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Analysis of the Impact of Cardiovascular Risk Factors on Carotid Intima-Media Thickness Progression: Postprint

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Abstract

Background Carotid intima-media thickening is a surrogate marker for atherosclerosis, and its prevention is beneficial for the primary prevention of atherosclerosis. The contribution degree of related risk factors to carotid intima-media thickening remains unclear. Objective To analyze the controllable influencing factors of carotid intima-media thickening in the general population (community residents without major diseases) and to conduct dominance analysis on each related controllable influencing factor to obtain the corresponding contribution ranking, thereby providing a reference basis for determining the focus of early prevention and control of cardiovascular diseases. Methods From 2019 to 2021, study subjects were recruited in Liuzhou City, Guangxi Zhuang Autonomous Region, with a total of 738 participants enrolled. Relevant information was collected through questionnaires and physical examinations. Fasting blood and urine samples were collected to detect various biochemical indicators. Carotid intima-media thickness (CIMT) was measured using a color Doppler ultrasound diagnostic instrument. Adaptive Lasso logit was used for variable screening, logistic regression models were constructed to analyze controllable influencing factors related to CIMT changes, and dominance analysis was employed to obtain the contribution ranking of each controllable influencing factor. Adaptive Lasso linear was used for variable screening to construct linear regression for sensitivity analysis. Results After adjusting for age, sex, and common carotid artery internal diameter, multivariate logistic regression showed that high systolic blood pressure (SBP), high total cholesterol (TC), high physical activity level, and high C-reactive protein (CRP) were risk factors for carotid intima-media thickening. The contribution ranking of controllable influencing factors from high to low was SBP (63.7%), CRP (16.1%), TC (12.4%), and physical activity level (7.8%). Sensitivity analysis indicated that the research results were relatively robust. Conclusion The contribution ranking of controllable risk factors differs in CIMT progression:

SBP > CRP > TC > physical activity level, suggesting that early prevention and control measures for cardiovascular diseases should be formulated more targetedly according to each controllable influencing factor and its contribution ranking.

Full Text

Analysis of the Effects of Cardiovascular Risk Factors on Carotid Intima-Media Thickness Progression

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Abstract

Background: Carotid intima-media thickening serves as a surrogate indicator of atherosclerosis, and its prevention is conducive to the primary prevention of atherosclerotic disease. However, the relative contribution of associated risk factors to carotid intima-media thickening remains unclear.

Objective: To analyze the controllable influencing factors for carotid intima-media thickening in a general population (community residents without major diseases) and to determine their contribution rank through dominance analysis, thereby providing evidence for prioritizing early prevention and control strategies for cardiovascular disease.

Methods: A total of 738 participants were recruited in Liuzhou, Guangxi Zhuang Autonomous Region from 2019 to 2021. Relevant information was collected through questionnaires and physical examinations. Fasting blood and urine samples were collected to measure biochemical indicators. Carotid intima-media thickness (CIMT) was measured using color Doppler ultrasonography. Adaptive Lasso logit regression was employed for variable screening, followed by logistic regression modeling to analyze controllable factors associated with CIMT changes. Dominance analysis was used to obtain the contribution rank of each controllable factor. Adaptive Lasso linear regression was performed for variable screening to construct a linear regression model for sensitivity analysis.

Results: After adjusting for age, sex, and common carotid artery internal diameter, multivariate logistic regression revealed that elevated systolic blood pressure (SBP), total cholesterol (TC), physical activity level, and C-reactive protein (CRP) were risk factors for carotid intima-media thickening. The contribution rank of controllable factors from highest to lowest was SBP (63.7%), CRP (16.1%), TC (12.4%), and physical activity level (7.8%). Sensitivity analysis demonstrated that the results were robust.

Conclusion: The contribution rank of controllable risk factors to CIMT progression differs, following the order SBP > CRP > TC > physical activity level. This suggests that more targeted early prevention and control measures for cardiovascular disease should be developed according to the specific contribution rank of each controllable factor.

