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Association between the C-reactive protein-triglyceride glucose index and incident hypertension across different blood pressure states: findings from the CHARLS

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Abstract

Background Hypertension is a major public health burden. Early detection of high-risk individuals is critical for prevention. The C-reactive protein-triglyceride glucose index (CTI), integrating insulin resistance and inflammation, may aid risk stratification, but its predictive value across different blood pressure (BP) states is unclear.

Methods This prospective study included 5494 non-hypertensive adults from the China Health and Retirement Longitudinal Study (CHARLS), classified into normal BP (< 120/70mmHg) and elevated BP (120–139/70-89mmHg) groups. CTI was calculated from triglyceride-glucose (TyG) index and C-reactive protein (CRP). Multivariable logistic regression examined the association between CTI and incident hypertension over 7 years. Restricted cubic splines and receiver operating characteristic analyses were employed to examine the dose-response relationship and predictive performance. The incremental predictive value of CTI was assessed by net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results During the 7-year follow-up, 1772 participants (32.2%) developed hypertension. A significant, linear dose-response relationship was observed between CTI and hypertension risk. In the fully adjusted model, each 1-unit increase in CTI was associated with a higher risk of hypertension in both the normal BP group (odds ratio [OR] = 1.19, 95% confidence interval [CI]: 1.07–1.33) and the elevated BP group (OR = 1.12, 95% CI: 1.03–1.21). When analyzed by quartiles, the association was most pronounced in the highest quartile (Q4), with a stronger effect size observed in the normal BP group (Q4 vs. Q1: OR = 1.57, 95% CI: 1.15–2.16) than in the elevated BP group (OR = 1.36, 95% CI: 1.10–1.68). Adding CTI to conventional risk factors significantly improved risk prediction overall (NRI = 0.114, P < 0.001). A significant interaction was found with alcohol consumption in the elevated BP group (P for interaction = 0.009), indicating a stronger association among drinkers. Sensitivity analyses confirmed the robustness of all findings.

Conclusions CTI is a robust predictor of future hypertension in both normal and elevated BP states, with a particularly strong effect in normotensive individuals. Its integration into clinical practice could enhance early-risk stratification for primordial and primary prevention.

Introduction

Hypertension is a major global public health challenge, affecting over one billion adults and contributing significantly to cardiovascular disease, stroke, and premature mortality worldwide [1, 2]. The recent 2024 European Society of Cardiology (ESC) guidelines formally recognized "Elevated Blood Pressure (BP)" [systolic BP (SBP) 120-139mmHg and/or diastolic BP (DBP) 70-89mmHg] as a distinct clinical category, underscoring the continuum of cardiovascular risk [3]. Individuals with elevated BP have a substantially higher risk of progressing to clinical hypertension than those with normal BP [4], making this subgroup a critical target for population-level primary prevention. Even among individuals with normal BP, underlying

metabolic and inflammatory disturbances can predispose them to future hypertension [5, 6], highlighting the need for effective tools for early risk identification in general populations.

The triglyceride-glucose (TyG) index, a well-validated and readily available surrogate marker of insulin resistance [7], has been consistently associated with an increased risk of incident hypertension across diverse populations [8-10]. The proposed mechanisms underpinning this association involve insulin-induced sympathetic nervous system overactivation [11], inflammation [12], oxidative stress [13], and endothelial dysfunction [14]. Separately, elevated levels of C-reactive protein (CRP), a canonical marker of systemic inflammation, have also been independently linked to future hypertension risk [15, 16]. Chronic, low-grade inflammation promotes vascular injury through oxidative stress, impaired nitric oxide bioavailability, and vascular smooth muscle cell proliferation, leading to increased arterial stiffness [17, 18].

Based on the established pathophysiological roles of insulin resistance and inflammation in hypertension, a composite indicator capable of simultaneously capturing both processes provides a compelling new approach for risk stratification. The C-reactive protein-triglyceride glucose index (CTI), which comprehensively reflects both insulin resistance and inflammation, has been demonstrated to predict the incidence of stroke and cardiovascular disease, as well as all-cause mortality [19-21]. However, its association with the risk of incident hypertension remains unexplored. Crucially, no study has yet evaluated whether CTI's predictive utility is consistent across individuals with normal and elevated BP—a key consideration for implementing stratified prevention strategies in public health and primary care settings.

To address this gap, we conducted a prospective analysis using data from the nationally representative China Health and Retirement Longitudinal Study (CHARLS). We aimed to investigate the association between CTI and incident hypertension and to evaluate its predictive performance across adults with normal and elevated BP. Our findings could inform the use of this simple, integrative biomarker for improving early detection and primordial prevention of hypertension in community-based populations.

Methods

Study participants and design

This study utilized data from the CHARLS, a nationally representative prospective cohort that employed a multi-stage, stratified probability sampling design to recruit participants aged 45 years and older from 28 provinces, 150 counties/districts, and 450 communities/villages across China [22]. The baseline survey was conducted in 2011, during which trained interviewers administered standardized face-to-face questionnaires to collect comprehensive demographic and health-related information. Follow-up surveys were carried out biennially to track health status changes. The CHARLS study protocol was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent. This study followed the Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) guidelines, and all methods were performed in accordance with relevant ethical regulations.

