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ORIGINAL ARTICLE

Association between Serum Total Bilirubin Levels and Diabetes Mellitus: a cross-sectional study of residents in Wuhu, China

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Abstract

BACKGROUND: This study aimed to investigate the relationship between serum total bilirubin (TBIL) and diabetes mellitus (DM) in a large health checkup population in China.

METHODS: A cross-sectional study was conducted in 2011-2016 at the Physical Examination Center of the First Affiliated Hospital of Wannan Medical College, involving 302,515 subjects. Logistic regression and restricted cubic splines were used to determine the associations between TBIL and DM. The relationship between TBIL and fasting plasma glucose (FPG) was explored through the application of generalized linear models.

RESULTS: Quartiles of TBIL were negatively associated with DM after multivariable adjustment, compared with Q1, the ORs of Q2, Q3 and Q4 for DM were 0.971 (95% CI: 0.923-1.022), 0.922 (95% CI: 0.876-0.971), and 0.880 (95% CI: 0.836-0.927), respectively ($p < 0.001$). The restricted cubic spline model showed a non-linear relationship between TBIL and DM ($p < 0.001$), with the ORs for DM increasing progressively, reaching a threshold at the TBIL level of 14.54 μmol/L. The relationship between TBIL and FPG was also non-linear, with a threshold at TBIL of 20.10 μmol/L. FPG decreased with TBIL when TBIL < 20.10 μmol/L and increased when TBIL ≥ 20.10 μmol/L ($p < 0.001$). After stratifying by gender and age, the results revealed similar patterns.

CONCLUSION: Our study identified that moderate to low levels of TBIL are significantly negatively correlated with DM. In contrast, high levels of TBIL are positively correlated with DM, with a threshold of 14.54 μmol/L. A non-linear relationship was also observed between TBIL and FPG, with a threshold of 20.10 μmol/L.

INTRODUCTION

Diabetes Mellitus (DM) is a significant global health threat and a substantial public health issue. The global diabetes prevalence in 20-79 year olds in 2021 was estimated to be 10.5% (536.6 million people), China has the most people with diabetes with estimates of over 140 million (Sun *et al.* 2022). Diabetes can cause a variety of complications such as heart disease, kidney failure, stroke, and dementia (Thomas, 2022; Van Sloten *et al.* 2020). Preventing and controlling diabetes remains a persistent and formidable global challenge.

Bilirubin, a metabolite of heme-containing proteins, is clinically associated with jaundice (Belay *et al.* 2022; Yang *et al.* 2019). This compound is not merely a marker of toxic waste and hepatobiliary disease but is also fundamentally associated with hepatic pathology and hemolytic disorders (Puerto-Carranza *et al.* 2023). It has been shown to have strong antioxidant and anti-inflammatory effects under physiological conditions (Vítek, 2012; Adin, 2021; Baranano *et al.* 2002; Vitek *et al.* 2023). Recent studies suggest that bilirubin also plays a role in reducing adiposity and preventing metabolic and cardiovascular diseases (Vitek *et al.* 2023; Hou *et al.* 2021). A 3-year follow-up prospective cohort study in individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) reported a protective association between TBIL levels and T2DM (5). Similarly, a population-based cohort study in South Korea with an average follow-up of 8.4 years also reported a protective association between TBIL levels and T2DM (Kwon *et al.* 2018). However, a cohort study in a Chinese population with a 4.5-year follow-up aged 60 years and older did not support the protective association of serum total bilirubin levels with T2DM (Wang *et al.* 2017). Additionally, a community-based study in middle-aged and older women with a 4.4-year follow-up demonstrated that elevated TBIL levels were significantly associated with T2DM in women, but not in men (Zhang *et al.* 2021). These inconsistent findings remain a subject of debate.

Previous studies, predominantly focusing on middle-aged and elderly populations while overlooking other age groups, could not comprehensively reflect the association between bilirubin levels and T2DM. Moreover, these studies categorized bilirubin into categorical variables (quartiles) rather than analyzing it as a continuous variable. Notably, grouping bilirubin into quartiles may overlook some of the details in its relationship with diabetes. In this study, we conducted a cross-sectional analysis using data from a large health checkup population of all age groups in China. To provide a more detailed analysis of the relationship between TBIL levels and DM, we employed restricted cubic splines and generalized linear models, treating TBIL as a continuous variable.

