Blood Pressure Reactivity to the Cold Pressor Test Predicts Hypertension Among Chinese Adults: The GenSalt Study

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BACKGROUND
Blood pressure (BP) hyper-reactivity to the cold pressor test (CPT) has been suggested as a predictor of hypertension. We examined whether BP reactivity to the CPT was associated with hypertension incidence among the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study participants from China.

METHODS
A total of 1,961 GenSalt study participants without any antihypertensive treatment completed the CPT at the baseline examination. Hypertension status was assessed at baseline (2003–2005) and 2 follow-up visits (2008–2009 and 2011–2012).

RESULTS
After adjustment for multiple covariates, both systolic BP (SBP) and diastolic BP reactivity to the CPT were significantly associated with hypertension incidence. For example, the multivariable adjusted odds ratios (ORs, 95% CI) of developing hypertension were 0.92 (0.66, 1.29), 1.42 (1.03, 1.97), and 1.45 (1.05, 2.00) for participants with maximum SBP responses of 6.7–12.0, 12.1–19.2, and ≥19.3 mm Hg, respectively, compared to those with responses of <6.7 mm Hg (*P* for trend = 0.006). Likewise, the multivariable-adjusted ORs (95% CI) of hypertension were 1.12 (0.79, 1.57), 1.62 (1.15, 2.29), and 1.82 (1.30, 2.55) for participants with the area under the curve of SBP responses of 3.0–16.0, 16.1–29.9, and ≥ 30.0 mm Hg·min, respectively, compared to those with responses of < 3.0 mm Hg·min (*P* for trend = 0.0001). The associations between BP reactivity variables and the risk of hypertension were not different among subgroups of sex, age, and baseline BP levels.

CONCLUSIONS
BP hyperreactivity to the cold stimulus may predict the risk of hypertension among Chinese adults.

Key Words: blood pressure; hypertension; risk factors; stress; sympathetic nervous system.

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Hypertension has become an enormous global health burden because of its high prevalence and related risk for cardiovascular disease and premature death.[1,2] Early detection of individuals at high risk for hypertension is crucial for its prevention. Cardiovascular hyperreactivity to stress has been hypothesized as an important risk factor for the development of hypertension and cardiovascular disease. The cold pressor test (CPT), which measures blood pressure (BP) reactivity to the stimulus of external cold, has been commonly used for the evaluation of cardiovascular reactivity to stress in normotensive and hypertensive subjects. In addition, BP reactivity to the CPT has been demonstrated to be a reproducible characteristic. Although individuals' response to the CPT may increase with aging, they tend to stay in a low or high track of response among people of the same age.[3–5]

Previous longitudinal studies have shown inconsistent findings with respect to the association between individual

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reactivity to the CPT and risk for hypertension.[6–15] A recent study has reported racial and sex differences in the association of BP reactivity to the CPT with the development of hypertension. Specifically, the effect of cold pressor reactivity on the risk of hypertension was apparent among whites and women, but not among blacks or men.[15] However, most previous studies only had 1 BP reading during the CPT, which was used to assess BP response to the stress test. A single BP measure during the CPT might not fully reflect the variation of BP reactivity among individuals. In addition, few studies have been conducted to examine the association between BP response to the CPT and the future risk for hypertension among the Chinese population.

In this study, we examined the association between BP reactivity to the CPT and the development of hypertension during a follow-up of more than 7 years among the Chinese participants of the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study. Participants' BP levels were measured at multiple time points during the CPT in the GenSalt study, which enabled a more comprehensive assessment of BP reactivity during the CPT. In addition, a previous GenSalt report showed that women, older age, and higher usual BP levels were associated with greater BP response during the CPT.[16] Therefore, we also examined whether the association of BP reactivity to the CPT with the risk of hypertension varied by these factors.

METHODS

Study subjects

All the study participants were from the GenSalt study, which was conducted in northern rural China. The GenSalt study was designed to identify genetic and environmental risk factors for BP responses to dietary sodium and potassium interventions and to the CPT.[17] A community-based BP screening was conducted among persons aged 18–60 years in the study villages to identify potential probands with systolic BP (SBP) of 130–160 mm Hg and/or diastolic BP (DBP) of 85–100 mm Hg and no use of antihypertensive medications. Probands and their parents, siblings, offspring, and spouses were recruited for the GenSalt study. Individuals who were older than 60 years; had stage 2 hypertension, secondary hypertension, or a history of clinical cardiovascular disease, diabetes, or chronic kidney disease; were using antihypertensive medication; or were pregnant were excluded from the CPT. A total of 1,961 study participants completed the CPT during baseline examination of the GenSalt study from 2003 to 2005. Two follow-up visits of the participants were conducted in 2008–2009 and 2011–2012, respectively. Among the 1,937 and 1,920 surviving participants with the CPT data at baseline, 1,759 (90.8%) and 1,698 (88.4%) were re-examined in the 2 follow-up visits, respectively. Institutional review boards at all participating institutes approved the GenSalt study. Written informed consent was obtained from each study participant.

