Original Article

OPEN

Rapid increases in infant adiposity and overweight/obesity in childhood are associated with higher central and brachial blood pressure in early adulthood

Laura D. Howe[a,b], Nishi Chaturvedi[c], Debbie A. Lawlor[a,b], Diana L.S. Ferreira[b], Abigail Fraser[a,b], George Davey Smith[a,b], Kate Tilling[a,b], and Alun D. Hughes[c]

Background: Small size at birth and greater BMI in childhood are associated with greater brachial blood pressure (BP) in later life. Aortic (central) BP differs from brachial BP and is more predictive of organ damage and cardiovascular events; the relationship between BMI in childhood and central BP is not known.

Methods: Using data from 3154 people from the Avon Longitudinal Study of Parents and Children, we assessed associations between repeated measures of BMI from birth to age 10 with central and brachial BP at age 17.

Results: Lower BMI at birth (thinness) was associated with greater central and brachial BP. No associations were seen between BMI in early childhood (<7 years) and later BP, but greater BMI from 7 to 10 years was associated with higher BP. Associations were similar for central and brachial SBP and for DBP, and were stronger in males compared with females. The highest BP was seen in participants who were low-birth-weight and overweight or obese at both the end of infancy (age 2) and at the time of BP assessment (age 17); mean central SBP was 104.2 mmHg (SD = 11.0) compared with 100.7 (SD = 10.5) in participants who were normal-birth-weight and overweight or obese at 2 and 17 years.

Conclusion: Small size at birth followed by rapid adiposity gain in infancy and continued overweight/obesity are associated with greater BP in young adulthood. These findings emphasize the importance of maintenance of normal weight in childhood for the prevention of high BP.

Keywords: ALSPAC, blood pressure, cause, epidemiology, life course, obesity, pediatrics

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BP, Blood pressure

INTRODUCTION

The prevalence of obesity in children and adolescents has risen dramatically in the recent decades [1,2], and childhood obesity is now recognized as a major public health challenge. Overweight and obesity in childhood increase the likelihood of overweight and obesity in adulthood [3]. Birth weight and the pattern of subsequent adiposity gain in early life may both be important for later cardiovascular health; there is extensive evidence that low birth weight is associated with higher BP in later life, and it has been suggested that the combination of small size at birth and high BMI in later life is particularly detrimental for cardiovascular health [4–7]. Greater weight or adiposity in childhood is associated with greater brachial blood pressure (BP) in childhood [8,9] and much of the recent rise in BP in children and adolescents has been attributed to increasing rates of overweight and obesity [10]. This trend can be predicted to result in a higher risk of hypertension [11] and coronary heart disease [12] in later life, and existing data show that higher BMI is associated with elevated mortality, including death from cardiovascular disease, in adolescents [13,14].

Existing studies investigating the influence of childhood growth or adiposity on later BP have almost exclusively used brachial measures of BP. Brachial BP predicts cardiovascular events [15]; however, brachial BP exceeds aortic (central) SBP by a variable extent [16]. The magnitude of the difference in adults is highly variable [17], but typically, differences between brachial and central pressure tend to be even greater in younger, fit people [18–20]. Noninvasive estimates of central BP are more closely correlated with target organ damage [21] and may be better predictors of future cardiovascular events than brachial BP [22]. The association of BMI throughout childhood with central BP has not been studied. We therefore assessed the relationship between BMI across infancy and childhood with central BP measured at age 17 years, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). We also tested the hypothesis that low birth weight

Journal of Hypertension 2014, 32:1789–1796

[a]MRC Integrative Epidemiology Unit at the University of Bristol, UK, [b]School of Social and Community Medicine, University of Bristol, Bristol and [c]National Heart and Lung Institute, Imperial College London, London, UK

Correspondence to Laura D. Howe, MRC Integrative Epidemiology Unit at the University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK. Tel: +44 117 3310134; e-mail: Laura.Howe@Bristol.ac.uk.

Received 19 January 2014 **Revised** 12 May 2014 **Accepted** 12 May 2014

DOI:10.1097/HJH.0000000000000269

followed by rapid weight gain in childhood is associated with higher BP.

METHODS

Avon Longitudinal Study of Parents and Children

Avon Longitudinal Study of Parents and Children is a population-based birth cohort that recruited pregnant women residing in the former county of Avon, South West England, with an expected delivery date between 1st April 1991 and 31st December 1992 [23,24]. In this study, 14 541 women were enrolled, with 14 062 children born. Full details of the cohort, including a fully searchable data dictionary, are available on the study website: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval was obtained from the ALSPAC Law and Ethics committee and local ethics committees.

