

## Influence of Dietary Approaches to Stop Hypertension-Type Diet, Known Genetic Variants and Their Interplay on Blood Pressure in Early Childhood

### ABCD Study

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**Abstract**—There is limited evidence on association between adherence to the Dietary Approaches to Stop Hypertension (DASH diet) and a lower blood pressure (BP) in children. In a population-based cohort study, among 1068 Dutch children aged 5 to 7, we evaluated the association between a DASH-type diet, 29 known genetic variants incorporated in a genetic risk score, and their interaction on BP. We calculated DASH score based on the food intake data measured through a validated 71-item food frequency questionnaire. In our sample, DASH score ranged from 9 (low adherence to the DASH diet) to 33 (median=21), and genetic score ranged from 18 (low genetic risk on high BP) to 41 (median=29). After adjustment for covariates, each 10 unit increase in DASH score was associated with a lower systolic BP of 0.7 mmHg ( $P=0.033$ ). DASH score was negatively associated with hypertension (odds ratio=0.96 [0.92–0.99],  $P=0.044$ ). Similarly, each SD increment in genetic score was associated with 0.5 mmHg higher diastolic BP ( $P=0.002$ ). We found a positive interaction between low DASH score and high genetic score on diastolic BP adjusted for BP risk factors ( $\beta=1.52$ ,  $P_{\text{interaction}}=0.019$  in additive scale and  $\beta=0.03$ ,  $P_{\text{interaction}}=0.021$  in multiplicative scale). Our findings show that adherence to the DASH-type diet, as well as a low (adult-derived) genetic risk profile for BP, is associated with lower BP in children and that the genetic basis of BP phenotypes at least partly overlaps between adults and children. In addition, we found evidence of a gene-diet interaction on BP in children. (*Hypertension*. 2020;75:59-70. DOI: 10.1161/HYPERTENSIONAHA.118.12292.) • [Online Data Supplement](#)

**Key Words:** blood pressure ■ DASH score ■ environment ■ interaction ■ phenotype ■ risk factors

Evidence from epidemiological studies collected over the past decades, examining blood pressure (BP) among children and adolescents, shows a significant increase in the prevalence of high BP.<sup>1</sup> The recent US national survey data of children 8 to 17, showed that prehypertension or hypertension in 19.2% of adolescent-age boys and 12.6% of girls, an estimated 38% increase compared with National Health and Nutrition Examination Survey III data collected from 1988 to 1994.<sup>2</sup>

Dietary factors are known to be involved in the cause of hypertension.<sup>3</sup> Although abundant studies have investigated the role of single foods or nutrients on the cause of disease,<sup>4</sup> more recent studies have recommended a holistic approach of dietary patterns in association studies between diet and

disease.<sup>5</sup> The Dietary Approaches to Stop Hypertension (DASH) diet, an initiative of the National Heart, Lung, and Blood Institute, is a dietary pattern that substantially lowers BP in hypertensive and normotensive adults in clinical trials.<sup>6,7</sup> The DASH diet is rich in fruits, vegetables, low-fat dairy products, and whole grains and low in (saturated) fats, sodium, and processed red meats.<sup>8,9</sup> Applying a DASH score (DS) on food intake data reflects the adherence to a DASH-style diet.<sup>10</sup> The effect of a DASH-style diet on BP in adults may be extrapolated to children. This is supported by preliminary evidence of a clinical trial investigating the effect of a DASH-style diet in adolescents 11 to 18 with a clinical diagnosis of prehypertension or hypertension. Results showed that in 50% of the participants BP normalization was achieved.<sup>11</sup> The results of

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this clinical trial showed a larger effect of the DASH diet on systolic BP (SBP) than on diastolic BP (DBP), which is consistent with DASH trials in adults.<sup>6,11</sup>

Genetic factors also play an important role in the development of hypertension throughout the life course. It is estimated that the heritability of BP is between 50% and 60% in both children and adults.<sup>12</sup> Large genome-wide association studies identified single nucleotide polymorphisms (SNPs) in adults of European ancestry that are related to SBP or DBP.<sup>13</sup> SNPs identified in adults may also influence childhood BP, but little is known about the age dependency of these BP related SNPs.<sup>12</sup>

There is growing evidence that complex interactions among various lifestyle factors and various genetic markers play an important role in determining an individual's risk of multiple common diseases, such as hypertension.<sup>14</sup> The interaction of environmental factors and genotype contributes to the total variance of BP.<sup>15</sup> To the best of our knowledge, no study has explored the interaction between dietary pattern and genetic markers in relation to children's BP. Therefore, with this study, we aimed to investigate in children aged 5 to 7 years: (1) the association between adherence to the DASH-style diet expressed in a DS and BP, (2) the association between the 29 genetic markers combined into a genetic risk score (GRS) and BP, and (3) the interaction of the DS and GRS on BP in children.

## Population and Methods

### Study Design

The data are not publically available because of ethical restrictions related to protecting patient confidentiality. The data sets analyzed during the current study are available from the corresponding author on reasonable request. The ABCD study (Amsterdam Born Children and their Development) is a large prospective community-based birth cohort in the Netherlands. Details concerning study protocol, design, and methods have been detailed elsewhere.<sup>16</sup> Briefly, between January 2003 and March 2004, all pregnant women living in Amsterdam were contacted for participation in the ABCD study (Figure). These women were approached by their obstetric care giver at their first antenatal appointment. In total 8266 women responded to the invitation of the study and returned a questionnaire on sociodemographic data, obstetric history, family history, and lifestyle. Of these women, 7863 had a singleton live-born baby, of which 6735 gave consent for follow-up (86%). Mothers received a questionnaire and a consent form for a health checkup of their children at the age of 5. A total of 4488 from the 6161 questionnaires were sent back (response rate 76%) to the Amsterdam Medical Center, and 4158 women gave consent for the health check of their children. Two weeks before the health check, the women got a notifying letter and a self-administered 71-item Food Frequency Questionnaire (FFQ).<sup>17</sup> Between 2008 and 2010, 3320 children of the age 5 to 6 had a health check, which included various health measurements.<sup>18</sup> Filled out FFQs were sent back by 2782 of the children. Of these children, 14 had >50% missing answers on one page or product sort and were, therefore, excluded. A sample of 2649 children had a complete filled out FFQ and a valid BP measurement (stage

1, sample used for evaluating the first research question). The genetic data were derived from the ABCD-GE study (ABCD-Genetic Enrichment) which was a substudy with 1192 ethnic Dutch children. DNA was extracted from the dried blood samples. A total of 1068 children with genetic data, filled out FFQ, and valid BP measurement was available (stage 2, sample used for evaluating the second and third research questions). The ABCD study protocol was approved by the Central Committee on Research Involving Human Subjects in The Netherlands, the medical ethics review committees of the participating hospitals, and the Registration Committee of the Municipality of Amsterdam. All ABCD participants gave written informed consent for data collection of the phenotypes. Regarding the DNA collection and analysis, an opt-out procedure was used (METC approval 2002\_039#B2013531).

