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Association of total homocysteine with blood pressure in a general population of Chinese adults: a cross-sectional study in Jiangsu province, China

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ABSTRACT

Objectives We aimed to evaluate the relation of total homocysteine (tHcy) concentrations with systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels, and examine the possible modifiers in the association among a general population of Chinese adults.

Design A cross-sectional study.

Setting The study was conducted within 21 communities in Lianyungang of Jiangsu province, China.

Participants A total of 26 648 participants aged ≥35 years and with no antihypertensive drug use were included in the final analysis.

Results Overall, there was a positive association between tHcy concentrations and SBP (per 5 µmol/L tHcy increase: adjusted β=0.45 mm Hg; 95% CI 0.29 to 0.61) or DBP levels (per 5 µmol/L tHcy increase: adjusted β=0.47 mm Hg; 95% CI 0.35 to 0.59). Compared with participants with tHcy <10 µmol/L, significantly higher SBP levels were found in those with tHcy concentrations of 10 to <15 (adjusted β=0.80 mm Hg; 95% CI 0.32 to 1.28) and ≥15 µmol/L (adjusted β=1.79 mm Hg; 95% CI 1.20 to 2.37; p for trend <0.001). Consistently, significantly higher DBP levels were found in participants with tHcy concentrations of 10 to <15 (adjusted β=0.86 mm Hg; 95% CI 0.49 to 1.22) and ≥15 µmol/L (adjusted β=2.01 mm Hg; 95% CI 1.57 to 2.46; p for trend <0.001), respectively as compared with those with <10 µmol/L. Furthermore, a stronger association between tHcy and SBP (p for interaction=0.009) or DBP (p for interaction=0.067) was found in current alcohol drinkers.

Conclusion Serum tHcy concentrations were positively associated with both SBP and DBP levels in a general Chinese adult population. The association was stronger in current alcohol drinkers.

Strengths and limitations of this study

- Our study included a total of 26 648 male and female adults with no antihypertensive drugs usage, by far the largest study of its kind.
- We evaluated the association between total homocysteine (tHcy) concentrations and systolic or diastolic blood levels, and examined the potential modifiers in the association among a general adult population.
- As a cross-sectional study, we were not able to determine the causal relationship between tHcy and blood pressure levels.

INTRODUCTION

Hypertension is one of the major risk factors for cardiovascular disease (CVD), chronic kidney disease (CKD) and peripheral arterial disease.[1 2] By 2025, the global number of adults with hypertension will be 1.56 billion.[3] A better understanding of the modifiable risk factors of hypertension is crucial for clinical decision-making and timely management, for it would lead to early detection and prevention, decreasing the huge burden of hypertension and its associated complications.

Previous studies have shown that total homocysteine (tHcy), an intermediate product in the metabolism of methionine, is a controllable risk factor for many chronic diseases, including CVD, stroke and CKD.[4–7] The Hordaland Homocysteine Study[8] and the Third National Health and Nutrition Examination Survey study[9] further found that there was a positive association between tHcy and blood pressure levels. Consistently, Li *et al* reported that hyperhomocysteinaemia was independently related to the elevated diastolic blood pressure (DBP).[10] Another study indicated that hyperhomocysteinaemia was significantly associated with the prevalence of hypertension in males, but not in females in the general adult population of rural Northeast China.[11] Recently, a meta-analysis of relevant randomised trials, including 7887 participants, also indicated that folic acid therapy was effective in reducing the blood

pressure and tHcy levels among patients with hypertension and hyperhomocysteinaemia.[12] However, in the China Stroke Primary Prevention Trial (CSPPT), folic acid therapy had no obvious effect on blood pressures in 20 702 hypertensive participants.[13] In fact, Fakhrzadeh *et al*[14] and Dinavahi *et al*[15] found no significant association between tHcy and blood pressure levels. Sundström *et al*[16] found no obvious relationship of tHcy levels with hypertension incidence or blood pressure progression. These results indicate that the relationship of tHcy with blood pressure remains controversial. The possible explanations included the differences in study populations, sample size and the concomitant drugs or diseases within the study populations. More importantly, although it has been suggested that age, sex, body mass index (BMI), smoking, alcohol drinking, fruit and vegetable consumption and life styles may affect the tHcy and blood pressure levels,[17] whether these factors could modify the association between tHcy and blood pressure had not been thoroughly investigated in these previous studies.

