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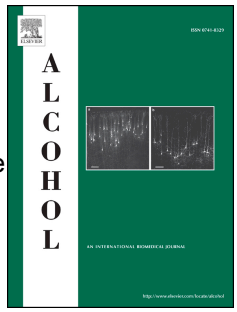

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Alcohol sensitivity, alcohol use and high-sensitivity C-reactive protein in older Chinese men: the Guangzhou Biobank Cohort Study

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Abstract

Compared to other ethnic groups Asians are more likely to be sensitive to alcohol, due to polymorphisms of alcohol-metabolizing enzymes. Although previous studies have found positive association between regular alcohol use and high-sensitivity C-reactive protein (HsCRP), whether this association is modified by alcohol sensitivity has not been clarified. We therefore sought to examined this potential effect modification in a cross-sectional community sample with high prevalence of alcohol sensitivity, using data from 2903 men aged ≥50years recruited during phase 1 of the Guangzhou Biobank Cohort Study. Information on alcohol consumption and sensitivity (facial flushing, palpitation or dizziness after drinking) was obtained by questionnaire and HsCRP was measured by an immunoturbidometric assay. Elevated HsCRP was defined as HsCRP level equal to or higher than 2.81mg/L(median).Excessive alcohol use was defined as use of ≥210g ethanol per week. After adjustment for age, educational level, occupation, smoking status, physical activity and history of cardiovascular disease, alcohol use was associated with HsCRP in a dose-response pattern. The risks of elevated HsCRP were higher in those who drank daily (odds ratio (OR) =1.38 (1.10, 1.72)) or drank excessively (1.57 (1.22, 2.02)), and were even higher in alcohol users with alcohol sensitivity (1.82 (1.24, 2.65) for daily users and 2.34 (1.48, 3.71) for excessive users). Results of this study have showed an important role of alcohol sensitivity in modifying the association between alcohol use and HsCRP level. Reduction of alcohol use should be an important public heath target, particularly among populations with high prevalence of alcohol

sensitivity.(253Words)

Key words: Alcohol sensitivity; alcohol use; high-sensitivity C reactive protein; China

INTRODUCTION

Animal and epidemiological studies have suggested an association between chronic alcohol use and atherosclerosis and cardiovascular mortality(Romelsjo et al., 2012; Shirpoor et al., 2012; Tang et al., 2013), but the underlying mechanism has not been fully elucidated. Previous research has focused on lipids and genetic factors, purported to be potential mediators of the vascular effects of alcohol(Brinton, 2010; Yao et al., 2011).However, accumulating evidence suggests alcohol may modify other factors through complex pathways that remain to be clarified (Brinton, 2010; Mukamal et al., 2001);as such alternative mechanisms of alcohol on atherogenesis may exist.

High-sensitivity C-reactive protein (HsCRP) is a marker of systemic inflammation and a predictor of cardiovascular risk (Cushman et al., 2009; Kaptoge et al., 2012; Otsuka et al., 2008). Population-base studies have shown an association between alcohol use and HsCRP(Albert et al., 2003), but the shape of the relationship remains inconclusive, with some earlier studies showing a J-shaped association between alcohol use and HsCRP(Imhof et al., 2001; Stewart et al., 2002), while a linear dose-response relationship was reported in a more recent study (Oliveira et al., 2010). Although the reason behind such discrepancy is not clear, it is possible that the effects of alcohol are modified by

intrinsic genetic differences. For example, compared to other ethnic groups Asians are more likely to have lower alcohol tolerance, due to polymorphisms of alcohol-metabolizing enzymes, such as acetaldehyde dehydrogenase(Wakabayashi, 2005). We have previously shown that alcohol sensitivity plays important role in the association between alcohol use and hypertension(Zhang et al., 2009; Zhang et al., 2013). Therefore, we sought to investigate whether alcohol sensitivity modifies the association of alcohol use with HsCRP in older Chinese males, using the data from the ongoing Guangzhou Biobank Cohort Study (GBCS).

