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POPULATION STUDY ARTICLE

Interaction between lifestyle behaviors and genetic polymorphism in *SCAP* gene on blood pressure among Chinese children

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BACKGROUNDS: Previous studies had revealed that sterol regulatory element-binding protein (*SREBP*) cleavage-activating protein (*SCAP*) rs12487736 polymorphism was associated with blood pressure (BP), but whether rs12487736 could interact with lifestyle behaviors on BP is unknown.

METHODS: A case–control study with 1092 Chinese children was conducted.

RESULTS: We found an interaction between rs12487736 and high calorie foods intake (fried chips/cakes/cookies) on systolic blood pressure (SBP) ($P_{interaction} = 0.027$), and rs12487736 was associated with SBP in the subgroup having high calorie foods at least once in the last week ($b = 2.19$, $P = 0.025$), but not in the subgroup not having high calorie foods. Also, interaction between protein intake (meat/fish/soy beans/egg) and rs12487736 on diastolic BP (DBP) was identified ($P_{interaction} = 0.049$); rs12487736 was associated with DBP in the subgroup consuming protein (meat/fish/soy beans/egg) <twice/day ($b = 3.38$, $P = 0.014$), but not in the subgroup ≥twice/day. There is combined effect between rs12487736 and physical activity on DBP. In the subgroup who were inactive (physical activity <1 h/day), rs12487736 was significantly associated with DBP ($b = 3.27$, $P = 0.046$), but not in the active group (physical activity ≥1 h/day). Similar combined effect between rs12487736 and soft drink was found.

CONCLUSIONS: Interactions or combined effects between *SCAP* and lifestyle behaviors on BP support the importance of promoting a healthy lifestyle in the children genetically predisposed to higher BP.

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INTRODUCTION

High systolic blood pressure (SBP) is one of the three largest risk factors of global disease burden in 2016; it was estimated that high SBP contributed to 122.2 million of global disability-adjusted life-years (DALYs) of men and 87.6 million of global DALYs of women.[1] There is a tracking phenomenon of BP, which means that without proper intervention or control the BP level of children with a high percentile of BP would remain a relatively high percentile in adulthood.[2] Pediatric high BP (HBP) can also lead to target organ diseases.[3] Therefore, exploring the etiology of HBP in childhood is necessary, which is also important for developing personalized interventions in early life.

Hypertension is a complex phenotype influenced by both environmental and genetic risk factors.[4,5] Until now, genetic risk factors are really hard to change or modify. However, environmental risk factors could be modifiable. Hence, the exploration of gene–environment interaction on BP will provide not only important information for the etiology of HBP but also practical implication for prevention and control measures of HBP- or BP-related cardiovascular diseases.

Sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP) plays an important role in the lipid biosynthesis. Under cholesterol-depleted condition, SCAP could transport SREBPs to the Golgi. In Golgi, the transcription activation domain of SREBP is released from the precursor protein. Then, the active form of SREBP activates transcription of lipid regulatory genes.[6]

A previous study has shown that genetic polymorphisms of *SCAP* gene is associated with obesity,[7] blood lipids,[8] and sudden cardiac death.[9] Our study group found that a common single-nucleotide polymorphism (SNP) rs12487736 (also known as *SCAP* A2386G polymorphism, *SCAP*-796I/V isoforms) is associated with SBP in children.[10]

However, whether this BP-related polymorphism of *SCAP* gene could interact with lifestyle factors, such as dietary behaviors and physical activity, has not been studied before. Thus, we conducted the present study to identify whether dietary behaviors and physical activity interact with rs12487736 on BP in Chinese children.