Data collection at baseline and follow-up visits

During the GenSalt baseline examination, a standard questionnaire was administered by trained staff to obtain data on demographic characteristics, medical history, and lifestyle risk factors, including cigarette smoking, alcohol drinking, and physical activity. Current cigarette smoking was defined as having smoked ≥100 cigarettes during a lifetime and smoking at survey, while current alcohol drinking was defined as consumption of 12 or more drinks in the past 12 months. The physical activity information obtained from the questionnaire was converted to metabolic equivalent hours per day. Body weight, height, and waist circumference were measured according to a standard protocol.

The CPT was conducted using a standardized protocol by trained and certified technicians during the baseline examination in 2003–2005. After the participant had remained seated for 20 minutes, 3 pre-CPT BP measurements were obtained using a standard mercury sphygmomanometer on the right upper arm before the ice water immersion. Then, participants immersed their left hand in the ice water bath (3–5 °C) to just above the wrist for 1 minute. BP measurements at 0, 1, 2, and 4 minutes were obtained using a standard mercury sphygmomanometer on the right upper arm after the left hand had been removed from the ice water bath.

During both baseline and follow-up visits, 3 BP measurements were obtained by trained and certified technicians every morning during 3 consecutive days using a random-zero sphygmomanometer according to a standard protocol. BP was measured with the participant in the sitting position after a 5-minute rest. Additionally, participants were advised to avoid alcohol, coffee/tea, cigarette smoking, and exercise for at least 30 minutes before their BP measurements. The mean of the 9 BP measurements was calculated to assess individual hypertension status for baseline and follow-up visits. Hypertension was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg or use of antihypertensive medications. Stage 2 hypertension was defined as SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg or use of antihypertensive medications.

Statistical analysis

Maximum response and the total area under the curve (AUC) were used to measure the magnitude of individual response to the CPT at baseline. Maximum response was defined as the largest BP difference between BP at any of the 4 CPT tested time points (0, 1, 2, and 4 minutes after hand removal from the ice water) and pre-CPT BP. Most participants achieved maximum BP response at 0 minutes after hand removal from the ice water (92.3% and 82.1% of participants for SBP and DBP responses, respectively). The total AUC of BP response above pre-CPT BP levels was defined as the difference between the area under the response curve and the area below pre-CPT BP levels (from the time point of immersing the hand in ice water to 4 minutes post-CPT). The AUC of BP response to the CPT summarizes the magnitude of BP increase from pre-CPT to peak response and its recovery from peak response.

Means or percentages of baseline characteristics were calculated overall and by sex. In the association analyses between BP response variables and hypertension incidence, subjects with complete BP data during either follow-up visit were included. Because the exact time of hypertension onset could not be determined, the typical time-to-event analysis (survival analysis) was not appropriate for our data.

Therefore, a mixed effects logistic regression model was used to assess the association between BP reactivity to the CPT and hypertension incidence. The assessments of hypertension status during the 2 follow-up visits were treated as repeated measurements in these mixed models. The correlation within families of the GenSalt study was also accounted for in these models. Specifically, the study participants and family relationships were treated as random effects, with participants nested within families. For the analyses of incident hypertension, the participants diagnosed with hypertension at baseline were excluded. Because all the participants were free of stage 2 hypertension at baseline, no participants were excluded from the analyses of incident stage 2 hypertension. Multiple covariates, including sex, age, field centers, follow-up duration, body mass index (BMI), baseline BP, education, current cigarette smoking and alcohol drinking status, and physical activity, were adjusted in the mixed models. Multivariable-adjusted hypertension incidences were calculated by quartiles of BP reactivity variables, and odds ratios (ORs) for hypertension were also compared among quartiles using the lowest quartile of each BP reactivity variable as the reference group. To test for linear trend, the median BP response in each response variable quartile was treated as a continuous variable in mixed models. To further test for linear association between BP reactivity to the CPT and hypertension incidence, BP response variables were treated as continuous variables in mixed models. These BP response variables were continuously and nearly normally distributed among the study participants.[16] The risks for hypertension associated with a 1 standard deviation (SD) increase in response variables were calculated to compare the magnitude of effects by different response variables. Specifically, each response variable was divided by its SD and the new variable was used as the explanatory variable in mixed effects logistic regression models. The exponential of the coefficient for the new variable would be the OR associated with 1 SD change in the corresponding response variable. The associations of BP reactivity to the CPT and hypertension incidence were also tested according to subgroups of sex, age, and baseline BP levels. The difference in the associations among subgroups was tested by adding interaction terms of these subgroup variables with BP reactivity variables in the mixed models. The Proc Glimmix procedures in SAS (version 9.2; SAS Institute, Cary, NC) were used to perform the generalized linear mixed model analyses.

