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Original Contribution

Maternal History of Hypertension and Blood Pressure Response to Potassium Intake

The GenSalt Study

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The relation between parental history of hypertension and blood pressure response to potassium intake is unknown. A 7-day high-sodium followed by a 7-day high-sodium plus potassium dietary-feeding study was conducted from 2003 to 2005 among 1,871 Chinese participants. Those with a maternal history of hypertension had larger systolic blood pressure responses to potassium compared with those without: −4.31 (95% confidence interval (CI): −4.99, −3.62) mm Hg versus −3.35 (95% CI: −4.00, −2.70) mm Hg, respectively ($P_{difference}$ = 0.002). A consistent trend was observed for diastolic blood pressure responses: −1.80 (95% CI: −2.41, −1.20) mm Hg versus −1.35 (95% CI: −1.95, −0.74) mm Hg, respectively (P = 0.07). Stronger associations between early onset maternal hypertension and blood pressure responses were noted, with systolic blood pressure decreases of −4.80 (95% CI: −5.65, −3.95) mm Hg versus −3.55 (95% CI: −4.17, −2.93) mm Hg and diastolic blood pressure decreases of −2.25 (95% CI: −3.01, −1.50) mm Hg versus −1.42 (95% CI: −1.99, −0.85) mm Hg among those with early onset maternal hypertension versus those without, respectively (P = 0.001 and 0.009, respectively). Odds ratios for high potassium sensitivity were 1.36 (95% CI: 0.96, 1.92) and 1.60 (95% CI: 1.08, 2.36) for those with maternal hypertension and early onset maternal hypertension, respectively (P = 0.08 and 0.02, respectively). Potassium supplementation could help to reduce blood pressure among those with a maternal history of hypertension.

blood pressure; dietary potassium; family history; hypertension

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; GenSalt, Genetic Epidemiology Network of Salt Sensitivity; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation.

Observational studies have identified a significant, inverse association between dietary potassium intake and blood pressure (1, 2). Randomized clinical trials have demonstrated the blood pressure-lowering effects of potassium among hypertensive and normotensive participants (3–5). Clinical trials have also documented that blood pressure responses to potassium intake are normally distributed in populations, with blood pressure reductions varying substantially between individuals (3, 6). Although the interindividual variability of blood pressure response to potassium is well described, relatively few determinants of this complex trait have been recognized (6). Identification of subgroups most sensitive to potassium intake could have important public health implications because these individuals may benefit most from dietary potassium intervention.

Parental history of elevated blood pressure is an important risk factor for hypertension development (7, 8). However, the association between parental history of hypertension and potassium sensitivity remains unknown. If a positive relation exists, this high-risk group would represent

an ideal population for targeted increased potassium intake (9). The current study examined the relation between parental history of hypertension and both systolic and diastolic blood pressure responses to potassium intake among participants of the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study. In addition, we explored the separate associations between maternal and paternal history of hypertension, as well as parental history of early onset hypertension, and potassium sensitivity. This unique analysis takes advantage of the large, multigenerational family-based design of the GenSalt Study, which provides directly ascertained measures of blood pressure and hypertension status among parents of intervention participants.

MATERIALS AND METHODS

Study population

The GenSalt Study was conducted between the years 2003 and 2005 in a Han Chinese population with habitually high sodium intake from rural areas of northern China. A community-based blood pressure screening was conducted among persons aged 18–60 years in the study villages to identify potential probands and their families. Those with a mean systolic blood pressure (SBP) between 130 and 160 mm Hg and/or a diastolic blood pressure (DBP) between 85 and 100 mm Hg and no use of antihypertensive medications were recruited, along with their parents, spouses, siblings, and offspring. Detailed eligibility criteria for the probands and their spouses, siblings, parents, and offspring have been presented elsewhere (10). Briefly, individuals were excluded from the study if they had stage 2 hypertension, secondary hypertension, clinical cardiovascular disease, chronic kidney disease, or diabetes; used antihypertensive medications; or were pregnant, heavy alcohol drinkers, or currently on a low-sodium diet. Only probands, siblings, spouses, and offspring were eligible for the dietary intervention. Of the 1,871 eligible participants for high-sodium and high-sodium plus potassium interventions, 1,843 (98.5%) completed the entire intervention.