Therefore, the present study aimed to evaluate the relation of tHcy concentrations with blood pressure levels, and examine the potential modifiers in the association among a general Chinese adult population.

METHODS

Study participants

We conducted an epidemiological study for identification, education and register of the high-risk population with both hypertension and elevated tHcy within 21 communities in Lianyungang of Jiangsu province, China, from July 2016 to September 2016. We recruited from the community through open recruitment rather than a random selection. All participants provided written informed consent.

Eligible participants were men and women aged 35 years and older. The lowest age limit was defined as 35 years old in order to improve the recruitment rate of patients with hypertensive. The exclusion criteria were as follows: (1) individuals with severe mental disorders; (2) individuals with abnormal laboratory tests or clinical manifestations who were unsuitable to participate as judged by the investigators and (3) anyone unwilling to participate in the study.

Patient and public involvement

Patient and public involvement was taken into consideration during the whole study. We performed a pilot study to evaluate the feasibility of the project and invited the participants to provide comments. The staff collected the comments of the participants for discussing and further updating the questionnaires and research design. As we have collaborated with local medical institutions to create archives of the participants and established long-term cohorts, our findings are regularly disseminated to the participants and local residents by the local medical institutions.

Data collection and measurements

Baseline data were collected by trained research staff according to standard operating procedure. Face-to-face interviews were conducted using a standardised questionnaire designed specifically for the present study, which included information on demographic characteristics, diet, lifestyle, history of disease and medication use. Anthropometric measurements, including height and weight, were taken using standard operating procedures. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with the subject wearing light clothing and no shoes. BMI was calculated as weight (kg)/height (m^2).

Current smoking was defined as having smoked ≥1 cigarette per day or ≥18 packs in the past year. Current alcohol drinking was defined as drinking alcohol at least two times per week in the past year. Diabetes was defined as having a history of diabetes or currently undergoing glucose-lowering therapy. Hyperlipidaemia was defined as having a history of hyperlipidaemia or currently undergoing lipid-lowering therapy. CVD was defined as having a history of stroke, coronary heart disease or heart failure. The question about standard of living was phrased as follows: 'How is your standard of living?' and a choice of three responses was given as follows: bad, medium and good. The question about fruit and green vegetable consumption was phrased as follows: 'How much fruit and green vegetables do you eat (count the annually averaged weekly intake of fruits and green vegetables)?' and a choice of three responses regarding weekly intake was given as follows: <500 g, 500–1500 g and ≥1500 g. The question about sleep quality was phrased as follows: 'How do you describe your sleep quality?' and a choice of three responses was given as follows: poor, medium and good. The question about sleep time was phrased as follows: 'How long do you sleep every night?' and a choice of three responses was given as follows: <5, 5–8 and ≥8 hours.

Trained research staff obtained systolic blood pressure (SBP) and DBP measurements after subjects had been seated for 10 min, using a validated automatic digital sphygmomanometer (Omron HEM 705IT device; Omron Healthcare), with appropriately sized cuffs. Triplicate measurements on the same arm were taken, with 1–2 min between readings. Each patient's SBP and DBP were calculated as the mean of the three independent measures. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg.

Blood sample collection and laboratory methods

A fasting vein blood sample was obtained from each subject. Serum or plasma samples were separated within 30 min of collection and stored at −80°C. Serum tHcy levels were determined using commercial kits (Homocysteine Assay Kit (Hcy); Ausa Pharmed, Shenzhen, China) by enzymatic assay according to standard procedures.

Statistical analysis

Means (SD) and proportions were calculated for population characteristics by tHcy categories (<10, 10 to <15 and ≥15 µmol/L). Differences in population characteristics were compared using analysis of variance tests or χ^2 tests, accordingly.