RESULTS

Characteristics of the participants and BP reactivity to the CPT at baseline are presented in Table 1. Men had greater BMI, higher levels of education and physical activity, and higher rates of smoking and drinking. SBP and DBP were higher for men than women. During the CPT at baseline, women exhibited greater maximum SBP response than men.

In general, all of the 4 BP reactivity variables were positively associated with the risk of hypertension in this study. Figures 1 and 2 show that the incidence of overall hypertension and stage 2 hypertension over the 7.4-year follow-up period consistently increased from the lowest quartile to the highest quartile of each BP reactivity variable. Compared with the lowest quartile of each reactivity variable (Table 2), the ORs for hypertension increased from the second to the highest quartile, and the linear trends were significant even after adjusting for multiple covariates (all *P* values for trend ≤ 0.002). The same trend was also observed for BP reactivity and stage 2 hypertension (all *P* values for trend ≤ 0.01).

Table 1. Participants' characteristics and blood pressure responses to the CPT at baseline

Variables	Overall (*N* = 1,961)	Women (*N* = 924)	Men (*N* = 1,037)	*P* value[a]
Age, years	39.9 ± 10.2	39.6 ± 10.2	40.1 ± 10.2	0.18
Body mass index, kg/m^2	23.3 ± 3.2	23.5 ± 3.2	23.1 ± 3.2	0.03
Secondary school or higher, %	64.8	49.8	78.2	<0.0001
Current cigarette smoking, %	31.6	0.3	59.4	<0.0001
Current alcohol drinking, %	29.8	3.0	53.6	<0.0001
Physical activity, MET	23.8 ± 11.5	21.5 ± 10.7	25.9 ± 11.8	<0.0001
SBP, mm Hg	117.4 ± 14.8	115.6 ± 16.0	119.1 ± 13.4	<0.0001
DBP, mm Hg	73.7 ± 10.4	71.7 ± 10.5	75.5 ± 9.9	<0.0001
Blood pressure ≥ 140/90 mm Hg, %	10.1	8.8	11.4	0.03
Response measures to CPT				
Maximum SBP response, mm Hg	13.9 ± 10.2	14.7 ± 10.4	13.3 ± 9.9	0.02
Maximum DBP response, mm Hg	7.8 ± 6.2	7.9 ± 6.5	7.7 ± 5.9	0.94
Total AUC of SBP, mm Hg·min	17.2 ± 22.9	17.4 ± 23.5	17.0 ± 22.4	0.84
Total AUC of DBP, mm Hg·min	10.9 ± 16.7	10.3 ± 17.2	11.4 ± 16.2	0.07

Values are presented as mean ± standard deviation or percentage.

Abbreviations: AUC, area under the curve; CPT, cold pressor test; DBP, diastolic blood pressure; MET, metabolic equivalent per week; SBP, systolic blood pressure.

[a]*P* values for comparisons between women and men.

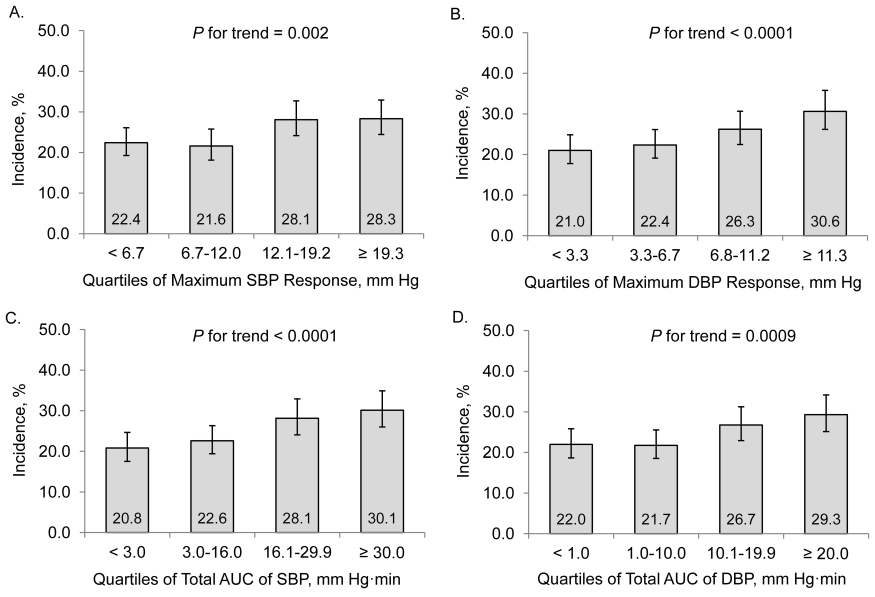

Figure 1. Multivariable-adjusted hypertension incidence over the 7.4-year follow-up by the quartiles of BP responses to the CPT among 1,762 participants without hypertension at baseline. Black bars show the 95% CI for incidence. Hypertension was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg, or taking antihypertensive medications. Sex, age, field centers, follow-up duration, body mass index, baseline BP, education, current cigarette smoking and alcohol drinking status, and physical activity were adjusted. BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