MATERIALS AND METHODS

Sources of data

The GBCS is a three-way collaborative project between Guangzhou No. 12 Hospital and the Universities of Hong Kong and Birmingham, and has been described elsewhere in detail(Jiang et al., 2006). Briefly, about 30,000 older (≥50 years) men and women from Guangzhou, the third largest city in China, were recruited from a community social and welfare association in three phases (2003-04, 2005-06, and 2006-08), with around 10,000 participants included in each phase. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants given written, informed consent before participation. All participants underwent a structured computer-assisted interview, as well as fasting biochemical and anthropometric measurements. HsCRP was measured during the first phase of recruitment of 10,413

participants, but not in the subsequent phases due to the limited resources. Hence the present analysis is restricted to phase 1 male participants (n=3064). We excluded females as only 8.6% reported to have ever used alcohol (0.4% being excessive users, defined in the following section). We also excluded former drinkers (n=98) to avoid reverse causation due to poor health status. A total of 2903 men with all variables information on all variables of interest were included.

Alcohol use and sensitivity

During the interview, participants were asked about their frequency of alcoholic beverage consumption and the usual quantity per occasion, from which we calculated the amount of alcohol use (g ethanol per week). We categorized alcohol use based on frequency into never, occasional, regular, and former drinkers. Occasional drinkers were those drinking less than once per week, or only on special occasions, such as wedding or major festival. Regular drinkers were people who drank at least once per week, and were further divided into moderate (less than 210g of ethanol per week) and excessive (drinking 210g or more ethanol per week) drinkers(Au Yeung et al., 2012).Former drinkers were those who stopped drinking for more than one year. We also categorized participants using another scheme into never, occasional, 1-6 times per week and daily drinkers. Self-reported alcohol use has been found to be reliable and valid in different populations(Midanik, 1988). For the GBCS, content and predictive validity of our exposure variables has been confirmed previously elsewhere(Schooling et al., 2009).

Alcohol sensitivity was assessed by the question 'Do you usually experience facial flushing, palpitation or dizziness after drinking alcohol?' Participants who gave an affirmative response were considered to have alcohol sensitivity(Itoh et al., 1997).

HsCRP

Blood samples were drawn using a vacutainer tube in the morning after an overnight fast. We used a latex agglutination turbid metric test with a detection limit of 0.06 mg/L (BioSystems SA, Costa Brava30, Barcelona, Spain) to measure HsCRP. Further details of this test were given previously (Lao et al., 2010).

Statistical analysis

HsCRP levels were logarithmically transformed and their geometric means are presented. We created a dichotomized variable for HsCRP using the median (2.81 mg/L) as the cut-off value. We first compared the demographic characteristics across alcohol use status and sensitivity (never drinkers, current drinkers without alcohol sensitivity, and current drinkers with alcohol sensitivity). We then performed logistic regression analyses to assess the association of alcohol sensitivity and alcohol use with the elevated HsCRP (≥2.81mg/L) adjusting for potential confounders, which included age, occupation (manual, non-manual, others), educational level, physical activity (as assessed by the International Physical Activity Questionnaire and categorized into active, moderate, and inactive)(Deng et al., 2008), smoking (never, former, current) and history of cardiovascular diseases. All analyses were performed using SPSS 16.0(SPSS Inc.,

Chicago, IL, USA).

RESULTS

The mean age of the 2903 men included was 66.2 years (SD 5.8), with two-third (67%) being never drinkers, 13% occasional drinkers, and 20% regular drinkers. Of the regular drinkers, 69% reported to drink daily and 53% consumed at least 210 g of ethanol every week. About 40% of the drinkers were sensitive to alcohol. Table 1 shows the characteristics of the participants according to drinking status and broken down by alcohol sensitivity. There was no difference in terms of age, education level and occupation between never and current drinkers, although drinkers were more likely to be current smokers and less likely to reported a history of cardiovascular disease.

Mean HsCRP levels were similar in never (2.51 mg/L; 95% CI 2.42, 2.61) and occasional (2.48; 2.27, 2.72) drinkers, but were significantly higher in regular drinkers (2.84; 2.65, 3.06; P=0.009) and those with alcohol sensitivity (2.87; 2.64, 3.12; P=0.03).

Table 2 shows the associations between alcohol use and elevated HsCRP (≥median, which is 2.81 mg/L), adjusting for age (Model 1)and additionally for other potential confounders (Model 2). Regular drinkers, particularly those who consumed daily or those who had ≥210 g ethanol per week had a significantly higher odds of having elevated HsCRP, when compared to never drinkers, with adjusted odds ratios being 1.38 (95%CI

1.10, 1.72) and 1.57 (1.22, 2.02), respectively. There was a statistically significant trend for elevated HsCRP risk with more frequent and heavy alcohol use (P for trend =0.01 and 0.004, respectively).Drinkers with alcohol sensitivity had a 40% increased odds of elevated HsCRP (95%CI 12%, 75%) compared to never drinkers. When compared to drinkers who were insensitive to alcohol, the odds ratio for elevated HsCRP was 1.32 (1.01, 1.72).

