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Original Contribution

Reproducibility of Blood Pressure Response to the Cold Pressor Test

The GenSalt Study

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An elevated blood pressure (BP) response to the cold pressor test (CPT) is associated with increased risk of hypertension and cardiovascular disease. However, it is still unclear whether BP response to the CPT is a stable and reproducible trait over time. Using the same study protocol, the authors repeated the CPT 4.5 years after initial administration among 568 Han Chinese in rural northern China (2003–2005 and 2008–2009). BP was measured using a standard mercury sphygmomanometer prior to and 0, 1, 2, and 4 minutes after the participants immersed their hand in ice water (3°C–5°C) for 1 minute. Absolute BP levels and BP responses during the CPT in the initial and repeated administrations were highly correlated. For example, the correlation coefficients were 0.67, 0.73, 0.71, and 0.72 for absolute systolic BP levels at 0, 1, 2, and 4 minutes after ice-water immersion (all P's < 0.0001). The correlation coefficients for systolic BP response were 0.41 at 0 minutes, 0.37 at 1 minute, 0.42 for maximum response, and 0.39 for the area under the curve during CPT (all P's < 0.0001). These data indicate that BP response to the CPT is a long-term reproducible and stable characteristic in the general population.

blood pressure; cardiovascular diseases; hypertension; reproducibility of results; stress, physiological

Abbreviations: AUC, area under the curve; BP, blood pressure; CPT, cold pressor test; DBP, diastolic blood pressure; GenSalt, Genetic Epidemiology Network of Salt Sensitivity; SBP, systolic blood pressure; SD, standard deviation.

Hypertension is a global public health challenge because of its high prevalence and the concomitant increase in risk of cardiovascular diseases (1). Cardiovascular hyperreactivity to stress has been hypothesized to be an important risk factor for the development of hypertension and cardiovascular diseases (2–4). The cold pressor test (CPT), which measures blood pressure (BP) response to the stimulus of external cold, has been used for the evaluation of cardiovascular reactivity to stress in normotensive and hypertensive subjects (5–8). It is important to establish the reproducibility of BP response to the CPT before it can be widely used for risk classification and prediction. Several studies have been conducted to investigate the short-term reproducibility of BP response to CPT based on test-retest intervals of days to months (9–12). Only a few studies have been conducted with intervals of longer than 1 year (13–15). The 2 studies with the longest test-retest intervals (10 years and 18 years, respectively) suggested that the reactivity of BP response to CPT is a relatively stable individual characteristic over time (14, 15). However, both studies tested the stability of BP response to CPT only among young healthy men and had limited sample sizes (74 subjects and 55 subjects, respectively). It is still unclear whether individual BP response to CPT is a stable trait in the general population, including both men and women of a wide range of ages.

The Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study and its follow-up study provided a unique opportunity to examine the long-term reproducibility of BP response to CPT in a general population. A total of 568 Chinese men and women aged 16–60 years completed the CPT during both the initial study and its 4.5-year follow-up study.

MATERIALS AND METHODS

Study participants

All of the study subjects were from the GenSalt Study, which was carried out in rural areas in northern China. The initial GenSalt Study was conducted from October 2003 to July 2005. The details of the study design and methods have been published elsewhere (16). In brief, community-based BP screening was conducted among persons aged 18–60 years in the study villages to identify potential probands and their families. Probands with mean systolic BP (SBP) of 130–160 mm Hg and/or diastolic BP (DBP) of 85–100 mm Hg and no use of antihypertensive medication were recruited, along with their parents, siblings, spouses, and offspring. Persons who were older than age 60 years; had stage 2 hypertension, secondary hypertension, or a history of clinical cardiovascular disease, diabetes, or chronic kidney failure; were using antihypertensive medication; or were pregnant were excluded from the CPT. A total of 2,007 subjects from 45 study villages completed the CPT in the initial GenSalt Study.

The GenSalt follow-up study was conducted from August 2008 to November 2009. In the follow-up study, 21 villages were sampled for repeat CPT. A total of 758 GenSalt participants were invited to undergo the second CPT, and 568 participants (74.9%) completed it. The average time of follow-up was 4.5 years (standard deviation, 0.8).

Institutional review boards or ethics committees at all participating institutions approved the study protocol. Written informed consent was obtained from each participant.

