Prevalence of Subclinical Carotid Atherosclerosis and Associated Risk Factors in Individuals Without Cardiovascular Risk Factors: Insights from General Population

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Abstract

Objective: Individuals without conventional cardiovascular risks (CVRFs) still have the risk of adverse outcomes, and subclinical carotid atherosclerosis is a known predictor of cardiovascular events. We aimed to assess the prevalence and associated risk factors of subclinical carotid atherosclerosis in CVRF-free population.

Methods: The cross-sectional study was conducted in rural northeast China in 2017-2018. CVRFs freedom was defined as untreated blood pressure < 140/90 mmHg, fasting plasma glucose < 7.0 mmol/L, untreated total cholesterol < 6.22 mmol/L, low-density lipoprotein cholesterol < 4.14 mmol/L, high-density lipoprotein cholesterol (HDL-C) ≥ 1.04 mmol/L, and no current smoking. This subgroup population included 1449 individuals, and ultrasound was used to detect carotid atherosclerosis.

Results: The mean carotid intima-media thickness is 0.74 ± 0.14 mm. The prevalence of carotid plaque is 23.4% (95%CI: 21.2%-25.6%) among CVRFs-free population, significantly higher in men than in women (37.1% vs 20.0%, p<0.001), and rises steeply with advancing age. 1.31% have moderate-to-severe carotid stenosis. Advancing age, man, glycosylated hemoglobin (OR, 1.90; 95% CI, 1.20-1.32), HDL-C level (OR, 2.31; 95% CI, 1.75-3.04), and pulse pressure (OR, 1.03; 95% CI, 1.01-1.05) are potentially related to presence of carotid atherosclerosis. Adjusted-dose-response association shows a linear relationship between HDL-C and prevalence of carotid atherosclerosis.

Conclusions: The prevalence of subclinical carotid atherosclerosis in CVRF-free population was relatively high, indicating poorly defined factors might contribute to the early atherogenesis. Moreover, we observed a paradoxical response between subclinical carotid atherosclerosis and HDL-C levels, suggesting that treatment targeting to increase HDL-C levels might not reduce future cardiovascular risks.

Background

Asymptomatic individuals without traditional cardiovascular risk factors (CVRFs) are considered to have low risk of cardiovascular events, and preventive strategies in healthy individuals without conventional cardiovascular risk factors are usually not recommended according to current preventive guideline.[1] However, previous studies consistently reported that nearly half individuals were reclassified as intermediate or high risk according to subclinical atherosclerosis detection.[2, 3] Individuals with unrecognized atherosclerosis continue to occur cardiovascular events, especially in young adults and women, because they were misclassified into low-risk population by conventional risk factors, and not receiving risk-reducing preventive therapies.[2, 4]

Moreover, high incidence of mortality in asymptomatic individuals free of CVRFs was confirmed previously. [5, 6] The CAFES-CAVE study showed that in asymptomatic individuals without CVRFs, the annual events rate was up to 3%-5%, on the contrary, the annual events rate was only 0.1% in the population without plaque.[5, 6] The mismatch between low conventional CVRFs, the presence of subclinical atherosclerosis and future cardiovascular events, further warranted subclinical atherosclerosis detection in a population absent from conventional CVRFs.[7]

Carotid ultrasound is a non-invasive and effective imaging for modality of assessing subclinical atherosclerosis.[8] However, current statements recommended against screening for asymptomatic carotid artery stenosis in general population in view to offer carotid surgery, they failed to address asymptomatic carotid atherosclerosis as a marker of cardiovascular adverse outcomes.[9, 10] Early detection of the underlying atherosclerosis before symptoms manifestation could improve risk stratification and provide a great opportunity to reduce future cardiovascular risks, in light of many effective nonpharmacologic and pharmacologic interventions.[2] Therefore, in the present study, we aimed to determine the prevalence of subclinical carotid atherosclerosis and potential related risk factors in the population free of major CVRFs, and to provide reliable data for formulating effective strategies to reduce cardiovascular risks in those individuals.

Methods

This present study derived from a cross-sectional survey conducted in rural areas of northeast China from September 2017 to May 2018. A multi-stage, geologically stratified and cluster random sampling method was employed to ensure the samples were representative. A total of 13 villages were randomly selected from 2 counties (Chaoyang and Lingyuan) of Liaoning province. All permanent residents aged more than 40 years old (n=6830) were recognized as eligible participants. Participants with pregnancy, cancer or mental disorders were excluded from the study. We finally enrolled 5838 (response rate: 85.5%) individuals into further analyses. The study protocol was approved by the central ethics committee of China National Center for Cardiovascular Disease. Written consents were obtained from all subjects. If the subjects were disabled, their proxies provided written informed consents for them.