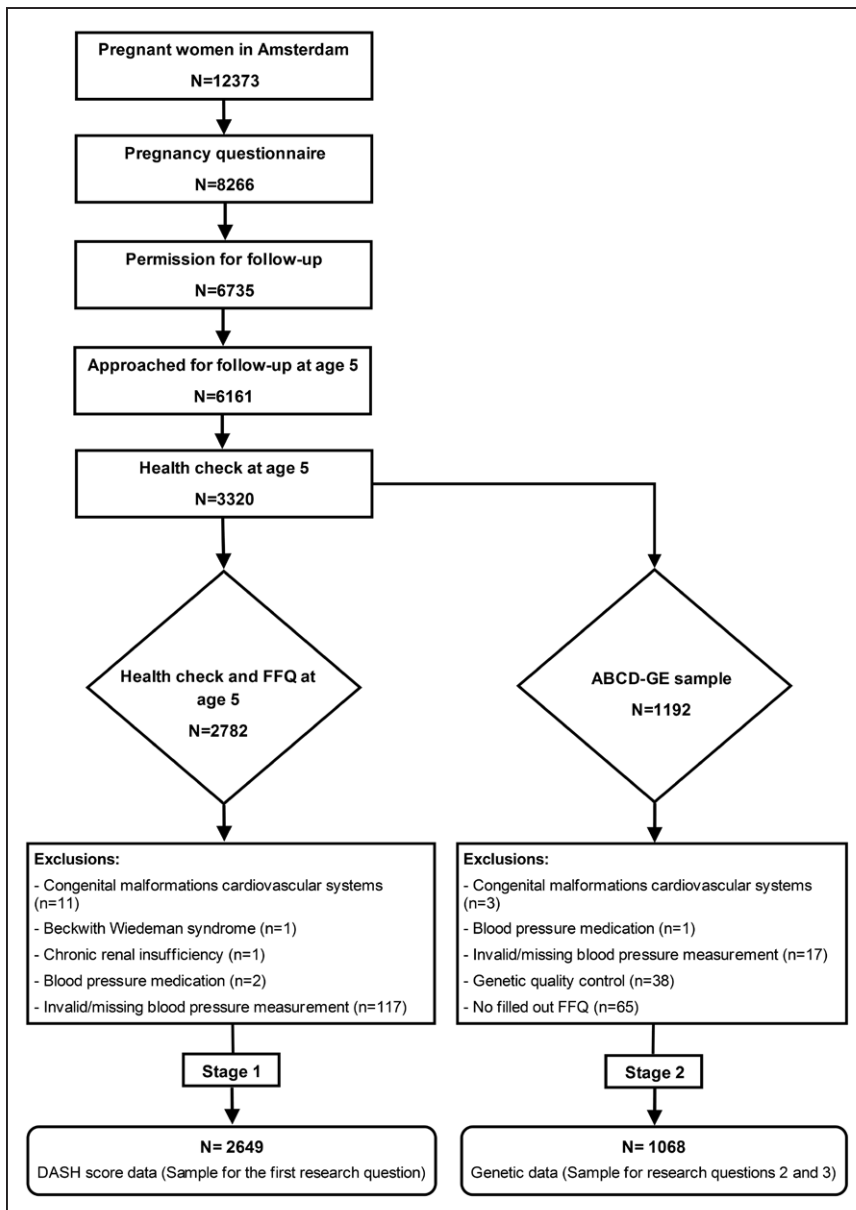
### Inclusion and Exclusion Criteria

To be eligible for the current study (stage 1), children had to meet the following criteria: singleton child participated in the 5-year health check and filled out the FFQ. Children were excluded from participation if they met the following criteria: congenital malformations of the cardiovascular system (n=11), Beckwith Wiedeman syndrome (n=1), chronic renal insufficiency (n=1), BP medication (n=2), and invalid or missing SBP and DBP measurements (n=117).<sup>19,20</sup> For the ABCD-GE sample (stage 2), the inclusion criteria were as follows: unrelated children that were of the Dutch ethnicity, availability of a blood sample, and good quality of extracted DNA for genotyping and the willingness to participate in genetic investigations. This resulted in 1192 participants. Participants were excluded based on: genetic quality control (due to call rate <95%; heterozygosity, phenotype-genotype gender mismatch, and relatedness; n=38), no filled out FFQ (n=65), BP medication (n=1), congenital malformations of the cardiovascular system (n=3), and invalid or missing SBP and DBP measurement (n=17). The Figure shows the flowchart of the 2 stages of this study.

### Health Check Measurements

The ABCD health check consisted of a finger prick, anthropometric measurements, cardiovascular function measurements, body composition measurements, and a cognitive test. Health measurements relevant for this research were described more in detail elsewhere.<sup>17</sup> Anthropometric measurements included height and weight. The children were asked to wear clothing appropriate for physical activity and no footwear. Height was measured with a Leicester height measure (Seca) in centimeter (cm) to the closest millimeter (mm). The weight of the children was measured with a Marsden Model MS-4102 weighing scale in kilograms (kg) and rounded off at 100 grams (g).<sup>20</sup> Body mass index (BMI) was defined as kg/m<sup>2</sup>.

BP was measured during the physical checkup by qualified staff of the Amsterdam Medical Center, according to a standardized procedure.<sup>17</sup> First, a test measurement was performed when the child was lying down in supine position on an examination bed. This was then followed by 4 minutes of rest. After the resting period, BP was measured twice in lying position. Children were then seated at a table and were given 1 minute to adapt. This was followed by 4 minutes of rest.



**Figure.** Flowchart of study participants included in the 2 stages of the current study. ABCD indicates Amsterdam Born Children and their Development; DASH, Dietary Approaches to Stop Hypertension; and FFQ, Food Frequency Questionnaire.