Hyperhomocysteinaemia has been defined as a tHcy concentration ≥10 µmol/L[17 18] or 15 µmol/L[19] in previous studies. Therefore, the clinical cut-off levels of tHcy were set at 10 and 15 µmol/L in our current study. Furthermore, to confirm the consistency of the results, multivariate linear regression models were performed to determine the associations between tHcy as a continuous variable, tHcy categories (<10 (reference), 10 to <15 and ≥15 µmol/L) based on the clinical definition or tHcy quartiles (Q1: <10.1 (reference), Q2: 10.1 to < 12.2, Q3: 12.2 to < 14.9 and Q4: ≥14.9 µmol/L) and SBP or DBP levels. Consistently, multivariate logistic regression models were performed to determine the associations between tHcy as a continuous variable, tHcy categories (<10 (reference), 10 to < 15 and ≥15 µmol/L), or tHcy quartiles (Q1: <10.1(reference), Q2: 10.1 to < 12.2, Q3: 12.2 to <14.9 and Q4: ≥14.9 µmol/L) and the prevalence of hypertension. All models were adjusted for age, sex, study communities, BMI, smoking and drinking status, living standard, fruit and vegetable consumption, sleep quality, history of diabetes, hyperlipidaemia and CVD. In the subgroup analyses, possible modifications of the association between tHcy and blood pressure were assessed for the variables, age (<60, ≥60), sex (male, female), BMI (<24, 24 to <28, ≥28 kg/m^2), current smoking (yes, no), current alcohol drinking (yes, no), living standard (good, medium, bad), fruit and vegetable consumption (<500, 500 to < 1500, ≥1500 g), sleep quality (good, medium and poor) and sleep time (<5, 5 to <8 and ≥8 hours). Interactions were examined by including interaction terms in the multivariable linear regression models. BMI was categorised as normal weight (<24.0 kg/m^2), overweight (24.0 to <28.0 kg/m^2) and obesity (≥28.0 kg/m^2) based on the guidelines of the Chinese Ministry of Health.[20]

A two-tailed p<0.05 was considered statistically significant in all analyses. All statistical analyses were performed by Empower(R) (www.empowerstats.com, X&Y Solutions, Boston, Massachusetts, USA) and statistical package R V.3.4.2 (http://www.r-project.org).

RESULTS

Baseline characteristics

A total of 26 648 participants (9262 males and 17 386 females) with complete data on blood pressure and tHcy levels and with no antihypertensive drugs use were included in the final analysis. We speculated that the use of antihypertensive drugs may decrease the blood pressure and affect the association between tHcy and blood pressure levels. Therefore, these participants were excluded from the current analyses. A flow chart of the participants is shown in online supplementary figure 1.

The participants on average were 57.9 (SD: 10.3) years old with a mean tHcy levels of 13.2 (6.1) µmol/L. The participants were divided into three groups based on their baseline tHcy concentrations (<10, 10 to <15 and ≥15 µmol/L). General characteristics of these three groups are presented in table 1. The tHcy concentrations were directly associated with age, male sex, smoking and alcohol drinking and was inversely associated with BMI.

Association between tHcy concentrations and blood pressure

Overall, there was a positive association between tHcy concentrations and SBP or DBP levels (continuous variable). Each 5 µmol/L tHcy increment was associated with 0.45 mm Hg (95% CI 0.29 to 0.61 mm Hg) increase in SBP levels and 0.47 mm Hg (95% CI 0.35 to 0.59) increase in DBP levels (figure 1 and table 2). Compared with participants with tHcy <10 µmol/L, significantly higher SBP levels were found in those with tHcy 10–15 µmol/L (adjusted β=0.80 mm Hg; 95% CI 0.32 to 1.28) or ≥15 µmol/L (adjusted β=1.79 mm Hg; 95% CI 1.20 to 2.37; p for trend <0.001). Consistently, significantly higher DBP levels were found in participants with tHcy 10–15 µmol/L (adjusted β=0.86 mm Hg; 95% CI 0.49 to 1.22) or ≥15 µmol/L (adjusted β=2.01 mm Hg; 95% CI 1.57 to 2.46; p for trend <0.001) as compared with those with tHcy <10 µmol/L.

