Is infant weight associated with childhood blood pressure? Analysis of the Promotion of Breastfeeding Intervention Trial (PROBIT) cohort

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Accepted 6 July 2011

Background Weight gain during infancy may programme later health outcomes, but examination of this hypothesis requires appropriate lifecourse methods and detailed weight gain measures during childhood. We examined associations between weight gain in infancy and early childhood and blood pressure at the age of 6.5 years in healthy children born at term.

Methods We carried out an observational analysis of data from a cluster-randomized breastfeeding promotion trial in Belarus. Of 17 046 infants enrolled between June 1996 and December 1997, 13 889 (81.5%) had systolic and diastolic blood pressure measured at 6.5 years; 10 495 children with complete data were analysed. A random-effects linear spline model with three knot points was used to estimate each individual’s birthweight and weight gain from birth to 3 months, 3 months to 1 year and 1–5 years. Path analysis was used to separate direct effects from those mediated through subsequent weight gain.

Results In boys, after controlling for confounders and prior weight gain, the change in systolic blood pressure per z-score increase in weight gain was 0.09 mmHg [95% confidence interval (95% CI) −0.14 to 0.31] for birthweight; 0.41 mmHg (95% CI 0.19–0.64) for birth to 3 months; 0.69 mmHg (95% CI 0.47–0.92) for 3 months to 1 year and 0.82 mmHg (95% CI 0.58–1.06) for 1–5 years. Most of the associations between weight gain and blood pressure were mediated through weight at the age of 6.5 years. Findings for girls and diastolic blood pressure were similar.

Conclusions Children who gained weight faster than their peers, particularly at later ages, had higher blood pressure at the age of 6.5 years, with no association between birthweight and blood pressure.
Introduction

Raised blood pressure, estimated to cause 7.6 million deaths/year worldwide, is a leading cardiovascular risk factor. Blood pressure tracks from childhood (especially school age) into adulthood and high blood pressure in childhood increases future cardiovascular disease risk. There are strong cohort effects in blood pressure, with declines in blood pressure among young people implying that exposures acting in early life may be determinants of later blood pressure. These data support the search for early-life factors that could be modified to prevent premature mortality associated with hypertension.

Birthweight is consistently inversely associated with blood pressure and coronary heart disease (CHD) risk. The adverse effects of low birthweight may be worsened by slow weight gain in infancy and faster weight gain later in childhood, which has been associated with increased CHD risk possibly mediated through blood pressure and other risk factors. In this case, slow infant weight gain would be a risk factor for later high blood pressure. Inverse associations of birthweight with blood pressure strengthen with adjustment for later size, suggesting that post-natal 'catch-up' weight gain may be more important than poor fetal development. However, these inverse associations between birthweight and outcome could also merely be induced by correlations between birthweight, later size and outcome.

Randomized controlled trials of feeding in preterm or small-for-gestational-age infants show that promoting faster early post-natal weight gain is detrimental for later blood pressure and cardiovascular disease risk. In observational analyses, faster early post-natal weight gain was positively associated with childhood and adult blood pressure, and other risk factors among adolescents. Singhal et al., in contrast to the studies cited above, proposed the 'weight gain acceleration' hypothesis: faster weight gain, particularly in early infancy and as a result of a nutrient-enriched diet, adversely programmes the principal components of the metabolic syndrome. Under this hypothesis (in contrast to the 'Barker' hypothesis above), faster weight gain throughout infancy, especially the immediate post-natal period and childhood would be a risk factor for later high blood pressure.

Analysis of lifecourse data poses statistical problems, in particular, because of correlations between repeated measures on the same subject. Two common approaches to examining the relationship between a changing exposure and later outcome are: z-score plots and lifecourse plots. The z-score plots show mean standardized exposure against time for those developing and not developing a given disease. This conditioning on disease status can induce associations in the absence of causal effects. Lifecourse plots show the coefficients from a series of conditional regressions of the outcome upon each exposure, adjusted for all prior exposures, against time. The interpretation of all coefficients except that for the last measure is subject to bias, since the model also includes subsequent measures (and is thus conditioning on variables which are on the causal pathway). These regression coefficients are also affected by collinearity; this problem increases with the number of prior exposures conditioned upon. Conditional weights (the residuals from each weight conditioned upon all previous weights) are sometimes used to overcome this problem of collinearity. Whereas the conditional weights are (by definition) independent, the regression equations used to derive them are likely to suffer from collinearity, and also rely on accurate and efficient modelling of each weight measure. These methods share two major disadvantages: the samples at each time-point must be the same and measurements for all individuals must be taken simultaneously. Thus better modelling of complex relationships along the lifecourse is important.