The methods of data collection have been described previously.[11] According to Adult Treatment Panel III CVRF definitions,[12] CVRF-free population was defined as follows: (1) no current smoking, (2) untreated systolic blood pressure (SBP) < 140 mm Hg and diastolic blood pressure < 90mmHg, (3) untreated fasting plasma glucose (FPG) < 7.0 mmol/L (126 mg/dl), (4) untreated total cholesterol (TC) < 6.22 mmol/L (240 mg/dl), low-density lipoprotein cholesterol (LDL-C) < 4.14 mmol/L (160 mg/dl), and high-density lipoprotein cholesterol (HDL-C) ≥ 1.04 mmol/L (40 mg/dl).[7] This subgroup population included 1449 (24.8%) individuals without CVRFs (Figure 1).

Ultrasound Protocol

All scans were performed using a high-resolution B-mode ultrasonography (Mindray M7, Shenzhen, China) with a broadband 7L4S linear array transducer. Carotid ultrasound was performed by a certified sonographer with >3 years of experience in vascular ultrasound imaging. All subjects were examined in prone position with both left and right carotids scanned. A transverse scan starting at the clavicle and moving cranially up to the mandible was performed for orientation firstly, thereby longitudinal images of carotid artery as well as plaque was obtained subsequently.

Plaque was displayed both in short-axis view and long-axis sweep, color and pulsed Doppler imaging were obtained if necessary. The highest peak systolic and end-diastolic velocity measurements from the common carotid artery and the internal carotid artery were obtained to confirm the degree of carotid stenosis.[13] The Doppler velocity thresholds were used to determine the degree of stenosis according to the criteria that were previously described. Moderate carotid stenosis was defined as the degree of carotid artery stenosis between 50%- 69%, and severe carotid stenosis was defined as the degree of carotid stenosis ≥ 70%.[13, 14]

Carotid atherosclerosis was defined as mean carotid intima-media thickness (CIMT) ≥ 1.0mm and/or presence of carotid plaque. [13, 15] For each participant, CIMT was measured within a region free of plaque from a common carotid artery video acquisition according to Mannheim consensus. [15] 3 mean CIMT measurements were taken on each artery (left/right side), and CIMT measurements from both sides were averaged to create mean CIMT. The presence of plaques was assessed in the common carotid artery, bulb, and internal carotid artery segments, defined as a focal thickness of CIMT ≥ 1.5mm, or focal intraluminal protrusion >50% of the surrounding CIMT according to Mannheim carotid intima-media thickness and plaque consensus.[15]

Statistical Analysis

Descriptive statistics were calculated for all variables. Continuous variables with normal distribution are reported as means and standard deviations. Otherwise, continuous variables are reported as medians and interquartile ranges. Differences between groups were compared using a c^2 test for categorical variables. Univariate and stepwise multivariate logistic regression analyses were performed to evaluate the association between parameters and subclinical carotid atherosclerosis. Statistical analyses were conducted by using SPSS22.0 (SPSS Inc., Chicago, IL, USA).

We employed the restricted cubic spline function of linear model to characterize C-R relationships between potential risk factors and subclinical carotid atherosclerosis. Concentration-response relationships (C-R relationships) were analyzed using the SAS 9.4 software (SAS, Institute, Cary, NC).

CIMT was examined twice after a 1-week interval in a blinded manner. Variability was determined by calculating coefficients of variation, which was calculated as the standard deviation of differences. Paired *t* test was employed to test the difference between the 2 measurements. *P* values <0.05 were considered statistically significant.

Results

Characteristics of the CVRFs-free population

The characteristics of the CVRFs-free individuals are shown in Table 1. The 1449 participants include 283 men (19.5%) and 1166 women (80.5%), whose average age is 54.7 ± 9.6 years. 52.4% have a primary school education or less, 27.0% have an annual income less than 5000 yuan (approximately $ 700). The plasma HbA1c is 5.32 ± 0.33%, and the plasma HDL-C is 2.24 ± 0.57 mmol/L.

