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ORIGINAL RESEARCH

The Association Between High-Sensitivity C-Reactive Protein and the Progression of Arteriosclerosis: The Kailuan Study

Weizhe Li[1,*], Pei Liang[2,*], Xueliang Ma[1], Yanling Gao[1], Xiaoxin Bai[1], Shasha An[3], Xin Wang[1], Shuohua Chen[4], Shouling Wu[4]

[1]Department of Emergency Internal Medicine No. 1, Handan Central Hospital, Handan, Hebei, 056001, People's Republic of China; [2]Department of Intensive Care Rehabilitation, Handan Mingren Hospital, Handan, Hebei, 056001, People's Republic of China; [3]Department of General Medicine, Handan Central Hospital, Handan, Hebei, 056001, People's Republic of China; [4]Department of Cardiology, Kailuan General Hospital, Tangshan, Hebei, 063001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xueliang Ma; Xin Wang, Department of Emergency Internal Medicine No. 1, Handan Central Hospital, NO. 15, Zhonghuanan Street, Hanshan District, Handan, Hebei, 056001, People's Republic of China, Tel +86 13333008705; +86 18103300116, Email mxlhsl@163.com; wangxin2167@163.com

Objective: To explore the association between high-sensitivity C-reactive protein (hs-CRP) and the progression of arteriosclerosis.

Methods: Using a prospective cohort study design, 11,577 participants from the Kailuan Study cohort who underwent at least two brachial-ankle pulse wave velocity (baPWV) examinations and met the inclusion criteria were included as the study subjects. Based on baseline hs-CRP levels, they were divided into three groups: hs-CRP <1 mg/L group, 1 mg/L≤hs-CRP≤3 mg/L group, and hs-CRP >3 mg/L group. Poisson regression analysis was employed for longitudinal comparison to assess the impact of different hs-CRP levels on baPWV≥1,400 cm/s.

Results: (1) After a mean follow-up of 5.12 ± 2.84 years, the detection rates of baPWV≥1,400 cm/s at the end of follow-up were 28.54%, 33.36%, and 36.25% in the hs-CRP<1 mg/L (n=5,998), 1 mg/L≤ hs-CRP≤3 mg/L (n=4,101), and hs-CRP>3 mg/L (n=1,578) groups, respectively (P<0.001). (2) Multivariable-adjusted Poisson regression analysis for baPWV≥1,400 cm/s showed that, after adjusting for confounding factors, compared to the hs-CRP<1 mg/L group, the 1 mg/L≤hs-CRP≤3 mg/L group had a 2.4% higher risk of arterial stiffness (RR: 1.024; 95% CI: 1.002 to 1.047; P<0.05) and hs-CRP>3 mg/L group had a 6.3% higher risk (RR: 1.063; 95% CI: 1.031 to 1.095; P<0.001). Sensitivity analysis validated the robustness of the results.

Conclusion: Elevated hs-CRP is an independent risk factor for arteriosclerosis progression.

Keywords: high-sensitivity C-reactive protein, brachial-ankle pulse wave velocity, arteriosclerosis, poisson regression

Introduction

Arteriosclerosis is a degenerative condition that occurs in the walls of large blood vessels and is one of the primary manifestations of vascular aging, Arteriosclerosis is not only a risk factor for cognitive impairment[1] and reduced cardiac function,[2] but it is also positively associated with an increased risk of cardiovascular and cerebrovascular events, such as myocardial infarction[3,4] and stroke.[5] Age is the major non-modifiable risk factor for arteriosclerosis. However, studies have confirmed that metabolic disorders of glucose and lipids, hypertension, and especially the level of inflammation in the body are positively correlated with the development of arteriosclerosis.[6,7] A meta-analysis found that individuals with elevated C-reactive protein (CRP) levels have a 1.19 to 3.96 times higher risk of developing arteriosclerosis.[8–12]

Previous studies on the association between CRP and arteriosclerosis have predominantly been cross-sectional studies.[9,11,13] However, arteriosclerosis lesions are a slowly progressing pathological process. Cross-sectional studies cannot accurately elucidate the relationship between inflammation and the progression of arteriosclerosis. To further clarify the link between inflammation and the progression of arteriosclerosis, we conducted an observational study using

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the Kailuan cohort (registration number: ChiCTR-TNC-11001489).[14] In this study, hs-CRP was used as an inflammation marker to analyze the impact of hs-CRP on the progression of baPWV.

