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Association between birth weight and adolescent systolic blood pressure in a caucasian birth cohort differs according to skin type, CRH promoter or 11β-HSD2 genotype

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ABSTRACT

Objective: To examine whether the inverse association between birth weight and blood pressure varies by skin pigmentation and/or related genotypes.

Study design: 671 children from a predominantly caucasian birth cohort were followed-up to adolescence (mean (SD) age 14.4 (0.64)).

Methods: Data on birth weight, socioeconomic status, maternal antenatal smoking, adolescent blood pressure and polymorphisms of candidate genes were obtained and analysed by multiple linear regression.

Results: An increase in birth weight of 1 kg was associated with an non-significant difference in adolescent systolic blood pressure of –0.53 mm Hg (95% CI –1.72 to 0.66) per kg after adjustment for child age and cohort entry criteria. The inverse association between birth weight and systolic blood pressure was stronger for those with darker skin (⩾2% melanin) (difference in effect, $p = 0.02$), those with more copies of the C allele of corticotropin-releasing hormone (CRH) +T1273C ($p = 0.06$), and those with more copies of the short (⩽236 bp) form of the 11β-HSD2{CA}n_{repeat} microsatellite ($p = 0.03$).

Conclusions: These findings add to the evidence that cortisol-related pathways may account for at least part of the observed birth weight–blood pressure associations.

What is already known on this topic

- Low birth weight has been associated with higher blood pressure in adult life.
- Glucocorticoids and the underlying hypothalamic–pituitary–adrenal axis may account for at least part of the observed birth weight–blood pressure associations.

What this study adds

- The inverse birth weight–blood pressure association varies by two cortisol-related genes, CRH promoter and 11β-HSD2 genotype.
- The inverse birth weight–blood pressure association also varies by skin pigmentation in a caucasian population.

An extensive body of research has shown that birth weight is related to adverse outcomes such as hypertension, risk of coronary heart disease and type 2 diabetes, with smaller babies having greater risk in later life.[1 2] The underlying mechanisms are still not clear, but genetic factors associated with both fetal growth restriction and increased risk of cardiovascular disease may be involved.[3]

There is currently considerable interest in this link because of the rapidly increasing burden of cardiovascular and metabolic disease in developing countries, where low birth weight and growth restriction of infants at birth are common. Further, it is likely that the prevalence of the relevant genotypes may vary by race. African–Americans, Aborigines, Polynesians and people from the Indian subcontinent have a higher risk of hypertension, coronary heart disease and type 2 diabetes than caucasians.[4–7] Some of these higher-risk groups have genotypes/phenotypes associated with long-term adaptation to living in warm climates near the equator, including an increase in skin pigmentation. In evolutionary terms, it has been proposed that famine may have forced selection for thrifty fat-storing genes among generations.[8] Similarly, polymorphisms associated with retaining sodium, such as the angiotensinogen gene (AGT) M235T polymorphism, may have been beneficial for those living in warmer climates.[8] This evolutionary perspective raises the question of whether genes associated with darker skin pigmentation may potentiate the association between low birth weight and adverse cardiovascular outcomes, an issue of public health significance.[2 9] There is conflicting evidence about the relative strength of the association between birth weight and systolic blood pressure (SBP) in black versus white children or adults.[10–13] These findings may be confounded by sociocultural factors related to skin pigmentation because people with different skin pigmentation may live in different sociocultural conditions. No study to date has examined the interaction between measured skin pigmentation and birth weight in relation to later sequelae in a relatively homogeneous ethnic group where genetic associations can be examined free of cultural confounding.

Candidate genes that may modify the association between low birth weight and blood pressure include those that meet the following four criteria: (1) have relevant biological functional effects; (2) are related

Table 1 Characteristics of subjects at birth and at adolescent follow-up in 2002–4

	Males (n = 470)	Females (n = 203)	All subjects (n = 673)
Birth weight in 1988 or 1989 (g)*	3338 (702)	2867 (757)	3204 (743)
Age in 2002–4 (years)	14.43 (0.65)	14.52 (0.62)	14.45 (0.64)
Cutaneous melanin in 2002–4 (%)	1.47 (1.53)	1.77 (1.51)	1.56 (1.53)
Systolic blood pressure in 2002–4 (mm Hg)	109.6 (10.7)	108.4 (10.5)	109.2 (10.7)
Diastolic blood pressure in 2002–4 (mm Hg)	55.7 (6.3)	58.0 (6.5)	56.4 (6.5)
Height in 2002–4 (cm)	166.8 (8.4)	159.6 (6.3)	164.4 (8.4)
Weight in 2002–4 (kg)	59.1 (14.0)	56.6 (11.4)	58.4 (13.3)