We further explored the potential effect modification by alcohol sensitivity. The results are shown in Table 3.Regular users with alcohol sensitivity had higher risk of elevated HsCRP compared to those who were insensitive. This effect was more marked among those consuming ≥210 g ethanol per week, with adjusted adds ratios being 2.34 (95%CI 1.48, 3.71) for the alcohol-sensitivity individuals, and 1.34 (1.00, 1.79) for those being insensitive to alcohol.

DISCUSSION

To the best of our knowledge, this is the first study on alcohol sensitivity, alcohol use and HsCRP in a community-based sample in Chinese men. Our results indicated that daily or excessive alcohol use was associated with a higher risk of inflammatory reaction, and the association was stronger for alcohol users who were sensitive to alcohol.

Previous studies on the effects of alcohol use on HsCRP were inconsistent. Results from

an animal study have shown ethanol consumption could lead to increase CRP levels (Shirpoor et al., 2012). A large population-based study in Portugal also reported a dose-dependent linear relationship between alcohol intake and HsCRP in men (Oliveira et al., 2010).Other studies, however, found a U-shaped relationship. A cross-sectional analysis of 9895 adults in the 1999-2004 cycles of the National Health and Nutrition Examination Survey (NHANES) showed that, among the obese participants, moderate alcohol users had lower HsCRP level than never users (Kantor et al., 2013). A prospective study in the USA with 959 men and 473 women (Pai et al., 2006) and a German study also showed a U-shaped relationship between alcohol consumption and HsCRP(Imhof et al., 2001). In the latter study, the lowest HsCRP levels were found among daily drinkers of 20-40 g ethanol for men 40-60 g for women (Imhof et al., 2001).Contrary to the studies above, a recent study in Greenland suggested heavy alcohol intake was associated with a decrease in HsCRP levels (Schaebel et al., 2013). It was also reported that there was no association between daily drinking and HsCRP in women with preclinical rheumatoid arthritis(Lu et al., 2010). In all, our data suggested that excessive alcohol use was associated with increased HsCRP, while no protective effect was observed among occasional or moderate drinkers, consistent with the findings by Oliveira et al.

Alcohol sensitivity is more common in East Asian than in Western populations(Chan, 1986), mainly due to polymorphisms of enzymes in alcohol-metabolism pathways, as well as synaptic neurotransmitter pathways involving dopamine signaling(Kong et al.,

2010; Morozova et al., 2014). Because of its uncommon occurrence in Western populations, alcohol sensitivity was seldom considered in previous studies on alcohol use and CRP levels. A study including 226 Han Chinese patients with acute myocardial infarction (AMI) found that the A allele in the ALDH2 gene the inactive form was positively associated with HsCRP after the onset of AMI(Bian et al., 2010). Another case-control study in China showed the ALDH2 was positively associated with HsCRP in patients with acute coronary syndrome(Xu et al., 2011). However, to our knowledge, the association between alcohol sensitivity and elevated HsCRPhas not been reported in an Asian community sample. Although alcohol-induced flushing, palpitation or dizziness are thought to be deterrent factors to heavy consumption of alcohol(Takeshita and Morimoto, 1998), this discomfort after drinking cannot completely prevent all such people from drinking, or from excessive drinking. In our study, about 40% of male alcohol users were sensitive to alcohol. Our data, suggest that alcohol sensitivity may augment HsCRP levels, which are already higher among regular drinkers. The mechanism behind this effect modification is unclear, but it is possible that the retention of alcohol in blood (due to slower metabolism) effective in increases the exposure of the cardiovascular system to alcohol, which has already shown to induce adverse vascular effects, ultimately leading to chronic systematic inflammatory.

There are some limitations for the current study. First, participants of the GBCS were relatively healthy and may not be fully representative of older people in Guangzhou. We

might have precluded excessive drinkers who may be less health-conscious, and those who had more severe chronic condition, as such we might have under-estimate the association between drinking and HsCRP levels. Second, we excluded women as there were few female drinkers in our sample. Third, the causal association of alcohol use and alcohol sensitivity with HsCRP cannot be ascertained because of the cross-sectional nature of this study.

