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Birth Weight and Carotid Intima-media Thickness: New Perspectives from the Atherosclerosis Risk in Young Adults (ARYA) Study

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PURPOSE: Although intrauterine growth retardation (IUGR) is associated with increased risk of cardiovascular disease (CVD) in adult life, it is unclear whether the relationship is present at younger ages. Furthermore, current debate suggests that postnatal factors might be at least as important as prenatal conditions. The authors investigated whether low birth weight leads to an increased risk of subclinical atherosclerosis in a population-based sample of 750 Dutch men and women, aged 27 to 30 years.

METHODS: Information about birth characteristics was available from the original charts of the Municipal Health Service, Utrecht, The Netherlands. Cardiovascular risk factors were evaluated by a questionnaire. The extent of atherosclerosis, assessed by carotid intima-media thickness (CIMT), was measured in both common carotid arteries.

RESULTS: Overall, birth weight was not related to common CIMT. However, in the lowest tertile of birth length an inverse association between birth weight and common CIMT was observed. Moreover, low birth weight was significantly associated with increased common CIMT in those who showed exaggerated postnatal growth.

CONCLUSION: These findings suggest that low birth weight is only associated with increased common CIMT in young adulthood in those who experienced severe IUGR and in those who showed exaggerated postnatal growth.

Ann Epidemiol 2004;14:8–16. © 2003 Elsevier Inc. All rights reserved.

KEY WORDS: Birth Weight, Carotid Intima-media Thickness, Postnatal Growth, Subclinical Atheroscelrosis, Young Adulthood.

INTRODUCTION

Several studies, largely restricted to middle-aged and elderly populations, have shown that small body size at birth may be associated with both atherosclerosis and cardiovascular disease (CVD) (1–4). Besides, evidence is accumulating in both young and elderly populations for a relationship between birth characteristics and raised blood pressure (5–7), high body mass index (BMI) (8), dyslipidemia (9), glucose intolerance (10), and elevated fibrinogen or clotting factor VII (11). The mechanisms underlying these relationships have initially been attributed to an unfavorable intrauterine environment that may induce permanent changes in the structure, metabolism and physiology of fetal organs, Barker's "fetal origin hypothesis" (12). However, Barker's theory has been criticized and discussed openly in recent literature (13), suggesting that postnatal growth in early childhood may be at least as important as intrauterine conditions in the mechanism underlying the relation between reduced birth weight and increased risk for CVD in adult life (14, 15).

Two concepts should be addressed in this context. First, intrauterine growth impairment might lead to underdeveloped vascular beds, i.e. unfavorable collagen to elastin ratio, and increased risk of atherosclerosis in adult life independent of conventional risk factors for CVD (16). Second, exaggerated postnatal growth, i.e. faster than based on genetic constitution ("detracking"), might play a key role in the development of vascular damage in later life since it might result in obesity during child- or adult-hood with increasing risk for atherosclerosis in later life (8, 17, 18).

High-resolution B-mode ultrasonography provides a noninvasive method to quantify arterial wall thickening and atherosclerosis progression. Carotid intima-media thickness (CIMT) has been shown to be a strong predictor of cardiovascular morbidity and mortality in middle-aged and elderly subjects (19, 20) and to be strongly related to cardiovascular risk factors in healthy young adults (21–24). Additionally,

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Received June 7, 2002; accepted March 27, 2003.

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360 Park Avenue South, New York, NY 10010

1047-2797/04/$–see front matter
doi:10.1016/S1047-2797(03)00068-1

common CIMT may be regarded as a valid marker of generalized atheroslcerosis since it is strongly associated with atherosclerosis in other parts of the arterial system (23, 25).

The objective of this study was to evaluate the relationship between birth weight and subclinical atherosclerosis, assessed by common carotid intima-media thickness, in healthy young men and women, aged 27 to 30 years. In addition, to further elucidate the underlying mechanism, the impact of severe IUGR and an exaggerated postnatal growth in young infancy on the relation between birth weight and common CIMT was studied.

MATERIALS AND METHODS

Study Design and Population

The Atherosclerosis Risk in Young Adults (ARYA) study consists of two birth cohorts of young adults. Vascular measurements were only performed in the Utrecht cohort and hence this article is restricted to that part of the ARYA study (26). The Utrecht cohort comprises 750 young adults born between 1970 and 1973, who attended secondary school in the city of Utrecht in The Netherlands and for whom original medical records were available from the Municipal Health Service.

