# Study on the Distribution Characteristics and Influencing Factors of Homocysteine in the Physical Examination Population

**Fang Bao** ( bfspg@163.com )
Affiliated Hospital of Nantong University https://orcid.org/0000-0003-2673-7249
**Ming Cui**
Affiliated Hospital of Nantong University
**Xiuying Shi**
Affiliated Hospital of Nantong University
**Shaoqing Ju**
Affiliated Hospital of Nantong University
**Hui Cong**
Affiliated Hospital of Nantong University

**Research article**

**Keywords:** homocysteine, creatinine, uric acid, high-density lipoprotein cholesterol

**Posted Date:** May 19th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-520296/v1

# Abstract

**Background:** Homocysteine (Hcy) is considered to be an independent risk factor for cardiovascular and cerebrovascular diseases. No study has evaluated the distribution of Hcy on a large-scale health examination. Accordingly, this study aimed to investigate the level and distribution of Hcy in the healthy physical examination population and the correlation with other biomarkers, and analyzed for cardiovascular and other diseases. The prevention provides an important scientific basis.

**Methods:** From February 2017 to April 2020, 8063 medical examination populations were selected for analysis. Determination of serum Hcy, TC, TG, LDL-c, HDL-c, ALT, ALP, γ-GT, TBIL, GLU, urea, Cr, UA and related metabolic risk factors. According to the multivariate regression model of age, gender, smoking, drinking, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP), the relationship between Hcy and other biochemical indicators was evaluated.

**Results:** Among 8063 cases, the age, BMI, SBP and DBP of the high-Hcy group were higher than those of the low-Hcy group, the difference was statistically significant ($P$<0.05), and the proportion of males, smoking and drinking were higher than the low In the Hcy group, the difference was statistically significant ($P$<0.05); the ALT, ALP, γ-GT, TBIL, Urea, Cr, UA, and TG in the high Hcy group were higher than those in the low Hcy group, and the difference was statistically significant ($P$<0.05 ); HDL-c in the high-Hcy group was lower than that in the low-Hcy group, and the difference was statistically significant ($P$<0.05). There was no statistically significant difference in TC, LDL-c, and GLU between the high- and low-Hcy groups ($P$>0.05). In multivariate analysis, lnHDL-C was negatively correlated with lnHcy (β=-0.038, SE=0.016, $P$<0.05), lnCr was positively correlated with lnHcy (β=0.055, SE=0.016, $P$<0.05), lnUA and lnHcy were positive correlation (β=0.043, SE=0.019, $P$<0.05).

**Conclusion:** Hcy is closely related to HDL-c, Cr and UA, which indicates that Hcy may affect the metabolism of HDL-c and UA, and can also be used as an auxiliary diagnostic index for kidney injury.


# Background

Homocysteine (homocysteine, Hcy) is a sulfur-containing amino acid produced during the metabolism of methionine in cells of the body. Folic acid and vitamin B12 participate in its metabolism. Its pathogenic mechanism is mainly through multiple mechanisms such as vascular endothelial damage, stimulating smooth muscle cell proliferation, affecting coagulation and thrombus activation, and elevated Hcy is considered to be an independent risk factor for cardiovascular and cerebrovascular diseases [1, 2]. In this paper, through the detection and analysis of Hcy and other biochemical indicators in the 8063 healthy physical examination population, the level and distribution of Hcy in the healthy physical examination population and the correlation with other biochemical indicators are analyzed, and the possible influencing factors are analyzed for cardiovascular and cerebrovascular diseases. The prevention provides an important scientific basis.

# Methods

The subjects of this study came from a total of 8063 cases of the physical examination population in our hospital from February 2017 to April 2020. This research protocol was approved by the Ethics Committee of Nantong University Affiliated Hospital. The distribution characteristics of Hcy, blood lipids and other biochemical indicators, systolic blood pressure, diastolic blood pressure, body mass index, and pulse of the physical examination population were observed. 8063 study subjects were divided into low-Hcy group (Hcy≤15μmol/L) and high-Hcy group (Hcy>15μmol/L) according to their Hcy levels. Male UA>420 umol/L is an abnormal UA group, female UA>360umol /L is the abnormal UA group [3]; According to the 2016 edition of the "Guidelines for the Prevention and Treatment of Dyslipidemia in Adults in China" [4], TG>1.7mmol/L is defined as the abnormal TG group; TC>5.2mmol/L is abnormal TC group; LDL-c>3.4mmol/L is abnormal LDL-c group; HDL-c<1mmol/L is abnormal HDL-c group. According to the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China" [5], GLU>6.1mmol/L was regarded as the abnormal GLU group. BMI<18.5 kg/$m^2$ means lean, BMI between 18.5~24.0 kg/$m^2$ means normal group, BMI between 24~28 kg/$m^2$ means overweight, BMI≥28 kg/$m^2$ is the obesity group[6]; systolic blood pressure>130mmHg and/or diastolic blood pressure>80mmHg is the abnormal blood pressure group[7]; have had smoking and drinking behaviors Defined as the abnormal smoking and drinking group; males with ALT between 9-50U/L are regarded as normal group, females with ALT between 7-40U/L are regarded as normal group; outside the range are abnormal ALT group; males with ALP between 45-125U /L is the normal group, women aged 20 to 49: ALP between 35 to 100 U/L is the normal group, women 50 to 79 years old: ALP is between 50 to 135 U/L is the normal group, outside the range is defined as abnormal ALP Group; male γ-GT between 10~60U/L is the normal group, female γ-GT between 7~45U/L is the normal group, all outside the range is defined as abnormal γ-GT group[8]; TBIL≤23.0μmol/L is the normal group, outside the range is defined as abnormal TBIL group[9]; 20~59-year-old male Cr between 57~97μmol/L is In the normal Cr group, 60-79-year-old men with Cr between 57-111μmol/L are considered normal Cr group, 20-59-year-old women with Cr between 41-73μmol/L are normal Cr group, 60-79-year-old women with Cr between 41~81μmol/L is the normal Cr group, all outside the range is defined as the abnormal Cr group; 20-59 year-old males with Urea between 3.1-8.0mmol/L are considered normal group, 60-79 year-old males with Urea between 3.6~ 9.5mmol/L is the normal group, 20-59 year old women with Urea between 2.6 and 7.5mmol/L are normal group, 60-79 year old women with Urea between 3.1 and 8.8mmol/L are normal group. All outside the scope is defined as the abnormal urea group[10].

