Genetic Influences on Trajectories of Systolic Blood Pressure Across Childhood and Adolescence

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Background—Blood pressure (BP) tends to increase across childhood and adolescence, but the genetic influences on rates of BP change are not known. Potentially important genetic influences could include genetic variants identified in genome-wide association studies of adults as being associated with BP, height, and body mass index. Understanding the contribution of these genetic variants to changes in BP across childhood and adolescence could yield understanding into the life course development of cardiovascular risk.

Methods and Results—Pooling data from 2 cohorts (the Avon Longitudinal Study of Parents and Children [n=7013] and the Western Australian Pregnancy Cohort [n=1459]), we examined the associations of allelic scores of 29 single-nucleotide polymorphisms (SNPs) for adult BP, 180 height SNPs, and 32 body mass index SNPs, with trajectories of systolic BP (SBP) from 6 to 17 years of age, using linear spline multilevel models. The allelic scores of BP and body mass index SNPs were associated with SBP at 6 years of age (per-allele effect sizes, 0.097 mm Hg [SE, 0.039 mm Hg] and 0.107 mm Hg [SE, 0.037 mm Hg]); associations with age-related changes in SBP between 6 and 17 years of age were of small magnitude and imprecisely estimated. The allelic score of height SNPs was only weakly associated with SBP changes. No sex or cohort differences in genetic effects were observed.

Conclusions—Allelic scores of BP and body mass index SNPs demonstrated associations with SBP at 6 years of age with a similar magnitude but were not strongly associated with changes in SBP with age between 6 and 17 years. Further work is required to identify variants associated with changes with age in BP. **(*Circ Cardiovasc Genet*. 2013;6:608-614.)**

Key Words: adolescent ■ blood pressure ■ genetics ■ humans

Although cardiovascular disease generally manifests in later life, evidence from autopsies suggests that the process of atherosclerosis (1 consequence of high blood pressure [BP]) starts in adolescence.[1] Furthermore, epidemiological evidence has demonstrated that levels of BP track from childhood into adulthood[2] and that BP in young adulthood is associated with carotid intima-media thickness[3] and mortality from cardiovascular events[4] later in life.

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In children and adolescents, BP tends to increase with age.[5–11] The causes of these age-related changes in BP are largely unexplored; some age-related changes are likely to be the result of height growth because height is a major determinant of BP in childhood and adolescence, with taller height associated with higher BP.[10] Other influences on age-related changes in BP in children and adolescents are likely to include increasing levels of adiposity, a decline in health-promoting behaviors, and uptake in potentially harmful behaviours.[12,13] Understanding age-related changes in BP in childhood and

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adolescence, and whether genetic variants are associated with greater or smaller age-related increases in SBP, could provide insight into cardiovascular disease pathogenesis and potentially inform prevention strategies that aim to slow down age-related increases and therefore reduce the level of BP attained in adulthood. Genetic variants related to BP, height, and body mass index (BMI) may all be determinants of patterns of change in BP across childhood and adolescence.

The International Consortium for Blood Pressure identified 29 single-nucleotide polymorphisms (SNPs) in 28 loci, 16 of which were novel, that are associated with BP in adulthood.[14] After accounting for the major nongenetic determinants of BP (age, age^2, sex, and BMI), the 29 SNPs explain ≈0.9% of the variance in both systolic BP (SBP) and diastolic BP and are associated with BP-related organ damage and clinical cardiovascular disease.[14] Genetic variants known to be associated with BMI[15] and height[16] have also been identified.

In this article, we pool data from 2 prospective cohort studies; the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Western Australian Pregnancy Cohort (Raine). We describe the associations of (1) an allelic score of 29 BP SNPs, (2) an allelic score of 180 height SNPs, (3) an allelic score of 32 BMI SNPs, and (4) each of the 29 BP SNPs individually with SBP trajectories from 6 to 17 years of age, modeled using linear spline multilevel models. This analysis will allow us to identify the total effect of currently known genetic influences on adult BP on trajectories of SBP across childhood and adolescence. In addition, it permits us to explore the effect of genetic variants related to 2 key environmental determinants of BP (ie, height and BMI) on its development in early life.

Methods

The ALSPAC

The ALSPAC is a longitudinal population-based birth cohort that recruited pregnant women residing in Avon, UK, with an expected delivery date between April 1, 1991, and December 31, 1992. A total of 14 541 women were enrolled, with 14 062 children born, of whom 13 988 were alive at 1 year (13 617 singletons). The cohort, including its representativeness, is described in detail on the Web site http://www.alspac.bris.ac.uk and elsewhere.[17,18] Ethics approval was obtained from the ALSPAC Law and Ethics Committee and relevant local ethics committees.