To enroll ARYA participants in Utrecht, a stepwise procedure was used: all available Municipal Health Service charts (n = 15,592) were checked for the presence of adequately registered birth weight (birth weight notations with a ± sign were excluded) and at least one blood pressure measurement during adolescence. All young adults with a complete chart (n = 4208; 26.9%) were invited by mail (last-known parental address) to participate in the study. 2191/4208 (52.1%) individuals did not respond despite regular mailings, 726/4208 (17.3%) letters were returned because of an inadequate address, 470/4208 (11.2%) subjects declined to take part and 821/4208 (19.5%) were willing to participate. Of the eligible 821 young adults, 14 were excluded because of pregnancy and 55 declined to participate after they had given informed consent. Two candidates did not appear at our clinic. Ultimately, 750 young adults completed participation in the Utrecht part of the ARYA study. From October 1999 to December 2000, the participants were asked to visit our out-patient clinic twice within a 3-week period.

The ARYA-study was approved by the Medical Ethical Committee of the University Medical Center Utrecht and all participants gave written informed consent.

Birth Characteristics

In The Netherlands virtually all babies attend mother-and-child clinics, a part of the Municipal Health Service, in their first 4 years of life. Growth and development are monitored, vaccinations are given and parental advice is given when needed. The first contact is scheduled when the newborn is about 4 weeks old and at that time data, provided by the mother, on pregnancy, delivery and birth characteristics are recorded.

For purposes of the ARYA study, birth weight, birth length, gestational age and information about the delivery were obtained from the original charts of the Municipal Health Service. Since the presence of information on birth weight was one of the inclusion criteria for participation in the ARYA study, it was known in all participants but one, who was included by mistake. In contrast, length at birth and gestational age were known in 581/750 (77.5%) and 599/750 (79.9%) participants, respectively. Premature birth (n = 32) was defined as babies born before 37 weeks of gestation. There was no difference in gender, mean common CIMT, birth length, and gestational age between participants with and without complete birth data. In contrast, birth weight was significantly lower in those without known birth length.

Postnatal Growth

Most reports concerning the issue of postnatal growth use *z*-scores and delta-*z*-scores as a measure to quantify postnatal growth. Since we used routinely-assessed measurements of infant growth, we were not able to use *z*-scores because our children were not measured at the same age, but over quite an age range. Hence, an alternative measure, which reflects the shift in the distribution was needed. In our study, postnatal growth within the first 2 years of life was defined as the difference in gender-specific decile of weight at the age of 6, 12, 18, or 24 months compared to the gender-specific decile of weight at birth. Difference in deciles (Δ-decile) was calculated in each of the 4 periods: between birth and 6 months of age (0–6 months), birth and 1 year of age (0–12 months), birth and 1.5 years of age (0–18 months) and birth and 2 years of age (0–24 months). So, a person who was in the 30th percentile at birth, and at the 90th percentile at 6 months of age obtained a Δ-decile for the 0–6 months period of 90-30. For a person that had the opposite, a 30-90 score was obtained. Next, to define the growth-pattern during infancy each Δ-decile was divided into tertiles of the distribution. The lowest, middle, and highest tertiles of Δ-decile were used as measure for minimal, constant, and exaggerated ("catch-up") growth in early life, respectively.

Cardiovascular Risk Factors at Young Adulthood

At each visit blood pressure was measured twice after 5 minutes rest and at an interval of 5 to 15 minutes, on the left arm in sitting position, with an automated device

(Dinamap) without replacing the cuff between the two measurements. Mean systolic and diastolic blood pressure were calculated as the average of the four measurements. During the first visit anthropometric measurements were performed. Height, weight, and waist-hip circumference were measured with indoor clothes without shoes (27). A written standardized questionnaire was completed on miscellaneous cardiovascular risk factors, like family history of CVD, smoking habits, alcohol intake, current drug use and physical activity.

During the second visit fasting venous blood samples were drawn. The samples were stored at −20°C until all participants were enrolled in the study. Total cholesterol, high-density-lipoprotein (HDL)cholesterol, triglycerides, and glucose were determined using Vitros950 dry-chemistry analyzer (Johnson & Johnson, Rochester, New York, USA). Low-density-lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (TC−HDL−(0.45 * TG)) when TG < 8.0 mmol/l.

Common Carotid Intima-media Thickness (CIMT)

Ultrasonography of both the left and right carotid artery was performed in all 750 participants, using a 7.5 MHz linear array transducer (Acuson Aspen). On a longitudinal two-dimensional ultrasound image of the carotid artery, the near and far walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance of the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicated the intima-media thickness. When an optimal longitudinal image was obtained, it was frozen on the R-wave of the electrocardiogram and stored on video tape (Figure 1). This procedure was repeated at 4 predefined angles per side (180°, 150°, 120°, 90° for the right carotid artery and 180°, 210°, 240°, 270° for the left carotid artery) using the Meijer's arc.

The actual measurements were performed off-line. The frozen images on the video tape were digitized and displayed on a screen using additional dedicated software as described in detail by Wendelhag et al. (28). In short, the interfaces of the distal common carotid artery were marked over a length of 10 mm using an automated edge detection approach. The beginning of the dilatation of the distal carotid artery served as a reference point for the start of the measurement. The average of the intima-media thickness of the 8 predefined angles was used for each subject as a measure for current wall thickness of the common carotid artery. Both sonographer and reader were unaware of participants' birth data.

