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ORIGINAL RESEARCH

Association Between Serine Concentration and Coronary Heart Disease: A Case–Control Study

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Purpose: Early identification of new residual risk factors for coronary heart disease (CHD) is warranted. In this study, we aim to investigate the association between the serine concentration, an important amino acid in one-carbon metabolism, and CHD in Chinese hospitalized patients.

Patients and Methods: This case–control study included 428 case–control pairs comprising patients with CHD with a maximum coronary artery stenosis degree of >70% and controls with stenosis of <30%. The individuals were matched by age, sex, and date of coronary angiography at Peking University First Hospital from January 1, 2016, to December 31, 2019. Conditional logistic regression was used to investigate the associations between the serine concentration and CHD.

Results: Patients with CHD were aged 63.48 ± 10.38 years, and 43.73% were male. Compared with controls, patients with CHD had a slightly lower serine concentration (13.35 ± 4.20 vs 13.77 ± 4.08 μg/mL), but the difference was not significant. In the multivariable conditional logistic regression analysis, for every 1 μg/mL increase in serine concentration, the odds of CHD decreased by 6% (95% confidence interval [CI] 0.90–0.99; $P = 0.010$). Patients with a serine concentration of ≥13.41 μg/mL had a lower CHD risk than those with a serine concentration of <13.41 μg/mL (odds ratio [OR] 0.57, 95% CI 0.39–0.84; $P = 0.004$). Subgroup analyses showed that sex interacted with the relationship between serine concentration and CHD ($P_{interaction} = 0.039$), which was more significant in males (OR 0.93, 95% CI 0.87–0.98; $P = 0.013$) than in females.

Conclusion: This study observed an inverse association between the serine concentration and CHD prevalence in Chinese hospitalized patients, which revealed that serine might play a protective role in CHD.

Keywords: serine, coronary heart disease, case–control, one-carbon metabolism

Introduction

Cardiovascular disease (CVD), as the leading cause of global mortality, accounts for 31% of deaths worldwide. In 2015, CVD accounted for approximately 17.7 million deaths, with coronary heart disease (CHD) being the most common type (7.4 million deaths).[1,2] Although the risk of CHD morbidity and mortality can be reduced by intervention targeted toward traditional risk factors, such as smoking, hypercholesterolemia, hypertension, and diabetes mellitus, residual risks still exist.[3] Therefore, the early identification of new risk factors is an urgent problem to be solved.

The key metabolites and associated gene polymorphisms of enzymes involved in one-carbon metabolism, such as homocysteine (Hcy) and methylenetetrahydrofolate reductase (MTHFR), are associated with CHD risk.[4,5] Serine is a non-essential amino acid and an essential metabolite in one-carbon metabolism in the human body. Serine participates in the folic acid cycle and the trans-sulfuration pathway of Hcy. In the folic acid cycle, using pyridoxal phosphate (PLP) as the coenzyme, serine hydroxymethyltransferase (SHMT) catalyzes the interaction between tetrahydrofolate and serine to produce 5,10-methylene tetrahydrofolate (5,10-CH_2-THF) and glycine.[6] Meanwhile, under the catalysis of PLP-

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dependent cysteine β-synthase (CBS), Hcy interacts with serine to produce cystathionine, which is transformed into cysteine through trans-sulfuration and finally converted to glutathione.[7]

Serine accelerates the growth of various tumors because its synthesis is linked to tumor cell proliferation.[8] Serine is also a useful biomarker and potential therapeutic target in senile dementia, as well as schizophrenia, depression, and other mental health conditions.[9–11] In addition, serine synthesis can delay vascular endothelial cell senescence.[12] Serine-related metabolism is also related to atherosclerotic lesions in patients with chronic thromboembolic pulmonary hypertension.[13] However, few studies have studied the relationship between serine and CHD.

On the basis of the important role of serine in folic acid and Hcy metabolism, as well as its possible regulation of oxidative stress upstream of glutathione production, we speculated that serine may be involved in the formation of coronary atherosclerosis and CHD. The purpose of this case–control study was to preliminarily explore the relationship between serine and coronary atherosclerosis severity. This research provides evidence that serine can be considered as a potential biomarker for CHD.

Materials and Methods

Participants

The flowchart of this case–control study is shown in Figure 1. The participants were hospitalized patients who underwent coronary angiography at the catheterization laboratory of the Department of Cardiology, Peking University First Hospital, from January 1, 2016, to December 31, 2019. Patients whose coronary angiography indicated that the coronary artery stenosis degree (anterior descending branch, circumflex branch, right coronary artery, and any one of the left main arteries) was >70% were enrolled in the case group. Individuals with the degree of coronary artery stenosis less than 30% and no CHD diagnosis upon discharge were included in the control group. The study exclusion criteria were 1) no signed informed consent for biological sample collection; 2) blood samples were not collected or retained; 3) a previous diagnosis of CHD through coronary angiography; 4) prior coronary intervention therapy or coronary artery bypass grafting; and 5) an admission diagnosis of acute myocardial infarction or myocardial injury biomarker elevation greater than the normal upper limit before coronary angiography.