Methods

Data Sources

From 2006 to 2007, health check-ups were conducted on active and retired employees at Kailuan General Hospital and its 11 affiliated hospitals. Subsequently, follow-up health check-ups were performed from 2008 to 2023, covering the 2nd to 9th rounds of health examinations. During the 3rd to 9th rounds, some individuals underwent baPWV measurements. Since the objective of this study was to explore the effect of inflammation on the progression of arteriosclerosis, we selected individuals who participated in at least two baPWV measurements as the study population. This study complies with the declaration of Helsinki and has been approved by the Ethics Committee of Kailuan General Hospital (No. 200605). Written informed consent was obtained from all participants.

Inclusion Criteria: (1) Participants from the Kailuan cohort;(2) Individuals who attended at least two baPWV measurements; (3) Participants who agreed to and signed an informed consent form.

Exclusion Criteria: (1) Individuals who completed two baPWV tests but had missing hs-CRP data;(2) Individuals with physical disabilities that prevented the examination; (3) Individuals with atrial fibrillation or lower limb venous thrombosis.

Data Collection

The investigators and examining physicians for this study were fixed personnel who received standardized training. They strictly adhered to the unified standards developed for this research when conducting the surveys and various examinations. The questionnaire survey was administered face-to-face by specially trained surveyors, who individually asked each participant about the contents of the questionnaire and carefully recorded the responses. The survey included demographic information, occupational status, behavioral habits (sleep, smoking, drinking, physical exercise, and diet), medical history, and family history. Physical examinations were conducted to gather data on Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), height, weight, waist circumference, etc. Body mass index (BMI) was determined as weight (kg) divided by height (m) squared. Mean Arterial Pressure (MAP) was calculated using the formula: MAP = DBP+ (SBP-DBP) /3. Smoking was defined as smoking at least one cigarette per day on average for at least one year during the past year. Drinking was defined as consuming at least 100 mL of white liquor (alcohol content greater than 50%) per day on average for at least one year during the past year. Physical exercise was defined as aerobic activities such as walking, jogging, and ball sports for at least 90 minutes per week.

In the Kailuan study, baPWV was assessed by a BP-203 RPE III networked arterial stiffness detection device manufactured by Omron Health Medical Co., Ltd. [Dalian China], which directly reads the data through a network connection. The temperature of the examination room was maintained between 22 and 25°C. Before measurement, participants were instructed not to smoke and to rest for at least 5 minutes. The patient's age, gender, height, and weight were recorded prior to the examination. At the start of the measurement, the subject remained quiet, lying flat with their head supported, and their palms facing upwards at their sides. The blood pressure cuffs were applied to the upper arms and lower legs at the ankle. The cuff's airbag mark was aligned with the brachial artery on the upper arm, and the lower edge of the cuff was 2–3 cm above the elbow crease. For the lower limbs, the airbag mark was positioned on the inner side of the leg, with the lower edge of the cuff 1–2 cm above the inner ankle. Electrocardiogram (ECG) electrodes were attached to the limbs, and one phonocardiogram (PCG) sensor was placed at the V4 position of the chest ECG lead. The four cuffs were inflated and deflated simultaneously while monitoring both the ECG and PCG signals. Each subject was measured twice, with the second measurement used for final analysis.

According to the classification criteria of arteriosclerosis in the Takashima study in Japan,[15] baPWV< 1400cm/s indicates normal peripheral arterial stiffness, while baPWV≥1400 cm/s suggests peripheral arterial sclerosis. In this study, the larger value between the left and right side baPWV was used for analysis. The annual growth rate of baPWV was determined by the following equation: the change in baPWV (baPWV values at the final visit minus baseline baPWV values) was divided by the duration of follow-up in years.