The reproducibility of the CIMT-measurement was assessed by scanning 21 subjects on a second occasion by another sonographer. Absolute mean difference (+ SE) of the repeated measurements between visits was 0.012 mm (0.004) for mean intima-media thickness of both carotid arteries. The intraclass correlation coefficient for repeated measurements was 0.84.

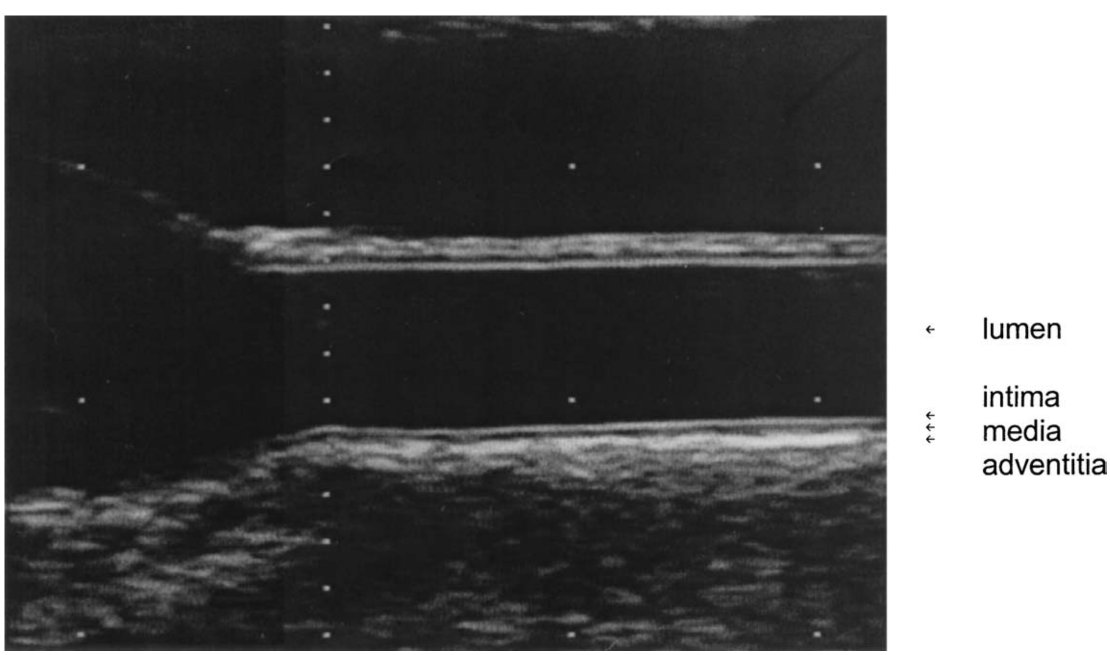

FIGURE 1. A characteristic longitudinal 2-D B-mode image of the distal common carotid artery from which intima-media thickness can be measured as the distance between the white line reflecting the lumen intima interface and the second white line reflecting the media-adventitita interface.

Statistical Analysis

The clinical and biochemical features of the population are presented as mean (standard deviation). The relationship between mean common CIMT, birth characteristics, and cardiovascular risk factors was evaluated by linear regression models. Common CIMT and birth weight were used as continuous variables in the analysis. Data on cardiovascular risk factors were analyzed either continuously or by tertiles of the distribution. Since there was a statistically significant difference in common CIMT between the two readers ($p \leq 0.001$) all analyses were adjusted for reader. All associations were expressed as linear regression coefficients with corresponding 95% confidence intervals.

The data were analyzed in four ways. A linear regression model with common CIMT as dependent variable and birth weight as independent variable was used, successively adjusted for reader and gender. To evaluate whether gender modifies the association between birth weight and CIMT, the model was repeated in men and women separately and was evaluated using a multiplicative interaction term. The second analysis step aimed to evaluate whether severe IUGR, defined as low birth weight combined with low birth length, modified the association by repeating the analysis in strata of tertiles of birth length. To be sure that our definition of severe IUGR reflects dysmaturity and not prematurity, the latter analysis was repeated after exclusion of the premature born babies. Third, in order to evaluate whether cardiovascular risk factors modify the relation of birth weight to carotid intima-media thickness, analyses were performed in tertiles of the risk factors—BMI, systolic and diastolic blood pressure, total- and LDL-cholesterol. Finally, to evaluate the effect of postnatal growth on the relationship between birth weight and common CIMT the analysis was performed in strata of growth-pattern in early infancy. In the group that showed exaggerated growth during infancy, mean common CIMT and BMI were compared between low birth weight (lowest quartile of birth weight), and normal birth weight infants to further elucidate the effect of infant growth on common CIMT.