We investigated associations of weight gain in early life with blood pressure at the age of 6.5 years. In line with the 'weight gain acceleration' hypothesis outlined above, we hypothesized that the magnitude of associations with childhood blood pressure would be larger for early-infant than late-infant weight gain, and that weight gain at all time periods would be positively associated with childhood blood pressure.

Materials and Methods

A detailed description of the original PROBIT trial has been published. Briefly, 31 maternity hospitals in the Republic of Belarus and 1 each of their affiliated polyclinics (out-patient clinics for routine health-care follow-up) were randomly assigned to a breastfeeding promotion intervention or to usual practice. Overall, 17,046 full-term (≥37 weeks of gestation), healthy singletons who weighed at least 2500 g, with Apgar score 5 at 5 min, and who initiated breastfeeding, were recruited between June 1996 and December 1997. These children were followed up at polyclinic visits at 1, 2, 3, 6, 9 and 12 months; home visits were made when polyclinic visits were missed. At the age of 6.5 years, 13,889 (82%) children attended a follow-up visit. The institutional review board of
the Montreal Children’s Hospital approved both the original PROBIT trial and the 6.5 year follow-up, and participating mothers signed consent forms (in Russian) before entry into PROBIT and the 6.5 year follow-up. Our study sample comprises 10 495 (76%) participants aged 6.5 years, who had complete data on all potential confounders (see below) and at least one measure of weight between birth and 5 years of age.

Exposures measured in infancy
Birthweight, gestational age, mother’s smoking in pregnancy and mother’s and father’s education were prospectively recorded during the post-partum stay.26 Weight was measured by paediatricians at the scheduled study visits26 with over 93% of the children attending all six visits. As differences in weight gain were not major hypotheses of PROBIT, measurements of weight were not standardized.

Data on weight and height from routine check-ups between 12 months and 5 years were abstracted retrospectively from medical records by the child’s paediatrician, while weight and height at a mean of 6.5 years were measured in duplicate at a scheduled research visit.27 Parental height and weight were obtained by interview with the parent accompanying the child; 1379 (10%) of the fathers and 161 (1%) of the mothers did not have data on their reported height and weight.

Outcomes
At the 6.5-year follow-up, systolic and diastolic blood pressures were measured, in duplicate while seated and after rest, using a digital oscillometric device (M1; Omron Healthcare, Milton Keynes, UK) with the blood pressure cuff specified for children.27 When blood pressure was unobtainable with the Omron M1, a standard clinic sphygmomanometer was used. The mean of the duplicate blood pressure measurements was used in the analysis. Paediatricians underwent a week-long training session in obtaining blood pressure and anthropometry involving a convenience sample of school-aged children27 and early data collection was independently monitored. An audit of the anthropometric and blood pressure measurement was carried out ~18 months after the 6.5-year follow-up clinic (range: 5.3–32.6 months) by paediatricians blinded to the measures obtained at the initial clinic visit. The Pearson correlation coefficients between the initial clinic measures and these further measures were: height 0.84, weight 0.89; systolic and diastolic blood pressure 0.55 and 0.45, respectively.27

Statistical analysis
As the intervention was not associated with blood pressure at the age of 6.5 years,27 the trial arms are pooled for this observational analysis with all models adjusting for trial arm.

First, we estimated birthweight and weight gain for each individual up to the age of 5 years. A priori, we chose weight gain up to 5 years to allow a 1.5-year time lag prior to the outcome, reducing the impact of current body size on the results; results based on weight gain up to the age of 6.5 years were very similar. Second, we estimated the associations of birthweight and weight gain with systolic and diastolic blood pressure at follow-up.

Estimating individual weight gain trajectories
We reduced the dimensionality of the data by estimating individual weight gain trajectories using a mixed-effects model28 fitted using MLWiN version 2.10 (www.cmm.bristol.ac.uk/MLwiN/index.shtml).29 Such models allow for changes in scale and variance of weight over time, and use all available data. We used fractional polynomials to find the best-fitting weight gain trajectory for boys and girls separately. We then fitted knot points at the planned clinic times and chose the model which best fitted the fractional polynomial. The best-fitting splines for both boys and girls had knots at 3 and 12 months. Thus, for both boys and girls, we fitted a mixed-effects model for weight, with linear gain between 0 and 3 months (‘early-infant weight gain’), 3 and 12 months (‘late-infant weight gain’) and 12 and 60 months (‘early-childhood weight gain’). Thus, weight for individual i at age j is given by:

\[
y_{ij} = \beta_0 + u_{0i} + (\beta_1 + u_{1i})s_{1j} + (\beta_2 + u_{2i})s_{2j} + (\beta_3 + u_{3i})s_{3j} + e_{ij} \times j
\]

where:

- \(\beta_0\) is the population average intercept and \(\beta_1\), \(\beta_2\) and \(\beta_3\) are the population average velocities of weight gain between 0 and 3 months, 3 and 12 months and 12 and 60 months, respectively (the fixed effects).
- \(u_{0i}\) is the deviation from the average intercept for child i, and \(u_{1i}\), \(u_{2i}\) and \(u_{3i}\) are the deviations for child i from the average velocities of weight gain between 0 and 3 months, 3 and 12 months and 12 and 60 months, respectively (the individual-level random effects), and
- \(s_{1j}\), \(s_{2j}\) and \(s_{3j}\) are the amount of time spent in each period for child i at age j. \(e_{ij}\) is the deviation from the predicted weight for child i at age j (the occasion-level random effects) and is related to age to allow for the increase in weight (and therefore the increase in the size of the measurement error of weight) with age.

The individual-level random effects correlation matrix was unstructured, thus each random effect could be correlated with all other random effects (Supplementary Table 1, available as Supplementary Data at IJE online). The occasion-level random effects were independent, thus we assumed that measurement error at one age was unrelated to measurement error for that individual at another age. Occasion- and individual-level random effects were independent.
From these models, individual estimates of birthweight and the three weight gain parameters were obtained for each child. These were then standardized (z-scored) by sex. Birthweight was additionally standardized (z-scored) by gestational age (in completed weeks, from 37 to 43 weeks). Additional standardization of early-infant weight gain by gestational age made no difference to the results (data available from the authors).

Estimating associations between weight gain and outcomes

Linear regression models related systolic or diastolic blood pressure (outcomes) to the individual estimates for each child of birthweight, early-infant weight gain, late-infant weight gain and early-childhood weight gain (exposures). Three models were fitted for each of the weight gain exposures. Model 1 adjusted only for treatment arm and clustering by polyclinic. Model 2 additionally adjusted for potential confounders [maternal and paternal heights, body mass indices (BMI) and highest educational levels]. Model 3 additionally adjusted for preceding weight measures (e.g. the model for the effect of late-infant weight gain on blood pressure, included birthweight and early-infant weight gain as covariates). Since correlations between weight gain parameters were relatively low (Supplementary Table 2, available as Supplementary Data at IJE online), there was no problem of collinearity.

Separate models were fitted for boys and girls a priori. We also fitted an overall model and tested the statistical interaction between sex and each weight gain parameter for each outcome. Only 2% of the mothers reported smoking during pregnancy; given this homogeneity, we did not include this variable in the models.

We used path analysis to distinguish the direct effects of each weight gain measure on later outcome (those effects not mediated through subsequent weight gain) from the indirect effects (those effects mediated through subsequent weight gain).25 Path analysis here is the simultaneous estimation of the regression of the outcome (blood pressure at the age of 6.5 years) on the exposures (summary measures of the weight gain trajectories) and the regressions of each of those summary measures of weight gain on preceding weight gains (and confounding variables).

Results

Table 1 shows the baseline characteristics of the study sample. The correlations between observed birthweight and observed weight gain between birth and the 3- and 12-month clinic visits are shown in Supplementary Table 1, available as Supplementary Data at IJE online. However, these correlations should be interpreted with caution due to mathematical coupling, which can induce a negative correlation between initial value and change, because initial value is also part of the expression for change and there is usually a positive correlation between consecutive measures for the same individual.30 For example, the strong negative correlation between observed early-infant weight gain and observed birthweight could be (at least partly) due to the strong positive correlation between weight at 0 and 3 months.30 The actual weights of the children at the approximate ages of selected clinic follow-ups are shown in Table 2, together with the weights predicted by the multi-level model. Weight gain velocity monotonically declined through childhood, with boys having faster weight gain velocity during the first year of life than girls, but slightly lower weight gain velocity between 1 and 5 years. Diastolic and systolic blood pressures at the age of 6.5 years were similar for boys and girls.