A total of 447 individuals met the criteria for inclusion in the control group and were matched 1:1 with patients with CHD according to the following conditions: 1) identical sex; 2) age range within 2 years; 3) coronary angiography date within 180 days of each other. Finally, 429 case–control pairs were enrolled. Because the serine concentration was too low to be measured in one subject, one case–control pair was further excluded, leading to the inclusion of 428 case–control pairs. This study was approved by the Ethics Committee of Peking University First Hospital, and all of the research processes were conducted in strict accordance with the Declaration of Helsinki.

Data Collection

The following information was collected from the participants' medical records: general information, including sex, age, body mass index (BMI), and blood pressure at hospital admission; medical history, such as history of hypertension, diabetes mellitus, dyslipidemia, depression, and tumor; lifestyle factors, such as the status of smoking and alcohol consumption; laboratory test results, including routine blood test and biochemical index results; and coronary angiography results.

Hypertension, diabetes mellitus, dyslipidemia, depression, and tumors were all determined from the discharge diagnosis. Smoking was defined as continuous smoking for more than half a year with smoking ≥1 cigarette per day. Quitting smoking was defined as being a former smoker who had not smoked for more than 6 months. Alcohol consumption was defined as drinking at least once per week for more than half a year. Abstinence was defined as abstaining from alcohol for more than 6 months. Drug history was based on admission records. Routine blood and biochemical index results were obtained from the first laboratory test after admission before coronary angiography. Coronary artery stenosis was calculated as the diameter stenosis rather than the area stenosis.

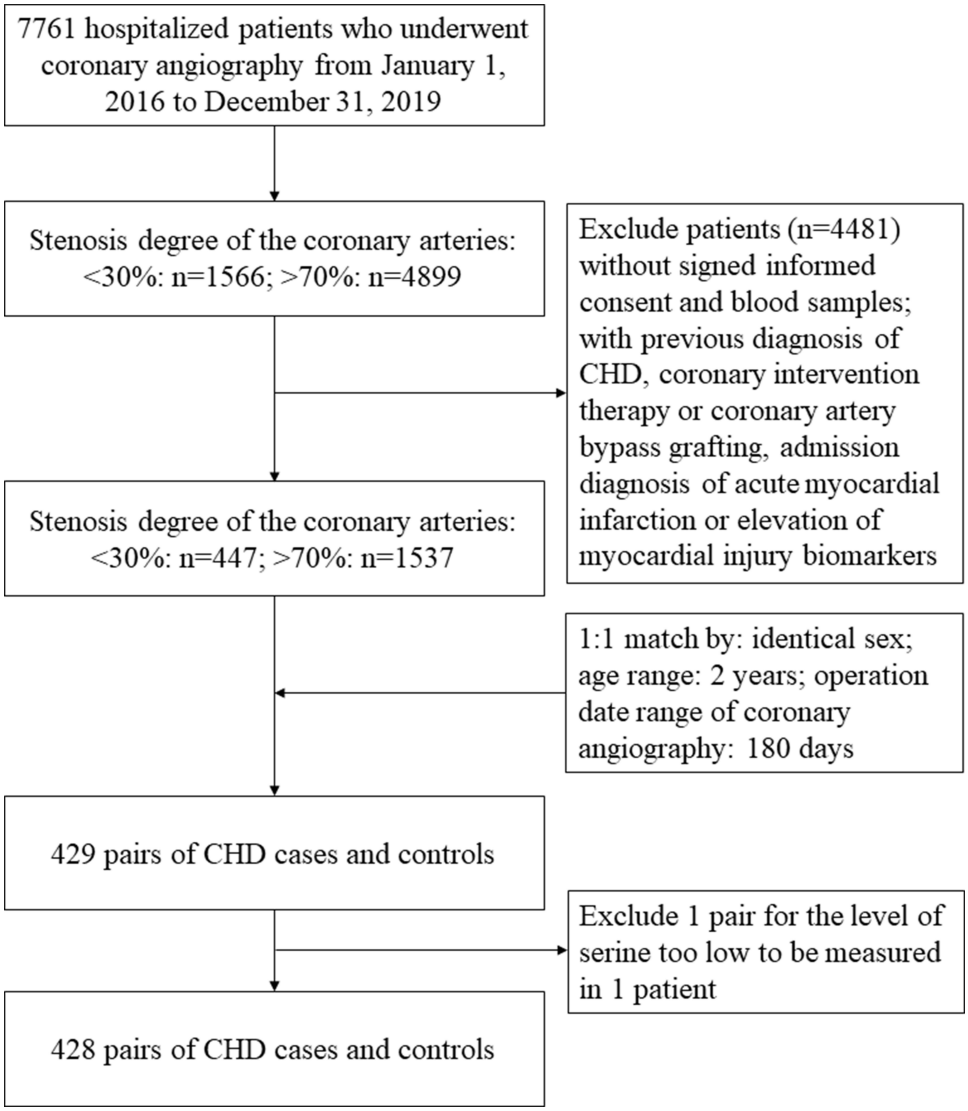

Figure 1 Study flowchart.
Abbreviation: CHD, coronary heart disease.

Serine Examination

With the informed consent of each patient, 10 mL blood was collected from the median cubital vein before coronary angiography and loaded into ethylenediaminetetraacetic acid anticoagulant blood tubes (Solebo Technology Co., Ltd., Beijing, China). All samples were immediately sent to the cardiology laboratory and centrifuged at 3000 rpm for 5 minutes (Xiangyi Laboratory Instrument Development Co., Ltd., Hunan, China). After centrifugation, the upper layer of clear plasma was absorbed, placed into an EP tube (1.5 mL) and stored at −80°C for later use.