Table 1
Characteristics of The Study Participants

	Male	Female	Total
Participant, n(%)	283(19.5)	1166(80.5)	1449(100.0)
Mean age, years	58.2 ± 10.3	53.8 ± 9.3	54.7 ± 9.6
40–49	23.3	38.8	35.7
50–59	29.0	33.4	32.5
60–69	33.9	21.8	24.2
70–79	11.3	4.9	6.1
>=80	2.5	1.2	1.4
Education			
Primary school or lower	37.5	56.1	52.4
Middle school	53.4	39.5	42.2
High school or above	9.2	4.4	5.3
Incoming, Yuan			
< 5000	29.3	26.4	27.0
5000–9999	23.0	23.6	23.5
10000–19999	20.5	23.8	23.1
>=20000	27.2	26.2	26.4
Current drinking	49.1	13.4	20.4
Lack of Exercise	12.7	11.2	11.5
Body mass index, kg/m^2	23.69 ± 3.33	24.27 ± 3.37	24.16 ± 3.37
Waist, cm	81.50 ± 8.88	79.85 ± 9.24	80.17 ± 9.19
Hipline, cm	92.46 ± 6.20	92.94 ± 6.67	92.85 ± 6.58
Systolic blood pressure, mmHg	123.66 ± 9.81	121.03 ± 11.12	121.54 ± 10.92
Diastolic blood pressure, mmHg	78.85 ± 6.46	77.91 ± 6.68	78.09 ± 6.65
Fasting plasma glucose, mol/L	5.51 ± 0.59	5.39 ± 0.56	5.41 ± 0.57
Glycosylated hemoglobin,%	5.28 ± 0.34	5.34 ± 0.33	5.32 ± 0.33
Total cholesterol, mol/L	4.54 ± 0.73	4.65 ± 0.75	4.63 ± 0.75

	Male	Female	Total
Triglyceride, mol/L	1.17 ± 0.77	1.31 ± 0.82	1.28 ± 0.81
High-density lipoprotein cholesterol, mol/L	2.15 ± 0.56	2.26 ± 0.57	2.24 ± 0.57
Low-density lipoprotein cholesterol, mol/L	1.78 ± 0.64	1.76 ± 0.63	1.77 ± 0.63

Prevalence of subclinical carotid atherosclerosis in CVRF-free population

Overall, among the 1449 participants without conventional CVRFs adults aged ≥ 40 years in rural northeast China, the mean cIMT is 0.74 ± 0.14 (men 0.80 ± 0.16, women 0.73 ± 0.13, respectively). The correlation coefficient between the first and second CIMT measurements is 0.88 ($p < 0.05$), with no significant difference. The mean difference and standard deviation is 0.02 ± 0.06 mm.

Among conventional CVRFs-free individuals, 339 have subclinical carotid atherosclerosis, including 82 have mean cIMT ≥ 1.0 mm, 316 have carotid plaques, 59 have both. The prevalence of subclinical carotid atherosclerosis is shown in Table 2. The overall prevalence of carotid plaque is 23.2% (95%CI: 21.2%-25.6%), significantly higher in men than in women (37.1% vs 20.0%, $p < 0.001$). It rises steeply with advancing age, ranging from 5.0% (95%CI: 3.1%-6.9%) among participants 40 to 49 years to 85.7% (95%CI: 69.4%-102.0%) among participants 80 years or older.

Table 2
Prevalence of subclinical carotid atherosclerosis among individuals without cardiovascular risk factors

Age group(years)	Male			Female			Total			*p* value
	No	Rate	95%CI	No	Rate	95%CI	No	Rate	95%CI	
40–49	8	12.1	4.0-20.2	18	4.0	2.2–5.8	26	5.0	3.1–6.9	0.011
50–59	17	20.7	11.8–29.7	63	16.2	12.5–19.9	80	17.0	13.6–20.4	0.320
60–69	52	54.2	44.0-64.3	103	40.6	34.5–46.6	155	44.3	39.1–49.5	0.022
70–79	21	65.6	48.2–83.0	39	68.4	56.0-80.9	60	67.4	57.5–77.3	0.787
>=80	7	100.0	-	11	78.6	54.0-103.2	18	85.7	69.4–102.0	0.521
Total	105	37.1	31.4–42.8	234	20.1	17.8–22.4	339	23.4	21.2–25.6	< 0.001

Among participants without conventional CVRFs, 19 (1.31%) had more than moderate-to-severe carotid stenosis, including 13 (0.90%) who were diagnosed with moderate carotid stenosis (50–69%), and 6 (0.41%) who have severe carotid stenosis (≥ 70%).

