Childhood body mass index and adult pro-inflammatory and pro-thrombotic risk factors: data from the New Delhi birth cohort

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Objective
Weight gain and growth in early life may influence adult pro-inflammatory and pro-thrombotic cardiovascular risk factors.

Methods
Follow-up of a birth cohort in New Delhi, India, whose weight and height were measured every 6 months until age 21 years. Body mass index (BMI) at birth, during infancy (2 years), childhood (11 years) and adulthood (26–32 years) and BMI gain between these ages were analysed in 886 men and 640 women with respect to adult fibrinogen, high-sensitivity C-reactive protein (hsCRP) and plasminogen activator inhibitor-1 (PAI-1) concentrations.

Results
All the pro-inflammatory/pro-thrombotic risk factors were higher in participants with higher adiposity. In women, BMI at birth and age 2 years was inversely related to fibrinogen ($P = 0.002$ and 0.05) and, after adjusting for adult adiposity, to hsCRP ($P = 0.02$ and 0.009). After adjusting for adult adiposity, BMI at 2 years was inversely related to hsCRP and PAI-1 concentrations ($P < 0.001$ and 0.02) in men. BMI gain between 2 and 11 years and/or 11 years to adulthood was positively associated with fibrinogen and hsCRP in women and with hsCRP and PAI-1 in men.

Conclusions
Thinness at birth or during infancy, and accelerated BMI gain during childhood/adolescence are associated with a pro-inflammatory/pro-thrombotic state in adult life. An altered inflammatory state could be one link between small newborn/infant size and adult cardiovascular disease. Associations between pro-inflammatory markers and childhood/adolescent BMI gain are probably mediated through adult adiposity.

Keywords
Birth weight, growth, C-reactive protein, fibrinogen, plasminogen activator inhibitor-1
Introduction
India is experiencing high and rising rates of cardiovascular disease (CVD) and type 2 diabetes. Coronary heart disease has been estimated to affect 10% of adults >35 years of age in Indian cities, and to have caused 1.5 million deaths in India in 2000. India is known as the diabetes capital of the world, because of the high burden of type 2 diabetes compared with other geographic regions; the number of patients with diabetes is predicted to rise from 50.8 million in 2010 to 87 million in 2030.

Recent evidence suggests that the inflammation–coagulation interface may contribute to the development of these diseases. Inflammation may increase cardiovascular risk through increasing platelet activity and coagulation factors, and down-regulating anticoagulant mechanisms and fibrinolysis. Fibrinogen and C-reactive protein (CRP) released in response to inflammation increase the risk of thrombosis by increasing the expression of tissue factor and plasminogen activator inhibitor-1 (PAI-1). The coagulation system can in turn increase inflammation by releasing mediators from platelets, activating cells and promoting cell–cell interaction. In prospective studies, fibrinogen, CRP and PAI-1 predict an increased risk of future atherosclerotic CVD and type 2 diabetes. Adipose tissue is a major source of pro-inflammatory cytokines and PAI-1, which could explain its role as a risk factor for the CVD and type 2 diabetes. Both pro-inflammatory cytokines and PAI-1 have been shown to be raised in South Asian populations compared with white Caucasians.

Environmental factors acting in early life influence the risk of developing adult CVD and type 2 diabetes. Low birth weight and/or infant weight, and accelerated weight gain during childhood, are associated with an increased risk of both disorders. The underlying mechanisms are largely unknown, but activation of the innate immune system during critical periods of fetal/post-natal development may predispose to a pro-inflammatory state. Studies have shown associations of lower birth weight or infant weight, and/or greater weight gain during childhood with increased adult concentrations of fibrinogen, high-sensitivity CRP (hsCRP) and PAI-1. We now report associations of these pro-inflammatory/pro-thrombotic markers with BMI at birth and during infancy, childhood and adolescence in an Indian population.