Accordingly, the prevalence of hypertension (binary variables) increased with the increment tHcy (per 5 µmol/L increment: OR 1.07; 95% CI 1.04 to 1.09) (online supplementary figure 2 and table 2). The prevalence of hypertension was higher in subjects with higher tHcy concentrations: 26.2% in the tHcy <10 µmol/L group, 31.4% in the tHcy 10–15 µmol/L group and 39.2% in the tHcy ≥15 µmol/L group. Compared with those with tHcy <10 µmol/L, the adjusted ORs were 1.12 (95% CI 1.04 to 1.21) and 1.32 (95% CI 1.21 to 1.44) for the tHcy 10–15 µmol/L group and the tHcy ≥15 µmol/L group, respectively (p for trend <0.001, table 2).

Similarly, SBP and DBP levels and the prevalence of hypertension increased through the quartiles of tHcy concentrations as did the adjusted ORs (All p for trend <0.001) (figure 2).

Stratified analyses by potential effect modifiers

Stratified analyses were performed to assess the association between tHcy and SBP (figure 3) and DBP (online supplementary figure 3) levels in various subgroups. Alcohol drinking positively modified the association between tHcy and SBP (p for interaction=0.009) and DBP (p for interaction=0.067) levels. A stronger association between tHcy and SBP or DBP levels was found in current alcohol drinkers. Other variables, including age, sex, BMI, smoking, living standards, fruit and vegetable consumption, sleep quality and sleep time, did not significantly modify the relationship of tHcy with SBP or DBP levels.

Table 1 Characteristics of the participants by tHcy categories (n=26 648)

Variables	tHcy, µmol/L <10	10 to <15	≥15	P values
N (%)	6483 (24.3)	13 689 (51.4)	6476 (24.3)	
Age, year	54.4±9.5	57.8±9.7	61.7±10.9	<0.001
Sex, male (%)	1338 (20.6)	4417 (32.3)	3507 (54.2)	<0.001
Body mass index, kg/m^2	24.9±3.8	24.9±3.6	24.7±3.7	<0.001
tHcy, µmol/L	7.8±2.2	12.3±1.4	20.4±7.9	<0.001
Current smoking (%)	597 (9.6)	1919 (14.7)	1482 (24.6)	<0.001
Current alcohol drinking (%)	719 (11.6)	2208 (16.9)	1513 (25.1)	<0.001
Self-reported hyperlipidaemia	370 (5.9)	798 (6.1)	378 (6.3)	0.745
Self-reported diabetes mellitus	331 (5.3)	631 (4.8)	263 (4.4)	0.050
Self-reported cardiovascular diseases	491 (7.9)	1320 (10.1)	867 (14.4)	<0.001
SBP, mm Hg	126.7±16.1	129.1±16.1	131.9±16.2	<0.001
DBP, mm Hg	80.7±11.6	82.0±12.1	84.1±12.7	<0.001
Medication use, n (%)				
Lipid-lowering drugs	38 (0.6)	50 (0.4)	30 (0.5)	0.084
Glucose-lowering drugs	183 (2.8)	365 (2.7)	129 (2.0)	0.004
Living standards				<0.001
Good	734 (11.8)	1850 (14.2)	866 (14.4)	
Medium	4835 (77.7)	10 046 (77.0)	4539 (75.4)	
Bad	652 (10.5)	1149 (8.8)	613 (10.2)	
Fruit and vegetable consumption, g/week				<0.001
<500	291 (4.7)	498 (3.8)	352 (5.8)	
500–1500	1465 (23.5)	3079 (23.6)	1498 (24.9)	
≥1500	4465 (71.8)	9468 (72.6)	4168 (69.3)	
Sleep quality				<0.001
Good	2784 (44.7)	5821 (44.6)	2906 (48.3)	
Medium	2266 (36.4)	4846 (37.1)	2141 (35.6)	
Poor	1172 (18.8)	2396 (18.3)	974 (16.2)	
Sleep time, hours				<0.001
<5	476 (7.5)	1177 (8.8)	568 (9.1)	
5–8	3843 (60.4)	8123 (60.8)	3591 (57.4)	
≥8	2043 (32.1)	4070 (30.4)	2099 (33.5)	

For continuous variables, values are presented as mean±SD.
DBP, diastolic blood pressure; SBP, systolic blood pressure; tHcy, total homocysteine.