Data collection

The same study protocol was applied for the initial study and the follow-up study. Trained staff administered a standard questionnaire to collect information on demographic characteristics, personal and family medical history, and lifestyle risk factors (including cigarette smoking, alcohol drinking, and physical activity). Body weight and height were measured twice in light indoor clothing without shoes. Waist circumference was measured 1 cm above the participant's naval during light breathing. Three BP measurements were obtained by trained and certified technicians every morning during the 3-day baseline observation with 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 taken during the 3-day baseline evaluation was considered the baseline BP level.

The CPT was conducted using the same protocol in the initial and follow-up studies. After the participant had remained sitting 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 the participant immersed his or her left hand in the ice-water bath (3°C–5°C) to a point just above the wrist for 1 minute. BP measurements were obtained using a standard mercury sphygmomanometer on the right upper arm at 0, 1, 2, and 4 minutes after the left hand had been removed from the ice-water bath.

Statistical analysis

Participants' characteristics in the initial and follow-up studies were calculated and compared. The statistical significance of the differences was examined by paired *t* test for continuous variables and by χ^2 test for categorical variables. In order to determine whether people who responded initially in a low or high range continued to respond in a low or high range after approximately 5 years of follow-up, we utilized the Pearson correlation coefficient to assess the reproducibility of absolute BP levels during CPT and BP response to CPT, including the BP response at 0 minutes and 1 minute, the maximum BP response, and the area under the curve (AUC) above pre-CPT BP. Responses at the time points of 0 and 1 minute were calculated as the difference between BP at 0 and 1 minute and pre-CPT BP levels, respectively; maximum response was defined as the largest BP difference between BP at any of the 4 CPT tested time points and pre-CPT BP; and the 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 CPT summarizes the magnitude of BP increase (from pre-CPT to 0 minute) and its recovery from response peak to baseline (from 0 minutes to 4 minutes). In addition, partial correlation coefficients were obtained by adjusting for age, sex, field center, time intervals, baseline BP levels, and differences in room temperature and ice-water temperature during CPT between the initial and follow-up studies. Additionally, Bland-Altman graphical approaches (17) were employed to test whether, for each BP response variable, the difference between the 2 measurements varied in a systematic way from the mean of the 2 measurements.

All analyses were conducted using the SAS statistical package (version 9.2; SAS Institute, Inc., Cary, North Carolina).

RESULTS

The characteristics of the 568 participants during the initial and follow-up studies are shown in Table 1. The average age of the participants was 39.0 years at the initial examination, and 54.1% of the participants were male. Mean body mass index (weight (kg)/height (m)^2), waist

Table 1. Characteristics of 568 Participants in the Initial and Follow-up Studies, GenSalt Study, China, 2003–2005 and 2008–2009

	Initial Study (2003–2005)						Follow-up Study (2008–2009)						*P* Value[a]
	Men ($n = 307$)		Women ($n = 261$)		Total ($n = 568$)		Men ($n = 307$)		Women ($n = 261$)		Total ($n = 568$)		
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	
Age, years		39.5 (8.7)		38.3 (8.2)		39.0 (8.5)		44.0 (8.8)		43.1 (8.8)		43.6 (8.8)	
High school education or higher	13.0		8.8		11.1		13.0		8.8		11.1		
Current cigarette smoking	61.9		0		33.5		61.9		0.4		33.6		0.87
Current alcohol drinking	49.4		0.8		27.3		54.1		3.1		30.6		0.03
Body mass index[b]		23.4 (2.9)		23.9 (2.9)		23.6 (2.9)		24.2 (3.2)		24.7 (3.1)		24.4 (3.2)	<0.0001
Waist circumference, cm		81.4 (9.7)		78.3 (9.1)		79.9 (9.5)		84.6 (9.7)		80.2 (9.2)		82.6 (9.7)	<0.0001
Systolic blood pressure, mm Hg		119.0 (12.4)		116.4 (14.6)		117.8 (13.5)		125.9 (14.1)		120.4 (16.1)		123.4 (15.3)	<0.0001
Diastolic blood pressure, mm Hg		76.0 (9.5)		72.8 (9.9)		74.5 (9.8)		83.3 (9.8)		77.8 (9.4)		80.7 (10.0)	<0.0001

Abbreviations: GenSalt, Genetic Epidemiology Network of Salt Sensitivity; SD, standard deviation.
[a] *P* for initial study vs. follow-up study among all subjects.
[b] Weight (kg)/height (m)^2.

circumference, and BP levels increased significantly during the follow-up period of 4.5 years (all P's < 0.0001).