CONCLUSION

Alcohol sensitivity may augment the association of alcohol use and HsCRP, which, if confirmed by other studies, may provide new insight into the individual differences of alcohol-related health problems. Individuals with alcohol sensitivity could be at a higher risk and should therefore be advised to cut down or even quit drinking.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Authors Contribution: WS Zhang and SJ Xu contributed to study design, data analysis and manuscript writing, WS Zhang also contributed to data collection, manuscript revision and approval of final submission. CQ Jiang, KK Cheng, CM Schooling, L Xu, KB Lam, B Liu and YL Jin contributed to study design and data collection, TH Lam contributed to study design, manuscript revision.

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Table 1 Sample characteristics by status of alcohol use and alcohol sensitivity on 2903 older Chinese men in Phase 1 of Guangzhou Biobank Cohort Study

		Current Drinkers (occasional and regular)		P-value
	Never drinkers	Alcohol insensitive	Alcohol sensitivity	
No. of participants	1942(66.9)	573(19.7)	388(13.4)	—
Age,years(SD)	66.1 (5.7)	66.2 (6.1)	66.4 (5.7)	0.62
Educational level				0.11
Primary or less	582(30.0)	202(35.3)	132(34.0)	
Middle	985(50.7)	271(47.3)	191(49.2)	
College or above	375(19.3)	100 (17.5)	65(16.8)	
Lifelong occupation				0.61
Manual	904(46.5)	275(48.0)	182(46.9)	
Non-manual	956(49.2)	276(48.2)	196(50.5)	
Others	82(4.2)	22(3.8)	10(2.6)	
Smoking status				<0.001
Never smokers	984(50.7)	142(24.8)	120(30.9)	
Current smokers	439(22.6)	237(41.4)	130(33.5)	
Ex-smokers	519(26.7)	194(33.9)	138(35.6)	
Physical activity				0.04
Inactive	28(1.4)	16(2.8)	10(2.6)	
Minimally active	772(39.8)	237(41.4)	135(34.8)	
HEPA[a]active	1142(58.8)	320(55.8)	243(62.6)	
History of cardiovascular disease[b]				0.04
No	1224(63.0)	394(68.8)	252(64.9)	
Yes	718(37.0)	179(31.2)	136(35.1)	

Abbreviations: SD, standard deviation; MET, metabolic equivalent

[a]Health-enhancing physical activity was defined as vigorous activity achieving at least 1,500 MET-minutes per week on at least 3 days per week or activity achieving at least 3,000 MET-minutes per week on all 7 days of the week.

[b]Included self-reported history of hypertension, hyperlipidaemia, coronary heart disease, stroke, angina and myocardial infarction.

All values are expressed as n (%) unless otherwise specified.

Table 2 Association of alcohol use and alcohol sensitivity with elevated high-sensitivity C-reactive protein

	n	Elevated HsCRP; %	Odds ratio (95% CI)	
			Model 1	Model 2
Alcohol use				
Status				
Never	1942	47.8	1.00	1.00
Occasional	376	49.5	1.07 (0.86, 1.34)	1.09 (0.87, 1.36)
Regular	585	55.9	1.37 (1.14, 1.65)***	1.34 (1.11, 1.62)**
P for trend			0.001	0.01
Frequency				
1-6 days/week	182	53.8	1.28 (0.94, 1.73)	1.27 (0.93, 1.72)
Daily	403	56.8	1.42 (1.14, 1.76)**	1.38 (1.10, 1.72)**
P for trend			0.001	0.01
Quantity				
<210 g/week	276	51.4	1.14 (0.89, 1.47)	1.14 (0.88, 1.47)
≥210 g/week	309	59.9	1.62 (1.27, 2.07)***	1.57 (1.22, 2.02)***
P for trend			<0.001	0.004
Alcohol sensitivity				
No	573	51.3	1.15 (0.95, 1.38)	1.13 (0.93, 1.37)
Yes	388	56.4	1.41 (1.13, 1.75)**, #	1.40 (1.12, 1.75)**, #

HsCRP: High-sensitivity C-reactive protein; CI: confidence interval

Referent group: never drinkers

Elevated HsCRP: HsCRP ≥ median (2.81 mg/L)

Model 1 adjusted for age; model 2 additionally adjusted for educational level, occupation, smoking, physical activity and history of cardiovascular disease.