The Western Australian Pregnancy Cohort (Raine)

Recruitment of the Western Australian Pregnancy Cohort (Raine) has previously been described in detail.[19] Between 1989 and 1991, 2900 pregnant women were recruited at King Edward Memorial Hospital (Perth, Western Australia) before 18 weeks of gestation into a randomized, controlled trial to evaluate the effects of repeated ultrasound in pregnancy. The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from caregivers at all follow-ups and participants at the 17-year-of-age follow-up. Further details about this study can be found at the study Web site http://www.rainestudy.org.au.

Genotyping

Within ALSPAC, 9912 subjects were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK, and the Laboratory Corporation of America, Burlington, NC. Individuals were excluded on the basis of having incorrect sex assignments; minimal or excessive heterozygosity (<0.32 and >0.345 for the Sanger data and <0.31 and >0.33 for the LabCorp data); disproportionate levels of individual missingness (>3%); evidence of cryptic relatedness (>10% identity-by-descent); and being of non-European ancestry (EIGENSTRAT analysis revealed no additional obvious population stratification, and genome-wide analyses with other phenotypes indicate a low λ). The resulting data set consisted of 8365 individuals. SNPs with a minor allele frequency of <1% and call rate of <95% were removed. Furthermore, only SNPs that passed an exact test of Hardy-Weinberg equilibrium (P>5E–7) were considered for the analysis. Genotypes were subsequently imputed with MACH 1.0.16 Markov Chain Haplotyping software, using CEPH individuals from phase 2 of the HapMap project as a reference set (release 22).

Within Raine, DNA was collected at the follow-ups at 14 years (74% of all adolescents) and 17 years (additional 5% of all adolescents) of age using standardized procedures. High-throughput genome-wide SNP genotyping using the genome-wide Illumina 660 Quad Array was performed for each individual. Genotype data were imputed against Hapmap phase2 build 36 release 22 using MACH version 1.0.16 after quality control (minor allele frequency, >1%; Hardy-Weinberg equilibrium, $>5\times10^{-7}$; call rate per SNP and population, >95%). Principal components analysis of genome-wide SNP data with EIGENSTRAT[20] has revealed evidence of population stratification in the Raine sample, so the first 4 principal components were included as cofactors in all analyses. This procedure has been used previously in genetic analyses of the Raine cohort.[21,22]

BP Measurement

A maximum of 7 measures of SBP were available for ALSPAC participants from research clinics held when the participants were ≈7, 9, 10, 11, 13, 15, and 17 years old (mean ages at clinic attendance of 7.5, 9.9, 10.6, 11.7, 12.8, 15.4, and 17.8 years; Figure I in the online-only Data Supplement). At each clinic, SBP was measured twice with the child sitting and at rest with the arm supported, using a cuff size appropriate for the child's upper arm circumference. The mean of the 2 measures is used in our analyses. A Dinamap 9301 Vital Signs Monitor (Morton Medical, London) was used at the 7-, 9-, and 11-year clinics; an Omron MI-5 was used at the 10-year clinic; a Dinamap 8100 Vital Signs Monitor (Morton Medical) was used at the 13-year clinic; and an Omron IntelliSense M6 (Omron Healthcare, Kyoto, Japan) was used at the 15- and 17-year clinics.

Within Raine, a maximum of 5 measures of SBP were available from research clinics held when the participants were ≈6, 8, 10, 14, and 17 years old (mean ages at clinic attendance of 6.0, 8.1, 10.6, 14.1, and 17.1 years; Figure I in the online-only Data Supplement). BP was measured by trained research assistants on participants rested in a seated position for 5 minutes. Right arm circumference was measured, and the appropriate cuff size was used. Measurements were recorded using an oscillometric sphygmomanometer (DINAMAP vital signs monitor 8100, DINAMAP XL vital signs monitor, or DINAMAP ProCare 100) automating readings per 2-minute intervals. Earlier ages (6–10 years) each took 3 recordings, and older ages (14 and 17 years) had 6 BP recordings taken. The first BP measure was discarded, and the mean of the remaining measures was used to represent SBP.