The study subjects were instructed to fast for more than 8 hours and blood samples (5 mL) were collected from the antecubital vein between 7:00 AM and 9:00 AM in ethylenediamine tetraacetic acid (EDTA) vacuum tubes. The blood samples were centrifuged at 3000g for 10 minutes at room temperature. The upper serum was then analyzed within 4 hours for total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), fasting blood glucose (FBG), and hs-CRP. The serum hs-CRP level was measured using an immunoturbidimetric method, with reagents provided by Kanto Chemical Co., Ltd., Japan (Nihonbashi Muromachi, Chuo-ku, Tokyo, Japan). Between 2006 and 2009, the Ministry of Health evaluated the laboratory's CRP testing proficiency (Laboratory Proficiency Testing, PT) as 100%. Additionally, each sample was tested twice daily, with at least a 2-hour interval between measurements, and samples were measured over 20 days. The measurement precision analysis showed an intra-assay coefficient of variation (CV) of 6.53%, an inter-assay CV of 4.78%, a day-to-day CV of 6.61%, and a total CV of 9.37%. Fasting blood glucose was measured using the hexokinase method, with reagents provided by Zhongsheng Beikong Biotechnology Co., Ltd (Beijing, china). The CV for this test was <2%. All analyses were performed on a Hitachi 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan). The operations were conducted strictly following the reagent instructions, with quality control conducted for each batch, and performed by professional laboratory technicians.

Follow-up

The follow-up started in 2010–2011 when the first baPWV measurement was completed. The endpoint event was defined as the follow-up conclusion when baPWV≥1400 cm/s.

Statistical Analysis

The health examination data were entered by designated personnel, trained uniformly at each hospital, and uploaded to the server of the Kailuan General Hospital computer room via the network, forming an Oracle 10.2 database (Oracle Corporation, Redwood, USA). Statistical analysis was performed using SAS 9.4 software. Normally distributed continuous data are described using the mean and standard deviation (SD), compared with the one- way ANOVA. Count data were expressed as percentages (%), and comparisons of proportions were made using the chi-square (χ^2) test. Poisson regression models were employed to analyze the association between baseline hs-CRP levels and incident baPWV≥1400 cm/s events, with results expressed as RR (95% CI). Two multifactorial adjustment models were constructed: Model 1, controlled for age and gender; Model 2, controlled for age, gender, MAP, FBG, LDL-C, follow-up time, smoking, alcohol intake, BMI, physical activity.

Sensitivity Analysis: To avoid the influence of acute-phase inflammation (hs-CRP>10 mg/L), tumors, and medications (antihypertensive, lipid-lowering, or antidiabetic drugs) on hs-CRP, this population was excluded. A further Poisson regression analysis was performed to assess the effect of hs-CRP on baPWV≥1400 cm/s. A bilateral $P<0.05$ was deemed statistically significant.

Results

General Characteristics of the Study Population

A total of 24,201 participants who underwent at least two baPWV measurements were initially included in the study. After excluding individuals with missing baseline hs-CRP data and those with baPWV≥1400 cm/s (12,624 cases), 11,577 participants were ultimately included in the statistical analysis. Among these, 6,123 were male and 5,454 were female. Baseline hs-CRP data were obtained from the first baPWV measurement during the initial health check-up. Participants were then divided into three groups based on their baseline hs-CRP levels: hs-CRP<1 mg/L, 1 mg/L hs-CRP≤3 mg/L, and hs-CRP>3 mg/L.[16] As the baseline hs-CRP concentration increased, baPWV, MAP, FBG and BMI showed a gradual increase, with statistically significant differences observed ($P<0.001$; Table 1).

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Table 1 Comparison of Baseline Characteristics Among Different Hs-CRP Groups

Characteristics	hs-CRP<1 mg/L	1 mg/L≤hs-CRP≤3 mg/L	hs-CRP>3 mg/L	F/X^2	*P*-value
Participants, n	5998	4101	1578		
$baPWV_1$, cm/s	1219.57±116.99	1231.11±113.08	1236.55±112.11	19.92	<0.001
Age, years	41.73±9.16	41.91±9.85	41.81±10.04	0.42	0.656
Male, n (%)	2894 (49.07)	2358 (57.50)	871 (55.20)	72.9	<0.001
MAP, mmHg	90.57±10.33	92.24±10.39	93.16±10.45	52.1	<0.001
FBG, mmol/L	5.12±1.14	5.27±1.02	5.52±3.09	43.14	<0.001
LDL-C, mmol/L	2.58±0.72	2.75±0.79	2.75±0.88	18.53	<0.001
BMI, kg/m^2	23.70±3.23	24.97±3.43	26.02±3.90	334.56	<0.001
Follow-up, year	5.18±2.91	5.08±2.80	4.99±2.67	3.28	0.037
Current smoker, n (%)	1333 (26.04)	1137 (31.15)	382 (28.03)	27.52	<0.001
Current drinker, n (%)	1542 (35.06)	1249 (42.18)	486 (42.01)	44.92	<0.001
Physical activity, n (%)	277 (12.20)	167 (11.57)	55 (10.42)	1.384	0.500