Institutional review boards at all of the participating institutions approved the GenSalt Study. Written, informed consents for the baseline observation and for the intervention program were obtained from each participant.

Data collection

A standard questionnaire was administered by trained staff at the baseline examination to collect information on family structure, demographic characteristics, personal and family medical history, and lifestyle risk factors including cigarette smoking, drinking, and physical activity. Physical activity information obtained from the questionnaire was converted to metabolic equivalent-hours per day, which were calculated by multiplying the number of hours spent in each activity intensity category by its corresponding metabolic equivalent weight (11). Body weight and height were measured twice in light indoor clothing without shoes during the baseline examination. Body mass index was calculated as weight (kg)/height $(m)^2$. Three morning blood pressure measurements were obtained according to a standard protocol during each of the 3 days of baseline observation and on days 5, 6, and 7 of each intervention period. All blood pressure readings were measured by trained and certified observers using a random-zero sphygmomanometer (12). Blood pressure was measured with the participant in the sitting position after 5 minutes of rest. In addition, participants were advised to avoid alcohol, cigarette smoking, coffee/tea, and exercise for at least 30 minutes prior to their blood pressure measurements. All blood pressure observers were blinded to the participant's dietary intervention.

Parental history of hypertension

Parental history of hypertension was directly ascertained from parents of intervention participants at the GenSalt baseline examination. Proband spouses who took part in the dietary intervention were excluded from the current study because information on parental history of hypertension was not collected for these individuals ($n = 62$). Parental history of hypertension was defined as having a mother or father who had hypertension (SBP $\geq$140 mm Hg and/or DBP $\geq$90 mm Hg and/or taken antihypertension medication within the past 30 days). Maternal and paternal history of hypertension was defined as having a mother and father, respectively, with hypertension. For the 192 participants whose father ($n = 146$) or mother ($n = 49$) was not available for examination, self-reported family history information was used to assess his/her hypertension status. Eighty-three participants whose parents were not available for examination and were missing self-reported information on family history were excluded from the analysis. Data on parental history of hypertension were available for 1,698 (95.3%) probands, siblings, and offspring who participated in the dietary intervention. Parental history of early onset hypertension was defined as having a father or mother with hypertension who was either under 65 years of age at the time of the baseline examination or reported a diagnosis of hypertension before the age of 65 years.

Potassium supplementation intervention

The GenSalt dietary intervention participants received a low-sodium diet (51.3 mmol of sodium per day) for 7 days followed by a high-sodium diet (307.8 mmol of sodium per day) for 7 days. After that, they received a 60 mmol potassium supplementation while continuing on the high-sodium diet for another 7 days. One 20 mmol potassium pill (Klor-Con M20 potassium tablets; Upsher-Smith Laboratories, Maple Grove, Minnesota) was given during breakfast, lunch, and dinner. All study foods were cooked without salt, and prepackaged salt was added to the individual study participant's meal when it was served by the study staff. To ensure study participants' compliance with the intervention program, they were required to have their breakfast, lunch, and dinner at the study kitchen under supervision of the study staff during the entire study period. The study participants were instructed to avoid consuming any foods that were not provided by study personnel. Three

timed urinary specimens were collected at baseline and at the end of each phase of intervention (days 5, 6, and 7) to monitor compliance with the dietary sodium and potassium interventions among all participants. The results showed excellent compliance with the study diet: The means of 24-hour urinary excretions of sodium and potassium were 242.4 (standard deviation (SD), 66.7) mmol and 36.9 (SD, 9.6) mmol at baseline; 47.5 (SD, 16.0) mmol and 31.4 (SD, 7.7) mmol during the low-sodium intervention; 244.3 (SD, 37.7) mmol and 35.7 (SD, 7.5) mmol during the high-sodium intervention; and 251.9 (SD, 36.9) mmol and 77.3 (SD, 12.6) mmol during the potassium intervention, respectively.