Subsequently, BP was measured twice when sitting, while resting the right arm on a table. BP was measured with the automatic oscillometric method, using an Omron 705 IT (Omron Healthcare Inc, Bannockburn, IL) with a proper cuff size (arm circumference 17–22 cm) on the nondominant arm. The cuff was around the upper arm. The arm was laying on the bed. So the arm was more supported (compared with sitting position when the arm could only be supported by the elbow).<sup>16</sup> The usage of Omron 705 IT was validated for home BP measurement in children and adolescents.<sup>21</sup> Each BP assessment procedure consisted of 2 consecutive SBP and DBP measurements. These measurements were considered valid only if the difference between the 2 was smaller than 10 mmHg. In the event of a larger difference, a third measurement was performed. Eventually, the average was calculated of the 2 closest measurements for SBP and DBP. In this study, we used BP in supine position, since the arm of the child was more supported in this position, compared to the sitting position and BP measurements were more stable in supine position.

### Demographic Questionnaire

Information was retrieved from the pregnancy questionnaire about ethnicity categorized as Dutch, Turkish, Moroccan, Surinamese, Western, and non-Western, physical activity of their child in hours per week, prepregnancy maternal BMI that was calculated from self-reported height and prepregnancy weight, smoking during pregnancy in cigarettes per day, and maternal educational level in years after elementary school. Other information was acquired from the Dutch Perinatal Registration and the Youth Health Care Registration such as gestational age in weeks and additional days, birth weight of the child in grams, and breastfeeding duration.

### Genotyping

The finger prick yielded fasting capillary blood samples for DNA extraction. Subsequently, the DNA samples were genotyped, using the Illumina Human Core Exome Beadchip (Illumina, San Diego, CA). The Illumina Human Core Exome Beadchip included over 540,000 genetic markers. Before

imputation, SNPs were excluded if they had high levels of missing data (SNP call rate <95%), strong departures from Hardy-Weinberg equilibrium ( $P < 1 \times 10^{-6}$ ), or low minor allele frequencies (<1%). Genetic markers were imputed using the IMPUTE2 software and the 1000 Genomes References Panel (phase 1 release v3, build 37). Genotypes for the SNPs of interest were extracted from the imputed genome-wide association studies data set. The mean quality of the imputed genotypes ( $r^2$ ) of SNPs included in this study was 0.996, ranging from 0.95 to 1.00. Of the 29 SNPs of interest, 3 (rs3774372, rs13107325, and rs1799945) were not present in the genome-wide association studies data set. For this reason the following proxies within 500 kb with linkage disequilibrium  $r^2 > 0.8$  in the CEU population panel were chosen for each of the missing SNPs: rs9873207 ( $r^2 = 1$  with rs3774372), rs13135092 ( $r^2 = 0.93$  with rs13107325), and rs129128 ( $r^2 = 0.93$  with rs1799945).

### Food Frequency Questionnaire

Parents were asked to complete a validated 71-item FFQ (developed by the TNO Food and Nutrition organization, Zeist, the Netherlands) about their children's dietary pattern.<sup>22</sup> The FFQ included questions concerning 71 food items, based on the most frequently consumed foods and drinks by Dutch children.<sup>16</sup> Per food item, consumption frequency, portion size, and the type of product consumed over the past 4 weeks was reported by the mother of the child. Frequency options were never or less than once a week, once a week, 2 to 3 times a week, 4 to 5 times a week, and 6 to 7 times a week. Food items were assessed in units (eg, a piece of fruit and a slice of bread) and in household units (eg, a glass and a tablespoon).

### DASH Score

Dietary pattern is defined as "The quantities, proportions, variety or combination of different foods, drinks, and nutrients in diets, and the frequency in which they are habitually consumed."<sup>23</sup> The dietary pattern quality was measured through the FFQ and by comparing the food intake data with a DASH-style diet. Dietary elements of the FFQ that were specifically relevant for this study were based on a DASH-style diet and divided in 7 equally weighted food groups: whole grain products, fruit, vegetables, legumes and nuts, low-fat dairy products, red processed meat, and sweetened beverages.<sup>10</sup> The sodium component of the DASH diet was not included in the current constructed DS because this was not well measured by the FFQ that was used in this study. A DS was calculated based on the food intake data to estimate the diet quality of the children. Children were classified into quintiles according to their intake in grams per day per food component. This was done by summing all the foods in one food component, and then the resulting total intake (g/d) was divided into quintiles, on which the highest quintile portrays a high intake. A summary on the DASH components and their corresponding FFQ food items is provided in Table S1 in the [online-only Data Supplement](#). The consumption of the healthy food component (ie, whole grain products, fruits, vegetables, legumes and nuts, and low-fat dairy products) were scored positively. The food components were scored on a scale from 1 to 5. This means that if the intake of a child was ranked in quintile 5, it was awarded with 5 points, and if the child was ranked in quintile

1, it was awarded with 1 point. For the unhealthy food components, where a lower intake was recommended, the scoring was reversed. Thus, the consumption of unhealthy food components (ie, processed meats and sugar-sweetened beverages) was scored negatively. The total DS ranges from 7 to 35, in which a high score is a high adherence to a DASH-style diet and a low score is a low adherence to a DASH-style diet. The DS was used continuous but also dichotomized based on the median value of 21, with a DS > 21 indicating a high adherence to the DASH diet.

### Genetic Risk Score

A large international genome-wide association studies performed in adults found 29 SNPs that are associated with an increased risk of hypertension.<sup>13</sup> These 29 SNPs were adopted for the genetic markers in the participating children. A GRS can be generated to estimate the cumulative risk of these 29 SNPs. An unweighted GRS was computed by the sum of outcome-increasing alleles, assuming equal risks of the SNPs. Consequently, the GRS could be ranged from 0 to 58. The GRS in our analyses (ranged, 18–41) was used continuous, but also dichotomized, based on the median value of 29. The low GRS was the reference group in the analyses. A GRS < 29 indicates a low (adult-derived) genetic risk profile for high BP. We used this approach because we had combined SBP and DBP SNPs in one GRS.

### Outcomes

Hypertension is established based on the classification criteria for children that are sex, age, and height specific. Normal BP has been previously defined as an SBP and DBP < 90th percentile. Prehypertension is established when SBP and DBP is  $\geq 90$ th percentile but < 95th percentile. Hypertension is determined in children when their SBP and DBP are in or above the 95th percentile.<sup>24</sup> The outcome measurements were high BP (including prehypertension and hypertension; yes/no) and hypertension (yes/no) as dichotomous dependent variables as well as SBP and DBP as the continuous outcomes.