Blood pressure measurements

Blood pressure was measured at clinic when participants were approximately 17 years old (mean age 17.8 years). Brachial BP was measured using an automated device validated in children and adolescents (705IT; Omron, Kyoto, Japan) [25]. Arm girth was measured and appropriate cuff sizes used according to the manufacturer's instructions. Central SBP was measured by radial artery applanation tonometry (Sphygmocor; Atcor, West Ryde, Australia) calibrated using brachial BP. While augmentation index was measured, it was not analysed since the majority of participants had negative augmentation indices and under these circumstances it cannot be used as a valid measure of reflection [26].

Childhood growth data

Length (before age 2 years), height (after age 2 years) and weight data for the participants were obtained from several sources. Birth length (crown-heel) was measured by the ALSPAC staff who visited newborns soon after birth (median 1 day, range 1–14 days), using a Harpenden Neonatometer (Holtain Ltd., Crymych, Pembs, UK) Birth weight was extracted from the medical records. From birth to 5 years, length and weight measurements were extracted from health visitor records, which form part of the standard child care in the UK. In this cohort, up to four measurements were taken, on average at 6 weeks, 10, 21, and 48 months of age; previous work has shown these measurements to have good accuracy [27]. For a random 10% of the cohort, length/height and weight measurements were made at research clinics held between the ages of 4 months and 5 years. From age 7 years upwards, all children were invited to annual clinics. Details of measuring equipment used in the clinics are in the supplementary material. Across all ages, parent-reported child heights and weights were also available from questionnaires. BMI was calculated as weight (kg) divided by height squared (m^2). All available growth measurements were used to model growth trajectories, using multilevel models as described previously [28,29].

Multilevel models are an appropriate tool for the analysis of longitudinal data, since they account for repeated measurements within people, and can estimate a full trajectory for each person with one or more measurement under a missing at random assumption [28,30,31]. Such models estimate the average pattern of growth, as well as each person's trajectory. They also take account of the change in scale and variance of BMI over time and the differential measurement error in clinic and parent-reported measurements of height and weight. Full details of the methodology used to develop the growth trajectories are available elsewhere [28,29]. Briefly, participant trajectories of height and weight between birth and 10 years were estimated using multilevel linear spline models (two levels: measurement occasion and individual), fitted using the runmlwin command [32] in Stata version 12 [33], which calls the MLwiN program [34]. Previous work has demonstrated that models estimating different linear growth rates between 0 and 3 months, 3 months and 1 year, 1 and 3 years, 3 and 7 years, and 7 and 10 years fit the observed data well in this and other cohorts [28], and provide interpretable summaries of the pattern of growth across childhood. Interaction terms model the differences in birth size and growth rates between males and females. Person-level random effects describe how each child's birth size and rate of growth in each linear spline period differs from the average. Trajectories were not modelled beyond the age of 10 years since puberty would necessitate individual spline points due to variation in age at onset of puberty, and in order to give an appropriate time separation between our exposure (childhood BMI) and our outcome (BP at age 17), as is appropriate in a prospective study. We use the height and weight trajectories to predict participants' heights and weights at the end of each linear spline period, that is, birth, 3 months, 1, 3, 7 and 10 years, and calculate BMI for each of these ages. These predicted BMI measurements were converted to z-scores by subtracting the mean and dividing by the SD, separately by sex.

Other variables

We considered maternal age (extracted from obstetric records), education, pre-pregnancy BMI and parity (all self-reported in an antenatal questionnaire) as the key potential confounders. Maternal education was categorized into four levels: below the level equivalent to today's UK General Certificate of Secondary Education (GCSE), to GCSE, above GCSE, but below the university degree or university degree or above.

Statistical analysis

A total of 5081 participants attended the research clinic at 17 years. Of these, brachial and central BP were measured for 3974 participants, because the equipment was not available at the start of the clinic. We restricted our analyses to participants with data on at least one measure of BMI in childhood, and all potential confounders, giving a final sample size of 3154.

We used linear regression to assess the association between each predicted BMI z-score (birth, 3 months, 1, 3, 7 and 10 years) and each measure of BP (brachial and central systolic and brachial diastolic). Analyses were initially adjusted for sex and age at BP assessment. We subsequently adjusted for all potential confounders,

including earlier BMI measurements (e.g. BMI at 1 year was adjusted for BMI at birth and 3 months, but not for later measures). Finally, we further adjusted analyses for BMI at the time of BP assessment in order to assess whether any associations between early childhood BMI and later BP were mediated by contemporary BMI. We assessed whether there was any evidence of sex interactions in these associations.

As a sensitivity analysis to confirm the validity of using the multilevel models to predict BMI, we repeated our main analysis using observed BMI measurements instead of those predicted from the multilevel models of weight and height.

