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Original Article

Total bilirubin independently predicts incident metabolic syndrome among community-dwelling women

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ABSTRACT

Background: Metabolic syndrome (MetS) is related to the increased risk of major cardiovascular diseases (CVD). The link between high serum total bilirubin (TBL) is cross-sectionally related to MetS and its components. However, whether serum TBL predicts incidence of MetS and its components remains inconclusive.

Methods: The present study included 893 women aged 70 ± 9 years from a rural village. We examined the relationship between serum TBL and MetS based on the modified criteria of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP) III report in a cross-sectional (N = 893) and cohort (N = 288) data.

Results: In the cross-sectional study, serum TBL ($\beta = 0.536$, $p < 0.001$) as well as age, alcohol consumption, exercise habits, history of CVD, SUA, GGT, and ALT was significantly and dependently associated with number of MetS components, but in the cohort study serum TBL was not associated with number of MetS components. Compared with the 1st tertile of serum TBL (0.20–0.55 mg/dL), multivariate-adjusted odds ratio (95% confidence interval) for the 2nd -3rd tertiles of serum TBL (0.54–2.00 mg/dL) was 0.70 (0.51–0.95) in the cross-sectional study and 0.41 (0.21–0.81) in the cohort study.

Conclusions: Our data demonstrated an independently negative association between serum TBL and MetS in Japanese community-dwelling women.

1. Introduction

Metabolic syndrome (MetS), or a clustering of cardiovascular risk factors, such as central obesity, elevated blood pressure, elevated triglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels, and elevated fasting glucose, has been recognized as a major cause of type 2 diabetes [1,2] and cardiovascular diseases (CVD) [3,4]. Moreover, it has become one of the major public health challenges worldwide. An increasing number of studies confirm that oxidative stress, chronic inflammation and angiogenesis all play important roles in the pathogenesis of MetS [5,6]. Oxidative stress and a state of lost balance between the oxidative and anti-oxidative systems of the cells and tissues, results in the over production of oxidative free radicals and reactive oxygen species (ROS) [6].

Serum bilirubin is a major end product formed in heme metabolism occurring in the systemic circulation. Recent studies have suggested that serum TBL is an endogenous antioxidant that may have important protective roles against atherosclerotic processes such as inflammatory and oxidative stress-induced disease [7]. During the past few years, many studies have shown that serum bilirubin levels are inversely associated with MetS and systemic inflammation in adults [8–10]. In particular, central obesity has been correlated with low serum bilirubin levels [10,11]. Thus, most studies were cross-sectional in design [12]. Lee et al. [13] reported that serum TBL level was negatively associated with incident MetS in healthy Korean men over a 4-year period. Among components of MetS, serum bilirubin was found to be negatively associated with only the risk of incident hypertriglyceridaemia. On the contrary,

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Oda et al. [14] reported that serum TBL was not associated with incident MetS in a cohort study in Japanese men and women. These findings raise the possibility that serum TBL could be a confounding factor for MetS, but whether baseline TBL can be a predictor of incident MetS remains controversial.

To address this hypothesis, we investigated the relationship between baseline TBL and potential risk factors such as age, smoking status, drinking status, exercise habits, presence of CVD, low-density lipoprotein cholesterol (LDL-C), serum uric acid (SUA), and estimated glomerular filtration ratio (eGFR) using cross-sectional and prospective cohort data from community-dwelling women. In the follow-up period, we examined whether serum TBL levels were associated with the development of MetS in these patients.

2. Materials and methods

2.1. Subjects

The study group was recruited from the Nomura Health and Welfare Center in a rural town in Ehime prefecture of Japan through an annual health checkup process closely related to the area [15]. This study was started in 2014, and included 1014 community-dwelling women aged 29–90 years. Participants with serum T-B >2.0 mg/dL or alanine transaminase (ALT) ≥100 IU/L or gamma glutamyl transpeptidase (GGT) ≥100 IU/L were excluded to avoid confounding factors because the probability of potential Gilbert syndrome and hepatobiliary disease is high. Follow-up assessment cycles are being performed every three years

In the present study, data from the assessment cycles of 2014 and 2017 was included. Blood samples were obtained only from respondents who participated in the medical interviews. For the cross-sectional analyses, data of the 2014 cycle (n = 893) was used as all five components of MetS were measured in this cycle. For the longitudinal analyses, a sub-cohort of the 2014 cycle was used and it included only participants in whom MetS was not prevalent at baseline in 2014 (n = 288). Fig. 1 presents a flowchart of the participants included.