Related risk factors for prevalence of subclinical carotid atherosclerosis among CVRFs-free population

According to the results of the multivariate regression model, our results identify that advancing age, man (OR, 1.87; 95% CI, 1.26–2.77), glycosylated hemoglobin (HbA1c) (OR, 1.90; 95% CI, 1.20–1.32), HDL-C level (OR, 2.31; 95% CI, 1.75–3.04), and pulse pressure (OR, 1.03; 95% CI, 1.01–1.05) are risk factors for presence of subclinical carotid atherosclerosis. However, ever smoking does not significantly correlated to the presence of subclinical atherosclerosis.

What is noteworthy is that participants with higher HDL-C and HbA1c levels were likely to have a high prevalence of carotid atherosclerosis in individuals without CVRFs (Table 3). We further chose HDL-C and HbA1c levels that were encoded using restricted cubic spline function with 3 knots, located at the fifth, 50th, 95th percentiles, after adjusted age, sex, current drink, triglyceride, TG, LDL-C, BMI, waist, hipline, lack of exercise, education, and pulse pressure, we found linear relationships between HDL-C and subclinical carotid atherosclerosis. In individuals without conventional CVRFs, the prevalence of subclinical carotid atherosclerosis increased significantly with high levels of HDL-C after adjusting other risk factors ($p < 0.05$) (Fig. 2).

Table 3
Association of risk factors with subclinical carotid atherosclerosis

	OR	95% CI	P value
Sex			
Female	1.00	-	
Male	1.87	1.26–2.77	0.002
Age Group, Years			
40-	1.00		
50-	2.63	1.62–4.27	< 0.001
60-	7.62	4.64–12.52	< 0.001
70-	17.29	8.80-33.99	< 0.001
80-	53.99	14.44-201.83	< 0.001
Incoming, Yuan			
< 5000	1.00	-	
5000–9999	0.64	0.43–0.94	0.021
10000–19999	0.53	0.35–0.80	0.003
>=20000	0.47	0.30–0.74	0.001
Waist, cm	1.02	1.00-1.03	0.051
HDL-c, mmol/L	2.31	1.75–3.04	< 0.001
HbA1c, mmol/L	1.90	1.20–3.02	0.007
Ever smoking	1.56	0.95–2.56	0.077
Pulse pressure	1.03	1.01–1.05	0.003

Adjusted factors: sex, incoming, age, current drinking, ever smoking, education, overweight or obesity, lack of exercise, fasting plasma glucose, waist, hipline, neck circumference, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), pulse pressure, glycosylated hemoglobin (HbA1c).

Discussion

The major findings of the present study are: 1) the prevalence of subclinical carotid atherosclerosis in CVRFs-free individuals is 23.2%, which rises steeply with advanced age; 2) the prevalence of subclinical carotid atherosclerosis in men is higher than in women; 3) the HDL-C and HbA1c levels are potentially related to high rate of subclinical carotid atherosclerosis. These findings indicate that additional poorly defined factors are likely to contribute to the process of atherogenesis in individuals without conventional CVRFs. Moreover, a significant number of individuals without conventional CVRFs have subclinical carotid atherosclerosis, which indicates that the assessment of subclinical atherosclerosis in this population might provide substantial yield. In addition, the association between HDL-C and the presence of subclinical carotid atherosclerosis is not expected, further suggesting that using pharmacologic inhibitor to increase HDL-C levels might not reduce the rate of cardiovascular events in individuals without conventional CVRFs, and a fundamental assessment of the clinical importance of HDL-C should be warranted.

Atherosclerotic cardiovascular diseases remain to be the major cause of premature death globally.[16] Conventional risk factors for atherosclerosis including smoking, dyslipidemia, hypertension and diabetes are used within the risk factor-based approach to identify high-risk groups, such as Framingham risk scores and pooled cohort equation risk scores.[17] However, only nearly 40% of cardiovascular events occur in those high-risk group, and approximately 40–60% adverse outcomes occur in the low-risk individuals, accounting for 1/3 of the population. [18] Therefore, the validity of conventional risk factors assessment in identifying risk factors in the next 10 years remains controversial. In our study cohort, up to 23.2% of individuals had carotid atherosclerosis, including 1.31% of participants who have moderate-to-severe carotid stenosis, indicating the clinical importance of carotid atherosclerosis screening.