Given the postulated influences of low birth weight and rapid BMI gains in infancy on later BP, we wished to test various hypotheses about the ways in which body size across infancy and childhood could influence later BP, using the methodology proposed by Mishra *et al.* [35]. We defined three key ages as birth, age 2 (the end of infancy, i.e. the time during which rapid BMI gains are thought to be particularly harmful) and age 17 (the same time as BP was measured). For each age, a binary indicator of body size was created: low (bottom third) or normal (top two-thirds) birth weight, normal BMI or overweight/obese at 2 years and normal BMI or overweight/obese at 17 years. BMI at 2 years was predicted from the multilevel models as detailed above, and BMI at 17 years was measured in the research clinic. Overweight/obesity at 2 and 17 years was defined according to age and sex-specific thresholds [36]. Using these binary measures of body size at birth, 2 and 17 years, participants were separated into eight groups (each potential combination of low/normal birth weight, overweight/normal BMI at 2 years, overweight/normal BMI at 17 years). We used these eight groups to test the following hypotheses regarding size at birth, 2 and 17 years:

1. Accumulation, equal effects: low birth weight, overweight/obesity at age 2 and overweight/obesity at age 17 all have the same magnitude of association with BP at age 17.
2. Accumulation, differing effects: low birth weight, overweight/obesity at age 2 and overweight/obesity at age 17 each influence BP at 17 with differing magnitudes.
3. Critical period at age 17: overweight/obesity at 17 years is the only body size measure associated with BP at 17.
4. Mobility between birth and 2 years: overweight/obesity at age 17 is associated with BP at age 17, and there is an additive effect of moving from low birth weight to overweight/obese at age 2. In this model, low birth weight and overweight/obese at age 2 only contribute if the participant experiences both.
5. Mobility between birth and 17 years: overweight/obesity at age 17 is associated with BP at age 17, and there is an additive effect of moving from low birth weight to overweight/obese at age 17. In this model, low birth weight only contributes if the participant is overweight/obese at age 17; overweight/obese at age 2 does not contribute.
6. Persistent risk: overweight/obesity at age 17 is associated with BP at age 17, and there is an additive effect of moving from low birth weight to overweight/obese at both ages 2 and 17. In this model, low birth weight and overweight/obese at age 2 only contribute if both are experienced in addition to overweight/obese at age 17.

In order to evaluate these alternative hypotheses, we fit a series of nested linear-regression models and used likelihood ratio tests to compare each model with a fully saturated model (including body size at all ages and all possible interaction terms); large P values from these tests indicate that the simpler, nested model adequately describes the data, that is, a large P value supports the hypothesis. Additionally, we present the rout mean standard error (RMSE) for each model; this is a test of model fit with lower values indicating better fit. We also used each model to predict the mean BMI and BP in each group, and compared these with the observed values to provide evidence of which model was the closest match to the data. Due to the small number of participants in some groups, sex differences in these associations were not assessed.

RESULTS

Participants who attended the 17-year clinic tended to have higher birth weight, lower BMI from age 1 year onwards, and mothers with higher educational status, older age, lower BMI and lower parity than ALSPAC participants who did not attend this clinic (Supplementary Table 1, http://links.lww.com/HJH/A364). Amongst participants who attended the 17-year clinic, those excluded from our analyses due to missing data on childhood growth or confounders tended to have higher BMI than participants included in our analyses, but no differences were observed in terms of BP (Supplementary Table 2). The growth trajectory models fit the observed data well (Supplementary Table 3), and almost all (99%) participants had at least four weight and height measurements.

Mean central SBP was lower than mean brachial SBP and this difference was greater in males (Table 1). For all measures of BP (central and brachial SBP and DBP), greater BMI at birth was associated with lower BP (Table 2). There was little convincing evidence of an association between BMI at birth and prior to age 7 and BP at age 17, but there was a clear positive association between BMI at age 7 and 10 years and central and brachial BP at age 17 years.

The magnitude of associations between childhood BMI and central or brachial SBP was broadly similar with associations being slightly stronger for brachial SBP at all ages, but with overlapping confidence intervals (CIs) providing no statistical evidence of differences. Associations tended to be weaker with DBP. Whereas growth trajectories were similar by sex (Supplementary Table 1), from age 7 years onwards, associations between BMI and BP were markedly stronger in males than females; for example, a 1 SD (z-score) increase in BMI at age 10 was associated with 4.2 mmHg (95% CI 3.1–5.3) higher central SBP in males compared with 2.5 mmHg in females (95% CI 1.4–3.5) (P for gender interaction = 0.03; Table 2).