Values are mean (SD) (ie, sample mean (sample SD)).
*Birth weight (SD) for the entire eligible sample (n = 1443) was 3160 (798) for males and 2769 (763) for females.

to cardiovascular or metabolic outcomes; (3) are related to birth size or modify the association between birth size and adverse outcomes; (4) are related to skin pigmentation or differ across racial groups with differing skin pigmentation. In this report, we have focused on polymorphisms of the eight genes shown in table 2. Detailed information is provided in the Appendix, but genes that met our criteria were (i) angiotensin I-converting enzyme (ACE),[14–19] (ii) AGT,[20–24] (iii) apolipoprotein E (APOE),[25–27] (iv) paraoxonase 2 (PON2) polymorphism,[28 29] (v) proinsulin converting enzyme 1 (PC1),[30–34] (vi) proopiomelanocortin (POMC),[35–37] (vii) 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2)[38–41] and (viii) corticotropin-releasing hormone (CRH).[42–47]

The three cortisol-related genes (POMC, CRH, 11β-HSD2) are of particular interest because there has been accumulating evidence since the inception of this study that glucocorticoids and the underlying hypothalamic–pituitary–adrenal (HPA) axis may account for at least part of the observed birth weight–blood pressure associations.[48 49]

We have previously reported an inverse association between birth weight and childhood blood pressure in a follow-up of predominantly caucasian infants.[50 51] There are unlikely to be major socioeconomic differences associated with skin pigmentation. We aimed to examine how the birth weight–blood pressure association varied by skin pigmentation. Further, we aimed to examine how the birth weight–blood pressure association varied by selected genetic polymorphisms, particularly those involved in cortisol-related pathways.

METHODS

Subjects

During the years 1988–1995, 10 569 children were recruited soon after birth into the Tasmanian Infant Health Study, which had been established to investigate sudden infant death syndrome.[52] The selection of eligible singleton subjects was based on scores allocated for each of six risk factors for sudden infant death syndrome (young maternal age, male infant, low birth weight, month of birth, maternal intention to bottle feed, and duration of the second stage of labour).[52] Cohort eligibility was automatic for multiple births. Of the 1498 eligible infants born during 1988 or 1989 in southern Tasmania (a defined geographical region), 1443 (96.3%) were recruited into the Tasmanian Infant Health Study. They included 1283 singletons, of whom 1028 were traced to the enrolment list of a school in southern Tasmania in 1996 (1988 cohort) or 1997 (1989 birth cohort), and 779 participated in follow-up studies during those years.[51 53] In 2002, 87.5% (682/779) of the participants in 1996–7 were retraced in adolescence to an address in southern Tasmania, and 98.7% (673/682) of those retraced subsequently participated in this further study. They represented 52.5% (673/1283) of the total pool of eligible singletons in the 1988 and 1989 birth cohorts.

This study was approved by the Human Research Ethics Committee (Tasmania), and parental written consent was obtained.

Measurements

At birth or early infant life

Routinely collected obstetric data (gestational age in completed weeks, placental weight, birth weight, crown-to-heel length, head circumference) were extracted from the infant's hospital records at birth. Secondly, the study nurses administered a questionnaire to their mothers in an in-hospital interview soon after birth, and direct measurements of the infants were made at that time.[52]

In childhood

Children who provided informed consent underwent measurements of anthropometrics, blood pressure, blood chemistry and lifestyle factors at follow-up in 1996 or 1997.[51 53]

In adolescence

Blood pressure was measured three times using a Critikon Dinamap Adult/Pediatric Vital Signs Monitor or was determined elsewhere. Weight was measured without shoes or heavy clothing using bathroom scales that were calibrated daily using known weights. Skin reflectance was measured using a Minolta spectrophotometer at the upper inner arm, a site exposed to relatively little sun. The reflectance readings at wavelengths of 400 nm and 420 nm were used to calculate the percentage concentration of cutaneous melanin at that site using the method described in detail elsewhere.[54]

Genetic analyses

DNA collection

Duplicate buccal mucosa swabs were collected by brushing inside the cheek with Gentra PureGene (Gentra Systems, Minneapolis, MN, USA) collection brushes which were placed in lysis solution immediately afterwards. In total, 671 samples were collected, but DNA quality and quantity was not adequate in some samples (table 2).