Serine was identified by liquid chromatography–tandem mass spectrometry (LC–MS/MS) at Shenzhen Tailored Medical Laboratory. The specific method of LC–MS/MS was as follows. The plasma protein precipitation was pre-treated, and serine-d3 was used as the internal standard (standard solution was from Inorganic Ventures, VA, US). The Waters ACQUITY UPLC® BEH HILIC (2.1 × 100 mm, 1.7 μm) chromatographic column (US Waters Company) was used, with 0.5% acetic acid water (containing 10 mmoL ammonium acetate) and 95% acetonitrile water (containing 0.5% acetic acid, 10 mmoL ammonium acetate) used as the mobile phase for gradient elution (for each 10 μL injection, the elution flow rate was set to 0.4 mL/min). An electrospray ion source, positive ion ionization mode, and the multi-reactive ion monitoring mode were adopted for mass spectrometry detection. The corresponding internal standard ion pair m/z of serine was 106.1→ 60.1.

Statistical Analysis

The data are expressed as the mean ± standard deviation for normally distributed continuous variables, or as the median (interquartile range) for non-normally distributed continuous variables. The Student's *t*-test or Mann–Whitney *U*-test was used to identify differences between the cases and controls. Categorical data are expressed as number (percentage), and differences between the two groups were identified using the Chi-square test.

First, a smooth curve (restricted cubic spline) was used to explore the dose–effect relationship between serine and CHD risk. Then, conditional logistic regression was applied to analyze the association of serine (as a continuous variable, as quartiles, and as a dichotomic variable divided by cut-off point) with CHD. Adjusted variables included BMI, systolic blood pressure (SBP), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), plasma creatinine, smoking status, drinking status, hypertension, diabetes mellitus, hyperlipidemia, anti-hypertensive treatment, hypoglycemic treatment, and lipid-lowering treatment. Finally, because of the different characteristics of the above covariates, further subgroup and interaction analyses were performed to explore the differences in the relationship between serine and CHD in the different subgroups. Statistical analyses were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using EmpowerStats software (Version 2.0, http://www.empowerstats.com) and R software (Version 4.3.1, http://www.R-project.org).

Results

Baseline Characteristics of All Participants

In this study, 856 subjects were enrolled, including 428 cases and 428 controls (Table 1). The mean age of the cases and controls was 63.89 ± 10.49 years and 63.06 ± 10.27 years, respectively. Participants in the case group had a lower LDL-

Table 1 Characteristics of the Cases and Controls

Variables	Non-CHD Controls	CHD Cases	*P* value
N	428	428	
Male, n (%)	200 (46.73%)	200 (46.73%)	1.000
Age, years	63.06 ± 10.27	63.89 ± 10.49	0.243
BMI, kg/m^2	26.21 ± 3.72	25.93 ± 3.65	0.271
SBP, mm Hg	132.79 ± 16.02	133.50 ± 16.63	0.532
LDL-C, mmol/L	2.39 ± 0.82	2.28 ± 0.81	0.047
FPG, mmol/L	6.50 ± 2.48	7.52 ± 3.45	<0.001
Crea, μmol/L	74.20 (63.80–84.73)	76.40 (65.94–89.72)	0.014
Smoking status, n (%)			0.005
Never	272 (64.15%)	227 (53.66%)	
Ever	64 (15.09%)	93 (21.99%)	
Current	88 (20.75%)	103 (24.35%)	
Drinking status, n (%)			0.946
Never	296 (69.98%)	293 (69.60%)	
Ever	42 (9.93%)	40 (9.50%)	
Current	85 (20.09%)	88 (20.90%)	
Comorbidities, n (%)			
Hypertension	280 (65.42%)	319 (74.53%)	0.004
Diabetes mellitus	139 (32.48%)	221 (51.64%)	<0.001
Hyperlipidemia	316 (73.83%)	352 (82.24%)	0.003
Medications, n (%)			
Anti-hypertensive	226 (52.80%)	249 (58.18%)	0.114
Hypoglycemic	97 (22.66%)	166 (38.79%)	<0.001
Lipid-lowering	170 (39.72%)	240 (56.07%)	<0.001
Serine, μg/mL	13.77 ± 4.08	13.35 ± 4.20	0.133

Notes: For continuous variables, the data are presented as the mean ± standard deviation or median (interquartile range) depending on their distribution.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; Crea, plasma creatinine; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

C; higher FPG and creatinine levels; and a higher prevalence of current smoking, hypertension, diabetes mellitus, hyperlipidemia, hypoglycemic, and lipid-lowering medications. For the other baseline characteristics, there was no significant difference between cases and controls. Table S1 shows that no significant differences were found among the participants in the four serine concentration quartiles, except for SBP and drinking status.

Relationships Between Serine and CHD

The restricted cubic spline demonstrated a linear negative relationship between serine and CHD risk (Figure 2). In the univariable conditional logistic regression analysis, CHD risk showed a downward trend with an increase in the serine concentration. After adjusting for other confounding covariates, for every 1 μg/mL increase in serine concentration, the risk of CHD significantly decreased by 6% (95% CI 0.90–0.99; $P = 0.010$) (Table 2). Furthermore, the risk of CHD in the third and fourth serine concentration quartiles was reduced by 45% and 46% ($P_{trend} = 0.008$) compared with the first quartile. Compared with subjects with a serine concentration of <13.41 μg/mL, those with a serine concentration of ≥13.41 μg/mL had a 43% lower risk of CHD (OR 0.57, 95% CI 0.39–0.84; $P = 0.004$).