The study complies with the Declaration of Helsinki, and obtained written informed from each subject with the approval of the Ehime University Graduate School of Medicine ethics committee.

2.2. Evaluation of risk factors

Information on demographic characteristics and risk factors was collected using clinical files. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by the square of height (in meters). Other characteristics such as smoking status, drinking habit, exercise habit, and medication were investigated by individual interviews conducted using a structured questionnaire. Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack year), and the participants were classified into never smokers, past smokers, light smokers (<30 pack year), and heavy smokers (≥30 pack year). Daily drinking habit was measured using the Japanese liquor unit in which a unit corresponds to 23 g of ethanol, and the participants were classified into never drinkers, occasional drinkers (<1 unit/day), and daily drinkers (light, <2 unit/day, heavy, ≥2 unit/day). We measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) with an appropriate-sized cuff of the right upper arm of the subjects using an automatic oscillometric BP recorder in a seated position after at least 5 min. The average of two consecutive measurements was used for the analysis.

Overnight fasting plasma samples were available for all these individuals. TG, HDL-C, LDL-C, hemoglobin A1c (HbA1c), SUA, creatinine (Cr), GGT, and ALT were measured during an overnight fast of more than 11 h eGFR was calculated using CKD-EPI equations modified by a Japanese coefficient ($eGFR_{CKDEPI}$): Male, $Cr \leq 0.9$ mg/dl, $141 \times (Cr/0.9)^{-0.411} \times 0.993^{age} \times 0.813$; $Cr > 0.9$ mg/dl, $141 \times (Cr/0.9)^{-1.209} \times 0.993^{age} \times 0.813$; Female, $Cr \leq 0.7$ mg/dl, $144 \times (Cr/0.7)^{-0.329} \times 0.993^{age} \times 0.813$; $Cr > 0.7$ mg/dl, $144 \times (Cr/0.7)^{-1.209} \times 0.993^{age} \times 0.813$ [16].

2.3. MetS

MetS was determined according to the revision standard of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP - ATP III) [17]. MetS was present if three or more of the following five criteria were met: 1) high waist circumference (women ≥80 cm) based on the adjusted Japanese waist circumference criterion [18] and/or BMI ≥25.0 kg/m^2 according to the guidelines of the Japanese Society for the Study of Obesity [19] if waist circumference was not available; 2) elevated BP {systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg, and/or antihypertensive medication use}; 3) high TG (≥150 mg/dL); 4) low HDL cholesterol (men <40 mg/dL and women <50 mg/dL, and/or current treatment for dyslipidemia); and 5) elevated FPG level {≥100 mg/dL (equivalent to HbA1c = 5.6%) and/or current treatment for diabetes mellitus}.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation (SD) for normal distribution or as median with lower and upper quartiles for non-normal distribution. (i.e., TG, HbA1c, GGT, and ALT). For all analyses, parameters with non-normal distributions were used after log-transformation. Statistical analyses were performed using a statistical computer program IBM SPSS Statistics Version 20 (Statistical Package for Social Science Japan, Inc., Tokyo, Japan). Subjects were divided into three groups according to the baseline TBL tertile (1st and 2nd-3rd), and differences between two groups were analyzed by student's t-test for the continuous variables or the χ^2 -test for the categorical variables. Multiple logistic regression analysis was performed to evaluate the contribution of the baseline confounding factors (i.e., age, smoking status, drinking habit, history of CVD, SUA, eGFR, GGT, and ALT) for incident MetS after the 3-year follow-up. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of participants

Baseline characteristics of the subjects according to baseline TBL in the cross-sectional and cohort studies are shown in Table 1. The study included 893 women aged 70 ± 9 (range, 29–90) years and 288 women aged 66 ± 9 (range, 29–84) years. In the cross-sectional study, TG and HbA1c, and number of MetS components were significantly higher in the 1st tertile group of TBL than the 2nd-3rd tertile group, but HDL-C and LDL-C were significantly lower in the 1st tertile group of TBL. In the cohort study, there were no differences in all the characteristics.