The subjects were fasted for 12 hours and collected 5 mL of venous blood into a vacuum test tube containing separation gel. After the blood coagulated, the serum was separated by centrifugation at 2062g for 10 minutes within 2 hours and tested on the machine. All tests are carried out under the condition that the instrument and reagents are in normal condition and the indoor quality control is under control, and are carried out in strict accordance with the reagent and instrument operating procedures (SOP). All biochemical index testing instruments are American Beckman-Coulter automatic biochemical analyzer testing. Hcy (enzyme cycling method) kit and calibrator were purchased from Qiangsheng

Biotechnology Co., Ltd., quality control products were provided by Shanghai Kunlai Biotechnology Company; ALT (lactate dehydrogenase method), ALP (NPP substrate-AMP buffer method) ), γ-GT (rate method), TBIL (diazonium method), TG (GPO-POD method), TC (cholesterol oxidase method), LDL-c (direct method), HDL-c (direct method), GLU (hexokinase method), BUN (urease-glutamate dehydrogenase method), Cr (sarcosine oxidase method), UA (uricase-peroxidase method) are tested by Beckman-Coulter Original kits and calibrators, quality control products are provided by Bio-Rad.

### Statistical analysis

Statistical software stata20.0 was used for data analysis, skewness and kurtosis normality test (sktest), the numerical variables of the normal distribution were expressed by the mean ± standard deviation, and the comparison between the two groups was performed by the t test; the numerical variables of the non-normal distribution The median (interquartile range) was used to express, the Mann-Whiteney U test was used for comparison between the two groups, the count data were all expressed by the number of cases (percentage), and the chi-square test was used for comparison between groups. This study analyzed the relationship between Hcy and TC, TG, LDL-c, HDL-c, ALT, ALP, TBIL, γ-GT, Urea, Cr and UA through single factor, multivariate linear regression and logistic regression models. The skewed numerical variables are analyzed after natural logarithmic transformation, and the multivariate regression is adjusted for age, gender, smoking, drinking, pulse and body mass index. Two-sided $P$<0.05 was considered statistically significant.

## Results

### General characteristics

This study included 8063 patients with an average age of (50.88±11.92) years old, body mass index (25.02±3.39) kg/$m^2$, systolic blood pressure (130.54±18.85) mmHg, diastolic blood pressure (78.66±11.96) mmHg, pulse ( 77.54±11.31) times/min. Among them, 5478 cases were male, accounting for 67.94%, aged 20-79 years old, and 2585 cases were female, accounting for 32.06%, aged 20-79 years old. The body mass index, systolic blood pressure, diastolic blood pressure, and glucose of men were higher than women, the difference was statistically significant ($P$<0.0001), while the pulse rate of men was lower than that of women, the difference was statistically significant ($P$<0.0001). Among men, the proportion of smoking is 23.95% and the proportion of drinking is 64.8%, which is much higher than that of women. Male ALT, γ-GT, TBIL, TG, LDL-c, Urea, Cr, UA are all higher than females, the difference is statistically significant ($P$<0.0001), TC, HDL-C are lower than females ($P$<0.001 ), there was no statistical difference in ALP between the

### Comparison of various indicators grouped by Hcy high and low

The age, body mass index, systolic blood pressure, and diastolic blood pressure of the high-Hcy group were higher than those of the low-Hcy group, the difference was statistically significant ($P$<0.05), and the

proportion of men, smoking and drinking was higher than that of the low-Hcy group, and the difference was statistically significant Academic significance ($P$<0.05).

The results of blood lipids showed that the TG of the high-Hcy group was significantly higher than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05). The HDL-c of the high-Hcy group was significantly lower than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05). There was no statistically significant difference in TC and LDL-c between the high and low Hcy groups ($P$>0.05); the liver function results showed that the ALT, ALP, γ-GT and TBIL in the high-Hcy group were higher than those in the low-Hcy group, and the difference was statistically significant ($P$<0.05); Renal function results showed that Urea, Cr and UA in the high-Hcy group were significantly higher than those in the low-Hcy group, and the difference was statistically significant ($P$<0.05). See Table 2 for details.

## Comparison of high and low Hcy indicators by gender

Among men, the age, systolic blood pressure, and diastolic blood pressure of the high-Hcy group were higher than those of the low-Hcy group, and the difference was statistically significant ($P$<0.05). The GLU between the high-Hcy group was lower than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05); the γ-GT and TBIL of the high-Hcy group were higher than those of the low-Hcy group, and the difference was statistically significant ($P$<0.05); the TG of the high-Hcy group was significantly higher than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05). The Cr and UA of the high-Hcy group were higher than those of the low-Hcy group, and the difference was statistically significant ($P$<0.05).

Among women, the age, BMI, systolic blood pressure and diastolic blood pressure of the high-Hcy group were significantly higher than those of the low-Hcy group, and the difference was statistically significant ($P$<0.05). The ALP of the high-Hcy group was higher than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05). The TG of the high-Hcy group was significantly higher than that of the low-Hcy group, and the difference was statistically significant ($P$<0.05), while the HDL-C was lower than the low-Hcy group, and the difference was statistically significant ($P$<0.05); Both Cr and UA were significantly higher than the low-Hcy group, and the difference was statistically significant ($P$<0.05). See Table 3 for details.