### Statistical Analysis

The participants' characteristics were compared across DS (low and high). Demographic characteristics of the study participants were presented in percentages, means, and SD. Overall missing values of all variables ranged from 0% to 1.2%. Therefore, complete cases were used for the analyses. Before the analyses, a nonresponse analysis was performed.

To answer the first research question (the association between DS and BP) and the second one (the association between GRS and BP), a series of linear regression models (SBP and DBP as continuous outcomes) and logistic regression models (high BP and hypertension as dichotomous outcomes) were used. First, separate crude models for both DS and GRS on BP were built. All the variables were checked for normal distribution by visually inspecting the histogram and normal quantile plot. The independent variables were also analyzed dichotomously with the outcomes for the interaction assessment. Finally, the adjusted models were developed. The most important covariates were chosen a priori from literature on the determinants of hypertension in childhood.<sup>20</sup> The first



adjusted model included age (continuous), sex, and height (continuous). The second model was additionally adjusted for BMI-Z score child (continuous), ethnicity (nominal), gestational age (continuous), birth weight (continuous), breastfeeding duration (categorical, as presented in Table 1), maternal prepregnancy BMI (continuous), smoking during pregnancy (dichotomous: yes/no), physical activity (PA) (continuous), and maternal educational level (continuous: years after elementary school).

To answer the third research question (the interaction between DS and GRS on BP), both multiplicative and additive interaction were studied, as recommended.<sup>25</sup> Additive interaction is present when the combined association of a higher DS and a lower GRS with BP is higher or lower than the sum of the individual associations for a higher DS and a lower GRS. Multiplicative interaction is present when the combined association of a higher DS and a lower GRS with BP is higher or lower than the product of the individual associations for a higher DS and a lower GRS. For the dichotomous outcomes (high BP and hypertension), we first evaluated the multiplicative interaction in a series of logistic regression models and a product term. Subsequently, additive interaction was assessed using the relative excess risk due to interaction (RERI) and its 95% CI by the delta method provided in the spreadsheet tool by Knol and VanderWeele.<sup>26</sup> While a RERI >0 indicates a positive additive interaction and a RERI <0 shows a negative additive interaction, a RERI=0 indicates absence of interaction on the additive scale. For the continuous outcomes (SBP and DBP), the multiplicative interaction was assessed by using log-linear regression models and additive interaction by using linear regression models.<sup>25</sup> In these models, the regression coefficients of the product terms indicated deviation from multiplicative or additive interaction. The modeling strategies included the assessment of the interaction without and with adjustment for the covariates. The statistical analysis was performed by IBM SPSS Statistics software version 20.0 (IBM Corp, Armonk, NY). Statistical significance was set at a  $P < 0.05$ .

## Results

### Population Characteristics

The participants' characteristics for the stage 1 are presented in Table 1. The mean age of the children was 5.7 years ( $SD \pm 0.5$ ). The distribution of boys and girls was nearly equal with 50.7% boys. Most children (71.2%) had a Dutch ethnicity. Mean SBP in the whole group was 99.3 mmHg ( $SD \pm 7.2$ ) and mean DBP was 57.1 mmHg ( $SD \pm 6.0$ ). Of the 2649 children, 314 (11.9%) were classified as prehypertensive or hypertensive and 137 (5.2%) as hypertensive. Systolic hypertension ( $SBP \geq 95$ th percentile) was seen in 122 (4.6%) children, and diastolic hypertension ( $DBP \geq 95$ th percentile) was seen in 33 (1.2%) children, while 18 children had both systolic and diastolic hypertension. Low DS (low adherence to DASH diet) was seen in 1224 children and high DS (high adherence to DASH diet) in 1425 children. Children with a low DS had on average a lower birth weight and gestational age, were less physically active, their mothers had a higher prepregnancy BMI and smoked relatively more during pregnancy. Furthermore, children with a

high DS were on average younger, more often from Dutch origin, had higher educated mothers and their mothers breastfed them longer after birth.

### Nonresponse Analysis

In total, 6161 mothers and children at age 5 were approached to participate in phase 3 of the ABCD cohort (Figure). Of this population, 2649 children (43%) with health measurements were eligible for inclusion in this study and 3512 children (57%) were in the nonresponse group for various reasons. Comparing the responders and nonresponders of the initial approached group showed that the responders were more frequently of Dutch origin, and the gestational age, birth weight, and maternal education after primary school were higher among them. Additionally, in the nonresponders group, the frequency of mothers that smoked during pregnancy was slightly higher (Table S2).

### DS Analysis

Table 2 displays the associations between continuous and dichotomous DS and SBP, DBP, hypertension, and high BP. In the fully adjusted models, the continuous DS was significantly associated with SBP but not with DBP. Each 10 unit increment of DS was associated with a lower SBP of 0.7 mmHg (95% CI,  $-0.13$  to  $-0.01$ ;  $P = 0.03$ ). The continuous DS was also significantly associated with hypertension, a one-unit increment in DS decreased the odds of hypertension by a factor of 0.04 (odds ratio=0.96, 95% CI, 0.92–0.99,  $P = 0.04$ ). We found no association between dichotomous DS and SBP, DBP, hypertension, or high BP. When we restricted our sample to the Dutch children which were used for the stage 2 (research questions 2 and 3) of the study and repeated the analyses, we found almost the same results (there was a significant association between continuous DS and SBP, Table S3).

### GRS Analysis

In our study, population ( $n = 1068$ ) mean GRS was 29.4 ( $SD = 3.6$ ). Table 3 shows the results of the analyses of the dichotomous and continuous GRS on SBP, DBP, hypertension, and high BP. Each SD increase in BP GRS (3.6) was associated with 0.50 mmHg higher DBP in children (95% CI, 0.06–0.23,  $P = 0.002$ ). We did not observe any significant association between the continuous GRS and SBP nor with hypertension or high BP. A  $GRS \geq 29$  (high genetic risk; versus  $< 29$ ) was significantly associated with a higher DBP of 0.70 mmHg (95% CI, 0.07–1.34,  $P = 0.029$ ). No significant associations were found between dichotomous GRS and SBP, hypertension, and high BP.

