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Childhood adiposity, adult adiposity, and the *ACE* gene insertion/deletion polymorphism: evidence of gene—environment interaction effects on adult blood pressure and hypertension status in adulthood

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Abstract

Background: Genetic variants may modify the associations of adiposity measures with blood pressure (BP) and hypertension. The insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme (*ACE*) gene is an attractive candidate.

Aims: To examine interaction effects between I/D polymorphism and adiposity measures (BMI, waist circumference, waist-to-hip ratio, and skinfold thickness) during childhood and adulthood in relation to adult BP and hypertension.

Methods: Data were available for 4835 participants from three prospective cohort studies. Multivariable linear regression models for adult SBP and DBP, and multivariable logistic regression models for hypertension were fit that included interaction effects between child or adult adiposity and I/D polymorphism.

Results: Evidence for interaction effects on BP/hypertension were found across the three studies. Compared with childhood measures, the effect modification appeared to be more consistent when using adult adiposity. In particular, the adverse effects of greater adult waist

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Conflicts of interest

There are no conflicts of interest.

circumference on increasing adult SBP and DBP appeared to be larger among carriers of *ACE* DD (or GG) [adjusted linear regression coefficients 0.26, 95% CI (0.21–0.31) and 0.28 (0.24–0.32) for SBP and DBP, respectively] and ID (or AG) genotypes [0.25 (0.21–0.29) and 0.25 (0.21–0.28), respectively], whereas those with II (or AA) genotypes had smaller effects [0.15 (0.09–0.21) and 0.19 (0.13–0.23)].

Conclusion: *ACE* genetic variation may modify the effect of adult adiposity on increasing BP and risk of hypertension in adulthood. Individuals with *ACE* DD (or GG) and/or ID (or AG) genotypes, compared with those with II (or AA) genotype, appear more vulnerable to the impact of excess adiposity.

Keywords

adiposity; angiotensin-converting enzyme; blood pressure; genes and environment interaction; longitudinal cohort study; renin-angiotensin aldosterone system

INTRODUCTION

The epidemic of obesity worldwide is tied to rising rates of serious medical consequences such as hypertension, type 2 diabetes mellitus, and cardio-vascular disease (CVD) [1,2]. It has been estimated that 60–70% of adult hypertension may be directly attributable to adiposity [3]. Hypertension alone affects 1.36 billion persons worldwide, 31.1% of the adult population in 2010 [4]. Globally, type 2 diabetes mellitus affects 415 million people in 2015, 9% of the adult population [5]. In 2013, 32% of global deaths were attributable to CVD [6]. In view of divergent cardiometabolic outcomes among individuals with similar adiposity levels, considerable effort is being made to identify the genes that confer susceptibility to obesity, and, in particular, its impact on hypertension.

A previous study found angiotensin-converting enzyme (*ACE*) gene deletion (DD) genotype (rs1799752), compared with the insertion/deletion (I/D) or insertion (II) genotype, was associated with larger increases in body weight, blood pressure (BP), and higher incidence of overweight in an aging population [7]. Furthermore, studies showed that the I/D polymorphism (rs1799752), a valid marker of *ACE* gene functional polymorphism [8], accounts for about half of the variation in this enzyme level in healthy Caucasians [9]. Caucasians who carry the DD genotype had the highest plasma ACE concentration ($494.1 \pm 88.3 \mu\text{g/l}$), nearly twice that found in individuals with the II genotype (299.3 ± 49.0); those with the ID genotype had intermediate level of plasma ACE (392.6 ± 66.8). Alternative single nucleotide polymorphisms of *ACE*, which is in nearly complete linkage disequilibrium with *ACE* I/D genotypes (e.g. rs4343), have also been reported [10,11]. As ACE plays an essential role in cardiovascular pathophysiology and has been implicated in various conditions including obesity [7,12–14] and hypertension [15], *ACE* appears to be a candidate gene that may influence adiposity [7,12], BP (rs4646994) [7,16], and CVD (rs1799752) [17]. In particular, evidence suggests a central role for ACE in converting Angiotensin I to potent vasoconstrictor, Angiotensin II, a key modulator of the renin–angiotensin system in adipose and vascular tissue with systemic functions such as regulation of BP [18,19]. However, gene-BP/hypertension association studies have reported inconsistent findings [16,20]. Although the exact reasons for the inconsistent findings are

not clear, many studies that have been conducted to date have been limited by small sample sizes [21,22]. Failing to include possible interaction effects in data analyses may be another potential contributing factor towards the common lack of replication of gene-disease associations [23,24]. Excess adiposity is well established as a risk factor for elevated BP [25], thereby making it appropriate to determine gene identification studies in the context of this environmental factor [26].

