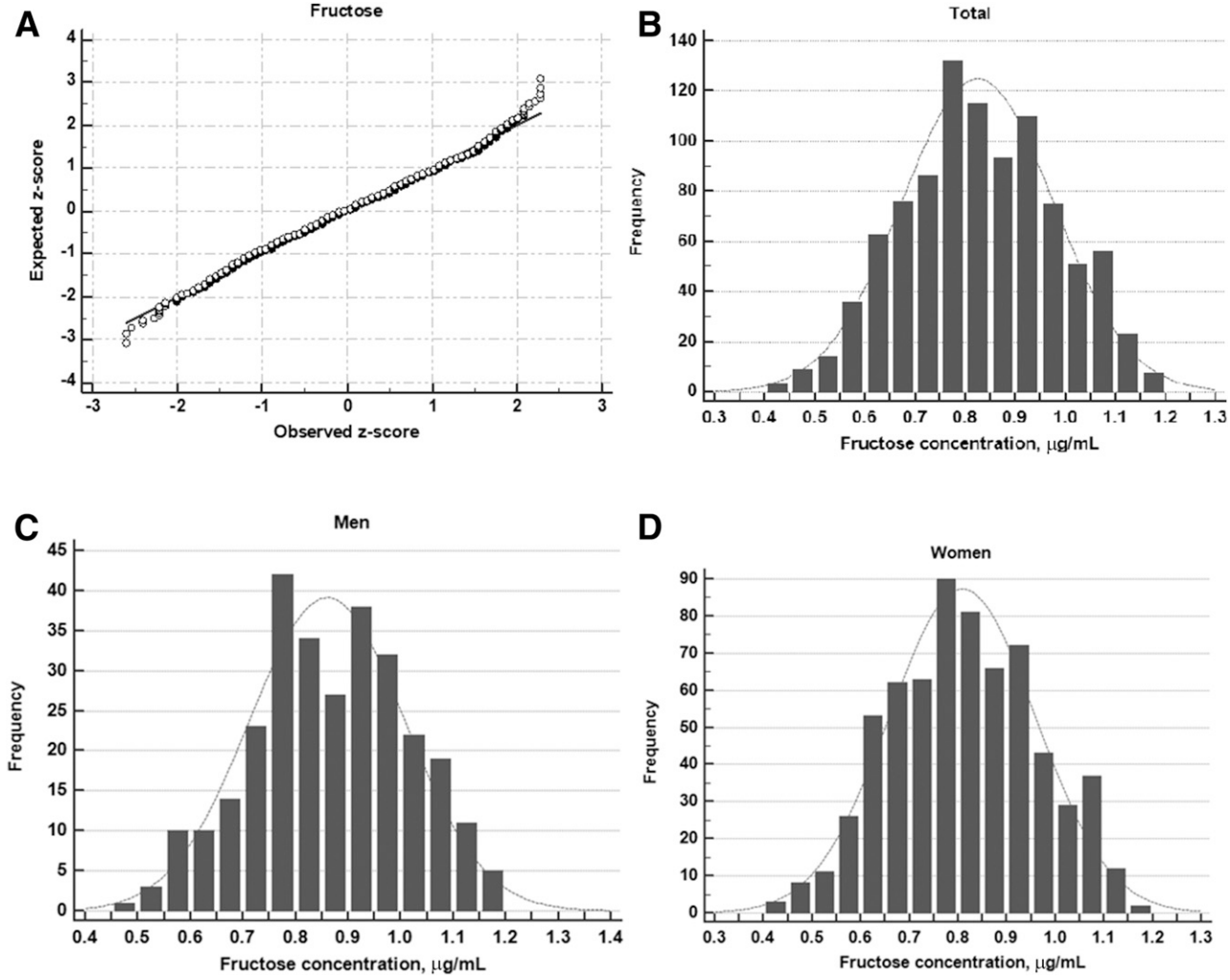


**Figure 1**—Distribution of fasting serum fructose concentrations in all participants and in men and women separately.

concentrations was associated with a 33% (1.33 [1.07–1.65], $P = 0.010$) increased risk of incident diabetes. Furthermore, a subgroup analysis was performed in participants with exclusion of frequent SSB consumption (≥1 serving per day), and the association of fasting serum fructose levels with incident diabetes remained, with a 30% increased risk of incident diabetes by 1-SD increase of fructose concentrations (1.30 [1.04–1.62], $P = 0.023$) (Supplementary Table 2).