Abbreviations: $baPWV_1$, First measurement of brachial-ankle pulse wave velocity; MAP, Mean arterial pressure; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; BMI, Body Mass Index.

Table 2 Comparison of baPWV Among Different Hs-CRP Groups

Characteristics	hs-CRP<1 mg/L	1 mg/L≤hs-CRP≤3 mg/L	hs-CRP>3 mg/L	F/X^2	*P*-value
Participants, n	5998	4101	1578		
$baPWV_1$, cm/s	1219.57±116.99	1231.11±113.08	1236.55±112.11	19.92	<0.001
$baPWV_2$, cm/s	1326.55±201.60	1346.63±202.15	1361.08±211.37	23.24	<0.001
$PWV\__d$, cm	106.97±174.12	115.52±174.91	124.52±190.99	7.11	<0.001
baPWV≥1400cm/s, n (%)	1683 (28.54)	1368 (33.36)	572 (36.25)	47.01	<0.001

Abbreviations: $baPWV_1$, First measurement of brachial-ankle pulse wave velocity; $baPWV_2$, Brachial-ankle pulse wave velocity at the most recent health check-up; PWV_d, Difference in brachial-ankle pulse wave velocity between the first and last measurements.

baPWV Measurement in the Study Population

Among the 11,577 participants included in the statistical analysis, the average baPWV at the end of follow-up for the hs-CRP<1 mg/L group, the 1 mg/L≤hs-CRP≤3 mg/L group, and the hs-CRP>3 mg/L group were 1326.55, 1346.63, and 1361.08 cm/s, respectively. The differences between the groups were statistically significant (P<0.001). The average follow-up duration was 5.12 ± 2.84 years, during which the average increase in pulse wave velocity was 106.97, 115.52, and 124.52 cm/s for each group. The detection rates of baPWV≥1400 cm/s were 28.54%, 33.36%, and 36.25%, respectively, with statistically significant differences between the groups (P<0.001; Table 2).

Poisson Regression Analysis of Factors Influencing baPWV≥1400 cm/s

Using baPWV as the dependent variable (baPWV<1400 cm/s coded as 1, baPWV≥1400 cm/s coded as 2), Poisson regression analysis was performed to assess the impact of baseline hs-CRP levels on baPWV. In Model 1, after adjusting for age and gender, hs-CRP1 group was used as the reference. The RR (95% CI) for developing baPWV≥1400 cm/s in the hs-CRP 2 and hs-CRP 3 groups were 1.029 (95% CI: 1.016 to 1.043, P<0.001) and 1.053 (95% CI: 1.034 to 1.072, P<0.001), respectively. Model 2 further adjusted for MAP, FBG, LDL-C, follow-up time, smoking, alcohol intake, BMI and physical activity. In this model, the RR (95% CI) for developing baPWV≥1400 cm/s in the hs-CRP 2 and hs-CRP 3 groups were 1.024 (95% CI: 1.002 to 1.047, P<0.05) and 1.063 (95% CI: 1.031 to 1.095, P<0.001), respectively (Table 3).