SUBJECTS AND METHODS

Subjects

Participants were selected from the study of Comprehensive Prevention project for Overweight and Obese Adolescents (CPOOA). As described in previous studies,[11–13] the CPOOA study included 1093 children and adolescents aged 7–18 years from three elementary schools and two middle schools in Haidian

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Table 1. General characteristics and behavior characteristics of the study population

Variables	Category	Non-HBP ($n = 942$)	HBP ($n = 150$)	Total ($N = 1092$)	P*	P'
Sex	Boys	510 (54.1)	101 (67.3)	611 (56)	**0.003**	
	Girls	432 (45.9)	49 (32.7)	481 (44)		
Age (year)		11.2 ± 2.9	12.8 ± 2.4	11.4 ± 2.9	**<0.001**	
BMI (kg/m^2)		21 ± 3.8	25.8 ± 4.6	21.6 ± 4.3	**<0.001**	
SBP (mmHg)		101.9 ± 10.9	130.8 ± 9.7	105.9 ± 14.7	**<0.001**	
DBP (mmHg)		49 ± 14.2	58.6 ± 17.7	50.3 ± 15.1	**<0.001**	
Protein intake (meat/fish/soy beans/egg)	<twice/day	502 (62.6)	83 (61)	585 (62.4)	0.728	0.737
	≥twice/day	300 (37.4)	53 (39)	353 (37.6)		
Fruits and vegetables intake[a]	<twice/day	587 (72.7)	97 (72.4)	684 (72.7)	0.933	0.461
	≥twice/day	220 (27.3)	37 (27.6)	257 (27.3)		
Fried chips/cakes/cookies	No	185 (23.3)	41 (30.4)	226 (24.3)	0.075	0.277
	Yes	610 (76.7)	94 (69.6)	704 (75.7)		
Western food	No	539 (68.0)	87 (64.9)	626 (67.5)	0.486	0.084
	Yes	254 (32.0)	47 (35.1)	301 (32.5)		
Soft drink	No	346 (42.4)	49 (35.8)	395 (41.4)	0.145	0.951
	Yes	470 (57.6)	88 (64.2)	558(58.6)		
Physical activity	≥1 h/day	359 (44.8)	65 (47.8)	424 (45.2)	0.511	0.525
	<1 h/day	443 (55.2)	71 (52.2)	514 (54.8)		
Screen time	<2 h/day	522 (64.5)	76 (55.1)	598 (63.1)	**0.033**	0.845
	≥2 h/day	287 (35.5)	62 (44.9)	349 (36.9)		

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *HBP* high blood pressure
P* value was calculated with t test (quantitative variables) or χ^2 test (categorical variables). P' value was adjusted for age, sex, age square, and BMI. P values <0.05 were set in bold
[a]For fruit and vegetable intake category, twice/day means either fruits or vegetables intake twice/day, and ≥twice/day means both fruits and vegetables ≥twice/day

District, Beijing. One participant was excluded for the absence of BP measurement; therefore, totally 1092 participants were included in the current study. The detailed sampling strategies of the CPOOA study have also been reported before.[14,15]

HBP was defined as SBP and/or diastolic BP (DBP) ≥the age- and sex-specific 95th percentile of a representative Chinese children population.[16] This study has been approved by the Ethic Committee of Peking University Health Science Center. Written informed consents were provided by participants and their parents.

Measurement

Anthropometric measurements, including weight, height, and BP, were measured according to standard protocols. Weight and height were measured twice, and the mean value was used for the analysis. Body mass index (BMI) was calculated by weight divided by height squared (kg/m^2). BP was calculated by averaging three measurements at one visit. It was measured three times with a 5-min time interval. BP was measured according to the recommendation of the National High Blood Pressure Education Program Working Group for Children and Adolescents,[17] using an auscultation mercury sphygmomanometer with an appropriate cuff size for children. BP measurements were taken at least 5 min after resting. SBP was defined as the onset of "tapping" Korotkoff sound (K1), and DBP was defined as the fifth Korotkoff sound (K5).

Dietary behaviors, including consumption of fruits, vegetables, high calorie foods (fried chips/cakes/cookies), protein intake (meat/fish/soy beans/egg), western food, and soft drink, were measured by a questionnaire, which has been described in detail in the previous study.[13] The frequency of eating fruit, vegetable, high calorie foods (fried chips/cakes/cookies), and soft drink was investigated with the options of "Never," "1–3 times," "4–6 times," "daily," "twice per day," "3 times per day," or "more than 3 times per day." Physical activity and screen time were also measured by the questionnaire.[12] Daily time spent on physical activity was measured with the options of "Never," 0–0.5 h per day," "0.5–1 h per day," "1–2 h per day," "2–3 h per day," "3–4 h per day," and "more than 4 h per day."