Subgroup and Interaction Analyses

The subgroup analyses based on different sexes, age groups, BMI values, creatinine concentrations, smoking and drinking statuses, hypertension, diabetes mellitus, and hyperlipidemia are shown in Table 3. Sex modified the relationship between serine concentration and CHD, which was more significant (OR 0.93, 95% CI 0.87–0.98; $P = 0.013$) in males, while no correlation was seen in females ($P_{interaction} = 0.039$). The interaction tests of the other covariates were not

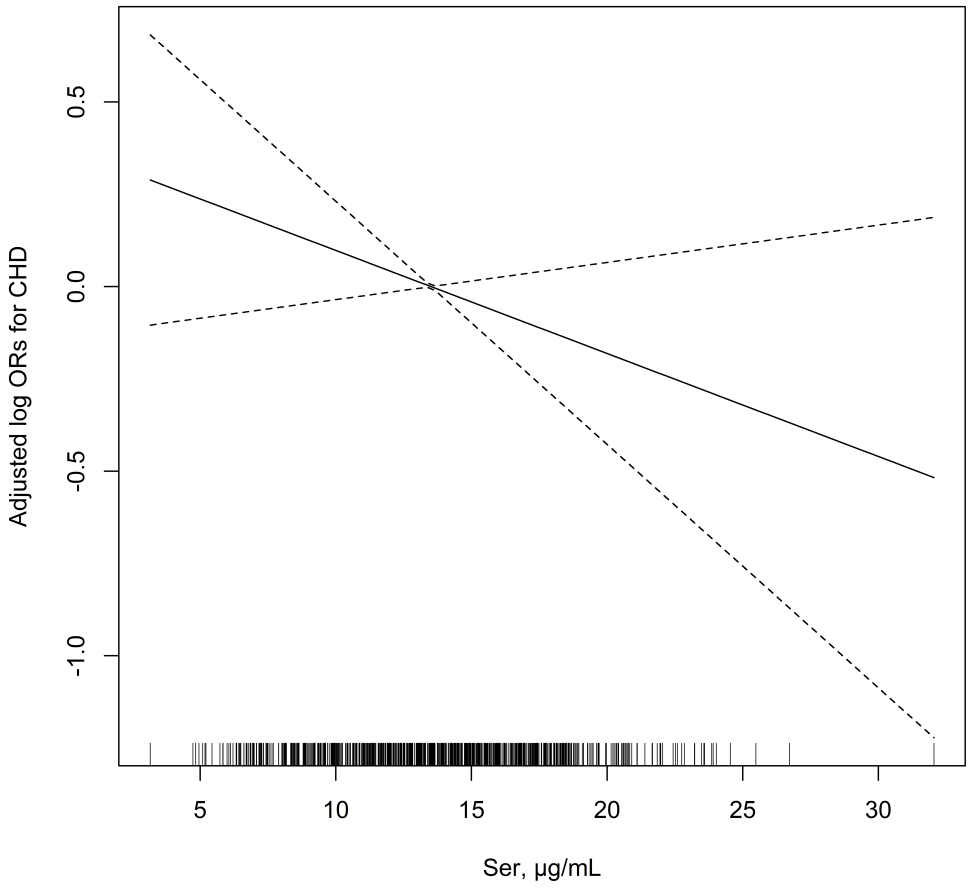

Figure 2 Smooth curve of the association between the serine concentration and CHD risk. The restricted cubic spline was adjusted for sex, age, BMI, SBP, FPG, LDL-C, Crea, smoking status, drinking status, hypertension, diabetes mellitus, hyperlipidemia, anti-hypertensive treatment, hypoglycemic treatment, and lipid-lowering treatment.
Abbreviations: BMI, body mass index; CHD, coronary heart disease; Crea, plasma creatinine; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.

Table 2 Association of the Serine Concentration with CHD Risk

Variables	Cases, n (%)	Crude Model		Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Serine, per 1 μg/mL	428 (50.0)	0.98 (0.94, 1.01)	0.133	0.97 (0.94, 1.01)	0.100	0.94 (0.90, 0.99)	0.010
Quartiles, μg/mL							
Q1 (<10.62)	115 (53.74)	Ref		Ref		Ref	
Q2 (10.62-<13.41)	116 (54.21)	1.02 (0.70, 1.49)	0.923	0.98 (0.66, 1.45)	0.902	0.92 (0.54, 1.55)	0.746
Q3 (13.41-<16.27)	97 (45.33)	0.71 (0.49, 1.04)	0.082	0.66 (0.43, 0.99)	0.046	0.55 (0.32, 0.95)	0.031
Q4 (≥16.27)	100 (46.73)	0.76 (0.52, 1.10)	0.147	0.70 (0.46, 1.06)	0.095	0.54 (0.31, 0.93)	0.028
P for trend					0.033		0.008
Groups, μg/mL							
<13.41 (Q1 + Q2)	231 (53.97%)	Ref		Ref		Ref	
≥13.41 (Q3 + Q4)	197 (46.03%)	0.73 (0.56, 0.95)	0.020	0.69 (0.51, 0.92)	0.013	0.57 (0.39, 0.84)	0.004

Notes: Conditional logistic regression Model 1 was conditioned on the matching factors of age, sex, and operation time; Model 2 was conditioned on the matching factors of age, sex, and operation time, and adjusted for BMI, SBP, FPG, LDL-C, Crea, smoking status, drinking status, hypertension, diabetes mellitus, hyperlipidemia, anti-hypertensive treatment, hypoglycemic treatment, and lipid-lowering treatment.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; Crea, plasma creatinine; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.