From an initial pool of 11847 participants with available blood samples at baseline, we applied the following exclusion criteria during the 7-year follow-up period (2011–2018): (1) prevalent hypertension or lack of hypertension diagnosis information at baseline (n = 5961); (2) missing data on fasting plasma glucose (FBG), triglycerides (TG), and CRP (n = 101); (3) age < 45 years or missing demographic data (n = 247); (4) extreme CTI values (exceeding ± 3 standard deviations from the mean) (n = 44). After these exclusions, 5494 participants were included in the final analysis. The study cohort comprised 2178 participants with normal BP (defined as SBP < 120mmHg and DBP < 70mmHg) and 3316 participants with elevated BP (defined as SBP 120–139mmHg and/or DBP 70–89mmHg) at baseline [3]. A detailed flowchart of participant selection is presented in Fig. 1.

Calculation of CTI

The CTI index is calculated by using the following formula [23]: CTI = 0.412 × Ln (CRP [mg/L]) + Ln (TG [mg/dL] × FPG [mg/dL])/2.

Assessment of hypertension

Hypertension was defined as either: (1) having an average SBP ≥ 140mmHg and/or DBP ≥ 90mmHg based on objective measurement [3], or (2) self-reported physician-diagnosed hypertension in response to the standardized question: “Have you been diagnosed with hypertension by a doctor?”, or (3) current use of antihypertensive medication. Participants meeting any of these criteria were classified as having hypertension. BP measurement was performed using an Omron™ HEM-7112 monitor (Omron Healthcare Co., Ltd., Dalian, China). Participants were seated in a comfortable position with feet flat on the floor and the left arm supported at heart level, palm facing upward. The cuff was placed directly on the skin approximately 1.5 cm above the elbow, ensuring proper alignment of the air tube along the midline of the arm. After initiating the device, the cuff automatically inflated and subsequently displayed SBP, DBP, and pulse rate before deflating. Three consecutive readings were taken on the left arm with a rest interval of 45–60 seconds between each measurement. The average of these three readings was used as the baseline BP value [22].

Assessment of covariates

Data on a comprehensive set of covariates was collected through standardized interviews, physical examinations, and laboratory tests. These included sociodemographic characteristics (age, gender, educational level, residence, and marital status), lifestyle factors (smoking status and alcohol consumption), anthropometric measurements (SBP, DBP, and body mass index [BMI]), and self-reported medical history (stroke, heart disease, diabetes, dyslipidemia, kidney disease, and liver disease).

Laboratory analyses included measurements of FBG, glycated hemoglobin (HbA1c), total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and CRP.

Statistical analysis

Continuous variables are presented as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Categorical variables are expressed as frequencies (percentages). Group differences for continuous variables were assessed using one-way ANOVA for normally distributed data or the Kruskal–Wallis test for non-normally distributed data, while Pearson's chi-square test was used for categorical variables. Participants were categorized into four groups based on quartiles of CTI. To enhance the robustness of our findings, CTI was evaluated both as a continuous variable and as a categorical variable (quartiles). Although the proportion of missing data was low, we performed multiple imputation by chained equations (MICE) under the assumption of missing at random (50 iterations) to maximize the sample size and preserve statistical power. Detailed information regarding the extent of missingness and the specific imputation procedures is provided in Supplementary Table S1.

Logistic regression models were constructed to examine the association between CTI and hypertension incidence, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). CTI was incorporated both as a continuous variable and as a categorical variable based on quartiles. Three models were developed: Model 1 was unadjusted; Model 2 was adjusted for age, gender, marital status, education level, residence, smoking status, and drinking status; Model 3 further adjusted for diabetes, dyslipidemia, heart disease, stroke, kidney disease, liver disease, BMI, LDL-c, and TC on the basis of Model 2. To examine potential non-linear associations, restricted cubic spline (RCS) models were fitted for the overall cohort and separately stratified by baseline BP status (normal and elevated BP). Receiver operating characteristic (ROC) analysis was further employed to evaluate and compare the predictive performance of CTI, TyG, and CRP for hypertension incidence. To quantify the incremental predictive value of CTI beyond established risk factors, we calculated the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The analysis compared the fully adjusted clinical model (Model 3) against the same model with the addition of CTI.