In the current study, we investigated whether *ACE*I/D polymorphism confer different risks in the development of adult hypertension (BP elevation) among participants with different adiposity levels in childhood and adulthood using three large population-based longitudinal cohort studies from the International Childhood Cardiovascular Cohort (i3C) Consortium [27]. No large-scale, prospective population-based cohort studies have investigated these factors. We have yet to understand why some obese individuals develop hypertension whereas others maintain normal BP, hampering the development of effective preventive strategies [28]. The pooling of consortium data will provide insights into the evolution of CVD risk factors in early life with greater power than has been available previously.

METHODS

Study populations

Details of the design and conduct of the Childhood Determinants of Adult Health Study (CDAH), the Muscatine Study and the Cardiovascular Risk in Young Finns Study (YFS) have been published elsewhere [29–32]. After excluding cohort members with missing information for *ACE* genotypes (I/D rs13447447 for CDAH and rs4343 for Muscatine and YFS), BP, and 177 participants who reported ‘yes’ on antihypertensive medication use in adulthood (yes, no, or unknown), 4835 participants were included in our analysis. These included 2285 children examined in 1985 and re-examined as young adults in 2004–2006 from the CDAH, 1875 children examined in 1980 and re-examined as young adults in 2007 from the YFS, and 675 children examined in 1970–1977 and re-examined as young adults in 1996–1998 from the Muscatine Study. The mean (SD) length of follow-up across the three cohorts was 23.6 (3.2) years. Details of the methods used for *ACE* genotyping and other covariates in each study are provided in the supplement (<http://links.lww.com/HJH/A955>). Each study was approved by the appropriate ethics committee and institutional review boards, and written informed consent was obtained from study participants and from their parents or guardians when recruited in childhood.

Outcomes

Adult BP was measured from the right arm while seated after a 5-min rest using an OMRON HEM907 Digital Automatic Blood Pressure Monitor in CDAH, and a random zero sphygmomanometer (Hawksley & Sons Ltd, Lancing, UK) in the YFS and Muscatine Study. The mean of the three measurements was used for analysis in all studies. We classified participants as having hypertension if they had a SBP of 140mmHg or higher, or a DBP of 90mmHg or higher [33].

Statistical analysis

Means and SDs or, for skewed variables, medians and interquartile ranges were calculated for description of childhood and adulthood characteristics. We also performed gene main effect analysis and Pearson correlation analysis for adiposity measures. Childhood triceps skinfold thickness was log transformed as the exposure prior to analysis because of skewness in the distribution. Base two logarithms were calculated so that a change of one unit of log-transformed triceps skinfold thickness represented a doubling in that value.

As children are still growing, age-standardized and sex-standardized BMI and waist circumference (z scores) were generated based on 1990 British growth chart using the *zanthro* function in Stata 14 (StataCorp, College Station, Texas, USA) [34,35]. To reduce the potential impact of outliers on the findings, we examined the prospective associations between childhood adiposity (skinfold thickness, BMI and waist circumference z scores) and adult SBP and DBP using robust linear regression models. We also performed logistic regression when hypertension (yes/no) was used as an outcome. The evidence for an additive genetic model for the *ACEI/D* polymorphism was inconsistent (i.e. the effect often suggested a dominant based on the estimates from the general model coding II/AA as 0, ID/AG as 1, and DD/GG as 2), therefore, we chose the general effect specification rather than the additive genetic effect. In the regression models, interaction effects were examined as global effects (two degrees of freedom) using the cross product of the genotypes (a categorical variable) and a childhood adiposity measure. To make the adult adiposity measures independent of childhood adiposity measures, we used the residual of the adult adiposity measures that regressed on childhood adiposity measures. We followed the same procedure for adult waist circumference, but used childhood BMI z score as the surrogate measure when childhood waist circumference was not available. Interaction effects were assessed using a cross-product of the genotypes and adult adiposity (using residual that regressed on childhood adiposity) in the regression models. We used the likelihood ratio test to assess the evidence for interaction between *ACE* genotype and adiposity in relation to BP or hypertension. These associations are presented adjusted for current age and sex, which were controlled in previous studies, and for covariates found to change the estimates of association by at least 10% when added to the multivariable model.