** p<0.01; *** p<0.001.

Additionally adjusted for the quantity of alcohol use; compared with drinkers without sensitivity, the ORs(95%CI) of elevated HsCRP in drinkers with alcohol sensitivity were 1.32(1.01, 1.72) both in Model 1 and Model 2 ($^{\#}$p<0.05)

Table 3 Association between alcohol use with and without alcohol sensitivity and elevated high-sensitivity C-reactive protein

Interaction		n	Elevated HsCRP; %	Odds ratio (95% CI)	
				Model 1	Model 2
Alcohol use	**Sensitivity**				
Never	Any	1942	47.8	1.00	1.00
Occasional	No	190	49.5	1.07 (0.80, 1.44)	1.08 (0.80, 1.46)
	Yes	186	49.5	1.08 (0.80, 1.45)	1.10 (0.81, 1.49)
Regular					
<210 g/week	No	190	49.5	1.07 (0.80, 1.44)	1.08 (0.80, 1.46)
	Yes	186	49.5	1.08 (0.80, 1.45)	1.10 (0.81, 1.49)
≥210 g/week	No	218	56.0	1.39 (1.05, 1.85)*	1.34 (1.00, 1.79)*
	Yes	91	69.2	2.42 (1.53, 3.81)***,#	2.34 (1.48, 3.71)***,#

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval

Referent group: never drinkers

Model 1 adjusted for age; model 2 additionally adjusted for educational level, occupation, smoking, physical activity and history of cardiovascular disease.

* $p<0.05$; *** $p<0.001$.

#: Referent group: drinkers drinking >=210g/w without alcohol sensitivity. The ORs(95%CI) of elevated HsCRP in those with alcohol sensitivity were 1.81(1.07, 3.05) in model 1 and 1.79(1.05, 3.04) in model 2;# $p<0.05$.

Appendix table 1 Biomarkers by alcohol use and alcohol sensitivity in 2903 older Chinese men in Phase 1 of Guangzhou Biobank Cohort Study

	Never drinkers	Current Drinkers (occasional and regular)		P-value
		Alcohol insensitive	Alcohol sensitivity	
Number of participants (%)	1942(66.9)	573(19.7)	388(13.4)	—
ALT (U/L),mean	27.3	26.2	28.2	0.05
AST (U/L),mean	27.7	27.9	28.4	0.54
Creatinine (μmol/L),mean	95.2	94.6	96.4	0.59
TCHO (mmol/L),mean	5.51	5.51	5.66	0.03
TG (mmol/L),mean	1.53	1.56	1.58	0.73
HDL-C (mmol/L), mean	1.55	1.59	1.63	<0.001
LDL-C (mmol/L), mean	2.82	2.86	2.92	0.006
White blood cell count(*10^9/L), mean	6.29	6.76	6.73	0.18

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transaminase; TCHO, total cholesterol; TG, Triglycerides; HDL-C, Highdensity lipoprotein cholesterol; LDL-C, Lowdensity lipoprotein cholesterol

Appendix table 2.1 Association of alcohol use and alcohol sensitivity with elevated high-sensitivity C-reactive protein in 2855 older Chinese men in Phase 1 of Guangzhou Biobank Cohort Study

	n	*Elevated HsCRP; %*	*Odds ratio (95% CI)*	
			Model 1	*Model 2*
Alcohol use				
Status				
Never	*1911*	*48.0*	*1.00*	*1.00*
Occasional	*368*	*50.0*	*1.08 (0.87, 1.36)*	*1.08 (0.86, 1.35)*
Regular	*576*	*56.3*	*1.38 (1.14, 1.67)****	*1.34 (1.11, 1.62)***
P for trend			*0.001*	*0.01*
Frequency				
1-6 days/week	*179*	*54.2*	*1.28 (0.94, 1.74)*	*1.26 (0.92, 1.72)*
Daily	*397*	*57.2*	*1.43 (1.15, 1.78)***	*1.39 (1.10, 1.74)***
P for trend			*0.001*	*0.01*
Quantity				
<210 g/week	*272*	*51.8*	*1.15(0.89, 1.48)*	*1.11 (0.86, 1.44)*
≥210 g/week	*304*	*60.2*	*1.63 (1.28, 2.09)****	*1.61 (1.25, 2.09)****
P for trend			*<0.001*	*0.004*
Alcohol sensitivity				
No	*560*	*51.6*	*1.15 (0.95, 1.39)*	*1.13 (0.93, 1.38)*
Yes	*384*	*57.0*	*1.43 (1.15, 1.78)**,#*	*1.38 (1.10, 1.74)**,#*

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.

