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# Birth Weight and Carotid Artery Intima-Media Thickness

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**Objectives** To determine the association between birth weight and carotid artery intima-media thickness (CIMT), a measure of atherogenesis, in a population of 11-year-old children.

**Study design** CIMT measured by high-resolution ultrasound, and birth registry data were available for 670 children of the Southern California Children's Health Study. Multivariate regression analyses were performed to investigate the association between birth weight and CIMT, with adjustment for child's health status and lifestyle, pregnancy information, and parental health.

**Results** Mean CIMT was 0.57 mm (SD 0.04). We found a nonlinear association between birth weight and CIMT, with an increase in CIMT of 0.014 mm in the fifth (*P* value .01) compared with the third birth weight quintile. These associations were robust in subsample analyses in children considered normal-weight by gestational age or in term-born children. No significant association with CIMT was found for the lowest quintile.

**Conclusions** Greater birth weight was significantly associated with increased CIMT at age 11 years. No evidence for an impact of lower birth weight was found. The predictive value of childhood CIMT on future cardiovascular outcomes is largely unknown, but strong associations between childhood cardiovascular disease risk factors and adult vascular disease suggest that increased CIMT in childhood may be clinically important. *(J Pediatr 2013;162:906-11)*.

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The hypothesis of the developmental origins of cardiovascular disease (CVD) was first raised by Barker and Osmond[1] in the year 1986. Since then, evidence in support of the hypothesis and the importance of intrauterine exposures and birth outcomes has grown. In various studies authors have shown early changes of the vasculature in childhood and the long-term clinical importance of early cardiovascular risk factors in children,[2,3] as well as the adverse impact of specific intrauterine exposures such as maternal smoking[4] or maternal hypercholesterolemia.[5] However, the question as to whether birth weight, as a proxy for the intrauterine environment and development, is associated with CVD remains unclear.

In general, studies on birth weight and vascular properties yield stronger associations with small for gestational age (SGA) and intrauterine growth restriction (IUGR) than with low birth weight.[6-9] Studies in newborns raise the question of the observations being a transient phenomenon.[9,10] This objection is partly refuted by studies in adult populations showing an association of birth weight and intima-media thickness (IMT); however, studies in adults remain inconsistent.[7,11,12] Interestingly, the greater birth weight range or children large for gestational age (LGA) remains understudied, although obesity in childhood has been associated with vascular health[13-15] and fetal overnutrition is associated with childhood obesity and metabolic dysfunction,[16] both main determinants of cardiovascular health. On the basis of these uncertainties, we investigated the hypothesis that both lower and greater birth weight is associated with carotid artery intima-media thickness (CIMT) in a population-based study of schoolchildren.

## Methods

This study was nested in the ongoing Southern California Children's Health Study.[17] From the 5341 kindergarten and first graders who were first en-

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| AGA | Appropriate weight for gestational age |
| BMI | Body mass index |
| CHS | Children's Health Study |
| CIMT | Carotid artery intima-media thickness |
| CVD | Cardiovascular disease |
| IMT | Intima-media thickness |
| IUGR | Intrauterine growth restriction |
| LGA | Large for gestational age |
| SGA | Small for gestational age |

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rolled in 2002, we sampled 738 children in 2007 to participate in a study of atherosclerosis. The children were recruited from public schools in 8 communities. Information was collected on personal, parental, and sociodemographic characteristics through questionnaire assessment; systolic/diastolic blood pressure, heart rate, height, and weight were measured; and B-mode carotid artery ultrasound was performed for assessment of CIMT. Heart rate, CIMT, and blood pressure were assessed by a single imaging specialist from the USC Atherosclerosis Research Unit, Core Imaging and Reading Center. The birth record for each participant was obtained from the state of California following necessary approvals.

Of the 738 eligible participants, 47 were excluded because they were born outside the State of California, inability to match to birth record, or indeterminate birth weight, leaving 691 participants in the study population. We excluded an additional 18 children born as part of a multiple pregnancy and 3 children with missing data on covariates, leaving 670 children for analyses.

The study protocol was approved by the institutional review board for human studies at the University of Southern California. Written informed consent was provided by a parent of the study subject, and verbal assent was provided by the participant.