3.2. Relationship between tertile of baseline total bilirubin and number of MetS components in the cross-sectional and cohort studies

As shown in Fig. 2, the number of MetS components of the participants in the cross-sectional study was significantly greater in participants with a 1st tertile baseline TBL than those with a 2nd-

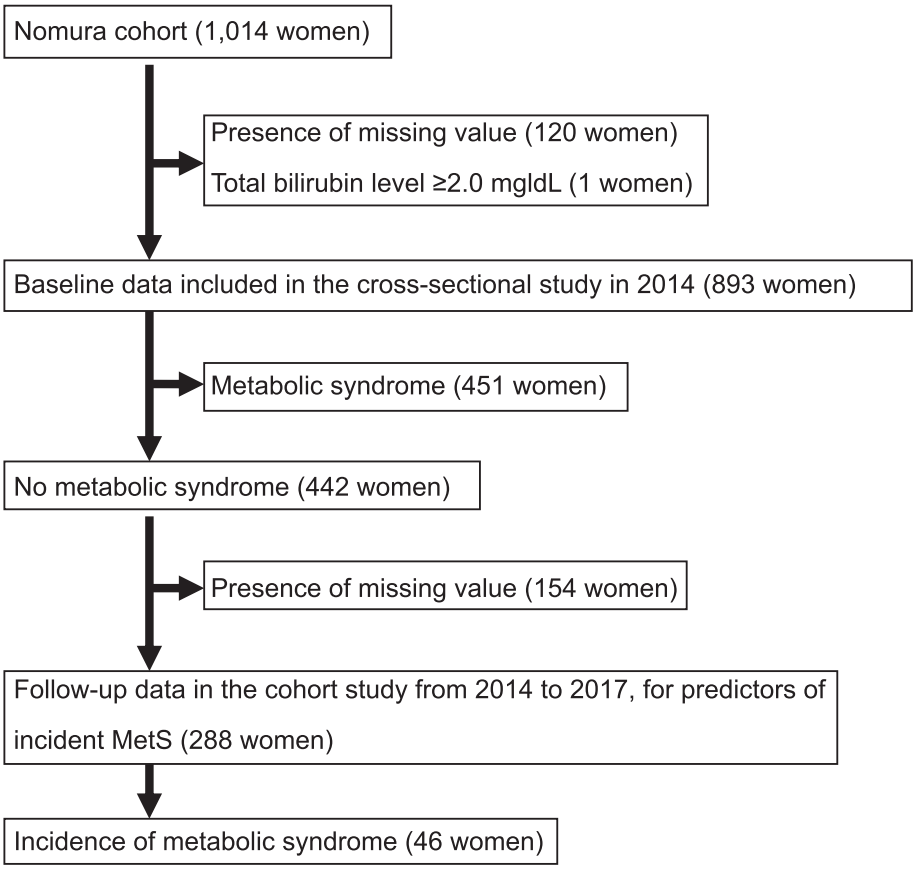

Fig. 1. Flowchart of participants in the cross-sectional and cohort studies.

3rd tertile. In the cohort study, number of MetS components in participants with a 1st tertile baseline TBL was significantly increased after 3 years but the number of MetS components in those with a 2nd-3rd tertile baseline TBL was not increased.

3.3. Relationship between baseline characteristics including serum TBL level and number of MetS in the cross-sectional and cohort studies

In Table 2, Pearson's correlation coefficient and multiple linear regression analysis were used to evaluate the contribution of each confounding factor for number of MetS components. In the cross-sectional study, serum BTL levels as well as age, daily drinking habits, exercise habits, history of CVD, SUA, GGT, and ALT were significantly and dependently associated with number of MetS components. In the cohort study, SUA and GGT were significantly and dependently associated with number of MetS components.