Model 1 adjusted for age; model 2 additionally adjusted for education, occupation, smoking, physical activity and history of cardiovascular disease and BMI.

*Comparing with nondrinkers: ** p<0.01; *** p<0.001*

Comparing with drinkers without sensitivity after adjusting for the amount of alcohol use:#p<0.05.

Appendix table 2.2 Association of alcohol use with and without alcohol sensitivity with elevated high-sensitivity C-reactive protein in 2855 older Chinese men in Phase 1 of Guangzhou Biobank Cohort Study

Interaction		n	Elevated HsCRP; %	Odds ratio (95% CI)	
				Model 1	Model 2
Alcohol use	***Sensitivity***				
Never	*Any*	*1911*	*48.0*	*1.00*	*1.00*
Occasional	*No*	*184*	*50.0*	*1.08 (0.80, 1.47)*	*1.06 (0.78, 1.45)*
	Yes	*184*	*50.0*	*1.09 (0.81, 1.48)*	*1.10 (0.80, 1.49)*
Regular					
<210 g/week	*No*	*162*	*47.5*	*0.97 (0.80, 1.47)*	*0.95 (0.69, 1.32)*
	Yes	*110*	*58.2*	*1.48 (1.00, 2.19)**	*1.41 (0.95, 2.09)*
≥210 g/week	*No*	*214*	*56.1*	*1.39 (1.04, 1.84)**	*1.39 (1.04, 1.87)**
	Yes	*90*	*70.0*	*2.49 (1.57, 3.94)***, #*	*2.34 (1.46, 3.75)***, #*

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.

Model 1 adjusted for age; model 2 additionally adjusted for education, occupation, smoking, physical activity and history of cardiovascular disease and BMI.

*Comparing with nondrinkers: * p<0.05; *** p<0.001*

Comparing with regular drinkers (>=210g/week) without alcohol sensitivity: # p<0.05.

Appendix table 3.1Association of alcohol use and alcohol sensitivity with elevated high-sensitivity C-reactive protein

	n	*Elevated HsCRP; %*	*Odds ratio (95% CI)*	
			Model 1	*Model 2*
Alcohol use				
Status				
Never	*1914*	*47.6*	*1.00*	*1.00*
Occasional	*375*	*49.6*	*1.09 (0.87, 1.36)*	*1.10 (0.88, 1.38)*
Regular	*581*	*55.6*	*1.37 (1.13, 1.65)****	*1.33 (1.10, 1.61)***
P for trend			*0.001*	*0.01*
Frequency				
1-6 days/week	*181*	*53.6*	*1.27 (0.94, 1.73)*	*1.26 (0.93, 1.72)*
Daily	*400*	*56.5*	*1.41 (1.13, 1.75)***	*1.37 (1.09, 1.71)***
P for trend			*0.001*	*0.01*
Quantity				
<210 g/week	*275*	*51.3*	*1.14(0.89, 1.47)*	*1.10 (0.88, 1.38)*
≥210 g/week	*306*	*59.5*	*1.61 (1.26, 2.06)****	*1.55 (1.20, 2.00)****
P for trend			*<0.001*	*0.004*
Alcohol sensitivity				
No	*570*	*51.2*	*1.15 (0.96, 1.39)*	*1.13 (0.93, 1.37)*
Yes	*386*	*56.2*	*1.41 (1.13, 1.75)***	*1.40 (1.12, 1.75)***

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.

Model 1 adjusted for age; model 2 additionally adjusted for education, occupation, smoking, physical activity and history of cardiovascular disease and BMI.

*Comparing with nondrinkers: ** p<0.01; *** p<0.001.*

Appendix table 3.2 Association of alcohol use with and without alcohol sensitivity with elevated high-sensitivity C-reactive protein in 2860 older Chinese men in Phase 1 of Guangzhou Biobank Cohort Study