Methods
During 1969–72, married women living in a 12 km² area of Delhi (N = 20 755) were followed up. There were 9169 pregnancies, and 8181 live births. Babies’ weights and lengths were recorded within 72 h of birth and every 6 months until 14–21 years. Measurements were interrupted in 1972–73 and 1980–82. At recruitment, 60% of families had incomes of >50 rupees per month (national average 28 rupees) and 15% of parents were illiterate (national average 66%). Forty-three percent of families lived in one room. Hindus were the majority religious group (84%), followed by Sikhs (12%), Christians (2%), Muslims (1%) and Jains (1%).

Current study
In 1998–2002, we retraced 2584 (32%) of the cohort and 1583 agreed to participate. They were visited at home by a social worker who administered a questionnaire to obtain data on schooling, occupation, household possessions, alcohol consumption, tobacco use, physical activity, family history and (in women) parity. Participants then attended a clinic after an overnight fast. Weight, height, waist circumference and skinfold thicknesses (triceps and subscapular) were measured using standardized techniques.

Blood samples were drawn in the fasting state for measurement of plasma fibrinogen, PAI-1, glucose and insulin, and serum hsCRP and lipids. For glucose, a further sample was drawn 120 min after a 75-g oral glucose load. Glucose was measured on the day of collection. For all other parameters serum and plasma were aliquoted and stored at −70°C until analysis. Glucose, cholesterol and triglyceride concentrations were analysed by enzymatic methods using Randox kits on a Beckman autoanalyzer, and high-density lipoprotein (HDL) cholesterol using the same method after phosphotungstic acid precipitation.

Insulin concentrations were measured by radioimmunoassay (Coat-a-Count insulin kit, Diagnostic Products, USA). Impaired glucose tolerance and diabetes were defined using World Health Organization criteria. Metabolic syndrome was defined using NCEP-ATPIII (National Cholesterol Education Program, Adult Treatment Panel III) criteria.

Fibrinogen was determined using the Clauss method. hsCRP and PAI-1 were measured using Enzyme Linked Immunosorbent Assay (ELISA) kits from BioCheck Inc. (CA, USA) and Diagnostica Stago (Asnieres, France) respectively.

The study was approved by the All India Institute of Medical Sciences Research Ethics Committee, and informed consent was obtained.

Statistical analyses
The distributions of fibrinogen, hsCRP, PAI-1, triglyceride and glucose concentrations and insulin resistance were skewed and were transformed to normality using inverse square roots (hsCRP only) or logarithms. Using all recorded data from the original cohort, not just those for subjects recruited for the current study, we generated BMI and height standards so as to derive internal sex-specific standard deviation (SD) scores.
Participants had a mean (SD) of 23 (5.5) observations between birth and the age of 21 years. We modelled the progress of the median, spread and skewness of the measurements as age increased. For each subject we interpolated values linearly between successive SD scores to estimate SD scores at 6 months and at birthdays from 1 to 21 years. The interpolated values were used if measurements were made within 6 months (up to 1 year), 1 year (age 2 years), 1.5 years (age 3 years) and 2 years (all older ages). Back-transformation provided estimates of measurements at these ages. In order to measure changes in early-life BMI and height (growth), we used the conditional SD scores method.\textsuperscript{34,35} We divided growth into three periods: birth to 2 years (infancy), 2–11 years (pre-pubertal childhood growth) and 11 years to adulthood (adolescent growth). To describe growth during each interval, for example between 2 and 11 years, we regressed SD scores at the end of the interval (11 years) on SD scores at the beginning (2 years) and at all preceding time-points (birth, 6 months, 1 year), and expressed the residuals as SD scores. This produces uncorrelated variables describing change between specific ages (‘conditional SD scores’). Quadratic terms were included when relationships between measurements at different ages were non-linear.

Associations between size and conditional growth in early life and adult outcomes were examined using regression, adjusting for age in all models, and for potential confounding variables as described. There were a number of interactions between sex and BMI (both early-life and adult BMI) in relation to the outcomes; we therefore analysed the data separately for men and women. Analyses were carried out using Statistical Package for Social Sciences version 15.0.