Next, we addressed the differences in the association between fasting serum fructose levels and incident diabetes among the subgroups according to age, sex, glucose tolerance status, BMI, and family history of diabetes (Fig. 2). The association was similar in individuals aged <60 or ≥60 years, with or without prediabetes, with BMI <25 kg/m$^2$ or ≥25 kg/m$^2$, and with or without family history of diabetes (all $P$ for heterogeneity ≥ 0.10). However, the association was stronger in men than in women ($P$ for heterogeneity = 0.037). In men, each SD increase in fasting serum fructose levels was associated with a 78% (HR 1.78 [95% CI 1.20–2.65]) increased risk for incident diabetes in the final adjusted model, whereas the association was not detected in women (1.13 [0.86–1.49]).

Besides, we investigated the incremental predictive value of fasting fructose levels when added to the models derived from traditional diabetes risk factors. For the noninvasive predictor model that was based on age, sex, BMI, family history of diabetes, and smoking and alcohol consumption, each SD increment in the basic clinical model was associated with a 31% increased risk of future diabetes ($P = 0.0027$). For combined noninvasive variables and fasting fructose concentration, each SD increment was associated with a 44% increased risk of future diabetes. We assessed the predictive performance of clinical models with and without fasting fructose concentration. The basic clinical model had an LHR of 9. Addition of fasting fructose concentration to the noninvasive predictor improved model fit with an LHR of 18, whereas adding fasting blood glucose, postprandial blood glucose, and $HbA_{1c}$ to noninvasive predictors yielded LHRs of 21, 27, and 10, respectively. Similar patterns were observed with changes in the C-statistic across different models (Supplementary Table 3).

### Oral SSB Challenge Test

The characteristics of the 11 participants in the SSB challenge test are presented in Supplementary Table 4. The time course of serum fructose concentration is shown in Supplementary Fig. 1. A time-dependent increase in serum fructose

**Table 1—Baseline characteristics of participants with and without incident type 2 diabetes: demographics and laboratory values**

| | No diabetes ($n$ = 770) | Incident diabetes ($n$ = 179) | $P$ value |
|---|---|---|---|
| Age (years) | 55 ± 8 | 57 ± 8 | 0.044 |
| Male sex | 233 (30) | 58 (32) | 0.58 |
| BMI (kg/m$^2$) | 24.0 ± 3.2 | 24.8 ± 3.3 | 0.0057 |
| Glucose metabolism | | | |
| Fasting plasma glucose (mmol/L) | 5.66 ± 0.52 | 5.83 ± 0.48 | <0.0001 |
| 2-h postload glucose (mmol/L) | 7.00 ± 1.59 | 7.69 ± 1.75 | <0.0001 |
| $HbA_{1c}$ (%) | 5.6 ± 0.4 | 5.7 ± 0.4 | 0.034 |
| $HbA_{1c}$ (mmol/mol) | 38 ± 3.2 | 39 ± 3.2 | — |
| Fasting serum fructose (μg/mL) | 0.82 ± 0.15 | 0.85 ± 0.15 | 0.0053 |
| Smoking status | | | |
| Smoker | 96 (13.2) | 17 (10.0) | 0.26 |
| Nonsmoker | 634 (86.8) | 153 (90.0) | |
| Drinking status | | | |
| Drinker | 59 (8.0) | 17 (9.9) | 0.43 |
| Nondrinker | 676 (92.0) | 155 (90.1) | |
| Blood pressure (mmHg) | | | |
| Systolic | 127 ± 18 | 134 ± 19 | <0.0001 |
| Diastolic | 79 ± 10 | 82 ± 11 | 0.0010 |
| Lipid profile | | | |
| TC (mmol/L) | 4.55 ± 1.00 | 4.73 ± 1.01 | 0.025 |
| TG (mmol/L) | 1.53 ± 1.15 | 1.78 ± 1.15 | 0.0079 |
| LDL-C (mmol/L) | 2.56 ± 0.75 | 2.65 ± 0.75 | 0.15 |
| HDL-C (mmol/L) | 1.24 ± 0.33 | 1.23 ± 0.36 | 0.91 |
| Liver function | | | |
| ALT (units/L) | 14.8 ± 10.2 | 17.7 ± 11.6 | 0.0007 |
| AST (units/L) | 19.1 ± 8.4 | 21.8 ± 10.3 | 0.0002 |
| Family history of diabetes | 51 (6.80) | 15 (8.47) | 0.44 |
| SSBs (servings/week) | 0.31 ± 2.13 | 0.19 ± 0.92 | 0.43 |
| Uric acid (μmol/L) | 323.8 ± 92.6 | 336.6 ± 95.3 | 0.096 |
| eGFR (mL/min/1.73 m$^2$) | 96.4 ± 12.8 | 95.4 ± 12.4 | 0.34 |