To further investigate the association between CTI and hypertension incidence, subgroup analyses were conducted separately among participants with normal BP and those with elevated BP. Stratification and interaction tests were performed based on age (< 60 and ≥ 60 years), gender, smoking status, drinking status, BMI (< 24 and ≥ 24 kg/m²), diabetes status, and dyslipidemia. To evaluate the robustness of the findings, multiple sensitivity analyses were carried out: Firstly, we reanalyzed the data after excluding all participants with missing values; Secondly, we excluded non-fasting individuals; Thirdly, we removed participants with less than 2 years of follow-up. Additionally, E-values were calculated to estimate the minimum strength of association that an unmeasured confounder would need to have with both CTI and hypertension to fully explain the observed association. All statistical analyses were performed using R

software (version 4.4.1). Two-sided tests were applied, and a P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of participants by BP status

A total of 5494 participants from the CHARLS dataset were included in this study, with a mean age of 57.62 ± 8.81 years, and 47.5% were male. Participants were classified into a normal BP group (n=2178; 39.6%) and an elevated BP group (n=3316; 60.4%). Significant differences were observed in several baseline characteristics between the groups. Compared with the normal BP group, the elevated BP group had a higher mean age (57.81 ± 8.85 vs. 57.31 ± 8.75 years), a greater proportion of males (49.2% vs. 44.9%), a lower percentage of rural residents (83.2% vs. 85.6%), and a higher prevalence of current drinkers (32.8% vs. 29.7%). Moreover, the elevated BP group showed significantly higher values in BMI, FBG, TC, TG, LDL-c, CRP, TyG, and CTI (all P < 0.001), along with lower HDL-c levels (P < 0.001). The distribution of HbA1c levels also significantly differed between the groups, with a shift towards higher values in the elevated BP group (P < 0.001). The detailed baseline characteristics are presented in Table 1. A further characterization of the cohort, stratified by incident hypertension status, revealed that participants who developed the condition were significantly older and had a more adverse cardiometabolic profile at baseline (Table S2).

Table 1 Baseline characteristics of participants

Characteristics	Overall	Normal BP	Elevated BP	P value
N	5494	2178	3316	
Gender, n (%)				0.002
Male	2608 (47.5)	977 (44.9)	1631 (49.2)	
Female	2886 (52.5)	1201 (55.1)	1685 (50.8)	
Age, years	57.62 ± 8.81	57.31 ± 8.75	57.81 ± 8.85	0.039
Marital status, n (%)				0.348
Married	4711 (85.7)	1880 (86.3)	2831 (85.4)	
Other	783 (14.3)	298 (13.7)	485 (14.6)	
Education level, n (%)				0.048
Elementary school or below	3758 (68.4)	1530 (70.2)	2228 (67.2)	
Middle school	1582 (28.8)	587 (27.0)	995 (30.0)	
College or above	154 (2.8)	61 (2.8)	93 (2.8)	
Residence, n (%)				0.022
Rural	4624 (84.2)	1864 (85.6)	2760 (83.2)	
Urban	870 (15.8)	314 (14.4)	556 (16.8)	
Smoking status, n (%)				0.097
Never	3322 (60.5)	1353 (62.1)	1969 (59.4)	
Former	436 (7.9)	159 (7.3)	277 (8.4)	
Current	1736 (31.6)	666 (30.6)	1070 (32.3)	
Drinking status, n (%)				0.008
Never	3370 (61.3)	1355 (62.2)	2015 (60.8)	
Former	391 (7.1)	177 (8.1)	214 (6.5)	
Current	1733 (31.5)	646 (29.7)	1087 (32.8)	
Stroke, n (%)	73 (1.3)	31 (1.4)	34 (1.3)	0.707
Heart disease, n (%)	456 (8.3)	179 (8.2)	277 (8.4)	0.899
Diabetes, n (%)	216 (3.9)	72 (3.3)	144 (4.3)	0.062
Dyslipidemia, n (%)	325 (5.9)	121 (5.6)	204 (6.2)	0.391

Kidney disease, n (%)	313 (5.7)	133 (6.1)	180 (5.4)	0.317
Liver disease, n (%)	188 (3.4)	87 (4.0)	101 (3.0)	0.069
SBP, mmHg	117.58 ± 11.68	107.12 ± 7.42	124.44 ± 8.43	<0.001
DBP, mmHg	70.02 ± 8.87	62.05 ± 5.51	75.27 ± 6.40	<0.001
BMI, kg/m2	22.48 (20.39, 24.82)	21.83 (19.94, 24.03)	22.92 (20.76, 25.39)	<0.001
FBG, mg/dl	100.98 (93.42, 110.34)	99.18 (92.34, 108.54)	102.06 (94.14, 112.14)	<0.001
HbA1c, %	5.10 (4.90, 5.40)	5.10 (4.80, 5.40)	5.10 (4.90, 5.40)	<0.001
TG, mg/dl	98.24 (71.68, 141.60)	92.93 (69.03, 130.10)	101.78 (74.34, 147.79)	<0.001
TC, mg/dl	190.60 ± 37.29	186.65 ± 35.88	193.20 ± 37.97	<0.001
HDL-c, mg/dl	52.53 ± 15.30	53.54 ± 15.16	51.86 ± 15.36	<0.001
LDL-c, mg/dl	115.42 ± 33.55	112.19 ± 31.58	117.54 ± 34.62	<0.001
CRP, mg/dl	0.90 (0.50, 1.88)	0.81 (0.47, 1.74)	0.95 (0.53, 1.95)	<0.001
TyG	8.58 ± 0.60	8.51 ± 0.58	8.63 ± 0.61	<0.001
CTI	8.61 ± 0.77	8.51 ± 0.75	8.67 ± 0.77	<0.001

Abbreviation: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein; TyG, triglyceride-glucose; CTI, C-reactive protein-triglyceride glucose index.