Results

Of the 1583 men and women who agreed to participate, 57 were excluded (24 were pregnant, 2 left after recruitment and 31 were unreliably linked to earlier data) leaving 1526 (59% of those traced and 19% of the original cohort). Fibrinogen values were available for 1492, hsCRP for 1472 and PAI-1 for 1469. Compared with the original birth cohort, 7% more of the participants in this study were male, maternal literacy was 6% higher, and mean birth weight was 32 g heavier. BMI and height in infancy, childhood and adolescence were ~0.1 SD lower. Mean concentrations of the pro-inflammatory/pro-thrombotic variables are shown in Table 1. HsCRP concentrations were positively correlated with fibrinogen and PAI-1 ($r = 0.21$ and 0.14, $P < 0.001$ for all, adjusted for age and sex).

Associations of outcomes with current (adult) factors

All the pro-inflammatory/pro-thrombotic outcomes, especially hsCRP, were positively related to adult adiposity. Correlations coefficients ($r$) for BMI with fibrinogen, hsCRP and PAI-1 were 0.09, 0.26 and 0.20 in men and 0.13, 0.44, 0.09 in women, respectively ($P < 0.05$ for all), and there were similar correlations with sum of skinfolds and waist circumference. All outcomes were higher in participants with metabolic syndrome ($N = 435$, 29%) than in the rest of the cohort: fibrinogen (2.94 vs 2.72 g/l; $P = 0.001$) in women; PAI-1 in men (100.1 vs 83.3 ng/ml; $P < 0.001$); and hsCRP in both sexes (2.25 vs 1.86 mg/l; $P = 0.003$ in men and 3.45 vs 1.64 mg/l; $P < 0.001$ in women).

In men, fibrinogen and PAI-1 rose with increasing socio-economic status ($P = 0.05$ and 0.01) and PAI-1 rose with increasing alcohol intake ($P = 0.005$). In women, hsCRP rose with increasing parity ($P = 0.008$), PAI-1 was lower in those reporting more physical activity ($P = 0.05$). hsCRP and PAI-1 were higher in men, and hsCRP was higher in women with a positive family history of CVD or diabetes ($P < 0.01$ for all). None of the outcomes was related to tobacco use.

Associations of outcomes with BMI in early life

In women, BMI at birth and 2 years was inversely related to adult fibrinogen and hsCRP concentrations (Table 2 and Figure 1). Similar associations to those with BMI at birth were present with birth weight [fibrinogen $P = 0.01$; hsCRP (after adjustment for adult BMI) $P = 0.003$]. There were no associations between size at birth and adult outcomes in men. None of the findings was changed after adjusting for gestational age at birth.

In men, BMI at 2 years was inversely related to hsCRP and PAI-1 concentrations and BMI at 11 years was positively related to adult hsCRP concentration in both sexes after adjusting for adult BMI (Table 2 and Figure 1). Adult BMI was positively related to all outcomes in both sexes.

Conditional regression analyses showed that greater BMI gain from 2 to 11 years and/or 11 years to adulthood was associated with higher adult hsCRP concentrations (both sexes), higher PAI-1 in men, and higher fibrinogen in women (Table 3). These positive associations were attenuated after adjusting for adult adiposity (BMI or sum of skinfolds and waist circumference).

We analysed the outcomes in relation to combinations of BMI at birth or during infancy with adult BMI or conditional adult BMI, to determine whether the adverse effects of adult BMI were greater in individuals with lower early BMI. The highest fibrinogen, hsCRP and PAI-1 values tended to be in participants who were small at birth (women) or 2 years (both sexes) and adipose as adults (Supplementary Table 1; Supplementary data are available at IJE online). However, for fibrinogen and hsCRP, there were no interactions of either BMI at birth or 2 years with adult BMI or conditional BMI gain (11 years adult).
For PAI-1, there was a greater increase in concentrations with conditional adult BMI in men who had lower 2 years BMI.