Table 2 presents BP levels before the CPT and at the 4 time points of 0, 1, 2, and 4 minutes after ice-water immersion. Compared with BP levels before the CPT, both SBP and DBP significantly increased at 0 and 1 minute after the CPT. The average BP returned to pre-CPT levels 4 minutes after the CPT (Figure 1). BP levels during the CPT were highly correlated between the initial and follow-up studies (all P's < 0.0001). After adjustment for multiple covariates, the correlation coefficients for BP at different time points did not change significantly. The partial correlation coefficients ranged from 0.66 to 0.71 for SBP and from 0.55 to 0.59 for DBP during the CPT, respectively. SBP showed higher test-retest correlation than did DBP at any time point.

Table 3 shows mean values, correlation coefficients for BP responses to CPT at 0 and 1 minute, maximum BP responses, and the AUC of BP responses to CPT in the initial and follow-up studies. Figure 2 displays the scatterplots of BP responses to CPT in the initial study versus those in the follow-up study. The correlation coefficients for BP responses to CPT between the initial and follow-up studies were moderate but highly significant (all P's $<$ 0.0001). The correlation coefficients ranged from 0.37 to 0.42 for SBP response and from 0.25 to 0.31 for DBP response, respectively. In general, SBP response to CPT had higher test-retest correlations than DBP response. The maximum SBP response to CPT had the highest correlation coefficient among all response variables ($r = 0.42$, 95% confidence interval: 0.35, 0.49).

Bland-Altman plots of BP responses to CPT in the initial and follow-up studies are presented in Figure 3. In general, we did not observe obvious relations between the differences and the means. Given differences in BP characteristics between men and women, we also conducted sex-stratified analyses. However, we did not observe significant sex differences in the reproducibility of BP response to CPT.

DISCUSSION

To our knowledge, this is the largest study to date to have investigated the long-term reproducibility of BP response to CPT in the general population. Correlations of BP responses to CPT over a 4.5-year follow-up period were moderate but highly statistically significant. These findings indicate that BP response to CPT is not a random phenomenon but a reproducible measure of cardiovascular reactivity to stress.

The CPT has been commonly used to assess cardiovascular reactivity, a person's physiologic responsiveness to environmental stimuli, and has been implicated in the etiology and development of both hypertension and cardiovascular disease. Prospective cohort studies have indicated that exaggerated cardiovascular response to the CPT is a predictor of future BP increase and the development of hypertension (18–21). For example, in a 28-year follow-up study (20), it was reported that the relative risk of hypertension

Table 2. Blood Pressure Levels (mm Hg) During the Cold Presser Test and Correlation Coefficients for the Initial Study Versus the Follow-up Study, GenSalt Study, China, 2003–2005 and 2008–2009

	Mean Blood Pressure		CC*	95% CI	Partial CC[a]	95% CI
	Initial Study (2003–2005)	Follow-up Study (2008–2009)				
Before CPT						
SBP	119.6 (13.7)[b]	123.7 (15.8)	0.72	0.68, 0.76	0.71	0.67, 0.75
DBP	74.9 (10.3)	80.4 (10.2)	0.56	0.50, 0.61	0.56	0.50, 0.61
0 minutes after CPT						
SBP	132.9 (17.5)	134.8 (18.8)	0.67	0.62, 0.71	0.66	0.61, 0.70
DBP	82.0 (11.8)	86.3 (11.6)	0.54	0.47, 0.59	0.55	0.49, 0.61
1 minute after CPT						
SBP	123.9 (15.1)	127.8 (17.0)	0.73	0.69, 0.76	0.70	0.66, 0.74
DBP	77.6 (10.6)	83.0 (10.7)	0.60	0.54, 0.65	0.59	0.54, 0.64
2 minutes after CPT						
SBP	120.2 (14.2)	124.7 (16.1)	0.71	0.67, 0.75	0.70	0.65, 0.74
DBP	75.7 (10.3)	81.4 (10.3)	0.58	0.52, 0.63	0.58	0.53, 0.63
4 minutes after CPT						
SBP	118.6 (14.0)	122.8 (15.7)	0.72	0.68, 0.76	0.71	0.67, 0.75
DBP	74.6 (10.4)	80.1 (10.3)	0.57	0.51, 0.62	0.56	0.50, 0.61

Abbreviations: CC, correlation coefficient; CI, confidence interval; CPT, cold pressor test; DBP, diastolic blood pressure; GenSalt, Genetic Epidemiology Network of Salt Sensitivity; SBP, systolic blood pressure.

