Letter to the Editor

Sex-specific and Dose-response Relationship between the Incidence of Gallstones and Components of the Metabolic Syndrome in Jinchang Cohort: A Prospective Study*

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Gallstones is a very common gastrointestinal disease, involving the formation of masses in the gall bladder or biliary tract, due to abnormally high concentrations of cholesterol or bilirubin in the bile[1]. There is a 10%–20% prevalence of gallstones worldwide, and > 20% of patients with gallstones show clinical symptoms, implying a substantial disease burden[1]. Metabolic syndrome (MS) comprises a series of cardiovascular risk factors, including obesity, abnormal lipid metabolism, high blood glucose or insulin resistance, and hypertension[2]. The prevalence of MS in China increased from 0–10% in 2002[3] to 24.2% in 2014[4]. The prevalence of MS ranges from 10% to 84% across the world, with nearly 30% of people in the United States and one in four in Europe having this syndrome[5].

The association between gallstones and MS has been a focus of some studies recently. MS is known to be strongly associated with lifestyle, and if MS is proved to be related to gallstone, we may reduce the prevalence of gallstones through lifestyle interventions, and form the basis of primary prevention by lifestyle changes[6]. Many previous studies tried to clarify this association, but they might be carried out without sufficient evidence. First, some studies were conducted with cross-sectional designs. As we all know, cross-sectional designs may be insufficient to capture the direct links between MS and gallstones. Second, most of these studies did not exclude people with cholecystectomy. However, those people should be excluded due to a history of gallstones at baseline in the cohort. In addition, those people with cholecystectomy for other reasons will hardly develop gallstones, so they also should be excluded in order to prevent them from assigning to the control group mistakenly, which may cause a large bias. Third, the associations of gallstones with MS as a whole were evaluated, but not those with specific components of MS. Last but not least, most studies did not explore potential sex differences. Thus, there is a need for more appropriate study design and statistical methods to be adopted to assess these associations. Consequently, we aimed to conduct a prospective study using Jinchang Cohort, to determine the dose-response relationships between gallstones and MS and its components, and explore the potentially sex differences.

This study used the Jinchang Cohort, established in June 2011, whose design and methods have been previously described in detail[7]. Because waist circumference (WC) data were collected from December 2012, this study included participants who entered the cohort after December 2012, making a total of 21,716. After excluding 620 individuals with missing data regarding the MS, 9,097 who were lost to follow-up, 976 with gallstones at baseline, and 477 who had undergone cholecystectomy, data from 10,419 participants remained to be analyzed in the

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present study.

Cox regression analysis was used to determine the relationships of MS as a whole, specific components of the MS, and the number of components of the MS present, with the incidence of gallstones. Because the incidence of gallstones and the related risk factors differed between the sexes, HRs (95% *CI*s) were calculated separately for men and women. Two models were used in the analysis: Model 1 was unadjusted, whereas Model 2 was adjusted for age, smoking status, alcohol intake status, physical exercise, and mean monthly income. We also investigated the dose-response relationship between components of the MS and risk of gallstones using the stratified analysis method and the restricted cubic splines function (RCS). Statistical analysis of the data was performed using SPSS 20.0 (IBM Inc., Armonk, NY, USA) and SAS 9.4 (SAS Institute Inc. Cary, NC, USA) software, and graphic rendering using R 3.6.1.

A total of 10,419 participants were included in this study, of whom 59.7% (6,223) were men and 40.3% (4,196) were women. Their mean age was 46.86 ± 13.74 years (Table 1). The adjusted HRs (95% *CI*) for gallstones were 7.92 (95% *CI*: 3.38–18.57) for women (P_{trend} < 0.05) and 5.01 (95% *CI*: 2.65–9.48) for total population (P_{trend} < 0.05) when five component of the MS were present, but this was not significant in men (P_{trend} > 0.05) (Table 2). Indeed, many studies conducted around the world have found that MS has a greater impact on the risk of gallstones in women than in men[8]. The mechanism for this may involve sex hormones, because estrogen enhances hepatic synthesis and secretion of cholesterol, and progesterone can reduce the secretion of bile salts and affect gall bladder emptying, which leads to a higher incidence of gallstones[9].

