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No association between elevated homocysteine levels and carotid atherosclerosis in a rural population in China

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ABSTRACT

Objectives: We wish to determine if homocysteine (Hcy) is an independent risk factor for carotid atherosclerosis in a rural Chinese population.

Methods: 2291 individuals (1016 men and 1275 women), aged 64.6±7.4 years, from Lvliang, China participated in this study. Tests performed included carotid artery ultrasound scan and blood analysis, to measure Hcy levels and other blood components.

Results: The mean serum Hcy level was 24.7±18.0 µmol/L. The overall detection rate of carotid atherosclerotic lesions was 76.3% and the detection rate of plaque was 48.6%. Participants were divided into 4 groups based on their Hcy levels, <14.49, 14.49–19.43, 19.44–28.30, and ≥28.30 µmol/L. The relative risk of carotid atherosclerosis for each quartile as compared with the risk for the lowest quartile was estimated as the OR derived from the logistic regression coefficients. After adjusting for age and gender, the OR of carotid atherosclerosis in the third and fourth quartiles of Hcy were 1.219 (95% CI 0.922 to 1.612) and 1.156 (95% CI 0.859 to 1.555; p>0.05), respectively. After controlling for demographic variables (age, gender, current smoker, fasting blood glucose, low-density lipoprotein and systolic blood pressure) the OR of carotid plaque(s) in the third and fourth quartiles were 1.246 (95% CI 0.967 to 1.606) and 1.259 (95% CI 0.963 to 1.646; p>0.05).

Conclusions: The mean value of Hcy among participants in this study was much higher than that previously reported. However, no significant correlation between elevated Hcy and carotid atherosclerosis was found.

INTRODUCTION

Homocysteine (Hcy) is a sulfur-containing amino acid. The metabolism of Hcy is influenced by folic acid and vitamin B_{12}, deficiencies of which can lead to high Hcy levels in the blood.[1 2] In 1969, McCully[3] made initial observations linking plasma Hcy concentrations and arteriosclerotic vascular disease. Many subsequent studies have shown that high Hcy levels may present a risk factor for atherosclerosis;[4–6] however, there is little consensus among epidemiological investigations or case–control studies.[6–12] These generally involved using participants from economically developed areas,[6–9] where most participants demonstrated normal or slightly elevated Hcy levels.[6–11] As a result, it remains unclear if high Hcy levels are related to atherosclerosis onset.

Lvliang city is one of the poorest areas of Shanxi Province, China. It has the highest incidence of neural tube defects (NTDs) in the world.[13] NTDs may be related to local environmental conditions and eating habits.[14] The use of folic acid has significantly reduced the incidence of NTDs in pregnant women in Lvliang city.[14] Therefore, it was hypothesised that blood folic acid levels may be low while the levels of Hcy may be high among individuals aged 55 years and older. The aim of this cross-sectional study was to describe the relationship between carotid atherosclerosis, as assessed by ultrasonography, and serum concentrations of Hcy in this region.

Methods

This study was approved by the Research Ethics Committee of the Shanxi Medical University. Written informed consents were obtained from the patients.

Participants

From August to November 2012, a team of researchers (physicians and senior medical students) from the First Hospital of Shanxi Medical University travelled to Lvliang, Shanxi Province of China to study villagers born before 1 January 1958 who resided at least 2 months of the year in one of the four towns located there; namely, Xiajiaying, Kangchen, Gaojiagou or Caijiaya. A population of 9286 people aged 55 years and older was provided by the household registry

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department in each town. Of the 3005 participants who volunteered to complete the study questionnaires, 2304 completed carotid ultrasound examinations and blood tests. Thirteen participants were excluded because of incomplete data, and the remaining 2291 were evaluated, of which 1016 were men and 1275 were women.

A survey was carried out in the village clinics. Two days before the survey, villagers were informed of the survey through posters, radio advertising and telephone. For those volunteers who agreed to participate in the study, a face-to-face structured questionnaire was administered by the medical research team. After signing an informed consent form, participants underwent carotid ultrasound examinations and blood tests. Participants for statistical analysis included those who completed the questionnaire, carotid ultrasound examination and blood tests.