Associations between BMI across childhood and BP at age 17 were broadly similar in analyses adjusted only for age at BP assessment and in analyses further adjusted for

TABLE 1. Characteristics of participants included in our analyses

	Overall ($N = 3154$)	Males ($n = 1421$)	Females ($n = 1733$)
Maternal education			
Less than O-level	566 (18.0%)	239 (16.8%)	327 (18.9%)
O-level	1080 (34.2%)	466 (32.8%)	614 (35.4%)
A-level	903 (28.6%)	429 (30.2%)	474 (27.4%)
Degree or above	605 (19.2%)	287 (20.2%)	318 (18.4%)
Maternal pre-pregnancy BMI (kg/m^2)	22.83 (3.69)	22.88 (3.66)	22.78 (3.71)
Maternal age (years)	29.42 (4.59)	29.58 (4.62)	29.29 (4.55)
Maternal parity	0.74 (0.87)	0.73 (0.87)	0.75 (0.87)
Birth weight (kg)	3.42 (0.53)	3.49 (0.57)	3.37 (0.48)
BMI at birth (kg/m^2)[a]	13.12 (1.46)	13.11 (1.58)	13.12 (1.36)
BMI at 3 months (kg/m^2)[a]	16.29 (1.47)	16.65 (1.55)	15.99 (1.33)
BMI at 1 year (kg/m^2)[a]	17.61 (1.40)	17.81 (1.38)	17.44 (1.39)
BMI at 3 years (kg/m^2)[a]	16.10 (1.12)	16.24 (1.06)	15.99 (1.15)
BMI at 7 years (kg/m^2)[a]	15.63 (1.52)	15.57 (1.41)	15.68 (1.61)
BMI at 10 years (kg/m^2)[a]	17.61 (2.57)	17.35 (2.41)	17.82 (2.68)
BMI at 17 year clinic (kg/m^2)	22.67 (3.96)	22.38 (3.62)	22.91 (4.21)
Age at 17 year clinic (years)	17.76 (0.36)	17.75 (0.36)	17.76 (0.37)
Central SBP at 17-year clinic (mmHg)	96.95 (9.34)	100.29 (8.82)	94.22 (8.85)
Brachial SBP at 17-year clinic (mmHg)	116.76 (11.63)	122.51 (10.89)	112.05 (9.99)
Amplification of brachial SBP at 17-year clinic (mmHg)[b]	19.8 (4.7)	22.2 (4.5)	17.8 (4.0)
DBP at 17-year clinic (mmHg)	64.58 (7.51)	64.33 (7.46)	64.78 (7.54)

Values are mean (SD) or number (percentage).
[a]Predicted from multilevel models of height and weight.
[b]Brachial–central SBP.

potential confounders, including earlier BMI measures (Table 2 and Supplementary Table 4). After adjustment for BMI at age 17, associations between childhood BMI and BP were attenuated, suggesting that mediation by continued adiposity is an important pathway in associations between childhood BMI and later BP (Supplementary Table 4). A similar overall pattern of association was also seen when using observed measures of BMI instead of those predicted from the multilevel model (Supplementary Table 5).

When separating participants into eight mutually exclusive groups defined by being in the bottom versus middle or top-thirds of birth weight, and being overweight or obese versus normal or low BMI at ages 2 and 17 years, the groups with the highest observed BMI at age 17 were those who went from the middle or top-third of birth weight to being overweight or obese at both 2 and 17 years [group N-O-O in Table 3, $N = 125$, mean (SD) BMI 29.3 (4.4) kg/m^2]. The mean (SD) central SBP in this group was 100.7 (10.5) mmHg. Despite having a slightly lower mean BMI at age 17 [28.3 (3.5) kg/m^2], participants who moved from the lowest third of birth weights to being overweight or obese at both 2 and 17 years had a higher central SBP (group L-O-O in Table 3, $N = 32$, mean = 104.2 mmHg, SD = 11.0). Testing the various hypothesized ways in which the combination between size at birth and overweight/obesity at 2 and 17 years could influence BP, the data were most compatible (largest P value and closest agreement between observed and predicted central SBP) with the 'persistent risk' model; this model specifies that BMI at age 17 influences BP and that there is an additional effect on BP from being in the lowest third of birth weight and being overweight/obese at both 2 and 17 years. The RMSE, however, did not reveal substantial differences in model fit across the various models. Similar results were observed for brachial SBP and DBP; for these BP measures, larger P values supported other hypothesized models, but the closest match between observed and predicted BP measurements was for the 'persistent risk' model (Supplementary Tables 6 and 7).