Associations of outcomes with height in early life
In comparison with BMI, there were only weak associations of height in early life with the adult pro-inflammatory markers (Supplementary Tables 2 and 3; Supplementary data available at IJE online). Height at birth, 2 and 11 years was inversely related to hsCRP in women, and height at 11 years was inversely related to hsCRP in men, after adjusting for adult BMI. Height at 2 and 11 years was positively related to PAI-1 in men, but these associations were attenuated after BMI adjustment. Shorter adult height was associated with higher fibrinogen concentrations in women and
### Table 2

Mean plasma fibrinogen, serum CRP and plasma PAI-1 concentrations according to body mass index (BMI) at birth, at age 2, 11 years and in adulthood

| Fifths of BMI at Birth | N min, max | Plasma fibrinogen (g/l) | Serum CRP (mg/l) | Plasma PAI-1 (ng/ml) | Birth | 12.2, 14.1 152, 161 2.46 1.91 83.4 10.4, 13.8 113, 115 2.68 1.50 79.4 21.2, 23.7 169, 173 2.52 1.58 78.0 20.1, 23.2 125, 127 2.52 1.80 78.7 15.5, 16.4 159, 162 2.52 1.90 88.9 153, 163 112, 116 2.74 1.91 79.5 16.4, 16.5 163, 165 2.59 2.22 103.8 163, 239 116, 118 2.81 2.25 81.2 16.4, 28.5 171, 174 2.53 2.27 108.6 20.1, 28.5 112, 116 2.76 2.64 77.0 16.4, 28.5 171, 174 2.53 2.27 108.6 20.1, 28.5 112, 116 2.76 2.64 77.0 | P-value | 0.08 (0.01 to 0.15) | 0.11 (0.04 to 0.18) | 0.00 (0.01 to 0.16) | 0.29 (0.22 to 0.36) | 0.21 (0.14 to 0.28) | 0.08 (0.01 to 0.16) | 0.41 (0.35 to 0.48) | 0.07 (0.00 to 0.15) | <0.001 | <0.001 | <0.001 | <0.001

The means presented are unadjusted. The summary effect size estimates [regression coefficient (B) and 95% confidence intervals (CIs)] and P-values are derived from linear regression analyses, using all variables (measures of BMI in early-life and adult pro-inflammatory markers) as continuous standardized variables. These estimates are presented adjusted first for age alone, and then adjusted for adult BMI and other covariates as follows: alcohol consumption (four levels from none to heavy), tobacco use (never, ex-user, current user), socio-economic status in childhood [father's occupation, ranging from 1 (low class) to 6 (high class)], adult socio-economic status derived from education level, household possessions and occupation [ranging from 1 (low class) to 17 (high class)] and family history of high blood pressure, angina, myocardial infarction, stroke or diabetes in a first-degree relative.
higher CRP concentrations in men after BMI adjustment. Less height gain between 11 years and adulthood was associated with higher PAI-1 concentrations in women.

All analyses were repeated after excluding participants on medication that could alter inflammatory markers (corticosteroids, \(N = 1\); oral contraceptives, \(N = 23\); aspirin and other anti-platelet medications, \(N = 4\); non-steroidal anti-inflammatory drugs, \(N = 33\)) and antibiotics (indicating current infection, \(N = 12\)). The findings were unchanged.

**Discussion**

The study reports an inverse association of birth weight and BMI at birth and 2 years with hsCRP concentration in both sexes and with fibrinogen in

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**Table 3** Multiple linear regression analyses using conditional BMI SD scores in earlier life to predict adult outcomes