3.4. Multivariate-adjusted odds ratios and 95% CI for MetS and its components of participants according to baseline total bilirubin in the cross-sectional and cohort studies

Table 3 shows the prevalence and risk for MetS and abnormalities of its components according to tertile of serum TBL in the cross-sectional study. Of the participants, 451 women (50.5%) had MetS at baseline. As shown in Table 4, after adjustments for the baseline parameters, namely, age, smoking status, drinking status, exercise habits, presence of CVD, LDL-C, SUA, eGFR, GGT, and ALT, multivariate-adjusted odds ratios (Ors) and 95% confidence interval (CI) for MetS (0.70; 0.51–0.95) and central obesity (0.74; 0.55–0.99) were significantly decreased in participants with 2nd-3rd tertile TBL compared to those with the 1st tertile. Table 4 shows the prevalence and risk for MetS, and abnormalities of its components according to tertile of serum TBL in the cohort study. Multivariate-adjusted ORs and 95% CI for MetS (0.41; 0.21–0.81) and elevated BP (0.47; 0.26–0.84) were significantly decreased in participants with 2nd-3rd tertile TBL compared with those with the 1st tertile.

4. Discussion

In the present study where data from the Nomura studies in 2014 and 2017 were used, our data demonstrated that low serum TBL levels are associated with an increased risk of both baseline and follow-up MetS, with the presence of central obesity at baseline, and with elevated BP after a 3-year follow-up. To our knowledge, few epidemiologic studies have quantified the link between serum TBL and incident MetS in Japanese community-dwelling women.

Many cross-sectional studies have reported that serum TBL was inversely associated with an increased risk of MetS [8,10,20]. For example, a recent cross-sectional study involving 5231 adults in Koreans suggested that elevated serum direct Bilirubin was associated with a decreased risk of MetS [9]. From 5266 women aged >40 years enrolled in the Korean Genomic Rural Cohort, TBL level appears to be inversely associated with the prevalence of MetS [21]. In 1423 middle-aged and elderly Chinese recruited from an urban community in Shanghai, serum TBL levels within the physiological range were inversely associated with MetS and insulin resistance, hyperinsulinemia, and systemic inflammation [11]. The 4-year retrospective cohort involving 6205 Korean men without MetS

Table 1
Baseline characteristics of participants according to baseline total bilirubin in the cross-sectional and cohort study.

Baseline characteristics	Baseline total bilirubin					
	Cross-sectional study N = 893			Cohort study N = 288		
	1st tertile 0.20–0.53	2nd-3rd tertile 0.54–2.00	*P*-value*	1st-2nd tertile 0.20–0.55	3rd tertile 0.56–2.00	*P*-value*
	N = 302	N = 591		N = 91	N = 197	
Age (years)	70 ± 8	69 ± 9	0.544	67 ± 8	66 ± 9	0.421
Body mass index (kg/m^2)	22.7 ± 3.2	22.5 ± 3.2	0.409	20.8 ± 2.1	20.9 ± 2.4	0.712
Waist circumference (cm)	80.7 ± 9.2	80.3 ± 9.1	0.527	75.2 ± 6.9	75.6 ± 7.0	0.591
Smoking status†, %	97.0/1.3/1.3/0.3	97.0/2.4/0.3/0.3	0.264	95.6/2.2/1.1/1.1	95.1/2.5/1.0/1.0	0.998
Drinking habits‡, %	70.5/21.2/6.3/2.0	71.4/22.5/3.4/2.7	0.215	70.3/19.8/6.6/3.3	67.5/23.9/4.1/4.6	0.661
Exercise habits, %	38.7	36.9	0.609	38.5	40.1	0.897
History of CVD, %	4.6	4.1	0.727	4.4	2.0	0.267
Systolic blood pressure (mmHg)	137 ± 18	136 ± 17	0.326	130 ± 18	129 ± 18	0.843
Diastolic blood pressure (mmHg)	77 ± 10	77 ± 9	0.738	74 ± 9	74 ± 9	0.974
Antihypertensive medication, %	43.4	43.3	1.000	23.1	19.3	0.530
Triglycerides (mg/dL)	87 (68–122)	85 (64–114)	**0.030**	77 (59–103)	73 (55–95)	0.086
HDL cholesterol (mg/dL)	66 ± 16	69 ± 17	**0.004**	72 ± 16	74 ± 16	0.299
LDL cholesterol (mg/dL)	120 ± 28	126 ± 29	**0.004**	122 ± 27	128 ± 28	0.053
Antilipidemic medication, %	31.8	27.4	0.185	6.6	8.1	0.813
Hemoglobin A1c, %	5.7 (5.5–6.0)	5.7 (5.4–5.9)	**0.012**	5.6 (5.3–5.7)	5.6 (5.3–5.8)	0.887
Antidiabetic medication, %	7.0	4.7	0.213	1.1	0.5	0.533
Serum uric acid (mg/dL)	4.7 ± 1.2	4.7 ± 1.1	0.749	4.4 ± 1.1	4.5 ± 1.0	0.704
Estimated GFR (ml/min/1.73 m^2)	71.4 ± 12.8	73.0 ± 10.6	0.075	74.1 ± 11.9	75.9 ± 9.8	0.193
GGT (IU/L)	17 (13–24)	16 (13–23)	0.859	14 (12–22)	15 (12–22)	0.776
ALT (IU/L)	16 (13–21)	17 (13–21)	0.567	16 (12–18)	16 (13–19)	0.863
Number of MetS components, %	2.7 ± 1.2	2.5 ± 1.2	**0.022**	1.4 ± 0.7	1.5 ± 0.7	0.551