DISCUSSION

We show that BMI at birth and BMI later in childhood have distinctive associations with central BP in young adulthood. Low BMI at birth was associated with higher central (and brachial) BP, whereas higher BMI from age 7 onwards was associated with higher BP; this latter relationship was stronger in males than in females. This finding mirrors a systematic review of studies examining BMI in childhood with coronary heart disease in adulthood, which found that the association did not emerge until age 7 [12]. Those who had low birth weight and then became obese or overweight at age 2 and maintained this status throughout childhood had the highest BP, despite having lower BMI at age 17 than other obese or overweight young adults. We did not observe differences in BP between participants who were in the lowest versus middle/top third of birth weights, normal BMI at age 2 and overweight/obese at age 17. This may suggest that any detrimental effect of low birth weight combined with later obesity is most marked in to those who experience rapid weight gain in infancy and become obese at an early age.

Non-invasive estimates of central BP are more strongly associated with target organ damage [21] and there is some evidence that they are better predictors of future cardiovascular events than brachial BP [22]. The association of BMI throughout childhood with central BP has not been studied. Despite differences between brachial and central BP, which may have important implications for the definition of hypertension in children, our analyses demonstrate similar associations between BMI in childhood and

TABLE 2. Associations between BMI in childhood and blood pressure measured at age 17 years ($N = 3154$)

BMI z-scores at each age	Brachial SBP (mmHg)			Central SBP (mmHg)			DBP (mmHg)		
	Females ($n = 1733$)	Males ($n = 1421$)	*P* interaction[a]	Females ($n = 1733$)	Males ($n = 1421$)	*P* interaction[a]	Females ($n = 1733$)	Males ($n = 1421$)	*P* interaction[a]
Adjusted for child's age at outcome assessment and confounders[b] including previous body size measures									
Birth	−0.7 (−1.2 to −0.2) $P = 0.004$	−0.6 (−1.2 to −0.02) $P = 0.04$	0.82	−0.7 (−1.2 to −0.3) $P = 0.001$	−0.5 (−0.9 to 0.02) $P = 0.06$	0.70	−0.4 (−0.8 to −0.02) $P = 0.04$	−0.3 (−0.7 to 0.1) $P = 0.22$	0.80
3 months	0.2 (−0.3 to 0.8) $P = 0.39$	0.5 (−0.1 to 1.2) $P = 0.12$	0.60	0.04 (−0.4 to 0.5) $P = 0.87$	0.4 (−0.1 to 0.9) $P = 0.14$	0.27	0.1 (−0.3 to 0.5) $P = 0.71$	0.1 (−0.4 to 0.5) $P = 0.77$	0.92
1 year	0.2 (−0.4 to 0.8) $P = 0.50$	0.1 (−0.6 to 0.8) $P = 0.71$	0.78	0.03 (−0.5 to 0.5) $P = 0.92$	−0.2 (−0.7 to 0.4) $P = 0.52$	0.81	−0.1 (−0.6 to 0.3) $P = 0.54$	−0.4 (−0.9 to 0.1) $P = 0.10$	0.54
3 years	0.3 (−0.5 to 1.1) $P = 0.45$	0.9 (−0.01 to 1.9) $P = 0.05$	0.44	−0.1 (−0.8 to 0.6) $P = 0.84$	0.4 (−0.4 to 1.1) $P = 0.34$	0.50	−0.1 (−0.7 to 0.4) $P = 0.64$	0.1 (−0.5 to 0.8) $P = 0.73$	0.96
7 years	1.6 (0.9 to 2.3) $P < 0.001$	2.7 (1.9 to 3.5) $P < 0.001$	0.04	1.4 (0.8 to 2.0) $P < 0.001$	2.1 (1.4 to 2.7) $P < 0.001$	0.10	1.1 (0.5 to 1.6) $P < 0.001$	1.2 (0.6 to 1.7) $P < 0.001$	0.66
10 years	2.6 (1.4 to 3.8) $P < 0.001$	4.9 (3.5 to 6.3) $P < 0.001$	0.01	2.5 (1.4 to 3.5) $P < 0.001$	4.2 (3.1 to 5.3) $P < 0.001$	0.03	2.0 (1.1 to 2.9) $P < 0.001$	2.5 (1.5 to 3.5) $P < 0.001$	0.58

[a]*P* interaction tests the null hypothesis that the coefficients are the same for males and females.
[b]Confounders are maternal age, education, pre-pregnancy BMI and parity.

measures of brachial and central BP in early adulthood. Further research is now needed to determine whether brachial and SBP demonstrate differing associations with measures of cardiovascular structure and function in young adults. Our findings with regard to the relationship between birth weight and subsequent BMI in childhood and central and brachial BP are also consistent with previous studies that only measured brachial BP [37–40]. Similarly, previous longitudinal studies of the associations between change in BMI in childhood and brachial BP have also found that the highest levels of BP are observed in participants who move from low birth weight to being overweight/obese in childhood [41,42]. One previous cross-sectional clinic-based study of 149 adolescents aged 10–17 [42] found that central SBP was highest in obese participants who had a history of low birth weight, which is also in keeping with our findings. Typically, brachial SBP is higher than central (aortic) SBP, although this difference tends to diminish with age [18]. The difference between brachial and central SBP in our study was substantial (mean of the difference = 19.8 mmHg) and the difference was greater in young men than women. These observations are very similar to a previous report that measured central BP in a cross-sectional sample that included a relatively small number of people below the age of 20 years [18].