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>BMI at birth (SD score)</th>
<th>BMI change birth to 2 years (SD)*</th>
<th>BMI change 2–11 years (SD)*</th>
<th>BMI change 11 years–adult (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (SD)</td>
<td>-0.01 -0.09 to 0.07 0.8</td>
<td>0.08 -0.00 to 0.15 0.06 0.07 -0.01 to 0.14 0.1</td>
<td>0.03 -0.04 to 0.11 0.4</td>
<td></td>
</tr>
<tr>
<td>hsCRP (SD)</td>
<td>0.01 -0.06 to 0.08 0.8</td>
<td>-0.03 -0.11 to 0.04 0.4 0.14 0.07 to 0.22 &lt;0.001</td>
<td>0.29 0.22 to 0.36 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PAI-1 (SD)</td>
<td>-0.03 -0.10 to 0.05 0.5</td>
<td>-0.05 -0.12 to 0.03 0.2 0.10 0.03 to 0.18 0.008</td>
<td>0.14 0.07 to 0.22 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (SD)</td>
<td>-0.14 -0.23 to -0.05 0.003</td>
<td>-0.06 -0.15 to 0.03 0.2 0.04 -0.05 to 0.13 0.4</td>
<td>0.12 0.03 to 0.21 0.01</td>
<td></td>
</tr>
<tr>
<td>hsCRP (SD)</td>
<td>-0.01 -0.09 to 0.07 0.9</td>
<td>0.00 -0.08 to 0.08 1.0 0.14 0.06 to 0.22 0.001</td>
<td>0.44 0.35 to 0.52 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PAI-1 (SD)</td>
<td>-0.03 -0.12 to 0.06 0.5</td>
<td>-0.00 -0.10 to 0.09 0.9 0.07 -0.03 to 0.16 0.2</td>
<td>0.07 -0.02 to 0.17 0.1</td>
<td></td>
</tr>
</tbody>
</table>

*BMI changes are calculated as conditional measures (see Statistical methods section). The continuous outcome variables were normalized so that \(B\) (regression coefficient) values indicate the SD change in the outcome per SD change in the predictor. All analyses are adjusted for age and alcohol consumption (four levels, from none to heavy), tobacco use (never, ex-user, current user), socio-economic status in childhood [father's occupation, ranging from 1 (low class) to 6 (high class)], adult socio-economic status derived from education level, household possessions and occupation [ranging from 1 (low class) to 17 (high class)] and family history of high blood pressure, angina, myocardial infarction, stroke or diabetes in a first-degree relative.
women, and BMI at 2 years with PAI-1 concentration in men. In contrast, greater BMI gain after infancy (between 2 and 11 years and/or 11 years and adulthood) was associated with an increase in all pro-inflammatory/pro-thrombotic markers, associations that diminished after adjusting for adult adiposity. Participants who were thin at birth (women) or 2 years (both sexes) and had a high BMI as adults had the highest hsCRP, fibrinogen and PAI-1 levels.

CRP
An inverse relation of birth weight with adult hsCRP concentrations has been reported in the MIDSPAN study from the UK after adjusting for adult BMI, and in the Northern Finland birth cohort study.23 The Finnish study also showed, consistent with our findings, that greater weight gain from birth to 14 years, and 14–31 years, was associated with higher hsCRP concentrations. In the Pelotas birth cohort (Brazil), there were positive associations between weight gain at all ages >1 year and adult hsCRP concentrations.22 In contrast, the Barry-Caerphilly study (UK) showed no association with weight velocity between 1 and 5 years.23

Fibrinogen
Our finding of an association of lower birth weight with higher fibrinogen in women and not men is consistent with the Atherosclerosis Risk In Communities (ARIC) study,26 the associations were stronger for white Caucasians than African Americans, suggesting ethnic differences. Other reports of associations between birth weight and fibrinogen have been inconsistent.20,21,23,37,38 Lower birth weight is associated with higher clottable fibrinogen concentrations within dizygotic but not monozygotic twins,39 suggesting that genetic factors could contribute to the association. The inconsistencies among studies could be due to ethnic genetic differences. Low weight at 1 year in men (but not women) was associated with higher adult fibrinogen concentrations in the Hertfordshire study.20,40 In the Caerphilly study, weight velocity in infancy was not related to adult fibrinogen concentrations.23