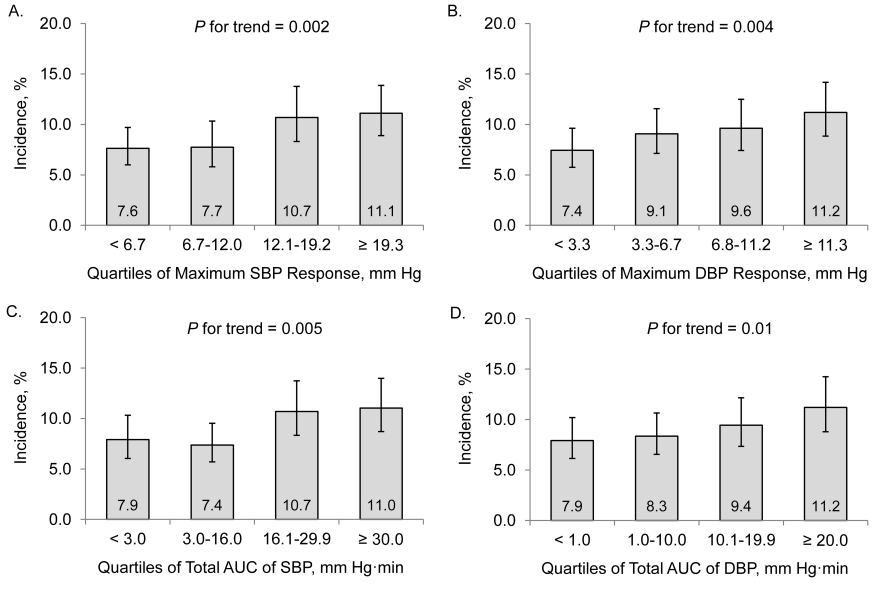

Figure 2. Multivariable-adjusted stage 2 hypertension incidence over the 7.4-year follow-up by the quartiles of BP responses to the CPT among 1,961participants without stage 2 hypertension at baseline. Black bars show the 95% CI for incidence. Stage 2 hypertension was defined as SBP ≥160 mm Hg or DBP ≥100 mm Hg, or taking antihypertensive medications. Sex, age, field centers, follow-up duration, body mass index, baseline BP, education, current cigarette smoking and alcohol drinking status, and physical activity were adjusted. BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Taking the BP response variables as continuous variables, we calculated the ORs for hypertension associated with a 1 SD increase in each response variable in the overall population (Table 3) and by subgroups of sex, age, and baseline BP levels (Table 4). Overall, all of the 4 BP response variables were positively associated with the risk of hypertension after adjusting for multiple covariates (model 3). In addition, the association between BP response to the CPT and hypertension incidence did not differ among these subgroups after correcting for multiple testing (Table 4).

DISCUSSION

In this study, we observed a significant positive association between BP reactivity to the CPT and hypertension incidence among the GenSalt participants. To the best of