Table 3 Subgroup and Interaction Analyses for the Association Between the Serine Concentration and CHD

Subgroups	N	Cases, n (%)	OR (95% CI)*	*P* value	*P* for Interaction
Sex					0.039
Male	400	200 (50.0)	0.93 (0.87, 0.98)	0.013	
Female	456	228 (50.0)	1.01 (0.96, 1.06)	0.828	
Age, years					0.552
<65	456	212 (46.5)	0.96 (0.92, 1.01)	0.153	
≥65	400	216 (54.0)	0.99 (0.93, 1.04)	0.601	
BMI, kg/m^2					0.126
<24	230	124 (53.9)	1.01 (0.94, 1.08)	0.808	
24–28	384	192 (50.0)	0.93 (0.88, 0.99)	0.015	
≥28	228	106 (46.5)	1.01 (0.94, 1.09)	0.803	
SBP tertiles, mm Hg					0.309
<126	269	138 (51.3)	1.01 (0.95, 1.08)	0.690	
126-<139	282	137 (48.6)	0.95 (0.89, 1.02)	0.157	
≥139	286	142 (49.7)	0.95 (0.89, 1.01)	0.104	
Crea, μmol/L					0.442
<75.2	426	197 (46.2)	0.99 (0.94, 1.04)	0.628	
≥75.2	426	230 (54.0)	0.96 (0.91, 1.01)	0.139	
Glycine tertiles, μg/mL					0.471
<21.79	285	148 (51.9)	0.97 (0.89, 1.06)	0.514	
21.79-<27.94	285	145 (50.9)	0.90 (0.81, 1.00)	0.046	
≥27.94	285	135 (47.4)	0.96 (0.90, 1.04)	0.330	
Smoking status					0.137
Never	499	227 (45.5)	1.00 (0.95, 1.05)	0.957	
Ever	157	93 (59.2)	0.91 (0.82, 1.01)	0.071	
Current	191	103 (53.9)	0.94 (0.87, 1.01)	0.092	
Drinking status					0.801
Never	589	293 (49.7)	0.98 (0.94, 1.02)	0.337	
Ever	82	40 (48.8)	0.93 (0.82, 1.06)	0.307	
Current	173	88 (50.9)	0.97 (0.89, 1.05)	0.454	

(*Continued*)

Table 3 (Continued).

Subgroups	N	Cases, n (%)	OR (95% CI)*	*P* value	*P* for Interaction
Hypertension					0.435
No	276	116 (42.0)	0.95 (0.89, 1.02)	0.150	
Yes	572	308 (53.8)	0.98 (0.94, 1.03)	0.430	
Diabetes					0.470
No	516	220 (42.6)	0.96 (0.91, 1.01)	0.121	
Yes	334	205 (61.4)	0.99 (0.93, 1.04)	0.644	
Dyslipidemia					0.482
No	276	120 (43.5)	1.00 (0.92, 1.08)	0.974	
Yes	562	298 (53.0)	0.97 (0.93, 1.01)	0.108	
Anti-hypertensive treatment					0.687
No	276	116 (42.0)	0.96 (0.91, 1.02)	0.203	
Yes	572	308 (53.8)	0.98 (0.93, 1.03)	0.422	
Hypoglycemic treatment					0.703
No	516	220 (42.6)	0.97 (0.92, 1.01)	0.165	
Yes	334	205 (61.4)	0.98 (0.92, 1.05)	0.576	
Lipid-lowering treatment					0.540
No	276	120 (43.5)	0.98 (0.94, 1.03)	0.479	
Yes	562	298 (53.0)	0.96 (0.91, 1.02)	0.161	

Notes: *Logistic regression models were adjusted, if not stratified, for sex, age, BMI, SBP, FPG, LDL-C, Crea, smoking status, drinking status, hypertension, diabetes mellitus, hyperlipidemia, anti-hypertensive treatment, hypoglycemic treatment, and lipid-lowering treatment.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; Crea, plasma creatinine; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.

significant. In terms of the characteristics of males and females, Table S2 shows that compared with females, males were younger; had lower SBP, LDL-C, and FPG values; and had a lower prevalence of hypertension, diabetes mellitus, and all three types of medication. Moreover, males more frequently smoked and consumed alcohol, and they had a higher creatinine concentration.

Although the subgroup and interaction analyses based on smoking status (never, ever, and current) were not statistically significant, a non-significant reverse association between the serine concentration and CHD was observed in ever and current smokers, but not in never smokers. Further subgroup analyses (Table S3) identified similar results, especially when combining ever and current smokers as one group and dividing the serine concentration into quartiles, where the $P_{\text{interaction}}$ value changed to 0.023, suggesting that the protection effect of serine may mainly exist in ever/current smokers.