The dietary behaviors and physical activity variables were classified into two categories based on the national recommendation of nutrition and physical activity for Chinese children[18] (Table 1). Screen time included time spent on the television/video viewing and computer/video game playing, and were categorized into <2 h/day or ≥2 h/day according to the American Academy of Pediatrics[19] (Table 1).

Genotyping

Genomic DNAs of participants were isolated from blood leukocytes by the phenol–chloroform extraction method. The *SCAP* rs12487736 polymorphism was assayed by using the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Agena). All the experiments were conducted by investigators who were blind to the phenotypes. The genotyping call rates of rs12487736 were 99.5%.

Statistical analyses

The Hardy–Weinberg equilibrium was tested with the χ^2 test for the genotype data of the non-HBP group. The quantitative variables were described as mean and standard deviations (SD), while the categorical variables were described as percentages. Differences between HBP group and non-HBP group were compared with t tests/Mann–Whitney U test (quantitative variables with normal distribution/skewed distribution) or χ^2 tests (categorical variables). The effect of rs12487736 on BP phenotypes (quantitative variables) and interaction terms (genotype × lifestyle

Table 2. Interaction between lifestyle behaviors and *SCAP* rs12487736 polymorphism on SBP

Lifestyle variables	Category	Genotype	*N*	Mean	SD	*b*	SE	*P* value	$P_{interaction}$
Protein intake (meat/fish/soy beans/egg)	<twice/day	GG	154	107.8	17.1	0.18	1.11	0.871	0.181
		GA/AA	427	105.5	14.0				
	≥twice/day	GG	105	104.9	13.9	2.33	1.29	0.071	
		GA/AA	247	107.0	14.9				
Fruits and vegetables intake[a]	<twice/day	GG	196	107.41	16.0	0.87	0.99	0.379	0.386
		GA/AA	484	106.19	14.4				
	≥twice/day	GG	65	103.72	14.4	2.55	1.56	0.102	
		GA/AA	191	105.63	14.1				
Fried chips/cakes/cookies	No	GG	62	112.6	15.9	−2.13	1.70	0.211	**0.027**
		GA/AA	162	107.4	14.0				
	Yes	GG	195	104.9	15.5	2.19	0.97	**0.025**	
		GA/AA	506	105.6	14.5				
Western food	No	GG	175	107.5	15.9	0.85	1.00	0.392	0.782
		GA/AA	447	106.4	14.1				
	Yes	GG	82	105.4	15.5	1.26	1.59	0.429	
		GA/AA	218	105.3	14.9				
Soft drink	No	GG	111	105.8	15.2	1.05	1.20	0.383	0.974
		GA/AA	281	105.5	13.6				
	Yes	GG	155	107.3	16.3	1.21	1.12	0.282	
		GA/AA	401	106.5	14.9				
Physical activity	<1 h/day	GG	120	108.4	16.3	0.43	1.26	0.731	0.335
		GA/AA	302	107.2	14.3				
	≥1 h/day	GG	144	105.2	15.4	2.10	1.11	0.060	
		GA/AA	367	105.3	14.4				
Screen time	<2 h/day	GG	170	105.6	15.9	0.79	1.00	0.429	0.715
		GA/AA	425	104.8	13.6				
	≥2 h/day	GG	96	108.9	15.8	1.45	1.49	0.332	
		GA/AA	251	108.4	15.3				