## Linear regression model analysis of the effect of serum Hcy level on blood lipid level

As shown in Table 3, the single factor linear regression model analysis results show that lnHcy is negatively correlated with lnHDL-c, and lnHcy is positively correlated with lnTG, lnALT, lnALP, lnγ-GT, lnTBIL, lnUrea, lnCr, and lnUA. The adjusted multivariate linear regression model analysis of gender, age, BMI, smoking and drinking showed that lnTG was positively correlated with lnHcy (β=0.080, SE=0.021, $P$<0.05), and lnHDL-c was negatively correlated with lnHcy (β= -0.021, SE=0.008, P<0.05), lnALT was negatively correlated with lnHcy (β=-0.053, SE=0.018, $P$<0.05), and lnTBIL was positively correlated with lnHcy (β=0.054, SE=0.014, $P$<0.05) ), lnCr was positively correlated with lnHcy (β=0.065, SE=0.006,

*P*<0.05), and lnUA was positively correlated with lnHcy (β=0.069, SE=0.009, *P*<0.05). For the abnormal Hcy group (Hcy>15μmol/L), in univariate analysis, lnTC was negatively correlated with lnHcy (β=-0.032, SE=0.016, *P*<0.05), and lnHDL-c was negatively correlated with lnHcy (β=- 0.060, SE=0.017, *P*<0.05), lnALP is positively correlated with lnHcy (β=0.062, SE=0.022, *P*<0.05), and lnUrea is negatively correlated with lnHcy (β=-0.045, SE=0.021, *P*<0.05) , LnCr was positively correlated with lnHcy (β=0.065, SE=0.016, *P*<0.05), and lnUA was positively correlated with lnHcy (β=0.062, SE=0.020, *P*<0.05). In multivariate analysis, lnTC was negatively correlated with lnHcy (β=-0.036, SE=0.016, *P*<0.05), lnHDL-C was negatively correlated with lnHcy (β=-0.038, SE=0.016, *P*<0.05), lnALP It is positively correlated with lnHcy (β=0.068, SE=0.022, *P*<0.05), lnUrea is negatively correlated with lnHcy (β=-0.054, SE=0.027, *P*<0.05), and lnCr is positively correlated with lnHcy (β=0.055, SE =0.016, *P*<0.05), lnUA and lnHcy were positively correlated (β=0.043, SE=0.019, *P*<0.05). See Table 4 for details.

### Logistic regression model analysis of serum Hcy on each index

The single factor logistic regression model showed that high lnHcy is the occurrence of high TG (OR: 1.870, 95% CI: 1.581-2.212, *P*<0.05), low HDL-C (OR: 1.803, 95% CI: 1.404-2.316, *P*< 0.05), abnormal γ-GT (OR: 1.270, 95%CI: 1.028-1.569, *P*<0.05), high TBIL (OR: 2.456, 95%CI: 1.741-3.464, *P*<0.05), high UA (OR: 3.106, 95%CI: 2.439-3.956, *P*<0.05) risk factors. High lnHcy is a protective factor for abnormal ALP (OR: 0.692, 95%CI: 0.531-0.900, *P*<0.05) and abnormal Cr (OR: 0.737, 95%CI: 0.565-0.960, *P*<0.05); multivariate logistic regression Model analysis results show that high lnHcy is high TG (OR: 1.281, 95%CI: 1.078-1.523, *P*<0.05), high UA (OR: 2.008, 95%CI: 1.565-2.575, *P*<0.05), abnormal TBIL (OR: 1.707, 95% CI: 1.205-2.418, *P*<0.05) risk factors. High lnHcy is a protective factor for abnormal Cr (OR: 0.663, 95% CI: 0.508-0.866, *P*<0.05) and high LDL-c (OR: 0.820, 95% CI: 0.699-0.962, *P*<0.05). For the abnormal Hcy group (Hcy>15μmol/L), single-factor logistic regression showed that high lnHcy is low HDL-C (OR: 1.772, 95% CI: 1.184-2.653, *P*<0.05), abnormal ALP (OR: 1.940, 95%CI: 1.093-3.444, *P*<0.05), high UA (OR: 1.485, 95%CI: 1.052-2.096, *P*<0.05), abnormal Cr (OR: 2.086, 95%CI: 1.271-3.366, *P*< 0.05) risk factors; multivariate logistic regression analysis results show that high lnHcy is low HDL-C (OR: 1.558, 95% CI: 1.017-2.386, *P*<0.05), abnormal ALP (OR: 1.992, 95% CI : 1.111-3.571, *P*<0.05), high UA (OR: 1.487, 95%CI: 1.037-2.131, *P*<0.05), abnormal Cr (OR: 2.241, 95%CI: 1.364-3.681, *P*<0.05) Risk factors. See Table 5 for details.

## Discussion

The baseline data collected in this study showed that the proportion of men smoking and drinking was higher, BMI, systolic blood pressure, diastolic blood pressure, GLU, Hcy, ALT, γ-GT, TBIL, TG, LDL-c, Urea, Cr, UA Both are higher than women, while TC and HDL-c are lower than women. This may be related to multiple factors such as genetics, lifestyle and eating habits. There is no significant difference in ALP between the two groups, which may be related to the average age of the subjects we included Too big related. Folic acid, vitamin B12, estrogen, etc. in the human body can promote the metabolism of Hcy. Generally, the concentration of Hcy in women is lower than that in men [11-14]. In this study, the average concentration of Hcy was 10.2 (8.3-12.8), and males were much higher than females. In addition,

smoking can indirectly lead to the reduction or lack of folic acid and vitamin B12 levels in the blood and affect the decomposition and metabolism of Hcy. This may also be the reason why the level of Hcy in men is higher than that in women.

