High Birth Weight Is Associated With Obesity and Increased Carotid Wall Thickness in Young Adults

The Cardiovascular Risk in Young Finns Study

Michael R. Skilton, Niina Siitonen, Peter Würtz, Jorma S.A. Viikari, Markus Juonala, Ilkka Seppälä, Tomi Laitinen, Terho Lehtimäki, Leena Taittonen, Mika Kähönen, David S. Celermajer, Olli T. Raitakari

Objective—There is some evidence that people born with high birth weight may be at increased risk of cardiovascular disease in adulthood. Details of the underlying mechanisms remain unknown. We sought to determine whether people born large for gestational age have poor arterial health, increased adiposity, and a poor cardiovascular risk factor profile.

Approach and Results—Carotid intima-media thickness, brachial flow–mediated dilatation, and cardiovascular risk factors were compared between young adults (24–45 years) born at term who were large for gestational age (birth weight >90th percentile; n=171), and a control group with normal birth weight (50–75th percentile; n=525), in the Cardiovascular Risk in Young Finns Study. Those born large for gestational age had higher body mass index throughout childhood, adolescence, and as young adults (26.4 kg/m² [SD 4.9], versus normal birth weight 25.1 kg/m² [SD 4.6]; P=0.002), and 2-fold greater risk of obesity. Other cardiovascular risk factors and arterial function did not differ; however, carotid intima-media thickness was increased in people born large for gestational age (0.60 mm [SD 0.09], versus normal birth weight 0.57 mm [SD 0.09]; P=0.003), independent of cardiovascular risk factors (P=0.001 after adjustment). Both obesity and high birth weight were independently associated with carotid intima-media thickness in a graded and additive fashion.

Conclusions—Young adults born large for gestational age are more likely to be obese, yet have an otherwise healthy cardiovascular risk profile. Nonetheless, they have increased carotid intima-media thickness, a marker of subclinical atherosclerosis, consistent with an increased risk of cardiovascular disease. (Arterioscler Thromb Vasc Biol. 2014;34:1064-1068.)

Key Words: atherosclerosis ■ fetal development ■ obesity

Impaired fetal growth is an emerging risk factor for adult cardiovascular disease. At the other end of the fetal growth spectrum, those born large for gestational age (LGA) may also be at increased risk of adult cardiovascular events, although evidence to support or oppose this is limited. Indeed, the majority of evidence for such an association has been inferred from the strengthening of the association of birth weight with adult cardiovascular disease when those born LGA are excluded, nonlinear associations, or nonsignificant increases in risk in this group.

We and other have previously demonstrated that those born with impaired fetal growth have higher arterial intima-media thickness (IMT) and impaired endothelial function from birth through early adulthood, indicating that the fetal environment may be an important modifier of postnatal vascular health. Whether LGA influences preclinical measures of arterial health and cardiovascular risk factors is poorly described and may provide important information concerning the relative cardiovascular risk in this group. One small study has previously described increased aortic IMT in LGA newborns, and a separate study demonstrated a nonlinear association of birth weight with carotid IMT in childhood, with a significantly higher carotid IMT in those in the highest quintile of birth weight when compared with those in the middle quintile. LGA is associated with increased systolic blood pressure and prevalence of obesity in childhood, although evidence concerning cardiovascular risk factors during adulthood in those born LGA is limited.

Accordingly, we examined whether cardiovascular risk factors and measures of vascular health, including measures of...
both arterial structure and function, are altered in young adults who were born LGA.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

LGA, Adiposity, and Cardiovascular Risk Factors

At birth, those born LGA had greater length and body mass index (BMI; Table 1). The difference in BMI between those born LGA and those with normal birth weight was 1.8 kg/m² (SE 0.9) at birth, 0.8 kg/m² (SE 0.3) at study enrolment in 1980 (3–18 years old), and 1.3 kg/m² (SE 0.4) during adulthood. This translated to those born LGA having an increased odds of overweight (odds ratio, 1.58 [95% CI 1.06, 2.38]) and obesity (odds ratio, 2.05 [95% CI 1.22, 3.44]; adjusted for age, sex, study center, and socioeconomic status) during adulthood.