Sensitivity Analyses

A positive correlation between serine and glycine (r = 0.70) was found with regard to the bidirectional transformation between serine and glycine. We performed sensitivity analyses adjusted for the glycine concentration (Table S4), and the results showed that the relationship between serine and CHD remained.

We included Hcy; other related nutrients, including methionine, vitamin B6, and B12; and white blood cell count into the multivariable-adjusted model and found that the main results did not change substantially (Table S5).

A history of depression (n = 10) and tumor (n = 96) was further adjusted in the multivariable conditional logistic regression analyses (Table S6). The main results did not change substantially. Further multivariable logistic regression analyses excluding participants with a history of depression and tumor produced similar results (not shown).

Discussion

To our knowledge, this is the first case–control study to observe a negative correlation between the serine concentration and CHD in Chinese individuals. Individuals with a serine concentration of ≥13.41 μg/mL had a significantly reduced

risk of CHD (43%) compared to those with a serine concentration of <13.41 μg/mL, suggesting that serine may be one of the protective factors for coronary artery atherosclerosis.

Recently, a cohort study investigated the relationship between CVD onset and plasma-free amino acid profiles in the general Japanese population, observing that elevated serine concentration was significantly associated with a decreased CVD risk.[14] Another trans-ancestry Mendelian randomization (MR) analysis investigated the association between 20 types of circulating amino acid and CVD.[15] Consistent with our study, per 1 unit increase in serine, the risk of CHD decreased by 12.6% (OR 0.874, 95% CI 0.836–0.914; $P_{\text{IVW-MRE}} = 3.37 \times 10^{-9}$) in the East Asian population, which indicated the potential of serine as a biomarker or therapeutic target for CHD in clinical scenarios. However, the specific mechanism underpinning the possible protective effect of serine against CHD remains unclear. We speculate that the following mechanisms may explain this phenomenon.

First, one way by which serine metabolism promotes cancer cell growth is by controlling the antioxidant and methylation abilities of cells,[16] which is speculated to be involved in the different effects of serine on tumors and CHD. Oxidative stress plays an important role in atherosclerosis, vascular damage, and CHD.[17–20] The metabolites of serine metabolism participate in various reactions that regulate oxidative stress. For example, tetrahydrobiopterin, participating in nitric oxide generation, is involved in serine metabolism.[21] Nitric oxide has vasodilatory, antiplatelet, anti-proliferative, and anti-inflammatory effects.[22] Furthermore, serine and Hcy can be transformed into glutathione, a crucial antioxidant cofactor.[23] Insufficient serine may inhibit the trans-sulfuration pathway, reduce glutathione production, and consequently decrease antioxidant power.[24] Therefore, we hypothesized that the antioxidant effect of serine metabolism might protect against CHD due to its role in one-carbon metabolism and glutathione generation.

In addition, some genetic mutations in serine metabolism have also demonstrated associations with CHD. The gene mutation *SHMT C1420T* (rs1979277) decreases SHMT activity, resulting in reduced serine metabolism.[25] Previous studies have found that CHD cases compared with control cases had a lower proportion of individuals with *SHMT C1420T* mutations and higher levels of oxidative stress markers.[26] Epigenomic studies have also shown that mutations such as *SHMT C1420T* are associated with the expression of genes related to oxidative stress, thereby influencing CHD susceptibility.[27] Interestingly, the *SHMT 1420TT* genotype was found to protect against CHD risk in a risk prediction model.[28] However, the frequency of *SHMT C1420T* gene polymorphism was not available in this study, and thus its relationship with serine and CHD could not be analyzed.

Serine and glycine can be transformed into each other,[29] and glycine may have a protective effect on the cardiovascular system. A cohort study in northern Europe found that glycine was inversely associated with myocardial infarction risk in angina patients.[30] A genome-wide association study demonstrated that genetically determined serum glycine protected against CHD in the Singaporean Chinese population,[31] consistent with findings from two other MR studies.[15,32] In addition, glycine supplementation could mitigate atherosclerosis development, reduce tissue injury, and treat metabolic disorders in multiple animal models.[33–35] Our data also showed a positive correlation between serine and glycine (r = 0.70, 95% CI 0.66–0.73; $P < 0.001$). However, the supplementary analysis (Table S3) showed that the serine-CHD relationship remained after further adjustment for the glycine concentration, suggesting that the protective effect of serine on CHD was not entirely dependent on glycine.

We also found that sex and smoking modified the relationship between serine and CHD, and their inverse relationship was mainly observed in males and ever/current smokers. However, the specific mechanism is unknown and needs to be further explored. Oxidative stress is speculated to play a critical role in sex differences, smoking, and serine concentration. The prevalence of CHD was higher in males than in females across all age groups.[36] Possible reasons for this include higher oxidative stress and lower antioxidant potential in males, making them more susceptible to oxidative stress.[37] Moreover, smoking has been proven to increase inflammation, endothelial dysfunction, and oxidative stress to initiate cardiovascular dysfunction.[18] Conversely, serine may attenuate oxidative stress and play a protective role in coronary atherosclerosis. Thus, serine may counteract the harmful effects of risk factors, such as male sex and smoking, on atherosclerosis.