METHODS

This cross-sectional study investigated 434,847 individuals who received physical examinations at the Physical Examination Center of the First Affiliated Hospital of Wannan Medical College between 2011 and 2016. The exclusion criteria were: (1) Under age 18 years; (2) Incomplete or missing data of age, gender, body mass index, blood pressure, and laboratory test results; (3) History of acute or chronic liver disease, hemolytic disorders, or biliary tract disease; (4) Pregnancy or lactation; and (5) Malignancy. According to these criteria, the final physical examination data of 302,515 participants were included in this study.

Ethics statement

The study was conducted in compliance with the Helsinki guidelines of the Helsinki Declaration of the World Medical Association and approved by the Ethics Committee of Wannan Medical College (Ethical Approval No. (2024) 7). Prior to study initiation, verbal informed consent was obtained from all participants after medical staff (who were independent of the research team) explained the study objectives and procedures. These medical staff were not involved in any other aspect of the research. Names, ID numbers, and contact information were permanently deleted from the dataset. All data were collected and analyzed in anonymized form, with strict confidentiality maintained throughout the study.

Questionnaire survey

Experts in epidemiology and clinical practitioners jointly designed the questionnaire. Demographic and behavioral characteristics, history of diseases, and operations were included in the questionnaire. Demographic characteristics included age, sex, and marital status. Smoking (at least one cigarette per day for at least one year) and drinking (consuming alcoholic beverages more than four times per week for at least one year) were categorized as behavioral characteristics. The column labeled 'History of the disease' contained comprehensive information on diabetes, hypertension, cardiovascular diseases, major surgeries, medication use, and instances of cancer.

Physical examination

Height and weight were measured using standardized, calibrated mechanical height rods and electronic scales. The examinee was instructed to wear light clothing and pants, remain barefoot, and stand naturally at the center of the scale platform with body posture stabilized during measurement. A mercury column sphygmomanometer was used to measure SBP and DBP. Subjects were asked to rest for 10 min, the blood pressure was measured twice and a mean was calculated. Body mass index (BMI) was calculated as weight (kg) divided by

the square of the height (m^2) (Eknoyan, 2008), with accuracy of 0.01 kg/m^2.

Laboratory measurements

In preparation for the physical examination, subjects should follow a light diet for three days prior. Morning blood samples were collected from each patient after a 12-hour fast. The general laboratory of the hospital performed routine blood tests and the serum samples were stored at -80°C until analysis. All biochemical assays were performed by professionals in the hospital.

Definitions

Hypertension (high blood pressure) was defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or taking antihypertensive medicine (Yin *et al.* 2022). Diabetes mellitus (DM) was diagnosed when the fasting plasma glucose level was ≥ 7.0 mmol/L (126 mg/dL), or when the subject had a previous definitive diagnosis, or had started taking relevant medication (ElSayed *et al.* 2023). Obesity is defined as having a body mass index (BMI) ≥ 28 kg/m^2.

Statistical Analysis

All data were analyzed using SPSS 26.0 (IBM, Armonk, NY, USA) and R software program (V.4.3.2). Continuous variables were described as mean ± SD or median (1st and 3rd quartiles) depending on distribution and compared by t-test or Mann–Whitney U-test. Categorical data are expressed as proportions and were analyzed using the chi-square test. Patients were categorized into four groups based on total bilirubin quartiles: Q1, TBIL ≤ 11.3 μmol/L; Q2, 11.3-14.4 μmol/L; Q3, 14.4-18.4 μmol/L; and Q4, TBIL > 18.4 μmol/L. Logistic regression, presented as odds ratio (OR) and 95% confidence interval (CI), was used to test the associations between TBIL and DM. We used four different models: a crude model; a model adjusted for age and sex; a model adjusted for age, sex, and BMI; and a model additionally adjusted for age, sex, BMI, smoking, drinking, hypertension, TG, HDL-C, LDL-C, and CRE. Furthermore, we applied a restricted cubic spline with four knots placed at the 5th, 35th, 65th, and 95th percentiles to model the association between TBIL and DM. A generalized smoothing spline was used to analyze the possible nonlinear relationship between TBIL and fasting plasma glucose levels, with the knot locations generated automatically in generalized additive models using the R package MGCV, and the analysis was grouped by gender and age. A probability value (*p* value) below 0.05 was considered to reflect a statistically significant difference.