SBP systolic blood pressure, *SD* standard deviation, *SE* standard error, *BMI* body mass index, *SCAP* SREBP cleavage-activating protein
P and $P_{interaction}$ were adjusted for sex, age, age square, and BMI. *P* values <0.05 were set in bold
[a]For fruit and vegetable intake category, twice/day means either fruits or vegetables intake twice/day, and ≥ twice/day means both fruits and vegetables ≥twice/day

variables) were estimated with multivariate general linear model with age, age square, sex, and BMI as covariates. For the effect on risk of HBP, multivariate logistic regression model, with age, age square, sex, and BMI as covariates, was conducted to test the interaction terms (genotype × lifestyle variables). All analyses were conducted under a dominant genetic model (GG = 0, GA/AA = 1) as the previous study, since GA and AA genotype carriers have similar average SBP/DBP levels that are significantly higher than GG genotype carriers.[10] In the present study, combined effect, or joined action or joint effect as a specific mode of interaction, is used to describe that two factors together contribute to the phenotype, without excluding the probability of complete independentability. The interaction term is used in a narrower or strict sense, which refers to a statistical level ($P_{interaction} < 0.05$).[20] The analyses were performed with SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics of the study population

The characteristics of our study population are presented in Table 1. A total of 1092 children with a mean age of 11.4 years were included in the study. HBP group had significantly higher BMI, SBP, and DBP than non-HBP group ($P < 0.001$). In the univariate analysis for the dietary behaviors and physical activity, there were no significant difference between HBP group and non-HBP group ($P > 0.05$). When the potential covariates were further adjusted, the associations between HBP and dietary behaviors or physical activity were still not significant ($P > 0.05$). For screen time, the children with ≥2 h/day of screen time had significantly higher risk of HBP than those with <2 h of daily screen time ($P = 0.033$), though the association were not significant when the covariates were further adjusted ($P = 0.845$). In total, 62.4% of the children had protein (meat/fish/soy beans/egg) less than twice per day; only 27.3% of the participants had both fruits and vegetables intake ≥twice every day. Totally, 54.8 and 36.9% of the participants had <1 h of daily physical activity and more than 2 h of daily screen time, respectively. The percentages of the participants had fried chips/cakes/cookies, western food, and soft drink in the past week were 75.7, 32.5, and 58.6%, respectively.

SCAP rs12487736 polymorphism and lifestyle behaviors interaction on SBP

Our previous study demonstrated that *SCAP* rs12487736 polymorphism was significantly associated with SBP ($\beta = 1.66$, $P = 0.003$) under a dominant genetic model with adjustment