Table 2. Hypertension risk by quartiles of blood pressure reactivity variables

Quartiles of reactivity	Odds ratio (95% CI) for hypertension[a]			Odds ratio (95% CI) for stage 2 hypertension[b]		
	Model 1[c]	Model 2[d]	Model 3[e]	Model 1[c]	Model 2[d]	Model 3[e]
Maximum SBP response, mm Hg						
<6.7	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
6.7–12.0	0.81 (0.59, 1.11)	0.78 (0.57, 1.07)	0.92 (0.66, 1.29)	0.93 (0.62, 1.42)	0.91 (0.59, 1.39)	1.06 (0.69, 1.62)
12.1–19.2	1.34 (0.98, 1.83)	1.26 (0.93, 1.72)	1.42 (1.03, 1.97)	1.40 (0.95, 2.07)	1.32 (0.89, 1.96)	1.56 (1.05, 2.34)
≥ 19.3	1.34 (0.98, 1.84)	1.30 (0.95, 1.78)	1.45 (1.05, 2.00)	1.76 (1.22, 2.53)	1.72 (1.19, 2.48)	1.79 (1.22, 2.61)
P for trend	0.01	0.02	0.006	0.0002	0.0005	0.0009
Maximum DBP response, mm Hg						
<3.3	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
3.3–6.7	0.95 (0.70, 1.30)	0.92 (0.67, 1.27)	1.08 (0.76, 1.52)	1.06 (0.74, 1.51)	1.08 (0.75, 1.56)	1.32 (0.89, 1.94)
6.8–11.2	1.20 (0.87, 1.65)	1.18 (0.85, 1.63)	1.45 (1.03, 2.04)	1.17 (0.81, 1.71)	1.19 (0.81, 1.75)	1.41 (0.92, 2.15)
≥11.3	1.31 (0.96, 1.78)	1.25 (0.91, 1.72)	1.75 (1.25, 2.45)	1.41 (0.98, 2.03)	1.39 (0.96, 2.03)	1.82 (1.20, 2.76)
P for trend	0.04	0.07	0.0002	0.05	0.07	0.006
Total AUC of SBP, mm Hg·min						
<3.0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
3.0–16.0	0.88 (0.64, 1.21)	0.87 (0.63, 1.19)	1.12 (0.79, 1.57)	0.79 (0.52, 1.20)	0.79 (0.52, 1.20)	0.87 (0.56, 1.35)
16.1–29.9	1.28 (0.92, 1.78)	1.21 (0.88, 1.68)	1.62 (1.15, 2.29)	1.12 (0.73, 1.71)	1.06 (0.69, 1.62)	1.48 (0.95, 2.30)
≥30.0	1.33 (0.97, 1.84)	1.34 (0.97, 1.85)	1.82 (1.30, 2.55)	1.46 (0.98, 2.16)	1.43 (0.97, 2.12)	1.64 (1.08, 2.49)
P for trend	0.02	0.02	0.0001	0.02	0.03	0.004
Total AUC of DBP, mm Hg·min						
<1.0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1.0–10.0	0.87 (0.63, 1.19)	0.87 (0.63, 1.19)	0.94 (0.67, 1.30)	0.92 (0.62, 1.35)	0.95 (0.64, 1.40)	1.08 (0.72, 1.63)
10.1–19.9	1.10 (0.80, 1.52)	1.07 (0.78, 1.47)	1.36 (0.96, 1.93)	1.05 (0.73, 1.51)	1.04 (0.72, 1.50)	1.27 (0.84, 1.93)
≥20.0	1.05 (0.75, 1.46)	0.99 (0.71, 1.39)	1.51 (1.07, 2.12)	1.10 (0.75, 1.62)	1.10 (0.74, 1.63)	1.66 (1.09, 2.55)
P for trend	0.48	0.76	0.004	0.48	0.55	0.01

Abbreviations: AUC, area under the curve; CI, confidence interval; CPT, cold pressor test; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Hypertension was defined as SBP ≥140 mm Hg or DBP ≥ 90 mm Hg, or taking antihypertensive medications.

[b]Stage 2 hypertension was defined as SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg, or taking antihypertensive medications.

[c]Model 1: Age, sex, field center, and the duration of follow-up were adjusted.

[d]Model 2: In addition to the covariates in Model 1, body mass index, education, current cigarette smoking, alcohol drinking, and physical activity were adjusted.

[e]Model 3: In addition to the covariates in Model 2, baseline blood pressure was adjusted.

our knowledge, our study provides the first evidence that BP reactivity to cold stress may predict hypertension in the Chinese population. In addition, BP reactivity to the CPT might be used to predict the risk of hypertension in both women and men, young to older adults, and persons with different baseline BP levels.

It has been hypothesized that individuals who exhibit a large BP response to cold stress are at increased risk for hypertension.[18] Some early efforts failed to identify the relationship between BP reactivity to the CPT and the incidence of hypertension.[6–9,11] Although the negative findings of early studies may be partially accounted for by insufficient statistical power due to small sample sizes (less than 200), the latest studies with larger sample sizes still obtained inconsistent study results.[11–15] In addition, the Coronary Artery Risk Development in Young Adults Study (CARDIA) reported a potential racial difference in the relationship between BP reactivity to cold stress and risk for hypertension. In their study, BP reactivity to cold stress could predict hypertension among whites, but not among blacks during a 13-year follow-up of the CARDIA participants.[15]

We did not observe that the association between BP response to the CPT and hypertension incidence varied among the subgroups of sex, age, and baseline BP levels in the Chinese population. Specifically, we did not observe a sex difference in the effects of CPT reactivity on hypertension incidence, which has been reported in the CARDIA study.[15] In addition, we did not observe any differences in the associations between BP reactivity to the CPT and incident hypertension by age groups. This finding does not support the conclusion of a previous study among Japanese subjects, which reported that the CPT only predicted the

Table 3. Hypertension risk associated with a 1 standard deviation increase in blood pressure reactivity variables