Keywords: Carotid intima-media thickness; Atherosclerosis; Risk factors; Dominance analysis; Primary prevention

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death. The *China Cardiovascular Disease Report* [1] indicates that CVD ranks first among causes of death in both urban and rural residents, with an estimated 290 million current patients, a number expected to increase further over time. The primary pathogenic mechanism of CVD involves atherosclerosis, stenosis, and occlusion of supplying blood vessels, leading to impaired vascular structure and function. As the disease progresses, plaque detachment and rupture can trigger adverse vascular events. As the main cause of CVD, atherosclerosis (AS) first affects the arterial intima, particularly in large and medium-sized arteries [2]. Studies have shown that carotid intima-media thickness (CIMT) can serve as a surrogate indicator of subclinical atherosclerosis, reflecting AS to some extent [3]. CIMT thickening precedes atherosclerotic plaque formation, and targeted interventions against cardiovascular risk factors can effectively reverse CIMT thickening [4,5,6]. Previous research has primarily focused on identifying risk factors, but the relative contribution of each factor to CIMT thickening remains unclear, which hinders primary prevention of CVD. Therefore, this study aims to clarify the contribution rank of different risk factors to CIMT thickening, providing evidence for early precision prevention and control of CVD.

1.1 Study Participants

From 2019 to 2021, 852 local residents were recruited from several townships in Guangxi using convenience sampling. Inclusion criteria were: (1) local residents aged 20-74 years; (2) fasting for at least 8 hours; (3) residing locally for the past year at the time of examination and agreeing to participate. Exclusion criteria included: (1) patients with major diseases including malignant tumors, paralysis, psychiatric disorders, or severe infectious diseases; (2) patients diagnosed with coronary heart disease, stroke, or peripheral arterial disease; (3) those taking lipid-lowering or vasodilator medications within the past 3 days; (4) pregnant or lactating women; (5) those with missing relevant data. Based on these criteria, 738 participants were ultimately included. This study was approved by the Ethics Committee of Guangxi Medical University [NO. 伦审【科】(2019-SB-094)], and all participants provided informed consent.

The participant screening flowchart is shown in [Figure 1: see original paper].

Figure 1 Flow chart of the study subjects screening

1.2.1 Survey Methods

This cross-sectional study employed on-site questionnaires, physical examinations, and laboratory testing. Baseline data collected through questionnaires included sex, age, smoking history, alcohol consumption history, current diseases, and medication use. Physical examinations included height, weight, and blood pressure measurements. Biochemical indicators from serum and urine samples included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose (GLU), C-reactive protein (CRP), apolipoprotein A (ApoA), apolipoprotein B (ApoB), lipoprotein(a) (LPA), aspartate transaminase (AST), alanine transaminase (ALT), microalbuminuria (ALB), and urine creatinine (UCR). These indicators were measured using Hitachi 7600-120 and 7600-020 automatic biochemical analyzers (Japan) with reagent kits from Shanghai Zhicheng Biological Technology Co., Ltd., performed by the Clinical Laboratory of the First Affiliated Hospital of Guangxi Medical University. ELISA was used to measure intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) using a Thermo Fisher Scientific FI-01620 microplate reader (USA) with reagent kits from Wuhan Huamei Biological Engineering Co., Ltd.

1.2.2 Carotid Intima-Media Thickness Measurement

CIMT was defined as the vertical distance from the intimal inner surface to the interface between the media and adventitia. Color Doppler ultrasonography (Mindray DC-33) with a 10 MHz probe was used to examine bilateral carotid arteries. Participants were placed in supine position with the head turned to the opposite side during examination to fully expose neck vessels. The common carotid artery, carotid bifurcation, and internal carotid artery were scanned sequentially. CIMT was measured at the distal common carotid artery, 1 cm from the bifurcation, at end-diastole on both sides (avoiding plaques if present), and the average value was calculated. CIMT < 1 mm was defined as normal, and CIMT ≥ 1 mm as thickened [7].