The correlation matrix from the multi-level model (Supplementary Table 2, available as Supplementary Data at IJE online) showed no correlation between birthweight and early-infant weight gain, with negative correlation between birthweight and late-infant weight gain and positive correlations between birthweight and early-childhood weight gain and between late-infant and early-childhood weight gains. This indicates that at least some of the negative correlation between birthweight and the differences calculated directly from the observed data (Supplementary Table 1, available as Supplementary Data at IJE online) was due to mathematical coupling. The correlations between the estimated weight gain parameters (Figures 1 and 2) have larger magnitude than these model estimates, because estimates for individuals with few weight measures are shrunk towards the mean.29 The associations between weight gain parameters and confounders are shown in Supplementary Table 3, available as Supplementary Data at IJE online, and between weight gain parameters and weight at the age of 6.5 years in Supplementary Table 4, available as Supplementary Data at IJE online.

Sex-specific associations of blood pressure with birthweight, early-infant, late-infant and early-childhood weight gain are shown in Tables 3 and 4. The unadjusted coefficients (Model 1) show that, for girls, a 1 standard deviation (SD) higher birthweight (≈0.36 kg) was associated with a 0.35 mmHg higher systolic blood pressure at the age of 6.5 years (Table 3). A 1 SD faster weight gain in infancy or childhood was associated with increases in systolic blood pressure of between 0.49 and 1.32 mmHg, with the magnitude of the associations increasing with age. After adjustment for confounding factors (Model 2), there was no evidence of a relationship between birthweight and systolic blood pressure. All other coefficients were attenuated upon adjustment (Models 2 and 3), but the same basic pattern remained. Associations were smaller for diastolic than
systolic blood pressure (Table 4), consistent with the ratio (~0.80) of the SDs of diastolic and systolic blood pressure. There was no strong evidence of interaction between sex and birthweight or each weight gain period (P-value for sex interaction >0.1 for all weight exposures and outcomes).

Figure 1 shows the direct effects (those not mediated through subsequent weight gain) and indirect effects (those mediated through subsequent weight gain) for systolic blood pressure, separately for boys and girls. There was some evidence (P < 0.1) of an interaction between sex and the relationships among the coefficients for weight up to 1 year. There was no direct effect of birthweight, with small, positive direct effects of early- and late-infancy weight gains, and a larger effect of early-childhood weight gain. Diastolic blood pressure showed a similar pattern (Figure 2).

The total effect of any weight gain parameter (Tables 3 and 4) can also be calculated by adding the direct and indirect effects from Figures 1 or 2. For example, the total effect of early-infancy weight gain on diastolic blood pressure for girls is given by (Figure 2): 0.15 + 0.26 × 0.35 + 0.26 × 0.40 × 0.73 + (−0.11 × 0.73) = 0.24 mmHg (as shown in Table 4).

We examined mediation of these direct associations by weight and height at 6.5 years (Supplementary Table 5, available as Supplementary Data at IJE online). Further adjustment for height at 6.5 years made little difference to any of the associations. Thus, most of the effect of weight gain in each period is mediated through weight at time of blood pressure measurement.

Discussion

In this cohort of healthy children born at term in the Republic of Belarus, we found that an individual’s weight gain during early-infancy (birth to 3 months), late-infancy (3 months to 1 year) and early-childhood (1–5 years) was positively associated with systolic and diastolic blood pressure at the age of 6.5 years. The stronger effects seen for early-childhood contrasted with our a priori hypothesis, which postulated that the initial post-natal period may be more ‘sensitive’ to any deviations from a normative weight gain trajectory. We also found no evidence of an inverse association between early weight gain and childhood blood pressure. Instead, we found that greater weight gain was associated with higher blood pressure at the age of 6.5 years, with the size of the association increasing with proximity to the blood pressure measure. Thus, we found no evidence in support of either the Singhal–Lucas ‘growth acceleration’ or the Barker ‘fetal origins’ hypotheses, although our results were more consistent with the former than the latter.
Table 2  Actual and predicted weight, estimated weight gain velocities and blood pressure at the age of 78 months, PROBIT Study 1996–2003