Statistical analysis was performed with the statistical package SPSS-9.0 for Windows.

RESULTS

Among the 750 participants (352 male and 398 females) mean (SD) common CIMT was 0.49 (0.05) mm. Men had higher common CIMT, systolic blood pressure, diastolic blood pressure, LDL cholesterol, fasting glucose, and triglyceride levels than women. HDL cholesterol was lower in men compared to women and more men were current smokers. No gender difference was seen with respect to BMI and total cholesterol. Furthermore, men were heavier and longer at birth compared to women despite similar gestational age (Table 1).

In the overall analysis, adjusted for reader and gender, we did not observe an association between birth weight and common CIMT (linear regression coefficient = 1.5 μm/kg; 95% CI, −4.4, 7.3). Gender did not modify the relationship as indicated by a non-significant multiplicative interaction term. In addition, since there was no difference in birth weight between parental level of social-economical status (SES), defined as the highest educational level of the father, the linear regression coefficients from the model including parental SES did not change materially. However, the relationship between birth weight and common CIMT was inverse and significant in the lowest tertile of birth length (linear regression coefficient = −12 μm/kg; 95% CI, −6, −18). Adjustment for gender did not change these findings. Exclusion of premature birth strengthened this association, with a linear regression coefficient of −16 μm/kg; 95% CI, −9, −23 (Figure 2).

A consistent inverse trend in the relationship between birth weight and common CIMT was seen in young adults in the highest tertiles of current BMI, and systolic and diastolic blood pressure levels. None of these trends, however, reached statistical significance. In contrast, in lean young adults (lowest BMI tertile) high birth weight was related to increased common CIMT (Table 2).

TABLE 1. Characteristics of the 750 men and women in the Atherosclerosis Risk in Young Adults (ARYA) study at birth and at 28 years of age

	Men (N = 352)	Women (N = 398)
Age (Yr)	28.4 (0.9)	28.4 (0.9)
Male (%)		
Systolic blood pressure (mmHg)	131 (12)	121 (12)
Diastolic blood pressure (mmHg)	73 (8)	71 (8)
Body mass index (kg/m^2)	24.7 (3.7)	24.6 (0.5)
Total cholesterol (mmol/l)	4.8 (1.0)	4.8 (0.8)
HDL-cholesterol (mmol/l)	1.3 (0.3)	1.6 (0.4)
LDL-cholesterol (mmol/l)	2.9 (0.9)	2.7 (0.8)
Triglycerides (mmol/l)	1.4 (0.9)	1.2 (0.6)
Glucose (mmol/l)	5.2 (1.6)	4.8 (0.4)
Current smoker (%)	36%	27%
Carotid intima-media thickness (mm)	0.50 (0.05)	0.48 (0.05)
Birth weight (gram)	3479 (541)	3364 (546)
Birth length (cm)	51.3 (2.5)	50.4 (2.5)
Gestational age (wk)	39.8 (1.8)	39.8 (2.0)
Parental social economical status[a]	Low: 55% Middle: 23% High: 22%	Low: 48% Middle: 23% High: 29%

Values are expressed as mean (standard deviation).
HDL = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein-cholesterol.
[a]Social economical status is based on the highest educational level of participants' fathers.