Modeling Trajectories of SBP

Multilevel models are an appropriate tool for the analysis of longitudinal data; they estimate average and individual-specific trajectories of the outcome, regardless of differences in the number and timing of measurements between individuals. Such models allow the clustering of repeated measurements within individuals, can account for change in scale and variance of measures over time, and use all available data from all eligible children under a missing at-random assumption.[23] The models allow individual variation in trajectories because random effects allow a separate trajectory to be estimated for each individual. Individual trajectories of SBP were estimated using linear spline multilevel models (2 levels: measurement occasion

and individual). These models estimate an intercept (SBP at the age of 6 years; note that for ALSPAC this is an extrapolation because the first available measure was at the age of 7 years) and different linear slopes between 6 and 11 years, 11 and 15 years, and 15 and 17 years (see Figure I in the online-only Data Supplement for details of raw data, Figure III and IV in the online-only Data Supplement for details of model selection, and Figures II, V, and VI in the online-only Data Supplement for details of the final model).[24] Mean intercepts and linear slopes were allowed to differ between men and women and between ALSPAC and Raine, and the variance of measurement occasion-level residuals (the differences between observed and predicted measurements) was allowed to vary with age and across cohorts. A binary indicator for the 10-year clinic in ALSPAC was included as a fixed effect to allow for the different measuring device. Four principal components and their interactions with the linear slopes were included in the models to account for population stratification in Raine. The trajectories were modeled in MLwiN version 2.25,[25] which was called from Stata version 12[26] using the runmlwin command.[27] All residuals were approximately normally distributed (results available from authors on request).

Statistical Analysis

For the 29 individual BP SNPs,[14] we used dosages (number of BP-increasing alleles) from imputed data. Allelic scores of the 29 BP SNPs, 180 height SNPs,[16] and 32 BMI SNPs[15] (details of SNPs are given in Table I and II in the online-only Data Supplement) were constructed by summing the number of BP/height/BMI-increasing alleles.

We estimated genetic differences in trajectories of SBP by including a fixed effect for the SNP/allelic score, which estimates the effect of the SNP/allelic score at baseline (6 years) and an interaction between age the SNP/allelic score in the linear spline multilevel model. The coefficients represent the mean difference in SBP (mm Hg) at 6 years or the mean difference in the rate of SBP change (mm Hg/y) per allele, with genotypes modeled on an additive scale. We tested for whether genotype effects of each allelic score differed by cohort or sex, but no differences were observed (all *P* values for sex differences, >0.1; for cohort differences, 1 *P* value of 0.06 was observed and all 11 other *P* values [differences for 1 intercept and 3 slopes for each of the 3 allelic scores were tested] were >0.4), so all genotype associations are presented for men and women and ALSPAC and Raine combined.

In addition to the longitudinal analyses, we used linear regression in the observed data to estimate the cross-sectional associations between each allelic score and SBP at the first (age, 6 years in Raine and 7 years in ALSPAC) and last (age, 17 years in both cohorts) clinics.

To place the genetic results in context, we assessed the relationships of height and BMI with SBP at the first and last clinics and the associations of the height and BMI allelic scores with height and BMI, respectively, at the first and last clinics.

As sensitivity analyses, we repeated all analyses using allelic scores that were weighted according to the effect sizes identified in adult genome-wide association study and repeated longitudinal analyses restricting to individuals who had BP measured at each possible time point.

Results

At least 1 SBP measure and genetic data were available for 7013 ALSPAC participants and 1459 Raine participants, with some indication that included participants tended to be of higher socioeconomic position than the full cohorts (Table III in the online-only Data Supplement). The median number of SBP measures was 6 in ALSPAC and 5 in Raine, and the interquartile range was 4 to 7 measures in ALSPAC and 4 to 5 in Raine. The model demonstrated good fit in both cohorts, with the differences between observed and predicted measurements falling within a reasonable range given the inherent measurement error in BP (Table IV in the online-only Data Supplement). Mean SBP was higher at the age of 6 years in Raine than in ALSPAC, but mean rates of SBP increase in childhood were higher in ALSPAC than in Raine. In both cohorts, an increase in SBP was observed between ages 6 and 11 years, followed by a steeper rate of increase between 11 and 15 years (Table 1). A decrease was seen in the mean pattern between 15 and 17 years of age in women from both cohorts, whereas little change was seen in ALSPAC male subjects between these ages, and an increase was seen in men from Raine (Table 1; Figure II in the online-only Data Supplement). All results were similar using unweighted and weighted allelic scores (results available from authors on request), so only analyses using the unweighted score are presented here. Results were also similar when including all individuals with ≥1 measures of BP or restricting to individuals with BP measured at all available time points (results available from authors on request), so only the former is presented here.