Statistical analysis

Potassium sensitivity was defined by using both continuous and discrete measures of blood pressure changes from high-sodium to high-sodium plus potassium supplementation interventions. Quantitative absolute SBP and DBP responses to potassium were calculated as the mean of 9 blood pressure measurements on days 5, 6, and 7 during the potassium intervention minus the mean of 9 blood pressure measurements during the high-sodium intervention. Dichotomous high potassium sensitivity was defined as a mean arterial blood pressure decrease in the top 10th percentile, which corresponded to an absolute mean arterial blood pressure decrease of greater than or equal to 7.5 mm Hg in response to potassium intake. Mean arterial blood pressure was calculated from measured blood pressure components as DBP + (SBP – DBP)/3.

The means and percentages of baseline characteristics were presented by parental history of hypertension. Statistical significance was determined by t tests for continuous variables and χ^2 tests for categorical variables. For the multivariable analyses, statistical methods that accounted for correlations among family members in the GenSalt Study were used. Differences in mean blood pressure responses to potassium intake according to parental, maternal, and paternal history of hypertension and early onset hypertension were examined separately by using mixed linear regression models. Generalized estimating equations were used to calculate the adjusted odds ratio of high potassium sensitivity associated with parental, maternal, and paternal history of hypertension and early onset hypertension. Multivariable models were adjusted for age, gender, high school education, marital status, current drinking, current smoking, physical activity, body mass index, and baseline urinary sodium and potassium excretions. A similar multivariable model with an additional adjustment for baseline blood pressure was also examined. To test the robustness of study findings for the dichotomous potassium-sensitivity phenotype, sensitivity analyses defined potassium sensitivity with alternative cutpoints in the top 25th, 15th, and 5th percentiles of mean arterial blood pressure responses. To determine whether the use of a common age threshold for defining maternal and paternal history of early hypertension may have influenced study findings, we conducted a sensitivity analysis still classifying early maternal hypertension as a maternal diagnosis before 65 years of age but reclassifying early paternal hypertension as a paternal diagnosis before 55 years of age. In addition, to determine whether the use of differentially reported information on maternal and paternal history of hypertension may have influenced study findings, we conducted a sensitivity analysis including only those participants who had directly ascertained information on parental hypertension status from both parents ($n = 1{,}506$). All reported P values are 2 sided. All statistical analyses were conducted by using SAS, version 9.2, statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Approximately 65.8% of GenSalt Study participants had a parental history of hypertension. Among those with a parental history of hypertension, the average age of parental diagnosis was 65.1 (SD, 11.1) years for maternal hypertension and 63.6 (SD, 11.1) years for paternal hypertension. Among those with a parental history of early hypertension, the average age of parental diagnosis was 62.4 (SD, 9.1) years for maternal hypertension and 54.7 (SD, 7.1) years for paternal hypertension. As expected, those with a parental history of hypertension had higher SBP and DBP, and they were more likely to be hypertensive than those with no parental history (Table 1).

Table 2 shows the multivariable-adjusted mean blood pressure responses to dietary potassium intake according to parental, maternal, and paternal history of hypertension. On average, those with a maternal history of hypertension had larger SBP decreases in response to potassium intake compared with those with no maternal history of hypertension. For example, those with a maternal history of hypertension had mean multivariable-adjusted SBP responses = −4.31 (95% confidence interval (CI): −4.99, −3.62) mm Hg compared with −3.35 (95% CI: −4.00, −2.70) mm Hg among those without maternal history of hypertension ($P_{\text{difference}} = 0.002$). Although not statistically significant, a similar trend was observed for DBP. These findings remained significant after additional adjustment for baseline blood pressure. Neither parental nor paternal history of hypertension was associated with potassium sensitivity in the current analysis.