We found a nonlinear dose-response relationship between the risk of gallstones and WC across the cohort as a whole and in women specifically (Table 3 and Figure 1). In a previous survey conducted in China, the prevalence of obesity was 25%, and the author thought the more serious the obesity was, the higher the incidence of gallstones[10]. Studies have shown that obesity has been associated with more cholesterol. Cholesterol is excessively secreted from the liver into the bile due to the upregulation of HMG-CoA reductase activity among obese people[11]. In addition, reduced bile acid and phospholipid production in obese people may lead to more lithogenic bile. Furthermore, studies have found gallbladder capacity and residual volumes are higher in obese women, and their gallbladder motility is lower[12]. The above may explain the present finding.

In the present study, there was a positive linear dose-response relationship between the risk of gallstones and TG concentrations in total population and in women specifically (Table 3 and Figure 1). However, it is thought that the relationship between TG and gallstones is more complex. Some reports have suggested that supersaturated fatty acids may be produced in obese people with high TG concentrations, but it may also be that a high triglyceride concentration itself can reduce gall

Table 1. The characteristics of participants in Jinchang cohort at baseline (2012–2013)

Variable	All participants (*n* = 10,419)
Age (years), mean ± SD	46.86 ± 13.74
Gender, *n* (%)	
men	6,223 (59.7)
women	4,196 (40.3)
Average monthly income (yuan), *n* (%)	
< 1,000	414 (4.0)
1,000–1,999	4,300 (41.3)
2,000–4,999	5,503 (52.8)
≥ 5,000	202 (1.9)
Smoking, *n* (%)	
yes	4,499 (43.2)
no	5,920 (56.8)
Drinking, *n* (%)	
yes	2,392 (23.0)
no	8,027 (77.0)
Physical exercise, *n* (%)	
yes	8,608 (82.6)
no	1,811 (17.4)
WC (cm), mean ± SD	84.31 ± 10.34
TG (mmol/L), mean ± SD	1.91 ± 1.40
HDL-C (mmol/L), mean ± SD	1.37 ± 0.35
SBP (mmHg), mean ± SD	124.26 ± 20.12
DBP (mmHg), mean ± SD	78.38 ± 12.56
FPG (mmol/L), mean ± SD	5.30 ± 1.41

Note. WC, Waist circumference; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting plasma glucose; SD, standard deviation.

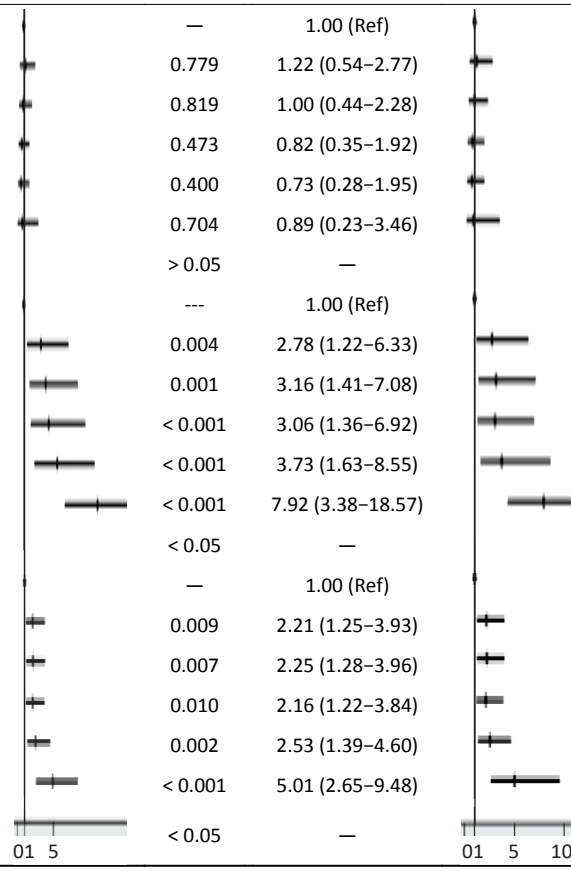
bladder contraction, which predisposes towards gallstone development[13]. Therefore, the relationship between gallstones and triglyceride must be confirmed in further studies.