<table>
<thead>
<tr>
<th>Variable</th>
<th>Girls</th>
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<th>Boys</th>
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<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>5%</td>
<td>95%</td>
<td></td>
<td>Mean (SD)</td>
<td>5%</td>
<td>95%</td>
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<tr>
<td><strong>Actual weight (kg), months</strong></td>
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<tr>
<td>Birth</td>
<td>5051</td>
<td>3.4 (0.4)</td>
<td>2.8</td>
<td>4.1</td>
<td>5444</td>
<td>3.5 (0.4)</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>3</td>
<td>5016</td>
<td>5.9 (0.6)</td>
<td>5.0</td>
<td>7.0</td>
<td>5407</td>
<td>6.3 (0.7)</td>
<td>5.3</td>
<td>7.5</td>
</tr>
<tr>
<td>12</td>
<td>5037</td>
<td>10.3 (1.0)</td>
<td>8.8</td>
<td>12.0</td>
<td>5425</td>
<td>10.8 (1.0)</td>
<td>9.4</td>
<td>12.5</td>
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<tr>
<td>12–24</td>
<td>4343</td>
<td>11.4 (1.4)</td>
<td>9.3</td>
<td>14.0</td>
<td>4653</td>
<td>12.0 (1.5)</td>
<td>10.0</td>
<td>14.5</td>
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<tr>
<td>24–36</td>
<td>3702</td>
<td>13.2 (1.7)</td>
<td>11.0</td>
<td>16.0</td>
<td>3962</td>
<td>13.7 (1.7)</td>
<td>11.0</td>
<td>16.6</td>
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<tr>
<td>36–48</td>
<td>2624</td>
<td>15.4 (2.0)</td>
<td>12.5</td>
<td>19.0</td>
<td>2841</td>
<td>15.8 (2.0)</td>
<td>13.0</td>
<td>19.1</td>
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<tr>
<td>48–60</td>
<td>2500</td>
<td>17.6 (2.5)</td>
<td>14.0</td>
<td>22.0</td>
<td>2674</td>
<td>18.0 (2.5)</td>
<td>14.7</td>
<td>22.0</td>
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<tr>
<td><strong>Actual weight (kg)—predicted weight (kg), months</strong></td>
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<tr>
<td>Birth</td>
<td>0.0 (0.1)</td>
<td>−0.1</td>
<td>0.2</td>
<td>0.0 (0.1)</td>
<td>−0.2</td>
<td>0.2</td>
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<tr>
<td>3</td>
<td>−0.1 (0.2)</td>
<td>−0.4</td>
<td>0.3</td>
<td>−0.1 (0.2)</td>
<td>−0.4</td>
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<tr>
<td>12</td>
<td>−0.3 (0.4)</td>
<td>−0.9</td>
<td>0.4</td>
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<tr>
<td>12–24</td>
<td>−0.1 (0.7)</td>
<td>−1.1</td>
<td>1.0</td>
<td>−0.1 (0.7)</td>
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<td>24–36</td>
<td>−0.1 (0.7)</td>
<td>−1.2</td>
<td>1.1</td>
<td>−0.1 (0.7)</td>
<td>−1.2</td>
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<tr>
<td>36–48</td>
<td>0.0 (0.7)</td>
<td>−1.0</td>
<td>1.0</td>
<td>−0.0 (0.7)</td>
<td>−1.0</td>
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<tr>
<td>48–60</td>
<td>0.2 (0.8)</td>
<td>−0.9</td>
<td>1.5</td>
<td>0.2 (0.8)</td>
<td>−0.9</td>
<td>1.5</td>
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<tr>
<td><strong>Estimated weight gain velocity (kg/year), months</strong></td>
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<tr>
<td>0–3</td>
<td>10.3 (1.4)</td>
<td>8.1</td>
<td>12.6</td>
<td>11.36 (1.53)</td>
<td>9.11</td>
<td>14.00</td>
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<tr>
<td>3–12</td>
<td>6.3 (0.9)</td>
<td>5.0</td>
<td>7.7</td>
<td>6.4 (0.9)</td>
<td>5.0</td>
<td>8.0</td>
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<tr>
<td>12–60</td>
<td>1.9 (0.4)</td>
<td>1.3</td>
<td>2.6</td>
<td>1.9 (0.4)</td>
<td>1.3</td>
<td>2.6</td>
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<td><strong>Outcomes aged 78 months</strong></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>97.0 (9.5)</td>
<td>82.0</td>
<td>113.0</td>
<td>97.5 (9.1)</td>
<td>83.0</td>
<td>112.5</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>57.6 (7.8)</td>
<td>46.0</td>
<td>71.5</td>
<td>57.4 (7.3)</td>
<td>46.5</td>
<td>70.0</td>
<td></td>
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</tr>
<tr>
<td><strong>Age at blood pressure measurement (months)</strong></td>
<td>79.5 (3.2)</td>
<td>76.7</td>
<td>86.0</td>
<td>79.7 (3.3)</td>
<td>76.7</td>
<td>86.4</td>
<td></td>
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</tbody>
</table>

Predictions were estimated from the multi-level model based on children aged <5 years’ weight measurements. Weights were predicted at time points using individual coefficients from the multi-level model.