DISCUSSION

Typically, Chinese populations are characterised by elevated tHcy, a high prevalence of the methylenetetrahydrofolate reductase (MTHFR) C677T mutation, and no dietary folic acid fortification, rendering the current study population best suitable for examining the association between tHcy and blood pressure levels.[21–23] Our study included a total of 26 648 male and female adults with no antihypertensive drugs usage, by far the largest study of its kind. Our study has provided some new insights. First, there was a significantly linear association between tHcy and SBP or DBP levels in the general population. Second, alcohol drinking was an important modifier for the association between tHcy and SBP or DBP levels.

MTHFR is the main regulatory enzyme for folate/homocysteine metabolism. Polymorphism of MTHFR 677C>T leads to a reduction in enzyme activity, resulting in increased concentrations of plasma Hcy and lower levels of serum folate. MTHFR C677T polymorphism has been reported to be associated with hypertension or high blood pressure. In line with our results, the studies by Heifetz and Birk had shown that tHcy may contribute to the effect of MTHFR C677T genotypes on blood pressure levels.[24] More importantly, Saraswathy *et al*[25] also

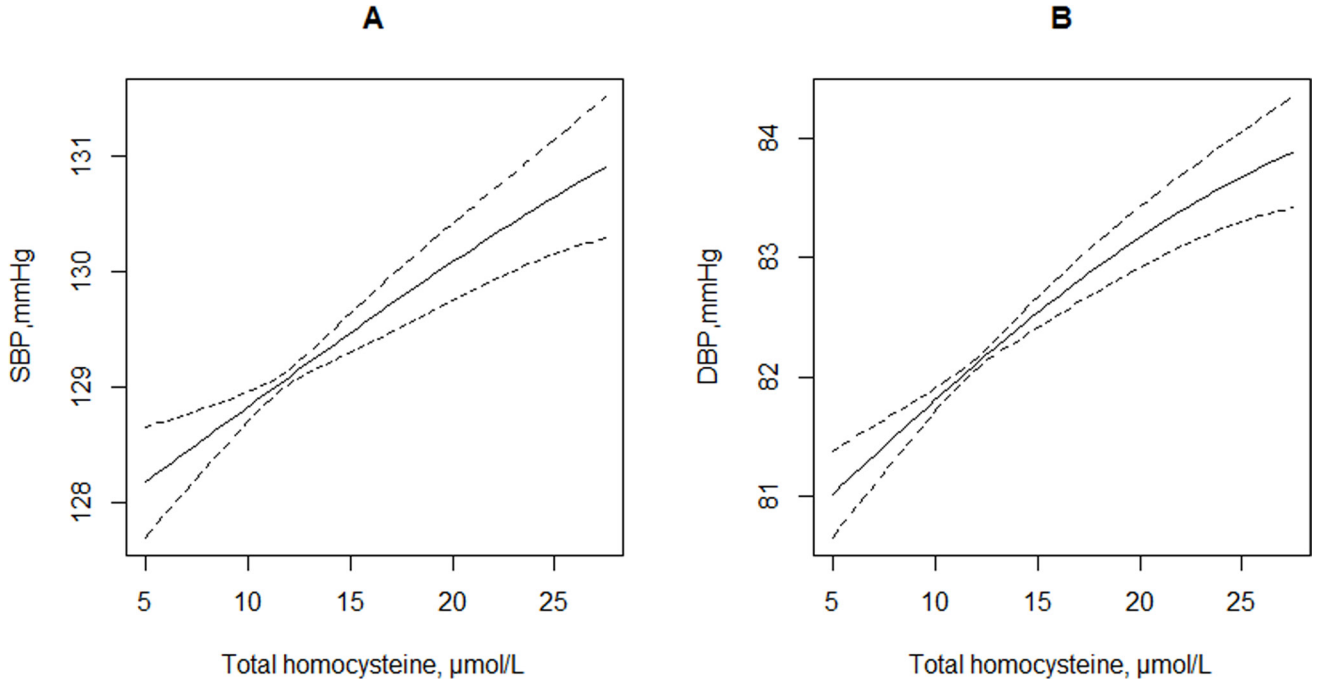

Figure 1 The relationship of total homocysteine concentrations with SBP (A) and DBP (B) levels. Adjusted for age, sex, study communities, body mass index, smoking and drinking status, living standards, fruit and vegetable consumption, sleep quality, history of diabetes, hyperlipidaemia and cardiovascular disease. DBP, diastolic blood pressure; SBP, systolic blood pressure.

suggested that MTHFR 677TT genotype and elevated tHcy levels (even in the upper limits of the normal range of 5–15 μmol/L) are significantly associated with hypertension regardless of age and gender in a Northeastern population with East Asian ancestry.