* $P < 0.0001$ for all CCs.

[a] Adjusted for age, sex, field center, time interval between the initial study and the follow-up study, and differences in room temperature and cold water temperature between the initial study and the follow-up study.

[b] Numbers in parentheses, standard deviation.

for persons with an SBP response to CPT of ≥15 mm Hg was 1.37 (95% confidence interval: 1.10, 1.71) compared with those with an SBP response less than 15 mm Hg.

The exaggerated sympathetic nervous system response during the cold stimulus has been considered one of the major mechanisms mediating the cardiovascular response to CPT (22, 23). Sympathetic stimulation is known to be a trophic factor for vascular hypertrophy (24, 25). In the CPT, the cold stimulus can induce α-adrenergic vasoconstriction with increased total peripheral resistance (26). It has been suggested that frequent surges of sympathetic activity may develop into sustained increased total peripheral resistance and then hypertension (27). The observed long-term stability of BP response to CPT may suggest that sympathetic nervous responsiveness is relatively stable over time as well. Therefore, our finding may further support the important role of high sympathetic activity in the pathogenesis of hypertension.

The reproducibility or reliability of the cardiovascular response to CPT has been examined in several studies (21). Most of these studies examined the short-term reproducibility of BP response to CPT and indicated that BP response to CPT is a relatively stable individual characteristic, at least for a short test-retest interval. In a study of 42 young men (10), the correlation coefficients over a 2-week test-retest interval were 0.85 and 0.78 for SBP and DBP responses to CPT, respectively. Similar results were observed in 113 normotensive white college men (9).

A few studies have investigated the long-term reproducibility of BP response to CPT (13–15). In a 10-year follow-up study among 55 men who were college undergraduates aged 18–22 years at initial testing, the correlation coefficients were 0.586 ($P < 0.001$) for SBP and 0.238 ($P > 0.05$) for DBP response to CPT, respectively (14). The magnitudes of the correlations were similar to those of our findings. In another longitudinal study of 81 men aged 19 years at initial testing (15), significant correlations for SBP response to CPT ($r = 0.25$, $P < 0.05$) and DBP response ($r = 0.34$, $P < 0.01$) were reported. In that study, intraarterial measurement on the first occasion was replaced by a Finapres noninvasive beat-to-beat BP recorder (Finapres Medical Systems BV, Amsterdam, the Netherlands) on the second occasion (15). Therefore, in addition to the longer test-retest interval, the different methods used in the two tests might explain the relatively low correlation between BP response and CPT observed in that study. Nevertheless, our results and those from the previous studies suggest that BP response to CPT remains relatively stable over a long period of time. Few data are available on the reproducibility of the CPT in women.

The correlation between absolute BP levels was much higher than the correlation between BP changes (responses) during the CPT in our study. The correlation coefficients for absolute SBP and DBP levels during the CPT were near 0.7 and 0.6, respectively. This was also noticed in a meta-analysis of the reproducibility of BP response to a