The greater impact of childhood adiposity gain on BP in males compared with females is supported by the findings in adults [43,44]. One potential explanation for our finding is that equivalent adiposity gain, as measured by BMI, may mask sex differences in ectopic fat deposition, particularly visceral fat, which may in turn be a stronger determinant of BP than BMI [2]. However, previous longitudinal analysis in ALSPAC do not show that directly assessed fat mass measured at 9–12 years is more strongly associated with BP at age 15–16 than BMI, although this study examined whole-body fat mass, and not the regional fat patterning [45]. An alternative explanation is that female sex hormones buffer adverse effects of stressors, such as weight gain, on BP. Animal studies show that oestrogen acts on the central oestrogen receptor to protect against renin–angiotensin–aldosterone system over-activation, autonomic dysfunction and hypertension [46,47]. Given the lower rates of hypertension in premenopausal, but not in postmenopausal women compared to men, it is plausible that such a mechanism may also operate in humans.

Key strengths of our study include the availability of brachial and central SBP and DBP on a large population-based birth cohort of 17-year-olds, in contrast to most previous studies that only have brachial BP measurements. We had sufficient numbers to observe sex differences in the impact of BMI change on BP. We were also able to examine the associations of BMI throughout childhood with BP in young adulthood, in contrast to most previous studies that have few measures of childhood BMI. Our statistical methods allowed us to exploit detailed data on childhood BMI to construct growth trajectories, which enable the prediction of BMI measures at the same ages for all children, regardless of when and how often they were measured. This methodology enables all available measures to be included in analyses and therefore reduces the problem of missing data, whilst also taking account of

TABLE 3. Life course models for the association between trajectories of body size and central systolic blood pressure at age 17 ($N = 3154$)

Trajectory of body size[a]				Mean (SD) BMI at 17 years (kg/m^2)	Mean (SD) observed central SBP (mmHg)	Predicted mean (SE) central SBP (mmHg)				
Birth	2 years	17 years	*N*			Accumulation, equal effects	Accumulation, differing effects	Critical period at 17 years	Mobility birth – 2 years	Mobility birth – 17 years	Persistent risk
N	N	N	1498	21.0 (2.0)	95.5 (8.8)	95.5 (0.2)	95.6 (0.2)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)
L	N	N	737	20.8 (2.1)	96.4 (9.4)	97.7 (0.2)	96.2 (0.3)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)
N	N	O	352	28.6 (3.4)	101.5 (9.0)	97.7 (0.2)	101.4 (0.4)	101.5 (0.4)	101.5 (0.4)	101.3 (0.4)	101.3 (0.4)
L	N	O	157	28.6 (3.1)	101.4 (8.5)	100.0 (0.4)	102.0 (0.4)	101.5 (0.4)	101.5 (0.4)	101.9 (0.7)	101.3 (0.4)
N	O	O	125	29.3 (4.4)	100.7 (10.5)	100.0 (0.4)	101.0 (0.5)	101.5 (0.4)	101.5 (0.4)	101.3 (0.4)	101.3 (0.4)
L	O	O	32	28.3 (3.5)	104.2 (11.0)	102.2 (0.6)	101.6 (0.6)	101.5 (0.4)	100.9 (1.0)	101.9 (0.7)	104.2 (1.6)
N	O	N	196	22.2 (1.8)	95.7 (9.0)	97.7 (0.2)	95.2 (0.5)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)	95.8 (0.2)
L	O	N	57	22.0 (1.7)	93.3 (6.8)	100.0 (0.4)	95.8 (0.5)	95.8 (0.2)	95.9 (1.0)	95.8 (0.2)	95.8 (0.2)
P value against the null hypothesis that the model has the same fit as the fully saturated model						<0.001	0.06	0.05	0.03	0.03	0.09
Root mean square error[b]					9.2	9.0	9.0	9.0	9.1	9.0	9.0

[a]L represents the lowest third of birth weight at birth and O represents overweight or obese (defined on age and sex-appropriate cut-offs using the UK 1990 growth reference) at 2 and 17 years. *N* represents the middle or top third of birth weight, and normal or low BMI at 2 and 17 years.
[b]RMSE is a measure of model fit; lower values indicate better fit.