We performed data pooling for three cohorts if the cohort-specific analysis showed consistency of estimates across three studies, adjusting for current age, sex, antihypertensive medication use, length of follow-up, and a cohort indicator variable. We also conducted a sensitivity analysis by including 177 participants who indicated current use of antihypertensive medications. All analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA).

RESULTS

The distribution of the *ACEI/D* genotypes (CDAH) and the rs4343 genotypes (Muscatine and YFS) did not differ from the expectations of Hardy-Weinberg equilibrium in any of the cohorts.

Baseline characteristics of the pooled sample and the individual cohort

Tables S1–4, <http://links.lww.com/HJH/A956> describe the childhood and adult characteristics in according to *ACE*I/D genotypes for the pooled sample and the individual cohorts. After excluding 177 participants who were reported taking antihypertensive medication, 226 participants had hypertension (169 from CDAH, 20 from YFS and 37 from Muscatine) at the time of the adult examination.

Results of correlation analysis for different adiposity measures, the effect of adiposity on BP and hypertension, and gene main effect analysis in the pooled sample and in each study are shown in the supplement, <http://link-s.lww.com/HJH/A955>.

Findings from interaction analysis between adiposity and angiotensin-converting enzyme

In the pooled sample, the effect of increased adult adiposity measures (BMI, waist circumference, and waist-to-hip ratio) on elevating SBP and DBP (marginal effect for waist-to-hip ratio) was greater in carriers with at least one *ACE* D(G) allele - *ACE* ID (AG) or DD (GG), compared with those with II (or AA), after adjusting for current age, sex, length of follow-up, and cohort indicator (Table 1 and Fig. 1). We detected a weaker signal of interaction in the pooled sample when using hypertension as the outcome.

Tables S5 (<http://links.lww.com/HJH/A956>) to S7 (<http://links.lww.com/HJH/A956>) presents results of interaction analysis for adult adiposity exposures from individual cohorts. Table S5 (<http://links.lww.com/HJH/A956>) demonstrates a similar pattern of an interaction effect between adult BMI (using residual that regressed on childhood BMI z score) and *ACE* gene variants was evident when considering the variation of adult BP in the CDAH and Muscatine. Also in the CDAH and Muscatine, carriers of *ACE* gene deletion genotype had larger adverse effect of increased adult BMI on hypertension, compared with those with insertion and insertion deletion genotypes. YFS showed no evidence of adult BMI and *ACE* gene variants interaction effect. With respect to adult waist circumference, in the CDAH, Table S6 (<http://links.lww.com/HJH/A956>) demonstrates a strong interaction effect on both adult SBP and DBP (marginal effect for hypertension), with participants carrying *ACE* deletion genotype having the largest adverse effect of increased adult waist circumference (using residual that regressed on childhood adiposity). Those with insertion genotypes had the smallest effect, and those with insertion deletion genotype had an intermediate, but closer to deletion than to insertion, effect, after adjusting for confounders listed in the footnote. The interaction effect was also shown in the Muscatine study, although more evident for DBP and marginal for SBP and hypertension. Those with AA (II proxy) and AG (ID proxy) genotypes had a smaller effect than that with GG (DD proxy), after adjusting for confounders listed in the footnote. We noted that in the YFS, there was a similar increased effect of waist circumference on BP in both AG and GG (ID and DD proxy) genotypes, compared with those with AA (II proxy) genotypes, after adjusting for confounders listed in the footnote. When we used adult waist-to-hip ratio as another central obesity measure, there was no strong evidence of interaction in the CDAH and Muscatine (Interaction $P=0.11$ for DBP; Table S7, <http://links.lww.com/HJH/A956>). YFS showed strong evidence of interaction with an increased effect of waist-to-hip ratio on BP in GG (DD proxy) and AG (ID proxy) genotypes, compared with those with AA (II proxy) genotypes. In both the

CDAH and Muscatine, we did not observe strong interaction effect of adult triceps skinfold thickness and *ACE* gene variants on the development of adult BP or hypertension (data not shown).