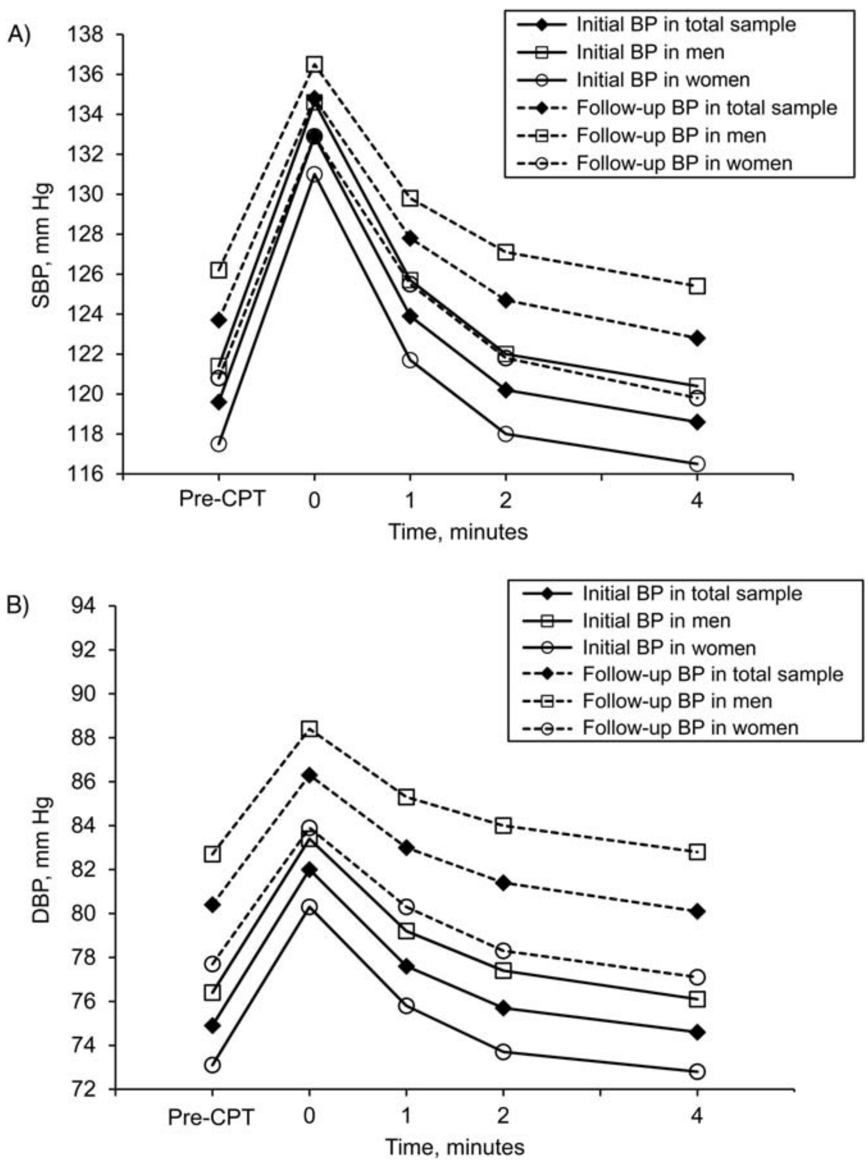

Figure 1. Levels of A) systolic blood pressure (SBP) and B) diastolic blood pressure (DBP) during the cold pressor test (CPT) in initial and follow-up studies, Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study, China, 2003–2005 and 2008–2009. (BP, blood pressure).

variety of stressors (28). The relatively weak correlation for BP changes is most likely due to increased measurement error, because BP changes are based on 2 separate measurements (15).

Our study had several important strengths. First, the large sample size enabled more accurate estimation of the long-term reproducibility of BP response to CPT. Second, both men and women from the general population, with a wide age range, were included. In the previous studies, only a small number of male college students were tested (14, 15). Therefore, our study findings may be more generalizable than those of previous studies. Furthermore, standardized and identical CPT protocols were applied for both the initial study and the follow-up study. This minimized the influence of different study methods. Finally, we adjusted for multiple confounding factors by calculating partial correlation coefficients.

A potential limitation of our study is that we did not measure heart rate during the CPT, which has shown good reproducibility in short-term test-retest studies (29). In the follow-up study, we compared persons who responded to the invitation to participate in the follow-up study with nonrespondents and found that the respondents tended to be younger, with a higher body mass index, lower baseline SBP, and lower SBP response at 0 minutes than nonrespondents.

In summary, our study indicates that BP response to the CPT is a reproducible measurement of cardiovascular reactivity to stress over time. Furthermore, these findings may

Table 3. Blood Pressure Response (mm Hg) to the Cold Pressor Test and Correlation Coefficients for the Initial Study Versus the Follow-up Study, GenSalt Study, China, 2003–2005 and 2008–2009