Association between the CTI and hypertension incidence according to BP status

Logistic regression model were employed to assess the association between the CTI and the risk of incident hypertension, stratified by baseline BP status. In individuals with normal BP, each 1-unit increase in CTI was associated with a significantly elevated risk of hypertension in all models (Model 1: OR = 1.26, 95% CI: 1.14-1.40; Model 2: OR = 1.25, 95% CI: 1.12-1.38; Model 3: OR = 1.19, 95% CI: 1.07-1.33). When analyzed by CTI quartiles, compared to the lowest quartile (Q1), participants in Q3 (Model 3: OR = 1.38, 95% CI: 1.01-1.88) and Q4 (Model 3: OR = 1.57, 95% CI: 1.15-2.16) had a significantly higher risk of developing hypertension after full adjustment. Similarly, in the elevated BP group, a positive association was also found between per 1-unit increase in CTI and hypertension risk across all models (Model 3: OR = 1.12, 95% CI: 1.03-1.21). The quartile analysis revealed that only the highest quartile (Q4) was significantly associated with an increased risk compared to Q1 in the fully adjusted model (Model 3: OR = 1.36, 95% CI: 1.10-1.68). The strength of the association was more pronounced in the normal BP group than in the elevated BP group. Detailed results of the regression analyses are presented in Table 2.

Table 2 Association between the CTI and hypertension incidence according to BP status

	Event,n	Model 1		Model 2		Model 3	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Normal BP							
CTI (per 1 unit)	427	1.26 (1.14, 1.40)	<0.001	1.25 (1.12, 1.38)	<0.001	1.19 (1.07, 1.33)	0.002
Q1	100	Ref		Ref		Ref	
Q2	106	1.23 (0.91, 1.67)	0.168	1.18 (0.87, 1.60)	0.288	1.17 (0.86, 1.59)	0.310
Q3	105	1.45 (1.07, 1.97)	0.016	1.40 (1.03, 1.91)	0.030	1.38 (1.01, 1.88)	0.043
Q4	116	1.82 (1.35, 2.46)	<0.001	1.75 (1.29, 2.37)	<0.001	1.57 (1.15, 2.16)	0.005
Elevated BP							
CTI (per 1 unit)	1345	1.14 (1.06, 1.22)	<0.001	1.14 (1.06, 1.22)	<0.001	1.12 (1.03, 1.21)	0.005
Q1	266	Ref		Ref		Ref	
Q2	305	1.07 (0.87, 1.32)	0.496	1.06 (0.86, 1.31)	0.578	1.03 (0.83, 1.27)	0.778
Q3	361	1.23 (1.00, 1.50)	0.049	1.18 (0.96, 1.45)	0.113	1.14 (0.93, 1.40)	0.213
Q4	413	1.45 (1.19, 1.77)	<0.001	1.43 (1.17, 1.76)	<0.001	1.36 (1.10, 1.68)	0.005

Model 1: Unadjusted model

Model 2: Adjusted for age, gender, marital status, education level, residence, smoking status and drinking status; Model 3: Model 2+ diabetes, dyslipidemia, heart disease, stroke, kidney disease, liver disease, BMI, TC, LDL-c.

Abbreviation: CTI, C-reactive protein-triglyceride glucose index; BP, blood pressure; OR, odds ratio; CI, confidence interval; BMI, body mass index; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol

RCS analyses demonstrated a significant, linear dose–response relationship between CTI and hypertension risk in the overall population (P-nonlinear = 0.322) and in both the normal BP (P-nonlinear = 0.899) and elevated BP (P-nonlinear = 0.301) groups (Fig. 2). ROC analysis showed that the predictive performance of CTI (AUC = 0.613) was comparable to that of the TyG index (AUC = 0.614) and CRP (AUC

= 0.606) in the overall population, with similar trends observed across BP subgroups (Figure S1). Stratified analyses confirmed the incremental predictive value of CTI (Table 3). In the overall population, adding CTI significantly improved both continuous NRI (0.114, P < 0.001) and IDI (0.0051, P < 0.001). A similar pattern was seen in the elevated BP group. In the normal BP group, IDI improvement remained significant (0.0043, P = 0.009), while the NRI increase was positive but nonsignificant (P = 0.072).

Table 3 Incremental predictive value of CTI for incident hypertension

Study population	Model	NRI (95%CI)	P value	IDI (95%CI)	P value
Overall	Basic model	Ref	-	Ref	-
	+ CTI	0.114 (0.057, 0.170)	<0.001	0.0051 (0.0030, 0.0070)	<0.001
Normal BP	Basic model	Ref	-	Ref	-
	+ CTI	0.097 (-0.009, 0.203)	0.072	0.0043 (0.0011, 0.0075)	0.009
Elevated BP	Basic model	Ref	-	Ref	-
	+ CTI	0.074 (0.005, 0.143)	0.036	0.0024 (0.0007, 0.0040)	0.004

The basic model included age, gender, marital status, education level, residence, smoking status, drinking status, diabetes, dyslipidemia, heart disease, stroke, kidney disease, liver disease, BMI, TC, and LDL-c. NRI, net reclassification improvement; IDI, integrated discrimination improvement; CTI, C-reactive protein-triglyceride glucose index; BP, blood pressure; CI, confidence interval.