Early onset maternal hypertension was strongly associated with SBP and DBP responses to potassium (Table 3). Significantly increased blood pressure responses to potassium intake were observed among those with compared with those without a history of early onset maternal hypertension: −4.80 (95% CI: −5.65, −3.95) mm Hg versus −3.55 (95% CI: −4.17, −2.93) mm Hg, respectively, for SBP response ($P_{\text{difference}} = 0.001$); and −2.25 (95% CI: −3.01, −1.50) mm Hg versus −1.42 (95% CI: −1.99, −0.85) mm Hg, respectively, for DBP response ($P_{\text{difference}} = 0.009$). Additional adjustment for blood pressure did not change the results. Moreover, parental history of early onset hypertension was also significantly associated with increased SBP responses to potassium ($P = 0.03$), with a similar nonsignificant trend observed for DBP responses ($P = 0.08$). Post hoc analysis demonstrated a nonsignificant association between parental history of early hypertension and SBP

Table 1. Characteristics of GenSalt Proband, Sibling, and Offspring Dietary Intervention Participants According to Parental History of Hypertension in China, 2003–2005

	Parental History of Hypertension				*P* Value
	No ($n = 580$)		Yes ($n = 1,118$)		
	%	Mean (SD)	%	Mean (SD)	
Age, years		36.5 (9.6)		39.9 (8.4)	<0.0001
Male	57.2		53.5		0.14
High school graduate	15.0		13.6		0.43
Married	88.8		94.8		<0.0001
Current drinker	28.1		32.4		0.07
Current smoker	32.4		31.7		0.75
Physical activity, METs		23.4 (11.4)		24.7 (11.6)	0.04
Body mass index[a]		23.2 (3.2)		23.5 (3.1)	0.03
Baseline urinary excretion, mmol					
Sodium		239.1 (64.6)		245.6 (68.2)	0.06
Potassium		36.8 (9.8)		36.9 (9.7)	0.87
Baseline blood pressure, mm Hg					
Systolic		114.0 (13.1)		119.3 (14.2)	<0.0001
Diastolic		71.9 (9.8)		75.3 (10.3)	<0.0001
Hypertension	5.2		12.7		<0.0001

Abbreviations: GenSalt, Genetic Epidemiology Network of Salt Sensitivity; MET, metabolic equivalent; SD, standard deviation.

[a] Body mass index: weight (kg)/height $(m)^2$.

response to potassium after additional adjustment for maternal history of early onset hypertension ($P = 0.41$), suggesting that our findings were driven by the strong influence of history of early maternal hypertension. Findings for parental history of early hypertension were also only marginally significant after additional adjustment for baseline SBP. There was no association between paternal history of early onset hypertension and blood pressure responses to potassium. Using an earlier age threshold to define history of early paternal hypertension did not change the results (data not shown).

Findings for the high-potassium sensitivity phenotype were consistent with those of the quantitative analyses (Table 4). For example, in multivariable analysis, maternal history of hypertension and early onset hypertension were marginally and significantly associated with high potassium sensitivity, respectively (odds ratio (OR) = 1.36, 95% CI: 0.96, 1.92 and OR = 1.60, 95% CI: 1.08, 2.36, respectively) ($P = 0.08$ and $P = 0.02$, respectively); parental history of early onset hypertension was marginally associated with high potassium sensitivity (OR = 1.41, 95% CI: 0.97, 2.03) ($P = 0.07$); and findings for parental history of hypertension and paternal history of hypertension and early onset hypertension were not significant.