When data from across the entire birth weight spectrum were analyzed, there was a nonlinear association of birth weight as a continuous variable with BMI in adulthood, kg/m² 25.1 (4.6) 26.4 (4.9) 0.002. There was a nonlinear association of birth weight as a continuous variable with carotid IMT across the entire birth weight spectrum (P=0.02 for nonlinear association; results for birth weight categories presented in Figure III in the online-only Data Supplement). When restricted to participants with birth weight >10th percentile, the association between birth weight and BMI was linear (P<0.0001 for linear association, P=0.88 for nonlinear association).

In addition to BMI, those born LGA also had greater waist circumference during adulthood (Table 1), and increased odds of having a high risk waist circumference consistent with an increased risk of metabolic complications (odds ratio, 1.83 [95% CI 1.15, 2.91]) and substantially increased risk of metabolic complications (odds ratio, 2.04 [95% CI 1.27, 3.28]; adjusted for age, sex, study center, and socioeconomic status).

Despite having increased adiposity, those born LGA did not have altered lipids, blood pressure, glucose, or C-reactive protein as young adults (Table 1).

LGA, Carotid IMT, and Brachial Flow–Mediated Dilatation

Carotid IMT was greater in those born LGA, when compared with those born with normal birth weight (Table 1), similar across adult BMI categories (Figure, Figure IV in the online-only Data Supplement), and independent of age, sex, study center, socioeconomic status, cardiovascular risk factors, and BMI during both adulthood and childhood (Table 2, Table I in the online-only Data Supplement). These results remained unchanged after further adjustment for additional childhood risk factors including low-density lipoprotein–cholesterol, high-density lipoprotein–cholesterol, triglycerides, and systolic blood pressure (LGA, β=0.020 mm [95% CI 0.005, 0.034], P=0.008 compared with normal birth weight). Adjustment for height or carotid end-diastolic diameter did not alter the results (LGA, β=0.025 mm [95% CI 0.011, 0.040], P=0.0007, base model adjusted for height; LGA, β=0.024 mm [95% CI 0.010, 0.039], P=0.0008, adjusted for carotid diameter). Sensitivity analyses using cut points of 25–75th percentile for normal birth weight gave essentially similar results. There was a nonlinear association of birth weight as a continuous variable with carotid IMT across the entire birth weight spectrum (P=0.02 for nonlinear association; results for birth weight categories presented in Figure III in the online-only Data Supplement). When restricted to participants with birth weight >10th percentile, the association between birth weight and carotid IMT was linear (P<0.0001 for linear association, P=0.88 for nonlinear association).
participants with birth weight >10th percentile, the association of birth weight with carotid IMT remained nonlinear ($P=0.02$ for nonlinear association).

Brachial flow-mediated dilatation did not differ between those born LGA and those born with normal birth weight (Table 1). Adjustment for age, sex, smoking, study center, socioeconomic status, and brachial artery diameter did not change this result (LGA, $\beta=0.1\%$ [95% CI, $−0.6$ to $0.9$] compared with normal birth weight). The association of birth weight as a continuous variable with brachial flow-mediated dilatation across the entire birth weight spectrum was linear ($P=0.001$ for linear association, $P=0.50$ for nonlinear association; results for birth weight categories presented in Figure III in the online-only Data Supplement). When restricted to participants with birth weight >10th percentile, the association of birth weight with brachial flow-mediated dilatation remained linear ($P=0.007$ for linear association, $P=0.18$ for nonlinear association).