### Multiplicative and Additive Interaction Analysis

In our study, 234 children among those with a high GRS ( $n = 516$ ) had a low DS (45.3%), and 237 children among those with a low GRS group ( $n = 552$ ) had a low DS (42.9%). Multiplicative and additive interactions between continuous and dichotomous DS/GRS and the outcomes are presented in Table 4. In the fully adjusted models, we found evidence of a positive interaction between a high GRS and a low DS on DBP in children both on the multiplicative scale (regression coefficient=0.026 [95% CI, 0.004–0.048],  $P = 0.021$ ) and on the additive scale (regression

**Table 1. General Characteristics of the Participants With FFQ Data (Stage 1) as a Function of DASH-Score Low/High (Median Split)**

Covariates	Total	Low DASH Score (DS ≤21)	High DASH score (DS >21)	P Value
N	2649	1224 (46.2%)	1425 (53.8%)	
Children characteristics				
DASH score	20.90 (4.3)	17.2 (2.4)	24.1 (2.6)	<0.001
Age, y	5.70 (0.5)	5.72 (0.5)	5.68 (0.5)	0.022
Sex (% boys)	1343 (50.7)	609 (49.8)	732 (51.4)	0.411
Height, cm	116.6 (5.7)	116.5 (5.7)	116.7 (5.7)	0.511
Ethnicity				0.001
Dutch	1886 (71.2%)	837 (68.4%)	1049 (73.6%)	
Surinamese	112 (4.2%)	67 (5.5%)	45 (3.2%)	
Turkish	54 (2.0%)	30 (2.5%)	24 (1.7%)	
Moroccan	105 (3.9%)	56 (4.6%)	49 (3.4%)	
Western	338 (12.8%)	149 (12.2%)	189 (13.3%)	
Non-Western	153 (5.8%)	85 (6.9%)	68 (4.8%)	
Birth weight, g	3492 (539)	3450 (544)	3528 (533)	<0.001
BMI, kg/m <sup>2</sup>	15.5 (1.4)	15.4 (1.5)	15.5 (1.4)	0.127
Physical activity per week (hours)	14.42 (6.3)	13.62 (6.4)	14.6 (6.1)	<0.001
SBP, mm Hg	99.3 (7.2)	99.5 (7.4)	99.1 (7.1)	0.111
DBP, mm Hg	57.1 (6.0)	57.3 (6.0)	56.9 (6.1)	0.095
High BP (BP≥90th %) (% yes)	314 (11.9)	158 (14.8)	156 (12.3)	0.120
HTN (BP≥95th %) (% yes)	137 (5.2)	78 (6.8)	59 (4.3)	0.010
Maternal characteristics				
Prepregnancy BMI, kg/m <sup>2</sup>	23.0 (4.0)	23.2 (4.1)	22.8 (3.8)	0.004
Smoking during pregnancy (% yes)	231 (8.7)	130 (10.6)	101 (7.1)	0.001
Gestational age, wk	39.9 (1.7)	39.8 (1.7)	40.00 (1.6)	<0.001
Breastfeeding duration				<0.001
None	449 (16.9%)	238 (19.4%)	211 (14.8%)	
<1 mo	183 (6.9%)	109 (8.9%)	74 (5.2%)	
1–2.9 mo	674 (25.4%)	306 (25.0%)	368 (25.8%)	
3–5.9 mo	830 (31.3%)	384 (31.4%)	446 (31.3%)	
≥6 mo	480 (18.1%)	171 (14.0%)	309 (21.7%)	
Education after primary school, y	10.1 (3.4)	9.6 (3.6)	10.6 (3.2)	<0.001

Means and SD are shown for continuous variables; frequency numbers and percentages are shown for dichotomous/categorical variables; DASH score ranging from 7 to 35, reflects the adherence to the DASH diet (higher adherence is a higher DASH score); *P* value reflects the difference between low and high DASH score. High BP (BP≥90th %), prehypertension + hypertension. BMI indicates body mass index; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DS, DASH score; FFQ, Food Frequency Questionnaire; HTN, hypertension; and SBP, systolic blood pressure.

coefficient=1.52 [95% CI, 0.25–2.80], *P*=0.019). In other words, children with a high GRS and a low DS had a higher DBP than expected based on the individual associations of GRS and DS. We found no evidence of additive or multiplicative interaction on SBP, hypertension, or high BP.

Table 5 shows the mean (and SD) of SBP and DBP across quintiles of GRS and DS in our study population. For DBP, the magnitude of effect was highest (mean DBP =58.8 mm Hg, SD 5.7) with the fifth quintile of GRS (poor genetic) and the first quintile of DS (poor DASH diet).

## Discussion

In this community-based birth cohort study, we found that a higher DS (higher adherence to the DASH diet) was associated with a lower SBP and lower odds of having hypertension in children aged 5 to 7 years. Whereas a higher GRS (higher adult-derived genetic risk profile for high BP) was associated with a higher DBP. We found also a positive interaction on additive and multiplicative scales between a low DS and a high GRS on DBP in children.

Saneei et al<sup>9</sup> performed a cross-over randomized clinical trial and found that adherence to the DASH-style diet

**Table 2. Associations Between DASH Score as Dichotomous/Continuous Independent Variables and BP Outcomes in Children**

Outcomes		Crude Model			Adjusted: Model 1			Adjusted: Model 2		
Continuous DS	Mean (SD)	B	SE	P value	B	SE	P value	B	SE	P value
SBP, mm Hg	99.3 (7.2)	−0.08	0.03	0.014*	−0.08	0.03	0.009*	−0.07	0.03	0.033*
DBP, mm Hg	57.1 (6.0)	−0.06	0.03	0.037*	−0.05	0.03	0.071	−0.01	0.03	0.648
Continuous DS	n (%)	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
High BP	314 (11.9%)	...	...	...	0.97	0.95–0.99	0.041	0.98	0.95–1.01	0.156
HTN	137 (5.2%)	...	...	...	0.94	0.91–0.98	0.005*	0.96	0.92–0.99	0.044*
Dichotomous DS	Mean (SD) (low DS/ high DS)	B	SE	P value	B	SE	P value	B	SE	P value
SBP, mm Hg	99.5 (7.4)/99.1 (7.1)	0.45	0.28	0.111	0.49	0.27	0.072	0.34	0.27	0.205
DBP, mm Hg	57.3 (6.0)/56.9 (6.1)	0.39	0.23	0.095	0.34	0.23	0.137	0.001	0.23	0.995
Dichotomous DS	n (%) (low DS/ high DS)	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
High BP	158 (12.9%)/156 (10.9%)	†	...	...	1.21	0.95–1.53	0.120	1.07	0.83–1.38	0.609
HTN	78 (6.4%)/59 (4.1%)	...	...	...	1.58	1.11–2.23	0.010*	1.34	0.93–1.94	0.117