This study has several limitations. First, this study's case–control design did not allow causality determination. Cohort and randomized trials should be conducted to provide further evidence. Second, a family history of CVD; inflammation markers, such as C-reactive protein; and other potential confounding factors that may influence serine concentrations,

were not available from the participants' medical records and were thus not included in the analyses. Finally, we chose patients with coronary artery stenosis of <30% rather than those with normal coronary arteries (no stenosis) as control subjects. Nevertheless, none of the controls were diagnosed with CHD at discharge, and most had nearly normal coronary angiography. Meanwhile, we chose those with coronary artery stenosis of >70% as cases, as all of these individuals were considered as having definite CHD. Patients whose coronary angiography indicated that the coronary artery stenosis degree was 30%–70%, which is an intermediate status, were not enrolled in this study. Therefore, whether the conclusions can be extrapolated to this population should be further evaluated in the future.

Conclusions

This case–control study of Chinese individuals is the first to report a negative correlation between the serine concentration and CHD, suggesting that serine may play a protective role in coronary atherosclerosis. This relationship was more robust in males, suggesting the existence of an interaction by sex. However, these findings need to be further verified in more extensive cohort studies, and the specific pathophysiological mechanisms need to be explored through animal and cell experiments.

Abbreviations

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; Crea, plasma creatinine; CVD, cardiovascular disease; FPG, fasting plasma glucose; Hcy, homocysteine; LDL-C, low-density lipoprotein cholesterol; MR, Mendelian randomization; OR, odds ratio; PLP, pyridoxal phosphate; SBP, systolic blood pressure; SHMT, serine hydroxymethyltransferase; 5,10-CH_2-THF, 5,10-methylene tetrahydrofolate.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Peking University First Hospital (reference number: 2020-447), and all the research processes were performed in strict compliance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1–25. doi:10.1016/j.jacc.2017.04.052
2. Purcell C, Dibben G, Hilton Boon M, et al. Social network interventions to support cardiac rehabilitation and secondary prevention in the management of people with heart disease. *Cochrane Database Syst Rev*. 2023;2023(6). doi:10.1002/14651858.CD013820.pub2
3. Giubilato S, Lucà F, Abrignani MG, et al. Management of residual risk in chronic coronary syndromes. clinical pathways for a quality-based secondary prevention. *J Clin Med*. 2023;12(18):5989. doi:10.3390/jcm12185989
4. Zhang C-Y, Xu R-Q, Wang X-Q, et al. Comprehensive transcriptomics and metabolomics analyses reveal that hyperhomocysteinemia is a high risk factor for coronary artery disease in a Chinese obese population aged 40–65: a prospective cross-sectional study. *Cardiovasc Diabetol*. 2023;22(1). doi:10.1186/s12933-023-01942-0
5. Mehlig K, Leander K, de Faire U, et al. The association between plasma homocysteine and coronary heart disease is modified by the MTHFR 677C>T polymorphism. *Heart*. 2013;99(23):1761–1765. doi:10.1136/heartjnl-2013-304460
6. Appaji Rao N, Ambili M, Jala VR, Subramanya HS, Savithri HS. Structure–function relationship in serine hydroxymethyltransferase. *BBA*. 2003;1647(1–2):24–29. doi:10.1016/s1570-9639(03)00043-8
7. Bao L, Vlcek C, Paces V, Kraus JP. Identification and tissue distribution of human cystathionine beta-synthase mRNA isoforms. *Arch Biochem Biophys*. 1998;350(1):95–103. doi:10.1006/abbi.1997.0486
8. Sun W, Liu R, Gao X, et al. Targeting serine-glycine-one-carbon metabolism as a vulnerability in cancers. *Biomarker Res*. 2023;11(1). doi:10.1186/s40364-023-00487-4
9. Piubelli L, Murtas G, Rabattoni V, Pollegioni L. The role of d-amino acids in Alzheimer's disease. *J Alzheimers Dis*. 2021;80(2):475–492. doi:10.3233/jad-201217
10. de Bartolomeis A, Vellucci L, Austin MC, De Simone G, Barone A. Rational and translational implications of D-Amino acids for treatment-resistant schizophrenia: from neurobiology to the clinics. *Biomolecules*. 2022;12(7):909. doi:10.3390/biom12070909
11. MacKay M-AB, Kravtsenyuk M, Thomas R, Mitchell ND, Dursun SM, Baker GB. D-serine: potential therapeutic agent and/or biomarker in schizophrenia and depression? *Frontiers in Psychiatry*. 2019;10. doi:10.3389/fpsyt.2019.00025
12. Wu Y, Tang L, Huang H, et al. Phosphoglycerate dehydrogenase activates PKM2 to phosphorylate histone H3T11 and attenuate cellular senescence. *Nat Commun*. 2023;14(1):1323. doi:10.1038/s41467-023-37094-8
13. Liu J, Chang Z, Zhang Z, et al. Clinical features and metabolic reprogramming of atherosclerotic lesions in patients with chronic thromboembolic pulmonary hypertension. *Front Cardiovasc Med*. 2022;9:1023282. doi:10.3389/fcvm.2022.1023282
14. Takeshita M, Tabara Y, Setoh K, et al. Development of a plasma-free amino acid-based risk score for the incidence of cardiovascular diseases in a general population: the Nagahama study. *Clin Nutr*. 2023;42(12):2512–2519. doi:10.1016/j.clnu.2023.10.024
15. Hu S, Lin Z, M-J H, et al. Causal relationships of circulating amino acids with cardiovascular disease: a trans-ancestry Mendelian randomization analysis. *J Transl Med*. 2023;21(1). doi:10.1186/s12967-023-04580-y
16. Yang M, Vousden KH. Serine and one-carbon metabolism in cancer. *Nat Rev Cancer*. 2016;16(10):650–662. doi:10.1038/nrc.2016.81
17. Yan Q, Liu S, Sun Y, et al. Targeting oxidative stress as a preventive and therapeutic approach for cardiovascular disease. *J Transl Med*. 2023;21(1). doi:10.1186/s12967-023-04361-7
18. Klein J, Diaba-Nuhoho P, Giebe S, Brunssen C, Morawietz H. Regulation of endothelial function by cigarette smoke and next-generation tobacco and nicotine products. *Pflügers Archiv*. 2023;475(7):835–844. doi:10.1007/s00424-023-02824-w
19. Li K, Li K, Yao Q, et al. The potential relationship of coronary artery disease and hyperuricemia: a cardiometabolic risk factor. *Heliyon*. 2023;9(5). doi:10.1016/j.heliyon.2023.e16097
20. Suman S, Biswas A, Kohaf N, et al. The diabetes-heart disease connection: recent discoveries and implications. *Curr Prob Cardiol*. 2023;48(11):101923. doi:10.1016/j.cpcardiol.2023.101923
21. Crabtree MJ, Tatham AL, Hale AB, Alp NJ, Channon KM. Critical role for tetrahydrobiopterin recycling by dihydrofolate reductase in regulation of endothelial nitric-oxide synthase coupling. *J Biol Chem*. 2009;284(41):28128–28136. doi:10.1074/jbc.M109.041483
22. Kawashima S. the two faces of endothelial nitric oxide synthase in the pathophysiology of atherosclerosis. *Endothelium*. 2009;11(2):99–107. doi:10.1080/10623320490482637
23. Ferreira MJ, Rodrigues TA, Pedrosa AG, et al. Glutathione and peroxisome redox homeostasis. *Redox Biol*. 2023;67. doi:10.1016/j.redox.2023.102917
24. Cueto R, Shen W, Liu L, et al. SAH is a major metabolic sensor mediating worsening metabolic crosstalk in metabolic syndrome. *Redox Biol*. 2024;73:103139. doi:10.1016/j.redox.2024.103139
25. Komlósi V, Hitre E, Pap É, et al. SHMT1 1420 and MTHFR 677 variants are associated with rectal but not colon cancer. *BMC Cancer*. 2010;10(1). doi:10.1186/1471-2407-10-525
26. Vijaya Lakshmi SV, Naushad SM, Seshagiri Rao D, Kutala VK. Oxidative stress is associated with genetic polymorphisms in one-carbon metabolism in coronary artery disease. *Cell Biochem Biophys*. 2013;67(2):353–361. doi:10.1007/s12013-011-9322-1
27. Lakshmi SVV, Naushad SM, Reddy CA, et al. Oxidative stress in coronary artery disease: epigenetic perspective. *Mol Cell Biochem*. 2013;374(1–2):203–211. doi:10.1007/s11010-012-1520-7
28. Naushad SM, Hussain T, Indumathi B, Samreen K, Alrokayan SA, Kutala VK. Machine learning algorithm-based risk prediction model of coronary artery disease. *Mol Biol Rep*. 2018;45(5):901–910. doi:10.1007/s11033-018-4236-2
29. Razak MA, Begum PS, Viswanath B, Rajagopal S. Multifarious beneficial effect of nonessential amino acid, glycine: a review. *Oxid Med Cell Longev*. 2017;2017:1–8. doi:10.1155/2017/1716701
30. Ding Y, Svingen GFT, Pedersen ER, et al. Plasma glycine and risk of acute myocardial infarction in patients with suspected stable angina pectoris. *J Am Heart Assoc*. 2015;5(1). doi:10.1161/jaha.115.002621