Subgroup analysis

Subgroup analyses were conducted to examine whether the association between CTI and incident hypertension was modified by key demographic and clinical factors, with results stratified by baseline BP status. Among participants with normal BP (Table 4), the positive association between elevated CTI quartiles and hypertension risk was generally consistent across all subgroups, including those defined by age, gender, smoking status, drinking status, BMI, diabetes, and dyslipidemia. No statistically significant interaction was observed for any of these variables (all P for interaction > 0.05). In the elevated BP group (Table 5), a significant interaction was identified between CTI and drinking status on hypertension risk (P for interaction = 0.009). Specifically, the association was stronger among drinkers, with those in the highest CTI quartile exhibiting substantially increased odds of hypertension (OR = 1.94, 95% CI: 1.35–2.78) compared to non-drinkers. No other significant interactions were detected for the remaining variables in this group (all P for interaction > 0.05).

Table 4 Subgroup analysis of the association between CTI and hypertension in normal BP participants

Variable	Q1	Q2	Q3	Q4	P for interaction
Age					0.623
<60	Ref	1.12 (0.75, 1.66)	1.24 (0.82, 1.87)	1.77 (1.19, 2.63)	
≥60	Ref	1.31 (0.82, 2.10)	1.44 (0.90, 2.31)	1.43 (0.87, 2.33)	
Gender					0.547
Male	Ref	1.43 (0.93, 2.19)	1.31 (0.83, 2.06)	1.65 (1.05, 2.58)	
Female	Ref	1.00 (0.65, 1.54)	1.35 (0.89, 2.06)	1.59 (1.04, 2.43)	
Smoking					0.252
Yes	Ref	1.05 (0.63, 1.74)	0.90 (0.52, 1.54)	1.17 (0.69, 1.99)	
No	Ref	1.31 (0.90, 1.92)	1.65 (1.12, 2.41)	1.98 (1.35, 2.91)	
Drinking					0.299
Yes	Ref	1.59 (0.94, 2.69)	1.14 (0.64, 2.03)	1.73 (0.99, 3.04)	
No	Ref	1.02 (0.70, 1.49)	1.40 (0.97, 2.02)	1.61 (1.12, 2.33)	
BMI					0.438
<24	Ref	1.15 (0.82, 1.61)	1.33 (0.93, 1.89)	1.42 (0.98, 2.05)	
≥24	Ref	1.47 (0.73, 2.97)	1.53 (0.78, 2.97)	2.45 (1.30, 4.64)	
Diabetes					0.879
Yes	Ref	0.64 (0.09, 4.54)	0.51 (0.07, 3.48)	0.95 (0.17, 5.26)	
No	Ref	1.20 (0.88, 1.63)	1.36 (0.99, 1.85)	1.67 (1.22, 2.29)	
Dyslipidemia					0.891
Yes	Ref	0.88 (0.23, 3.39)	1.13 (0.33, 3.79)	1.12 (0.31, 4.05)	
No	Ref	1.20 (0.88, 1.64)	1.32 (0.96, 1.82)	1.69 (1.23, 2.32)	

Abbreviation: CTI, C-reactive protein-triglyceride glucose index; BP, blood pressure; BMI, body mass index

Table 5 Subgroup analysis of the association between CTI and hypertension in elevated BP participants

Variable	Q1	Q2	Q3	Q4	P for interaction
Age					0.898
<60	Ref	1.08 (0.83, 1.42)	1.10 (0.84, 1.43)	1.25 (0.96, 1.64)	
≥60	Ref	0.97 (0.69, 1.36)	1.14 (0.82, 1.58)	1.28 (0.91, 1.80)	
Gender					0.086
Male	Ref	1.19 (0.89, 1.59)	1.06 (0.79, 1.42)	1.47 (1.09, 1.97)	
Female	Ref	0.89 (0.65, 1.20)	1.15 (0.86, 1.54)	1.09 (0.81, 1.46)	
Smoking					0.459
Yes	Ref	1.05 (0.73, 1.51)	0.93 (0.64, 1.34)	1.25 (0.86, 1.83)	
No	Ref	1.03 (0.79, 1.33)	1.23 (0.95, 1.58)	1.29 (1.00, 1.66)	
Drinking					0.009
Yes	Ref	1.12 (0.78, 1.60)	1.13 (0.78, 1.62)	1.94 (1.35, 2.78)	
No	Ref	0.98 (0.75, 1.27)	1.10 (0.85, 1.41)	1.02 (0.79, 1.32)	
BMI					0.415
<24	Ref	1.09 (0.85, 1.40)	1.10 (0.85, 1.41)	1.14 (0.87, 1.49)	
≥24	Ref	0.92 (0.61, 1.38)	1.14 (0.79, 1.66)	1.41 (0.98, 2.02)	
Diabetes					0.581
Yes	Ref	2.64 (0.49, 14.15)	2.57 (0.52, 12.77)	2.14 (0.51, 9.00)	
No	Ref	1.01 (0.82, 1.25)	1.09 (0.89, 1.35)	1.25 (1.01, 1.54)	
Dyslipidemia					0.236
Yes	Ref	0.54 (0.20, 1.45)	0.90 (0.34, 2.43)	0.68 (0.26, 1.75)	
No	Ref	1.06 (0.85, 1.31)	1.11 (0.90, 1.37)	1.32 (1.06, 1.63)	