Childhood adiposity and *ACE* genotypes in relation to BP and hypertension showed inconsistent estimates of interactions across the three cohorts (Tables 2 and 3). The magnitude of association of childhood BMI z score with adult DBP seemed stronger among the CDAH participants carrying *ACE* deletion and insertion deletion genotypes (D allele carriers) than those with insertion genotype (Table 2). However, we did not detect evidence of interaction effect of childhood BMI z score and *ACE*/D variants in relation to SBP and hypertension. In contrast to the CDAH, there was evidence that *ACE* AA (II proxy) genotype carriers in the YFS had the largest adverse effect of increased childhood BMI z score on adult SBP (marginal evidence) and hypertension, those with AG (ID proxy) genotype had an intermediate effect, and those with GG (DD proxy) genotypes had the smallest effect. Finally, examining associations with childhood triceps skinfold thickness in CDAH revealed evidence for interaction effects with the *ACE*/D polymorphism in relation to DBP and hypertension (marginal evidence for SBP) in Table 3. Per doubling of triceps skinfold thickness was associated with a 4.85 mmHg rise in DBP among those with deletion genotype, a 1.15 mmHg rise in DBP among those with insertion deletion genotype, and a 0.33 mmHg rise among those with insertion genotype. In the YFS, a similar pattern of interactions was observed (Tables 2 and 3) for SBP and hypertension. Muscatine showed no evidence of childhood adiposity and *ACE* gene variants interaction effect. In CDAH, no interaction effect was seen between childhood waist circumference and *ACE* genotypes for either SBP or DBP or hypertension (data not shown).

In sensitivity analysis, including participants who indicated current use of antihypertensive medications did change some of the reported estimates. Therefore, we present results excluding participants with antihypertensive medication use.

DISCUSSION

In this study consisting of three prospective cohort studies from the i3C Consortium [27], a consistent effect of increased adult adiposity interacting with *ACE* gene variants on elevating adult BP was evident across three studies, particular for adult waist circumference. Both *ACE* deletion (or GG) and insertion deletion (or AG) genotype carriers had larger adverse magnitude of effect of increased adult waist circumference on elevating both adult SBP and DBP (DBP for Muscatine only), compared with those carrying insertion (or AA) genotypes. There was weaker evidence that *ACE* genes variants moderate the effect of childhood adiposity on adult BP and hypertension. Specifically, our findings showed that in CDAH and YFS, participants carrying the *ACE* deletion genotype had greater effect of increased childhood adiposity (both BMI and triceps skin fold thickness, but not waist circumference) on elevating adult DBP (weak evidence for SBP) and increased risk of hypertension (for triceps skinfold thickness only), compared with other genotype carriers. In YFS, a different pattern of interaction was shown for SBP (weak evidence for DBP) and hypertension, with participants carrying AA genotype (II proxy) having the largest effect of increased childhood adiposity (both BMI and triceps skinfold thickness) on elevating BP and risk of

hypertension. In the pooled sample and in three individual studies, there was no evidence that *ACE* gene polymorphism was associated with either BP, or hypertension, or adiposity measures. It is possible, that the increased ACE levels resulting from the polymorphisms are associated with only mildly elevated BP at the population level. This might be the reason why many studies did not find an association between the polymorphisms and BP [36].