Sensitivity Analysis

To minimize the impact of other factors on hs-CRP levels, individuals with acute-phase inflammation, tumors, or those taking antihypertensive, lipid-lowering, or antidiabetic medications were excluded. Poisson regression analysis showed consistent results with the previous analysis. Compared to the hs-CRP 1 group, both the hs-CRP 2 and hs-CRP 3 groups

Table 3 Poisson Regression Analysis of Baseline Hs-CRP and baPWV ≥1400 cm/s

hs-CRP (mg/L)	SE	Wald value	RR (95% CI)	*P*-value
Model 1				
hs-CRP1			Ref.	
hs-CRP2	0.0067	18.72	1.029 (1.016–1.043)	<0.001
hs-CRP3	0.0091	32.59	1.053 (1.034–1.072)	<0.001
Model 2				
hs-CRP1			Ref.	
hs-CRP2	0.0111	4.72	1.024 (1.002–1.047)	0.0298
hs-CRP3	0.0154	15.87	1.063 (1.031–1.095)	<0.001

Note: hs-CRP1 represent the hs-CRP < 1 mg/L group, hs-CRP2 represent the 1 mg/L ≤ hs-CRP ≤ 3 mg/L group, and hs-CRP3 represent the hs-CRP > 3 mg/L group. Model 1 was adjusted for age (continuous) and gender (male or female); Model 2 was adjusted for age (continuous), gender (male or female), MAP (continuous), FBG (continuous), LDL-C (continuous), follow-up time (continuous), current smoking (yes or no), current drinking (yes or no), BMI (continuous), physical activity (active or inactive).
Abbreviations: SE, Standard Error; RR, relative risk; CI, confidential intervals.

Table 4 Sensitivity Analysis Result

hs-CRP (mg/L)	SE	Wald value	RR (95% CI)	*P*-value
Model 1				
hs-CRP1			Ref.	
hs-CRP2	0.0069	15.7	1.027 (1.013–1.041)	<0.001
hs-CRP3	0.01	25.55	1.051 (1.031–1.072)	<0.001
Model 2				
hs-CRP1			Ref.	
hs-CRP2	0.0114	4.63	1.024 (1.002–1.048)	0.0315
hs-CRP3	0.0167	9.34	1.052 (1.018–1.087)	0.0022

Notes: Model 1 was adjusted for age (continuous) and gender (male or female); Model 2 was adjusted for age (continuous), gender (male or female), MAP (continuous), FBG (continuous), LDL-C (continuous), follow-up time (continuous), current smoking (yes or no), current drinking (yes or no), BMI (continuous), physical activity (active or inactive).
Abbreviations: SE, Standard Error; RR, relative risk; CI, confidential intervals.

showed statistically significant differences ($P<0.05$), with RR (95% CI) of 1.024 (95% CI:1.002 to 1.048, $P < 0.05$) and 1.052 (95% CI:1.018 to 1.087, $P<0.01$), respectively (Table 4).

Discussion

This study, based on an average follow-up of 5.12±2.84 years for 11,577 participants, found that hs-CRP is an independent risk factor for the progression of arteriosclerosis. The level of systemic inflammation was positively associated with the progression of arteriosclerosis. This positive association is independent of traditional risk factors, including aging.

First, we observed a positive correlation between the progression of arteriosclerosis and the level of inflammation in the body. As the hs-CRP group increased, the progression of arteriosclerosis accelerated, with the progression speed rising from 106.97 cm/s in the hs-CRP1 group to 124.52 cm/s in the hs-CRP3 group. The average annual increase in the hs-CRP3 group was as high as 24.32 cm/year, compared to only 20.89 cm/year in the hs-CRP1 group. Our findings are consistent with previous studies on inflammation and the progression of arteriosclerosis. For instance, Andrew Agbaje[17] found that in adolescent populations, an increase in CRP levels preceded an increase in carotid-femoral pulse wave velocity (cfPWV). The Caerphilly prospective study[18] showed that baseline CRP levels in elderly individuals were independently associated with a 20-year increase in aortic pulse wave velocity (aPWV), with multiple linear regression analysis showing a β value of 0.35 (P=0.002). Additionally, the acceleration of aPWV was strongly correlated with

cumulative CRP exposure. These results suggest that individuals with high levels of inflammation experience an accelerated aging of large blood vessels.