Figure 1  Directed acyclic graph showing relationships between birthweight (z-score adjusted for gestational age), weight gain (z-score) and systolic blood pressure (mmHg), adjusted for confounding factors, PROBIT Study 1996–2003. Coefficients (standard errors) shown are in red for girls and blue for boys.
Since we used z-scores of weight gain during each period, we have examined relative (rather than absolute) associations, and thus this larger association for later weight gain is not due to the longer length of the later weight gain period compared with the earlier periods. Associations were independent of birthweight and prior weight gain, and remained after controlling for confounding factors. No association was observed between birthweight and either systolic or diastolic blood pressure at the age of 6.5 years, after controlling for confounding variables.

## Strengths and limitations

A key strength of our study lies in the advantages of the statistical methods used here over previously used methods. Our multi-level modelling approach allowed examination of within-subject variation, reduced the problem of collinearity between repeated weight

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Table 3  Associations between systolic blood pressure (mmHg) aged 78 months and birthweight (z-score adjusted for gestational age) and early-infant, late-infant and childhood weight gain (z-score), PROBIT Study 1996–2003

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th>P-values</th>
<th>Model 2</th>
<th>P-values</th>
<th>Model 3</th>
<th>P-values</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$\beta$ (95% CI)</td>
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<td>$\beta$ (95% CI)</td>
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<td>$\beta$ (95% CI)</td>
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<tr>
<td><strong>Girls, n = 5051</strong></td>
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<tr>
<td>Birthweight</td>
<td>0.35 (0.12 to 0.59)</td>
<td>0.003</td>
<td>0.13 (–0.11 to 0.38)</td>
<td>0.3</td>
<td>0.13 (–0.11 to 0.38)</td>
<td>0.3</td>
</tr>
<tr>
<td>Weight gain (months)</td>
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</tr>
<tr>
<td>0–3</td>
<td>0.49 (0.25 to 0.73)</td>
<td>&lt;0.001</td>
<td>0.39 (0.15 to 0.63)</td>
<td>0.002</td>
<td>0.38 (0.14 to 0.62)</td>
<td>0.002</td>
</tr>
<tr>
<td>3–12</td>
<td>1.02 (0.79 to 1.26)</td>
<td>&lt;0.001</td>
<td>0.93 (0.69 to 1.17)</td>
<td>&lt;0.001</td>
<td>0.94 (0.69 to 1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12–60</td>
<td>1.32 (1.09 to 1.56)</td>
<td>&lt;0.001</td>
<td>1.17 (0.93 to 1.42)</td>
<td>&lt;0.001</td>
<td>0.97 (0.71 to 1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Boys, n = 5444</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>0.26 (0.05 to 0.48)</td>
<td>0.02</td>
<td>0.09 (–0.14 to 0.31)</td>
<td>0.5</td>
<td>0.09 (–0.14 to 0.31)</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight gain (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>0.50 (0.28 to 0.72)</td>
<td>&lt;0.001</td>
<td>0.42 (0.20 to 0.64)</td>
<td>&lt;0.001</td>
<td>0.41 (0.19 to 0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3–12</td>
<td>0.76 (0.55 to 0.98)</td>
<td>&lt;0.001</td>
<td>0.69 (0.47 to 0.91)</td>
<td>&lt;0.001</td>
<td>0.69 (0.47 to 0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12–60</td>
<td>1.05 (0.84 to 1.27)</td>
<td>&lt;0.001</td>
<td>0.94 (0.71 to 1.16)</td>
<td>&lt;0.001</td>
<td>0.82 (0.58 to 1.06)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

For Model 1, each weight gain parameter is adjusted for clinic and treatment arm. Model 2 is as 1 but adjusted for the heights, BMIs and highest educational level of the mother and the father. Model 3 is as Model 2 but each weight gain parameter is also adjusted for previous weight gains and birthweight.

*a*Change in blood pressure (mmHg) per z-score change in weight gain.
measures made over short time periods, and allowed better handling of missing data than would be the case with commonly used methods.