Abbreviation: CTI, C-reactive protein-triglyceride glucose index; BP, blood pressure; BMI, body mass index.

Sensitivity analysis

To assess the robustness of our findings, we performed three sensitivity analyses. First, after excluding all participants with missing data, the association between CTI and hypertension risk remained significant in both normal and elevated BP groups (Table S3). Second, the results were consistent after further excluding non-fasting individuals (Table S4). Third, a similar pattern was observed when participants with less than two years of follow-up were removed (Table S5). Furthermore, the E-values calculated based on the Model 3 were 1.47 for the overall population, 1.50 for the normal BP group, and 1.36 for the elevated BP group. These values suggest that an unmeasured confounder would need to be moderately associated with both CTI and hypertension to fully explain away the observed associations.

Discussion

In this prospective, national cohort study, we demonstrated that the CTI was significantly associated with an increased risk of incident hypertension among middle-aged and older Chinese adults. RCS analyses revealed a positive and linear dose-response relationship between CTI and hypertension risk in the overall population and across BP strata. This association remained robust after adjusting for a wide range of demographic, behavioral, and clinical confounders and was consistently observed in both normal and elevated BP groups at baseline, with a more pronounced effect size in the former. The predictive performance of CTI was comparable to that of its individual components, the TyG index and CRP, as indicated by ROC analysis. The stability of our results was further confirmed through extensive sensitivity analyses and quantitative evaluation of unmeasured confounding using E-values.

Our study builds upon the established concept of the CTI, initially developed by Ruan et al. [23], as a composite marker integrating the TyG index, a reliable surrogate of insulin resistance, and CRP, a canonical biomarker of systemic inflammation. Substantial evidence from observational studies has established a positive association between the TyG index and the risk of hypertension [8, 10, 24]. Notably, this association is supported by genetic evidence; bidirectional Mendelian randomization analyses confirm that elevated TyG index levels are causally linked to an increased risk of incident hypertension [25]. Furthermore, long-term cohort studies have demonstrated that longitudinal trajectories of the TyG index are significantly correlated with hypertension development [26]. Similarly, a comprehensive meta-analysis encompassing 14 prospective cohorts indicated that higher circulating CRP levels are associated with an elevated risk of hypertension [27].

While the CTI was initially conceptualized to integrate metabolic and inflammatory pathways, its utility specifically for predicting hypertension in a nationally representative cohort remained unexplored. Our study validates the application of this composite biomarker in this new context, demonstrating its strong and independent association with incident hypertension. To the best of our knowledge, this is the first study to establish CTI as a robust predictor of hypertension risk in a large, prospective cohort.

Importantly, our stratified analyses provide crucial new insights by revealing that this association holds significant predictive value across the entire BP spectrum. The particularly pronounced effect observed among individuals with normal BP at baseline underscores the potential of CTI as a tool for early risk stratification in this subpopulation, for whom preventive interventions could be most beneficial.

The robust association between CTI and hypertension risk is strongly supported by the well-established pathophysiological roles of its two core components. The TyG index, reflecting insulin resistance [7], contributes to hypertension through multiple mechanisms. It can trigger sympathetic nervous system overactivation [11] and promotes renal sodium reabsorption, leading to increased blood volume and BP [28]. Furthermore, the metabolic consequences of insulin resistance, such as hyperglycemia and dyslipidemia, synergize with hypertensive processes to induce vascular endothelial dysfunction and microvascular damage [29]. For instance, insulin resistance can activate tissue inflammation [12] and oxidative stress [13], accelerate arterial stiffness [14], and interact with obesity-related mechanisms like hyperinsulinemia to drive the pathological progression of hypertension [29].

Concurrently, the CRP component of CTI captures the role of chronic low-grade inflammation. Inflammation contributes to hypertension primarily by causing vascular dysfunction and endothelial injury [30]. Mechanistically, inflammatory cytokines enhance vascular smooth muscle cell contractility and impair vascular relaxation, resulting in increased vascular tone [17, 18]. This process is often mediated by the activation of oxidative stress signaling [17]. Moreover, chronic inflammation can directly impair microvascular function and activate immune pathways, such as promoting the release of pro-inflammatory cytokines, thereby serving as a key driver of hypertension development [31].