Associations of an Allelic Score and 29 Individual BP SNPs With Trajectories of SBP

Using an allelic score of BP SNPs, each additional BP-increasing allele was associated with 0.097mm Hg higher SBP at the age of 6 years (SE, 0.039 mm Hg ; *P*=0.013; equivalent to a 0.017SD increase in SBP; Table 2). There was little evidence of an association between the allelic score and change in SBP between 6 and 11 years. There was weak evidence of an association between the allelic score and SBP change between 11 and 15 years; the magnitude of the effect was similar to the association with SBP at 6 years, but it was estimated with lower precision (each BP-increasing allele increased the rate of change in SBP by 0.015 SD; SE, 0.008; *P*=0.062). There was no evidence of an association between the BP allelic score and SBP changes between 15 and 17 years. Because the allelic score was associated with starting SBP at 6 years but only weakly with changes in SBP between ages 6 and 17, the difference between individuals of high and low genetic risk remained

Table 1. Mean Trajectories of Systolic Blood Pressure by Cohort and Sex Predicted by the Multilevel Model

	Mean Predicted (SD) Intercept (mm Hg) and Slopes (mm Hg/mt) in Female Subjects	Mean Predicted (SD) Intercept (mm Hg) and Slopes (mm Hg/mt) in Male Subjects
ALSPAC, n	3496	3517
6 y*	97.48 (5.47)	97.71 (5.32)
6–11 y	1.21 (0.15)	1.34 (0.15)
11–15 y	4.40 (0.56)	5.99 (0.54)
15–17 y	–2.47 (0.49)	–0.92 (0.47)
Raine, n	711	748
6 y	103.27 (5.69)	102.57 (5.33)
6–11 y	0.72 (0.18)	0.86 (0.18)
11–15 y	1.22 (0.55)	2.81 (0.57)
15–17 y	–0.74 (0.48)	0.81 (0.53)

ALSPAC indicates Avon Longitudinal Study of Parents and Children.

*Note that in ALSPAC the earliest blood pressure measurement was at 7 years; we extrapolated the multilevel model back to 6 years to match the earliest measurement available in Raine.

Table 2. Associations Between the Blood Pressure, Height, and BMI Allelic Scores and SBP Trajectories

	SBP at Age 6, mm Hg	SBP at Age 6–11 y, mm Hg/mo	SBP at Age 11–15 y, mm Hg/mo	SBP at Age 15–17 y, mm Hg/mo
Mean SBP, mm Hg (SD), or rate of SBP change, mm Hg/mo (SD)	98.51 (5.77)	1.19 (0.25)	4.65 (1.54)	–1.39 (1.13)
BP allelic score, mm Hg	0.097 (0.039) *P*=0.013	0.002 (0.009) *P*=0.862	0.023 (0.012) *P*=0.062	–0.010 (0.020) *P*=0.619
BP allelic score, SD	0.017 (0.007)	0.008 (0.036)	0.015 (0.008)	–0.009 (0.018)
Height allelic score, mm Hg	0.007 (0.015) *P*=0.668	0.001 (0.004) *P*=0.713	–0.006 (0.005) *P*=0.231	0.017 (0.008) *P*=0.029
Height allelic score, SD	0.001 (0.003)	0.004 (0.016)	–0.004 (0.003)	0.015 (0.007)
BMI allelic score, mm Hg	0.107 (0.037) *P*=0.004	0.012 (0.009) *P*=0.174	0.008 (0.012) *P*=0.470	–0.034 (0.019) *P*=0.076
BMI allelic score, SD	0.019 (0.006)	0.048 (0.036)	0.005 (0.008)	–0.030 (0.017)

BMI indicates body mass index; BP, blood pressure; and SBP, systolic blood pressure. Results are from pooled data from Avon Longitudinal Study of Parents and Children and Raine, adjusted for cohort, sex, and population stratification within Raine. Coefficients (SE) are reported as the mean difference per risk allele (increasing BP, height, or BMI) for SBP at 6 years, change in SBP between 6 and 11 years, 11 and 15 years, and 15 and 17 years; coefficients and SEs are reported both in terms of mm Hg/mm Hg per month and in terms of SDs and are predicted values from the multilevel models.

fairly stable across this age range (Figure). Cross-sectional analysis at 17 years showed that each additional BP-increasing allele was associated with a 0.163-mm Hg increase in SBP (SE, 0.050; *P*=0.001; Table V in the online-only Data Supplement); this is similar to the mean per-allele difference predicted by the multilevel model at 17 years (0.177 mm Hg; SE, 0.036 mm Hg; *P*<0.001). The allelic score explained 0.06% of the variation in SBP at the first clinic (6/7 years) and 0.23% at the 17-year clinic (Table VI in the online-only Data Supplement). The highest quintile of the BP allelic score had, on average, a higher SBP than the lowest quintile by 1.23 mm Hg (SE, 0.34 mm Hg) at the first clinic (6/7 years) and by 1.37 mm Hg (SE, 0.51 mm Hg) at the last clinic at 17 years (Table 3).

Four of the 29 single SNPs demonstrated an association with SBP at 6 years at *P*<0.05 (rs1173771, rs1378942, rs17608766, and rs1813353; Table VII in the online-only Data Supplement). A small number of SNPs also demonstrated associations of *P*<0.05 with change in SBP across childhood and adolescence. rs1813353 showed strong positive associations with SBP at 6 years and with SBP changes between 11 and 15 years and then a strong negative association with SBP change between 15 and 17 years. None of these associations would be significant under Bonferroni corrections; we report them here as exploratory findings.