N, number; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR glomerular filtration ratio; GGT, gamma glutamyltransferase; ALT, alanine aminotransferase. Data presented are mean ± standard deviation. Data for triglycerides, hemoglobinA1c, total bilirubin, and alanine aminotransferase were skewed, and presented as median (interquartile range) values, and were log-transformed for analysis. †Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack· year), and the participants were classified into never smokers, past smokers, light smokers (<30 pack year) and heavy smokers (≥30 pack year). ‡Daily alcohol consumption was measured using the Japanese liquor unit in which a unit corresponds to 22.9 g of ethanol, and the participants were classified into never drinkers, occasional drinkers, daily drinkers (light <2 unit/day, heavy ≥2 unit/day). * *P*-value: Student's t-test for the continuous variables or the χ^2 -test for the categorical variables. Bold values indicate significance ($p < 0.05$).

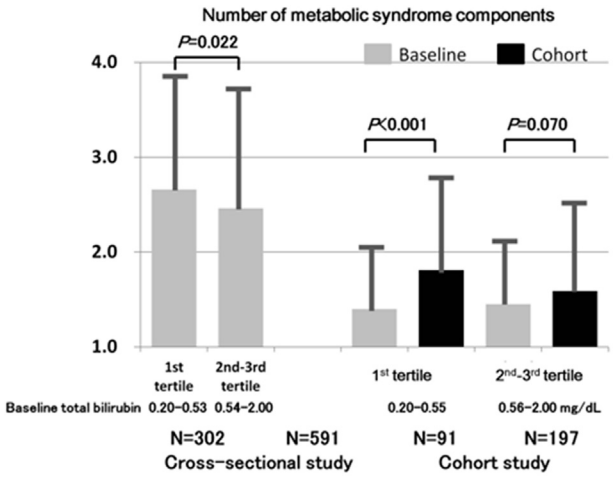

Fig. 2. Prevalence and incidence of metabolic syndrome components of participants in the cross-sectional and cohort studies.

revealed that TBL levels were inversely associated with the development of MetS [13]. In apparently healthy middle-aged and nonsmoking men, increased serum TBL was inversely associated with a risk of incident MetS, but the inverse correlation was attenuated in current smokers [22]. In addition, in a cross-sectional and longitudinal study including 2435 Japanese men and 1436 Japanese women, the adjusted hazard ratios of developing MetS for the higher quartiles of TBL compared with the lowest quartile were not significant [14]. In our study of women who were non-smokers, serum TBL was significantly and inversely associated with incident MetS in both the cross-sectional and cohort studies.

In line with these negative relationships between serum bilirubin levels and MetS, a negative association between bilirubin levels and central obesity per se has been shown in several recent studies [10,11,20,21]. Jenko-Pražnikar et al. [23] also demonstrated that serum bilirubin levels were negatively associated with central obesity in overweight healthy middle-aged individuals. As weight loss is known to improve several cardiovascular risk factors, Andersson et al. [24] have demonstrated in the results of their study that each 1% decrease in weight loss causes a linear increase in serum bilirubin level within the reference range in men and women. In our study, a negative association between serum TBL levels and central obesity per se was observed.

In our cohort study, increased serum TBL levels showed a significant relationship with elevated BP, which may be due to several reasons. In a prospective study of 3989 men and women without hypertension during a median follow-up of 10.7 years, baseline TBL was approximately log-linearly associated with hypertension risk, and age- and sex-adjusted hazard ratio for hypertension per 1-SD increase in $\log_e$ TBL was 0.86 (95% CI: 0.81–0.92; $p < 0.001$), which was attenuated to 0.94 (0.88–0.99; $p = 0.040$) after further adjustment for established risk factors [25].