Studies have found that Hcy is related to early renal damage [15]. High UA enhances oxidation, promotes lipid peroxidation through oxidative stress, and accelerates the production of oxygen free radicals and coronary artery The progression of the disease is related to cardiovascular and cerebrovascular diseases such as hypertension, coronary atherosclerosis, heart failure, and stroke. Many researchers regard UA as an independent risk factor for coronary heart disease. Therefore, in this study, we evaluated Cr and UA as basic data and found that Cr and UA in the high-Hcy group were significantly higher than those in the low-Hcy group. Univariate and multivariate analysis of Hcy normal group and abnormal group showed that Hcy was positively correlated with Cr and UA. In the follow-up study, we will follow up the study subjects to further clarify the relationship between Hcy and kidney injury and other related diseases.

TC, TG, HDL-c, LDL-c are involved in the metabolism of lipids and cholesterol in the blood, and are closely related to the occurrence and development of cardiovascular and cerebrovascular diseases. HDL-c is significantly different, which is consistent with related literature reports [16, 17]. High Hcy can damage blood vessel walls and affect lipid metabolism. In this study, both the univariate and multivariate linear regression model analysis results of Hcy in the normal group showed that Hcy was negatively correlated with HDL-c and positively correlated with TG; while in the high Hcy group, Hcy and HDL-c were still negatively correlated with TC. There is a negative correlation. The existing literature reports that high Hcy is negatively related to HDL-c, but the correlation between TC and TG is not consistent in the literature [18]. This may be related to the source of the research object, the geographical distribution, the degree of fasting before sample collection, the number of samples included in the study, and the factors used for correction in the multivariate analysis.

Hcy is a sulfur-containing amino acid produced during the metabolism of methionine in the body. Its main physiological function is to provide methyl groups for many important physiologically active substances such as DNA, protein and phospholipids in the body. Under normal circumstances, the production and metabolism of Hcy in the body maintain a dynamic balance [19], so that the concentration of Hcy in the blood is maintained at 5-15mmol/L. There are many factors that affect the level of Hcy. In addition, under certain pathological conditions, taking drugs that interfere with metabolism can affect the metabolism of Hcy. The superoxide and peroxide produced can cause vascular endothelial cell damage and vascular smooth muscle cell proliferation. The structural damage of the wall and the increase of lipid deposits in the blood vessel wall accelerate the process of atherosclerosis. Hcy can also destroy the normal coagulation mechanism, increase the chance of thrombosis, and easily increase the risk of arteriosclerotic diseases such as stroke, coronary heart disease, and peripheral vascular disease. Studies have pointed out that for every 5 μmol/L increase in blood Hcy, the risk of ischemic heart disease increases by 32%, and every 3 μmol/L decrease in Hcy, the risk of disease is reduced by 16% [20]. A large number of studies have shown that hyperHcyemia is closely related to the occurrence, development and

prognosis of a variety of cardiovascular and cerebrovascular diseases, hypertension, diabetes, and kidney diseases.

There are still some shortcomings in this study. For example, the fasting state of the study subjects may not be completely consistent, and the liver function is not judged in conjunction with imaging, so detailed evaluation was not performed.

# Conclusion

This study shows that Hcy may participate in or affect the metabolism of HDL-c, Cr, UA, etc. The content of Hcy should be paid attention to in clinical work to provide data support for clinical monitoring of cardiovascular and cerebrovascular diseases and renal function.

# Abbreviations

Hcy: Homocysteine; TC: Total cholesterol; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; γ-GT: γ-glutamyltransferase; TBIL: Total bilirubin; GLU: Blood glucose; Cr: Creatinine; UA: Uric acid; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

# Declarations


### Acknowledgements

The authors greatly appreciate Prof. Jing Xiao for assistant with statistical analysis.


### Authors' contributions

FB contributed to the conception and design of the study, and participated in the performance of the research, statistical data analysis and interpretation, and drafting and revision of the manuscript. MC participated in the design of the study, performance of the research, statistical data analysis. XS participated in the performance of the research. SJ participated in the performance of revision of the manuscript. HC participated in the performance of the research and revised the manuscript.


### Funding

No funding was obtained for this study.


### Availability of data and material

The datasets used and/or analyzed during the current study are de-identifed and available from the corresponding author on reasonable request. Identifying/confdential patient data should not be shared.

### Ethics approval and consent to participate

This research protocol was approved and exemption from informed consent by the Ethics Committee of Nantong University Affiliated Hospital.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

1 Department of Laboratory Medicine; 2 Department of Blood Transfusion, Affiliated Hospital of Nantong University, #20 Xisi Road, Nantong 226001, China

## References

1. Nam KW, Kwon HM, Jeong HY, et al. Serum homocysteine level is related to cerebral small vessel disease in a healthy population. Neurology. 2019, 92(4): e317-25.
2. Cianciolo G, De Pascalis A, Di Lullo L, et al. Folic acid and homocysteine in chronic kidney disease and cardiovascular disease progression: which comes first? Cardiorenal Med. 2017, 7(4): 255-66.
3. Multi-Disciplinary Expert Task Force on Hyperuricemia and its related disease. Chinese multi-disciplinary consensus on the diagnosis and treatment of hyperuricemia and its related disease. Chin J Intern Med. 2017, 56(3): 235-48.
4. Junren Zhu, Runlin Gao, Shuiping Zhao, et al. Guidelines for the prevention and treatment of dyslipidemia in adults in China (revised in 2016). Chinese Circulation Journal. 2016, 31(10): 937-52.
5. Chinese Diabetes Society. China □ guidelines for the prevention and treatment of type 2 diabetes. Chin J Diabetes Mellitus. 2018, 10(1): 4-64.
6. Dongfeng Gu. Guideline on the assessment and management of cardiovascular risk in China. Chinese Journal of Preventive Medicine. 2019, 53(1): 13-34.
7. Chuanchuan Li, Yan Zhang. Considerations on the international hypertension society 2020 International Hypertension Practice Guidelines and hypertension prevention and treatment strategies in China. Chinese Journal of Hypertension. 2020, 9: 815-817.
8. Health industry standard of the People's Republic of China. WS/T 404.1-2012. http://www.nhc.gov.cn/wjw/s9492/201301/9b2e494990ce4825a48b4b476f6f928b.shtml
9. Health industry standard of the People's Republic of China. WS/T 404.4-2018. http://www.nhc.gov.cn/wjw/s9492/201805/67aa364588f74ec69a1de85f893ed2c4.shtml
10. Health industry standard of the People's Republic of China. WS/T 404.5-2015. http://www.nhc.gov.cn/wjw/s9492/201504/b396412bcbd84e1ea2b7f9e0e131ae80.shtml