	Mean Blood Pressure Response						CC[a]*	95% CI	Partial CC[a,b]	95% CI
	Initial Study (2003–2005)			Follow-up Study (2008–2009)						
	Men	Women	Total	Men	Women	Total				
Response at 0 minutes										
SBP	13.2 (10.5)[c]	13.5 (9.6)	13.3 (10.1)	10.3 (9.8)	12.0 (9.1)	11.1 (9.5)	0.41	0.34, 0.48	0.42	0.35, 0.48
DBP	7.0 (6.6)	7.2 (6.3)	7.1 (6.5)	5.7 (6.2)	6.2 (5.7)	5.9 (6.0)	0.30	0.22, 0.37	0.25	0.17, 0.33
Response at 1 minute										
SBP	4.3 (6.2)	4.2 (5.8)	4.2 (6.0)	3.6 (6.0)	4.7 (5.9)	4.1 (6.0)	0.37	0.30, 0.44	0.32	0.25, 0.39
DBP	2.8 (4.3)	2.7 (4.5)	2.8 (4.4)	2.6 (4.3)	2.5 (4.4)	2.6 (4.3)	0.31	0.23, 0.38	0.27	0.19, 0.35
Maximum response										
SBP	13.5 (10.1)	13.7 (9.4)	13.6 (9.8)	11.1 (9.0)	12.5 (8.7)	11.7 (8.9)	0.42	0.35, 0.49	0.42	0.35, 0.49
DBP	7.7 (6.0)	7.8 (6.0)	7.7 (6.0)	6.8 (5.6)	6.9 (5.1)	6.8 (5.4)	0.27	0.19, 0.34	0.23	0.15, 0.31
Total area under the curve										
SBP	17.4 (21.7)	17.5 (20.7)	17.4 (21.2)	14.5 (21.8)	17.1 (19.1)	15.7 (20.6)	0.39	0.32, 0.46	0.37	0.29, 0.44
DBP	10.9 (15.3)	10.6 (15.7)	10.8 (15.4)	10.2 (15.1)	9.0 (14.5)	9.7 (14.8)	0.25	0.17, 0.32	0.22	0.14, 0.29

Abbreviations: CC, correlation coefficient; CI, confidence interval; DBP, diastolic blood pressure; GenSalt, Genetic Epidemiology Network of Salt Sensitivity; SBP, systolic blood pressure.

* $P < 0.0001$ for all CCs.

[a] CCs are for the total sample.

[b] Adjusted for age, sex, field center, time interval between the initial study and the follow-up study, baseline blood pressure in the initial study, and differences in room temperature and cold water temperature between the initial study and the follow-up study.

[c] Numbers in parentheses, standard deviation.