RESULTS

Characteristics of subjects

Table 1 showed the baseline characteristics of participants. Compared with people with normal glucose

Tab. 1. Baseline characteristics of study participants according to diabetes

	Total (n = 302,515)	Normal (288,100)	Diabetes (14,415)	$t/\chi^2/z$	*p*
Age (years)	47.59 ± 13.57	47.02 ± 13.40	58.98 ± 11.71	-118.78	<0.001
Sex (male (%))	176,147 (58.23)	165,475 (57.44)	10,672 (74.03)	1554.78	<0.001
BMI (kg/m^2)	23.80 ± 3.24	23.70 ± 3.21	25.64 ± 3.24	-70.82	<0.001
SBP (mmHg)	119.25 ± 16.86	118.68 ± 16.58	130.73 ± 18.27	-77.60	<0.001
DBP (mmHg)	77.39 ± 9.95	77.17 ± 9.88	81.95 ± 10.37	-54.12	<0.001
FPG (mmol/L)	5.19 (4.84-5.62)	5.16 (4.82-5.55)	8.13 (7.42-9.69)	202.94	<0.001
TG (mmol/L)	1.24 (0.87-1.86)	1.22 (0.86-1.82)	1.77 (1.21-2.69)	71.25	<0.001
HDL-C (mmol/L)	1.37 ± 0.35	1.38 ± 0.35	1.30 ± 0.33	28.58	<0.001
LDL-C (mmol/L)	2.56 ± 0.77	2.56 ± 0.77	2.66 ± 0.89	-13.87	<0.001
AST (U/L)	21.00 (17.00-26.00)	21.00 (17.00-26.00)	22.00 (18.00-30.00)	22.88	<0.001
ALT (U/L)	21.00 (14.00-32.00)	20.00 (14.00-32.00)	26.00 (18.00-41.00)	47.82	<0.001
CRE (μmol/L)	70.03 ± 18.84	69.93 ± 18.59	72.09 ± 23.20	-11.00	<0.001
TBIL (μmol/L)	15.62 ± 6.41	15.60 ± 6.41	15.96 ± 6.41	-6.62	<0.001
Drinking (n (%))	100,930 (33.36)	94,792 (32.90)	6,138 (42.58)	578.38	<0.001
Smoking (n (%))	81,820 (27.05)	76,814 (26.66)	5,006 (34.73)	452.59	<0.001
Hypertension (n (%))	56,774 (18.77)	50,841 (17.65)	5,933 (41.16)	4977.82	<0.001
Obesity (n (%))	29,841 (9.86)	26,845 (9.32)	2,996 (20.78)	2029.87	<0.001

BMI: body massive index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRE: creatinine; TBIL: total bilirubin.

Tab. 2. Association of DM with quartiles (Q) of TBIL

	Q1 (n = 75,937) (≤11.3 μmol/L)	Q2 (n = 76,999) (11.3-14.4 μmol/L)	Q3 (n = 74,104) (14.4-18.4 μmol/L)	Q4 (n = 75,475) (>18.4 μmol/L)	*p* value for trend
Model 1	1.0 (Reference)	0.927 (0.883-0.972)	0.864 (0.823-0.907)	0.839 (0.800-0.880)	<0.001
Model 2	1.0 (Reference)	1.046 (0.995-1.099)	1.035 (0.985-1.088)	1.029 (0.979-1.081)	0.613
Model 3	1.0 (Reference)	1.036 (0.986-1.090)	1.004 (0.955-1.056)	0.980 (0.932-1.030)	0.103
Model 4	1.0 (Reference)	0.971 (0.923-1.022)	0.922 (0.876-0.971)	0.880 (0.836-0.927)	<0.001

Model 1: Unadjusted
Model 2: Adjusted for age and sex
Model 3: Adjusted for age, sex, and BMI
Model 4: Adjusted for age, sex, BMI, TG, HDL-C, LDL-C, CRE, hypertension, smoking, and drinking.

levels, individuals in the diabetic group had significantly higher TBIL levels (15.96 ± 6.41 vs. 15.60 ± 6.41 μmol/L, $p < 0.001$). Significant differences were also observed among the two groups in other demographic characteristics and biochemical parameters.

Association between TBIL with diabetes

Table 2 showed the results from the multivariate-adjusted logistic regression models. In Model 1, compared with Q1, the odds ratios (OR) for diabetes were 0.927 (95% CI: 0.883-0.972), 0.864 (95% CI: 0.823-0.907), and 0.839 (95% CI: 0.800-0.880), respectively ($p < 0.001$). Further adjustments for potential confounders showed that the ORs were 0.971 (95% CI: 0.923-1.022), 0.922 (95% CI: 0.876-0.971), and 0.880 (95% CI: 0.836-0.927), respectively ($p < 0.001$). These findings indicate a significant negative correlation between TBIL and DM after controlling for multiple variables.