Data are mean ± SD or $n$ (%).

levels was observed after an oral SSB load. A peak concentration of serum fructose was achieved at 0.5 h and returned to baseline at 6.0 h.

## CONCLUSIONS

In the current study, using a targeted liquid chromatography–tandem mass spectrometry method, we quantified fasting fructose concentration in the circulation. We discovered that elevated fasting serum fructose levels were significantly associated with increased risk of incident diabetes in middle-aged and older Chinese. This association was independent of established diabetes risk factors. The association appeared to be dose-responsive, and each SD (0.2 μg/mL) increase in fasting serum fructose levels was associated with a 33% increase in incident diabetes risk. To our knowledge, this study evaluated for the first time the association between serum fructose concentration and the risk of incident diabetes.

Fructose is a monosaccharide that is found naturally in its free form in honey, fruits, and other plants and in a combined form as half of the disaccharide sucrose. Fructose is also present in added sugars, mainly from high-fructose corn syrup. Epidemiologic studies have shown that sugar consumption, particularly in the form of SSBs, contributes to the increased risk of obesity, fatty liver, type 2 diabetes, cardiovascular disease, and mortality (6,7). The administration of beverages containing 25% fructose to overweight subjects caused more visceral obesity and insulin resistance compared with subjects administered 25% glucose (20). Mice fed a high-fat diet supplemented with fructose developed more pronounced obesity, glucose intolerance, and fatty liver compared with mice fed a glucose-supplemented high-fat diet, despite similar caloric intake (21). Thus, fructose intake possibly increases the risk of development of obesity, fatty liver, and type 2 diabetes. In addition to diet, fructose can be produced endogenously in the body by aldose reductase and the polyol pathway. Physiologically, endogenously synthesized fructose is the primary energy source for sperm and may be important for fertility (22). Of note, overproduction of hepatic endogenous fructose could cause systemic metabolic changes (10). However, the association of fasting serum fructose concentrations with incident diabetes has not been evaluated previously. Our data presented here demonstrate a longitudinal link between serum fructose levels and incident diabetes in humans.

When ingested by mouth, fructose is initially absorbed by the small intestine and metabolized mostly in the liver. As a consequence of the high rate of extraction of fructose by liver, corresponding low-fructose concentrations are found in the circulation. Estimated serum concentrations of fructose in humans range from 0.008 to 0.12 mmol/L (23). Although fructose circulates in micromolar concentrations (only ~1/1,000 of glucose levels in