There was a negative linear dose-response relationship between the risk of gallstones and HDL-C in total population and in women specifically (Table 3 and Figure 1). Studies conducted in many western countries have shown that low HDL-C is associated with a high incidence of gallstones, which may be the result of the associations between low HDL-C and insulin resistance, and insulin resistance and gallstones[14]. Wang et al.[15] found that HDL-C concentration affects the treatment of gallstones; specifically, the higher the HDL-C concentration is, the more likely gallstones are to be treated successfully. HDL-C is mainly synthesized in the liver, which can help cholesterol that is from peripheral sources transported to the liver and metabolized into bile, in which form it is expelled from the body.

Several studies have shown that hypertension is positively correlated with gallstones. Here, we show that this correlation is mainly the result of SBP, and that there is a positive linear dose-response relationship between the risk of gallstones and SBP in total population and in women specifically, but not in men (Table 3 and Figure 1). Insulin resistance might underpin this relationship between hypertension and gallstones[16], because it is associated with a higher rate of biliary cholesterol secretion, which promotes gallstone formation. Other studies have shown that a lower frequency of defecation is a risk factor for gallstones, and patients with hypertension may have more sympathetic

Table 2. HRs and 95% *CI*s for gallstones with the number of metabolic syndrome components in Jinchang cohort

	No. of components	Model 1*		Model 2#	
		HR (95% *CI*)	*P*	HR (95% *CI*)	*P*
Men	normal	1.00 (Ref)	—	1.00 (Ref)	—
	1	1.12 (0.50–2.52)	0.779	1.22 (0.54–2.77)	0.630
	2	0.91 (0.40–2.05)	0.819	1.00 (0.44–2.28)	0.995
	3	0.74 (0.32–1.70)	0.473	0.82 (0.35–1.92)	0.641
	4	0.66 (0.25–1.74)	0.400	0.73 (0.28–1.95)	0.533
	5	0.77 (0.20–2.95)	0.704	0.89 (0.23–3.46)	0.871
	P_{trend}	—	> 0.05	—	> 0.05
Women	normal	1.00 (Ref)	---	1.00 (Ref)	---
	1	3.32 (1.47–7.51)	0.004	2.78 (1.22–6.33)	0.015
	2	4.02 (1.82–8.90)	0.001	3.16 (1.41–7.08)	0.005
	3	4.41 (1.99–9.79)	< 0.001	3.06 (1.36–6.92)	0.007
	4	5.60 (2.49–12.56)	< 0.001	3.73 (1.63–8.55)	0.002
	5	11.11 (4.82–25.61)	< 0.001	7.92 (3.38–18.57)	< 0.001
	P_{trend}	—	< 0.05	—	< 0.05
Total	normal	1.00 (Ref)	—	1.00 (Ref)	—
	1	2.13 (1.21–3.77)	0.009	2.21 (1.25–3.93)	0.007
	2	2.17 (1.24–3.79)	0.007	2.25 (1.28–3.96)	0.005
	3	2.11 (1.20–3.70)	0.010	2.16 (1.22–3.84)	0.009
	4	2.53 (1.41–4.53)	0.002	2.53 (1.39–4.60)	0.002
	5	4.94 (2.65–9.23)	< 0.001	5.01 (2.65–9.48)	< 0.001
	P_{trend}	—	< 0.05	—	< 0.05



Note. *Model 1 was unadjusted for the confounding factors; #Model 2 was adjusted for age, smoking status, alcohol intake status, physical exercise, and mean monthly income. HR, Hazard ratio; *CI*, Confidence interval.

Table 3. HRs and 95% *CI*s for gallstones with components of the metabolic syndrome in Jinchang cohort[#]