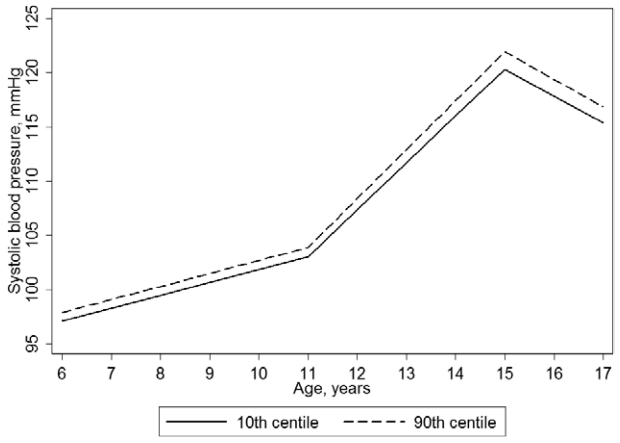

Figure. Mean predicted trajectories of systolic blood pressure with age for individuals with the 10th and 90th percentiles of the blood pressure allelic score. This figure represents the mean predicted trajectory for Avon Longitudinal Study of Parents and Children (ALSPAC) females with the 10th and 90th percentile of the blood pressure allelic score. ALSPAC females were chosen for illustrative purposes only, no evidence of heterogeneity in genetic effects was found across sex or cohorts.

Associations of an Allelic Score of 180 Height SNPs With Trajectories of SBP

Height is strongly associated with SBP in childhood, explaining 5% and 15% of the variance in SBP at the first and last clinics, respectively. The allelic score of height SNPs is strongly associated with height, with the association increasing with age; the proportion of variation in height explained by the allelic score increases from 0.9% to 5% between the first and last clinics.

Despite height being an important determinant of SBP, there is little evidence of associations between the allelic score of 180 height SNPs and trajectories of SBP (Table 2; Figure VII in the online-only Data Supplement). There is no evidence of association before 15 years of age, but there is some evidence that the height allelic score is associated with SBP changes between 15 and 17 years, with each increasing allele associated with a 0.015-SD increase in the rate of SBP change (SE, 0.007 SD; *P*=0.029). At 17 years, each additional height-increasing allele is associated with a 0.045-mm Hg increase in SBP (SE, 0.019; *P*=0.020; Table V in the online-only Data Supplement); a slightly smaller difference at 17 years is predicted by the multilevel model (0.024 mm Hg; SE, 0.014 mm Hg; *P*=0.078). The allelic score explains 0.03% of the variance in SBP at the first clinic and 0.12% at the last clinic (Table VI in the online-only Data Supplement). The SBP difference between the top and bottom quintiles of the height allelic score increases from 6 to 17 years, from 0.38 mm Hg (SE, 0.34 mm Hg, representing a 0.04-SD increase in SBP) to 1.47 mm Hg (SE, 0.51 mm Hg, representing a 0.13-SD increase in SBP). This difference at 17 years is of a magnitude similar to that of the comparison between the top and bottom quintiles of the BP allelic score (Table 3).

Associations of an Allelic Score of 32 BMI SNPs With Trajectories of SBP

BMI is strongly associated with SBP in childhood, explaining 9% and 8% of the variance at the first and last clinics. The BMI allelic score explains ≈1% of the variation in BMI at the first clinic, rising to 2% at the final clinic.

Table 3. Systolic Blood Pressure Differences Comparing Top and Bottom Quintiles of the Blood Pressure, Height, and BMI Allelic Scores at the First and Last Clinics (7 and 17 Years in the Avon Longitudinal Study of Parents and Children or 6 and 17 years in Raine)

	Mean Difference (SE) in Systolic Blood Pressure Comparing Top and Bottom Quintiles of Allelic Score, mm Hg		Mean Difference (SE) in SDs of Systolic Blood Pressure Comparing Top and Bottom Quintiles of Allelic Score	
Allelic Score	First Clinic	Last Clinic	First Clinic	Last Clinic
Blood pressure	1.23 (0.34)	1.37 (0.51)	0.13 (0.04)	0.12 (0.05)
Height	0.38 (0.34)	1.47 (0.51)	0.04 (0.04)	0.13 (0.05)
BMI	1.51 (0.34)	1.21 (0.51)	0.16 (0.04)	0.11 (0.05)

BMI indicates body mass index.