Results of sensitivity analyses examining high-potassium sensitivity defined by cutpoints at the upper 25th, 15th, and 5th percentiles of mean arterial blood pressure responses were consistent with the primary analysis for maternal history of hypertension (OR = 1.22, 95% CI: 0.94, 1.58; OR = 1.20, 95% CI: 0.88, 1.63; and OR = 2.03, 95% CI: 1.27, 3.26, respectively) ($P = 0.13$, 0.26, and 0.003, respectively); for early onset maternal hypertension (OR =1.40, 95% CI: 1.05, 1.87; OR = 1.42, 95% CI: 0.99, 2.04; and OR = 1.76, 95% CI: 1.03, 2.99, respectively) ($P = 0.02$, 0.06, and 0.04, respectively); and for early onset parental hypertension (OR = 1.23, 95% CI: 0.94, 1.63; OR = 1.34, 95% CI: 0.95, 1.87; and OR = 1.37, 95% CI: 0.82, 2.28, respectively) ($P = 0.13$, 0.09, and 0.23, respectively). Similar to the overall findings, there was no association between parental history of hypertension or early onset hypertension and high potassium sensitivity in this sensitivity analysis. Furthermore, limiting the analyses to only those participants who had directly ascertained information on both maternal and paternal history of hypertension did not change study findings (data not shown).

DISCUSSION

The current study identified a significant association between maternal history of hypertension and blood pressure responses to potassium intake. The effects of maternal history appeared to be even more pronounced among those with early onset maternal hypertension. Although there was some evidence of association between early onset parental hypertension and potassium sensitivity, these findings were driven by the strong effect of early onset maternal hypertension. In contrast, there was no association between paternal history of hypertension and any of the potassium

Table 2. Mean Blood Pressure Responses to Potassium Intervention According to Parental History of Hypertension Among GenSalt Participants in China, 2003–2005

	No History of Hypertension		History of Hypertension[a]		*P* Value
	Mean	95% CI	Mean	95% CI	
Parental					
No.	580		1,118		
Systolic					
Age and gender adjusted	−3.34	−3.85, −2.84	−3.51	−3.90, −3.13	0.58
Multivariable adjusted[b]	−3.67	−4.37, −2.96	−3.89	−4.53, −3.24	0.48
Multivariable + SBP adjusted[c]	−3.64	−4.34, −2.95	−3.62	−4.24, −2.99	0.93
Diastolic					
Age and gender adjusted	−1.42	−1.88, −0.96	−1.38	−1.68, −1.07	0.86
Multivariable adjusted[b]	−1.58	−2.25, −0.91	−1.56	−2.12, −0.99	0.94
Multivariable + DBP adjusted[c]	−1.57	−2.25, −0.90	−1.45	−2.02, −0.89	0.66
Maternal					
No.	880		818		
Systolic					
Age and gender adjusted	−3.00	−3.43, −2.56	−3.93	−4.37, −3.50	0.003
Multivariable adjusted[b]	−3.35	−4.00, −2.70	−4.31	−4.99, −3.62	0.002
Multivariable + SBP adjusted[c]	−3.29	−3.93, −2.64	−4.00	−4.67, −3.34	0.02
Diastolic					
Age and gender adjusted	−1.17	−1.54, −0.79	−1.62	−1.97, −1.27	0.08
History of HTN[a]multivariable adjusted[b]	−1.35	−1.95, −0.74	−1.80	−2.41, −1.20	0.07
Multivariable + DBP adjusted[c]	−1.33	−1.93, −0.72	−1.68	−2.29, −1.08	0.16
Paternal					
No.	1,013		685		
Systolic					
Age and gender adjusted	−3.54	−3.92, −3.17	−3.34	−3.86, −2.81	0.51
Multivariable adjusted[b]	−3.89	−4.51, −3.30	−3.70	−4.44, −2.96	0.54
Multivariable + SBP adjusted[c]	−3.77	−4.38, −3.17	−3.41	−4.13, −2.69	0.25
Diastolic					
Age and gender adjusted	−1.50	−1.83, −1.17	−1.24	−1.65, −0.83	0.31
History of HTN[a]multivariable adjusted[b]	−1.67	−2.26, −1.07	−1.42	−2.04, −0.81	0.34
Multivariable + DBP adjusted[c]	−1.62	−2.23, −1.02	−1.31	−1.92, −0.70	0.21

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

[a] History of hypertension was defined as having a parent/mother/father with hypertension (currently taking medication or had a SBP/DBP ≥140/90).

[b] Multivariable-adjusted model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, and baseline urinary potassium excretion.