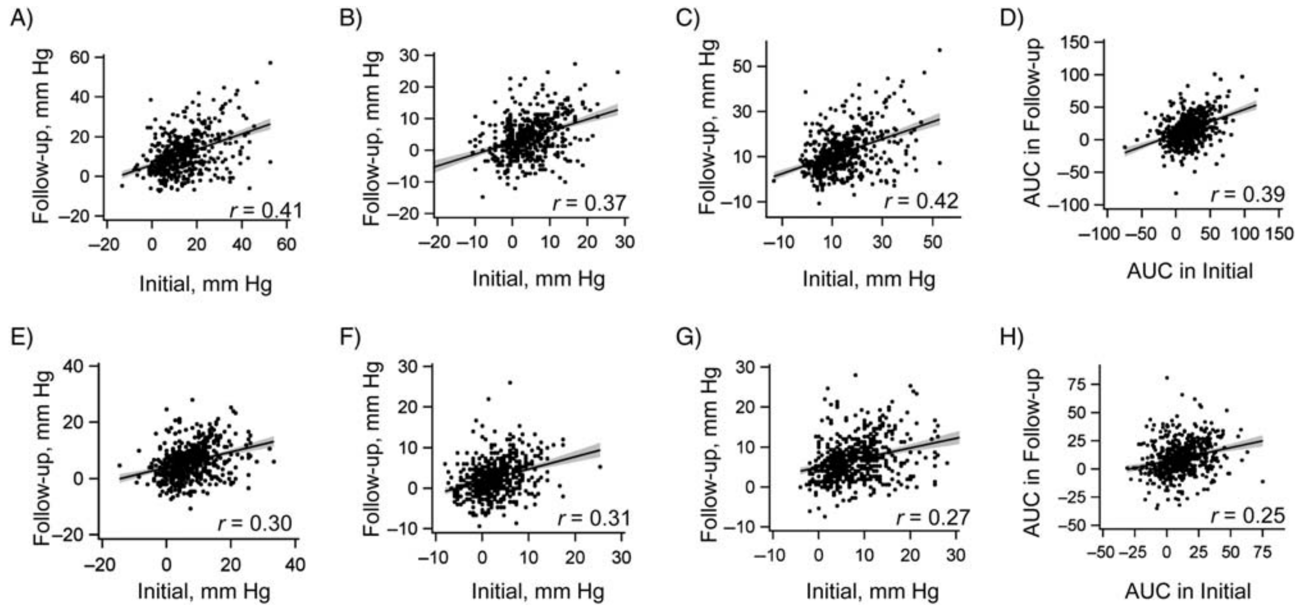

Figure 2. Scatterplots of systolic blood pressure (top) and diastolic blood pressure (bottom) responses to the cold pressor test in initial and follow-up studies, Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study, China, 2003–2005 and 2008–2009. Sections A and E show response at 0 minutes; sections B and F show response at 1 minute; sections C and G show maximum response; and sections D and H show the total area under the curve (AUC) above baseline. All P values for correlation coefficients (r) were less than 0.0001. Shaded areas show the 95% confidence intervals for mean predicted values.

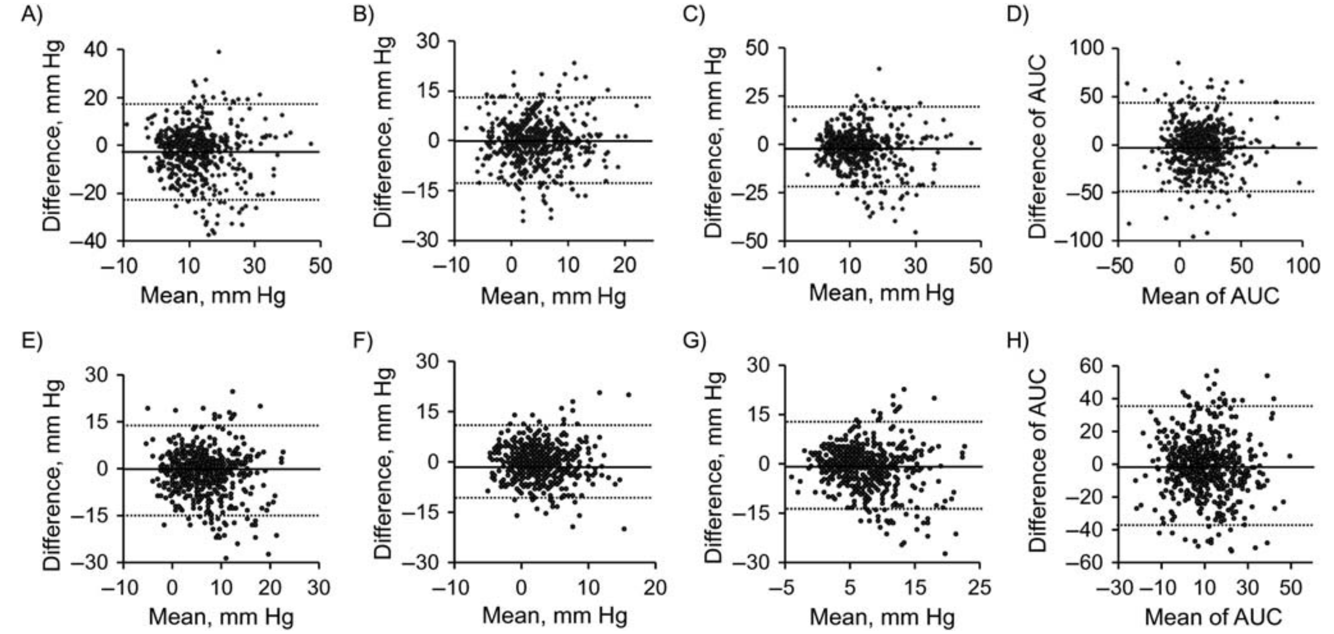

Figure 3. Bland-Altman plots of systolic blood pressure (top) and diastolic blood pressure (bottom) responses to the cold pressor test in initial and follow-up studies, Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study, China, 2003–2005 and 2008–2009. Sections A and E show response at 0 minutes; sections B and F show response at 1 minute; sections C and G show maximum response; and sections D and H show the total area under the curve (AUC) above baseline. The *x* axis represents the mean of 2 measurements from the initial study and the follow-up study, and the *y* axis represents the difference between those measurements from the initial study and the follow-up study. The middle line represents the mean difference and the upper and lower lines represent the limits of agreement (mean ± 2 standard deviations), respectively.

support further studies of the application of BP response to CPT in the risk classification and prediction of hypertension in the future.

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