Multi-level models are more time-consuming to fit than simpler regression, although once derived, the exposures may be used for more than one outcome.20,31 Where there are many exposures (e.g. weight measured every 6 months during childhood), or short time-intervals between exposures, multi-level models may help to identify periods of linear change, and thus reduce the dimensionality and collinearity of the exposures. Where many subjects are missing exposure measure(s), then estimating trajectories using a multi-level model is one way to impute the missing data and thus increase power. Finally, if the individual times at which exposures were measured vary (e.g. a clinic visit planned for 2 months of age, where actual age varies between 1 and 3 months, or routinely collected data where there was no planned schedule), then using a multi-level model to derive trajectories would reduce the measurement error associated with trying to group exposures according to common ages. An alternative to our two-stage approach would be to fit both the weight trajectories and their relationship with the outcome in one latent growth model (or structural equation model). However, this one-stage approach is more complex, and a different latent growth curve model would need to be fitted for every outcome analysed.

A further strength of this study is that the large number of weight gain measures available allowed us to identify biological trajectories, defined prior to analysis of associations with blood pressure, rather than conducting analyses at multiple time-points and then choosing those showing the largest associations with blood pressure. Path analysis enabled the separation of ‘direct’ and ‘indirect’ effects.

There are five important limitations of our study. First, although PROBIT was a randomized trial, our results are based on an observational analysis of the cohort and thus we must be cautious about inferring causality. Our weight gain–blood pressure associations were attenuated after controlling for confounding, but the degree of attenuation (between 10% and 20%) suggests that residual confounding, although a theoretical possibility, probably does not fully explain the results. Belarus has a low index of income inequality,32 so socio-economic confounding may be less than in other settings.

Second, anthropometric measurements in infancy and years 1–5 were not standardized; the error in measuring weight is likely to have been non-differential, thus attenuating associations towards the null. If measurement error varied during the differing weight gain periods, that may influence comparisons between the coefficients for the different periods. Measurement error in the outcomes (as indicated by the modest correlations between clinic measures and those taken again 18 months later) would increase the width of the confidence intervals around the effect sizes, but would be unlikely to introduce bias to these results.

Third, blood pressure was measured at a mean of 6.5 years. Blood pressure of school-age children tracks

Table 4 Associations between diastolic blood pressure (mmHg) aged 78 months and birthweight (z-score adjusted for gestational age) and early-infant, late-infant and childhood weight gain (z-score), PROBIT Study 1996–2003

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>βa (95% CI)</td>
<td>P-values</td>
<td>βa (95% CI)</td>
</tr>
<tr>
<td>Girls, n = 5051</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>0.36 (0.16 to 0.56)</td>
<td>0.001</td>
<td>0.19 (–0.02 to 0.40)</td>
</tr>
<tr>
<td>Weight gain (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>0.33 (0.13 to 0.54)</td>
<td>0.001</td>
<td>0.26 (0.05 to 0.46)</td>
</tr>
<tr>
<td>3–12</td>
<td>0.70 (0.50 to 0.90)</td>
<td>&lt;0.001</td>
<td>0.62 (0.41 to 0.82)</td>
</tr>
<tr>
<td>12–60</td>
<td>1.00 (0.79 to 1.20)</td>
<td>&lt;0.001</td>
<td>0.88 (0.67 to 1.08)</td>
</tr>
<tr>
<td>Boys, n = 5444</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>0.19 (0.01 to 0.38)</td>
<td>0.04</td>
<td>0.04 (–0.15 to 0.23)</td>
</tr>
<tr>
<td>Weight gain (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>0.34 (0.15 to 0.53)</td>
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</tr>
<tr>
<td>3–12</td>
<td>0.47 (0.28 to 0.65)</td>
<td>&lt;0.001</td>
<td>0.41 (0.22 to 0.59)</td>
</tr>
<tr>
<td>12–60</td>
<td>0.79 (0.61 to 0.98)</td>
<td>&lt;0.001</td>
<td>0.69 (0.50 to 0.88)</td>
</tr>
</tbody>
</table>

For Model 1, each weight gain parameter is adjusted for clinic and treatment arm. Model 2 is as 1 but adjusted for the heights, BMIs and highest educational level of the mother and the father. Model 3 is as Model 2 but each weight gain parameter is also adjusted for previous weight gains and birthweight.

aChange in blood pressure (mmHg) per z-score change in weight gain.
into adulthood, with tracking correlation coefficients of approximately 0.4, and is associated with increased cardiovascular disease risk. However, we were unable to investigate associations between weight gain in childhood and blood pressure in adolescence or adulthood.