The allelic score of 32 BMI SNPs was strongly associated with baseline SBP; each additional BMI-increasing allele was associated with a 0.107-mm Hg increase in SBP at 6 years (0.019 SD; SE, 0.006 SD; P=0.004; Table 2; Figure VIII in the online-only Data Supplement). The magnitude of the association between the BMI allelic score and SBP changes between 6 and 11 years was greater than for the BP or height allelic scores, but the coefficient was imprecisely estimated (each BMI-increasing allele was associated with a 0.048-SD increase in the rate of SBP change; SE, 0.036; P=0.174). There was little evidence of association between the BMI allelic score and SBP changes between 11 and 15 years. There was some evidence that higher values of the BMI allelic score (greater number of BMI-increasing alleles) were associated with slower rates of SBP increase between 15 and 17 years, although this association was imprecisely estimated (each increasing allele associated with a 0.030-SD slower rate of SBP increase or faster rate of SBP decrease; SE, 0.017; P=0.076). Cross-sectional analysis at 17 years shows that the BMI allelic score is associated with SBP to approximately the same magnitude as the BP allelic score; each additional BMI-increasing allele is associated with a 0.124-mm Hg (SE, 0.048 mm Hg; P=0.010) increase in SBP (Table V in the online-only Data Supplement); a similar difference at 17 years is predicted by the multilevel model (0.132 mm Hg; SE, 0.034 mm Hg; P<0.001). Compared with the BP allelic score, the BMI allelic score explains a greater proportion of the variation in SBP at the first clinic but a similar proportion at the final clinic (0.16% by the BMI score compared with 0.23% by the BP score; Table VI in the online-only Data Supplement). The SBP of individuals in the top quintile of the BMI allelic score is, on average, 1.51 mm Hg (SE, 0.34 mm Hg) higher than the bottom quintile at the first clinic, with the magnitude of this difference reducing slightly (to 1.21 mm Hg; SE, 0.51 mm Hg) between 7 and 17 years (Table 3).

Discussion

BP is influenced by height, adiposity, environmental factors, and genetics. On average, BP tends to increase with age across childhood and adolescence, with some studies showing that BP in women decreases in late adolescence[7–11] and then increases with age in adulthood in both men and women in most Western populations.[28]

In children and adolescents, age-related changes in SBP are poorly understood. Some of these changes are likely to represent normal growth and development; SBP would be expected to increase as children grow taller. Understanding the changes in SBP during childhood and adolescence may yield understanding into the life course development of cardiovascular risk and potentially inform prevention strategies aiming to lower the level of SBP reached in early adulthood.

We demonstrated that an allelic score of the 29 SNPs identified in genome-wide association study of adult BP was associated with SBP at 6 years but not with SBP changes through 17 years. From our data, it would seem that these SNPs are associated with BP from a early age but are not responsible for the changes in BP through childhood and adolescence. The percentage of the variance of SBP explained by the allelic score was 0.2 at 17 years compared with the 0.9% explained in the discovery sample of adults.[14] One previous study has examined the association between 13 BP-related SNPs and BP in childhood and adolescence.[29] Using data from the Cardiovascular Risk in Young Finns cohort and the Bogalusa Heart Study (combined sample size, 3551), Oikonen et al[29] show that an allelic score of the 13 SNPs is associated with BP at 9 years but that the association diminishes in adolescence before reappearing at 24 years. This is in contrast to our findings that show that the effect of the allelic score of BP-related variants remains largely constant between 6 and 17 years. Several factors may explain this difference. First, Oikonen et al[29] adjust for BMI, whereas our aim was to explore the associations between genetic variants and BP trajectories without adjusting for BMI, height, or any other determinant of BP. Second, differences in the populations under study may explain the differences; participants in the Young Finns cohort were born between 1962 and 1977 compared with the early 1990s for ALSPAC and Raine participants, who, therefore, experienced a more obesogenic environment during their childhood. For example, mean BMI at 9 years in the Young Finns was 16.7 kg/m^2 compared with 17.7 kg/m^2 in ALSPAC, rising to 20.2 and 21.5 kg/m^2 in the respective cohorts at 15 years. A further difference between the 2 studies (although perhaps less likely to explain the observed differences) is that our allelic score incorporates 16 additional SNPs discovered since the publication of the article of Oikonen.

In this study, we demonstrated only weak association between an allelic score of height SNPs and trajectories of SBP between 6 and 17 years although the association did increase with age. The height SNPs used in our analyses have previously been shown to be associated with height growth in infancy and childhood, with weak associations observed for birth length and growth infancy and stronger associations

for later childhood growth.[30] The inability of the allelic score of currently identified height variants to explain much of the age-related changes in SBP may reflect, in part, the increasing magnitude of associations between the allelic score of height variants and height across childhood.[30] It also suggests that there are likely to be additional genetic variants associated with growth and development that underlie some of the age-related SBP changes during childhood and adolescence. Analyzing genome-wide influences on SBP trajectories may yield new insights; however, conducting genome-wide association study on longitudinal models is computationally intensive,[31] and methodological work is required to assess the feasibility of this.