Data collection

The collected survey data included demographic information and cerebrovascular disease risk factors. Demographic characteristics included gender, date of birth, education, occupation and marital status. Cerebrovascular disease risk factors included history of smoking, hypertension and diabetes. Participants' blood pressure (BP), height and weight were recorded. A qualified nurse took a fasting venous blood sample. Information regarding the participants' medical history was self-reported or obtained through medical records. For the purposes of this study, history of smoking was defined as smoking continuously for 6 months or more and within 30 days prior to the survey.[15] History of drinking was defined as a daily alcohol intake of more than 25 mg (80 mL of liquor, 200 mL of wine and 600 mL of beer).[16]

For each participant, the same researcher measured the BP twice, between 08:00 and 10:00, with the participant seated and using the same calibrated sphygmomanometer. Participants were asked to rest for at least 15 min, not to smoke and to empty their bladder up to 30 min beforehand. Average values of the systolic and diastolic BP (SBP and DBP, respectively) were used for analysis. Hypertension was defined as SBP≥140 mm Hg or DBP≥90 mm Hg, according to the 2010 Chinese guidelines for the management of hypertension. Height and weight were measured indoors. Body mass index (BMI; kg/m^2) was calculated as an index of obesity.[16] The WHO cut-off points of BMI<25.0 for non-obese and ≥25.0 for obese adults in Asian populations were used.

Table 1 Sex and age distribution of the targeted population and participants, and participation rates

	N	Per cent	Response rate (%)
Targeted population	9286	100.0	–
Female	4830	52.0	–
Age			
55–64	4997	53.8	–
65–74	2567	27.6	–
75+	1722	18.6	–
Participants	2291	100.0	24.7
Female	1275	55.7	26.4
Age			
55–64	1302	56.8	26.1
65–74	693	30.2	27.0
75+	296	13.0	17.2

Biochemical determinations

Blood was drawn from the antecubital vein, to measure fasting blood glucose (FBG). Blood samples were centrifuged within 1 hour and frozen at −70°C. Blood samples were analysed at the First Hospital of Shanxi Medical University clinical laboratory. A Beckman UniCel DxC 800 Synchron Clinical System Analyzer (Beckman Coulter) was used to detect total cholesterol (TC), high-density lipoprotein (HDL) cholesterol (Immuno FS, DiaSys), triglycerides (TGs; Beckman Coulter) and uric acid (UA; Beckman Coulter). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation for participants who had TG levels <400 mg/dL.

Hcy was measured using an enzyme cycling method with a Beckman UniCel DxC 800 Synchron Clinical System Analyzer (Beckman Coulter). All the participants were divided into four groups according to the Hcy level of four quantiles.

Measurement of carotid atherosclerosis

Carotid artery ultrasound scan was performed by a qualified sonographer, using a colour Doppler ultrasound scanner (Logic E, American GE). Participants were inspected in the supine position, with the head upright and the anterior portion of the neck fully exposed. The proximal internal carotid artery (ICA), ICA bulb and distal ICA were detected in sequence. The distance from the ICA lumen-intima border to the media-outer border was measured as the intima media thickness (IMT), in longitudinal images at the diastolic phase. The proximal part of the vessel wall to a plaque was measured, where there was a plaque. According to Mannheim carotid IMT consensus[17] and carotid stenosis ultrasound diagnostic criteria,[18] IMT≥1.0 mm was defined as IMT thickening. IMT≥1.5 mm or above the lumen was defined as a plaque. Participants showing one or several stenotic lesions, with a stenosis rate of <50% and no change in blood flow velocity (BFV), were not recorded. A stenosis rate of more than 50% and altered BFV was recorded. We defined IMT thickening and or carotid plaque(s) as carotid atherosclerosis.

Statistical analysis

Data were checked, verified and recorded using Epidata software (V.3.1). Results are reported as means±SDs. Quantitative variables between groups were compared by

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t-test, approximate t-test and variance analysis, whereas classifications of variable rate were compared using the χ^2 test. Logistic regression was used to estimate ORs and 95% CIs. Statistical significance was defined as a p value <0.05. All statistical analyses were performed using SPSS (V.13.0).