Plasminogen activator inhibitor
In the only published study of birth weight in relation to PAI-1, a strong inverse association after adjusting for adult BMI was found in 70-year-old men.26 Genetic determinants are a stronger influence on concentrations of PAI-1 in South Asian population, which could explain weaker associations in our study.41 Small-for-gestational-age newborns have high cord blood hsCRP concentrations (after excluding known infected pregnancies), perhaps supporting a programming effect.42 Associations with fibrinogen, hsCRP and PAI-1 [factors released from the liver in response to interleukin-6 (IL-6) and chiefly cleared by the kidneys], may indicate impaired development of hepatic and/or renal tissue due to in utero or early post-natal influences. Up-regulation of inflammatory cytokines has been proposed as a mechanism of in utero ‘thriftiness’, inducing muscular insulin resistance in order to preserve the glucose supply to the brain.43 Increased maternal circulating glucocorticoids, due to stressful environmental factors, could influence the fetus via transplacentental transfer of glucocorticoids and other hormones, or stimulation of the fetal adrenal axis, causing a persistent inflammatory response. Post-natal stressors could have a similar effect during infancy; smaller newborns are more prone to infection, and maltreated children have higher inflammatory markers in adult life.44 Impaired intrauterine growth followed by infection postnatally could further augment the inflammatory response.

Adipose tissue is a major source of IL-6, the main stimulus for hsCRP and fibrinogen production. Our data suggest that the positive relationships of the adult outcomes to earlier BMI gain (especially BMI gain from 11 years) is observed because BMI gain at this stage of the life course is strongly related to the development of adult adiposity.28 Alternatively, a sub-clinical inflammatory state could cause BMI gain.45,46 Regulation of metabolism and food intake by cytokines, regulation of the hypothalamo-pituitary–adrenal axis by cytokines, leptin deficiency and resistance to leptin are possible mechanisms. Thus, an inflammatory state caused by early life factors could potentially cause excessive adipose tissue gain during childhood and adolescence. In the absence of measures of inflammatory markers in early life, it is impossible to ascertain whether inflammation drives excess adipose tissue acquisition or vice versa. Sex differences in the relative deposition of lean and adipose tissue during childhood could account for the sex differences we observed in associations between early BMI growth and adult pro-inflammatory markers. Another possible explanation for the sex differences is a greater impact on liver development in the growth-restricted female fetus, than in the male. Studies in the Finnish birth cohort showed an association between short birth length and coronary heart disease in women but not men.47

Potential mechanisms
Associations of lower BMI at birth and during infancy, with higher hsCRP, fibrinogen and PAI-1, may indicate persisting effects of the intra-uterine and early post-natal environment or genetic effects.

Strengths and limitations of the study
Strengths of the study were that it was population-based and children were measured by trained personnel, with frequent follow-up throughout childhood. Like other birth cohorts, there was considerable loss
to follow-up and participants are likely to be unrepresentative of the original sample. Only 19% of the original cohort participated. There was a slightly higher percentage of men among the participants than in the original cohort, probably because women are more likely to move away when they marry, and maternal education was higher in the study sample than in the original cohort, which probably reflects the influence of social factors on where people settle in adult life. The differences in their mean size at birth and during infancy and childhood, however, were trivial. In a within-sample analysis, loss to follow-up would introduce bias only if associations between early BMI/weight and later disease differed between those studied and not studied, which seems unlikely because inclusion was based only on subjects' availability. Another limitation is that we did not collect data on infection at the time of the data collection.

In summary, thinness at birth and/or in infancy is associated with higher fibrinogen, hsCRP and PAI-1 in adulthood. Both in utero influences and greater adiposity due to BMI gain in childhood/adolescence could be implicated consolidating the need to prevent excessive BMI gain in childhood.

Supplementary Data
Supplementary data are available at IJE online.

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Conflict of interest: None declared.

KEY MESSAGES
- Thinness at birth and accelerated BMI gain during childhood are associated with an increased risk of adult cardiovascular disease. Several studies have suggested that these associations may be mediated by inflammation.
- We have examined the relationship of BMI and height growth in early life to adult pro-inflammatory/pro-thrombotic markers (fibrinogen, CRP and PAI-1 concentrations) in a birth cohort from Delhi, India.
- Lower BMI at birth (women) and during infancy (both sexes), and accelerated BMI gain during childhood were associated with higher adult fibrinogen, CRP and PAI-1 concentrations.

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