**Table 2—Baseline characteristics of participants according to quartiles of fasting serum fructose levels**

| | Fasting serum fructose levels | | | | |
|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *P* for trend |
| Fasting serum fructose (μg/mL) | <0.71 | 0.71–0.82 | 0.82–0.93 | ≥0.93 | |
| Participants, *n* | 222 | 240 | 238 | 249 | |
| Age (years) | 54.9 ± 7.9 | 55.6 ± 8.0 | 55.3 ± 7.2 | 56.3 ± 7.5 | 0.074 |
| Sex, *n* male/*n* female (%) | 43/179 (23.4) | 73/167 (25.3) | 76/162 (25.1) | 99/150 (26.2) | <0.0001 |
| BMI, kg/m$^2$ | 24.1 ± 3.6 | 23.8 ± 3.0 | 24.3 ± 3.2 | 24.5 ± 3.2 | 0.088 |
| Glucose metabolism | | | | | |
| Fasting plasma glucose (mmol/L) | 5.46 ± 0.51 | 5.67 ± 0.50 | 5.75 ± 0.50 | 5.86 ± 0.50 | <0.0001 |
| 2-h postload glucose (mmol/L) | 6.64 ± 1.51 | 7.04 ± 1.56 | 7.29 ± 1.66 | 7.49 ± 1.72 | <0.0001 |
| $HbA_{1c}$ (%) | 5.6 ± 0.4 | 5.7 ± 0.4 | 5.7 ± 0.4 | 5.7 ± 0.4 | 0.0027 |
| $HbA_{1c}$ (mmol/mol) | 38 ± 3.2 | 39 ± 3.2 | 39 ± 3.2 | 39 ± 3.2 | — |
| HOMA-IR | 1.58 ± 0.83 | 1.65 ± 0.85 | 1.84 ± 0.90 | 1.92 ± 0.97 | <0.0001 |
| HOMA-IS | 0.80 ± 0.43 | 0.78 ± 0.45 | 0.69 ± 0.42 | 0.66 ± 0.35 | <0.0001 |
| Smoking status | | | | | |
| Current smoker | 22 (10.6) | 27 (12.0) | 32 (14.0) | 32 (13.4) | 0.30 |
| Nonsmoker | 186 (89.4) | 198 (88.0) | 196 (86.0) | 207 (86.6) | |
| Drinking status | | | | | |
| Current drinker | 9 (4.3) | 17 (7.5) | 19 (8.3) | 31 (12.9) | 0.0012 |
| Nondrinker | 202 (95.7) | 220 (92.5) | 209 (91.7) | 210 (87.1) | |
| Blood pressure (mmHg) | | | | | |
| Systolic | 129 ± 19 | 128 ± 19 | 127 ± 17 | 128 ± 18 | 0.45 |
| Diastolic | 79 ± 10 | 79 ± 10 | 80 ± 10 | 80 ± 10 | 0.11 |
| Lipid profile | | | | | |
| TC (mmol/L) | 4.42 ± 0.95 | 4.74 ± 1.07 | 4.55 ± 0.98 | 4.61 ± 0.99 | 0.25 |
| TG (mmol/L) | 1.31 ± 0.82 | 1.60 ± 1.14 | 1.73 ± 1.54 | 1.64 ± 0.96 | 0.0013 |
| LDL-C (mmol/L) | 2.49 ± 0.71 | 2.66 ± 0.81 | 2.51 ± 0.71 | 2.63 ± 0.76 | 0.22 |
| HDL-C (mmol/L) | 1.21 ± 0.34 | 1.29 ± 0.35 | 1.22 ± 0.32 | 1.22 ± 0.31 | 0.60 |
| Liver function | | | | | |
| ALT (units/L) | 14.6 ± 11.4 | 14.6 ± 8.5 | 15.8 ± 10.5 | 16.3 ± 11.5 | 0.045 |
| AST (units/L) | 18.7 ± 9.3 | 19.6 ± 7.2 | 19.6 ± 7.8 | 20.7 ± 10.5 | 0.020 |
| Family history of diabetes | 19 (8.8) | 12 (5.2) | 18 (7.7) | 17 (7.0) | 0.74 |
| SSBs (servings/week) | 0.44 ± 3.43 | 0.22 ± 1.14 | 0.28 ± 1.12 | 0.23 ± 1.34 | 0.33 |
| Uric acid (μmol/L) | 307.5 ± 85.5 | 324.2 ± 94.4 | 328.6 ± 93.0 | 342.5 ± 96.0 | <0.0001 |
| eGFR (mL/min/1.73 m$^2$) | 97.3 ± 16.6 | 96.3 ± 10.3 | 96.2 ± 10.5 | 95.3 ± 12.8 | 0.10 |

Data are mean ± SD, *n* (%), or median (interquartile range) unless otherwise indicated.

the circulation), fructose is much more reactive in terms of mediating pathology processes in vivo. Therefore, we used a targeted approach that coupled liquid chromatography with a triple quadrupole tandem mass spectrometer to quantify serum fructose concentration.