Our study not only found that the progression of arteriosclerosis is positively correlated with the level of systemic inflammation, but also confirmed that high inflammation levels are a risk factor for arteriosclerosis. Compared to the hs-CRP1 group, the risk of developing arteriosclerosis progressively increased with the rise in hs-CRP levels, from 2.4% in the hs-CRP2 group to 6.3% in the hs-CRP3 group. While no similar studies have been published, a study conducted in Rotterdam[11] found that for the development of isolated systolic hypertension as the endpoint for arteriosclerosis, each standard deviation increase in hs-CRP raised the risk of developing isolated systolic hypertension by 19%. Similarly, the Whitehall II study[19] showed that in a middle-aged European population, for every doubling of baseline CRP levels, the aPWV increased by 130 cm/s in men and 140 cm/s in women after 16 years of follow-up. These results suggest a dose-response relationship between baseline hs-CRP levels and the progression of arteriosclerosis. To the best of our knowledge, this is the first study to report the impact of hs-CRP on the progression of baPWV≥1400 cm/s.

CRP, as a non-specific marker of inflammation, is influenced by various confounding factors. To ensure the robustness of our findings, we re-analyzed the data after excluding individuals with acute-phase inflammation (hs-CRP>10mg/L), cancer, those taking antihypertensive, lipid-lowering, or antidiabetic medications. The results remained consistent with our main findings. Moreover, with increasing hs-CRP levels, there was a trend of aggregation of traditional risk factors, such as mean arterial pressure, fasting blood glucose, and BMI. However, after model adjustment, hs-CRP levels were still statistically significantly associated with the progression of arteriosclerosis. Sensitivity analyses further confirmed the relationship between hs-CRP and the progression of arteriosclerosis.

Current understanding suggests that inflammation contributes to the development of arteriosclerosis through the following mechanisms: (1) Reactive oxygen species (ROS) generated during inflammation activate the activity of matrix metalloproteinases on endothelial and smooth muscle cells, leading to the degradation of tissue inhibitors of metalloproteinases. This results in the breakdown of elastin, proliferation of smooth muscle cells, and inhibition of collagen and elastin crosslinking. The increased collagen content subsequently contributes to the progression of arteriosclerosis.[20–22] (2) C-reactive protein directly suppresses the expression of endothelial nitric oxide synthase (eNOS). Inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-1, inhibit eNOS activation by receptor-dependent agonists and promote the expression of inducible nitric oxide synthase, further inhibiting eNOS activity. Additionally, ROS generated during the inflammatory process further deplete nitric oxide (NO). Together, these factors lead to reduced NO bioactivity, diminished vasodilation capacity, and accelerated progression of arteriosclerosis.[22,23] (3) Inflammation induces a osteoblast-like phenotype in smooth muscle cells, increasing the expression of osteoblastic markers while downregulating the expression of vascular calcification inhibitors, such as fetuin-A, ultimately resulting in vascular wall calcification and increased arterial stiffness.[24] Our findings are consistent with the conclusions of the Swedish Malmo Diet and Cancer study.[25] Therefore, we recommend hs-CRP as a prospective biomarker for assessing the rate of arteriosclerosis progression.

Strengths and Limitations

Although this study confirms that hs-CRP is an independent risk factor for arteriosclerosis, there are certain limitations. (1) The cohort study grouped participants based on the baseline hs-CRP levels at the start of follow-up, without considering the impact of dynamic changes in hs-CRP on baPWV; (2) There are numerous confounding factors that influence baPWV. Although we adjusted for potential risk factors, not all influencing factors were included in the analysis, which may affect the accuracy of the results; (3) Although cfPWV is the gold standard for assessing aortic stiffness, baPWV has a strong correlation with cfPWV, and thus the results still offer valuable reference.

Conclusion

This study is the first to demonstrate that elevated hs-CRP serves as an independent risk factor for the progression of arteriosclerosis in the general population of northern China. As a simple and effective inflammatory biomarker, hs-CRP may help identify individuals at high risk of developing arterial stiffness at an early stage.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The Kailuan study was approved by the Kailuan General Hospital's ethics committee (No. 200605). Before participation, all individuals provided written informed consent. Acknowledgments We sincerely express our gratitude to all the staff and participants of the Kailuan Cohort for their invaluable contributions to this project.

Acknowledgments

We sincerely express our gratitude to all the staff and participants of the Kailuan Cohort for their invaluable contributions to this project.

Disclosure

The authors declared no conflicts of interest in this work.

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