the differential measurement error between measured and parent-reported growth measurements. The models had good fit to the observed data. The pattern of results using raw BMI measurements was similar to those using measurements predicted by our growth trajectory models, providing further reassurance that the use of our growth trajectories was appropriate. In our main analyses, we adjusted each BMI measure for all previous BMI measurements, but not future measures; for example, BMI at 1 year was adjusted for BMI at birth and 3 months, but not for BMI measures after 1 year. This approach is intended to remove the confounding by earlier BMI and shed light on the role of BMI at different ages. In unadjusted models, children with a higher BMI at age 7 are likely also to have had a higher BMI at earlier ages; therefore an unadjusted regression coefficient for BMI at age 7 encompasses all BMI changes prior to age 7. In contrast, when adjusting for previous BMI measurements, the two hypothetical people being compared have the same BMI at birth, 3 months, and 1 and 3 years, and only differ in their BMI change between 3 and 7 years. We use BMI as a measure of adiposity; the appropriateness of BMI in young children has been questioned, but at least from age 9 onwards, it shows similar associations with cardiovascular risk factors to other adiposity measures [45]. Despite our results being consistent with other studies [41,42], our conclusions with respect to the interplay of low birth weight and subsequent adiposity should be tempered by the fact that there were only 32 participants in the group who had low birth weight and were overweight or obese at 2 and 17 years, meaning that statistical power for this comparison was low and we cannot exclude the possibility that this is a chance finding.

Our results provide further evidence for the hypothesis that adiposity gain in childhood is detrimental for later BP. Importantly, we show this influence is evident for central BP, the pressure to which the heart is exposed and which shows a closer correlation with target organ damage and cardiovascular events in later life. We also show that this adverse effect of adiposity gain is worse for boys than girls. The magnitude of the associations we observe is large: the difference in central SBP observed between our lowest risk category (low birth weight, overweight at 2 years, not overweight at 17 years) and our highest risk category (low birth weight, overweight and obese at both 2 and 17 years) is 10 mmHg. In adults, a 20 mmHg difference in SBP is associated with a doubling in cardiovascular disease risk [15]. There is now evidence that overweight children who return to a healthy BMI in later life can, at least to some extent, normalize their cardiovascular risk [45,48], highlighting the importance of interventions to prevent and reverse overweight and obesity in children and young people.