Genotyping

A conservative substitution in the CRH promoter at position +1273 (CRH+T1273C) was detected as described by Gonzalez-Gay *et al*.[55] Single base substitutions (A to G in the PON2 gene at codon 148 (PON2 Ala148Gly); C to T at codon 235 of the AGT gene (AGT Met235Thr); A to C at codon 121 in plasma cell membrane glycoprotein PC1 (PC1 Lys121Gln)) were detected as described by Hegele *et al*,[28] Russ *et al*[56] and Kubaszek *et al*,[33] respectively. Two substitutions (C to T at codon 112 and C to T at codon 158 in APOE (APOE Cys112Arg, Cys158Arg)) were detected as described by Ossendorf and Prellwitz.[57] For the ACE gene, the insertion/deletion alleles (ACE I/D) in intron 16 were detected as described by Chiu and McCarthy.[58] The POMC insertion/deletion alleles at exon 3 (POMC I/D), described by Morris *et al*,[59] were amplified using a Hex-labelled forward primer, POMCF 5′-AGTACGTCATGGGCCACTTC-3′, and an unlabelled reverse primer, POMCR 5′-CATGGAGTAGGAGCGCTTG-3′. Products were then sized on an ABI PRISM 310 Genetic Analyser

Table 2 Mean levels of birth weight, systolic blood pressure (SBP) and melanin density of adolescent subjects classified by genotype

Genotype	No of subjects	Birth weight (g)	SBP (mm Hg)	Cutaneous melanin (%)
Angiotensin 1-converting enzyme insertion/deletion (ACE I/D)				
D/D	190	3203 (51)	110.8 (0.74)	1.48 (0.11)
I/D	308	3157 (40)	109.4 (0.57)	1.46 (0.09)
I/I	144	3269 (58)	109.7 (0.84)	1.66 (0.13)
Linear trend		p = 0.47	p = 0.28	p = 0.31
Angiotensinogen Met235Thr (AGT Met235Thr)				
Met/Met	158	3222 (55)	110.4 (0.80)	1.36 (0.13)
Met/Thr	200	3206 (49)	109.3 (0.71)	1.56 (0.11)
Thr/Thr	65	3222 (87)	108.2 (1.22)	1.67 (0.20)
Linear trend		p = 0.94	p = 0.13	p = 0.14
Apoprotein E (ApoE)				
ε4/ε4	18	3298 (165)	107.5 (2.3)	1.81 (0.37)
ε4/ε3	148	3084 (59)	109.5 (0.8)	1.39 (0.13)
ε4/ε2	16	3057 (181)	117.2 (2.7)	0.77 (0.37)
ε3/ε3	398	3215 (36)	109.8 (0.5)	1.61 (0.08)
ε2/ε2 or ε2/ε3	79	3334 (78)	109.6 (1.1)	1.46 (0.17)
ε2/ε2	4	2851 (374)	109.7 (5.0)	0.63 (0.73)
Difference of means		p = 0.14	p = 0.11	p = 0.13
Paraoxonase 2 (Pon2 Ala148Gly)				
Ala/Ala	365	3185 (38)	109.7 (0.5)	1.55 (0.08)
Ala/Gly	237	3183 (47)	110.5 (0.7)	1.46 (0.10)
Gly/Gly	53	3254 (98)	108.1 (1.4)	1.62 (0.22)
Linear trend		p = 0.66	p = 0.76	p = 0.86
Plasma cell membrane glycoprotein-1 (PC1 Lys121Gln)				
Ala/Ala	487	3228 (32)	109.8 (0.5)	1.52 (0.07)
Ala/Gly	167	3090 (56)	110.0 (0.8)	1.50 (0.12)
Gly/Gly	11	3145 (216)	109.0 (3.0)	1.55 (0.47)
Linear trend		p = 0.04	p = 0.99	p = 0.91
Corticotropin-releasing hormone (CRH+T1273C)				
T/T	527	3195 (31)	109.7 (0.4)	1.49 (0.06)
T/C	107	3169 (69)	110.9 (1.0)	1.55 (0.15)
C/C	10	3069 (229)	111.4 (3.3)	1.97 (0.51)
Linear trend		p = 0.57	p = 0.23	p = 0.42
Proopiomelanocortin exon 3 insertion/deletion (POMC I/D)				
D/D	597	3173 (29)	110.1 (0.4)	1.50 (0.06)
D/I	70	3342 (84)	107.6 (1.2)	1.67 (0.19)
I/I	3	2574 (449)	104.2 (5.5)	2.97 (0.95)
Linear trend		p = 0.24	p = 0.03	p = 0.16
11β-Hydroxysteriod dehydrogenase CA repeat (11β-HSD2{CA}$_n$)				
238+/238+	576	3187 (30)	109.9 (0.4)	1.52 (0.06)
238+/<238	76	3241 (82)	108.8 (1.2)	1.42 (0.18)
<238/<238	6	2756 (310)	120.0 (4.6)	2.69 (0.68)
Linear trend		p = 0.88	p = 0.71	p = 0.67

Values are mean (SE) (ie, sample mean (estimated SE)).