The strengths of the study include three independent large population-based samples, all samples of European ancestry limiting concerns with regard to population stratification, collection of a range of potential confounders and use of four different adiposity measures including BMI, triceps skinfold thickness, waist circumference, and waist-to-hip ratio. A consideration of the environmental contexts in which genetic susceptibility is suspected to be most evident could lead to confirmation of a hypothesized gene-environment interaction and thus may increase the confidence that the genetic or environmental factor under study is a true risk factor of the disease [37]. We were also able to examine the interaction between *ACE* genotypes and childhood adiposity for the development of adult higher BP and hypertension, reducing concerns with regard to reverse causality. The availability of population-based cohorts also reduces the problem of selection bias that has been an issue for an earlier case-control study on this issue [38]. A potential limitation of our study is that the range of measures included in the current study are not gold-standard measures of body composition. The use of different adiposity measures, however, may provide clues to the underlying mechanisms [39]. BMI is closely related to over-all subcutaneous fat mass [40]. In contrast, measures such as waist circumference, a centrally distributed adiposity measure, are more strongly correlated with abdominal and visceral fat mass. In a previous cohort study, waist circumference has also been shown to predict adult cardiometabolic health risk beyond that explained by BMI [41]. The waist-to-hip ratio may provide a better measure of central adiposity than waist circumference or BMI, but mainly among the elderly [42]. It is plausible that BMI may be less sensitive than waist circumference or waist-to-hip ratio at capturing the underlying and disparate metabolic effects of fat depots. For example, in the CDAH, we have shown that childhood waist circumference is superior for predicting long-term cardiometabolic health [43], indicating visceral fat mass accumulation may underlie the adverse metabolic profile associated with obesity. We measured BP in the right arm only as it is impractical to measure it three times in each arm in large population-based studies. Previous studies reported the prevalence of left-handed individuals are 3–10% and those with BP difference between left and right arm of at least 10mmHg is 2.7–31.2% [44,45]. However, a recent study suggests that BP measured in one arm is substitutable with that of the other arm because of a lack of an association of difference in BP measurements between arms with the dominant hand [46]. Hypertension as a clinical relevant outcome was not prevalent among these young adult populations, limiting the ability to assess this. Although it is true that having a homogeneous sample is good for statistical power, it does limit the generalizability of the current findings to other ethnic population. Although there are issues with missing data in three cohorts because of loss of follow-up as with all cohort studies, we have shown the representativeness of Muscatine study, YFS, and CDAH previously [47–49]. For both YFS and Muscatine study, *ACE*I/D genotypic information was not available, however, we used *ACE*rs4343, which is in nearly complete linkage disequilibrium with *ACE*I/D genotypes. Further more, 235 YFS participants had both *ACE*rs4343 and I/D

genotype (rs1799752) data for cross validation. Future association studies involving *ACE* I/D genotype and BP should also measure plasma ACE levels as the *ACE* I/D genotype only serves as a proxy for ACE levels and this relationship may not be strong in each individual [11].

Our findings from three studies support the concept that *ACE* genotype differences may modify the effect of increased adult adiposity on elevating BP and increasing risk of hypertension in adulthood. The effect size of such interaction seemed modest. For example, the difference in effect for 1 cm increase in adult waist circumference was 0.11 (0.26 – 0.15) mmHg for SBP and 0.09 (0.28 – 0.19) mmHg for DBP (details in Table 1), respectively, in the pooled sample between the two extreme genotype groups (DD/GG versus II/AA). In support of our finding, a previous case-control study found the prevalence of hypertension was 86% among participants who carried DD genotype and were obese, compared with 60% among those who only had one of these risk factors, and 40% among those with neither of them, indicating an additive effect of obesity and *ACE* DD genotype on hypertension [50]. A second case-control study, which examined *ACE* I/D polymorphisms, hypertension, and obesity among participants with and without type 2 diabetes, also reported evidence of an interaction effect [38]. The underlying mechanisms in this study, however, may be difficult to generalize as *ACE* DD genotype is causally related to diabetic nephropathy, a risk factor for hypertension [8].

Our findings from two of the three studies, CDAH and YFS, support that *ACE* I/D genotype differences may also prospectively modify the effect of increased adiposity during childhood on elevating BP and increasing risk of hypertension in adulthood, although the interaction pattern may differ by population. Comparing with the adult adiposity, the effect size of this interaction was greater. For example, in CDAH, the expected difference in DBP was 4.52 (4.85 – 0.33) mmHg between the two extreme genotype groups (DD versus II, details in Table 3), for comparing two childhood triceps values that were two-fold different, for example, comparing 2 mm with 4 mm, 4 mm with 8 mm, or 10 mm with 20 mm. We are unable to explain the finding that YFS participants with AA (II proxy) genotype carriers had the largest magnitude of adverse effect of increased childhood adiposity on elevating BP and increasing risk of hypertension. It could be chance finding, as consistency was not demonstrated across studies.