11. Xu R, Huang F, Wang Y, et al. Gender- and age-related differences in homocysteine concentration: a cross-sectional study of the general population of China. Sci Rep. 2020, 10(1): 17401.
12. Li X, Yuan J, Han J, et al. Serum levels of Homocysteine, Vitamin B12 and folate in patients with multiple sclerosis: an updated meta-analysis. Int J Med Sci. 2020, 17(6): 751-61.
13. Zhenfei Chen, Jing Zhang, Jun Feng, et al. Higher serum level of Cystatin C: An additional risk factor of CAD. Medicine (Baltimore). 2021, 100(2): e24269.
14. Mohetaboer Momin, Jia Jia, Fangfang Fan, et al. Relationship between plasma homocysteine level and lipid profiles in a community-based Chinese population. Lipids Health Dis. 2017, 16(1) : 54.
15. Dervisoglu E, Kozdag G, Etiler N, et al. Association of glomerular filtration rate and inflammation with left ventricular hypertrophy in chronic kidney disease patients. Hippokratia. 2012, 16(2): 137-42.
16. Mahalle N, Kulkarni MV, Garg MK, et al. Vitamin B12 deficiency and hyperhomocysteinemia as correlates of cardiovascular risk factors in Indian subjects with coronary Artery disease[J]. J Cardiol. 2013, 61(4): 289-94.
17. Momin M, Jia J, Fan F, et al. Relationship between plasma homocysteine level and lipid profiles in a community-based Chinese population[J]. Lipids Health Dis, 2017, 16(1): 54.
18. Namita Mahalle, Mohan V Kulkarni, Mahendra K Garg, et al. Vitamin B12 deficiency and hyperhomocysteinemia as correlates of cardiovascular risk factors in Indian subjects with coronary artery disease. J Cardiol. 2013, 61(4): 289-94.
19. Moein S, Vaghari-Tabari M, Qujeq D, et al. Association between serum folate with inflammatory markers, disease clinical activity and serum homocysteine in patients with inflammatory bowel disease. Does folate level have an effect on maintaining clinical remission? Acta Biomed. 2020, 91(4): e2020106.
20. Kimball SM, Mirhosseini N, Rankin BD, et al. Retrospective analysis of cardiovascular disease risk parameters in participants of a preventive health and wellness program. Integr Med (Encinitas). 2019, 18(3): 78-95.

# Tables

**Table 1 Distribution characteristics of the study population grouped by gender**

| | Total（n=8063） | Male（n=5478） | Female（n=2585） | *P* |
|---|---|---|---|---|
| Age (year-old), mean ± SD | 50.88 ± 11.92 | 49.98 ± 11.49 | 52.87 ± 12.59 | <0.0001 |
| BMI (kg/$m^2$), mean ± SD | 25.02 ± 3.39 | 25.54 ± 3.22 | 23.91 ± 3.48 | <0.0001 |
| SBP (mmHg), mean ± SD | 130.54 ± 18.85 | 131.49 ± 17.28 | 128.52 ± 21.68 | <0.0001 |
| DBP (mmHg), mean ± SD | 78.66 ± 11.96 | 81.13 ± 11.46 | 73.43 ± 11.30 | <0.0001 |
| Pulse (bpm), mean ± SD | 77.54 ± 11.31 | 76.77 ± 11.18 | 79.19 ± 11.42 | <0.0001 |
| Smoking status, N (%) | | | | <0.0010 |
| Current and former | 1312 (16.27 ) | 1312 (23.95) | 0 (0.00) | |
| never | 6751 (83.73) | 4166 (76.05) | 2585 (100) | |
| Alcohol dringking, N (%) | | | | <0.0010 |
| Current and former | 1930 (23.94) | 1928 (35.20) | 2 (0.08) | |
| never | 6133 (76.06) | 3550 (64.80) | 2583 (99.92) | |
| Hcy (μmol/L), M ( P25-P75) | 10.2 (8.3 - 12.8) | 10.9 (9 - 13.8) | 8.6 (7.1 - 10.7) | <0.0001 |
| ALT (U/L), M ( P25-P75) | 24 (18 - 34) | 26.5 (20 - 38) | 19 (15 - 26) | <0.0001 |
| ALP (U/L), M ( P25-P75) | 81 (67 - 96) | 81 (69 - 95) | 80 (65 - 98) | 0.0544 |
| γ-GT (U/L), M ( P25-P75) | 28 (19 - 45) | 33 (23 - 53) | 18 (14 - 27) | <0.0001 |
| TBIL (μmol/L), M ( P25-P75) | 13.7 (10.8 - 17.3) | 14.4 (11.6 - 18.1) | 12 (9.6 - 15.1) | <0.0001 |
| GLU (mmol/L), M ( P25-P75) | 5.3 (4.9 - 5.8) | 5.3 (5 - 5.8) | 5.2 (4.9 - 5.6) | <0.0001 |
| TC (mmol/L), M ( P25-P75) | 5.1 (4.5 - 5.8) | 5.1 (4.5 - 5.7) | 5.2 (4.6 - 5.8) | <0.0001 |
| TG (mmol/L), M ( P25-P75) | 1.4 (0.95 - 2.1) | 1.54 (1.05 - 2.32) | 1.14 (0. 81 - 1.67) | <0.0001 |
| HDL-c (mmol/L), M ( P25-P75) | 1.27 (1.09 - 1.49) | 1.2 (1.05 - 1.39) | 1.44 (1.24 - 1.67) | <0.0001 |
| LDL-c (mmol/L), M ( P25-P75) | 3.06 (2.54 - 3.57) | 3.07 (2.56 - 3.59) | 3.01 (2.51 - 3.53) | 0.0133 |
| Urea (mmol/L), M ( P25-P75) | 5.3 (4.5 - 6.1) | 5.4 (4.6 - 6.3) | 5 (4.1 - 5.9) | <0.0001 |
| Cr (μmol/L), M ( P25-P75) | 67 (57 - 76) | 72 (66 - 80) | 53 (48 - 59) | <0.0001 |
| UA (μmol/L), M ( P25-P75) | 332 (269 - 393) | 363 (313 - 416) | 256 (218 - 304) | <0.0001 |