RESULTS

The local housing registry department provided a list of 9286 residents. Of the 3005 participants who volunteered to complete the study questionnaires, 2304 completed carotid ultrasound examinations and blood tests. Incomplete information was provided by 13 participants.

Table 2 Research overview of study participants

	N=2291	Men N=1016	Women N=1275
Age (year)	64.6±7.4	65.4±7.8	64.0±7.0
Homocysteine (μmol/L)	24.7±18.0	29.3±20.8	21.0±14.5
Folic acid (nmol/L)	11.2±13.0	10.6±14.7	11.6±11.5
Atherosclerosis	1747 (76.3%)	854 (84.1%)	893 (70.0%)
Thickening of IMT only	633 (27.6%)	265 (26.1%)	368 (28.9%)
Plaque formation only	982 (42.9%)	514 (50.6%)	468 (36.7%)
Stenosis or occlusion	132 (5.8%)	75 (7.4%)	57 (4.5%)

IMT, intima media thickness.

Of the 2291 participants included in the statistical analysis, 1016 were men and 1275 were women. Table 1 shows the age and sex distribution of the targeted population and participants, as well as the participation rates.

The overall average detection rate of carotid atherosclerotic lesions was 76.3% and the detection rate of plaque was 48.6%. We observed that 84.1% of men and 70.0% of women showed atherosclerotic lesions. The characteristics of all participants involved are presented in table 2.

Table 3 shows the background factor classified by the presence of carotid atherosclerosis. The prevalence of men, Hcy, age, SBP, TG, UA, FBG, smoking and drinking was higher in the groups with carotid atherosclerosis. Table 4 shows the background factor classified by the presence of carotid plaque(s). The prevalence of men, Hcy, age, SBP, TG, UA, smoking, drinking and education was higher in the groups with carotid plaque(s).

Participants were divided into four groups according to their Hcy concentrations: <14.49, 14.49–19.44, 19.44–28.30 and ≥28.30 μmol/L. The prevalence rates of carotid atherosclerosis in these four groups were 70.33%, 76.47%, 78.09% and 80.14%, respectively (p=0.001). The prevalence rates of carotid plaque(s) in these four groups were 40.7%, 45.8%, 52.8% and 55.2%, respectively (p=0.000). There were differences between the groups in terms of age, SBP, TC, TG, HDL, LDL, UA, gender, smoking, diabetes, hypertension and family history of stroke (p<0.05; table 5).

Logistic regression was used with carotid atherosclerosis as the dependent variable. Hcy quartiles were modelled with indicator variables to represent the three

Table 3 Comparison of demographic characteristics in participants with or without carotid atherosclerosis

	Carotid atherosclerosis		
	No N=544	Yes N=1747	p Value
Age (year)	61.9±6.0	65.4±7.5	0.000
BMI (kg/m^2)	24.4±3.5	23.7±3.3	0.000
SBP (mm Hg)	136.9±18.6	140.3±20.8	0.000
DBP (mm Hg)	83.6±10.7	83.3±11.3	0.602
Total cholesterol (mmol/L)	4.3±1.2	4.4±1.1	0.538
Triglycerides (mmol/L)	1.6±1.1	1.5±1.1	0.004
HDL-C (mmol/L)	1.2±0.4	1.2±0.4	0.110
LDL-C (mmol/L)	2.5±0.9	2.5±0.8	0.109
Uric acid (μmol/L)	241.3±71.3	253.8±74.0	0.001
Homocysteine (μmol/L)	22.4±16.0	25.4±18.6	0.000
FBG (mmol/L)	5.2±1.2	5.4±1.5	0.000
Hypertension (%)	213 (39.2%)	683 (39.1%)	0.980
Diabetes mellitus (%)	32 (5.9%)	142 (8.1%)	0.084
Dyslipidaemia (%)	66 (12.1%)	131 (7.5%)	0.001
Family history of stroke (%)	44 (8.1%)	117 (6.7%)	0.268
Current smoker (%)	164 (30.1%)	810 (46.4%)	0.000
Drink (%)	34 (6.3%)	167 (9.6%)	0.017
Education—junior high school (%)	110 (20.2%)	336 (19.2%)	0.611
Sex (male, %)	162 (29.8%)	854 (48.9%)	0.000

BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

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Table 4 Comparison of demographic characteristics in participants with or without carotid plaque(s)

	Carotid plaque(s)		
	No N=1177	Yes N=1114	p Value
Age (year)	62.8±6.5	66.5±7.8	0.000
BMI (kg/m^2)	24.1±3.4	23.6±3.4	0.000
SBP (mmHg)	137.7±19.6	141.3±21.0	0.000
DBP (mmHg)	83.3±11.0	83.4±11.3	0.877
Total cholesterol (mmol/L)	4.3±1.1	4.4±1.1	0.012
Triglycerides (mmol/L)	1.6±1.1	1.4±1.0	0.004
HDL-C (mmol/L)	1.2±0.4	1.2±0.4	0.176
LDL-C (mmol/L)	2.4±0.8	2.6±0.9	0.000
Uric acid(μmol/L)	243.5±70.7	258.6±75.8	0.000
Homocysteine (μmol/L)	23.2±17.2	26.2±18.7	0.000
FBG (mmol/L)	5.3±1.4	5.4±1.5	0.183
Hypertension (%)	449 (38.1%)	447 (40.1%)	0.177
Diabetes mellitus (%)	71 (6.0%)	103 (9.2%)	0.002
Dyslipidaemia (%)	116 (9.9%)	81 (7.3%)	0.016
Family history of stroke (%)	93 (7.9%)	68 (6.1%)	0.055
Current smoker (%)	417 (35.4%)	557 (50.0%)	0.000
Drink (%)	91 (7.7%)	110 (9.9%)	0.041
Education—junior high school (%)	249 (21.2%)	197 (17.7%)	0.020
Sex (male, %)	427 (36.3%)	589 (52.9%)	0.000

BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 5 Baseline characteristics and laboratory profiles by quartile of Hcy level

	First quartile N=573	Second quartile N=578	Third quartile N=566	Fourth quartile N=574	p Value
Age (year)	62.9±6.6	64.2±7.2	65.3±7.3	65.9±7.9	0.000
BMI (kg/m^2)	23.7±3.6	23.8±3.2	23.9±3.5	24.0±3.3	0.477
SBP (mm Hg)	138.4±20.4	138.8±20.9	140.2±20.5	140.5±19.6	0.219
Triglycerides (mmol/L)	1.4±1.1	1.5±1.0	1.6±1.2	1.5±1.0	0.004
HDL-C (mmol/L)	1.1±0.4	1.2±0.4	1.2±0.4	1.2±0.4	0.000
LDL-C (mmol/L)	2.3±0.9	2.6±0.9	2.6±0.9	2.6±0.8	0.000
Uric acid (μmol/L)	211.5±72.5	253.4±66.5	265.4±66.8	273.2±72.5	0.000
FBG (mmol/L)	5.4±1.5	5.4±1.8	5.4±1.3	5.3±1.3	0.186
Current smoker (%)	196 (34.2%)	221 (38.2%)	245 (43.3%)	312 (54.4)	0.000
Drink (%)	39 (6.8%)	52 (9.0%)	52 (9.2%)	57 (9.9%)	0.273
Dyslipidaemia (%)	53 (9.3%)	41 (7.1%)	50 (8.8%)	53 (9.2%)	0.511
Education—junior high school (%)	116 (20.2%)	114 (19.7%)	98 (17.3%)	118 (20.6%)	0.502
Sex (male, %)	177 (30.9%)	220 (38.1%)	261 (46.1)	358 (62.4)	0.000
Atherosclerosis (%)	403 (70.3%)	442 (76.5%)	442 (78.1%)	460 (80.1%)	0.001
Plaque(s) (%)	233 (40.7%)	265 (45.8%)	299 (52.8%)	317 (55.2%)	0.000

Continuous variables are shown as mean±SD. Quantitative variables between groups were compared by t-test, approximate t-test or variance analysis, whereas classification of variable rate was compared by χ^2 test.
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

highest quartiles. The relative risk of the carotid atherosclerosis for each quartile as compared with the risk for the lowest quartile was estimated as the OR derived from the logistic regression coefficients. The OR of carotid atherosclerosis was higher in the second, third and fourth quartiles than in the first quartile by 1.371-fold, 1.504-fold and 1.702-fold ($p<0.05$), respectively. After further adjusting for age and gender, the OR of carotid atherosclerosis in the third and fourth quartiles of Hcy were 1.219 (95% CI 0.922 to 1.612) and 1.156 (95% CI 0.859 to 1.555; $p>0.05$; table 6), respectively.