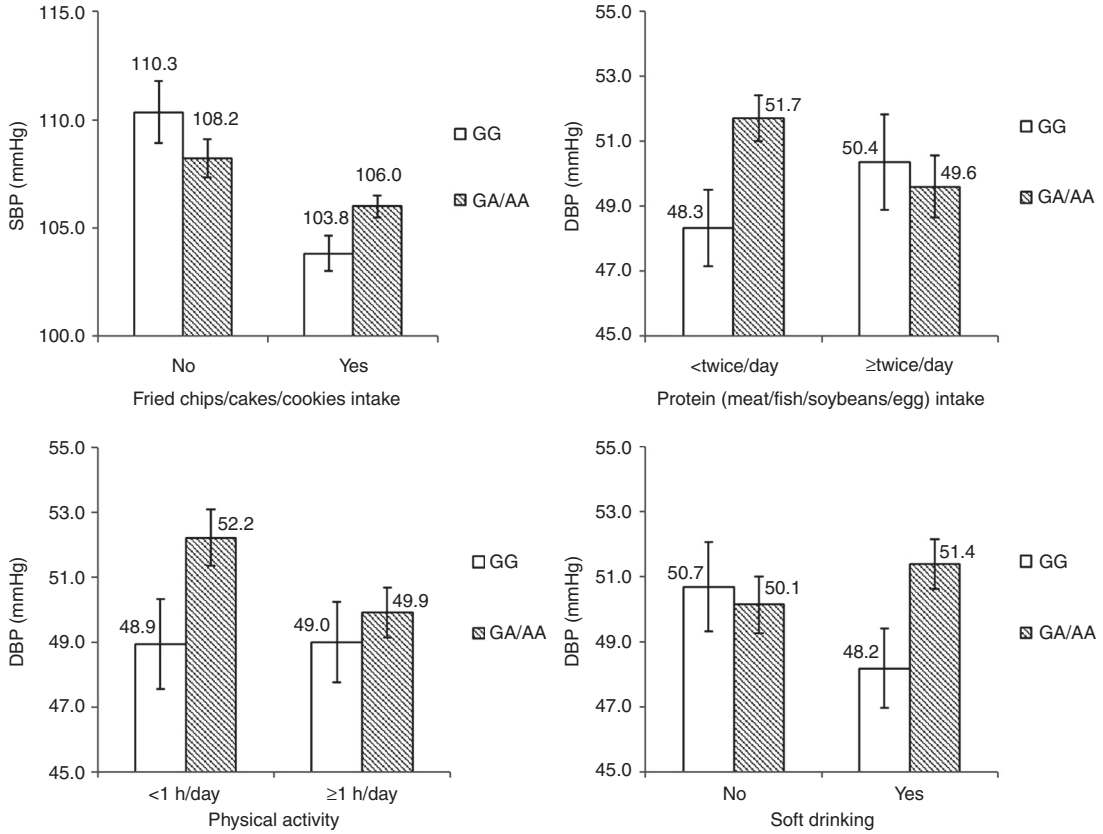

Fig. 1 Adjusted means and standard errors of blood pressure stratified by SREBP cleavage-activating protein (*SCAP*) rs12487736 polymorphism and lifestyle variables. SBP: systolic blood pressure; DBP: diastolic blood pressure. Adjusted means and standard errors were estimated under general linear regression model with adjustment for age, age square, sex, and BMI

for potential covariates. Here we further explored the interaction between rs12487736 and lifestyle behaviors on BP. Table 2 showed the associations between rs12487736 and SBP stratified by lifestyle variables. There was a significant interaction between high calorie food (fried chips/cakes/cookies) intake and rs12487736 polymorphism on SBP ($P_{interaction} = 0.027$). In the subgroup having high calorie foods at least once in the last week, rs12487736 polymorphism GA/AA genotype carriers had significantly higher SBP level than the GG genotype carriers ($b = 2.19$, SE = 0.97, $P = 0.025$), but no significant association was found in the subgroup having high calorie foods less than once. The adjusted SBP levels were showed by rs12487726 genotype and high calorie foods group in Fig. 1a. No interactions with protein intake (meat/fish/soy beans/egg), fruits and vegetables intake, dairy intake, western food intake, soft drink, physical activity, and screen time were found for rs12487736 on SBP.

SCAP rs12487736 polymorphism and lifestyle behaviors interaction on DBP

The stratified associations between rs12487736 and DBP by lifestyle variables are shown in Table 3. A significant interaction between protein intake (meat/fish/soy beans/egg) and rs12487736 on DBP ($P_{interaction} = 0.049$) was found. In the subgroup consuming protein (meat/fish/soy beans/egg) less than twice per day, rs12487736 polymorphism GA/AA genotype carriers had significantly higher DBP level than the GG genotype carriers ($b = 3.38$, SE = 1.38, $P = 0.014$), but no significant association was found in the subgroup consuming protein (meat/fish/soy beans/egg) at least twice per day. Additionally, there were combined effects between soft drink and physical activity with rs12487736 on DBP. A significant association between rs12487736 and DBP was found in the subgroup having soft drink in the last week ($b = 3.20$, SE = 1.44, $P = 0.027$), but not significant in the subgroup not having soft drink ($b = -0.55$, SE = 1.62, $P = 0.732$). In the subgroup having <1 h of physical activity, rs12487736 was also significantly associated with DBP ($b = 3.27$, SE = 1.63, $P = 0.046$), but not significant in the group having at least 1 h of physical activity ($b = 0.91$, SE = 1.46, $P = 0.535$). The adjusted DBP level with standard error by rs12487726 genotype and lifestyle factors is shown in Fig. 1b–d. No interactions between fruits and vegetables intake, dairy intake, western food, soft drink, and screen time with rs12487736 were detected on DBP.

Furthermore, the associations between rs12487736 and risk of HBP, as well as the interaction between rs12487736 and lifestyle behaviors on risk of HBP, were not significant (Table S1).