Interaction		n	Elevated HsCRP; %	Odds ratio (95% CI)	
				Model 1	Model 2
Alcohol use	***Sensitivity***				
Never	*Any*	*1911*	*47.6*	*1.00*	*1.00*
Occasional	*No*	*189*	*49.7*	*1.09 (0.81, 1.47)*	*1.10 (0.81, 1.49)*
	Yes	*186*	*49.5*	*1.08 (0.8, 1.46)*	*1.11 (0.82, 1.50)*
Regular					
<210 g/week	*No*	*165*	*47.3*	*0.97 (0.71, 1.34)*	*0.97 (0.70, 1.34)*
	Yes	*110*	*57.3*	*1.45 (0.98, 2.14)*	*1.43 (0.97, 2.12)*
≥210 g/week	*No*	*216*	*55.6*	*1.38 (1.04, 1.83)**	*1.33 (0.99, 1.78)*
	Yes	*90*	*68.9*	*2.39 (1.52, 3.77)****	*2.32 (1.46, 3.67)****

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.
Model 1 adjusted for age; model 2 additionally adjusted for education, occupation, smoking, physical activity and history of cardiovascular disease and BMI.
*Comparing with nondrinkers: * p<0.05; *** p<0.001.*

Appendix table 4.1 Association of alcohol use and alcohol sensitivity with HsCRP (mg/L) in older Chinese men

	n	*Crude HsCRP means(95%CI)*	*Adjusted HsCRP means(95%CI)*	
			Model 1	*Model 2*
Drinking status				
Nondrinkers	*1942*	*2.51(2.42, 2.61)*	*2.51(2.42, 2.61)*	*2.68(2.42, 2.96)*
Occasional drinkers	*376*	*2.48(2.27, 2.72)*	*2.49(2.28, 2.72)*	*2.65(2.33, 3.01)*
Regular drinkers	*585*	*2.84(2.65, 3.06)***	*2.84(2.64, 3.05)***	*3.00(2.67, 3.37)***
F-value, P-value		*4.689, 0.009*	*3.490, 0.015*	*3.769, 0.023*
t-value, P for trend		*2.692, 0.007*	*2.663, 0.008*	*2.454, 0.014*
Frequency of drinking				
Regular drinkers,1-6times/week	*182*	*2.73(2.39, 3.12)*	*2.74(2.40, 3.11)*	*2.90(2.48, 3.40)*
Regular drinkers, daily	*403*	*2.90(2.66, 3.16)***	*2.89(2.65, 3.15)***	*3.05(2.69, 3.46)***
F-value, P-value		*3.306, 0.019*	*3.201, 0.022*	*2.631, 0.049*
t-value, P for trend		*2.921, 0.004*	*2.881, 0.004*	*2.663, 0.008*
Amount of drinking				
Regular drinkers,<210g/week	*276*	*2.77(2.50, 3.08)*	*2.69(2.42, 2.99)*	*2.94(2.55, 3.37)*
Regular drinkers,≥210g/week	*309*	*2.91(2.63, 3.22)***	*2.89(2.62, 3.20)**	*3.06(2.67, 3.50)**
F-value, P-value		*3.272, 0.020*	*2.568, 0.053*	*2.612, 0.050*
t-value, P for trend		*2.885, 0.004*	*2.860, 0.004*	*2.639, 0.008*
Alcohol sensitivity				
Drinkers without sensitivity	*573*	*2.59(2.40, 2.79)*	*2.59(2.40, 2.78)*	*2.75(2.44, 3.08)*
Drinkers with Sensitivity	*388*	*2.87(2.64, 3.12)***	*2.86(2.62, 3.13)**#*	*3.05(2.68 3.46)*,#*
F-value, P-value		*3.580, 0.028*	*3.525, 0.030*	*3.188, 0.041*
t-value, P for trend		*2.546, 0.011*	*2.527, 0.012*	*2.355, 0.019*

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.
Model 1 adjusted for age;
Model 2 additionally adjusted for education, occupation, smoking, physical activity and history of cardiovascular disease.
*Comparing with nondrinkers: * p<0.05; ** p<0.01*
#: Comparing with drinkers without sensitivity after adjusting for the amount of alcohol use :p<0.05.

Appendix table 4.2Association of alcohol use and alcohol sensitivity with HsCRP (mg/L) in older Chinese men