There are several potential mechanisms by which increased tHcy could contribute to high blood pressure. Raised tHcy has been shown to be associated with increased oxidative stress, hypertrophy of vascular muscle and changes in DNA methylation.[26–28] Furthermore, tHcy may induce endothelial dysfunction via increased asymmetric dimethylarginine, increased inflammation and decreased bioavailability of endothelium-derived NO.[27] Higher tHcy could also activate metalloproteinase and induces collagen synthesis and causes imbalances of elastin/collagen ratio. More importantly, elevated tHcy promoted ACE activity that may lead to upregulation of angiotensin II and subsequently hypertension.[29]

Our data also showed that a stronger association between tHcy and SBP or DBP levels was found in current alcohol drinkers. There are several possible explanations. First, it has been reported that acetaldehyde, a production of ethanol metabolite, could inhibit homocysteine remethylation by affecting the methionine synthase.[30] Furthermore, previous studies have also suggested that alcohol consumption may lead to folate deficiency due to the malabsorption, and increased urinary excretion.[31] Additionally, alcohol drinkers usually had a significantly higher frequency of MTHFR C677T mutation.[32] Therefore, alcohol drinkers may experience more severe tHcy-related vascular damage, which could partly explain the stronger association between tHcy and blood pressure levels in the current alcohol drinkers seen in this study. However, the exact mechanisms regarding the relationship of tHcy and alcohol drinking with the blood pressure levels remain to be further investigated, and our findings also warrant further confirmation.

It has been reported that higher folate intake is associated with a lower incidence of hypertension as seen in both the Nurses' Health Study[33] and the Coronary Artery Risk Development in Young Adults study.[34] Williams *et al*,[35] van Dijk *et al*[36] and a recent meta-analysis[12] of relevant randomised trials among patients with hypertension and hyperhomocysteinaemia reported that tHcy lowering with folic acid therapy may reduce the blood pressure levels. Our previous study[37] also suggested that elevated tHcy concentration significantly decreased the antihypertensive effect of both short-term and long-term enalapril-based antihypertensive treatment. However, studies by Moens *et al*,[38] Doshi *et al*[39] and the CSPPT study[13] found no obvious effect between folic acid therapy and blood pressure levels. We speculate that the folic acid fortification of enriched cereal grain in North American countries effective since January 1998, and the concomitant use of antihypertensive drugs may possibly have modified the treatment effect in previous studies. Therefore, the power for detecting the beneficial effect of folic acid therapy on blood pressure may be limited in previous studies. A large-scale clinical trial is needed to further investigate and confirm the effect of tHcy lowering on blood pressure levels with and without the concomitant use of antihypertensive drugs.

Several potential concerns or limitations are worth mentioning. First, as a cross-sectional study, we were not

Table 2 The relationship of total homocysteine with SBP and DBP levels, and the prevalence of hypertension

Total Homocysteine, μmol/L	N	Mean±SD	Unadjusted β (95% CI)	P values	Adjusted* β (95% CI)	P values
SBP, mm Hg						
Per 5 μmol/L increase	26648	129.2±16.3	1.16 (1.00 to 1.32)	<0.001	0.45 (0.29 to 0.61)	<0.001
Categories						
<10	6483	126.7±16.1	Ref.		Ref.	
10 to <15	13689	129.1±16.1	2.43 (1.95 to 2.90)	<0.001	0.80 (0.32 to 1.28)	0.001
≥15	6476	131.9±16.2	5.26 (4.71 to 5.82)	<0.001	1.79 (1.20 to 2.37)	<0.001
P for trend				<0.001		<0.001
DBP, mm Hg						
Per 5 μmol/L increase	26648	82.2±12.2	0.86 (0.74 to 0.98)	<0.001	0.47 (0.35 to 0.59)	<0.001
Categories						
<10	6483	80.7±11.6	Ref.		Ref.	
10 to <15	13689	82.0±12.1	1.37 (1.01 to 1.73)	<0.001	0.86 (0.49 to 1.22)	<0.001
≥15	6476	84.1±12.7	3.44 (3.02 to 3.86)	<0.001	2.01 (1.57 to 2.46)	<0.001
P for trend				<0.001		<0.001
			Unadjusted		Adjusted	
Hypertension†	N	Events (%)	OR (95% CI)	P values	OR (95% CI)	P values
Per 5 μmol/L increase	26648	8536 (32.0)	1.14 (1.12 to 1.17)	<0.001	1.07 (1.04 to 1.09)	<0.001
Categories						
<10	6483	1700 (26.2)	Ref.		Ref.	
10 to <15	13689	4296 (31.4)	1.29 (1.20 to 1.37)	<0.001	1.12 (1.04 to 1.21)	0.003
≥15	6476	2540 (39.2)	1.82 (1.69 to 1.96)	<0.001	1.32 (1.21 to 1.44)	<0.001
P for trend				<0.001		<0.001