The restricted cubic spline was utilized to flexibly model and visualize the relationship between predicted TBIL and DM after adjusting for confounders. The analysis revealed a non-linear relationship (p for non-linearity < 0.001) between predicted TBIL and the DM, with the ORs for DM increasing progressively. Notably, at TBIL levels of 14.54 μmol/L, the odds ratio for DM risk was 1.0 (Fig. 1).

Relationship between TBIL and FPG

Adjusted analyses demonstrated that FPG decreased as TBIL increased when TBIL < 20.10 μmol/L, and FPG increased as TBIL increased when TBIL ≥ 20.10 μmol/L ($p < 0.001$) (Fig. 2a). Specific analysis was performed on men and women respectively. In females, FPG decreased as TBIL increased when TBIL < 25.05 μmol/L, and FPG increased as TBIL increased when TBIL ≥ 25.05 μmol/L ($p < 0.001$) (Fig. 2b). In males, FPG decreased as TBIL increased when TBIL < 19.95 μmol/L, and FPG increased as TBIL increased when TBIL ≥ 19.95 μmol/L ($p < 0.001$) (Fig. 2c). Age stratification showed TBIL thresholds at 20.50 μmol/L for < 65-year-olds ($p < 0.001$) (Fig. 2d) and 19.00 μmol/L for ≥ 65-year-olds ($p < 0.001$) (Fig. 2e).

DISCUSSION

To the best of our knowledge, this is the largest cross-sectional study on the relationship between TBIL and DM. In this study, we found that moderate to low TBIL levels are negatively correlated with DM, while high TBIL levels are positively correlated with DM, with a threshold value of 14.54 μmol/L.

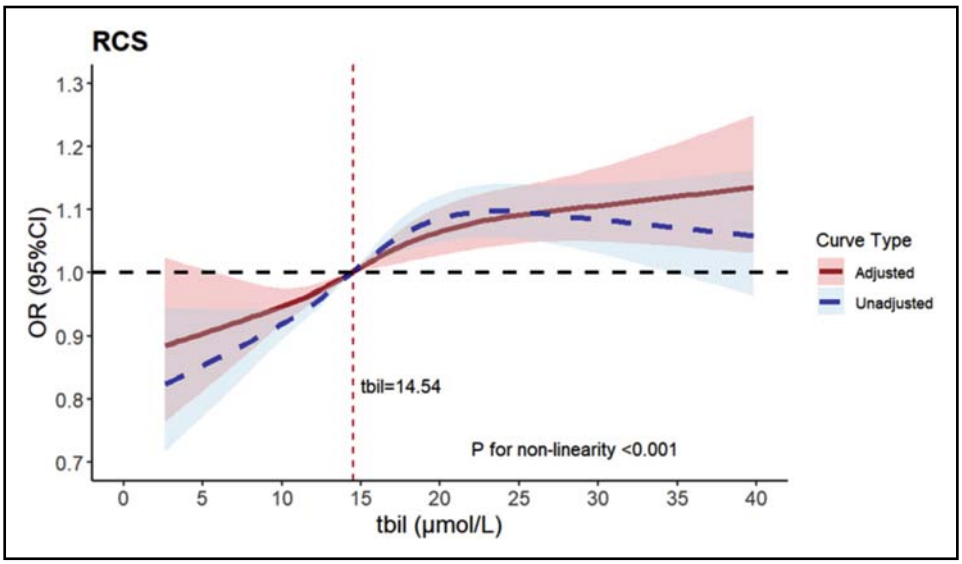

Fig. 1. Associations of TBIL with DM (The horizontal axis represents various levels of TBIL and the vertical axis is the odds ratio risk of DM). Blue line: without adjustment; red line: adjustment for sex, age, BMI, TG, HDL-C, LDL-C, CRE, hypertension, smoking, and drinking. The shaded area shows the 95% confidence interval.