[c] Multivariable-adjusted + blood pressure model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, baseline urinary potassium excretion, and systolic or diastolic blood pressure.

sensitivity phenotypes. The novel information gained from this research may have important clinical and public health implications. Easily obtainable information on maternal history of hypertension could be used to identify individuals who may receive enhanced benefits of potassium supplementation, substantially reducing their blood pressure and subsequent hypertension risk (3).

To our knowledge, this is the only study to examine the relation between parental history of hypertension and blood pressure responses to potassium intake. Other study attributes include the large, family-based design of the GenSalt Study, which allowed for direct ascertainment of parental hypertension status rather than relying primarily on offspring-reported information. In addition, very few intervention participants took antihypertensive medications ($n = 6$), minimizing the potentially confounding effects of this variable. Measurement error was reduced and power enhanced by the large number of blood pressure measurements that

Table 3. Mean Blood Pressure Responses to Potassium Intervention According to Parental History of Early Onset Hypertension Among GenSalt Participants in China, 2003–2005

	No History of Early Onset Hypertension		History of Early Onset Hypertension[a]		*P* Value
	Mean	95% CI	Mean	95% CI	
		Parental			
No.	1,093		593		
Systolic					
Age and gender adjusted	−3.17	−3.55, −2.79	−3.86	−4.40, −3.32	0.04
Multivariable adjusted[b]	−3.58	−4.20, −2.95	−4.29	−5.05, −3.53	0.03
Multivariable + SBP adjusted[c]	−3.46	−4.07, −2.84	−3.96	−4.69, −3.22	0.12
Diastolic					
Age and gender adjusted	−1.21	−1.53, −0.89	−1.64	−2.08, −1.21	0.11
Multivariable adjusted[b]	−1.44	−2.02, −0.86	−1.91	−2.56, −1.25	0.08
Multivariable + DBP adjusted[c]	−1.40	−1.98, −0.82	−1.78	−2.44, −1.13	0.15
		Maternal			
No.	1,282		404		
Systolic					
Age and gender adjusted	−3.11	−3.48, −2.75	−4.35	−4.96, −3.73	0.001
Multivariable adjusted[b]	−3.55	−4.17, −2.93	−4.80	−5.65, −3.95	0.001
Multivariable + SBP adjusted[c]	−3.42	−4.02, −2.81	−4.43	−5.23, −3.62	0.005
Diastolic					
Age and gender adjusted	−1.17	−1.47, −0.87	−1.96	−2.49, −1.43	0.01
Multivariable adjusted[b]	−1.42	−1.99, −0.85	−2.25	−3.01, −1.50	0.009
Multivariable + DBP adjusted[c]	−1.37	−1.95, −0.80	−2.12	−2.87, −1.36	0.02
		Paternal			
No.	1,399		287		
Systolic					
Age and gender adjusted	−3.38	−3.72, −3.05	−3.58	−4.40, −2.76	0.65
Multivariable adjusted[b]	−3.76	−4.38, −3.14	−3.95	−4.91, −2.99	0.66
Multivariable + SBP adjusted[c]	−3.60	−4.20, −3.00	−3.62	−4.55, −2.69	0.96
Diastolic					
Age and gender adjusted	−1.39	−1.68, −1.10	−1.27	−1.95, −0.59	0.74
Multivariable adjusted[b]	−1.60	−2.17, −1.02	−1.47	−2.26, −0.69	0.73
Multivariable + DBP adjusted[c]	−1.54	−2.12, −0.96	−1.35	−2.13, −0.57	0.60

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

[a] History of early onset hypertension was defined as having a parent/mother/father diagnosed with hypertension (currently taking medication or had a SBP/DBP ≥140/90) before the age of 65 years.

[b] Multivariable-adjusted model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, and baseline urinary potassium excretion.