High-resolution B-mode ultrasound images of the right common carotid artery were obtained with a portable Biosound MyLab 25 ultrasound system (Esaote North America, Inc, Indianapolis, Indiana) attached to a 10-MHz linear array transducer and read by a single operator. The imaging protocol, as described previously,[18,19] standardizes the timing, location, and distance over which CIMT is measured, ensuring comparability across participants (patents 2005, 2006, 2011). The jugular vein and carotid artery were imaged transversely and then longitudinally with the jugular vein stacked above the carotid artery. All images contained internal anatomical landmarks for reproducing probe angulation, and a 3-lead electrocardiogram was recorded simultaneously with the B-mode image to ensure that CIMT was measured at the R-wave in the cardiac cycle. Common carotid artery far-wall IMT was determined as the average of 70 to 100 measurements between the intima-lumen and media-adventitia interfaces along a 1-cm length defined by an electronic ruler proximal to the carotid artery bulb by automated computerized edge detection with an in-house developed software package (Prowin, patents 2005, 2006, 2011).[18,19]

Immediately after the IMT scan, blood pressure and heart rate were measured by standard techniques after the subject was recumbent for at least 10 minutes. Blood pressure was measured 3 times in 1-minute intervals with the use of an OMRON blood pressure monitor (OMRON, Tokyo, Japan) with automatic cuff inflation and deflation. Heart rate was measured with a 3-lead electrocardiogram as part of the Biosound MyLab 25 ultrasound system. The subject's standing height with the subject in stocking feet was measured to the nearest centimeter by the use of a metal measuring tape placed perpendicularly to the floor through the use of a construction-type bubble level and a measurement block to properly align head orientation. Weight was measured to the nearest pound with a medical-grade scale calibrated before each day's testing with the use of predetermined calibration weights.

Birth weight, gestational age, mode of delivery, and other reproductive data were obtained from California birth records. Birth certificate information for California-born children who participated in the Children's Health Study (CHS) was obtained by computerized linkage of participants with the California Department of Public Health, Birth Statistical Master Files, and Birth Cohort Files. Data obtained from California birth certificates included birth weight, gestational age, maternal age at birth, maternal residence postal code at birth, parity, pregnancy complications, and marital status. The estimated date of conception was assigned by the use of the birth date and gestational age, corrected for the average 2-week difference between the last menstrual period and conception. Gestational age was recorded for 640 children. Missing data were imputed by the use of weeks of prematurity if reported by the mother on the baseline questionnaire ($n = 6$) and otherwise a normal duration of pregnancy of 280 days was assumed ($n = 73$). Appropriate weight for gestational age (AGA) was defined as a birth weight between the 10th and 90th percentile on the basis of the sex-specific intrauterine growth curves by Olsen et al.[20] SGA was defined as <10th percentile for gestational age and sex and LGA correspondingly >90th percentile.

The study questionnaire included questions on medical history of the biological mothers and fathers, such as stroke, heart failure, heart attack, or angina. In addition, parents were asked whether they had ever had high blood pressure, high cholesterol, or diabetes. Further covariates on health, sociodemographic, and lifestyle characteristics were taken from the yearly surveys since first enrollment in 2002. Parental health information and pregnancy characteristics were reported in the first survey. Children's health and lifestyle data were collected at each survey.

## Statistical Analyses

Basic descriptive analyses and univariate associations between CIMT and birth characteristics, sociodemographic, and lifestyle factors were investigated for the analytic sample and compared with the total study population. Second, multivariate regression analyses were performed in the full analytic sample and in the following subsamples: (1) singleton births who were AGA as determined by the intrauterine weight curves of Olsen et al[20] ($n = 562$); and (2) singletons born at term ($n = 531$). Term born was defined as birth between gestational weeks 37-41. The final model was adjusted for child's sex, age, body mass index (BMI), systolic blood pressure measurement, and asthma status at time of CIMT measurement; maternal cardiovascular and metabolic pregnancy complications; delivery mode; annual household income; and race/ethnicity and study community. Additional covariates evaluated but not included in the final regression