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

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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 future 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].

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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., Crymlyn, 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 (m²). 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/obesity at age 2 and overweight/obesity at age 17 years, 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/obese 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 age 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 root 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...
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 moved 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 (SD) BMI 29.3 (4.4) kg/m\(^2\)].

**TABLE 1. Characteristics of participants included in our analyses**

| Maternal education                      | Overall \((N = 3154)\) | Males \((n = 1421)\) | Females \((n = 1733)\) |
|-----------------------------------------|-------------------------|----------------------|------------------------|
| 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 \((kg/m^2)\)              | 13.12 (1.48)            | 13.11 (1.58)         | 13.12 (1.36)           |
| BMI at 3 months \((kg/m^2)\)           | 16.29 (1.47)            | 16.65 (1.55)         | 15.99 (1.33)           |
| BMI at 1 year \((kg/m^2)\)             | 17.61 (1.40)            | 17.81 (1.38)         | 17.44 (1.39)           |
| BMI at 3 years \((kg/m^2)\)            | 16.10 (1.12)            | 16.24 (1.06)         | 15.99 (1.15)           |
| BMI at 7 years \((kg/m^2)\)            | 15.63 (1.52)            | 15.57 (1.41)         | 15.68 (1.61)           |
| BMI at 10 years \((kg/m^2)\)           | 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 \((mmHg)\) | 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).

aPredicted from multilevel models of height and weight.

bBrachial–central SBP.

central SBP: 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)     |             |
| Birth                     | -0.7 (-1.2 to -0.2) | -0.6 (-1.2 to -0.2) | 0.82       |
|                           | P=0.004            | P=0.004            |            |
| 3 months                  | 0.2 (-0.3 to 0.8)  | 0.5 (-0.1 to 1.2)  | 0.60       |
|                           | P=0.39             | P=0.12             |            |
| 1 year                    | 0.2 (-0.6 to 0.8)  | 0.2 (-0.7 to 0.4)  | 0.78       |
|                           | P=0.50             | P=0.87             |            |
| 3 years                   | 0.3 (-0.5 to 1.1)  | 0.9 (-0.01 to 1.9) | 0.44       |
|                           | P=0.45             | P=0.05             |            |
| 7 years                   | 1.6 (0.9 to 2.3)   | 2.7 (1.9 to 3.5)   | 0.04       |
|                           | P=0.001            | P=0.001            |            |
| 10 years                  | 2.6 (1.4 to 3.8)   | 4.9 (3.5 to 6.3)   | 0.01       |
|                           | P=0.001            | P=0.001            |            |
| Females                   |                     |                     |            |
| Males                     |                     |                     |            |
| P interaction             |                     |                     |            |
| Birth                     | 0.5 (-0.9 to 0.2)  | 0.5 (-0.9 to 0.2)  | 0.70       |
|                           | P=0.001            | P=0.006            |            |
| 3 months                  | 0.4 (-0.4 to 0.5)  | 0.4 (-0.1 to 0.9)  | 0.27       |
|                           | P=0.04             | P=0.14             |            |
| 1 year                    | 0.2 (-0.7 to 0.4)  | 0.2 (-0.7 to 0.4)  | 0.81       |
|                           | P=0.92             | P=0.52             |            |
| 3 years                   | 0.1 (-0.6 to 0.3)  | 0.4 (-0.9 to 0.1)  | 0.54       |
|                           | P=0.54             | P=0.10             |            |
| 7 years                   | 0.9 (0.8 to 2.0)   | 2.1 (1.4 to 2.7)   | 0.10       |
|                           | P=0.001            | P=0.001            |            |
| 10 years                  | 2.5 (1.4 to 3.5)   | 4.2 (3.1 to 5.3)   | 0.03       |
|                           | P=0.001            | P=0.001            |            |
| Females                   |                     |                     |            |
| Males                     |                     |                     |            |
| P interaction             |                     |                     |            |
| Birth                     | -0.4 (-0.8 to -0.2) | -0.3 (-0.7 to 0.1) | 0.80       |
|                           | P=0.04             | P=0.22             |            |
| 3 months                  | 0.1 (-0.3 to 0.5)  | 0.1 (-0.4 to 0.5)  | 0.92       |
|                           | P=0.71             | P=0.71             |            |
| 1 year                    | -0.1 (-0.6 to 0.3) | -0.4 (-0.9 to 0.1) | 0.54       |
|                           | P=0.54             | P=0.10             |            |
| 3 years                   | 0.1 (-0.7 to 0.4)  | 0.1 (-0.5 to 0.8)  | 0.96       |
|                           | P=0.64             | P=0.73             |            |
| 7 years                   | 1.1 (0.5 to 1.6)   | 1.2 (0.6 to 1.7)   | 0.66       |
|                           | P=0.001            | P=0.001            |            |
| 10 years                  | 2.0 (1.1 to 2.9)   | 2.5 (1.5 to 3.5)   | 0.58       |
|                           | P=0.001            | P=0.001            |            |

*P interaction tests the null hypothesis that the coefficients are the same for males and females.

Confounders are maternal age, education, pre-pregnancy BMI and parity.

The greater impact of childhood adiposity gain on BP in males compared to females is supported by the findings of a previous study [41]. The observed difference between brachial and central SBP in our study was substantial (mean difference = 3.8 mmHg) and similar to that found in a young (aged 10-17 years) [12]. Our findings are also in keeping with previous studies [37–40] that measured central BP and brachial and central BP in early adulthood. Further research is now needed to determine whether males and females demonstrate differing associations with measures of central and brachial BP in early adulthood. BMI in childhood and brachial BP have also been found to move from lower levels of BMI to being overweight/obese in adolescence [14,42]. Typically, brachial BP was consistently lower than central BP in early adulthood. The associations of BMI with BP throughout childhood tended to diminish with age [10]. The difference between brachial and central SBP is higher in males with BMI in childhood and brachial BP have also been found to move from lower levels of BMI to being overweight/obese in adolescence [14,42]. Typically, brachial BP was consistently lower than central BP in early adulthood.
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.

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Importantly, we show this influence is evident for central SBP, 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 the adverse effect of adiposity gain is worse for boys than girls. 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 importance of interventions to prevent and reverse overweight and obesity in children and young people cannot exclude the possibility that this is a chance finding. Our statistical power for this comparison was low and we cannot make specific statements about the age of onset of adiposity gain in children. Although there is now evidence that overweight children and nurses.

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Our results provide further evidence that this is a chance finding and that adiposity gain in childhood is detrimental for later BP. Furthermore, our results show this influence is evident for central SBP, 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 the adverse effect of adiposity gain is worse for boys than girls.

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Conflicts of interest
There are no conflicts of interest.

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