The relative risk of the carotid plaque(s) for each quartile as compared with the risk for the lowest quartile was estimated as the OR derived from the logistic regression coefficients. After controlling for other demographic variables (age, gender, current smoker, FBG,

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Table 6 ORs (95% CIs) for the presence of carotid atherosclerosis by quartile of Hcy level

Hcy quartile	Crude	OR (95% CI) Model 2	Model 3
First quartile	1.00	1.00	1.00
Second quartile	1.371 (1.054 to 1.783) p=0.019	1.296 (0.992 to 1.692) p=0.057	1.253 (0.957 to 1.640) p=0.101
Third quartile	1.504 (1.150 to 1.966) p=0.003	1.334 (1.014 to 1.755) p=0.040	1.219 (0.922 to 1.612) p=0.164
Fourth quartile	1.702 (1.296 to 2.235) p=0.000	1.465 (1.107 to 1.938) p=0.007	1.156 (0.859 to 1.555) p=0.339

Reference group: first quartile. Model 2: adjusted for age, model 3: adjusted for age and gender.
Hcy, homocysteine.

Table 7 ORs (95% CIs) for the presence of carotid plaque(s) by quartile of Hcy level

Hcy quartile	Crude	OR (95% CI) Model 4	Model 5	Model 6
First quartile	1.00	1.00	1.00	1.00
Second quartile	1.235 (0.978 to 1.560) p=0.076	1.162 (0.915 to 1.475) p=0.218	1.117 (0.877 to 1.422) p=0.369	– –
Third quartile	1.634 (1.292 to 2.066) p=0.000	1.454 (1.142 to 1.852) p=0.002	1.335 (1.044 to 1.709) p=0.022	1.246 (0.967 to 1.606) p=0.089
Fourth quartile	1.800 (1.424 to 2.275) p=0.000	1.580 (1.241 to 2.011) p=0.000	1.324 (1.040 to 1.730) p=0.023	1.259 (0.963 to 1.646) p=0.093

Reference group: first quartile. Model 4: adjusted for age, model 5: adjusted for age and gender, model 6: adjusted for age, gender, current smoker, FBG, LDL and SBP.
FBG, fasting blood glucose; Hcy, homocysteine; LDL, low-density lipoprotein; SBP, systolic blood pressure.

LDL and SBP) the OR of carotid plaque(s) in the third and fourth quartiles were 1.246 (95% CI 0.967 to 1.606) and 1.259 (95% CI 0.963 to 1.646; p>0.05; table 7), respectively.

DISCUSSION

The average value of serum Hcy in this study was 24.7±18.0 μmol/L, which is much higher than the normal range of Hcy (5–15 μmol/L).[19] The mean values of serum Hcy were 29.3±20.8 μmol/L for men and 21.0±14.5 μmol/L for women. These results are much higher than those of the general population in the western world (13 μmol/L for men, 10 μmol/L for women),[19] also higher than China's coastal rural population[20] and the Japanese rural general population[9] (12.0 μmol/L for men, 9.6 μmol/L for women in China; 12.6 μmol/L for men, 9.8 μmol/L for women in Japan). The differences in plasma Hcy concentration described in various reports could be due to different inclusion criteria and ethnic or geographic differences. The average value for folic acid was 11.2±13.0 nmol/L, and 68.1% of folic acid levels measured was below 11 nmol/L. These data confirm our hypothesis that villagers aged 55 years and older have high levels of Hcy and low levels of folic acid.