Screening for asymptomatic carotid stenosis was based on the concept that it was possible to prevent stroke by stenting or operating moderate to severe carotid stenosis.[9] However, recent studies reported that carotid operation such as carotid endarterectomy or carotid stent might cause more stroke than it can prevent, which indicated the recommendation against screening for asymptomatic carotid stenosis in view of surgery is now outmoded.[19, 20] In addition, previous study reported that the presence of plaque, no matter the size, was a marker of increased risk of cardiovascular events.[9] Therefore, subclinical atherosclerosis in regard of selecting optimal medical therapy to reduce cardiovascular risks should be recommended. Previous study suggested that carotid ultrasound is a more readily available and reliable imaging modality for detecting early atherosclerosis when compared to CAC scan.[2] Therefore, in the present study, we used ultrasound to evaluate the subclinical atherosclerosis in CVRFs-free population.

LDL-C and HDL-C are crucially involved in the development of atherosclerosis. In contrast to LDL-C promotes the vascular atherosclerotic process, HDL-C was thought to act as a protective agent by preventing endothelial dysfunction.[21] Previous studies reported that low concentration of HDL-C was inversely associated with the risk of adverse cardiovascular outcomes in general population.[22, 23] However, there are growing evidences suggesting that HDL-C might lose its protective properties in certain conditions.[22] Elevated HDL-C levels failed to decrease cardiovascular events and high levels of HDL-C was not correlated with reduced CIMT.[24, 25] Our findings indicated that the inverse relationship between HDL-C and atherosclerosis may not apply to the individuals without CVRFs, further suggested that using pharmacologic inhibitor of the cholesterol-ester transfer protein to increase HDL-C levels might not reduce the rate of cardiovascular events in individuals without conventional CVRFs. In addition, PESA study indicated that in CVRF-free middle-aged individuals, LDL-C was independently correlated with the presence of atherosclerosis, even in currently considered normal levels.[7] However, in our population, we did not find the correlation, possibly because of the different population selection and definition of atherosclerosis.

Previous study reported that HbA1c was linked to increased CAC and cIMT in 2340 nondiabetic participants.[26] In addition, other study reported that HbA1c concentration was independently associated with cIMT progression and adverse cardiovascular outcomes in nondiabetic prospective series.[27] In the present study, we found HbA1c level was independently associated with the presence of subclinical carotid atherosclerosis, which consistent with previous studies. [26, 27] This finding might be partially explained by the association between prediabetes and increased cardiovascular risk.

Smoking is an important modifiable risk factor for atherosclerosis, and current smoking and cumulative exposure are significantly related to cardiovascular risks.[28] Therefore, smoking cessation is crucially important in reducing cardiovascular risks. In the present study, we did not find any significant association between subclinical atherosclerosis and ever smoking, coincident with previous studies,[28] which indicated smoking-related damage to the artery is irreversible, and smoking cessation should be emphasized.

The strengths of the study include its population-based design in Chinese population and a comprehensive estimation of subclinical carotid atherosclerosis by ultrasound. However, this present study also had several limitations. Firstly, we can only provide implications for the association between risk factors and subclinical carotid atherosclerosis, but the causality of this association still needs more longitudinal studies to validate. Secondly, we use carotid ultrasound as a surrogate of subclinical carotid atherosclerosis, which may have led to underestimation of atherosclerosis prevalence. However, atherosclerosis is a systemic disorder, and previous study suggested that screening atherosclerosis by carotid ultrasound is likely to provide the highest yield to detect atherosclerosis.[2] Thirdly, our population originated from the rural areas of northeast China, whether our results are suitable to the population in different geographic and economic conditions also needs further studies to confirm. Lastly, women comprised 80.5% of the population, and selection bias was inevitable as women usually had better access to prevention strategies, and were more likely to obey the health education.[29]

Conclusions

The present study provides insight into the presence of subclinical carotid atherosclerosis and related risk factors in a representative population in rural northeast China, observing 23.2% had subclinical carotid atherosclerosis, including 1.31% had moderate-to-severe carotid stenosis, indicating poorly-defined factors play a role in the early process of atherosclerosis, and early detection of subclinical atherosclerosis in sight of reducing cardiovascular risks should be recommended. Moreover, the HDL-C levels are potentially related to a high rate of subclinical carotid atherosclerosis, further indicated that increase HDL-C levels might not reduce the rate of cardiovascular events in individuals without conventional CVRFs.