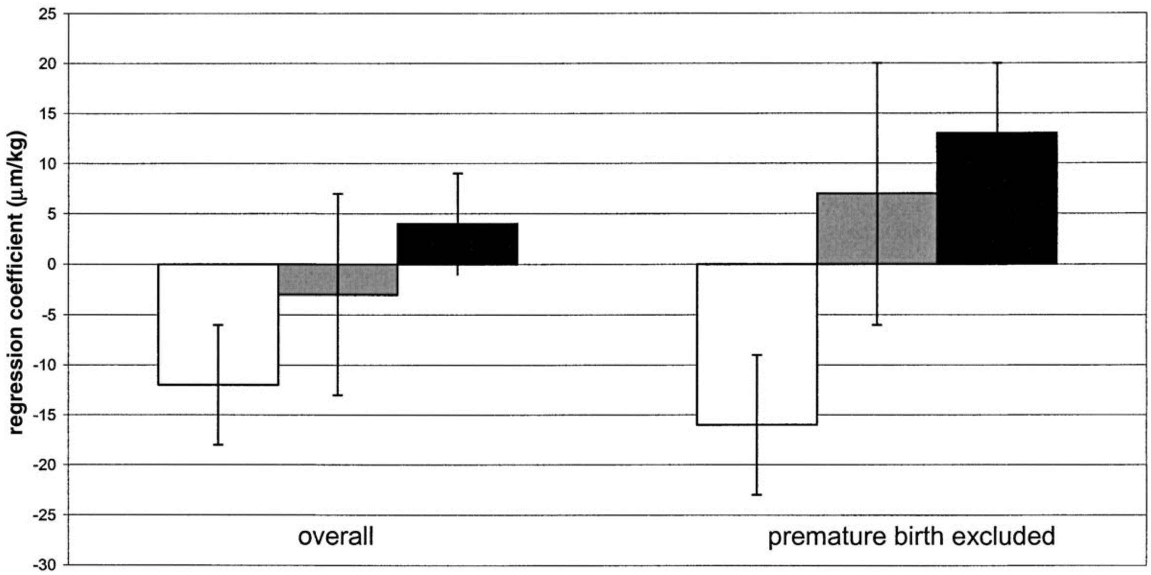

FIGURE 2. Association between birth weight and common carotid intima-media thickness, adjusted for gender and reader, by tertiles of birth length in young adults, participating in the Atherosclerosis Risk in Young Adults (ARYA) study in the Netherlands. The vertical lines represent the corresponding 95% confidence interval. (White bar Lowest tertile of birth length; gray bar Middle tertile of birth length; black bar Highest tertile of birth length.)

Birth weight was positively associated with common CIMT in subjects who showed minimal growth during infancy (linear regression coefficient for 0–24 months = 26 μm/kg; 95% CI, 9, 43). In contrast, birth weight was inversely associated with increased common CIMT in the participants who showed exaggerated ("catch-up") growth during infancy over a period of 2 years with a linear regression coefficient of –35 μm/kg; 95% CI, −18, −52 (Figure 3). Table 3 and 4 show mean common CIMT and BMI, respectively, in the group that experienced exaggerated growth in early infancy. Within this group, the highest common CIMT and BMI levels were seen in infants born in the lowest quartile of birth weight. Analysis in the group that showed constant growth over time revealed no difference in common CIMT and adult BMI while in the group of minimal growth, the children who were heavy at birth (highest quartile of birth weight) showed higher CIMT and higher adult BMI compared to the rest of the cohort (data not shown).

DISCUSSION

In ARYA participants who were short at birth, lower birth weight was associated with higher common CIMT at young adulthood independent of gender. Additionally, low birth weight was associated with an increased common CIMT in those who had experienced an exaggerated ("catch-up") growth in early postnatal life.

TABLE 2. Linear regression coefficients for the association between birth weight and common carotid intima-media thickness according to tertiles of current cardiovascular risk factors in young adults, participating in the Atherosclerosis Risk in Young Adults (ARYA) study

	Lowest tertile		Middle tertile		Highest tertile	
	B	95% CI	b	95% CI	B	95% CI
Body mass index (kg/m^2)	11.1	2.1; 20.2	1.3	−7.3; 9.9	−5.8	−17.3; 5.7
Systolic blood pressure (mmHg)	3.1	−6.3; 12.4	9.0	−0.6; 18.5	−7.4	−18.6; 3.7
Diastolic blood pressure (mmHg)	3.6	−6.1; 13.2	11.3	1.2; 21.3	−10.3	−20.9; 0.3
Total cholesterol (mmol/l)	−0.4	−10.6; 9.9	3.0	−6.4; 12.4	2.9	−7.8; 13.6
LDL-cholesterol (mmol/l)	−3.8	−12.7; 5.2	5.2	−4.6; 15.0	3.3	−8.2; 14.9

B = linear regression coefficients, adjusted for gender and reader, reflecting changes in common CIMT (in μm) by 1 kg increase in birth weight; 95% CI = 95 percent confidence interval.