	Model 1[a]		Model 2[b]		Model 3[c]	
Reactivity variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Hypertension[d]						
Maximum SBP response	1.25 (1.07, 1.46)	0.005	1.23 (1.06, 1.43)	0.008	1.28 (1.10, 1.50)	0.001
Maximum DBP response	1.19 (1.03, 1.36)	0.02	1.16 (1.00, 1.34)	0.05	1.35 (1.17, 1.56)	< 0.0001
Total AUC of SBP	1.12 (1.02, 1.22)	0.01	1.11 (1.01, 1.21)	0.02	1.21 (1.10, 1.32)	< 0.0001
Total AUC of DBP	1.07 (0.99, 1.15)	0.10	1.04 (0.96, 1.13)	0.29	1.18 (1.08, 1.28)	< 0.0001
Stage-2 hypertension[e]						
Maximum SBP response	1.39 (1.18, 1.63)	< 0.0001	1.38 (1.17, 1.62)	< 0.0001	1.38 (1.16, 1.65)	0.0003
Maximum DBP response	1.30 (1.10, 1.54)	0.003	1.26 (1.06, 1.50)	0.008	1.40 (1.16, 1.69)	0.0004
Total AUC of SBP	1.13 (1.02, 1.25)	0.02	1.12 (1.02, 1.24)	0.02	1.18 (1.06, 1.31)	0.003
Total AUC of DBP	1.08 (0.98, 1.19)	0.12	1.07 (0.97, 1.17)	0.21	1.19 (1.08, 1.32)	0.0007

Abbreviations: AUC, area under the curve; CI, confidence interval; CPT, cold pressor test; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; SE, standard error.

[a]Model 1: Age, sex, field center, and the duration of follow-up were adjusted.

[b]Model 2: In addition to the covariates in Model 1, body mass index, education, current cigarette smoking, alcohol drinking, and physical activity were adjusted.

[c]Model 3: In addition to the covariates in Model 2, baseline blood pressure was adjusted.

[d]Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or taking antihypertensive medications.

[e]Stage 2 hypertension was defined as SBP ≥160 mm Hg or DBP ≥100 mm Hg, or taking antihypertensive medications.

hypertension incidence among subjects aged ≥40 years.[13] Two previous studies conducted in school children aged 7–17 years or young adults aged 18–30 years identified significant associations between BP reactivity to the CPT and future hypertension.[10,15] Collectively, these data indicated that BP reactivity to the CPT predicted hypertension incidence across all age groups. Finally, we did not observe that the effects of the BP reactivity on hypertension incidence varied among individuals with different BP levels at baseline.

Our study has several strengths. First, standardized protocols for the CPT and BP measurements were used throughout the study. Second, BP response to the CPT has been shown as a long-term reproducible and stable characteristic in the GenSalt participants.[3] Third, multiple BP readings were obtained during the CPT, which enabled a more comprehensive assessment of individuals' BP reactivity to the stress. Our study is the first to involve the area under the BP response curve in testing the association between BP reactivity and the risk of hypertension, which integrates the magnitude of BP increase from pre-CPT to peak response and its recovery from peak response. Fourth, multiple regression analyses were used to adjust for potential confounding factors. For example, cigarette smoking and alcohol drinking have been associated with hypertension and increased sympathetic nerve activity,[19–23] which is the major mechanism regulating cardiovascular reactivity to the CPT. However, they were not well controlled in previous studies testing the association between BP response to the CPT and hypertension incidence. Finally, the large community-based prospective study design enhanced generalizability of these findings among the Chinese population. The racial difference in the association between BP response to the CPT and hypertension incidence reported by the CARDIA study may suggest that genetic factors play an important role in the association. Previous studies have suggested that the variation of individuals' response to the CPT is substantially explained by genetic components.[24,25] Considering the shared genetic background among Chinese and Asians, our study findings may be valid for Chinese Americans and even other Asian Americans as well.

Nevertheless, our study does have limitations. Our data could not elucidate mechanisms underlying the observed associations. The exaggerated sympathetic nervous system response during the cold stimulus has been considered one of the major mechanisms mediating the cardiovascular response to the CPT.[26,27] Sympathetic stimulation is known to be a trophic factor for vascular hypertrophy. During the CPT, the cold stimulus can induce α-adrenergic vasoconstriction with increased total peripheral resistance.[28] It has been suggested that frequent surges of sympathetic activity may develop into sustained increased total peripheral resistance and then hypertension.[29] However, a recent study failed to observe significant associations between the level of catecholamine, an arterial sympathetic nervous transmitter, measured during the CPT, and subsequent BP levels.[30] Other mechanisms may also be involved in the pathogenesis of exaggerated reactivity of BP to stress leading to hypertension, such as endothelial dysfunction.[15] The value of the application of the CPT for identifying high risk individuals for hypertension at the population level or in clinical settings is uncertain. Further studies investigating the mechanisms underlying the relationship between BP reactivity to cold stress and the development of hypertension are likely to identify novel biomarkers and pharmaceutical targets for the prevention and treatment of hypertension. In addition, we compared the baseline characteristics of the subjects who missed follow-up visits with those of participants who were

Table 4. Hypertension risk[a] associated with a 1 standard deviation increase in reactivity variables by subgroups