Indexs		Men		Women		Total population	
		HR (95% *CI*)	*P*	HR (95% *CI*)	*P*	HR (95% *CI*)	*P*
WC (cm)	< 70*	_____		1.00 (Ref)		1.00 (Ref)	
	70–	1.00 (Ref)		2.06 (0.50–8.52)	0.318	2.74 (0.67–11.27)	0.162
	80–	1.19 (0.56–2.49)	0.655	3.83 (0.93–15.69)	0.063	5.23 (1.29–21.25)	0.021
	90–	1.34 (0.63–2.78)	0.437	6.84 (1.64–28.53)	0.008	7.48 (1.82–30.70)	0.005
	≥ 100‡	0.98 (0.37–2.55)	0.978	_____		2.84 (0.60–13.57)	0.191
	P_{trend}		0.910		< 0.001		< 0.001
TG (mmol/L)	< 1.4	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
	1.4–	1.13 (0.60–2.12)	0.715	1.17 (0.77–1.77)	0.474	1.24 (0.88–1.76)	0.218
	1.7–	0.73 (0.32–1.67)	0.459	1.04 (0.64–1.69)	0.867	1.06 (0.70–1.60)	0.780
	2.0–	2.02 (1.09–3.77)	0.027	1.41 (0.88–2.26)	0.158	1.75 (1.20–2.54)	0.040
	≥ 2.3	0.83 (0.47–1.48)	0.423	1.37 (0.94–2.00)	0.100	1.29 (0.94–1.76)	0.116
	P_{trend}		0.942		0.079		0.045
HDL-C (mmol/L)	< 0.8	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
	0.8–	3.15 (0.39–25.65)	0.283	0.87 (0.29–2.59)	0.803	1.08 (0.44–2.67)	0.872
	0.9–	1.53 (0.18–13.09)	0.699	0.45 (0.16–1.24)	0.124	0.67 (0.27–1.64)	0.375
	1.0–	2.92 (0.38–22.23)	0.301	0.35 (0.13–0.90)	0.029	0.78 (0.34–1.78)	0.557
	≥ 1.1	1.89 (0.26–13.67)	0.529	0.28 (0.13–0.64)	0.003	0.56 (0.26–1.19)	0.131
	P_{trend}		0.634		< 0.001		0.005
SBP (mmHg)	< 100	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
	100	1.28 (0.37–4.24)	0.712	2.29 (0.81–6.50)	0.118	2.07 (0.94–4.55)	0.072
	120	1.18 (0.36–3.88)	0.789	2.26 (0.82–6.26)	0.117	2.17 (1.00–4.69)	0.050
	140	0.55 (0.15–2.03)	0.372	2.73 (0.97–7.68)	0.057	2.13 (0.96–4.72)	0.063
	≥ 160	0.93 (0.24–3.53)	0.911	5.44 (1.91–15.50)	0.002	3.79 (1.68–8.53)	0.001
	P_{trend}		0.149		< 0.001		0.001
DBP (mmHg)	< 70	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
	70	1.09 (0.62–1.91)	0.774	1.23 (0.78–1.94)	0.384	1.22 (0.85–1.74)	0.274
	80	0.35 (0.17–0.72)	0.005	1.26 (0.80–1.99)	0.327	0.90 (0.61–1.31)	0.568
	90	0.63 (0.31–1.28)	0.203	1.65 (1.01–2.69)	0.045	1.25 (0.84–1.86)	0.275
	≥ 100	0.40 (0.16–1.01)	0.052	1.70 (0.99–2.91)	0.848	1.21 (0.76–1.90)	0.423
	P_{trend}		0.005		0.020		0.553
FPG (mmol/L)	< 4.5	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
	4.5	2.03 (0.78–5.27)	0.148	1.30 (0.66–2.56)	0.448	1.49 (0.86–2.59)	0.157
	5.0	1.71 (0.65–4.57)	0.289	1.09 (0.55–2.16)	0.801	1.23 (0.70–2.14)	0.481
	6.0	1.32 (0.45–3.91)	0.612	1.16 (0.56–2.37)	0.690	1.17 (0.64–2.13)	0.605
	≥ 6.0	1.21 (0.42–3.48)	0.728	1.50 (0.75–2.98)	0.252	1.43 (0.81–2.55)	0.221
	P_{trend}		0.345		0.325		0.808

Note. [#]Model 2 was adjusted for age, smoking status, alcohol intake status, physical exercise, and mean monthly income. [*]In the male population, no gallstones occurred when the waist circumference was less than 70 cm. [‡]In the female population, no gallstones occurred when the waist circumference was more than 100 cm.

nerve activity, which may inhibit defecation[17].

Although in recent years many studies have demonstrated relationships between diabetes and gallstones, and multiple studies have shown associations between blood glucose or insulin resistance and gallstones, the present prospective study has shown a positive linear dose-response relationship between gallstones and FPG only in women (Figure 1). Hyperglycemia may promote gallstone formation through a few mechanisms. Firstly, hyperglycemia in rats is associated with the upregulation of foxo1, which promotes the excretion of cholesterol in bile[18]. Alternatively, hyperglycemia may be associated with an inhibition of bile secretion, impaired gall bladder contraction and motor function, and altered crystal nucleation and mucus secretion into the bile[6].