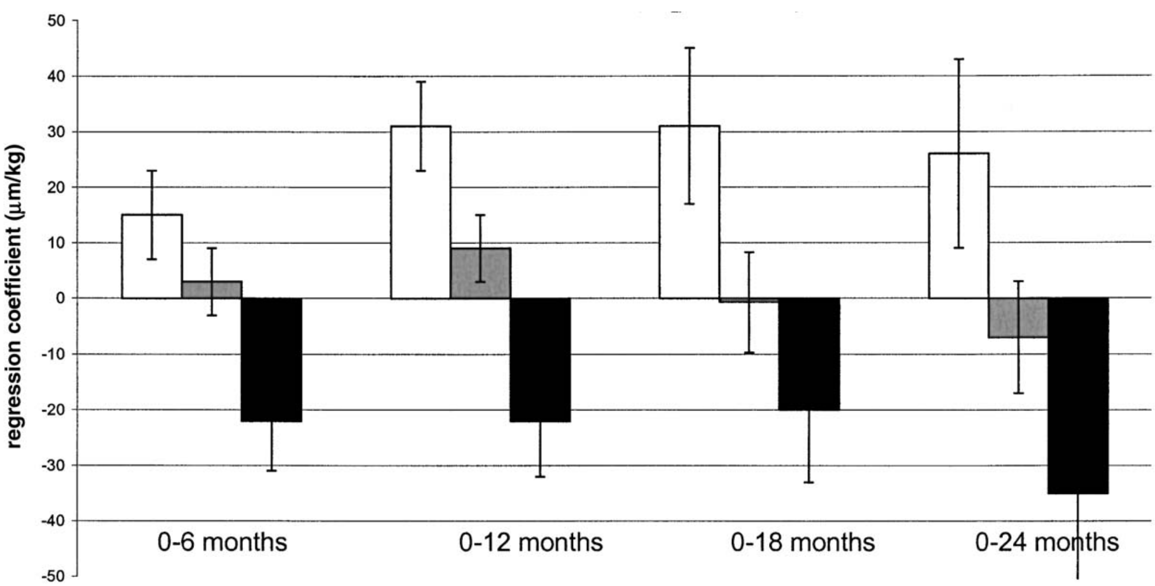

FIGURE 3. Association between birth weight and common carotid intima-media thickness, adjusted for gender and reader, according to postnatal growth pattern (evaluated over several periods) in young adults, participating in the Atherosclerosis Risk in Young Adults (ARYA) study in the Netherlands. The vertical lines represent the corresponding 95% confidence interval. (White bar Minimal postnatal growth; gray bar Constant postnatal growth; black bar Exaggerated postnatal growth.)

To appreciate these results some issues need to be addressed. The ARYA study was based on the 750 participants who were traced and agreed to attend the research clinic (18% of the 4208 letters sent). To evaluate whether selection bias might be an issue we collected information about birth weight, systolic and diastolic blood pressure as well as weight and height during adolescence from all charts matching our inclusion criteria in birth cohort 1970. None of these parameters was significantly different between responders and non-responders. Besides, the social and economical status as well as the educational level of our participants was comparable to mean population levels as provided by the Central Office for Statistics in The Netherlands (www.cbs.nl.). Moreover, since we have no reason to assume that the relationship between birth weight and common CIMT differs between responders and non-responders, we do not believe that our results are biased. Additionally, we were able to reduce misclassification of the birth characteristics to a minimum as we used written data from original

TABLE 3. Differences in mean common carotid intima-media thickness[a] at young adulthood between participants of the Atherosclerosis Risk in Young Adults (ARYA) study born in the lowest quartile of birth weight compared to the rest of the cohort who showed an exaggerated growth in several periods of early infancy

	Low birth weight[b]		Normal birth weight[c]	
	Mean	95% CI	Mean	95% CI
Birth–6 months (N = 191)	0.50	0.49, 0.51	0.49	0.48, 0.49
Birth–12 months (N = 145)	0.50	0.48, 0.51	0.48	0.47, 0.49
Birth–18 months (N = 82)	0.50	0.48, 0.53	0.49	0.47, 0.50
Birth–24 months (N = 59)	0.51	0.48, 0.53	0.47	0.46, 0.49

The first column represents the postnatal period in which the exaggerated growth, defined as the highest tertile of delta-decile, is calculated.
[a]Common CIMT is adjusted for reader and gender.
[b]low birth weight was defined as birth weight within the lowest quartile of the distribution.
[c]normal birth weight was defined as birth weight in the 2nd, 3rd or highest quartile of the distribution.
95% CI = 95 percent confidence interval.

TABLE 4. Differences in adult body mass index[a] between participants of the Atherosclerosis Risk in Young Adults (ARYA)-study born in the lowest quartile of birth weight compared to the rest of the cohort who showed an exaggerated growth in several periods of early infancy

	Low birth weight[b]		Normal birth weight[c]	
	Mean	95% CI	Mean	95% CI
Birth–6 months (N = 191)	24.8	23.4, 26.2	25.0	24.4, 25.6
Birth–12 months (N = 145)	25.1	23.7, 26.5	24.2	23.4, 25.0
Birth–18 months (N = 82)	26.2	24.4, 28.0	24.3	23.3, 25.3
Birth–24 months (N = 59)	25.9	23.2, 28.6	24.5	22.9, 26.1

The first column represents the postnatal period in which the exaggerated growth, defined as the highest tertile of delta-decile, is calculated.
[a]Body mass index is adjusted for gender.
[b]low birth weight was defined as birth weight with the lowest quartile of the distribution.
[c]normal birth weight was defined as birth weight in the 2nd, 3rd or highest quartile of the distribution.
95% CI = 95 percent confidence interval.

charts, which were filled in by the Municipal Health Service when the babies were about 1-month old, rather than relying on parental memory. An issue one should appreciate is that the sample size of the present study may be considered small, in particular for evaluating relations in subgroups.

With respect to our outcome measurement, CIMT is considered to be a good measure for generalized atherosclerosis (25, 29). It is strongly related to several conventional cardiovascular risk factors (30, 31) and has been shown to be a good predictor for CVD (19) in middle-aged and elderly subjects. Most conventional risk factors are already positively associated with subclinical atherosclerosis at a young age (22). Although direct evidence is lacking for the relation between common CIMT and future cardiovascular events in this age group, we feel that, given the relations with CVD risk factors and coronary calcification (23), individuals with the highest CIMT in young adulthood are more likely to be at higher risk to develop CVD in later life than subjects with the lowest CIMT.