Systemic fructose concentrations were greatly influenced by diet fructose intake. Our SSB challenge test showed that circulating fructose concentrations were increased by ~20-fold at 0.5–1 h and returned to baseline at 6 h. Herein, we measured circulating fructose concentration on fasting, which is relatively stable. Patel et al. (24) also reported that baseline fructose concentration during fasting was not affected by high- or low-fructose diet intake. We might speculate that postprandial fructose concentrations largely reflect dietary fructose intake and that fasting fructose concentrations largely represent endogenous fructose production. In multivariable-adjusted models, after adjustment for SSB consumption, the association of fasting fructose levels and the risk of incident diabetes did not change. Furthermore, a subgroup analysis in participants excluding frequent SSB intake showed that the association of fasting fructose levels with risk of incident diabetes still remained, with a 30% increase in risk by 1-SD increase of fasting serum fructose levels (HR 1.30 [95% CI 1.04–1.62]). Those results indicate that the association between fasting serum fructose concentration and incident diabetes is not influenced by SSB consumption.

Fructose intake also raises serum uric acid concentrations. Previous studies showed that phosphorylated fructose stimulates AMP deaminase to convert AMP to inosine monophosphate and then inosine monophosphate is converted to uric acid (25). Our results showed that fasting serum fructose and uric acid concentrations were correlated, whereas adjustment for uric acid partially attenuated the association of fasting serum fructose with diabetes, indicating that a mechanism other than uric acid may likely also contribute to the link between fructose and diabetes. Since fructose is excreted through the kidney, we further explored the effect of kidney function on the association of serum fructose and diabetes. In our study, eGFR was >60 mL/min/1.73 m$^2$ in almost all participants, with a mean eGFR of 96.1 ± 12.8 mL/min/1.73 m$^2$. Fasting serum fructose levels were not correlated with eGFR in our study participants, and yet further

**Table 3—HR of baseline fasting serum fructose levels on risk of incident diabetes**

| | Fasting serum fructose levels | | | | *P* for trend | HR (95% CI) for 1-SD increase |
|---|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | |
| Median, μg/mL | 0.62 | 0.76 | 0.87 | 1.02 | | |
| Cases, *n* | 34 | 42 | 46 | 57 | | |
| Incidence rate per 100 PYs | 15.1 | 17.2 | 19.3 | 22.9 | | |
| HR (95% CI) for: | | | | | | |
| Age- and sex-adjusted model | Ref. | 1.47 (0.93–2.32) | 1.57 (1.00–2.46) | 1.79 (1.17–2.76) | 0.0015 | 1.39 (1.13–1.69) |
| Multivariable model 1 | Ref. | 1.57 (0.98–2.54) | 1.61 (1.01–2.56) | 1.89 (1.20–2.98) | 0.0012 | 1.41 (1.15–1.74) |
| Multivariable model 2 | Ref. | 1.42 (0.86–2.34) | 1.67 (1.02–2.72) | 1.81 (1.13–2.91) | 0.0039 | 1.37 (1.11–1.70) |
| Multivariable model 3 | Ref. | 1.38 (0.83–2.27) | 1.59 (0.98–2.60) | 1.73 (1.07–2.79) | 0.0069 | 1.35 (1.09–1.67) |
| Multivariable model 4 | Ref. | 1.36 (0.82–2.25) | 1.61 (0.98–2.62) | 1.72 (1.07–2.78) | 0.0071 | 1.35 (1.08–1.67) |
| Multivariable model 5 | Ref. | 1.30 (0.79–2.14) | 1.52 (0.93–2.48) | 1.65 (1.02–2.65) | 0.011 | 1.33 (1.07–1.65) |
| Multivariable model 6 | Ref. | 1.30 (0.79–2.15) | 1.52 (0.93–2.48) | 1.65 (1.02–2.67) | 0.010 | 1.33 (1.07–1.65) |