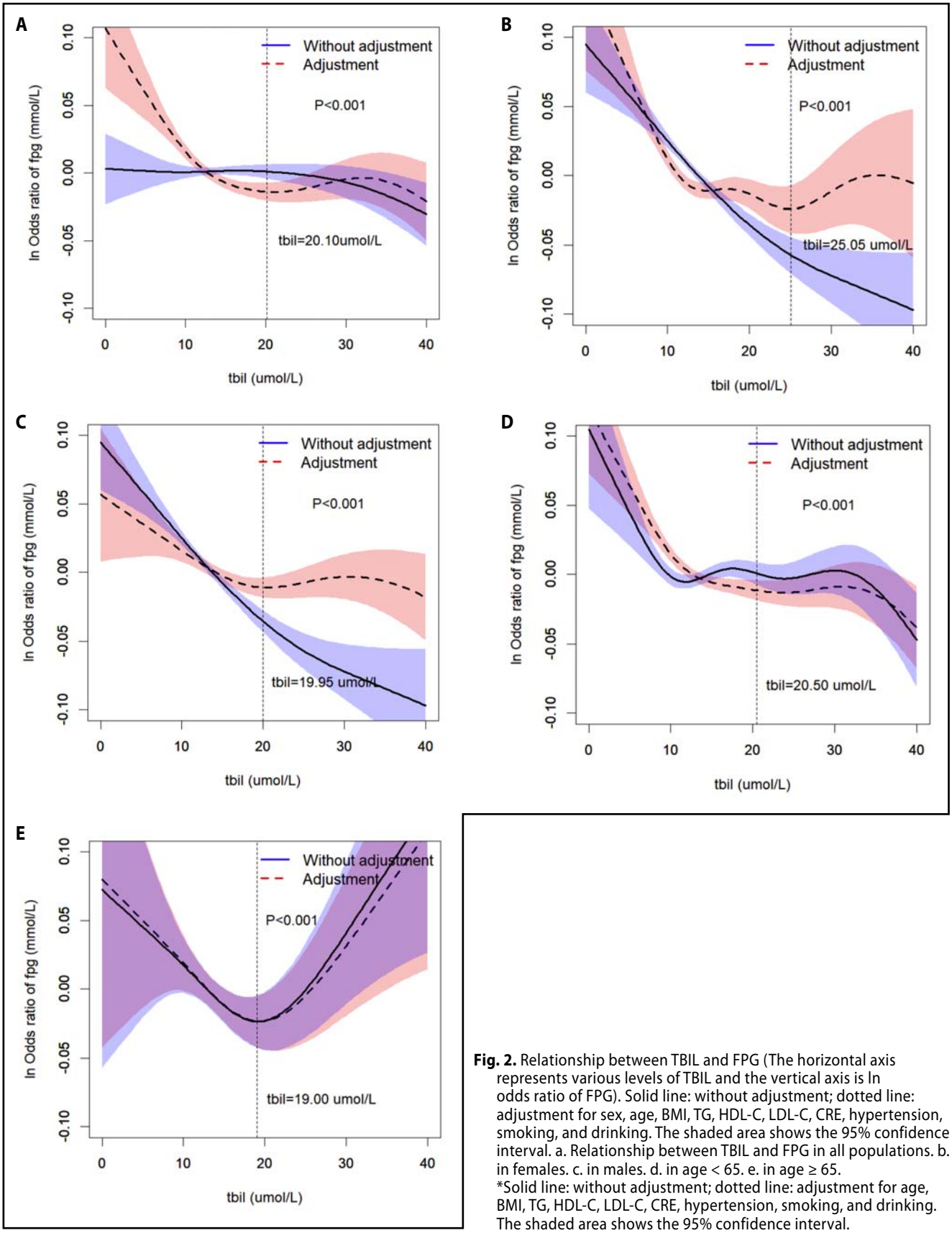

Fig. 2. Relationship between TBIL and FPG (The horizontal axis represents various levels of TBIL and the vertical axis is ln odds ratio of FPG). Solid line: without adjustment; dotted line: adjustment for sex, age, BMI, TG, HDL-C, LDL-C, CRE, hypertension, smoking, and drinking. The shaded area shows the 95% confidence interval. a. Relationship between TBIL and FPG in all populations. b. in females. c. in males. d. in age < 65. e. in age ≥ 65.
*Solid line: without adjustment; dotted line: adjustment for age, BMI, TG, HDL-C, LDL-C, CRE, hypertension, smoking, and drinking. The shaded area shows the 95% confidence interval.

Although high levels of TBIL are currently considered a protective factor against T2DM (Yang *et al.* 2019; Kwon *et al.* 2018; Mashili *et al.* 2024; Wei *et al.* 2021), some studies have reported conflicting results (Wang *et al.* 2017; Zhang *et al.* 2021). Most studies have focused on middle-aged and elderly populations, but bilirubin levels tend to be elevated with age (Stocker *et al.* 1987). As a result, these studies may not accurately represent all age groups. Our study aims to examine the relationship between TBIL and diabetes across a broader age range. Furthermore, we treated TBIL as a continuous variable instead of a categorical one, adding novelty to the study.