In summary, metabolic syndrome is associated with a higher risk of gallstones with potential heterogeneities by sexes, and the risk of gallstones increased with the number of metabolic syndrome components. In addition, there was a dose-response relationship between WC, TG, HDL-C, SBP, FPG, and the risk of gallstones in women, but not in men. The findings emphasize the probable role of metabolic syndrome for gallstones, and call for more studies on the risk of gallstones in a sex-specific manner.

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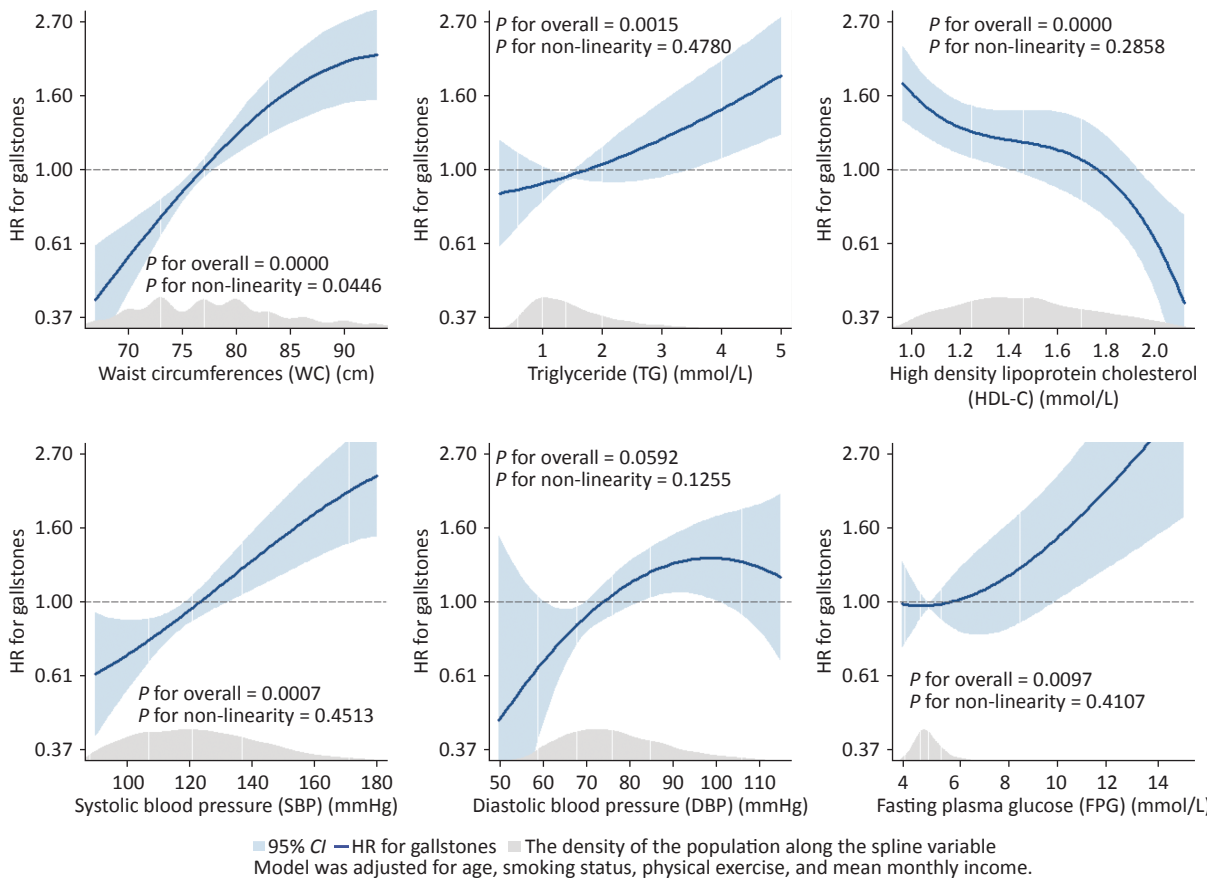

Figure 1. The dose-response relationship between metabolic syndrome components and the hazard risk of gallstones among women in Jinchang cohort.

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