The interaction effect appeared stronger when using adult waist circumference with weaker signals being detected using adult BMI, indicating more data from future studies are needed. The effect modification of *ACE* genotypes and BP by adiposity in the three studies is consistent with other work, which has shown that the adverse effect of *ACE* DD genotype on other cardiometabolic outcomes including triglycerides and insulin resistance to be more evident than other *ACE* I/D genotypes carriers [24]. Future studies on other cardiometabolic outcomes are clearly warranted. Our findings are also in line with a large body of work on the renin-angiotensin system in relation to obesity, hypertension, and CVD [19].

These findings could help explain that meta-analyses of the association between the *ACE* deletion genotype and hypertension have reported significant heterogeneity ($P < 0.001$) with overall a minor positive effect for the D allele, sometimes reported more evident in women

[8], although this is not evident in our cohorts. Biologically, the deletion genotype would be expected to be associated with higher serum ACE levels, increasing angiotensin 2 and thus reducing nitric oxide bioavailability and inducing endothelial dysfunction and also catabolizing bradykinin, a strong vasodilator [8]. Both obesity and *ACE* deletion genotype can also increase oxidative stress [51,52]. Further, obesity was found to upregulate gene expression for renin and ACE in adipocytes [53] and therefore, enhancement of the *ACE* deletion genotype by obesity is plausible.

The clinical implications of this international multicohort lifecourse investigation now require careful consideration. It is estimated that 10% (US\$372) of the world's overall healthcare expenditure was on hypertension in 2001 [54]. Considering the rising prevalence of elevated BP, the direct cost of elevated BP was expected to be over US\$ 908 billion globally in the current decade [54]. In an era of rising obesity, cardiometabolic morbidity and its related healthcare costs will continue to rise, should preventive efforts against obesity be more effective for those of varying genotypes, say carrying *ACE* deletion or insertion deletion genotypes? Future candidate association studies that use modern gold-standard adiposity measures, particularly in older populations, with a larger sample size, are clearly needed. This international lifecourse gene-environment investigation highlights both the potential and problems as personalized genomic medicine continues to evolve.

In conclusion, our data suggest that individuals with *ACE*DD (or GG) and/or ID (or AG) genotypes, compared with those carrying II (or AA) genotype, appear more vulnerable to the impact of excess adiposity, in particular in adulthood. In light of the worldwide epidemic of obesity, these findings may have important implications for reducing obesity-related hypertension among children and adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACE	angiotensin-converting enzyme
BP	blood pressure
CDAH	Childhood Determinants of Adult Health Study
CVD	cardiovascular disease
I/D	insertion/ deletion
YFS	Cardiovascular Risk in Young Finns Study

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FIGURE 1.

Estimated interaction effects for adult adiposity with *ACE* genotypes in multivariable regression models for adult blood pressure, pooled across cohorts. WC, waist circumference; WHR, waist-to-hip ratio

TABLE 1.

Estimated interaction effects for adult adiposity with ACE genotypes in multivariable regression models for adult blood pressure and hypertension, pooled across cohorts