Many experimental studies suggest oxidative stress can cause the development of hypertension and MetS [26]. Serum TBL level is a major contributor to the antioxidant capacity in blood plasma [27] and has been identified as an independent cardiovascular risk factor in cohort studies [25]. These clinical studies are supported by in vitro and in vivo experimental data and have demonstrated that bilirubin not only has an ability to scavenge overproduced reactive oxygen species (ROS) and inhibit vascular smooth muscle cell proliferation, but additionally has anti-inflammatory effects [28].

Table 2
Relationship between baseline characteristics and number of metabolic syndrome components in the cross-sectional and cohort study.

Baseline characteristics	Number of MetS components			
	Cross-sectional study N = 893		Cohort study N = 288	
	r (*P*-value)	β (*P*-value)	r (*P*-value)	β (*P*-value)
Age (years)	**0.247 (<0.001)**	**0.211 (<0.001)**	**0.123 (0.037)**	0.106 (0.181)
Smoking status	- 0.065 (0.054)	−0.059 (0.053)	- 0.024 (0.685)	0.015 (0.801)
Alcohol consumption	- **0.082 (0.014)**	- **0.091 (0.005)**	- 0.083 (0.161)	- 0.044 (0.489)
Exercise habits	- 0.059 (0.076)	- **0.073 (0.016)**	- 0.057 (0.339)	- 0.088 (0.136)
History of CVD	**0.109 (0.001)**	**0.072 (0.016)**	- 0.007 (0.909)	- 0.012 (0.835)
LDL cholesterol	- 0.049 (0.143)	- 0.021 (0.481)	0.081 (0.170)	0.087 (0.152)
Serum uric acid	**0.285 (<0.001)**	**0.238 (<0.001)**	**0.135 (0.022)**	**0.156 (0.019)**
eGFR	- **0.227 (<0.001)**	0.000 (0.997)	- 0.087 (0.140)	0.038 (0.660)
GGT (IU/L)	**0.218 (<0.001)**	**0.152 (<0.001)**	- 0.099 (0.094)	- **0.137 (0.042)**
ALT (IU/L)	**0.228 (<0.001)**	**0.143 (<0.001)**	- 0.063 (0.140)	0.108 (0.092)
Total bilirubin	- **0.082 (0.015)**	**0.536 (<0.001)**	- 0.081 (0.171)	- 0.099 (0.098)
R2	———	**0.218 (<0.001)**	———	**0.074 (0.027)**

r, Pearson's correlation coefficient; β, standard coefficient; R^2, multiple, coefficient of determination. Significant values ($p < 0.05$) are presented in bold. . (———) did not remain in the final model by stepwise multiple linear regression analysis. Data for total bilirubin, GGT and ALT were skewed, and log-transformed for analysis.

Table 3
Prevalence and odds ratio (95% CI) for metabolic syndrome and its components of participants according to baseline total bilirubin in the cross-sectional study.

Cross-sectional study	Baseline total bilirubin			
	Total	1st tertile 0.20–0.53	2nd-3rd tertile 0.54–2.00	*P*-value*
Dependent variable	N = 893	N = 302	N = 591	
Metabolic syndrome, N (%)	451 (50.5)	167 (55.3)	284 (48.1)	**0.048**
Adjusted odds ratio (95% CI)	**0.67 (0.55–0.82)**	Reference	**0.70 (0.51–0.95)**	**0.022**
Central obesity, N (%)	451 (50.5)	164 (54.3)	287 (48.6)	0.120
Adjusted odds ratio (95% CI)	**0.80 (0.66–0.97)**	Reference	**0.74 (0.55–0.99)**	**0.049**
Elevated blood pressure, N (%)	683 (76.5)	232 (76.8)	451 (76.3)	0.934
Adjusted odds ratio (95% CI)	0.93 (0.73–1.17)	Reference	0.98 (0.69–1.41)	0.920
Elevated triglycerides, N (%)	110 (12.3)	45 (14.9)	65 (11.0)	0.106
Adjusted odds ratio (95% CI)	0.91 (0.68–1.21)	Reference	0.68 (0.44–1.04)	0.076
Lowering HDL cholesterolemia, N (%)	331 (37.1)	124 (41.1)	207 (35.0)	0.079
Adjusted odds ratio (95% CI)	0.83 (0.67–1.01)	Reference	0.83 (0.61–1.14)	0.249
Elevated fasting glucose, N (%)	679 (76.0)	237 (78.5)	442 (74.8)	0.246
Adjusted odds ratio (95% CI)	0.83 (0.66–1.03)	Reference	0.78 (0.56–1.10)	0.163