Critically, these pathways are not isolated; they form a vicious cycle whereby insulin resistance amplifies inflammatory responses, and inflammation, in turn, exacerbates metabolic dysfunction [32]. The CTI, by integrating both pathways, provides a holistic measure of this synergistic adverse physiology, which may explain its strong association with hypertension risk. The comparable predictive performance of CTI to its individual components, as indicated by ROC analysis, does not diminish its clinical value but may reflect the substantial overlap in the pathophysiology captured by TyG and CRP. The value of CTI may therefore lie in its ability to identify a high-risk phenotype characterized by the confluence of significant metabolic and inflammatory derangements, which could be particularly valuable for guiding targeted interventions aimed at both pathways simultaneously.

Collectively, our findings position the CTI as a robust tool for refining hypertension risk assessment. The significant NRI (11.4%) and IDI establish CTI's value for enhancing individual risk stratification. This is a crucial distinction from its population-level discriminative capacity (AUC), which was comparable to its components, likely because the pathophysiological pathways of insulin resistance and inflammation are deeply intertwined and captured to some extent by both TyG and CRP. The NRI, however, demonstrates CTI's superior ability to correctly reclassify individuals into their true risk categories. This utility is further exemplified in specific high-risk subgroups; notably, alcohol consumption significantly amplified the CTI-associated hypertension risk among individuals with elevated BP (P for interaction = 0.009). This

suggests that CTI not only identifies baseline risk but is also sensitive to behaviorally modified risk, likely through alcohol-induced exacerbation of insulin resistance and inflammation [33, 34]. Consequently, CTI serves as a practical, integrative tool derived from routine parameters (TG, FBG, CRP), enabling early risk identification and guiding targeted interventions—such as prioritized alcohol moderation counseling—thereby advancing precise primordial and primary prevention strategies.

Limitation

Several limitations of our study should be considered. First, despite adjusting for a comprehensive set of covariates in our multivariable models, the possibility of residual confounding due to unmeasured or imperfectly measured factors (e.g., dietary habits, physical activity levels, genetic predisposition) cannot be entirely ruled out. However, we employed E-value analysis to quantify the potential impact of such confounding, and the results suggested that the observed associations were relatively robust. Second, the CTI and other laboratory parameters were based on a single measurement at baseline, which may not accurately reflect long-term exposure levels and could lead to potential misclassification bias, likely diluting the true effect sizes toward the null. Third, as our study cohort consisted of middle-aged and older Chinese adults, the generalizability of our findings to other ethnicities or younger populations requires further validation. Finally, while the CHARLS study is nationally representative, its complex survey design, though accounted for in some analyses, may introduce intricacies not fully captured in all our models.

Conclusion

In conclusion, our prospective study establishes the CTI as a robust and independent predictor of incident hypertension that significantly improves the reclassification of individual risk. Calculable from routine clinical parameters, the CTI provides a practical tool not only for the early identification of high-risk individuals but also for enhancing the precision of primordial and primary prevention strategies.

Abbreviations

ESC	European Society of Cardiology
BP	Blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TyG	Triglyceride-glucose
CRP	C-reactive protein
CTI	C-reactive protein-triglyceride glucose index
CHARLS	China Health and Retirement Longitudinal Study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
FBG	Fasting blood glucose
TG	Triglycerides
BMI	Body mass index
HbA1c	Glycated hemoglobin
TC	Total cholesterol
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
MICE	Multiple imputation by chained equations
OR	Odds ratio
CI	Confidence interval
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
AUC	Area under the curve

Declarations

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Author Contributions

LX and WS conceptualized and designed the study. LX performed the formal analysis, data curation, visualization, and wrote the original draft. WJ, TY, FQ, and ZT contributed to investigation and resources. JJX contributed to software, validation, and data curation. All authors participated in the interpretation of the results, critically reviewed the manuscript, and approved the final version for publication. WS provided supervision and project administration.

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Availability of data and materials

The data used in this study can be obtained from the publicly accessible CHARLS database (http://charls.pku.edu.cn). Additionally, any derived data generated during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (Approval Number: IRB00001052-11015 for the main household survey including anthropometric measurements, and IRB00001052-11014 for biomarker collection). All participants provided written informed consent prior to participation.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

