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ARTICLE

Sex-specific association between soluble corin and metabolic syndrome in Chinese adults

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Abstract

Soluble corin has been associated with cardiovascular disease and its risk factors, but whether it is associated with metabolic syndrome (MetS), a cluster of cardiometabolic disorders, remains unclear. We aimed to examine the association between soluble corin and MetS in Chinese men and women. We examined serum soluble corin using immunoassays in 962 men (mean age, 53 years) and 1536 women (mean age, 54 years) free of cardiovascular disease. Logistic regression was applied to examine the association between soluble corin and MetS in men and women. The results showed that participants in the 3rd and 4th quartiles of serum soluble corin had 1.99 (95% CI: 1.32–3.00) and 3.84 (95% CI: 2.54–5.83) times the risk of having MetS for men and 1.48 (95% CI: 1.06–2.06) and 1.53 (95% CI: 1.10–2.12) times the risk of having MetS for women compared to those in the lowest quartile. The magnitude of the association between serum soluble corin and MetS was significantly stronger for men than for women ($P < 0.001$). These results indicated that soluble corin was significantly associated with MetS, and this association was stronger for men than for women. Corin may contribute to cardiometabolic risks differently between men and women and thereby accounting, at least partly, for the sex difference in cardiovascular risk.

Keywords Cross-sectional study · Cardiometabolic risk factors · Metabolic syndrome · Soluble corin

Introduction

Metabolic syndrome (MetS), a cluster of cardiometabolic risk factors, including raised blood pressure, dyslipidemia, hyperglycemia, and central obesity, is associated with the morbidity and mortality of cardiovascular disease and chronic kidney disease [1, 2]. Understanding the mechanisms and risk factors of MetS is therefore critical for delivering the best management of cardiometabolic-associated disease burden. However, the underlying mechanisms are not very clear. The natriuretic peptide system plays an integral role in energy homeostasis [3–5], activation of lipolysis [6], lipid oxidation [7], mitochondrial respiration [8], and salt-water balance [9], all of which account for development and progress of MetS. Previous epidemiological studies reported that B-type natriuretic peptide was inversely associated with metabolic syndrome [10–12], and the Framingham Study also showed that people with metabolic syndrome had a lower adjusted circulating natriuretic peptide level than those without metabolic syndrome [13]. As a key activator of natriuretic peptides [14–16], corin may be a potential switching regulator of the natriuretic peptide system, thereby contributing to MetS and related complications.

Corin, a type II transmembrane serine protease highly expressed in the heart [17], can be shed from cells and enter the circulation. Its probable role in the development of MetS has been suggested by some studies. For example, basic studies found that body weight and blood pressure were increased in *corin* gene knockout mice [16], and corin is downregulated in mice with diabetes [15]. In humans, *CORIN* gene variants and mutations have been identified in

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association with hypertension and coronary artery disease [18–21]. Circulating levels of soluble corin have been associated with some MetS-related complications, e.g., myocardial infarction [22], heart failure [23, 24], atrial fibrillation [25], pregnant hypertension [26], and chronic kidney disease [27], in small-sample case–control studies. Our prior studies have found that serum soluble corin was associated with some components of MetS, such as hyperglycemia [3], hypertension [28], dyslipidemia [29], and central obesity [30], in an unselected population of Chinese adults. However, whether serum soluble corin was associated with clustering of these crosstalk cardiometabolic risk factors in this population, as well as other ethnic groups, is unknown. Further, sex-differences in circulating corin [31] and MetS prevalence [32] have been documented. Therefore, the goal of this study is to examine the sex-specific association between serum soluble corin and MetS in an unselected population of Chinese men and women.

Methods

Study participants

We conducted a cross-sectional study in a traditional but economically developed district of Suzhou city from January to May 2010. The study design, survey methods, and laboratory techniques have been described previously [28]. Briefly, 2706 participants signed the informed consent and participated in this study. We excluded 107 participants who lacked blood samples and 101 participants who met one of the following exclusion criteria: (1) clinical suspicion of diseases that may cause secondary hypertension (e.g., renal artery stenosis, coarctation, glomerulonephritis, pyelonephritis, pheochromocytoma, Cushing's syndrome, Conn's syndrome), (2) self-reported history of coronary heart disease, stroke, or tumors, (3) self-reported thyroid or parathyroid diseases, and (4) pregnancy. In total, 2498 participants were included in the final data analysis. The protocols of this study were approved by the Soochow University Ethics Committee.