**Discussion**

In this article, we demonstrate that young adults who were born LGA are more likely to be overweight and obese, with increased waist circumference and greater arterial wall thickness. Furthermore, this association of LGA with arterial wall thickness was only modestly attenuated when accounting for established cardiovascular risk factors and body size in childhood and adulthood, suggesting that other mechanisms are involved. Indeed, both obesity and LGA were independently associated with subclinical atherosclerosis in a graded and additive fashion. The association of LGA with arterial wall thickness seemed to be of similar magnitude to that previously observed in those born small for gestational age, at the other end of the birth weight spectrum, and was equivalent to a difference of 25 mm Hg higher systolic blood pressure, 4.4 mmol/L higher low-density lipoprotein–cholesterol concentration, 3.5 mmol/L lower high-density lipoprotein–cholesterol, and 8.0 kg/m$^2$ higher BMI in the same cohort.$^8$

By definition, LGA occurs in ≈10% of all live births$^{19}$ and, in the context of our findings, identifies a group at risk of obesity and subclinical atherosclerosis in adulthood, with likely implications for later risk of cardiovascular disease.

Previous evidence linking LGA with later cardiovascular disease has mostly been inferred from the strengthening of the inverse association of birth weight with adult cardiovascular disease when those born LGA are excluded,$^7$ nonlinear associations of birth weight with later disease,$^3$ or nonsignificant increases in risk.$^3,^4$ For example, in a meta-analysis of the association of birth weight with adult ischemic heart disease, the inverse association of birth weight with adult coronary heart disease was strengthened after excluding those with birth weight >4 kg.$^2$ In women, but not men, born in Iceland, there was a significant nonlinear association between birth weight and adult coronary artery disease, although those with the highest birth weights (>4000 g) did not have significantly increased odds when compared with those with normal birth weight.$^3$ Among both males and females born in Hertfordshire, there was some evidence for a small increase in the risk of mortality from cardiovascular disease.

**Table 2. Association of LGA With Carotid IMT**

<table>
<thead>
<tr>
<th>Risk adjusted</th>
<th>Mean Carotid IMT, mm</th>
<th>β-coefficient</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td></td>
<td>$0.026$</td>
<td>$0.012$, $0.040$</td>
<td>$0.0004$</td>
</tr>
<tr>
<td>Risk factor adjusted</td>
<td>LGA (vs normal birth weight)</td>
<td>$0.024$</td>
<td>$0.010$, $0.038$</td>
<td>$0.001$</td>
</tr>
<tr>
<td>Childhood and adulthood BMI adjusted</td>
<td>LGA (vs normal birth weight)</td>
<td>$0.021$</td>
<td>$0.007$, $0.036$</td>
<td>$0.003$</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>LGA (vs normal birth weight)</td>
<td>$0.022$</td>
<td>$0.007$, $0.036$</td>
<td>$0.003$</td>
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</tbody>
</table>

$β$-regression coefficients for mean carotid intima-media thickness (IMT; mm), derived from multivariable linear regression. Base model adjusted for age, sex, study center, employment status, and marital status. Risk factor–adjusted model adjusted as per base model, with additional adjustment for low-density lipoprotein–cholesterol, high-density lipoprotein–cholesterol, systolic blood pressure, triglycerides, glucose, C-reactive protein, and smoking status at time of IMT assessment. Childhood and adulthood body mass index (BMI)–adjusted model adjusted as per base model, with additional adjustment for BMI at study entry in 1980 and BMI at time of IMT assessment (2001 or 2007). Fully adjusted model adjusted as per base model, with additional adjustment for both risk factors and BMI during childhood and adulthood. CI indicates confidence intervals; and LGA, large for gestational age.
disease in those in the highest birth weight category, which the authors proposed may have been because of maternal diabetes mellitus, although the absolute number of events was low, and accordingly confidence limits were wide.4