[c] Multivariable-adjusted + blood pressure model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, baseline urinary potassium excretion, and systolic or diastolic blood pressure.

were collected for each participant. Furthermore, the participation rate was high (95.3%), and compliance with the study dietary sodium and potassium interventions, as assessed by urinary excretion of sodium and potassium during each intervention period, was excellent. Finally, stringent quality control procedures were used during measurement of blood pressure and the other study covariables, conduct of the dietary interventions, and data management and analysis. Although previous studies have used age cutpoints as young as 35, 45, 50, or 55 years to define early onset hypertension (8, 13–15), less than 0.5%, 5%, 7%, and 15% of GenSalt parents, respectively, were categorized with early onset hypertension using these thresholds. Compared with findings from a national examination survey

Table 4. Odds Ratio of High Potassium Sensitivity[a] According to Parental History of Hypertension and Early Onset Hypertension Among GenSalt Participants in China, 2003–2005

	History of Hypertension[b]			History of Early Onset Hypertension[c]		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
			Parental			
Age and gender adjusted	1.08	0.75, 1.56	0.68	1.38	0.95, 2.00	0.09
Multivariable adjusted[d]	1.09	0.75, 1.58	0.66	1.41	0.97, 2.03	0.07
Multivariable + HTN adjusted[e]	1.05	0.72, 1.52	0.80	1.37	0.95, 1.97	0.09
			Maternal			
Age and gender adjusted	1.35	0.96, 1.91	0.09	1.56	1.06, 2.31	0.02
Multivariable adjusted[d]	1.36	0.96, 1.92	0.08	1.60	1.08, 2.36	0.02
Multivariable + HTN adjusted[e]	1.32	0.93, 1.86	0.12	1.55	1.05, 2.28	0.03
			Paternal			
Age and gender adjusted	1.07	0.76, 1.51	0.70	1.12	0.69, 1.83	0.65
Multivariable adjusted[d]	1.07	0.76, 1.52	0.68	1.13	0.69, 1.85	0.62
Multivariable + HTN adjusted[e]	1.04	0.74, 1.46	0.84	1.11	0.68, 1.81	0.68

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

[a] High potassium sensitivity was defined as the top 10% of mean arterial pressure decreases in response to potassium.

[b] History of hypertension was defined as having a parent/mother/father with hypertension (currently taking medication or had a SBP/DBP ≥140/90).

[c] History of early onset hypertension was defined as having a mother/father with hypertension (currently taking medication or had a SBP/DBP ≥140/90) who was diagnosed before the age of 65 years.

[d] Multivariable-adjusted model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, and baseline urinary potassium excretion.

[e] Multivariable-adjusted + HTN model is adjusted for age, gender, high school education, marital status, current drinking status, current smoking, physical activity, baseline body mass index, baseline urinary sodium excretion, baseline urinary potassium excretion, and hypertension status.

conducted in China in 2000–2001, these estimates are low and likely reflect a limited access to health care rather than true prevalence estimates (16). Because 40.1% of mothers and 49.5% of fathers were not diagnosed with hypertension previous to the GenSalt baseline examination (resulting in a high average age of hypertension diagnosis), the current study used a threshold of 65 years to define early onset hypertension. Although this method may incorrectly categorize some participants as "early onset," such misclassification would likely dilute study findings, making the reported estimates conservative. Further, among those with a history of early parental hypertension, the average age of hypertension diagnosis was nearly 8 years younger for fathers compared with mothers (54 vs. 62 years), suggesting that differential misclassification using a common age threshold for early hypertension diagnosis could have resulted in stronger associations between early maternal hypertension and potassium sensitivity compared with early paternal hypertension. However, sensitivity analyses using an age threshold of 55 years in fathers did not change the results. Finally, more fathers than mothers lacked directly ascertained information on hypertension status. Because participant-reported information may be less accurate than directly ascertained data, we cannot exclude the possibility that survival bias could have diluted the association between history of paternal hypertension and potassium sensitivity. However, limiting the analysis to only those participants with directly ascertained information from both parents did not change the overall findings, suggesting that the findings should be robust to this issue.