Some of the age-related changes in SBP in this age range may also be attributable to factors such as worsening quality of diet, reducing levels of physical activity, and increasing adiposity that are potentially much stronger determinants of BP and changes in BP than currently identified genetic variants. In adults, BMI-related SNPs have been shown to be associated with BP to the extent predicted by their relationship to BMI.[32,33] However, in our study, although a strong association between an allelic score of BMI SNPs and SBP at 6 years was observed, this association did not strengthen with age. Thus, although BMI, along with genetic variants related to BMI, is an important determinant of SBP, our findings would suggest that it is largely not driving age-related changes in SBP during childhood and adolescence. This finding is consistent with analysis of multiple cohorts from across the life span, which found that age-related changes in BP were largely not explained by BMI.[28]

It is noteworthy that although having only weak statistical evidence, both the BMI and BP allelic scores demonstrated negative associations with SBP changes between 15 and 17 years. SBP tends to decrease across this age range (particularly among females), so higher numbers of BP- and BMI-increasing alleles are associated with more rapid decreases in SBP in adolescents. In contrast, the height allelic score demonstrated a positive (and statistically significant) association with SBP changes between 15 and 17 years, so a greater number of tall alleles is associated with slower rates of SBP decrease in adolescents. Thus, there may be competing influences on SBP changes across adolescence. The reasons for the reduction in SBP in adolescence and its associations with later cardiovascular health are not well understood, but our findings tentatively imply that a larger, more rapid decrease in SBP in this age may be associated with adverse cardiovascular health; further studies with data on both childhood and adult BP and cardiovascular health are required to investigate this hypothesis.

Strengths and Limitations

We have combined data from 2 large prospective cohort studies with multiple measures of SBP per child. We have used linear spline multilevel models to estimate trajectories of SBP across childhood and adolescence. Although the piecewise linear structure of the model clearly represents an implausible simplification of the nature of SBP changes with age, the model demonstrated good fit to the data and facilitates easily interpretable analyses of whether the associations between genetic variants and SBP trajectories differ during various periods of childhood and adolescence. The methods allow all individuals to be included in the analyses if they contribute ≥1 measures of SBP under a missing-at-random assumption (ie, assuming that the value of unmeasured SBP, once measured values are accounted for, is not the reason driving missingness, missing data will not have biased these analyses).

Using allelic scores of known variants for height, BMI, and BP enabled us to examine overall associations between common, moderate effect variants related to these traits and trajectories of SBP across childhood and adolescence. The analysis using the scores makes the assumption of uniform strength, direction, and timing of associations between each SNP and SBP trajectories. Although this assumption is not likely to hold, the scores provide a useful tool to explore the overall effect of variants related to adult height, BMI, and BP on trajectories of SBP in childhood and adolescence.

Our study has focused on trajectories of SBP; however, associations of known genetic variants for BP were similar for SBP and diastolic BP in both the adult genome-wide association study[14] and the existing study looking at the association of 13 BP-related SNPs and BP from childhood through adulthood.[29]

Conclusions

Allelic scores of BP and BMI SNPs demonstrated associations with SBP at 6 years with a similar magnitude but were not strongly associated with changes in SBP with age between 6 and 17 years. Further work is required to identify variants associated with changes with age in BP.

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Disclosures

None.