	Hypertension[b]				Stage 2 hypertension[c]			
	Maximum response		Total AUC		Maximum response		Total AUC	
Subgroups	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Sex								
Women	1.52 (1.22, 1.89)	1.38 (1.11, 1.70)	1.31 (1.15, 1.49)	1.20 (1.07, 1.36)	1.45 (1.13, 1.86)	1.25 (0.97, 1.61)	1.18 (1.02, 1.37)	1.17 (1.01, 1.34)
Men	1.11 (0.90, 1.36)	1.30 (1.07, 1.59)	1.12 (1.00, 1.25)	1.13 (1.02, 1.26)	1.33 (1.04, 1.70)	1.60 (1.26, 2.03)	1.16 (1.01, 1.34)	1.19 (1.05, 1.36)
P for difference by sex	0.02	0.92	0.19	0.69	0.22	0.27	0.62	0.97
Age (years)								
<35	1.04 (0.75, 1.45)	1.08 (0.81, 1.46)	1.06 (0.88, 1.26)	1.06 (0.89, 1.26)	1.39 (0.86, 2.25)	1.13 (0.82, 1.57)	1.21 (0.94, 1.56)	1.00 (0.82, 1.22)
35–44	1.55 (1.21, 2.01)	1.46 (1.16, 1.84)	1.34 (1.16, 1.55)	1.18 (1.05, 1.33)	1.39 (1.03, 1.88)	1.52 (1.14, 2.03)	1.13 (0.95, 1.35)	1.29 (1.11, 1.50)
≥45	1.29 (1.02, 1.64)	1.45 (1.14, 1.85)	1.23 (1.07, 1.41)	1.26 (1.10, 1.45)	1.35 (1.05, 1.74)	1.42 (1.08, 1.86)	1.15 (0.99, 1.34)	1.15 (0.99, 1.33)
P for difference by age	0.19	0.32	0.33	0.71	0.99	0.71	0.97	0.24
Baseline BP (mm Hg)								
<120/80	1.25 (0.96, 1.62)	1.39 (1.10, 1.75)	1.16 (0.99, 1.35)	1.16 (1.01, 1.33)	1.71 (1.25, 2.33)	1.49 (1.08, 2.08)	1.34 (1.08, 1.65)	1.24 (1.02, 1.52)
120–139/80–89	1.37 (1.11, 1.69)	1.21 (1.01, 1.44)	1.23 (1.10, 1.39)	1.08 (0.98, 1.19)	1.44 (1.10, 1.87)	1.20 (0.95, 1.51)	1.19 (1.01, 1.40)	1.11 (0.98, 1.25)
≥140/90	—	—	—	—	1.11 (0.83, 1.47)	1.56 (1.17, 2.06)	1.06 (0.91, 1.23)	1.10 (0.94, 1.28)
P for difference by baseline BP	0.78	0.57	0.42	0.67	0.15	0.58	0.26	0.61

Abbreviations: AUC, area under the curve; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Age, sex, field center, the duration of follow-up, body mass index, baseline blood pressure, education, current cigarette smoking and alcohol drinking status, and physical activity were adjusted; data are shown as odds ratio (95% confidence interval).

[b]Hypertension was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg, or taking antihypertensive medications.

[c]Stage 2 hypertension was defined as SBP ≥160 mm Hg or DBP ≥100 mm Hg, or taking antihypertensive medications.

followed. Participants lost to follow-up tended to be younger, were more likely to be male, and had a lower BMI, but had similar baseline BP levels and BP responses to the CPT, compared to those who participated in follow-up visits. The high follow-up rates in our study further suggest that the loss to follow-up is not likely to have significantly influenced our study results.

This is the first report that linked BP reactivity to cold stress and risk for hypertension in the Chinese population. The CPT may be a useful predictor for hypertension among both women and men, young and older adults, and persons with different baseline BP levels. Future studies are warranted to elucidate the underlying mechanisms of BP hyperreactivity and the risk of hypertension.