CI, confidence interval. *Multivariate-adjusted for age, smoking status, drinking status, exercise habits, presence of CVD, LDL cholesterol, serum uric acid, estimated GFR, γ-GTP, and ALT. Data for GGT and ALT were skewed, and log-transformed for analysis. Bold values indicate significance ($p < 0.05$).

Table 4
Prevalence and odds ratio (95% CI) for metabolic syndrome and its components of participants according to baseline total bilirubin after 4-year in the cohort study.

Cohort study	Baseline total bilirubin			
	Total	1 tertile 0.20–0.55	2nd-3rd tertile 0.56–2.00	*P*-value[a]
Dependent variable	N = 288	N = 91	N = 197	
Metabolic syndrome, N (%)	46 (16.0)	21 (23.1)	25 (12.7)	**0.037**
Adjusted odds ratio (95% CI)	**0.63 (0.41–0.96)**	Reference	**0.41 (0.21–0.81)**	**0.011**
Central obesity, N (%)	65 (22.6)	19 (20.9)	46 (23.4)	0.762
Adjusted odds ratio (95% CI)	1.03 (0.70–1.50)	Reference	1.05 (0.55–2.00)	0.878
Elevated blood pressure, N (%)	176 (61.1)	66 (72.5)	110 (55.8)	**0.009**
Adjusted odds ratio (95% CI)	**0.69 (0.50–0.96)**	Reference	**0.47 (0.26–0.84)**	**0.010**
Elevated triglycerides, N (%)	15 (5.2)	6 (6.6)	9 (4.6)	0.569
Adjusted odds ratio (95% CI)	0.86 (0.43–1.74)	Reference	0.60 (0.20–1.80)	0.359
Lowering HDL cholesterolemia, N (%)	47 (16.3)	16 (17.6)	31 (15.7)	0.733
Adjusted odds ratio (95% CI)	0.86 (0.57–1.29)	Reference	0.86 (0.43–1.71)	0.659
Elevated fasting glucose, N (%)	176 (61.1)	58 (63.7)	118 (59.9)	0.603
Adjusted odds ratio (95% CI)	0.90 (0.66–1.23)	Reference	0.82 (0.48–1.40)	0.457

[a] Multivariate-adjusted for age, smoking status, drinking status, exercise habits, presence of CVD, LDL cholesterol, serum uric acid, estimated GFR, GGT, and ALT. Data for GGT and ALT were skewed, and log-transformed for analysis. Bold values indicate significant.

There were several limitations of our study. First, serum TBL measurement was based on a single assessment, which might introduce a misclassification bias. Second, we could not rule out the possible effects of medications for hypertension, dyslipidemia, and hyperglycemia on the current findings. Third, the longitudinal analyses were limited by smaller sample sizes and discrepancies in the sequential measurements of the components of MetS in 2014 and 2017. The cohort was slightly younger and healthier compared

to participants not included in the longitudinal analyses, this might have caused an underestimation of incident MetS after three years of follow-up. Therefore the demographics and referral source may limit generalizability.

As a result, the present study showed that serum TBL levels are significantly associated with incident MetS among Japanese elderly community-dwelling women. The underlying mechanism behind this relationship is unknown, but it seems to be unrelated to confounding factors such as age, smoking status, drinking status, exercise habits, presence of CVD, LDL-C, SUA, eGFR, GGT, and ALT. Thus, serum TBL might provide an important marker for the assessment of risk as well as a therapeutic target for MetS. For healthy community-dwelling persons, prospective population-based studies are needed to investigate the underlying mechanisms of this association to determine whether intervention, such as medication and effective lifestyle modifications that control TBL in adults, will improve MetS.

Author disclosure statement

No competing financial interests exist for any of the authors.

Disclaimer

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.02.009.

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