Our study provides important information regarding increases in carotid IMT, a measure of subclinical atherosclerosis, and marked increase in the prevalence of obesity, in those born LGA. Other cardiovascular risk factors were similar in those born LGA when compared with those born with normal birth weight. Two studies have previously documented evidence of increased arterial wall thickness in those born LGA. One small study found that aortic IMT is increased in newborns born LGA, although for those born LGA to nondiabetic mothers this seemed to reflect proportional differences in body size.12 A separate study recently demonstrated a nonlinear association of birth weight with carotid intima-media thickness in childhood, with a significantly higher carotid intima-media thickness in those in the highest quintile of birth weight when compared with those in the middle quintile.13 Two other studies in adults have documented evidence that is potentially consistent with LGA being associated with increased carotid IMT; although neither has directly studied this association.10,11 Gale et al10 found a direct association of birth weight with later IMT in males, but not in females, however did not detail LGA specifically. Oren et al also detailed birth weight as a continuous variable and found a positive association of birth weight with later IMT in those who had the lowest postnatal growth. Although we have previously documented that those with LGA actually have high absolute postnatal weight gain,19 consistent with the increased BMI observed in our current study, Oren et al used change in percentiles to assess growth; a methodology that prohibits those with high birth weight from being defined as having increased growth.

Our findings extend these by demonstrating that the association of LGA with increased arterial IMT is independent of BMI and other cardiovascular risk factors during childhood and adulthood, and furthermore can coexist in a population in which small for gestational age is also associated with increased arterial IMT. Earlier studies have identified LGA as a risk factor for the metabolic syndrome.20,21 In the present study, individuals with LGA had nonsignificantly increased odds for the metabolic syndrome (results not shown), but our study may have been underpowered to show a significant association.

In this hypothesis-driven analysis, we have specifically focused on a key structural measure of vascular health, carotid IMT, and a key measure of arterial function, brachial flow–mediated dilatation, as per our previous study in people born with fetal growth restriction.8 Whether other markers of vascular health, such as coronary calcium score or measures of arterial stiffness, are altered in people born LGA may be the topic of future work. Although we were unable to identify the mechanisms involved in linking LGA with later subclinical atherosclerosis, we were able to identify risk factors that are unlikely to be involved, including established cardiovascular risk factors in childhood and adulthood. Genetic risk scores for fetal growth have previously been demonstrated to be associated with diabetic metabolism.22 Whether a similar association exists for atherosclerotic vascular disease is unknown. Although the unweighted genetic risk score analyses in our study only cover a fraction of the heritability of the metabolic risk factors, our results are consistent with the association of LGA with carotid IMT being independent of any such putative association (See online-only Data Supplement).

The lack of an association of LGA with arterial endothelial function, and the persistence of the association of LGA with carotid IMT after adjusting for cardiovascular risk factors, may indicate that the arterial damage is either acting via novel pathways or is the result of an early insult.23 Putative early life and parental risk factors that may be involved include maternal obesity,24 macrosomia resulting from gestational diabetes mellitus,12 and excessive weight gain during infancy.19 A lack of data concerning these potential maternal and early life risk factors is a limitation of the current work. The association of maternal glycemia with LGA seems complex. Although the association of pre-existing maternal diabetes mellitus and gestational diabetes mellitus with LGA is well described, there is also evidence of a U-shaped association between maternal glucose levels and risk of LGA.25 One small study has previously demonstrated that gestational diabetes mellitus is associated with higher arterial intima-media thickness in the exposed newborn offspring, independent of birth weight;25 however, whether such arterial abnormalities persist into adulthood and predispose to increased cardiovascular risk is unknown. Other limitations of the study include the lack of data on maternal diet during pregnancy, and paternal preconception overweight and obesity. Strengths of the current work include the relatively large sample, early recruitment during childhood and adolescence, and the long duration of follow-up.

Future studies may look to identify strategies to prevent this association of LGA with poor vascular health. For example, we have recently demonstrated that dietary or supplemental omega-3 fatty acids are associated with improved vascular health in those born small for gestational age.26 This seems to be mediated at least in part by alterations to blood pressure,26,27 and as such is unlikely to be of benefit for those born LGA, in whom there were no blood pressure disturbances. Our results suggest that weight maintenance in childhood and adulthood, although valuable from the perspective of potentially reducing the impact of overweight and obesity, would not seem to be a likely strategy to specifically limit the impact of LGA. One alternative however is that maternal interventions may be possible in the subgroup of those born LGA who are identified before birth.28

In conclusion, we have found that people born LGA have increased prevalence of obesity and central adiposity, and increased arterial wall thickness as young adults. These associations may contribute to an increased risk of cardiovascular disease in people born LGA.