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DISCLOSURE

There are no conflict of interest.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365:217–223.
2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; 367:1747–1757.
3. Zhao Q, Bazzano LA, Cao J, Li J, Chen J, Huang J, Chen J, Kelly TN, Chen CS, Hu D, Ma J, Rice TK, He J, Gu D. Reproducibility of blood pressure response to the cold pressor test: the GenSalt Study. *Am J Epidemiol* 2012; 176(Suppl 7):S91–S98.
4. Sherwood A, Girdler SS, Bragdon EE, West SG, Brownley KA, Hinderliter AL, Light KC. Ten-year stability of cardiovascular responses to laboratory stressors. *Psychophysiology* 1997; 34:185–191.
5. Hassellund SS, Flaa A, Sandvik L, Kjeldsen SE, Rostrup M. Long-term stability of cardiovascular and catecholamine responses to stress tests: an 18-year follow-up study. *Hypertension* 2010; 55:131–136.
6. Armstrong HG, Rafferty JA. Cold pressor test follow-up study for seven years on 166 officers. *Am Heart J* 1950; 39:484–490.
7. Harlan WR Jr, Osborne RK, Graybiel A. Prognostic value of the cold pressor test and the basal blood pressure. Based on an eighteen-year follow-up study. *Am J Cardiol* 1964; 13:683–687.
8. Eich RH, Jacobsen EC. Vascular reactivity in medical students followed for 10 yr. *J Chronic Dis* 1967; 20:583–592.
9. Thomas CB, Duszynski KR. Blood pressure levels in young adulthood as predictors of hypertension and the fate of the cold pressor test. *Johns Hopkins Med J* 1982; 151:93–100.
10. Wood DL, Sheps SG, Elveback LR, Schirger A. Cold pressor test as a predictor of hypertension. *Hypertension* 1984; 6:301–306.
11. Thomas J, Neser WB, Knuckles B, Semenya K, Thomas DJ, Gillum RF. Failure of the cold pressor test to predict hypertension in black physicians: the Meharry Cohort Study. *J Natl Med Assoc* 1988; 80:1185–1188.
12. Menkes MS, Matthews KA, Krantz DS, Lundberg U, Mead LA, Qaqish B, Liang KY, Thomas CB, Pearson TA. Cardiovascular reactivity to the cold pressor test as a predictor of hypertension. *Hypertension* 1989; 14:524–530.
13. Kasagi F, Akahoshi M, Shimaoka K. Relation between cold pressor test and development of hypertension based on 28-year follow-up. *Hypertension* 1995; 25:71–76.
14. Carroll D, Davey Smith G, Sheffield D, Willemsen G, Sweetnam PM, Gallacher JE, Elwood PC. Blood pressure reactions to the cold pressor test and the prediction of future blood pressure status: data from the Caerphilly study. *J Hum Hypertens* 1996; 10:777–780.
15. Matthews KA, Katholi CR, McCreath H, Whooley MA, Williams DR, Zhu S, Markovitz JH. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation* 2004; 110:74–78.
16. Zhang M, Zhao Q, Mills KT, Chen J, Li J, Cao J, Gu D, He J. Factors associated with blood pressure response to the cold pressor test: the GenSalt Study. *Am J Hypertens* 2013; 26:1132–1139.
17. GenSalt Collaborative Research Group. GenSalt: rationale, design, methods and baseline characteristics of study participants. *J Hum Hypertens* 2007; 21:639–646.
18. Hines EJ, Brown GE. The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. *Am Heart J* 1936; 11:1–9.
19. Shinozaki N, Yuasa T, Takata S. Cigarette smoking augments sympathetic nerve activity in patients with coronary heart disease. *Int Heart J* 2008; 49:261–272.
20. Husain K, Ansari RA, Ferder L. Alcohol-induced hypertension: Mechanism and prevention. *World J Cardiol* 2014; 6:245–252.
21. Virdis A, Giannarelli C, Neves MF, Taddei S, Ghiadoni L. Cigarette smoking and hypertension. *Curr Pharm Des* 2010; 16:2518–2525.
22. Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. *J Am Coll Cardiol* 2014; 64:1740–1750.
23. Grassi GM, Somers VK, Renk WS, Abboud FM, Mark AL. Effects of alcohol intake on blood pressure and sympathetic nerve activity in normotensive humans: a preliminary report. *J Hypertens Suppl* 1989; 7:S20–S21.
24. Mei H, Gu D, Rice TK, Hixson JE, Chen J, Jaquish CE, Zhao Q, Chen CS, Chen JC, Gu CC, Kelly TN, He J. Heritability of blood pressure responses to cold pressor test in a Chinese population. *Am J Hypertens* 2009; 22:1096–1100.
25. Roy-Gagnon MH, Weir MR, Sorkin JD, Ryan KA, Sack PA, Hines S, Bielak LF, Peyser PA, Post W, Mitchell BD, Shuldiner AR, Douglas JA. Genetic influences on blood pressure response to the cold pressor test: results from the Heredity and Phenotype Intervention Heart Study. *J Hypertens* 2008; 26:729–736.
26. Papanek PE, Wood CE, Fregly MJ. Role of the sympathetic nervous system in cold-induced hypertension in rats. *J Appl Physiol (1985)* 1991; 71:300–306.
27. Sun Z. Cardiovascular responses to cold exposure. *Front Biosci (Elite Ed)* 2010; 2:495–503.
28. Pickering TG, Gerin W. Cardiovascular reactivity in the laboratory and the role of behavioral factors in hypertension: A critical review. *Ann Behav Med* 1990; 12:3–16.
29. Folkow B. Pathophysiology of hypertension: differences between young and elderly. *J Hypertens Suppl* 1993; 11:S21–S24.
30. Flaa A, Eide IK, Kjeldsen SE, Rostrup M. Sympathoadrenal stress reactivity is a predictor of future blood pressure: an 18-year follow-up study. *Hypertension* 2008; 52:336–341.