31. Chang X, Wang L, Guan SP, et al. The association of genetically determined serum glycine with cardiovascular risk in East Asians. *Nutr Metab Cardiovasc Dis*. 2021;31(6):1840–1844. doi:10.1016/j.numecd.2021.03.010
32. Xu M, Zheng J, Hou T, et al. SGLT2 inhibition, choline metabolites, and cardiometabolic diseases: a mediation Mendelian randomization study. *Diabetes Care*. 2022;45(11):2718–2728. doi:10.2337/dc22-0323
33. Rom O, Liu Y, Finney AC, et al. Induction of glutathione biosynthesis by glycine-based treatment mitigates atherosclerosis. *Redox Biol*. 2022;52:102313. doi:10.1016/j.redox.2022.102313
34. Zaric BL, Radovanovic JN, Gluvic Z, et al. Atherosclerosis linked to aberrant amino acid metabolism and immunosuppressive amino acid catabolizing enzymes. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.551758
35. Wang W, Wu Z, Dai Z, Yang Y, Wang J, Wu G. Glycine metabolism in animals and humans: implications for nutrition and health. *Amino Acids*. 2013;45(3):463–477. doi:10.1007/s00726-013-1493-1
36. Martin SS, Aday AW, Almarzooq ZI, et al. 2024 heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149(8):e347–e913. doi:10.1161/CIR.0000000000001209
37. Kander MC, Cui Y, Liu Z. Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. *J Cell Mol Med*. 2017;21(5):1024–1032. doi:10.1111/jcmm.13038

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