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Disclosures

None.

References


Significance

There is an extensive body of evidence linking low birth weight with cardiovascular disease. We have previously demonstrated that people born with low birth weight have extensive modifications to their cardiovascular risk profile and poor vascular health. At the other end of the birth weight spectrum, people born with high birth weight may also be at risk of cardiovascular disease, although there is little direct evidence to support this.

Here, we demonstrate that young adults who were born with high birth weight (>90th percentile) have increased prevalence of obesity and carotid intima-media thickening; yet otherwise their cardiovascular risk profile seemed healthy. Both obesity and high birth weight were independently associated with subclinical atherosclerosis in a graded and additive fashion. These findings potentially identify a sizeable group of people at risk of obesity and arterial wall thickening independent of established cardiovascular risk factors.
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Supplemental results

The association of large for gestational age with increased carotid intima-media thickness (independent of age, sex, study center, socioeconomic status, cardiovascular risk factors and body mass index during both adulthood and childhood) remained unchanged after further adjustment for unweighted genetic scores for fetal growth, body mass index, height, waist:hip ratio, diabetes, blood pressure, coronary artery disease, intima-media thickness and carotid plaques (large for gestational age: $\beta = 0.025$ mm [95% CI 0.010, 0.041], $P = 0.001$ compared to normal birth weight).
Supplemental Table I. Association of LGA with maximum carotid IMT.

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<th>Maximum carotid IMT (mm)</th>
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<td></td>
<td>β-coefficient</td>
<td>95% CI</td>
<td>P-value</td>
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<tr>
<td><strong>BASE MODEL</strong></td>
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<tr>
<td>LGA (vs normal birth weight)</td>
<td>0.028</td>
<td>0.013, 0.043</td>
<td>0.0003</td>
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<td><strong>RISK FACTOR ADJUSTED</strong></td>
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<td>LGA (vs normal birth weight)</td>
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<td>0.011, 0.040</td>
<td>0.0008</td>
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<td><strong>CHILDHOOD &amp; ADULTHOOD BMI ADJUSTED</strong></td>
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<tr>
<td>LGA (vs normal birth weight)</td>
<td>0.023</td>
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<td>0.003</td>
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<td><strong>FULLY ADJUSTED</strong></td>
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<tr>
<td>LGA (vs normal birth weight)</td>
<td>0.023</td>
<td>0.008, 0.038</td>
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β-regression coefficients for maximum carotid IMT (mm), derived from multivariable linear regression. **Base model** adjusted for age, sex, study center, employment status, and marital status. **Risk factor adjusted** model adjusted as per base model, with additional adjustment for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, triglycerides, glucose, C-reactive protein and smoking status at time of IMT assessment. **Childhood and adulthood BMI adjusted** model adjusted as per base model, with additional adjustment for BMI at study entry in 1980 and BMI at time of IMT assessment (2001 or 2007). **Fully adjusted** model adjusted as per base model, with additional adjustment for both risk factors and BMI during childhood and adulthood.
Supplemental Figure I. Participant flow chart.

Children and adolescents randomly selected and invited to participate (n = 4320)

Baseline assessment [1980](n = 3596)

3 year follow-up [1983](n = 2991)
6 year follow-up [1986](n = 2779)

Birth weight data (n=2978)
- Born preterm (n = 311)

21 year follow-up visit [2001](n = 2283)
- Refused ultrasound examination (n = 18)
- Pregnant (n = 62)

27 year follow-up visit [2007](n = 2204)
- Refused ultrasound examination (n = 7)
- Pregnant (n = 37)

Non-pregnant non-preterm participants with data for birth weight, and carotid IMT or brachial FMD from 2001, or 2007 if missing from 2001 (n = 2028)
Supplemental Figure II. 3-month repeatability plots for mean carotid IMT, maximum carotid IMT, brachial FMD, and brachial diameter.