(Applied Biosystems, Foster City, CA, USA). HSD2 CA repeat alleles (11β-HSD2{CA}$_n$) were amplified using a Fam-labelled forward primer, HSDF 5′-GTGTGCAAGATGTGGGTGAC-3′, and an unlabelled reverse primer, HSDR 5′-CCTGCTGAGGAGGGGTACTT-3′. Reaction conditions and sizing were the same as for POMC. The 11β-HSD2{CA}$_n$ microsatellite varied from 230 bp to 248 bp and, by comparison, corresponded to alleles 141–159 bp, as reported by Agarwal *et al*,[60] and with alleles 140–158 bp, as reported by Lavery *et al*.[61] A microsatellite with a low repeat number of 236 bp and below was classified as short and denoted as 11β-HSD2{CA}$_{n = short}$. Reduced allelic repeat length has previously been associated with reduced 11β-HSD2 activity.[38]

We provide the *OMIM reference*,[62] reference NCBI database SNP ID[63] or GenBank accession code[64] for the genetic polymorphisms studied: (i) ACE, *106180*, rs13447447; (ii) AGT, *106150*, rs699; (iii) APOE *107741*, rs429358, rs7412; (iv) PON2, *602447*, rs12026; (v) PC1, *173335*, rs1044498; (vi) POMC, *176830*, rs10654394; (vii) 11β-HSD2, *218030*, GenBank AF071493; (viii) CRH, *122560*, GenBank x67661.

Data analysis

Means and standard deviations of variables were calculated from the original data or, where required, those data rescaled by appropriate transformations. Melanin concentrations were dichotomised at 2% for stratified analyses. This cut-off lies near the median for caucasian adults.[54] The strength of associations between variables are summarised by correlation coefficients and by linear regression coefficients. Linear trend was assessed from the test of the regression coefficient of a

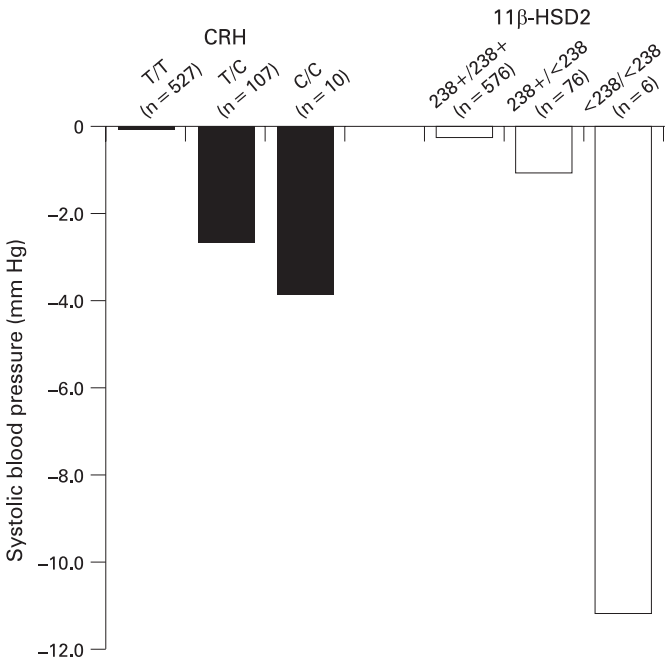

Figure 1 In the regression of adolescent systolic blood pressure (SBP) on birth weight, independently estimated differences in SBP associated with a 1 kg difference in birth weight for subjects classified by CRH and 11β-HSD2 genotype. The interactions between birth weight and the genes expressed on a linear (additive) scale were significant for both CRH ($p = 0.04$) and 11β-HSD2 ($p = 0.01$).

single predictor taking rank scores for ordered categories. In the regression of outcome factors on genotype, a binary (0/1) variable was used to represent each specific genotype other than the most common (reference group) genotype, with trend assessed using a single predictor coded for additive effects—that is, taking consecutive integer scores for genotypes ordered in decreasing frequency of the most common allele.