Maternal history of hypertension was strongly and significantly associated with potassium sensitivity in the current study. Although this work is the first to examine such a relation, past studies have implicated maternal history of hypertension as an important predictor of other blood pressure-related traits (8, 17–23). For example, a recent report by Tseng (17) showed increased SBP, DBP, and hypertension risk associated with maternal history of hypertension in a nationally representative sample of Taiwanese diabetes patients. Furthermore, the Johns Hopkins Precursor Study identified a 50% increased risk of hypertension among men with a maternal history of hypertension compared with those with no maternal history (8). The research presented here builds upon these past works, proposing dietary potassium-supplementation intervention as a particularly important approach for blood pressure reduction among this subgroup at increased risk for hypertension.

A significant association between both maternal and parental history of early onset hypertension and potassium sensitivity was also observed. A previous study implicated early onset parental hypertension as a substantially stronger predictor of hypertension incidence than late-onset hypertension (8), which suggested shared genetic susceptibility. However, the association of parental history of early onset

hypertension and potassium sensitivity observed in this study was driven solely by the strong effect of early onset maternal hypertension. Therefore, shared genetic factors are unlikely to explain the results because one would expect an equal contribution of both maternal and paternal phenotypes to potassium sensitivity, unless X-linked or mitochondrial inheritance could explain the finding. Given the complexity of the phenotype, inheritance in only these fashions seems unrealistic. Furthermore, additional analysis did not identify any gender differences in the relation between early maternal history of hypertension and potassium sensitivity (results not shown), providing a lack of evidence for X-linked inheritance.

The finding of a maternal but not paternal effect of hypertension on offspring potassium sensitivity is of particular interest. Although this phenomenon has not been studied previously, several studies have identified an enhanced effect of maternal compared with paternal history of hypertension on offspring blood pressure phenotypes (20–22). For example, data from the Framingham Offspring Study showed stronger correlations of maternal-offspring SBP levels compared with paternal-offspring SBP levels (20). Friedman et al. (22) showed that maternal history of hypertension was more predictive of offspring essential hypertension than paternal history of hypertension. These authors (22) go on to speculate that their results could be related to better detection of hypertension among mothers compared with fathers. Because parental hypertension status was ascertained through direct examination, any bias due to differential detection of hypertension should be minimized in the current study. Rather, these findings, combined with the pronounced effect of maternal early onset hypertension on blood pressure responses to potassium intake, could indicate that elevated maternal blood pressure during pregnancy influences offspring potassium sensitivity. This idea that the intrauterine environment may have long-term influences on human health was first described by Barker et al. (24) in 1989 and again by Barker (25) in 1995. Since that time, maternal hypertensive pregnancy has been associated with elevated blood pressure during childhood, hypertension, and cardiovascular diseases later in life (26–31). Hypertensive pregnancy has been purported to exert its adverse effects on offspring through inhibited fetal nutrient delivery, resulting in undernutrition, growth restriction, and adverse development of the fetal renal and vascular systems (32, 33). It has also been hypothesized that epigenetic modifications related to intrauterine stress could underlie alterations in gene expression that lead to hypertension development (34). In fact, upregulation of genes in the renin-angiotensin-aldosterone system as a result of fetal growth restriction has been documented extensively in animal experiments (34, 35). Given the well-established role of the renin-angiotensin-aldosterone system in sodium and potassium homeostasis and, subsequently, blood pressure regulation, the animal evidence lends some credence to the hypothesis of the fetal programming of potassium sensitivity (36). However, future studies that directly ascertain data on maternal pregnancy health and offspring potassium sensitivity will be necessary to further explore this relation.

In summary, this work identified a significant association between maternal history of hypertension and potassium sensitivity of blood pressure. A pronounced effect of early onset maternal hypertension on blood pressure responses to potassium was noted. The lack of an effect of paternal history of hypertension suggests that factors related to the intrauterine environment could explain the observed finding. Although more work is needed to confirm fetal programming of potassium sensitivity, these findings have important public health implications. Previous reports have demonstrated a relation between maternal history of hypertension and elevated blood pressure and hypertension risk among offspring. The current research contributes to these findings by suggesting potassium supplementation as a possible strategy for reducing blood pressure among this high-risk group.

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