DISCUSSION

In the present study, we found that there were interactions or combined effects between *SCAP* rs12487736 polymorphism and dietary behaviors, or physical activity on BP level among Chinese children. Briefly, the association between rs12487736 polymorphism and BP level only existed in the children with unfavorable lifestyle behavior (low protein intake "meat/fish/soy beans/egg" group, or fried chips/cakes/cookies intake group, or soft drink group or low physical activity level group), not in the children with favorable lifestyle behavior.

For interaction with dietary behaviors, a significant interaction between high calorie foods (fried chips/cakes/cookies) consumption and rs12487736 on children's SBP level was identified.

Table 3. Interaction between lifestyle behaviors and *SCAP* rs12487736 polymorphism on DBP

Lifestyle variables	Category	Genotype	*N*	Mean	SD	*b*	SE	*P* value	$P_{interaction}$
Protein intake (meat/fish/soy beans/egg)	<twice/day	GG	154	49.1	17.1	3.38	1.38	**0.014**	**0.049**
		GA/AA	427	51.5	14.1				
	≥twice/day	GG	105	50.5	15.8	−0.76	1.76	0.668	
		GA/AA	247	49.6	15.4				
Fruits and vegetables intake[a]	<twice/day	GG	196	49.7	16.7	1.58	1.31	0.227	0.825
		GA/AA	484	50.4	15.3				
	≥twice/day	GG	65	50.4	15.9	1.18	1.91	0.538	
		GA/AA	191	51.2	13.2				
Fried chips/cakes/cookies	No	GG	62	48.8	18.7	3.22	2.39	0.179	0.295
		GA/AA	162	51.1	14.5				
	Yes	GG	195	50.0	15.9	1.20	1.24	0.333	
		GA/AA	506	50.5	14.9				
Western food	No	GG	175	50.1	16.6	1.15	1.32	0.386	0.493
		GA/AA	447	50.3	14.5				
	Yes	GG	82	49.0	16.8	3.52	2.00	0.079	
		GA/AA	218	51.5	15.4				
Soft drink	No	GG	111	51.0	14.8	−0.55	1.62	0.732	0.093
		GA/AA	281	50.0	14.8				
	Yes	GG	155	48.8	17.5	3.20	1.44	**0.027**	
		GA/AA	401	51.1	14.6				
Physical activity	<1 h/day	GG	120	49.3	16.6	3.27	1.63	**0.046**	0.314
		GA/AA	302	52.1	14.8				
	≥1 h/day	GG	144	49.6	16.9	0.91	1.46	0.535	
		GA/AA	367	49.7	14.5				
Screen time	<2 h/day	GG	170	49.1	16.8	1.89	1.35	0.163	0.940
		GA/AA	425	50.4	14.8				
	≥2 h/day	GG	96	50.3	16.6	1.75	1.83	0.339	
		GA/AA	251	51.2	14.8				

DBP diastolic blood pressure, *SD* standard deviation, *SE* standard error, *BMI* body mass index, *SCAP* SREBP cleavage-activating protein
P and $P_{interaction}$ were adjusted for sex, age, age square, and BMI. *P* values <0.05 were set in bold
[a]For fruit and vegetable intake category, twice/day means either fruits or vegetables intake twice/day, and ≥twice/day means both fruits and vegetables ≥twice/day

Previous studies showed that the BP-related phenotype (BMI level/obesity) that attributed to genetic predisposition (32 BMI-associated variants) could be different in individuals with different behavior of fried food intake.[21] The potential mechanism of the gene–lifestyle interaction may due to the following reasons. First, previous studies found that DNA methylation may play an important role in the gene–lifestyle interaction on cardiovascular disease-related traits.[22] Hannah et al.[23] showed that unsaturated fatty acids, which is relatively low fried chips/cakes/cookies intake, could affect the expressing of transcription factor (SREBP) by DNA methylation. SCAP is an adaptor protein required for SREBP, which could combine with SCAP to regulate the lipogenesis.[24] Kalantarian's study may provide some clues for the mechanism of *SCAP*'s interaction with fried food, which found that *SREBP1* polymorphisms (rs2297508 and rs11656665) could interact with polyunsaturated fat on the atherosclerosis progression and the mean minimal coronary artery diameter,[25] which were both closely related with high BP. Second, recent animal studies showed that high fat diet could disrupt the circadian metabolic rhythms of this lipid pathway, leading to the disorder of fatty acid synthesis and oxidation, which would break the balance of the hepatic lipid metabolic process.[26] High BP, especially obesity-related high BP, is closely related with lipid levels.[27]