*Adjusted for age, sex, study communities, body mass index, smoking and drinking status, living standards, fruit and vegetable consumption, sleep quality, history of diabetes, hyperlipidaemia and cardiovascular disease.
†Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

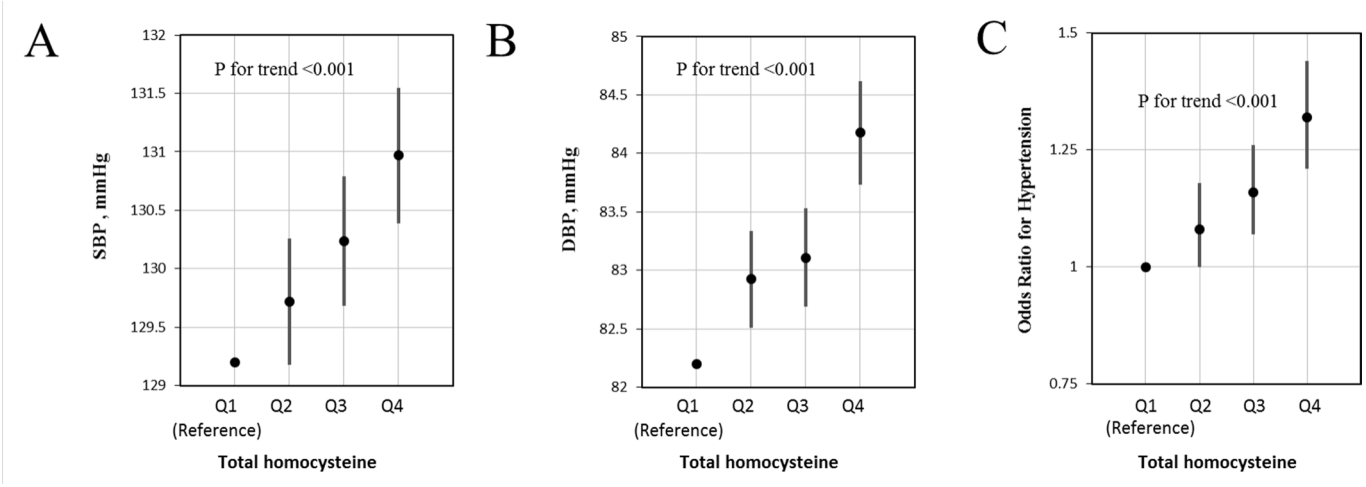

Figure 2 Systolic blood pressure (SBP) levels (**A**), diastolic blood pressure (DBP) levels (**B**) and the adjusted ORs of hypertension (**C**) by quartiles* of total homocysteine (tHcy) concentrations†. *tHcy quartiles: Q1:<10.1 (reference group), Q2:10.1 to <12.2, Q3: 12.2 to <14.9 and Q4: ≥14.9 μmol/L. †Adjusted for age, sex, study communities, body mass index, smoking and drinking status, living standards, fruit and vegetable consumption, sleep quality, history of diabetes, hyperlipidaemia and cardiovascular disease.