## Table 2 Distribution characteristics of the study population grouped by Hcy

| | Low Hcy (n=6958) | High Hcy (n=1105) | *P* |
|---|---|---|---|
| Age (year-old), mean ± SD | 50.65 ± 11.73 | 52.37 ± 13.00 | <0.0001 |
| Sex, N□%□ | | | <0.0010 |
| Male | 4479 (64.37) | 999 (90.41) | |
| Female | 2479 (35.63) | 106 (9.59) | |
| Smoking status, N (%) | | | <0.0010 |
| Current and former | 1066 (15.32) | 246 (22.26) | |
| never | 5892 (84.68) | 859 (77.74) | |
| Alcohol dringking, N (%) | | | <0.0010 |
| Current and former | 1580 (22.71) | 350 (31.67) | |
| never | 5378 (77.29) | 755 (68.33) | |
| BMI (kg/m$^2$), mean ± SD | 24.94±3.38 | 25.51±3.47 | <0.0001 |
| SBP (mmHg), mean ± SD | 129.89±18.80 | 134.60±18.69 | <0.0001 |
| DBP (mmHg), mean ± SD | 78.18±11.88 | 81.67±12.06 | <0.0001 |
| Pulse (bpm), mean ± SD | 77.62±11.31 | 77.07±11.36 | 0.1305 |
| ALT (U/L), M $_{(P25\text{-}P75)}$ | 23 (17-34) | 26 (19-37) | <0.0001 |
| ALP (U/L), M $_{(P25\text{-}P75)}$ | 80 (67-96) | 83 (69-98) | 0.0015 |
| γ-GT (U/L), M $_{(P25\text{-}P75)}$ | 27 (18-43) | 33 (22-54) | <0.0001 |
| TBIL (μmol/L), M $_{(P25\text{-}P75)}$ | 13.5 (10.7-17) | 14.8 (11.9-18.5) | <0.0001 |
| GLU (mmol/L), M $_{(P25\text{-}P75)}$ | 5.3 (4.9-5.8) | 5.3 (4.9-5.8) | 0.5542 |
| TC (mmol/L), M $_{(P25\text{-}P75)}$ | 5.1 (4.5-5.8) | 5.1 (4.5-5.8) | 0.7745 |
| TG (mmol/L), M $_{(P25\text{-}P75)}$ | 1.38 (0.93-2.07) | 1.58 (1.09-2.42) | <0.0001 |
| HDL-c (mmol/L), M $_{(P25\text{-}P75)}$ | 1.28 (1.1-1.51) | 1.22 (1.07-1.38) | <0.0001 |
| LDL-c (mmol/L), M $_{(P25\text{-}P75)}$ | 3.06 (2.54-3.57) | 3.06 (2.52-3.58) | 0.3710 |
| Urea (mmol/L), M $_{(P25\text{-}P75)}$ | 5.2 (4.4-6.1) | 5.4 (4.6-6.3) | <0.0001 |
| Cr (μmol/L), M $_{(P25\text{-}P75)}$ | 66 (56-75) | 74 (66-82) | <0.0001 |
| UA (μmol/L), M $_{(P25\text{-}P75)}$ | 325 (263-387) | 365 (314-426) | <0.0001 |

Note: Define low Hcy group (Hcy≤15μmol/L) and high Hcy group (Hcy>15μmol/L)