The 3-month between-visit differences in brachial FMD increased proportionally to the mean, and accordingly were log transformed for analysis. Solid lines represent no difference between visits; dotted lines on brachial FMD plot represent mean difference and 95% agreement limits.¹
Supplemental Figure III. Birth weight percentile and carotid intima-media thickness, brachial flow-mediated dilatation, and body mass index.

Data are mean (95% CI), adjusted for age, gender, study center, marital status and employment status; brachial flow-mediated dilatation further adjusted for resting brachial diameter. The associations of birth weight categories with: mean carotid IMT was nonlinear ($P = 0.003$); maximum carotid IMT was nonlinear ($P = 0.003$); flow-mediated dilatation was linear ($P = 0.002$); and body mass index was nonlinear ($P = 0.02$). All participants born at term ($\geq$37 weeks gestation). Birth weight percentiles for females: 10th = 2975 g, 25th = 3230 g, 50th = 3500 g, 75th = 3800 g, 90th = 4100 g; males: 10th = 3050 g, 25th = 3330 g, 50th = 3640 g, 75th = 3980 g, 90th = 4300 g.
Supplemental Figure IV. Large for gestational age and maximum carotid intima-media thickness, stratified by adulthood body mass index categories. Data are maximum carotid intima-media thickness, adjusted for age, sex, study center, marital status and employment status. P-values are for comparison with normal weight - normal birth weight category. For BMI categories: $P_{\text{trend}} < 0.0001$. For LGA: $P = 0.002$. For BMI category x birth weight category: $P_{\text{interaction}} = 0.59$. 
Supplemental references

MATERIALS AND METHODS

Participant population
In 1980, children and adolescents aged 3-18 years (n=3596) participated in the Cardiovascular Risk in Young Finns Study. The study was carried out in all 5 Finnish university cities with medical schools and their rural surroundings, with study participants chosen randomly from the national population register from these areas. The 21-year and 27-year follow-up visits were undertaken in 2001 and 2007. Data for birth weight, and carotid IMT or brachial artery flow-mediated dilatation were available for 2028 non-pregnant term-born participants from 2001, or 2007 if missing from 2001 (supplemental figure I).

The study complies with the Declaration of Helsinki, was approved by local ethics committees, and participants gave written informed consent.

Carotid IMT & Brachial flow-mediated dilatation
Ultrasound scans were undertaken at the five study centers, using standardized ultrasound equipment (Sequoia 512 with 13 MHz linear array transducer, Acuson, Mountain View, CA) and following standardized scanning protocols. Ultrasound measurements were undertaken in a central reading laboratory by a single blinded observer.

Carotid IMT and carotid diameter were assessed at end-diastole by high resolution noninvasive ultrasound, as previously described. Flow-mediated dilatation, expressed as percent change from resting arterial diameter, was assessed as previously described. A subset of 57 participants had a second ultrasound examination 3-months later, in order to assess between-visit repeatability (supplemental figure II). The 3-month between-visit repeatability coefficient was 0.12 mm for mean carotid IMT and 0.14 mm for maximum carotid IMT. For brachial FMD, about 95% of measures repeated at 3-months will be between 0.3 and 4.4 times that of the original measure. The 3-month between-visit repeatability coefficient for brachial diameter was 0.47 mm.

Assessment of socioeconomic, lifestyle and cardiovascular risk factors
Risk factors were measured in both 2001 and 2007. Fasting venous blood samples were drawn, and serum stored at -70ºC until analysis. Serum lipids were measured in duplicate as described previously, high-density lipoprotein cholesterol concentration was calculated, high-sensitive C-reactive protein was analyzed by latex turbidometric immunoassay (Wako Chemicals, Germany), and plasma glucose concentrations enzymatically (Olympus, Japan).