Adult adiposity measures	II (or AA) genotype (N = 955)			ID (or AG) genotype (N = 2316)			DD (or GG) genotype (N = 1449)			Interaction	
	Outcomes	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	P value ^a	
BMI	SBP	0.49 (0.31–0.67)	<0.001	0.72 (0.60–0.83)	<0.001	0.65 (0.51–0.80)	<0.001	0.65 (0.51–0.80)	<0.001	0.11	
	DBP	0.55 (0.40–0.69)	<0.001	0.71 (0.61–0.80)	<0.001	0.75 (0.64–0.87)	<0.001	0.75 (0.64–0.87)	<0.001	0.08	
	HT	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)			
		1.12 (1.05–1.21)	0.001	1.13 (1.09–1.18)	<0.001	1.21 (1.15–1.28)	<0.001	1.21 (1.15–1.28)	<0.001	0.12	
		II (or AA) genotype (N = 953)									
		ID (or AG) genotype (N = 2312)									
		DD (or GG) genotype (N = 1446)									
		β (95% CI)									
WC	SBP	0.15 (0.09–0.21)	<0.001	0.25 (0.21–0.29)	<0.001	0.26 (0.21–0.31)	<0.001	0.26 (0.21–0.31)	<0.001	0.01	
	DBP	0.19 (0.13–0.23)	<0.001	0.25 (0.21–0.28)	<0.001	0.28 (0.24–0.32)	<0.001	0.28 (0.24–0.32)	<0.001	0.01	
	HT	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)			
		1.05 (1.02–1.08)	0.001	1.05 (1.03–1.07)	<0.001	1.08 (1.05–1.10)	<0.001	1.08 (1.05–1.10)	<0.001	0.16	
		II (or AA) genotype (N = 953)									
		ID (or AG) genotype (N = 2312)									
		DD (or GG) genotype (N = 1446)									
		β (95% CI)									
W _{hr} ^b	SBP	2.73 (1.84–3.62)	<0.001	3.67 (3.02–4.31)	<0.001	3.68 (3.14–4.59)	<0.001	3.68 (3.14–4.59)	<0.001	0.08	
	DBP	2.74 (2.01–3.47)	<0.001	3.26 (2.74–3.79)	<0.001	3.51 (2.91–4.10)	<0.001	3.51 (2.91–4.10)	<0.001	0.20	
	HT	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)			
		2.16 (1.43–3.28)	<0.001	2.21 (1.64–2.98)	<0.001	2.04 (1.47–2.83)	<0.001	2.04 (1.47–2.83)	<0.001	0.92	

CI, confidence interval; DD, deletion; HT, hypertension (yes/no); ID, insertion deletion; II, insertion; WC, waist circumference; W_{hr}, waist-to-hip ratio.

Estimations adjusted for current age, sex, length of follow-up, and cohort indicator in the multivariable linear regression models. Adult adiposity (using residual that regressed on childhood BMI z score) were included in the models.

^aThe interaction P value is the two-degree freedom model with global (could be additive or nonadditive) genetic effects.

^bAdult waist-to-hip ratio (using residual that regressed on childhood BMI z score) multiplied by 10 in the models.

TABLE 2.

Estimated interaction effects for childhood BMI z score with *ACE* genotypes (Childhood Determinants of Adult Health Study) or rs4343 A/G genotypes (Young Finns and Muscatine Studies) in multivariable regression models for adult blood pressure and hypertension

Study	Outcomes	II genotype (N= 351)			ID genotype (N = 829)			DD genotype (N = 472)			Interaction	
		β	(95% CI)	P value	β	(95% CI)	P value	β	(95% CI)	P value	P value ^d	P value ^d
CDAH ^b	SBP	0.03	(-1.25 to 1.31)	0.96	0.80	(-0.00 to 1.59)	0.05	0.78	(-1.20 to 1.77)	0.12	0.57	0.57
	DBP	-0.66	(-1.74 to 0.42)	0.23	1.08	(0.40–1.75)	0.002	1.09	(0.26–1.92)	0.01	0.02	0.02
	HT	OR (95% CI)			OR (95% CI)			OR (95% CI)				
		1.04	(0.64–1.71)	0.86	0.96	(0.71–1.29)	0.78	1.23	(0.80, 1.91)	0.35	0.63	0.63
YFS ^c	SBP	1.38	(-0.63 to 3.39)	0.18	0.89	(-0.09–1.87)	0.08	-0.46	(-1.72 to 0.80)	0.48	0.17	0.17
	DBP	0.21	(-1.49 to 1.91)	0.81	0.80	(-0.03–1.63)	0.06	0.30	(-0.77 to 1.37)	0.58	0.70	0.70
	HT	OR (95% CI)			OR (95% CI)			OR (95% CI)				
		1.58	(1.03–2.43)	0.04	1.07	(0.86–1.34)	0.54	0.87	(0.64–1.17)	0.35	0.08	0.08
Muscatine ^d	SBP	3.23	(1.40–5.05)	0.001	2.30	(1.05–3.56)	<0.001	2.81	(1.22–4.40)	0.001	0.70	0.70
	DBP	2.15	(0.64–3.66)	0.005	2.28	(1.24–3.31)	<0.001	2.48	(1.17–3.79)	<0.001	0.94	0.94
	HT	OR (95% CI)			OR (95% CI)			OR (95% CI)				
		3.05	(1.43–6.52)	0.004	1.69	(1.02–2.79)	0.04	1.46	(0.78–2.72)	0.24	0.30	0.30