Indexes of metabolic syndrome

Body weight and height were measured using a regularly calibrated stadiometer and balance-beam scale with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the level of 1 cm above the umbilicus. Three consecutive sitting blood pressure measurements (30 s between each) were taken by trained staff using a standard mercury sphygmomanometer according to a standard protocol [33] after the subjects had been resting for at least 5 min. The first and fifth Korotkoff sounds were recorded as the systolic and diastolic blood pressure (SBP/DBP), respectively. The mean of three measurements was used in the analyses. Overnight fasting blood samples were collected from all participants. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting plasma glucose (FPG) were measured enzymatically on a Hitachi 7020 automatic biochemical analyzer using commercial reagents. Intra- and inter-assay coefficients of variation were less than 2% and 4%, respectively.

Definition of metabolic syndrome

MetS was defined as ≥3 of 5 abnormal findings, including increased blood pressure, dyslipidemia, hyperglycemia, and central obesity, according to the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention [34], which was described in Table 1. Central obesity was defined here as WC ≥ 85 cm for men and as WC ≥ 80 cm for women based on the recommendations of the Working Group on Obesity in China [35]. The MetS score (ranging from 0 to 5) was calculated by summing the number of abnormal components.

Measurement of serum soluble corin

Blood samples were obtained by venipuncture in the morning after a requested overnight fast (at least 8 h), and serum and plasma were frozen at −80 °C until laboratory testing. Serum corin was measured in duplicate by a quantikine human corin immunoassay (R&D Systems, Inc., Minneapolis, USA). Intra- and inter-assay coefficients of variation were less than 2.7% and 6.3%, respectively.

Confounding factors

Data on demographic information, lifestyle risk factors, personal medical history and family history of hypertension

Table 1 Definitions of metabolic syndrome components

Components	Definition
Central obesity	≥85 cm for men or ≥80 cm for women
Elevated triglyceride	≥1.70 mmol/L or under treatment
Reduced HDL-C	<1.00 mmol/L for men and <1.30 mmol/L for women or under treatment
Elevated blood pressure	≥130/85 mmHg or under treatment
Elevated fasting glucose	≥5.6 mmol/L or under treatment

(FHH) were gathered from standard questionnaires in the Chinese language administered by trained staff. Cigarette smoking was defined as having smoked at least 1 cigarette per day for 1 year or more and reporting current smoking. Alcohol consumption was defined as consuming any type of alcoholic beverage at least once per week during the last three years. A family history of hypertension (FHH) was defined as cases where one or more immediate family members, including the parents and siblings, were hypertensive.

Statistical analysis

Baseline characteristics were presented according to prevalent MetS in men and women. To examine the association between soluble corin and MetS score, we constructed a quantile regression model in which serum soluble corin was the dependent variable and MetS score was the independent variable, adjusting for age, smoking, drinking, and FHH. The quantile regression model was used here to account for the skewed distribution of serum soluble corin. To further examine the association between soluble corin and prevalent MetS, we constructed a nonconditional logistic regression model with prevalent MetS (y/n) as the independent variable and serum soluble corin (quartiles as a categorical variable) as the independent variable, adjusting for the covariates listed above. All models were repeated in men and women. To examine whether and to what extent sex affected the association between soluble and prevalent MetS, the interaction term of sex × soluble corin (continuous or categorical as quartiles) was included in the regression models. A significant interaction indicates a significant sex difference in the associations between soluble corin and MetS. A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS statistical software (version 9.4, Cary, North Carolina).