Multivariable model 1 adjusted for age, sex, BMI, family history of diabetes, and smoking and drinking status. Multivariable model 2 adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, and AST. Multivariable model 3 adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, AST, and basal glucose. Multivariable model 4 adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, AST, basal glucose, and SSB consumption. Multivariable model 5 adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, AST, basal glucose, SSB consumption, and uric acid. Multivariable model 6 adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, AST, basal glucose, SSB consumption, uric acid, and eGFR. PYs, person-years; Ref., referent.

adjustment for eGFR did not change the association. Intriguingly, fasting serum fructose concentrations are higher in men than in women. Meanwhile, a stronger association of serum fructose concentration with developing diabetes was also observed in men than in women. One explanation could be the impact of sex hormones on fructose metabolism.

Accumulating evidence has demonstrated that fructose is more lipogenic than glucose and that administration of fructose increases hepatic hexose-phosphate levels, activates ChREBP, and causes glucose intolerance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis in mice (26). Lanaspa et al. (10) reported that mice deficient in KHK, which is unable to metabolize fructose, were protected from an increased in energy intake and body weight, visceral obesity, fatty liver, and elevated insulin levels, even though blood and urinary fructose levels were markedly increased. Thus, elevated blood fructose itself is not deleterious; rather, fructose metabolism is essential for fructose-induced metabolic disease. Importantly, fructose-1-phophate, the fructose-specific metabolite converted by KHK, can promote glucokinase release from regulatory protein (GCKR) and enhance glycogen synthesis (27).

The polyol pathway, which is active in a wide range of tissues, is responsible for endogenous fructose formation. Therefore, serum fasting fructose may be a marker of polyol pathway activity. In this way, glucose is first reduced to sorbitol by aldose reductase. Sorbitol is then oxidized to fructose by sorbitol dehydrogenase. Previous studies showed that fructose produced through the polyol pathway could also be upregulated by high-fat diet and salt intake (28,29). Accordingly, we found that fasting fructose concentration was correlated not only with fasting glucose but also with other features of the metabolic syndrome. These findings suggested that fasting fructose produced endogenously could be promoted in individuals with metabolic dysfunction. All these metabolic disorders eventually contribute to a high risk of incident diabetes. We speculated that an active polyol pathway and endogenous fructose production might exist in patients with diabetes and even in individuals with prediabetes. We added fasting serum fructose to the traditional models to predict incident diabetes and found that the predictive value was improved. However, the slight difference in mean value of serum fructose limited its diagnostic value. Therefore, our findings demonstrate that fasting serum fructose could serve as a potential biomarker or contributor to incident diabetes.

The strengths of our study are as follows. First, we conducted this study in a well-characterized prospective cohort. The prospective cohort design minimizes selection and recall bias. The details and standardized collection of demographic, lifestyle, and other covariates allowed for adjustment of several relevant potential confounders. A large number of events provided appropriate statistical power. Second, we adopted a targeted liquid chromatography–tandem mass spectrometry method for quantification of serum fructose concentration at micromole levels, which was hardly differentiated from glucose. Our study also has several limitations. First, all participants in this study were middle-aged and older Chinese people, so the findings cannot be generalized to younger populations and other ethnicities. Second, we only measured serum fructose concentration at a single time point, which cannot reflect long-term exposure. The trajectory of serum fructose concentration may provide more information on diabetes risk than one time point.

In conclusion, elevated serum fructose level increases the risk of type 2 diabetes in middle-aged and older Chinese people. Although our population-based study cannot ascertain causality, our data suggest that higher fasting serum fructose levels might serve as a biomarker and/or a contributor to incident diabetes.