Fourth, Belarus is a developed country with low child, but high adult, mortality. Most previous studies have been in high-income countries, and, to our knowledge, this is the first such study from a middle-income former Soviet country with high rates of hypertension-related premature ischaemic heart and cerebrovascular disease. Belarus resembles Western developed countries in basic health services and sanitary conditions, but with lower rates of overweight or obesity in childhood (12–13% in our study) than the USA (30%). Associations may differ in countries with different rates of weight gain, levels of childhood obesity or adult mortality.

Fifth, our models assume a piece-wise linear relationship between weight gain and age. Alternative curvilinear forms (such as a nonlinear splines, complex polynomial or other non-linear model) may have resulted in closer approximation of the weight measures, but would have made the associations with blood pressure harder to interpret. We re-analysed these data using different knot points (6 and 12 months; 3 and 9 months) and obtained similar results (data available from the authors). Thus, it appears that our conclusions are not sensitive to the knot points chosen. We believe that these methods are a useful compromise between precision of growth modelling, and interpretable summaries of weight gain trajectory which can be related to subsequent outcomes.

Comparison with other studies in term infants

In line with our findings, a study of 679 term infants showed that weight gain in early infancy (0–3 months), late infancy (3–18 months) and up to 5 years had positive direct associations with systolic and diastolic blood pressure at the age of 25 years, after confounder adjustment. Positive associations have been shown between weight gain during early childhood (1–5 years) and later blood pressure, which were mediated by later size in some reports.

Weight gain after mid-childhood (~7 years of age) is also consistently positively associated with blood pressure and related morbidity in adulthood. However, few studies apart from Ben-Shlomo et al. have been able to investigate the weight gain acceleration hypothesis in any depth in term infants, because most data sets lack detailed measures of weight gain in early infancy. Two Finnish studies found a positive association of a change in weight z-score between birth and 1 year with systolic but not diastolic blood pressure at the ages 7 and 31 years, but could not distinguish between the effects of weight gains in early vs late infancy. Two other small studies (n ~ 100) reported that weight gain between birth and 3 or 6 months (but not later weight gain) were positively associated with cardiometabolic risk factors.

A pooled analysis from low- and middle-income countries suggested that weight gains in the first, second and between the second year and fourth year of life are positively associated with systolic blood pressure.

In contrast to our findings, most studies find that birthweight is inversely associated with systolic blood pressure, especially after controlling for body size at the time of blood pressure measurement, although the magnitude and public health importance of the effect is debated. In one large study (n = 25 874), the association of birthweight with later blood pressure increased with age at blood pressure assessment (age–birthweight interaction term P < 0.001) in support of a previously suggested ‘amplification’ hypothesis. Thus, our measurement of blood pressure at age 6.5 years may be too early to detect an effect of birthweight. The same hypothesis could explain the relatively small associations we found compared with studies with adult outcomes.

Mechanisms

The monotonic increase in the strength of our weight gain and blood pressure associations with age may simply reflect the fact that weight gain in early-life is associated with body size in later life, which is strongly and positively associated with systolic and diastolic blood pressure via acute and/or chronic mechanisms. Other mechanisms could operate through epigenetic modifications to DNA or histones, which may alter the expression of genes related to weight gain and blood pressure, metabolic or hormonal perturbations or common genes affecting both early weight gain and later blood pressure.

Conclusions

Novel statistical methods were used to overcome the problems usually encountered with life-course analyses. Faster weight gain during any stage of infancy or childhood was associated with an increase in childhood blood pressure, independent of birthweight, prior weight gain and confounding factors. Associations increased with age, and were not higher for the immediate post-natal period, as previously suggested.

Supplementary Data

Supplementary Data are available at IJE online.
Funding
The Canadian Institutes of Health Research; the European Union’s project on Early Nutrition Programming: Long-term Efficacy and Safety Trials (grant number FOOD-DT-2005-007036 to R.M.M. and G.D.S.); the MRC Centre for Causal Analyses in Translational Epidemiology (MRC PhD studentship to N.D.).

Acknowledgements
We thank Dr Robert Platt for comments on an earlier draft. M.S.K. is Senior Investigator of the Canadian Institutes of Health Research.

Conflict of interest: None declared.

KEY MESSAGES
- In this large cohort of healthy children who were born at term, children who gained weight faster than their peers had higher blood pressure at age 6.5 years.
- There was no evidence of an association between birthweight and blood pressure.
- The association between weight gain and blood pressure was stronger for weight gain at later ages.

References


Davies AA, Davey Smith G, May MT, Ben-Shlomo Y. Association between birth weight and blood pressure is robust, amplifies with age, and may be underestimated. *Hypertension* 2006;48:431–36.