Regression models included terms for subject age at blood pressure measurement and for cohort selection factors (mother's age, mother's intention to breast feed, duration of second stage labour, and child sex) to remove confounding that selection based on these factors may have introduced. Birth weight, another selection factor, was the main study factor and was included in most analyses. Interaction between birth weight and melanin density, between birth weight and genotype, and between genotypes was assessed from the coefficient and standard error of an interaction term formed from the product of the relevant covariates.[65] An extensive array of questionnaire-based measures of parental, family and domestic factors in infancy and childhood was available to control for confounding by socioeconomic situation.

RESULTS

General characteristics

Table 1 shows subject characteristics. The median of the measurements of cutaneous melanin was 1.5%, and the interquartile range (25th to 75th centile) was 0.3–2.9%. The highest melanin concentration recorded was 5.1%, and 94% (627/667) of the sample had a value less than 4%, consistent with a caucasian population. Similar proportions of boys (188/470) and girls (82/202) had more than 2% melanin in their skin ($p = 0.95$).

Birth weight, melanin density and SBP classified by genotype

Table 2 shows mean levels of birth weight and adolescent SBP for each of the genotypes.

Inverse association between birth weight and SBP in adolescence

In regression models with adjustment for age at examination and cohort selection factors, birth weight was weakly inversely associated with adolescent SBP. An increase in birth weight of 1 kg was associated with a change in SBP of –0.53 mm Hg (95% CI –1.72 to 0.66, $p = 0.33$). After adjustment for current height and weight, a 1 kg increase in birth weight was associated ($p<0.01$) with a change in SBP of –1.87 mm Hg (95% CI–3.01 to –0.73). Associations were similar for boys and girls.

Stronger association of birth weight with SBP in those with darker skin pigmentation

Darker skin pigmentation modified the association between birth weight and adolescent SBP (interaction between birth weight and increasing continuous melanin density, $p = 0.03$). To best illustrate this interaction, we dichotomised the continuous melanin measurements at 2%. For the 40% (267/

Table 3 Jointly estimated differences in systolic blood pressure (SBP) associated with a 1 kg difference in birth weight in the regression of adolescent SBP on birth weight: analysis of interaction effects showing that the change in SBP becomes more negative with darker skin type (≥2% melanin), each additional copy of the CRH+T1273C allele, and each additional copy of the shorter-sized 11β-HSD2{CA}$_n$ microsatellite

	Change in SBP (mm Hg)			
	Before further adjustment		Also adjusted for height and weight in 2002–4	
Predictor	β (95% CI)*	p Value	β (95% CI)*	p Value
Birth weight†	1.49 (–0.20 to 3.18)	0.08	–0.03 (–1.64 to 1.58)	0.18
Birth weight × melanin skin type‡	–2.71 (–4.91 to –0.51)	0.02	–2.64 (–4.70 to –0.57)	0.01
Birth weight × CRH+T1273C¶	–2.17 (–4.41 to 0.08)	0.06	–1.88 (–3.98 to 0.22)	0.08
Birth weight × 11β-HSD2{CA}$_n$§	–2.80 (–5.44 to –0.28)	0.03	–2.42 (–4.83 to –0.00)	0.05

*β (95% CI) = regression coefficient (95% confidence interval) adjusted for cohort selection factors other than birth weight, the age of the subject in 2002–4, melanin skin type (≥2%), C allele for CRH+T1273C and 11β-HSD2{CA}$_{\leq 236}$.
†Estimated difference in SBP per kilogram difference in birth weight for the reference group of subjects with <2% cutaneous melanin, T/T CRH+T1273C genotype and 238+/238+ 11β-HSD2{CA}$_n$ genotype.
‡Estimated additional difference in SBP per kilogram difference in birth weight for subjects with ≥2% melanin.
¶Estimated additional difference in SBP per kilogram difference in birth weight for each copy of the CRH+T1273C allele.
§Estimated additional difference in SBP per kilogram difference in birth weight for each copy of the shorter-sized 11β-HSD2{CA}$_n$ microsatellite.

Table 4 Estimated differences in systolic blood pressure (SBP) associated with a 1 kg difference in birth weight for cutaneous melanin, CRH+T1273C or 11β-HSD2{CA}$_n$ genotype separately in the regression of adolescent SBP on birth weight; effect of adjustment for gestational age