1.3 Definitions of Relevant Factors

Smoking: Never smoking was defined as <100 cigarettes in lifetime; former smoking as $ $100 cigarettes but none in the 30 days before survey; current smoking as $ $100 cigarettes and smoking within 30 days before survey [8]. **Alcohol consumption:** Never drinking was defined as <12 standard drinking units; former drinking as $ $12 units but <1 unit in the past year; current drinking as $ $12 units and $ $1 unit in the past year [9]. One standard unit was defined as 10 g of pure alcohol according to WHO recommendations. **Renal function:** Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [10], with eGFR \$ $90ml \cdot min^{\{-1\}\cdot(1.73m}$\{2\})^\{-1\}\$ defined as normal renal function. **Physical activity level** was calculated using the International Physical Activity Questionnaire (short form) [11] and expressed as metabolic equivalent (MET-min/week). **Overweight/obesity** was defined as BMI \$ $24kg/m$^\{2\}\$. **Diabetes** was defined as fasting glucose $ $7.0 mmol/L, current insulin or oral hypoglycemic medication use, or self-reported medical diagnosis. **Dyslipidemia** was defined as meeting any of the following: TC $ $200 mg/dL, HDL-C <40 mg/dL, LDL-C $ $130 mg/dL, TG $ $150 mg/dL, or current lipid-lowering medication use. **Metabolic syndrome** was defined according to the International Diabetes Federation criteria [12]. **Family history of disease** was defined as at least one first-degree relative (father, mother, sibling, son, or daughter) having the disease.

1.4 Lasso Regression Variable Selection

After fixing age and sex, potential influencing factors were selected based on literature reports. Variables included common carotid artery internal diameter, education level, waist circumference, overweight/obesity, physical activity level, TC, HDL-C, LDL-C, TG, CRP, GLU, ApoA/ApoB ratio, lipoprotein(a), ALT, AST, ALT/AST ratio, AST/ALT ratio, ICAM-1, VCAM-1, ALB, ACR, renal function, heart rate, SBP, DBP, smoking, alcohol consumption, dyslipidemia, diabetes, metabolic syndrome, family history of diabetes, family history of hypertension, and family history of coronary heart disease, totaling 39 variables after generating dummy variables. The optimal λ was determined using the adaptive method in Lasso regression.

1.5 Statistical Methods

Statistical analysis was performed using Stata 17. Continuous variables were expressed as mean ± standard deviation (±s) and compared between groups using Student' s t-test. Skewed data were expressed as median (25th percentile, 75th percentile) [M(p25, p75)] and compared using Mann-Whitney U test. Categorical variables were expressed as percentages (%) and compared using ^{2} test.

Logistic regression models were constructed with carotid intima-media thickening (normal/thickened) as the dependent variable, using Adaptive Lasso logit for variable screening to analyze controllable influencing factors. Dominance analysis [13] was then applied to estimate the contribution rank of each controllable factor. Sensitivity analysis was conducted using multivariate linear regression with natural log-transformed CIMT as the dependent variable, with variables selected via Adaptive Lasso linear regression. P<0.05 was considered statistically significant.

Results

2.1 Basic Characteristics of Study Participants

This study included 738 participants, with 45 in the CIMT thickening group (22 males, 48.9%) with a mean age of 63.5$±7.6*years*, *and*693*inthenormalCIMTgroup*(202*males*, 29.1±$10.2 years. The thickening group had significantly higher SBP, DBP, smoking proportion, common carotid artery internal diameter, TC, ACR, lipoprotein(a), VCAM-1, CRP, ALB, and physical activity level compared to the normal group (P<0.05).

Table 1 Baseline characteristics of the study subjects

[Note: The table content appears incomplete and fragmented in the original text. The translation would preserve the structure but the data appears to be missing or corrupted.]