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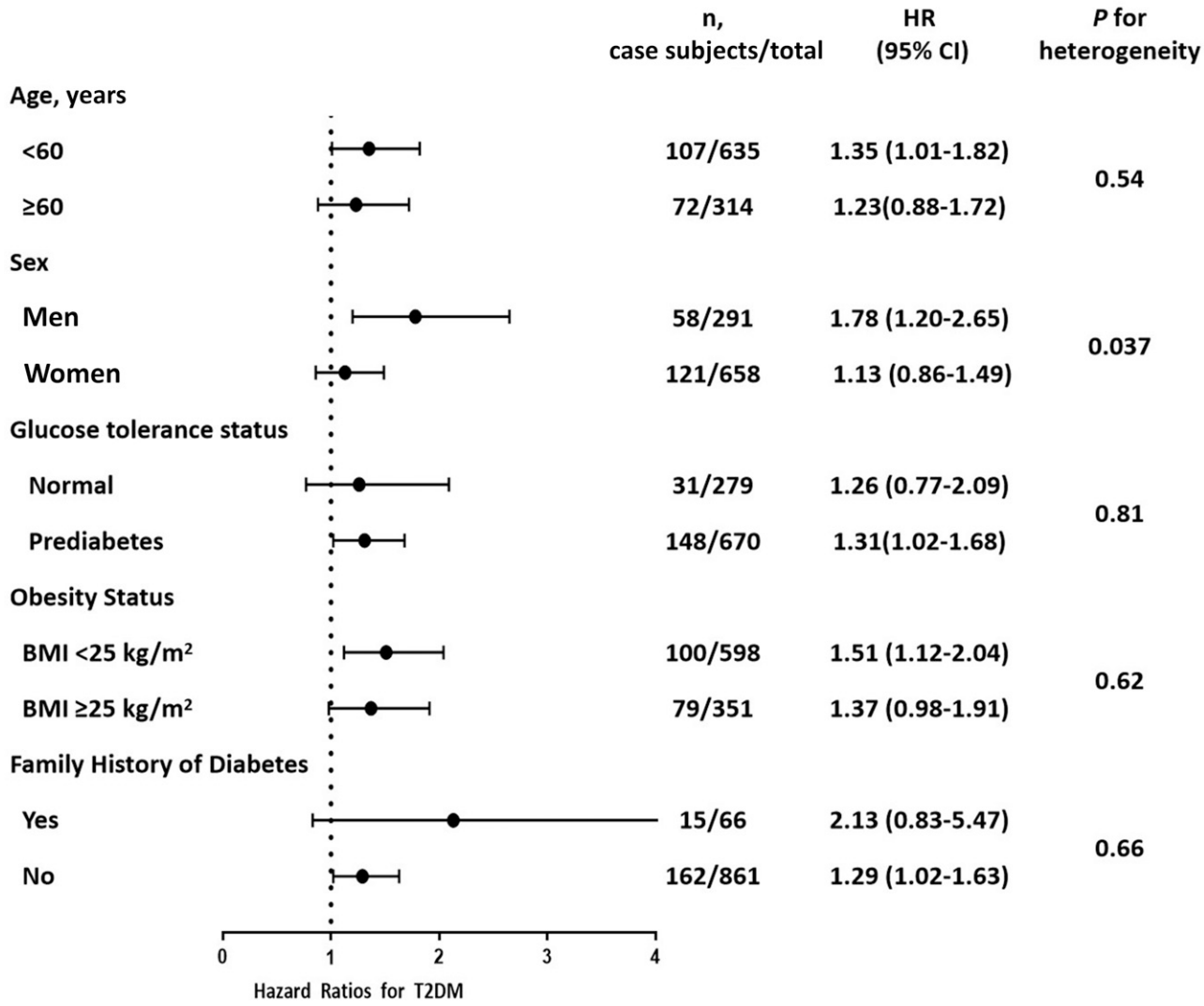


**Figure 2**—Subgroup analyses of risk of incident diabetes according to 1-SD increase of fasting serum fructose. The final model adjusted for age, sex, BMI, family history of diabetes, smoking and drinking status, systolic blood pressure, diastolic blood pressure, TC, TG, LDL-C, HDL-C, ALT, AST, basal glucose, SSB consumption, uric acid, and eGFR, except the strata variable. Risk is estimated by 1-SD increased fasting fructose level. T2DM, type 2 diabetes mellitus.

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