Subjects characterised by	No*	Difference in SBP (mm Hg)†	
		Before further adjustment	Adjusted also for gestational age
Cutaneous melanin			
<2% melanin (lighter)	267	0.42 (–1.06 to 1.89)	1.31 (–0.44 to 3.05)
⩾2% melanin (darker)	400	–2.22 (–3.91 to –0.53)	–1.18 (–3.20 to 0.83)
Interaction	667	–2.64 (–0.54 to –4.74)	–2.49 (–4.59 to –0.39)
CRH+T1273C genotype			
T/T	523	–0.02 (–1.40 to 1.39)	0.78 (–0.94 to 2.50)
T/C	106	–2.62 (–5.31 to 0.06)	–1.77 (–4.44 to 0.89)
C/C	9	–3.82 (–11.22 to 3.59)	–2.30 (–9.95 to 5.36)
Interaction	638	–2.29 (–4.53 to –0.04)	–2.13 (–4.38 to 0.12)
11β-HSD2{CA}$_n$ genotype			
238+/238+	570	–0.24 (–1.53 to 1.04)	0.84 (–0.83 to 2.52)
238+/<238	76	–1.04 (–3.94 to 1.85)	–0.29 (–3.27 to 2.70)
<238/<238	6	–11.19 (–20.41 to –1.97)	–9.82 (–19.11 to –0.52)
Interaction	652	–3.08 (–5.61 to –0.56)	–3.29 (–5.82 to –0.77)

*Number of subjects, which may differ slightly from those given elsewhere because of missing data on one or more of the adjustment factors.
†β (95% CI) = regression coefficient (95% confidence interval) adjusted for cohort selection factors other than birth weight, and for the age of the subject in 2002–4.

667) of subjects with more than 2% melanin, an increase in birth weight of 1 kg was associated with a more than 2 mm Hg reduction in SBP (–2.12 mm Hg (95% CI –3.82 to–0.41). For the remaining 60% (400/667) lighter-skinned subjects with less than 2% melanin, the association was weaker (0.42 mm Hg (95% CI –1.05 to 1.89), and the greater magnitude of the birth weight–SBP association in those with darker skin was significant (difference in effect, $p = 0.01$).

Modification of the birth weight–SBP association by CRH and 11β-HSD2 genotype

With the genotypes expressed on a linear (additive) scale, we found significant interactions between birth weight and these two gene variants in the explanation of SBP: $p = 0.04$ for any C allele for CRH+T1273C × birth weight and $p = 0.01$ for 11β-HSD2{CA}$_{n\,=\,short}$ genotype × birth weight (fig 1). For each of these, the inverse association between birth weight and SBP was strongest for subjects with two copies for the least common alleles (fig 1).

Independent modification of the association between birth weight and SBP by dark skin pigmentation or CRH and 11β-HSD2 genotype

Table 3 shows that the interaction between each of these three factors and birth weight on adolescent SBP persisted when the effects were considered in the same model. This indicates that interaction between birth weight and each of these cortisol-related genes or dark skin pigmentation could not be accounted for by the other interactions. Further adjustment for adolescent weight and height marginally reduced these interactions, with the greatest change occurring in the estimated interaction between birth weight and CRH+T1273C genotype ($\beta = -2.42$, $p = 0.05$ after adjustment).

Additional analyses

We conducted additional analyses to further investigate the potential influence of gestation and socioeconomic confounding on these main findings and we also examined gene epistasis.

Table 4 shows that the patterns observed for a stronger birth weight–adolescent SBP association by darker skin, genotype or 11β-HSD2{CA}$_{n\,=\,short}$ genotype persisted after adjustment for gestation. In addition, there was no evidence of interaction between gestation length and darker skin ($p = 0.17$), CRH+T1273C genotype ($p = 0.87$), or 11β-HSD2{CA}$_{n\,=\,short}$ genotype ($p = 0.45$) with regard to adolescent SBP. Thus gestation did not appear to explain the three interactions observed in table 3.

Melanin density in this sample did not appear to be a marker for socioeconomic status. Darker skin was weakly associated with birth weight ($r = –0.09$, $p = 0.02$) and adolescent SBP ($r = –0.10$, $p = 0.01$) but not with household income ($r = 0.01$, $p = 0.80$), maternal education ($r = –0.04$, $p = 0.27$), the number of persons sharing the household ($r = –0.05$, $p = 0.27$) or the density of persons per room ($r = –0.03$, $p = 0.49$). Nor was it associated with other recorded factors that have been linked to lower socioeconomic status, namely private health insurance, teenage motherhood or paternal unemployment (data not shown.) Similarly, markers of lower socioeconomic status were not associated with the CRH+T1273C variant or 11β-HSD2{CA}$_{n\,=\,short}$ (data not shown). We further adjusted for any maternal antenatal smoking, but this did not alter the results in tables 3 and 4.

Because both CRH and 11β-HSD2 are part of signalling via the HPA axis, we hypothesised that there may be gene–gene interaction, but this was not evident (data not shown).