Blood pressure was measured using a random zero sphygmomanometer (Hawksley & Sons, UK); the average of 3 measurements was used in the analysis. Height, weight and waist circumference were measured, and body mass index (BMI) calculated. BMI categories were defined as normal weight (BMI <25 kg/m²; 55% of non-pregnant term-born participants, including the 1.5% of participants with BMI <18.5 kg/m²), overweight (BMI 25-29.9 kg/m²; 32% of participants), obese (BMI ≥30 kg/m²; 12% of participants). Waist categories were defined as normal risk (men <94 cm, women <80 cm), increased risk (men 94-101.9 cm, women 80-87.9 cm), and substantially increased risk (men ≥102 cm, women ≥88 cm) of metabolic complications. A self-administered questionnaire recorded prior diagnosis of diabetes (type 1 diabetes if diagnosis prior to age 24 years, and/or if the treatment used is insulin; type 2 diabetes if the participant uses oral anti-diabetic drugs, and did not suffer from diabetes in their youth), employment, marital, and smoking status.
Birth weight
At follow-up visits in 1983 and 1986, the participants together with their parents, completed a detailed questionnaire, including information on birth weight and gestation. Birth characteristics were confirmed from participants’ records from well-baby clinics. In the case of discrepancies, birth weight was averaged between values recorded in 1983 and 1986. Sex-specific birth weight percentiles were calculated based on all 2667 participants born at term and with birth weight data in the Young Finns study. Normal birth weight was defined as birth weight between the 50-75th percentile (n = 525; females: 3510-3800 g; males: 3650-3980 g), and LGA as birth weight >90th percentile (n = 171; females: >4100 g; males: >4300 g). The definition of LGA is a commonly used clinical definition. The percentile cut-points for the control group were chosen based on identifying a group with the lowest risk of cardiovascular events, while maintaining a small gap with the LGA group to avoid effect dilution.

Unweighted genetic risk scores
Unweighted genetic risk scores for fetal growth (7 SNPs), body mass index (32 SNPs), height (180 SNPs), waist:hip ratio adjusted for body mass index (14 SNPs), type 2 diabetes (34 SNPs), blood pressure (29 SNPs), coronary artery disease (42 SNPs), intima-media thickness (4 SNPs) and carotid plaques (4 SNPs), identified in recent GWAS meta-analyses, were calculated as the arithmetic sum of risk alleles in these SNPs. Genotyping was performed with the Illumina BeadChip (Human 670k). Genotype imputation was performed using MACH 1.0 and HapMap II CEU (release 22) samples as reference.

Statistical analysis
The primary analysis consisted of a comparison of those born with normal birth weight, with those born LGA. Differences in participant characteristics, cardiovascular risk factors, carotid IMT and brachial artery flow-mediated dilatation between LGA and normal birth weight were determined by independent samples t tests for continuous variables and chi-square tests for nominal variables. The associations of LGA with our key outcomes of interest (BMI, carotid IMT and brachial flow-mediated dilatation) were further detailed by multivariable linear regression adjusting for age, sex, study center, and socioeconomic factors (marital, employment status). When associations persisted in this base model, further models were generated with additional adjustment for: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, triglycerides, glucose, C-reactive protein and smoking status at time of IMT assessment (risk factor adjusted model); BMI at study entry in 1980 and BMI at time of ultrasound assessment (childhood and adulthood BMI adjusted model); both risk factors and BMI during childhood and adulthood (fully adjusted model). As additional mechanistic considerations of the ultrasound techniques, brachial flow-mediated dilatation models also included brachial diameter as a covariate, and additional IMT models incorporated height and carotid diameter as covariates. Covariates used in analysis, such as cardiovascular risk factors, were from the same visit as carotid IMT or brachial flow-mediated dilatation, unless otherwise stated.

To assess linear trend, birth weight and BMI categories were numbered from lowest to highest, and analyzed as continuous variables by multivariable linear regression. Nonlinear associations were examined by mean-centralized second order polynomials.

Multinomial logistic regression, adjusting for covariates as per the multivariable linear regression base model, was used to examine the associations of LGA with BMI categories and waist circumference categories.

No sex-based differences were present (data not shown). Non-normally distributed variables were log transformed prior to analysis. Statistical analysis was undertaken using
IBM SPSS Statistics (version 21.0; IBM Corp., Somers, NY), and statistical significance inferred at two-sided $P$ value $<0.05$. 
REFERENCES