Low birth weight infants are considered to have suffered growth retardation in utero if their birth weight appeared to be lower than it was expected to be. Previous studies in middle-aged subjects have shown an inverse association between birth weight and atherosclerosis as well as cardiovascular morbidity and mortality in later life (1–4, 12, 32, 33). However, in our young study population we were not able to fully confirm these findings. It is possible that Barker's theory only applies to specific subgroups rather than to the population at large. Firstly, Barker's hypothesis was postulated in middle-aged individuals born before World War II. Our young population, born between 1970 and 1973, might differ from the older population in respect to intrauterine circumstances (e.g., severity of experienced growth retardation in utero). The severity of IUGR might play a key role in the vascular underdevelopment of low birth weight infants. It is possible that only those who experienced severe adverse conditions in utero, expressed by low birth weight combined with short birth length, are the individuals whose vasculature developed in such a way that they become more at risk for CVD in later life. Our finding that only in severely growth retarded newborns is low birth weight related to thicker common CIMT in young adults agrees with that reasoning. A second difference between the elderly cohort in which Barker's hypothesis was postulated and worked out and our younger population might concern the current risk profile for CVD and threshold beyond which vascular damage begins to develop. The arterial system of low birth weight infants might be more susceptible to the adverse effects of the conventional risk factors for CVD such as increased BMI, dyslipidemia, smoking and raised blood pressure than newborns with normal birth weight. From this perspective the strongest relationship between low birth weight and common CIMT is expected to be in the "high-risk" individuals. Alternatively, the relative contribution of (low) birth weight for common CIMT increment is smaller in subjects with increased risk factors for CVD. From this latter perspective the strongest relationship between low birth weight and high CIMT is expected to appear in the "low-risk" individuals. To be able to evaluate this hypothesis we stratified ARYA participants according to current risk profile. Although statistically significant levels were not reached in any of these analyses, an inverse trend between birth weight and common CIMT was seen in the young adults with the highest current levels of BMI and systolic and diastolic blood pressure. Current risk factors might play a more important role in the development of atherosclerosis than intrauterine growth. It is plausible that the adverse influence of conventional risk factors on the development of vascular damage has to exceed a particular threshold before vascular damage appears. As the exposure time for those conventional risk factors is rather short due to the relatively young age of our population, it is possible that such high levels of risk factors have not yet existed long enough to initiate manifest vascular damage.

Based on recent discussion in the literature, an alternative explanation for the observed relationship between low birth weight and increased common CIMT concerns the more pronounced role of postnatal catch-up growth abilities in the development of CVD (14, 15, 18), especially in those who were small at birth. Growth during infancy might modify the relation between birth weight and CIMT. To evaluate this theory we stratified ARYA participants into 3 groups: exaggerated ("catch-up"), minimal, and constant growth. The infants with the lowest birth weight had the thickest common CIMT at young adulthood if they showed exaggerated growth during their first 2 years of life. In contrast, within the group that showed minimal postnatal growth in early childhood an increase in birth weight was associated with an increase in common CIMT. A comparable phenomenon has been described earlier with respect to systolic blood pressure. Low as well as high birth weights were associated with raised levels of systolic blood pressure in young children (34). Adverse intrauterine circumstances leading to either decreased or increased size at birth may contribute to the increased risk for elevated blood pressure and higher common CIMT seen in those individuals in adult life.

The positive trend in the relation between birth weight and common CIMT, observed in those whose adult BMI is in the lowest tertile and in young adults who showed minimal postnatal growth disagree with Barker's hypothesis and our other findings. The positive relation between birth weight and CIMT in lean adults might be explained by the fact that adult BMI is determined by tracking in lean adults ($r = 0.18$; $p = 0.004$) while it is determined by detracking in obese adults (r = 0.08; p = 0.202). In addition, the relation between adult BMI and common CIMT is positive in both groups. Hence, within the lean adults, those with the highest adult BMI should have had a relative high birth weight and the highest common CIMT, explaining the positive relation between birth weight and CIMT observed in this group. In contrast, within the obese adults, those with the highest adult BMI should have been LBW-infants and have the highest common CIMT, explaining the negative trend between birth weight and CIMT observed in this group. The positive relation between birth weight and common CIMT observed in those who showed minimal growth during early infancy might be explained by the fact that within this group, the children who were born with a relatively high birth weight (highest quartile) had the highest common CIMT. These results support the idea, mentioned above, that a U-shaped relationship might exist between birth weight and common CIMT. However, the underlying mechanism remains unknown.