DISCUSSION

In this follow-up study, we tested the hypothesis that the relationship between birth weight and adolescent SBP in a caucasian sample differs by skin pigmentation and associated candidate genotypes. We found that the relationship between birth weight and adolescent blood pressure was modified by three factors: greater skin pigmentation of the upper inner arm (⩾2% melanin), the C allele of the CRH+T1273C allele, and short allele of the 11β-HSD2{CA}$_n$ microsatellite.

Markers of lower socioeconomic status were not associated with skin pigmentation or CRH+T1273C or 11β-HSD2{CA}$_n$

genotype, reducing the likelihood that these factors were markers of an adverse sociocultural environment that, in itself, may contribute to the birth weight–blood pressure association. Similarly, maternal antenatal smoking was not associated with these three characteristics, and adjustment for antenatal smoking did not alter the study findings in tables 3 and 4. Further, as shown by the lack of association of these genes with melanin concentration, CRH+T1273C and 11β-HSD2{CA}$_n$ genotype did not appear to be antecedents of skin pigmentation in this caucasian sample. The lack of association of ACE I/D and AGT Met235Thr with blood pressure is surprising, and suggests that the influence of these genes on blood pressure is via a pathway that is not associated with skin pigmentation.

The strengths of this study were: the sample was drawn from a relatively homogeneous caucasian population, reducing problems related to population stratification; the range of study measurements was comprehensive; the design was prospective. Because adjustment for adolescent weight may be inappropriate when studying the effect of birth weight on later outcomes if the putative effect is mediated by child growth or weight,[66] results were provided without adjustment for child size, and further results with adjustment for adolescent height and weight were supplied as supplementary analyses.

Limitations of this study include the inability to assess the influence of darker skin pigmentation across a wider range of skin types, thus these results cannot be extrapolated beyond a caucasian population. Further, owing to the sample size and predominance of males and the analytical aim of assessing interactions, we were not able to examine in detail sex-specific effects, which may be important. However, no differences in the birth weight–blood pressure association were observed between females and males.

The findings in relation to CRH+T1273C and 11β-HSD2{CA}$_n$ genotype add to the growing evidence that glucocorticoids, mineralocorticoids and the underlying HPA axis may account for at least part of the observed birth weight–blood pressure associations.[48 67]

Fetal exposure to cortisol is thought to reset the developing HPA axis, leading to raised cortisol in the offspring.[67] Growth-restricted infants have higher cord blood cortisol,[68] with increased HPA activity found in adulthood.[49] In Jamaican children, a strong dose–response between fasting plasma cortisol and SBP at age 8–9 has been reported.[48] Little work has been published on the effect of T to C polymorphism in the CRH promoter, and it has only recently been established that CRH reactivity varies between the promoter alleles.[42] However, a possible link to dysregulated HPA activity exists.[44] 11β-HSD2{CA}$_n$ genotype is linked to increased cortisol signalling in mineralocorticoid-sensitive tissues.[38] Given that both CRH and 11β-HSD2 genes are involved in cortisol-related pathways, we assessed epistasis between the two gene variants, but gene–gene interaction was not evident. Increasing the likelihood that the cortisol-related pathways are important, a third gene polymorphism, the I allele of POMC, was associated with lower blood pressure (table 2), consistent with the known effects of the POMC I form being associated with reduced adrenocorticotrophin-related hypertension.[69]

Our findings suggest that the inverse association between birth weight and adolescent SBP varies by genotype. In particular, genes pertaining to cortisol-related pathways and skin pigmentation appeared important in this caucasian adolescent population. A strength of this study was that we had available a range of markers of socioeconomic status with which to evaluate potential sociocultural confounding, but a limitation is that non-caucasian populations were not studied. The findings have added to other evidence that cortisol-related pathways may at least partly underlie the inverse association between size at birth and later blood pressure.

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APPENDIX

Table AI Selected gene variants of interest in relation to skin pigmentation, birth weight and blood pressure