Results

Baseline characteristics

This study included 2498 participants comprised of 962 men (average age, 53 years) and 1536 women (average age, 54 years). As expected, MetS was more prevalent in men ($n = 326$, 33.89%) than in women ($n = 448$, 28.66%). Men had a significantly higher level of serum soluble corin than women (median 2174.5 vs. 1515.1 pg/mL, $P < 0.001$). The baseline characteristics of the study participants are presented in Table 2. For men, compared to participants without MetS, those with MetS were more likely to have FHH and a higher level of BMI, WC, FPG, blood pressure, and lipids but less likely to be current smokers (all $P < 0.05$). These characteristics were similarly associated with MetS in women. In addition, for women, participants with MetS were more likely to be older than those without MetS ($P < 0.001$). The median level of serum soluble corin was significantly higher in participants with MetS than those without in both men (2425.5 vs. 2043.3 pg/mL, $P < 0.001$) and women (1577.2 vs. 1489.9 pg/mL, $P < 0.001$).

Sex-specific association between serum soluble corin and MetS score

Figure 1 shows the median levels of serum soluble corin according to MetS score in men and women. Participants with a higher MetS score had a significantly higher level of serum soluble corin in both men and women ($P < 0.001$). Quantile regression revealed that participants with per 1 additional MetS score would have a median of 154.26 pg/mL (95% CI: 110.88–193.12) and 32.48 pg/mL (95% CI: 18.79–55.49) higher level of serum soluble corin in men and women, respectively.

Sex-specific association between serum soluble corin and prevalence of MetS

For easier data interpretation, we further examined the association between serum soluble corin and the risk of having MetS. As shown in Table 3, compared to participants with the lowest level of serum soluble corin, those in the 3rd and 4th quartiles had 2.04 ($P = 0.001$) and 3.93 ($P < 0.001$) times the risk of having MetS in men, whereas those in the 3rd and 4th quartiles had 1.60 ($P = 0.004$) and 1.76 ($P < 0.001$) times risks of having MetS in women. Further adjusting for age, smoking, drinking, and FHH did not significantly change the magnitude of the associations between serum soluble corin and the prevalence of MetS in both men and women. Notably, the association between serum soluble corin and the prevalence of MetS in men was much stronger than that in women (all $P < 0.05$).

Discussion

While we previously found that serum soluble corin was significantly associated with hyperglycemia [3], hypertension [28], obesity [30], and dyslipidemia [29] in Chinese adults, whether MetS, a cluster of these metabolic abnormalities, is associated with serum soluble corin is unknown due to the phenomenon that these metabolic disorders usually cluster and intercorrelate with each other. To date, the association between serum soluble corin and MetS has not been studied in our study population or in other ethnic groups. Our current study demonstrated for the first time that serum soluble corin

Table 2 Characteristics of study participants according to metabolic syndrome by sex

Characteristics	Men			Women		
	MetS (−)	MetS (+)	*P*-value	MetS (−)	MetS (+)	*P*-value
No. of participants	636	326		1088	448	
Age, years	52.9 ± 9.5	53.7 ± 9.5	0.217	50.7 ± 9.5	56.4 ± 8.6	<0.001
Smoking, *n* (%)	402 (63.2)	170 (52.2)	<0.001	6 (0.6)	4 (0.9)	0.490
Drinking, *n* (%)	281 (44.2)	140 (42.9)	0.714	30 (2.8)	14 (3.1)	0.737
FHH, *n* (%)	157 (24.7)	104 (31.9)	0.017	287 (26.4)	125 (27.9)	0.540
BMI, kg/m^2	24.2 ± 3.5	27.3 ± 4.4	<0.001	23.7 ± 3.1	26.4 ± 3.0	<0.001
WC, cm	82.7 ± 7.9	91.4 ± 6.9	<0.001	77.9 ± 8.1	86.4 ± 7.2	<0.001
SBP[a], mmHg	128 (120, 138)	136 (128, 145)	<0.001	122 (114, 132)	138 (130, 148)	<0.001
DBP[a], mmHg	84 (80, 93)	91 (86, 96)	<0.001	80 (76, 86)	86 (82, 92)	<0.001
TC[a], mmol/L	4.94 (4.43, 5.50)	5.17 (4.68, 5.81)	<0.001	5.05 (1.49, 5.66)	5.36 (4.7, 6.04)	0.004
TG[a], mmol/L	1.03 (0.76–1.34)	1.89 (1.44, 2.69)	<0.001	0.91 (0.68, 1.23)	1.68 (1.13, 2.25)	<0.001
LDL-C, mmol/L	2.90 ± 0.70	3.01 ± 0.83	0.042	2.97 ± 0.75	3.18 ± 0.80	<0.001
HDL-C, mmol/L	1.5 ± 0.5	1.23 ± 0.34	<0.001	1.66 ± 0.40	1.36 ± 0.33	<0.001
FPG[a], mmol/L	5.0 (4.6, 5.4)	5.8 (5.2, 6.5)	<0.001	5.0 (4.6, 5.3)	5.8 (5.2, 6.3)	<0.001
Serum corin[a], pg/mL	2043.3 (1699.2, 2478.8)	2425.5 (1997.1, 2917.7)	<0.001	1489.9 (1257.5, 1734.1)	1577.2 (1354.1, 1817.4)	<0.001