DASH score, (range 7–35) reflects adherence to the DASH diet (higher DASH score: higher adherence); Model 1 adjusted model for age, sex, and height; Model 2 adjusted model for age, sex, height, ethnicity, child BMI, gestational age, birth weight, breastfeeding duration, maternal prepregnancy BMI, smoking during pregnancy, physical activity, and maternal education level; dichotomous: dichotomous DASH score (high DASH score reference group); continuous: the continuous DASH score; high BP (BP  $\geq$ 90th %): prehypertension + hypertension. *P* value reflects the significance of the regression coefficient or odds ratio. B indicates regression coefficient; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; HTN, hypertension; OR, odds ratio; and SBP, systolic blood pressure. \* $<0.05$ .

†Prehypertension and hypertension in the pediatric population are defined as BP between 90th and 95th percentile, and greater than 95th percentile, respectively, standardized for gender, age, and height. Therefore, the crude model results for high BP and HTN are left blank in the table.

prevented the rise in DBP but did not affect SBP in adolescent girls 11 to 18 diagnosed with metabolic syndrome. This was in contrast with the findings in our study showing only an association between DS and SBP. Two other previous randomized clinical trial's were more in concordance with the findings of our research; they reported a significant effect only on SBP among adolescents diagnosed with prehypertension or hypertension and children aged 3 to 6 years.<sup>11,27</sup> In addition, these trials all included a clinical population, whereas our study involved healthy children of the general population. However, a recent systematic review and meta-analysis of 24 trials in adults showed that the DASH diet lowered both SBP and DBP with a net effect for SBP of  $-7.6$  mm Hg (95% CI,  $-9.9$  to  $-5.3$ ) and for DBP of  $-4.2$  mm Hg (95% CI,  $-5.9$  to  $-2.6$ ).<sup>28</sup>

In contrast to the association between DS and SBP, we found only an association between the BP GRS and DBP and not with SBP. Punwasi et al<sup>29</sup> in a population-based prospective cohort study among 4137 children did not find an association of the adult-derived BP GRS (29 SNPs) on childhood SBP or DBP, whereas results of pooled data from 2 cohorts (the Avon Longitudinal Study of Parents and Children [n=7013] and the Western Australian Pregnancy Cohort [n=1459]) showed a significant association between the unweighted GRS (constructed from the same 29 SNP) and SBP in children at the age of 6 (per-allele effect sizes, 0.10 mm Hg [SE, 0.04 mm Hg]).<sup>30</sup> In the Young Finns study, the authors reported significant associations of GRS (constructed from 13 BP-associated SNPs) on both SBP and DBP in children at the age of 9, and the highest GRS risk demonstrated a

1.82-fold risk of hypertension later in adulthood.<sup>31</sup> Another study in young children showed a higher adult-derived GRS for SBP was related to higher SBP (0.37 [95% CI, 0.01–0.70]), but not to DBP, while a higher GRS for DBP was related to a higher SBP (0.66 [95% CI, 0.1–1.2]) but not to DBP.<sup>32</sup> The inconsistencies in findings between GRS and BP in children may be explained by the sample sizes of these studies, number of available SNPs used for making a GRS, the way of constructing the GRS (weighted or unweighted GRS, one general GRS for BP or separate GRSs for SBP and DBP), and the outcome definition.

Adherence to a DASH-style diet has been linked not only to a reduced risk on hypertension but also to a reduced body weight in adult randomized clinical trials.<sup>33,34</sup> Hypertension and body fat are interrelated implying that adherence to a DASH-style diet diminishes hypertension through a reduction in body fat. However, in our study controlling for child BMI and maternal prepregnancy BMI led to an amplification of the association between DS and BP (data not shown). This suggests that the mechanism by which the DASH-style diet has a protective effect on BP may be other than through effects on body fat.

### Strengths

There are several strengths to the present study. First, the study comprises a relatively large birth cohort sample and can be extrapolated to the diverse Dutch population of children 5 to 7 years old. Second, the dietary data were obtained through a validated FFQ. Third, all the measurements at the 5-year health check were performed by trained research assistants.

Table 3. Associations Between GRS as Dichotomous/Continuous Independent Variables and BP Outcomes in Children Using the ABCD-GE Sample (N=1068)

Outcomes		Crude Model			Adjusted: Model 1			Adjusted: Model 2		
Continuous GRS	Mean (SD)	B	SE	P value	B	SE	P value	B	SE	P value
SBP, mm Hg	98.6 (6.9)	0.05	0.06	0.416	0.04	0.06	0.488	0.02	0.06	0.697
DBP, mm Hg	56.6 (5.5)	0.16	0.05	0.001*	0.15	0.05	0.001*	0.14	0.05	0.002*
Continuous GRS	n (%)	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
High BP	102 (9.6%)	...	...	...	1.03	0.97–1.09	0.366	1.02	0.96–1.08	0.477
HTN	45 (4.2%)	...	...	...	1.08	0.99–1.17	0.093	1.08	0.99–1.17	0.095
Dichotomous GRS	Mean (SD) (high GRS/low GRS)	B	SE	P value	B	SE	P value	B	SE	P value
SBP, mm Hg	98.7 (7.1)/98.4 (6.7)	0.32	0.42	0.451	0.23	0.40	0.558	0.08	0.39	0.837
DBP, mm Hg	57.0 (5.4)/56.2 (5.5)	0.87	0.33	0.009*	0.80	0.33	0.016*	0.70	0.32	0.029*
Dichotomous GRS	n (%) (high GRS/low GRS)	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
High BP	54 (10.5%)/48 (8.7%)	†	...	...	1.23	0.82–1.85	0.326	1.19	0.78–1.81	0.428
HTN	25 (4.8%)/20 (3.6%)	...	...	...	1.35	0.74–2.47	0.322	1.31	0.70–2.44	0.393

GRS, (range 0–58) reflects genetic risk (higher GRS: higher genetic risk); Crude model; Model 1 adjusted model for age, sex, and height; Model 2 adjusted model for age, sex, height, child BMI, gestational age, birth weight, breastfeeding duration, maternal prepregnancy BMI, smoking during pregnancy, physical activity, maternal education level; dichotomous: dichotomous GRS (low GRS reference group); continuous: the continuous GRS; high BP (BP  $\geq$ 90th %): prehypertension + hypertension. ABCD-GE indicates Amsterdam Born Children and their Development-Genetic Enrichment; B, regression coefficient; BP, blood pressure; DBP, diastolic blood pressure; GRS, genetic risk score; HTN, hypertension; OR, odds ratio; and SBP, systolic blood pressure.