	Gene (OMIM* reference)							
	ACE Chr17q23 (106180)	**AGT Chr1q42-q43 (106150)**	**ApoE Chr 19q13.3 (107741)**	**PON2 Chr 7q21.3 (602447)**	**PC1 Chr 6q22q-23 (173335)**	**POMC Chr 2p23.3 (176830)**	**11β-HSD2 Chr 16q22 (218030)**	**CRH Chr 8q13 (122560)**
Name of measured polymorphism	ACE I/D, 288 bp insertion (I)/ deletion (D) in intron 16	AGT Met235Thr	APOE ε2, ε3, or ε4 ε2 = 112Cys/ 158Cys ε3 = 112Cys/ 158Arg ε4 = 112Arg/ 158Arg	PON2 Ala148Gly	PC1 Lys121Gln	POMC I/D, 9 bp insertion (I) or deletion (D) in exon 3	11β-HSD2$\{CA\}_n$ repeat with short alleles $\leqslant$236 bp	CRH+T1273C in 5′UTR promoter
(Reference NCBI database SNP ID or GenBank Accession Code)	(rs13447447)	(rs699)	Cys112Arg (rs429358) Arg158Cys (rs7412)	(rs12026)	(rs1044498)	(rs10654394)	(GenBank AF071493)	(GenBank x67661)
Functional effect of genetic variant	Circulating ACE levels highest in ACE D/D subjects, twice that of ACE I/I and intermediate in ACE I/D[14 15]	Met235Thr changes AGT gene expression and linked hypertension in some populations. Thr235Thr is the ancestral form, advantageous in salt scarcity[20]	APOE variants influence the efficiency and type of lipoprotein carriage. The most common (wild-type) = ε3/ε33, with ε4 allele associated with higher serum cholesterol[25]	PON2 hydrolyses the products of LDL oxidation, related to HDL-associated cardioprotection. Gly148Gly associated with higher mean fasting plasma glucose[28]	Allelic variants change insulin signalling at the site of the insulin receptor. Variants that upregulate PC1 inhibit insulin receptor activity[30]	POMC gene inactivation is associated with reduced ACTH and MSH production. The exon 3 insertion is associated with a loss of POMC function with I/D having 24% higher insulin than D/D and also lower insulin sensitivity[35]	The 11β-HSD2 gene controls enzyme activity for the breakdown of cortisol and related products. Defects in function result in higher circulating glucocorticoids. Short alleles are associated with fewer CA(n) repeats and reduced enzyme activity[38]	It has only recently been established that CRH reactivity varies between promoter alleles.[42] Psychotropics can inhibit the CRH gene,[43 44] so a possible link to dysregulated HPA activity exists
Association between genetic variant and disease	I/D ↑ insulin resistance, ↑ cardiovascular disease risk, especially in those with diabetes[16 17]	Thr235Thr is related to salt-sensitive hypertension[21]	ε4 allele is associated with adverse dyslipidaemia, particularly if ε4/ε4 (familial dyslipidaemia type V)[26]	Various PON2 variants are associated with CHD risk, Gly148Gly alleles associated with higher plasma glucose levels among diabetics[28]	121Gln Variant associated with altered insulin and plasma glucose after oral glucose test.[31] 121Gln Variant associated with primary insulin resistance in Indians and childhood obesity[32]	POMC inactivation is associated with early onset obesity, adrenal insufficiency and altered pigmentation[36]	Essential hypertension[39] and salt-sensitive hypertension[40] associated with reduced 11β-HSD2 activity	HPA activation by CRH is implicated in stress-induced hypertension and cortisol-related hypertension[45]
Association between genetic variant and perinatal factors	In low birth weight, ACE I → ↑ adult insulin secretion[18]	Thr235 allele associated with plasma triglycerides in neonates in Trinidad[22]	Effect of APOE genotype on LDL levels was found to be greater in low-birthweight babies[25]	Ala148Ala genotype associated with low birth weight in South Asians[29]	In a Finnish birth cohort, 121Gln allele was associated with type 2 diabetes in babies of low length (<49 cm) but not among longer infants[33]		Reduced 11β-HSD2 is associated with low birth weight and hypertension[41] Positive correlation between placental HSD11B2 activity and birth weight[41]	High CRH levels at 26 weeks' gestation are associated with subsequent preterm delivery[46]
Association between genetic variant and race or skin pigmentation	Conflicting results. ACE D allele over-represented in Afro-Caribbean compared with caucasians[19]	Thr235 allele more common in dark skin races.[23 20] M more common in white than Japanese[24]	ε4 allele is associated with a "thrifty" genotype re food scarcity. In Europeans, more common for higher latitude[27]	Not reported	121Gln variant higher in Asians than caucasians. Prevalence also high in Dominican republic[34]	POMC loss-of-function mutations result in a loss of pigmentation[37]	Skin melanogenesis, stimulated by glucocorticoids, could be affected by 11β-HSD2 activity because of the build up of cortisol	C gene is ancestral form, with T gene having a higher prevalence in caucasians(0.9) than Africans (0.3)[47]

ACTH, adrenocorticotrophin; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MSH, melanocyte stimulating hormone.