**Table 3 The characteristics of the population in the high and low Hcy groups are stratified by gender**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Low Hcy (n=4479) | High Hcy (n=999) | *P* | Low Hcy (n=2479) | High Hcy (n=106) | *P* |
| Age (year-old), mean ± SD | 49.66 ± 11.16 | 51.37 ± 12.78 | <0.0001 | 52.42 ± 12.50 | 61.79 ± 11.25 | <0.0001 |
| BMI (kg/m$^2$), mean ± SD | 25.54 ± 3.21 | 25.55 ± 3.28 | 0.9411 | 23.86 ± 3.40 | 25.14 ± 4.88 | 0.0002 |
| SBP (mmHg), mean ± SD | 130.92 ± 16.97 | 134.05 ± 18.36 | <0.0001 | 128.04 ± 21.59 | 139.77 ± 21.00 | <0.0001 |
| DBP (mmHg), mean ± SD | 80.90 ± 11.34 | 82.16 ± 11.96 | 0.0017 | 73.27 ± 11.24 | 77.00 ± 12.03 | 0.0009 |
| Pulse (bpm), mean ± SD | 76.71 ± 11.13 | 77.04 ± 11.41 | 0.3948 | 79.27 ± 11.43 | 77.32 ± 11.00 | 0.0849 |
| ALT (U/L), M ( P25-P75) | 26 (20 - 38) | 27 (19 - 38) | 0. 9502 | 19 (15 - 26) | 20 (14 - 25) | 0.7152 |
| ALP (U/L), M ( P25-P75) | 80 (68 - 95) | 82 (69 - 97) | 0.0559 | 80 (64 - 97) | 86.5 (71 - 108) | 0.0010 |
| γ-GT (U/L), M ( P25-P75) | 33 (23 - 52) | 34 (23 - 56) | 0.0233 | 18 (14 - 27) | 20 (15 - 30) | 0.0581 |
| TBIL (μmol/L), M ( P25-P75) | 14.3 (11.5 - 18) | 15.1 (12.1- 18.8) | 0.0002 | 12 (9.6 - 15.1) | 12.6 (10.6 - 15. 5) | 0.0593 |
| GLU (mmol/L), M ( P25-P75) | 5.3 (5 - 5.9) | 5.2 (4.9 - 5.7) | 0.0002 | 5.2 (4.9 - 5.6) | 5.3 (4.9 - 6.2) | 0.0109 |
| TC (mmol/L), M ( P25-P75) | 5.1 (4.5 - 5.7) | 5.1 (4.5 - 5.8) | 0.6519 | 5.2 (4.6 - 5.8) | 5.3 (4.6 - 5.9) | 0.3945 |
| TG (mmol/L), M ( P25-P75) | 1.53 (1.03- 2.29) | 1.6 (1.11 - 2.48) | 0.0106 | 1.13 (0.8 - 1.66) | 1.36 (0.97 - 2) | 0.0027 |
| HDL-c (mmol/L), M ( P25-P75) | 1.2 (1.04 - 1.4) | 1.2 (1.06 - 1.37) | 0.7750 | 1.44 (1.24 - 1.67) | 1.37 (1.19 - 1.55) | 0.0046 |
| LDL-c (mmol/L), M ( P25-P75) | 3.08 (2.57 - 3.6) | 3.06 (2.52 - 3.58) | 0.1974 | 3.01 (2.51 - 3.53) | 2.99 (2.47 - 3.55) | 0.5935 |
| Urea (mmol/L), M ( P25-P75) | 5.4 (4.6 - 6.2) | 5.4 (4.6 - 6.3) | 0.2280 | 4.9 (4.1 - 5.8) | 5.3 (4.4 - 6.3) | 0.0057 |
| Cr (μmol/L), M ( P25-P75) | 72 (65 - 79) | 75 (68 - 83) | <0.0001 | 53 (48 - 59) | 57.5 (52 - 66) | <0.0001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| UA (μmol/L), M ( P25-P75) | 361 (312 - 413) | 370 (324 - 429) | <0.0001 | 255 (218 - 301) | 290 (235 - 377) | <0.0001 |

Note: Define low Hcy group (Hcy≤15μmol/L) and high Hcy group (Hcy15μmol/L)

**Table 4 Analysis of linear regression model of serum Hcy on each index**

| | Single factor analysis | | Multiple-factor analysis | |
|---|---|---|---|---|
| | B（SE） | *P* | B（SE) | *P* |
| LnTC | | | | |
| lnHcy | 0.005 (0.007) | 0.458 | 0.009 (0.007) | 0.216 |
| Hcy (vs. Hcy≤15μmol/L) | -0.032 (0.016) | 0.046 | -0.036 (0.016) | 0.027 |
| LnTG | | | | |
| lnHcy | 0.212 (0.022) | <0.001 | 0.080 (0.021) | <0.001 |
| Hcy (vs. Hcy≤15μmol/L) | 0.090 (0.049) | 0.068 | 0.047 (0.047) | 0.324 |
| LnHDL-c | | | | |
| lnHcy | -0.087 (0.009) | <0.001 | -0.021 (0.008) | 0.011 |
| Hcy (vs. Hcy≤15μmol/L) | -0.060 (0.017) | 0.001 | -0.038 (0.016) | 0.019 |
| LnLDL-c | | | | |
| lnHcy | -0.004 (0.010) | 0.661 | -0.014 (0.010) | 0.169 |
| Hcy (vs. Hcy≤15μmol/L) | -0.021 (0.023) | 0.365 | -0.034 (0.023) | 0.140 |
| LnALT | | | | |
| lnHcy | 0.079 (0.019) | <0.001 | -0.053 (0.018) | 0.003 |
| Hcy (vs. Hcy≤15μmol/L) | 0.037 (0.043) | 0.389 | -0.020 (0.041) | 0.621 |
| LnALP | | | | |
| lnHcy | 0.037 (0.010) | <0.001 | 0.008 (0.011) | 0.401 |
| Hcy (vs. Hcy≤15μmol/L) | 0.062 (0.022) | 0.004 | 0.068 (0.022) | 0.002 |
| Lnγ-GT | | | | |
| lnHcy | 0.206 (0.025) | <0.001 | -0.031 (0.023) | 0.168 |
| Hcy (vs. Hcy≤15μmol/L) | 0.072 (0.057) | 0.210 | 0.036 (0.054) | 0.503 |
| LnTBIL | | | | |
| lnHcy | 0.122 (0.013) | <0.001 | 0.054 (0.014) | <0.001 |
| Hcy (vs. Hcy≤15μmol/L) | 0.014 (0.030) | 0.633 | 0.020 (0.030) | 0.506 |
| LnUrea | | | | |
| lnHcy | 0.070 (0.009) | <0.001 | 0.017 (0.009) | 0.058 |
| Hcy (vs. Hcy≤15μmol/L) | -0.045 (0.021) | 0.034 | -0.030 (0.021) | 0.159 |

| | | | | |
|---|---|---|---|---|
| lnCr | | | | |
| lnHcy | 0.177 (0.008) | <0.001 | 0.065 (0.006) | <0.001 |
| Hcy (vs. Hcy≤15μmol/L) | 0.065 (0.016) | <0.001 | 0.055 (0.016) | <0.001 |
| lnUA | | | | |
| lnHcy | 0.196 (0.010) | <0.001 | 0.069 (0.009) | <0.001 |
| Hcy (vs. Hcy≤15μmol/L) | 0.062 (0.020) | 0.002 | 0.043 (0.019) | 0.022 |

Note: Multivariate analysis adjusted for age, gender, smoking, drinking, and BMI. LnHcy is the logarithm of Hcy, which is a continuous variable, Hcy is a binary variable, vs. refers to the comparison group, high Hcy>15μmol/L vs. low Hcy≤15μmol/L.