Low to moderate levels of TBIL are negatively associated with DM and may be attributed to the antioxidant and anti-inflammatory effects of bilirubin (Adin, 2021). Firstly, bilirubin effectively scavenges free radicals and reactive oxygen species (ROS), which can damage Pancreatic β cells and impair their normal function (Stocker *et al.* 1987; Sedlak & Snyder, 2004). By inhibiting these free radicals, bilirubin protects beta cells from oxidative stress, enhancing insulin sensitivity and reducing insulin resistance (Tiwari & Ndisang, 2014). Additionally, researchers have found that bilirubin has an immunomodulatory effect. Bilirubin controls the inflammatory response by inhibiting NF-κB and inflammasome activation, such as NLRP3, and inhibiting the secretion of IL-1β (Li *et al.* 2020). This reduction in inflammation helps preserve the function of β cells. However, high levels of bilirubin increase the risk of DM. Elevated bilirubin levels enhance oxidative stress, which promotes endoplasmic reticulum stress and mitochondrial dysfunction, leading to β cell damage, decreased insulin secretion, and further exacerbation of insulin resistance and DM progression (Eguchi *et al.* 2021). Moreover, high bilirubin levels may be associated with cholestasis and hepatic dysfunction (Lu, 2022; Guerra Ruiz *et al.* 2021). Hepatic dysfunction can lead to abnormal lipid metabolism and increased fat accumulation in the liver, promoting the development of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MASLD). These liver diseases are closely associated with various components of metabolic syndrome, such as obesity, hyperlipidemia, and insulin resistance, significantly increasing the risk of DM (Badmus *et al.* 2022; Sakurai *et al.* 2021).

Later, we used a smoothed curve to explore the relationship between TBIL and FPG. The adjusted curve showed that FPG first decreased and then increased as TBIL levels increased. The adjusted curve showed that FPG exhibits a biphasic pattern: decreasing initially and then increasing as TBIL levels rise. Further analysis of the relationship between TBIL and FPG in different genders and age groups revealed that FPG exhibited a similar biphasic pattern: decreasing then increasing with rising TBIL levels across all subgroups. This finding further supports that low to medium levels of TBIL are negatively correlated with DM, while high levels of TBIL are positively correlated with DM.

This study has limitations. First, it was a cross-sectional study and causality could not be determined. Second, we only looked at the association between DM and TBIL levels and did not explore the exact mechanisms. Third, our adjusted analyses did not account for dietary factors, which may impact concentrations of FPG and TBIL in humans. Finally, all the samples in our study came from the same hospital. To confirm these results and enhance their reliability, larger samples and multicenter population studies are necessary.

In conclusion, we examined the association between TBIL and DM in a large health checkup population in China and found that low to moderate levels of TBIL were negatively associated with DM, while high levels of TBIL were positively associated with DM. The threshold value of 14.54 μmol/L may represent a point where the association between bilirubin and DM changes direction. Levels of TBIL below 14.54 μmol/L were negatively associated with DM, while the opposite effects were presented beyond the threshold. These findings provide new evidence that the levels of TBIL should be emphasized in the prevention of DM in the Chinese adult population.

DECLARATIONS

Ethics approval and consent to participate

This study's protocol has been approved by the Ethics Committee of Wannan Medical College, with data sourced from the Health Management Center at the First Affiliated Hospital of Wannan Medical College in Wuhu, China. Given that participants were hospital visitors for routine medical check-ups, the Medical Ethics Committee deemed verbal informed consent as sufficient. Therefore, necessary verbal informed consent was obtained from all subjects and/or their legal guardian(s). All methods in this study were conducted in accordance with the guidelines and regulations of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The authors collected participant data and uploaded it to a database. This system conveniently shields irrelevant data and effectively protects participant privacy. The data supporting this study's findings are available from the Health Management Center at the First Affiliated Hospital of Wannan Medical College, Wuhu, China. However, access to these data is restricted as they were used under license for this study and are not publicly available. Data can be provided upon reasonable request and with the Health Management Center's permission. For data requests, please contact Yufeng Wen, the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Tong Wang and Huan Wu wrote the main text of the manuscript; Xinyu Ma and Yue Wu prepared figures; Fan Su and Wendan Mei conducted the experiments; Yicheng Fang and Chenxu Wang analyzed the data; Yufeng Wen supervised the entire project. All authors reviewed the manuscript.

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