ACKNOWLEDGEMENTS

We are extremely grateful to the families who took part in the study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Funding sources: This work was supported by a UK Medical Research Fellowship (G1002375) to L.D.H. and by a Wellcome Trust grant to A.D.H., D.A.L., G.D.S. and N.C. L.D.H., A.F., G.D.S. and D.A.L. work in a unit that receives funding from the University of Bristol and the UK Medical Research Council (MC_UU_12013/5 and MC_UU_12013/9). The UK Medical Research Council, the Wellcome Trust and the University of Bristol provide core support for ALSPAC. AF is supported by a UK Medical Research Council Fellowship (G0701594).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obesity* 2006; 1:11–25.
2. Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. *Hypertension* 2013; 62:247–254.
3. Abraham S, Nordsiek M. Relationship of excess weight in children and adults. *Public Health Rep* 1960; 75:263–273.
4. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993; 341:938–941.
5. Barker DJP, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* 2002; 31:1235–1239.
6. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. *Hypertension* 2000; 36:790–794.
7. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Early growth and coronary heart disease in later life: longitudinal study. *BMJ* 2001; 322:949–953.
8. Howe LD, Tilling K, Benfield L, Logue J, Sattar N, Ness AR, *et al*. Changes in ponderal index and body mass index across childhood and their associations with fat mass and cardiovascular risk factors at age 15. *PLoS One* 2010; 5:e15186.
9. Tilling K, Davies N, Windmeijer F, Kramer MS, Bogdanovich N, Matush L, *et al*. Is infant weight associated with childhood blood pressure? Analysis of the Promotion of Breast feeding Intervention Trial (PROBIT) cohort. *Int J Epidemiol* 2011; 40:1227–1237.
10. Munter P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA* 2004; 291:2107–2113.
11. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: the Muscatine study. *Pediatrics* 1989; 84:633–641.
12. Owen CG, Whincup PH, Orfei L, Chou Q-A, Rudnicka AR, Wathern AK, *et al*. Is body mass index before middle age related to coronary heart disease risk in later life? Evidence from observational studies. *Int J Obesity* 2009; 33:866–877.
13. Sundstrom J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ* 2011; 342:d643.
14. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, *et al*. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; 373:1083–1096.
15. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903–1913.
16. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, *et al*. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009; 54:375–383.
17. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest* 1992; 102:1193–1198.
18. McEniery CM, Yasmin. Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005; 46:1753–1760.
19. McEniery CM, Yasmin. Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, *et al*. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension* 2005; 46:221–226.
20. Mahmud A, Feely J. Spurious systolic hypertension of youth: fit young men with elastic arteries. *Am J Hypertens* 2003; 16:229–232.
21. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, *et al*. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007; 50:197–203.
22. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; 31:1865–1871.
23. 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.
24. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey SG, *et al*. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013; 42:97–110.
25. Stergiou GS, Yiannes NG, Rarra VC. Validation of the Omron 705 IT oscillometric device for home blood pressure measurement in children and adolescents: the Arsakion School Study. *Blood Press Monit* 2006; 11:229–234.
26. Hughes AD, Park C, Davies J, Francis D, Thom S, Mayet J, *et al*. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. *PLoS One* 2013; 8:e59371.
27. Howe LD, Tilling K, Lawlor DA. Accuracy of height and weight data from child health records. *Arch Dis Childhood* 2009; 94:950–954.
28. Howe LD, Tilling K, Matijasevich A, Petherick ES, Santos AC, Fairley L, *et al*. Linear spline multilevel models for summarising childhood growth trajectories: a guide to their application using examples from five birth cohorts. *Stat Methods Med Res* 2013; doi 10.1177/0962280213503925. [Epub ahead of print].
29. Howe LD, Tilling K, Galobardes B, Smith GD, Gunnell D, Lawlor DA. Socioeconomic differences in childhood growth trajectories: at what age do height inequalities emerge? *J Epidemiol Commun Health* 2012; 66:143–148.
30. Anderson EL, Tilling K, Fraser A, Macdonald-Wallis C, Emmett P, Cribb V, *et al*. Estimating trajectories of energy intake through childhood and adolescence using linear spline multilevel models. *Epidemiology* 2013; 24:507–515.
31. 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 (6 Suppl):1808S–1813S.
32. Leckie G, Charlton C. runmlwin: Stata module for fitting multilevel models in the MLwiN software. Centre for Multilevel Modelling, University of Bristol; 2011.
33. StataCorp. Stata 12.0. Texas: StataCorp; 2011.
34. Rasbash J, Charlton C, Brown WJ, Healy M, Cameron B. MLwiN Version 2.24. Centre for Multilevel Modelling, University of Bristol 2011.
35. Mishra G, Nitsch D, Black S, De SB, Kuh D, Hardy R. A structured approach to modelling the effects of binary exposure variables over the life course. *Int J Epidemiol* 2009; 38:528–537.
36. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320:1240–1243.
37. Holland FJ, Stark O, Ades AE, Peckham CS. Birth weight and body mass index in childhood, adolescence, and adulthood as predictors of blood pressure at age 36. *J Epidemiol Commun Health* 1993; 47:432–435.
38. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000; 320:967–971.
39. Ben-Shlomo Y, McCarthy A, Hughes R, Tilling K, Davies D, Smith GD. Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly Growth Study. *Hypertension* 2008; 52:638–644.

40. Cheung YB, Low L, Osmond C, Barker D, Karlberg J. Fetal growth and early postnatal growth are related to blood pressure in adults. *Hypertension* 2000; 36:795–800.
41. Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, *et al*. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* 1996; 312:401–406.
42. Lurbe E, Carvajal E, Torro I, Aguilar F, Alvarez J, Redon J. Influence of concurrent obesity and low birth weight on blood pressure phenotype in youth. *Hypertension* 2009; 53:912–917.
43. Truesdale KP, Stevens J, Cai J. Effect of 3-year weight history on blood pressure: The Atherosclerosis Risk in Communities Study. *Obesity* 2008; 16:1112–1119.
44. Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the Tromso Study, 1986–1995. *Arch Intern Med* 2000; 160:2847–2853.
45. Lawlor DA, Benfield L, Logue J, Tilling K, Howe LD, Fraser A, *et al*. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. *BMJ* 2010; 341:c6224.
46. Xue B, Pamidmukkala J, Lubahn DB, Hay M. Estrogen receptor-á mediates oestrogen protection from angiotensin II-induced hypertension in conscious female mice. *Am J Physiol Heart Circ Physiol* 2007; 292:H1770–H1776.
47. Johnson MS, DeMarco VG, Heesch CM, Whaley-Connell AT, Schneider RI, Rehmer NT, *et al*. Sex differences in baroreflex sensitivity, heart rate variability, and end organ damage in the TGR(mRen2)27 rat. *Am J Physiol Heart Circ Physiol* 2011; 301: H1540–H1550.
48. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, *et al*. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med* 2011; 365:1876–1885.