Carotid IMT and plaques are both measures of atherosclerosis, perhaps having different attributes or risk associations but still closely related.[21 22] Sonographic characterisation of carotid IMT and plaque can be considered a measure of atherosclerosis quality. The overall detection rate of carotid atherosclerotic lesions was 76.3% and the detection rate of plaque was 48.6%. These detection rates are comparable to findings in a survey of the national population and related epidemiological findings.[23–26]

McCully[3] defined the normal value for Hcy as 6–10 μmol/L for women and 8–12 μmol/L for men. The Framingham Heart Study suggested a value >14 μmol/L for participants with normal folic acid, vitamins B_6 and B_{12}.[27] In most studies, hyperhomocysteinaemia was defined as ≥15 μmol/L.[19] Serum Hcy values in our study were much higher than normal.[19] The first quartile (serum Hcy<14.49 μmol/L) was normal and the fourth quartile (serum Hcy≥28.30 μmol/L) was even nearly onefold greater than the normal range.

Age is a strong risk factor of atherosclerotic diseases in Western countries[28 29] and China. Cigarette smoking has been reported to be a risk factor of coronary artery disease and stroke in many studies. Furthermore, smoking is well known to be a risk factor of arteriosclerosis obliterans.[30] In this study, the levels of Hcy were higher, the percentage of smokers was greater and the mean age of the participants was higher. After adjusting for age and gender, serum Hcy≥28.30 μmol/L did not increase the risk of carotid artery atherosclerosis compared with serum Hcy<14.49 μmol/L. After controlling for age, gender, current smoker and other known risk factors, elevated Hcy did not increase the risk of carotid plaque(s).

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Hyperhomocysteinaemia has been identified as a strong predictor of cardiovascular disease, independent of classical atherothrombotic risk factors.[31] However, not all disease predictors are risk factors in the strict definition. A biomarker commonly represents an early stage of the disease. Interventions aimed at optimising a biomarker may or may not be associated with reduced disease incidence depending on whether the treatment has an effect on a causal mechanism that underlies both the appearance of the biomarker as well as the occurrence of disease.[32] The mechanisms by which Hcy induces atherosclerosis are largely unknown. Several biological mechanisms have been proposed to explain cardiovascular pathological changes associated with Hcy. These include (1) endothelial cell damage and impaired endothelial function; (2) dysregulation of cholesterol and TG biosynthesis; (3) stimulation of vascular smooth muscle cell proliferation; (4) thrombosis activation; and (5) activation of monocytes.[5] Treatment that reduces the biomarker without affecting disease incidence is useless.

Folic acid intake is associated with reduced risk of ischaemic stroke in some epidemiological studies but not in others.[33] Most studies involving patients with established atherosclerotic vascular disease found no benefit in reducing Hcy by vitamin B complex therapy on clinical cardiovascular end points.[33] A substudy of the VITAmins TO Prevent Stroke (VITATOPS) trial reported that vitamin B complex did not reduce the change in carotid IMT.[10] Similarly, folic acid did not significantly affect carotid IMT in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST).[11] These findings show that the role of Hcy in atherosclerosis and cardiovascular events may be overvalued. Taken together, these results and our data indicate that Hcy has no significant effect on early atherosclerosis preceding stroke and myocardial infarction.

Routine screening for hyperhomocysteinaemia among patients with a recent ischaemic stroke or transient ischaemic attack (TIA) is not indicated (class III; level of evidence C). In adults with a recent ischaemic stroke or TIA who are known to have mild-to-moderate hyperhomocysteinaemia, supplementation with folate, vitamin B_6 and B_{12} safely reduces levels of Hcy but has not been shown to prevent stroke (class III; level of evidence B). These come from Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack 2014.[34] The role of Hcy in stroke is declining.

We are aware of the limitations of the present study. First, the response rate was low and this could lead to bias. Second, because of low awareness rate of hypertension and diabetes, the history of providing might influence the results.

In conclusion, the mean levels of Hcy among villagers aged 55 years and older in a rural region of Lvliang City, China was higher than that reported in other parts of China; however, there was no significant correlation between high Hcy and carotid atherosclerosis. Elevated Hcy was found not to be an independent determinant of carotid atherosclerosis.

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Contributors YL and LW planned the study, performed data analyses and wrote the manuscript. YF helped plan the study and collected the data. WZ performed data analyses and contributed to the revision of the manuscript. XN supervised the study and contributed to the revision of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Research Ethics Committee of the Shanxi Medical University.

Provenance and peer review Commissioned; externally peer reviewed.

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