Table note: SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides, TC=total cholesterol, ACR=urine albumin/creatinine ratio, eGFR=estimated glomerular filtration rate, ICAM-1=intercellular adhesion molecule-1, VCAM-1=vascular cell adhesion molecule-1, CRP=C-reactive protein, ALB=urine albumin, GLU=fasting blood glucose, ALT=alanine transaminase, AST=aspartate transaminase, PHYMET=physical activity level

2.2 Lasso Regression Variable Selection Results

In Lasso logit regression with carotid intima-media thickening as the dependent variable, coefficients for some variables were compressed to zero as the penalty coefficient λ increased. Eleven variables remained after compression: common carotid artery internal diameter, SBP, TC, overweight/obesity, urine albumin/creatinine ratio, physical activity level, CRP, lipoprotein(a), renal function decline, VCAM-1, and ApoA/ApoB ratio, with optimal λ=0.003. The coefficient path for each variable is shown in [Figure 2: see original paper]A. In Lasso linear regression with natural log-transformed CIMT as the dependent variable, optimal λ=0.002 retained 12 variables: common carotid artery internal diameter, SBP, TC, physical activity level, urine albumin/creatinine ratio, smoking, alcohol consumption, CRP, lipoprotein(a), ApoA/ApoB ratio, fasting glucose, and family history of diabetes. The coefficient path is shown in Figure 2B.

Figure 2 Lasso coefficient profile

2.3 Multivariate Logistic Regression and Dominance Analysis Results

After adjusting for age, sex, and common carotid artery internal diameter, multivariate logistic regression showed that elevated SBP, TC, physical activity level, and CRP were controllable risk factors for carotid intima-media thickening. Dominance analysis revealed the contribution rank of relevant variables from highest to lowest as: SBP (63.7%), CRP (16.1%), TC (12.4%), and physical activity level (7.8%), as shown in .

Table 2 Results of the related factors analysis and the dominance analysis in carotid intima-media thickness

[Note: The table appears incomplete in the original text. The translation would include the variables mentioned: SBP, TC, physical activity level, and CRP with their respective odds ratios and dominance weights.]

Table note: a indicates adjustment for age, sex, and common carotid artery internal diameter; b indicates per 10-unit increase; c indicates per 40-unit increase.

2.4 Sensitivity Analysis

Sensitivity analysis using multivariate linear regression showed that elevated SBP, TC, physical activity level, and current smoking were positively associated with carotid intima-media thickness. In the linear regression model, the contribution rank of included risk factors was: SBP (68.7%), smoking (19.9%), TC (8.8%), and physical activity level (2.6%), as shown in .

Table 3 Results of the sensitivity analysis based on the multivariate linear regression

[Note: The table appears incomplete in the original text. The translation would include the mentioned variables with their regression coefficients and dominance weights.]

Table note: a indicates adjustment for age, sex, and common carotid artery internal diameter; b indicates per 10-unit increase; c indicates per 40-unit increase.

Discussion

Atherosclerosis results from the combined effects of multiple cardiovascular risk factors that synergistically promote its development [14]. CIMT, as an early stage of AS, is first affected by cardiovascular risk factors. This study first analyzed controllable risk factors based on literature-defined categories of carotid intima-media thickening, then conducted sensitivity analysis using objectively measured, log-transformed CIMT as the dependent variable in linear regression. The results indicate that in the analysis using literature-defined categories, SBP, TC, physical activity level, and CRP are controllable risk factors for carotid intima-media thickening. Excluding inherent factors, the contribution rank of controllable risk factors from highest to lowest was SBP, CRP, TC, and physical activity level.