		n	Crude HsCRP means(95%CI)	Adjusted HsCRP means(95%CI)	
				Model 1	Model 2
Amount of drinking	Alcohol sensitivity				
Nondrinkers		1942	2.51(2.42, 2.61)	2.51(2.42, 2.61)	2.68(2.43, 2.96)
Occasional drinkers	No	190	2.45(2.12, 2.82)	2.45(2.26, 2.78)	2.61(2.23, 3.05)
	Yes	186	2.52(2.24, 2.84)	2.53(2.22, 2.87)	2.70(2.31, 3.16)
<210g/week	No	165	260(2.27, 2.99)	2.59(2.27, 2.97)	2.77(2.35, 3.26)
	Yes	111	3.04(2.60, 3.57)*	3.03(2.58, 3.58)*	3.22(2.67, 3.88)*
≥210g/week	No	218	2.71(2.40, 3.05)	2.71(2.41, 3.05)	2.86(2.46, 3.31)
	Yes	91	3.46(2.89, 4.14)***, #	3.45(2.88, 4.14)***, #	3.62(2.95, 4.46)**, #
F-value, P-value			2.833, 0.009	2.767, 0.011	2.431, 0.024
t-value, P for trend			3.241, 0.001	3.212, 0.001	3.001, 0.003

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.
Model 1 adjusted for age;
Model 2 additionally adjusted for education, occupation,smoking, physical activity and history of cardiovascular disease.
*Comparing with nondrinkers: * p<0.05; ** p<0.01; *** p<0.001.*
Comparing with daily or >=210g/week drinkers without alcohol sensitivity: # p<0.05

Appendix table 5.1 Association of alcohol use and alcohol sensitivity with elevated high-sensitivity C-reactive protein

	n	*Elevated HsCRP; %*	*Odds ratio (95% CI)*	
			Model 1	*Model 2*
Alcohol use				
Status				
Never	*6606*	*55.6*	*1.00*	*1.00*
Occasional	*380*	*51.3*	*0.86 (0.70, 1.06)*	*0.88 (0.71, 1.08)*
Regular	*227*	*59.9*	*1.18 (0.90, 1.55)*	*1.22 (0.93, 1.60)*
Frequency				
1-6 days/week	*98*	*62.2*	*1.33 (0.88, 2.01)*	*1.37 (0.90, 2.07)*
Daily	*129*	*58.1*	*1.08 (0.76, 1.54)*	*1.12 (0.79, 1.60)*
Quantity				
<210 g/week	*197*	*61.4*	*1.26 (0.94, 1.68)*	*1.30 (0.97, 1.75)*
≥210 g/week	*30*	*50.0*	*0.81 (0.39, 1.66)*	*0.81 (0.40, 1.67)*
Alcohol sensitivity				
No	*367*	*51.0*	*0.84 (0.68, 1.03)*	*0.86(0.69, 1.06)*
Yes	*240*	*60.0*	*1.21 (0.93, 1.57)*	*1.25 (0.96, 1.62)*

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.

Model 1 adjusted for age.

Model 2 additionally adjusted for educational level, occupation, smoking, physical activity, history of cardiovascular disease.

Appendix table 5.2Association of alcohol use with and without alcohol sensitivity with elevated high-sensitivity C-reactive protein in older Chinese women in Phase 1 of Guangzhou Biobank Cohort Study

Interaction		n	Elevated HsCRP; %	Odds ratio (95% CI)	
				Model 1	Model 2
Alcohol use	***Sensitivity***				
Never	*Any*	*6606*	*55.6*	*1.00*	*1.00*
Occasional	*No*	*213*	*45.5*	*0.68 (0.52, 0.90)***	*0.69 (0.53, 0.91)***
	Yes	*167*	*58.7*	*1.15 (0.84, 1.58)*	*1.18(0.86, 1.62)*
Regular					
<210 g/week	*No*	*129*	*58.9*	*1.13 (0.79, 1.61)*	*1.17(0.82, 1.67)*
	Yes	*68*	*66.2*	*1.55 (0.94, 2,57)*	*1.61(0.97, 2.67)*
≥210 g/week	*No*	*25*	*56.0*	*1.02 (0.46, 2.25)*	*1.01(0.46, 2.25)*
	Yes	*5*	*20.0*	*0.21 (0.02, 1.91)*	*0.22 (0.03, 2.01)*

HsCRP: High-sensitivity C - reactive protein; CI: confidence interval.

Model 1 adjusted for age.

Model 2 additionally adjusted for educational level, occupation, smoking, physical activity, history of cardiovascular disease.

Highlights

1. Higher levels of high sensitivity C-reactive protein (HsCRP) were previously found to be associated with regular alcohol use.

2. Asians have higher prevalence of alcohol sensitivity compared to other populations, but whether this would modify the association between alcohol use and HsCRP is not clear.

3. In a community-based sample of Chinese males, we found that alcohol sensitivity aggravated the effect of alcohol use on HsCRP.