Abbreviations

CIMT: carotid intima-media thickness; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin

Declarations

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Author' Contributions

SL was responsible for the concept and design of the study. YT and SZ were responsible for the study coordination and conduct. YT, SZ, and RL contributed to the drafting of the manuscript. WX, LX, GL, LZ, and LJ collected and analyzed the data. JY and CM interpreted the data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated for and analyzed in the study are not publicly available but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was granted approval by the Central Ethics Committee at the China National Center for Cardiovascular Disease (Clinical Research No.[2015]024. Beijing, China.). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

None.

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Figures

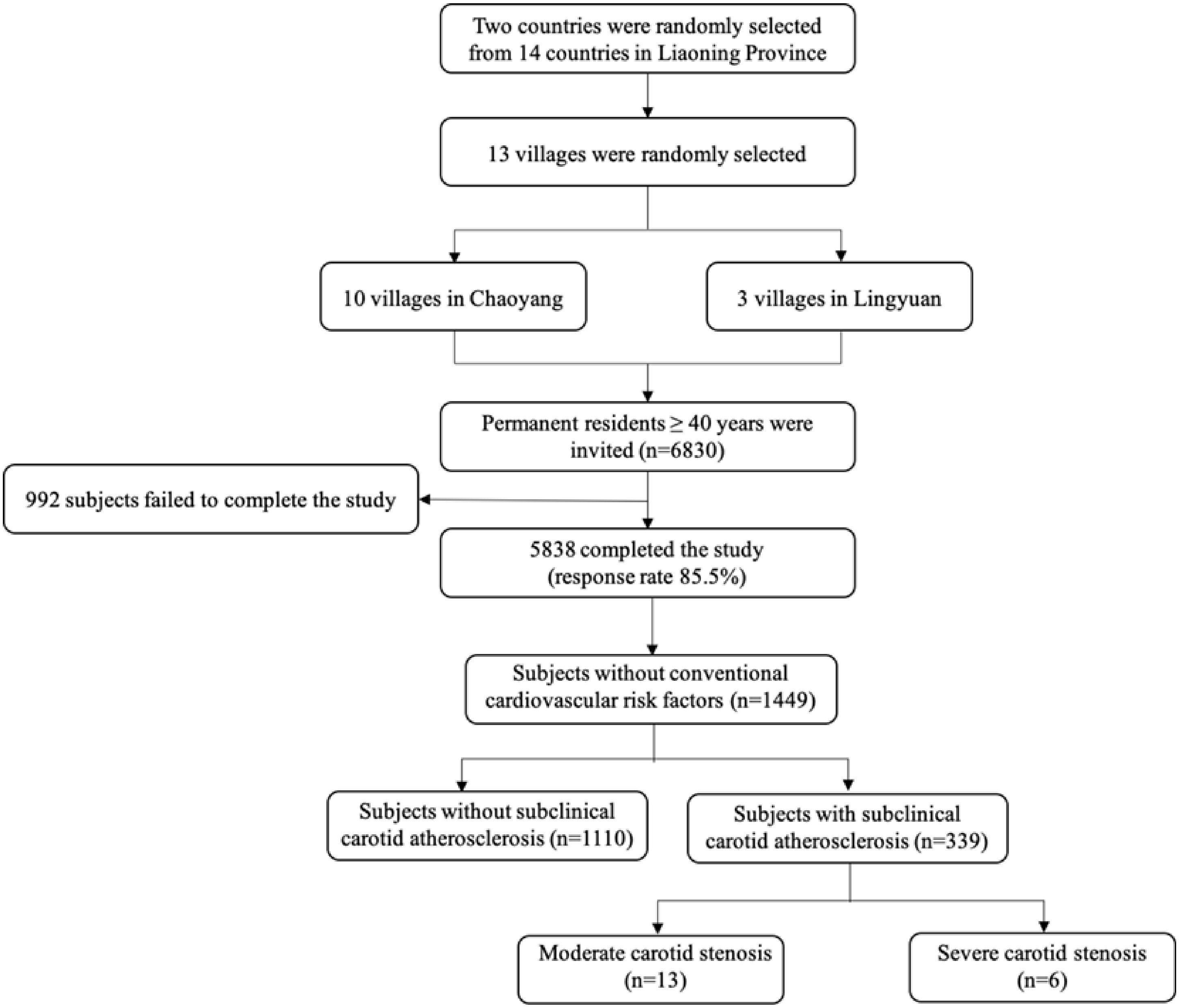

Figure 1

Flow chart of population selection.