MetS metabolic syndrome, *FHH* family history of hypertension, *BMI* body mass index, *WC* waist circumference, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FPG* fasting plasma glucose

[a]Results were expressed as median (interquartile range) unless otherwise noted

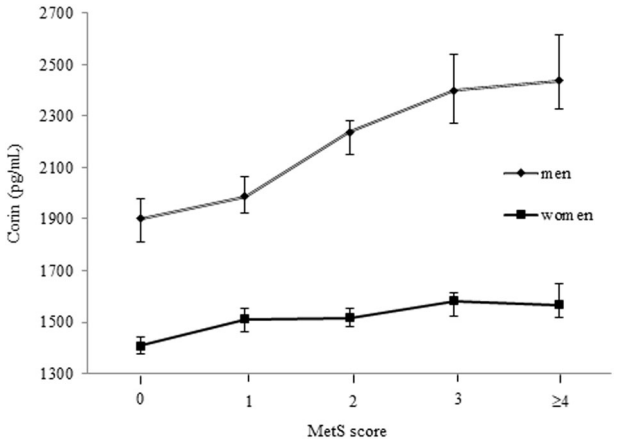

Fig. 1 Median levels and 95% CI of serum soluble corin according to metabolic syndrome score group by sex. There were 113, 221, 302, 217, and 109 men and 289, 388, 411, 280, and 168 women in the groups with a MetS score of 0, 1, 2, 3, ≥4, respectively

was significantly associated with the prevalence of MetS in Chinese men and women. As previous studies reported [23, 36], we similarly found that men had higher levels of serum soluble corin and were more likely to have MetS than women. In addition, we also found a sex-specific association between serum soluble corin and MetS. The association between corin and MetS was much stronger in men than in women. These results suggest that corin may be a potential contributor to the sex difference seen in cardiometabolic risk, although the underlying mechanisms remained unclear. Circulating corin may be a useful marker of cardiometabolic risk and therefore help identify individuals with a high risk of cardiovascular disease in the Chinese adult population, particularly men.

Prior studies have reported a sex difference in circulating corin similar to that in our study [23]. To eliminate the potential influence of sex on the association between serum soluble corin and MetS, we examined and found that the association was stronger in men than in women. Our prior study found a similar phenomenon, namely, that the association between serum soluble corin and stroke was much stronger in men than in women [36]. The mechanisms underlying the sex-specific contribution of corin to MetS and cardiovascular risk remain unclear. As a key activator of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), higher plasma corin levels vs. lower BNP have been observed in men than in women [31], indicating that men may have a lower activity of corin in processing BNP activation than women. Together with our findings, these studies suggest that corin may contribute to cardiometabolic risks differently in men and women, thereby accounting, at least partially, for the sex difference in cardiovascular disease profiles [37].