In conclusion, our findings suggest that severe IUGR, resulting in both low birth weight and short birth length, is associated with increased risk of subclinical atherosclerosis in young adults. Moreover, low birth weight was related to increased CIMT in young adults who showed exaggerated postnatal growth. The combined effect of severe IUGR and postnatal growth pattern should be further extended in future research. However, our findings support the view that an exaggerated growth postnatally may be at least as important as prenatal factors to explain the relation between low birth weight and subsequent risk of cardiovascular disease.

We gratefully thank Dr. A.A.A. Bak for her logistic support during enrolment; R. Meijer for his support in the acquisition of CIMT-images; the staff at Municipal Health Care Utrecht for sending the mailings; Marjon vd Meer and Janneke vd Brink for their contribution in the fieldwork; and the staff at our data-management section for data processing.
The study was funded by the Health research and development council of The Netherlands (ZON).

REFERENCES

1. Martyn CN, Gale CR, Jespersen S, Sherriff SB. Impaired fetal growth and atherosclerosis of carotid and peripheral arteries. Lancet. 1998;352:173–178.
2. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. BMJ. 1993;307:1519–1524.
3. Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ. 1993;306:422–426.
4. Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15,000 Swedish men and women born 1915–29. BMJ. 1998;317:241–245.
5. Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5–7 years. BMJ. 1989;299:587–591.
6. Seidman DS, Laor A, Gale R, Stevenson DK, Mashiach S, Danon YL. Birth weight, current body weight, and blood pressure in late adolescence. BMJ. 1991;302:1235–1237.
7. Barker DJ, Godfrey KM, Osmond C, Bull A. The relation of fetal length, ponderal index and head circumference to blood pressure and the risk of hypertension in adult life. Paediatr Perinat Epidemiol. 1992;6:35–44.
8. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet. 1996;348:1478–1480.
9. Barker DJ, Martyn CN, Osmond C, Hales CN, Fall CH. Growth in utero and serum cholesterol concentrations in adult life. BMJ. 1993;307:1524–1527.
10. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ. 1991;303:1019–1022.
11. Barker DJ, Meade TW, Fall CH, Lee A, Osmond C, Phipps K, et al. Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. BMJ. 1992;304:148–152.
12. Barker DJ. Fetal origins of coronary heart disease. Br Heart J. 1993;69:195–196.
13. Poulter NR. Birthweights, maternal cardiovascular events, and Barker hypothesis. Lancet. 2001;357:1990–1991.
14. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ. 1999;318:427–431.
15. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001;322:949–953.
16. Martyn CN, Greenwald SE. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. Lancet. 1997;350:953–955.
17. Vanhala MJ, Vanhala PT, Keinanen-Kiukaanniemi SM, Kumpusalo EA, Takala JK. Relative weight gain and obesity as a child predict metabolic syndrome as an adult. Int J Obes Relat Metab Disord. 1999;23:656–659.
18. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000;320:967–971.
19. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2000;151:478–487.
20. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997;96:1432–1437.
21. Raitakari OT. Imaging of subclinical atherosclerosis in children and young adults. Ann Med. 1999;31(suppl. 1):33–40.
22. Sass C, Herbeth B, Chapet O, Siest G, Visvikis S, Zannad F. Intima-media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure.J Hypertens. 1998;16:1593–1602.
23. Davis PH, Dawson JD, Mahoney LT, Lauer RM. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. The Muscatine study. Circulation. 1999;100:838–842.
24. Homma S, Hirose N, Ishida H, Ishii T, Araki G. Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke. 2001;32:830–835.
25. Bots ML, Hofman A, De Jong PT, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. Ann Epidemiol. 1996;6:147–153.
26. Oren A, Vos LE, Bos WJ, Safar ME, Uiterwaal CSPM, Gorrissen WHM, Grobbee DE, Bots ML. Gestational age and birth weight in relation

to aortic stiffness in healthy young adults. Two separate mechanisms? Am J Hypertension. 2003;16:76–79.

27. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults (1998). 2001. Available at: www.nhlbi.nih.gov. Accessed

28. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analyzing system. Clin Physiol. 1991;11:565–577.

29. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol. 1997;146:483–494.

30. Stensland-Bugge E, Bonaa KH, Joakimsen O. Age and sex differences in the relationship between inherited and lifestyle risk factors and subclinical carotid atherosclerosis: the Tromso study. Atherosclerosis. 2001;154:437–448.

31. Bonithon-Kopp C, Scarabin PY, Taquet A, Touboul PJ, Malmejac A, Guize L. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb. 1991;11:966–972.

32. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2:577–580.

33. Barker DJ, Fall CH. Fetal and infant origins of cardiovascular disease. Arch Dis Child. 1993;68:797–799.

34. Launer LJ, Hofman A, Grobbee DE. Relation between birth weight and blood pressure: longitudinal study of infants and children. BMJ. 1993;307:1451–1454.