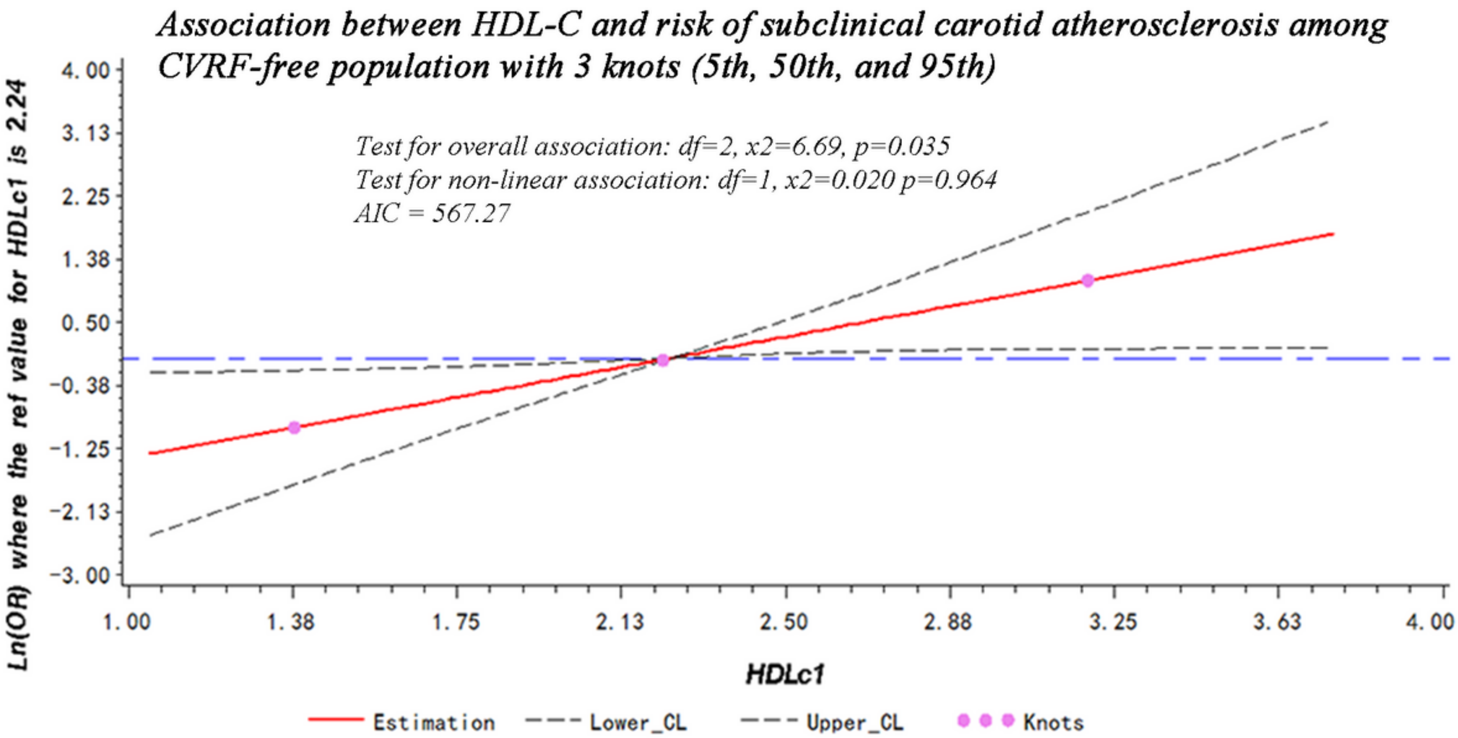

Figure 2

C-R association between HDL-C and presence of carotid atherosclerosis in individuals without conventional CVRFs. HDL-C levels were encoded using a restrictive cubic spline(RCS) function of linear model with 3 knots located at the 5th, 50th, and 95th percentiles of distribution. Y-axis values show the change of subclinical atherosclerosis between the indicated HDL-C (Fig.2B) values and the reference value. The dashed lines are the 95% confidence intervals. HDL-C, high-density lipoprotein cholesterol; CVRFs, cardiovascular risk factors.