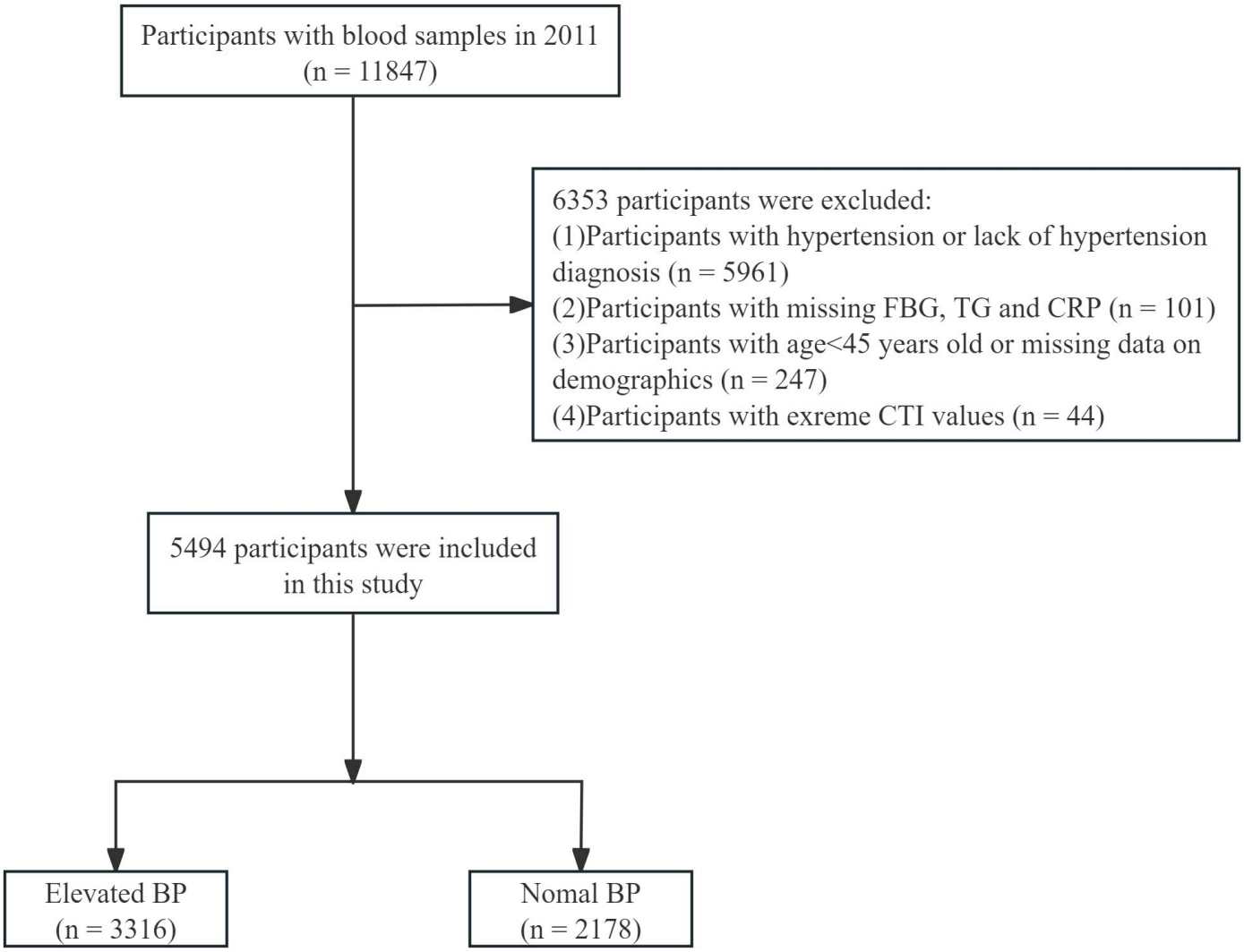


Figure 1

Flowchart of the study participants.

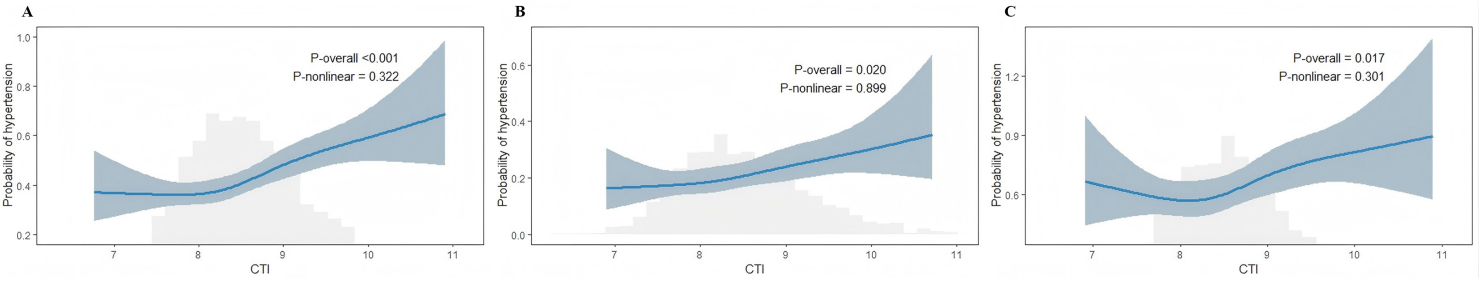


Figure 2

Restricted cubic spline analyses of the association between the CTI and incident hypertension risk in (A) the overall population, (B) individuals with normal BP, and (C) individuals with elevated BP. The model was adjusted for age, gender, marital status, education level, residence, smoking status and drinking status, diabetes, dyslipidemia, heart disease, stroke, kidney disease, liver disease, BMI, TC, LDL-c. CTI, C-reactive protein-triglyceride glucose index; BP, blood pressure; BMI, body mass index; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol.

Supplementary Files

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