In addition, there was a significant interaction between protein intake (meat/fish/soy beans/egg) and rs12487736 on DBP level. In the individuals with low protein intake (meat/fish/soy beans/egg), GA/AA genotype carriers had obviously higher level of DBP than GG genotype carriers, which was not detected in children with high protein consumption. According to our best knowledge, no gene–protein intake interaction of *SCAP* gene was reported before. However, Daily et al.[28] found that *BDNF* rs6265 polymorphism could interact with protein intake on risk of type 2 diabetes, and rs6265 Val/Val carriers are prone to have higher risk of type 2 diabetes when their protein intake was low. However, the potential mechanism of gene–protein intake interaction is still unclear, further researches should be warranted to explore it.

Furthermore, there were combined effects between soft drink and physical activity behavior and rs12487736 on BP level. Mastrocola et al.'s[29] study may provide explanation for the combined effect between *SCAP* and soft drink. In their study, they developed a mice model to resemble human's habit of consuming sugary drinks, and found that fructose intake could increase the expression and activity of SREBP1 and SCAP, and then mediate the fructose-induced lipogenesis of dyslipidemia and obesity, which is closely related with high BP.[27] However, the underlying mechanism of the combined effect between

rs12487736 polymorphism and lifestyle behaviors on BP levels still need more functional studies.

The *SCAP* gene, together with insulin-induced gene 1 (*INSIG1*), insulin-induced gene 2 (*INSIG2*), *SREBP1*, and *SREBP2*, are all important genes of INSIG-SCAP-SREBP pathway and play significant roles in regulating lipid metabolism. Previous studies usually focused on its effect on lipid regulation or obesity.[7,8] Recently, we found that the polymorphism of *SCAP* gene could individually[10] or combined with other lifestyle factors to affect BP levels. These results provide new clues for the function of INSIG-SCAP-SREBP pathway on BP regulation, and would be helpful for the early life risk assessment of hypertension and personalized lifestyle modification. In addition, different gene–lifestyle interaction or combined effects affect different BP component. For example, the interaction with high calorie foods (fried chips/cakes/cookies) affected SBP level, while other interaction or combined effects affect DBP level. Clinically, SBP and DBP has similar predictive value for death of stroke, but different in prediction for mortality of ischemic heart disease (IHD) and coronary heart disease (CHD). It was reported that SBP is superior to DBP for the prediction of IHD mortality,[30] but DBP is the strongest predictor for CHD.[31]

Several potential limitations should be considered when our results are interpreted. Given the case–control study design, only associations, but not causal relation, could be concluded for lifestyle behaviors. Because information of the diet and physical activity behavior was investigated by questionnaire, study with more precise measuring methods of diet or physical activity, such as 3 consecutive 24-h recalls of intake and accelerometer for physical activity measure, should be conducted to verify our findings.[32] There was a chance that the influence of lifestyle on variation effect was an error of skewed data; further researches in different population groups were necessary to confirm the present finding. Also, the mechanism of interaction between *SCAP* gene and lifestyle behaviors on children's BP awaits transcriptomic and proteomic studies. In conclusion, interactions between lifestyle behaviors, including consuming high calorie foods, protein intake, soft drink, and physical activity, and *SCAP* rs12487736 polymorphism could affect BP level. In addition, we found that there were combined effects between rs12487736 with soft drink and physical activity on DBP. Our results highlight the significance of reducing the unfavorable lifestyle behaviors in children genetically predisposed to HBP. Although children with rs12487736 GA/AA genotype may have an elevated BP level, the risk might be reduced by improving their behaviors.

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ADDITIONAL INFORMATION

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