**Table 5 Logistic regression model analysis of serum Hcy on each index**

| | Single factor analysis | | Multiple-factor analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* |
| TG<1.7 mmol/L | | | | |
| lnHcy | 1.870 (1.581 - 2.212)▯ | <0.001 | 1.281 (1.078 - 1.523) | 0.005 |
| Hcy (vs. Hcy≤15μmol/L) | 1.285 (0.928 - 1.780) | 0.131 | 1.116 (0.791 - 1.573)▯ | 0.533 |
| TC<5.2 mmol/L | | | | |
| lnHcy | 1.054 (0.911 - 1.219) | 0.479 | 1.083 (0.929 - 1.263)▯ | 0.307 |
| Hcy (vs. Hcy≤15μmol/L) | 0.795 (0.573 - 1.104)▯ | 0.171 | 0.743 (0.531 - 1.041) | 0.084 |
| HDL-C>1.0 mmol/L | | | | |
| lnHcy | 1.803 (1.404 - 2.316)▯ | <0.001 | 1.065 (0.835 - 1.359) | 0.613 |
| Hcy (vs. Hcy≤15μmol/L) | 1.772 (1.184 - 2.653)▯ | 0.005 | 1.558 (1.017 - 2.386) | 0.042 |
| LDL-c<3.4 mmol/L | | | | |
| lnHcy | 0.905 (0.776 - 1.055)▯ | 0.201 | 0.820 (0.699 - 0.962) | 0.015 |
| Hcy (vs. Hcy≤15μmol/L) | 0.859 (0.603 - 1.225)▯ | 0.401 | 0.819 (0.570 - 1.177) | 0.280 |
| γ-GT (10-60U/L (7-45U/L)) | | | | |
| lnHcy | 1.270 (1.028 - 1.569)▯ | 0.027 | 0.902 (0.729 - 1.116) | 0.343 |
| Hcy (vs. Hcy≤15μmol/L) | 1.186 (0.808 - 1.740)▯ | 0.384 | 1.108 (0.744 - 1.649) | 0.615 |
| ALT (9-50U/L (7-40U/L)) | | | | |
| lnHcy | 0.899 (0.720 - 1.123)▯ | 0.348 | 0.791 (0.627 - 0.998) | 0.048 |
| Hcy (vs. Hcy≤15μmol/L)▯▯ | 1.411 (0.880 - 2.260)▯ | 0.153 | 1.175 (0.717 - 1.924) | 0.522 |
| ALP (45-125U/L (35-100U/L)) | | | | |
| lnHcy | 0.692 (0.531 - 0.900)▯ | 0.006 | 0.726 (0.550 - 0.958) | 0.024 |
| Hcy (vs. Hcy≤15μmol/L) | 1.940 (1.093 - | 0.024 | 1.992 (1.111 - | 0.021 |

| | | | | |
|---|---|---|---|---|
| | 3.444)▯ | | 3.571) | |
| TBIL≤23μmol/L | | | | |
| lnHcy | 2.456 (1.741 - 3.464)▯ | <0.001 | 1.707 (1.205 - 2.418) | 0.003 |
| Hcy (vs. Hcy≤15μmol/L) | 1.211 (0.736 - 1.993)▯ | 0.452 | 1.241 (0.750 - 2.055) | 0.401 |
| Urea (3.1-8.8mmol/L) | | | | |
| lnHcy | 1.181 (0.767 - 1.817)▯ | 0.450 | 1.046 (0.675 - 1.623) | 0.839 |
| Hcy (vs. Hcy≤15μmol/L) | 0.817 (0.367 - 1.818)▯ | 0.620 | 0.963 (0.433 - 2.145) | 0.927 |
| UA (UA≤420 umol/L(UA≤360umol/L)) | | | | |
| lnHcy | 3.106 (2.439 - 3.956)▯ | <0.001 | 2.008 (1.565 - 2.575) | <0.001 |
| Hcy (vs. Hcy≤15μmol/L) | 1.485 (1.052 - 2.096)▯ | 0.024 | 1.487 (1.037 - 2.131) | 0.031 |
| Cr (57-97μmol/L (41-73μmol/L)) | | | | |
| lnHcy | 0.737 (0.565 - 0.960)▯ | 0.023 | 0.663 (0.508 - 0.866) | 0.003 |
| Hcy (vs. Hcy≤15μmol/L) | 2.068 (1.271 - 3.366)▯ | 0.003 | 2.241 (1.364 - 3.681) | 0.001 |

Note: Multivariate analysis adjusted for age, gender, smoking, drinking, and BMI. LnHcy is the logarithm of Hcy, which is a continuous variable, Hcy is a binary variable, vs. refers to the comparison group, high Hcy>15μmol/L vs. low Hcy≤15μmol/L. The normal reference value ranges of TBIL, Urea, ALP and Cr are indicated by brackets. If there are double brackets, the outer brackets indicate the normal reference value range for men, and the inner brackets indicate the normal reference value range for women. The normal range of Cr and Urea in parentheses indicates the 20-59 years old population, the 60-79 years old population Cr normal range is (57-111μmol/L (41-81μmol/L)); the 60-79 year old population Urea's normal range is ( 3.6-9.5mmol/L (3.1-8.8mmol/L))