References

1. McGill HC Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr*. 2000;72(suppl 5):1307S–1315S.
2. de Swiet M, Fayers P, Shinebourne EA. Blood pressure in first 10 years of life: the Brompton study. *BMJ*. 1992;304:23–26.
3. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283.
4. McCarron P, Smith GD, Okasha M, McEwen J. Blood pressure in young adulthood and mortality from cardiovascular disease. *Lancet*. 2000;355:1430–1431.
5. Beckett LA, Rosner B, Roche AF, Guo S. Serial changes in blood pressure from adolescence into adulthood. *Am J Epidemiol*. 1992;135:1166–1177.
6. Daniels SR, McMahon RP, Obarzanek E, Waclawiw MA, Similo SL, Biro FM, et al. Longitudinal correlates of change in blood pressure in adolescent girls. *Hypertension*. 1998;31:97–103.
7. Akahoshi M, Soda M, Carter RL, Nakashima E, Shimaoka K, Seto S, et al. Correlation between systolic blood pressure and physical development in adolescence. *Am J Epidemiol*. 1996;144:51–58.
8. Brotons C, Singh P, Nishio T, Labarthe DR. Blood pressure by age in childhood and adolescence: a review of 129 surveys worldwide. *Int J Epidemiol*. 1989;18:824–829.
9. Harding S, Whitrow M, Lenguerrand E, Maynard M, Teyhan A, Cruickshank JK, et al. Emergence of ethnic differences in blood pressure in adolescence: the determinants of adolescent social well-being and health study. *Hypertension*. 2010;55:1063–1069.
10. Kułaga Z, Litwin M, Grajda A, Kułaga K, Gurzkowska B, Góźdź M, et al.; OLAF Study Group. Oscillometric blood pressure percentiles for Polish normal-weight school-aged children and adolescents. *J Hypertens*. 2012;30:1942–1954.
11. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA*. 2004;291:2107–2113.
12. Ferreria I, Twisk JWR, Van Mechelen W, Kamper HCG, Stehouwer CDA. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years. *Arch Intern Med*. 2005;165:42–48.
13. Huang RC, de Klerk N, Mori TA, Newnham JP, Stanley FJ, Landau LI, et al. Differential relationships between anthropometry measures and cardiovascular risk factors in boys and girls. *Int J Pediatr Obes*. 2011;6:e271–e282.
14. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478:103–109.
15. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al.; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948.
16. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*. 2010;467:832–838.
17. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort profile: the 'children of the 90s': the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. 2013;42:111–127.
18. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol*. 2013;42:97–110.
19. Williams LA, Evans SF, Newnham JP. Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant. *BMJ*. 1997;314:1864–1868.
20. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38:904–909.
21. Whitehouse AJ, Bishop DV, Ang QW, Pennell CE, Fisher SE. CNTNAP2 variants affect early language development in the general population. *Genes Brain Behav*. 2011;10:451–456.
22. Paracchini S, Ang QW, Stanley FJ, Monaco AP, Pennell CE, Whitehouse AJ. Analysis of dyslexia candidate genes in the Raine cohort representing the general Australian population. *Genes Brain Behav*. 2011;10:158–165.
23. Goldstein H. *Multilevel Statistical Models*. 2nd ed. London: Edward Arnold; 1995.
24. Tilling K, Davies NM, Nicoli E, Ben-Shlomo Y, Kramer MS, Patel R, et al. Associations of growth trajectories in infancy and early childhood with later childhood outcomes. *Am J Clin Nutr*. 2011;94(suppl 6):1808S–1813S.
25. MLwiN Version 2.25. Bristol, UK: Centre for Multilevel Modelling, University of Bristol [computer program]. 2012.
26. Stata 12.0 [computer program]. College Station, TX: StataCorp; 2011.
27. runmlwin: Stata module for fitting multilevel models in the MLwiN software [computer program]. Bristol, UK: Centre for Multilevel Modelling, University of Bristol; 2011.
28. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med*. 2011;8:e1000440.
29. Oikonen M, Tikkanen E, Juhola J, Tuovinen T, Seppälä I, Juonala M, et al. Genetic variants and blood pressure in a population-based cohort: the Cardiovascular Risk in Young Finns study. *Hypertension*. 2011;58:1079–1085.
30. Paternoster L, Howe LD, Tilling K, Weedon MN, Freathy RM, Frayling TM, et al. Adult height variants affect birth length and growth rate in children. *Hum Mol Genet*. 2011;20:4069–4075.
31. Sikorska K, Rivadeneira F, Groenen PJ, Hofman A, Uitterlinden AG, Eilers PH, et al. Fast linear mixed model computations for genome-wide association studies with longitudinal data. *Stat Med*. 2013;32:165–180.
32. Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, et al. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. *Diabetes*. 2008;57:1419–1426.
33. Timpson NJ, Harbord R, Davey Smith G, Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. Does greater adiposity increase blood pressure and hypertension risk? Mendelian randomization using the FTO/MC4R genotype. *Hypertension*. 2009;54:84–90.

CLINICAL PERSPECTIVE

Blood pressure (BP) tends to increase across childhood and adolescence, but the genetic influences on rates of BP change are not known. Understanding the contribution of genetic variants to changes in BP across childhood and adolescence could yield understanding into the life course development of cardiovascular risk and hence potentially inform the design of intervention studies. In this analysis, we used data from 2 cohorts (the Avon Longitudinal Study of Parents and Children [n=7013] and the Western Australian Pregnancy Cohort [n=1459]) and examined the associations of allelic scores of 29 single-nucleotide polymorphisms for adult BP, 180 height single-nucleotide polymorphisms, and 32 BMI single-nucleotide polymorphisms with trajectories of systolic BP from 6 to 17 years using linear spline multilevel models. Allelic scores of BP and BMI single-nucleotide polymorphisms demonstrated associations with systolic BP at 6 years with a similar magnitude but were not strongly associated with changes in systolic BP with age between 6 and 17 years. Further work is required to identify variants associated with changes in BP with age.