CDAH, Childhood Determinants of Adult Health Study; CI, confidence interval; HT, hypertension (yes/no); YFS, the Cardiovascular Risk in Young Finns Study. Analysis was conducted using robust linear regression models to down weight effects of outliers (for SBP and DBP).

^aThe interaction P value is the two-degree freedom model with global (could be additive or nonadditive) genetic effects.

^bAdjusted for current age, sex, childhood socioeconomic status, and childhood 1.6 km run.

^cAdjusted for current age, sex, and parental education level.

^dAdjusted for current age, sex, and smoking (pack-years).

Table 3.

Estimated interaction effects for childhood triceps skinfold thickness (Log₂) with *ACE* genotypes (Childhood Determinants of Adult Health Study) or rs4343 A/G genotypes (Young Finns and Muscatine Studies) in multivariable regression models for adult blood pressure and hypertension

CDAH ^b	II genotype (N = 151)			ID genotype (N = 355)			DD genotype (N = 206)			Interaction	
	β (95% CI)	P value		β (95% CI)	P value		β (95% CI)	P value		P value	P value ^d
SBP	-0.59 (-3.95 to 2.77)	0.73		-1.24 (-3.62 to 1.13)	0.30		1.93 (-0.96 to 4.82)	0.19		0.19	0.19
DBP	0.33 (-2.43 to 3.09)	0.82		1.15 (-0.80 to 3.10)	0.25		4.85 (2.48-7.23)	<0.001		<0.001	0.01
Hypertension	OR (95% CI)			OR (95% CI)			OR (95% CI)			0.06	0.09
YFS ^c	AA genotype (N = 242)	0.64		AG genotype (N = 718)	0.43		GG genotype (N = 476)				
SBP	5.25 (2.09-8.42)	0.001		1.10 (-0.83 to 3.03)	0.27		0.68 (-1.55 to 2.90)	0.55		0.55	0.04
DBP	3.40 (0.73-6.08)	0.01		0.92 (-0.71 to 2.55)	0.27		1.21 (-0.67 to 3.09)	0.21		0.21	0.27
Hypertension	OR (95% CI)			OR (95% CI)			OR (95% CI)				
Muscatine ^d	AA genotype (N = 153)	0.004		AG genotype (N = 321)	0.87		GG genotype (N = 218)				
SBP	3.70 (1.18-6.20)	0.004		3.25 (1.48-5.02)	<0.001		2.20 (-0.03 to 4.42)	0.05		0.05	0.62
DBP	1.65 (-0.35-3.66)	0.11		2.81 (1.39-4.22)	<0.001		1.52 (-0.26 to 3.30)	0.09		0.09	0.41
Hypertension	OR (95% CI)			OR (95% CI)			OR (95% CI)			0.20	0.78

BP, blood pressure (mmHg); CDAH, Childhood Determinants of Adult Health Study; CI, confidence interval; DD, deletion; ID, insertion deletion; II, insertion; YFS, the Cardiovascular Risk in Yung Finns Study. Analysis was conducted using robust linear regression models to down weight effects of outliers (for SBP and DBP).

^aThe interaction P value is the two-degree freedom model with global (could be additive or nonadditive) genetic effects.

^bAll estimations adjusted for adult age, sex, childhood socioeconomic status, and childhood 1.6 km run.

^cAdjusted for adult age, sex, and parental education level.

^dAdjusted for adult age, sex, and smoking (pack-years).