Table 3 Associations between serum soluble corin and prevalent metabolic syndrome in men and women

Corin quartiles	MetS (%)	Unadjusted		Adjusted[a]	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Men					
≤1785.8	51 (21.3)	1.00 (ref)	—	1.00 (ref)	—
1785.9–2174.5	66 (27.4)	1.40 (0.92–2.13)	0.118	1.42 (0.93–2.17)	0.105
2174.6–2646.7	86 (35.5)	2.04 (1.36–3.07)	0.001	1.99 (1.32–3.00)	0.001
≥2646.8	123 (51.5)	3.93 (2.63–5.86)	<0.001	3.84 (2.54–5.83)	<0.001
Women					
≤1279.9	89 (23.1)	1.00 (ref)	—	1.00 (ref)	—
1280.0–1515.1	101 (26.4)	1.20 (0.86–1.66)	0.287	1.19 (0.85–1.68)	0.312
1515.2~1758.5	125 (32.5)	1.60 (1.16–2.20)	0.004	1.48 (1.06–2.06)	0.020
≥1758.6	133 (34.6)	1.76 (1.28–2.42)	<0.001	1.53 (1.10–2.12)	0.012

[a]Adjustment for age, smoking, drinking, and family history of hypertension

Corin deficiency led to a significant increase in body weight and blood pressure in *corin* gene knockout mice [16]. Significantly reduced corin expression at the mRNA and protein levels was also found in diabetic rats [15]. These experimental findings suggest a favorable effect of elevated corin on metabolic abnormalities. In humans, some small-sample case–control studies have examined circulating corin in some disease states with mixed results, such as cardiovascular disease [22, 38–40], stroke [36], pregnant hypertension [26, 41, 42], and chronic kidney disease [27]. Most of the above studies showed that the level of soluble corin decreased in cardiovascular disease, while it increased in hypertension during pregnancy. The varied corin levels in different disease states reflects a complex mechanism linking corin to different diseases.

The positive association between circulating corin and MetS identified in our study appeared to indicate that the relation of soluble corin with cardiovascular disease in humans is more complex than in animal experiments. Based on these conflicting findings in humans vs. animals, we speculated possible reasons for this inconsistency. First, there may be corin resistance among individuals with metabolic disorders, and corin activity might be a contributor to the conflicting findings. A previous study reported that corin expression was upregulated in heart failure, whereas corin activity did not increase [43]. Given that corin is a physiological activator of natriuretic peptides [14, 15], natriuretic peptides can be used as an indicator of corin activity. Natriuretic peptide levels were decreased in individuals with metabolic syndrome [10–12]. Corin activity may not increase proportionally in individuals with metabolic disorders although the level of corin is increased. Second, the increased circulating soluble corin levels in MetS may be a compensation for metabolic disorders. A study by Cui et al. [44] found that levels of corin mRNA and protein in the uterus were significantly lower in preeclampsia patients, whereas plasma corin levels were higher in preeclampsia patients than in nonpregnant women or women with a normal pregnancy. They considered that corin levels in the plasma did not reflect the levels in tissues, and plasma corin expression increased in response to high blood volume and high blood pressure in pregnancy. Third, corin may have unknown functions in addition to activating natriuretic peptides, or there may be unknown factors that influence corin levels. The biological function and metabolism of corin warranted further study and may help move forward the translation of corin into clinical practice.

The strengths of our study included sex-specific analysis of the association between serum soluble corin and MetS and comprehensive measurement and adjustment of confounding factors including lifestyles and family history of hypertension. Some limitations in our study should also be acknowledged. First, the cross-sectional study design precludes causal inference. It is still unclear whether increased serum soluble corin is a risk factor, consequence, or just an accompanying phenomenon of MetS. Second, as in most epidemiological studies, residual confounding is of concern. Although our results remained significant after controlling for known risk factors for MetS, some unmeasured confounding effects may exist. Third, our findings were derived from Chinese adults whose cardiovascular health profiles could be different from other populations with different ethnic backgrounds. Thus, the generalizability of our results to other ethnic populations or younger populations is unknown. Fourth, we did not obtain data regarding insulin resistance, which is important in the pathophysiology of MetS. The potential role of corin in insulin resistance has been rarely studied. However, the natriuretic peptide system has been associated with insulin resistance in many population studies [45, 46]. The association between soluble corin and insulin resistance warrants further study.

In conclusion, serum soluble corin is significantly and cross-sectionally associated with MetS in Chinese men and women, independent of lifestyle and a family history of

hypertension. The magnitude of this association is much stronger in men than in women. These results may indicate a sex-specific effect of corin on cardiometabolic risks. In light of our findings, circulating corin may be a potential marker to identify high-risk individuals of cardiovascular disease, especially in men.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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