\* $<0.05$ .

†Prehypertension and hypertension in the pediatric population are defined as BP between 90th and 95th percentile, and greater than 95th percentile, respectively, standardized for gender, age, and height. Therefore, the crude model results for high BP and HTN left blank in the table.

Fourth, detailed mother and child-related covariates were available with little missing information in the collected data of the participating children that was used for analysis.

### Limitations

There are some limitations to the present study as well. First, due to the cross-sectional design, no conclusions can be drawn from this study regarding the causal relationship between DS, GRS, and BP. Second, the definition we used to define the outcome is based on the Fourth Report of the Task Force on BP Control in Children<sup>24</sup> at the time of data analysis. Recently, a new guideline of the American Academy of Pediatrics for screening and management of high BP in children and adolescent<sup>35</sup> has updated the definition of high BP in children. Although it is relevant to update the analysis based on the current definitions, we expect the associations reported here between high BP and genetic and diet factors are still valid. Furthermore, we acknowledge the lack of ambulatory BP measures, lack of repeated BP measures over time to accurately classify hypertension status (due to the design of this study), and the use of the oscillometric device for BP measurement. The relatively high prevalence of hypertension or prehypertension for age 5 in our study could be attributed to the one visit BP measurement and the use of an automatic oscillometric device during laying position. While references are based on sitting BP recorded by auscultation, we assessed BP in supine position because of their ease of use and decrease in observer bias. SBP measurements are in general higher when measured with automatic oscillometric device. Because systolic hypertension in children is far more common than diastolic hypertension, the prevalence of prehypertension

might be overestimated, but this will probably not affect the investigated association. The current guidelines of American Academy of Pediatrics and the Scientific Council and the Working Group on Hypertension in Children and Adolescents of the European Society of Hypertension both advocate use of auscultated sitting BPs for diagnosis of hypertension as reviewed by Lurbe et al.<sup>35,36</sup>

Third, no sodium intake was measured through the FFQ. Sodium intake in adults is one of the most frequently studied and important aspects of the diet and it is one of the original DASH-score components. In children, sodium intake on BP has been studied less intensively. Two cross-sectional studies that investigated salt intake on BP in children 4 to 18 years found no significant association in prepubertal children but found a significant association in pubertal children on SBP.<sup>37,38</sup> In addition, results of a longitudinal study did not show a significant effect of salt intake on BP in children 5 to 17.<sup>39</sup> These studies suggest that the effect of salt intake on BP may not be eminent in early childhood. However, later in childhood salt intake may be of relevance, due to a higher salt sensitivity with an increase in age.<sup>38</sup> Thus, we think this limitation might not have led to a prominent bias of the results in the participating children of the age 5 to 7.

Fourth, selection bias may have occurred by unknowingly including children of families that tend to have a general healthier lifestyle. In the nonresponse analysis children in the response group had on average a higher gestational age and birth weight and their mothers smoked less during pregnancy and were more educated, compared to the nonresponse group. The inclusion of generally more healthy children may have led to an underestimation of the association



Table 4. Evaluation of Multiplicative and Additive Interactions Between GRS and DASH Score on BP Outcomes in Children

Dichotomous outcomes	Crude Model			Adjusted: Model 1			Adjusted: Model 2		
Multiplicative interaction									
Continuous GRS and DS	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
High BP	*	...	...	1.00	0.99 to 1.02	0.646	1.00	0.99 to 1.02	0.660
HTN	...	...	...	1.00	0.99 to 1.02	0.678	1.00	0.99 to 1.02	0.660
Dichotomous GRS and DS	...	...	...	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
High BP	...	...	...	1.52	0.67 to 3.47	0.316	1.61	0.68 to 3.83	0.282
HTN	...	...	...	1.66	0.49 to 5.63	0.418	1.68	0.47 to 6.02	0.424
Additive interaction									
Continuous GRS and DS	RERI	95% CI	<i>P</i> value	RERI	95% CI	<i>P</i> value	RERI	95% CI	<i>P</i> value
High BP	*	...	...	0.008	−0.05 to 0.07	0.793	0.008	−0.05 to 0.07	0.799
HTN	...	...	...	0.006	−0.08 to 0.09	0.897	0.007	−0.07 to 0.09	0.871
Dichotomous GRS and DS	...	...	...	RERI	95% CI	<i>P</i> value	RERI	95% CI	<i>P</i> value
High BP	...	...	...	0.54	−0.34 to 1.42	0.231	0.52	−0.32 to 1.36	0.225
HTN	...	...	...	0.89	−0.68 to 2.46	0.267	0.71	−0.69 to 2.11	0.318
Continuous outcomes									
Multiplicative interaction									
Continuous GRS and DS	B	SE	<i>P</i> value	B	SE	<i>P</i> value	B	SE	<i>P</i> value
SBP	−0.000021	0.000139	0.881	−0.000070	0.000132	0.599	−0.000041	0.000128	0.747
DBP	−0.000055	0.000190	0.771	−0.000100	0.000187	0.592	−0.000052	0.000184	0.777
Dichotomous GRS and DS	B	SE	<i>P</i> value	B	SE	<i>P</i> value	B	SE	<i>P</i> value
SBP	0.013	0.008	0.119	0.016	0.008	0.056	0.014	0.008	0.069
DBP	0.025	0.012	0.029†	0.029	0.011	0.012†	0.026	0.011	0.021†
Additive interaction									
Continuous GRS and DS	B	SE	<i>P</i> value	B	SE	<i>P</i> value	B	SE	<i>P</i> value
SBP	−0.001	0.01	0.914	−0.006	0.01	0.634	−0.003	0.01	0.787
DBP	−0.004	0.01	0.746	−0.006	0.01	0.575	−0.003	0.01	0.770
Dichotomous GRS and DS	B	SE	<i>P</i> value	B	SE	<i>P</i> value	B	SE	<i>P</i> value
SBP	1.31	0.85	0.123	1.53	0.81	0.058	1.42	0.79	0.070
DBP	1.49	0.67	0.026†	1.69	0.66	0.011†	1.52	0.65	0.019†