Hypertension is a well-known controllable risk factor for CVD, influenced by genetics, dietary habits, and environmental factors. Our study demonstrates that elevated SBP is significantly associated with carotid intima-media thickening. Previous research has shown that hypertensive patients have 1.55 times higher risk of carotid intima-media thickening [OR=1.55, 95%CI (1.03, 2.34)] [15]. Kiechl et al. [16] found that both SBP and arterial hypertension were positively associated with CIMT progression in adolescents, suggesting that the impact of hypertension on carotid intima-media thickness begins early in life and that early blood pressure management may delay CIMT progression. These findings support our results. Elevated SBP may cause carotid intima-media thickening by altering blood flow shear stress, enhancing oxidative stress, damaging the endothelial lining, and causing persistent endothelial injury with loss of vasoconstrictive function [17]. Notably, hypertension is the greatest risk factor for CVD [18]. Our study shows that, independent of inherent factors like age, dominance analysis revealed that SBP' s contribution proportion to carotid intima-media thickening far exceeds other controllable risk factors, suggesting that early prevention and control of carotid intima-media thickening in the general population should prioritize controlling elevated SBP.

Inflammation permeates the entire atherosclerotic process, and persistent inflammation is one cause of vascular endothelial cell injury. Previous studies have shown that inflammation can cause atherosclerosis even in the absence of classical cardiovascular risk factors [19]. High levels of inflammation may lead to excessive endothelial permeability, indicating loss of endothelial barrier integrity. Damaged endothelial cells further express adhesion molecules and chemokines, causing rolling leukocytes to adhere and enter the vascular wall, promoting vascular wall inflammation [20]. This study demonstrates that CRP' s contribution rank in CIMT progression is second only to SBP, indicating that early prevention and control of inflammation should not be overlooked.

Elevated TC is closely associated with CVD, with studies reporting a linear relationship between increasing TC and CVD mortality [21]. Azemi et al. [22] found that atherosclerotic model rats with higher TC levels had greater CIMT. Population data also show an association between TC levels and CIMT [23]. Our study shows that elevated TC promotes CIMT thickening, with dominance analysis indicating TC' s contribution rank is lower than SBP and CRP but higher than physical activity level.

The relationship between physical activity level and cardiovascular disease remains controversial. Previous studies have shown that moderate or high physical activity levels are associated with lower CVD risk compared to low activity levels [24]. Franklin et al. [25] reported a U-shaped or J-shaped dose-response relationship between exercise and adverse cardiovascular events. One possible reason for discrepancies among studies is that the high physical activity level group may have activity levels far exceeding the classification criteria. Our results show that increased physical activity level promotes CIMT progression, possibly because our participants were from economically disadvantaged townships where long-term high-intensity labor may cause compensatory structural changes in blood vessels.

Sensitivity analysis results were largely consistent with the main findings, but differed for CRP and smoking, with smoking ranking second in the sensitivity analysis versus CRP ranking second in the main analysis. This discrepancy may occur because the contribution rank in dominance analysis is relative and depends on the included factors. In this study, CRP and smoking were not simultaneously included in the dominance analysis, preventing direct comparison of their contributions. The contribution ranks for SBP, TC, and physical activity level were consistent between main and sensitivity analyses.

This study has several limitations. As a cross-sectional study, it cannot establish temporal relationships between exposure and outcome. With only one CIMT measurement, misclassification may occur. Additionally, participants were primarily from township areas, which may limit generalizability of the findings.

In summary, CIMT serves as an excellent surrogate endpoint for subclinical atherosclerosis that can predict adverse cardiovascular events. Preventing carotid intima-media thickening can reduce cardiovascular disease risk. The contribution rank of controllable risk factors differs in CIMT progression. Developing more targeted early prevention and control measures for cardiovascular disease based on this contribution rank can help precisionize interventions and facilitate rational allocation of medical resources.

Author Contributions

Chen Runlin, He Tufeng, Tao Lijun, Qin Lingqiao, Zhang Dacheng, Zhang Yifan, Zhao Min, and Zhang Dacheng conducted the study implementation, data collection, and data organization. Chen Runlin performed statistical analysis, results interpretation, and manuscript writing. Chen Runlin and Zhong Qiuan revised the manuscript. Zhong Qiuan conceived and designed the study, conducted feasibility analysis, and was responsible for quality control and final approval.

Conflicts of Interest

The authors declare no conflicts of interest.

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