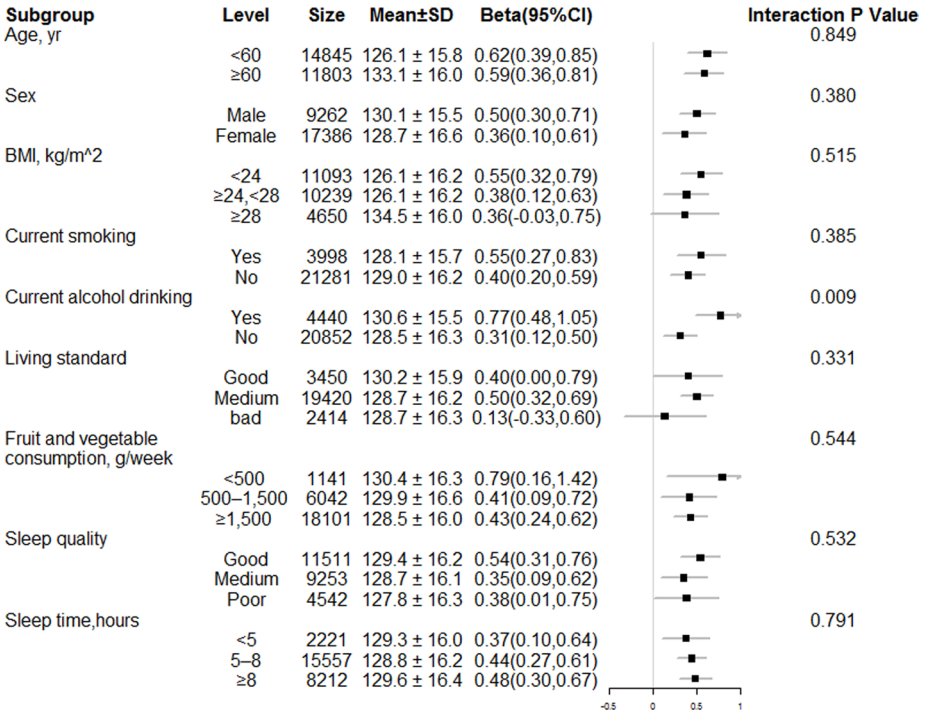

Figure 3 Stratified analyses by potential effect modifiers for the association between total homocysteine and systolic blood pressure levels. Adjusted for age, sex, study communities, body mass index (BMI), smoking and drinking status, living standards, fruit and vegetable consumption, sleep quality, history of diabetes, hyperlipidaemia and cardiovascular disease.

able to determine the causal relationship between tHcy and blood pressure levels. Second, the participants in our current study were recruited from the community through open recruitment rather than a random sampling strategy, which may have affected the representativeness of the population. The generalisability of our findings to other populations remains to be explored. Third, we did not measure the tHcy-related genetic variants, and could not evaluate the possible role of these variants in our current study. Fourth, although diabetes and dyslipidaemia had been included in the analyses, we did not have the actual values for blood glucose and lipids. Fifth, some of the information in our study was taken by questionnaire and this information could be biased. However, these questionnaires had been validated, and been applied to numerous previous projects.[2 40 41] In addition, we did not follow the Diagnostic and Statistical Manual of Mental Disorders criteria for the categorisation of alcoholics. Due to these limitations, confirmation of our findings in an independent study is essential.

CONCLUSIONS

Serum tHcy concentrations were positively associated with both SBP and DBP levels in a general Chinese adult population. The association was stronger in current alcohol drinkers. Our findings raise the possibility that a better understanding of the mechanism by which elevated Hcy effects blood pressure levels, may help to improve hypertension prevention and control, a burgeoning concern in clinical and community settings.

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Contributors Study concept and design: XX, HW, BW, QB, LC, DY, YY, YS, CL, JC, JZ, YZ, TZ, HZ, HG, GT, YZ, JL, YH, TZ and XQ. Conduct of study: HW, BW, YY, QB, LC, YS, JC, JZ, YZ, JL, GT, YZ, TZ, YH, TZ and XQ. Data management and statistical analysis: HW, BW, CL and XQ. Drafting of the manuscript: HW, BW and XQ. Critical review and revision of the manuscript for important intellectual content: XX, HW, BW, QB, LC, DY, YY, YS, CL, JC, JZ, YZ, TZ, HZ, HG, GT, YZ, JL, YH, TZ and XQ.

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