GRS (range 0–58); DASH score, (range 7–35) reflects adherence to the DASH-type diet (higher DASH-score: higher adherence); multiplicative: departure from multiplicativity; additive: departure from additivity; Model 1 adjusted model for age, sex and height; Model 2 adjusted model for age, sex, height, child BMI, gestational age, birth weight, breastfeeding duration, maternal BMI, smoking during pregnancy, physical activity, maternal education level; dichotomous: dichotomous DASH score and GRS (high DASH-score reference group and low GRS reference group); continuous: the continuous DASH score and GRS; high BP (BP ≥90th %): prehypertension + hypertension; *P* value reflects the significance of the product term. B indicates regression coefficient; BMI, body mass index; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; DS, DASH score; DBP, diastolic blood pressure; GRS, genetic risk score; HTN, hypertension; OR, odds ratio; RERI, relative excess risk due to interaction; and SBP, systolic blood pressure.

\*Prehypertension and hypertension in the pediatric population are defined as blood pressure between 90th and 95th percentile, and greater than 95th percentile, respectively, standardized for gender, age, and height. Therefore, the crude model results for high BP and HTN left blank in the table.

†<0.05.

between DS and BP. However, it has been shown that in spite of presenting a selective nonresponse in the ABCD study, selection bias was acceptably low and did not influence the main study questions.<sup>40</sup> Fifth, parents had to score the foods and drinks that their child had consumed over the past 4 weeks in an FFQ. Two disadvantages of the FFQ method are recall bias and it typically lists only common food items, which reduces the precision of the food intake data if a child consumes uncommon foods.<sup>41,42</sup> This may have led

to underreporting of the consumed foods and drinks in the FFQ, which in turn may have resulted in an underestimation of the association between DS and BP. Sixth, the aim of this study was purely explorative, and we did not take multiple testing into account.

Given the above limitations and the difficulties in measuring BP in young children that would suggest an analysis in this age group would more likely be negative than positive, the results are intriguing but need to be confirmed.

Table 5. Average Systolic Blood Pressure and Diastolic Blood Pressure Across Quintiles of GRS and DASH Score in Children

GRS Quintiles		DASH-Score Quintiles					
		1	2	3	4	5	Total
Systolic blood pressure							
1	Mean	99.1	98.6	98.2	100.0	97.8	98.8
	SD	9.5	5.9	7.2	6.9	6.8	7.2
	n	32	45	30	51	53	211
2	Mean	100.1	98.1	98.3	97.6	98.2	98.2
	SD	9.0	7.3	6.0	5.6	5.4	6.2
	n	10	19	22	38	20	109
3	Mean	99.6	97.2	96.9	98.7	98.6	98.2
	SD	7.7	5.0	6.0	6.6	6.6	6.4
	n	39	47	43	59	44	232
4	Mean	100.8	100.1	96.9	98.1	97.5	98.2
	SD	7.8	7.7	4.9	6.9	6.1	6.9
	n	31	50	31	58	38	208
5	Mean	100.0	98.6	98.5	98.5	98.5	99.1
	SD	7.4	7.6	6.4	6.9	6.1	6.9
	n	49	70	58	71	60	308
Total	Mean	99.9	98.6	97.8	98.6	98.1	98.6
	SD	8.0	6.9	6.2	6.7	6.6	6.9
	n	161	231	184	277	215	1068
Diastolic blood pressure							
1	Mean	56.6	55.3	54.7	56.8	55.9	55.9
	SD	5.8	4.6	5.8	5.0	8.3	6.1
	n	32	45	30	51	53	211
2	Mean	55.7	55.3	56.6	57.8	54.4	56.2
	SD	3.9	6.2	5.7	4.3	3.8	4.9
	n	10	19	22	38	20	109
3	Mean	56.5	55.5	56.2	57.2	56.3	56.4
	SD	4.7	4.5	4.5	5.9	5.8	5.2
	n	39	47	43	59	44	232
4	Mean	57.9	56.0	55.0	56.8	56.3	56.4
	SD	4.1	6.0	5.7	5.3	4.6	5.3
	n	31	50	31	58	38	208
5	Mean	58.8	58.0	57.4	56.3	56.8	57.4
	SD	5.7	4.8	4.9	5.0	6.0	5.3
	n	49	70	58	71	60	308
Total	Mean	57.4	56.4	56.2	56.8	56.2	56.5
	SD	5.2	5.2	5.2	5.1	6.2	5.4
	n	161	231	184	277	215	1068

GRS (range 0–58); DASH score, (range 7–35) reflects adherence to the DASH-type diet (higher DASH score: higher adherence). DASH indicates Dietary Approaches to Stop Hypertension; DS, DASH score; and GRS, genetic risk score.

## Conclusions

Adherence to the DASH diet and genetic predisposition were both associated with BP in children 5 to 7. In addition, a

gene-environment interaction was found between adherence to the DASH diet and genetic predisposition on BP. Children with a higher genetic predisposition to develop high BP may

have a greater benefit from having a specific healthy diet compared to children with a lower genetic risk.

### Perspectives

The association that has been found regarding adherence to the DASH diet and BP indicates a possible causal relationship that requires further research. We would recommend including children of a larger age range, 4 to 12 to study if there is age sensitivity to the DASH diet, as well as enrolling normotensive and hypertensive children in randomized clinical trials on the effect of the DASH diet on BP. If the effect of the DASH diet and its interplay with genetic risk on lowering BP among children is replicated in other studies, this may be applied as a strategy to prevent the development of hypertension at this early stage in life.

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### Disclosures

None.

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## Novelty and Significance

### What Is New?

- This is the first study to evaluate the relation of adherence to Dietary Approaches to Stop Hypertension-type diet, a genetic risk score and their interaction on blood pressure phenotypes in a large community-based cohort of young children.

### What Is Relevant?

- Both Dietary Approaches to Stop Hypertension-type diet and the adult-derived genetic risk score were associated with blood pressure phenotypes in young children.
- Low adherence to a Dietary Approaches to Stop Hypertension-type diet combined with a high genetic risk score resulted in the highest diastolic blood pressure

### Summary

Preventing hypertension through the Dietary Approach to Stop Hypertension diet could have public health benefits for children. Our study suggests that the genetic basis of blood pressure phenotypes at least partly overlaps between adults and children and these genetic variants identified by adult genome-wide association studies are associated with blood pressure in children.