Low Birthweight Is Associated With Narrower Arterioles in Adults

Gerald Liew, Jie Jin Wang, Bruce B. Duncan, Ronald Klein, A. Richey Sharrett, Frederick Brancati, Hsin-Chieh Yeh, Paul Mitchell, Tien Y. Wong; for the Atherosclerosis Risk in Communities Study

Abstract—Low birthweight is associated with increased risk of hypertension, but underlying mechanisms are obscure. We hypothesized structural microvascular alterations may be one such mechanism. We examined the association of birthweight and retinal arteriolar caliber in 3800 persons aged 51 to 72 years participating in a population-based study in 4 US communities (the Atherosclerosis Risk in Communities study). Participants reported full-term birth and their birthweight and had retinal photography. Retinal arteriolar and venular calibers were measured from digitized retinal photographs using a validated computer-assisted method. Lower birthweight was associated with narrower retinal arteriolar caliber, with each kg lower birthweight associated with 2.4 μm (95% confidence intervals, 1.3 to 3.5, \(P<0.001\)) narrower retinal arteriolar caliber, after controlling for age, gender, race, education, smoking, alcohol consumption, adult body mass index, and height. Additional adjustment for blood pressure averaged over the past 6 years and fasting glucose did not alter these findings, with each kg lower birthweight associated with a 1.7 μm (95% confidence intervals, 0.7 to 2.8, \(P<0.001\)) narrower retinal arteriolar caliber. This association was also present in persons without hypertension or diabetes. Lower birthweight was not associated with retinal venular caliber. These findings provide evidence that structural alterations in the arteriolar microcirculation may be a potential mechanism linking restricted fetal growth with subsequent risk of hypertension. (Hypertension. 2008;51:933-938.)

Key Words: birthweight ■ hypertension ■ developmental origins hypothesis ■ Barker hypothesis

Hypertension is the major cause of morbidity and mortality worldwide.\(^1\) In the last decade, epidemiological and experimental data have shown that fetal growth restriction, commonly measured by low birthweight for gestational age, is associated with an increased risk of hypertension,\(^2-4\) and related conditions including diabetes,\(^2,5,6\) coronary heart disease,\(^7\) and stroke.\(^8\) This led to the concept that fetal “programming” during critical phases of development in utero\(^2,9\) may result in long-term structural changes in the vascular system.\(^10,11\) However, the underlying vascular mechanisms are not known, but their elucidation is clearly important in further understanding the etiology of hypertension and cardiovascular disease.\(^12\)

It has been hypothesized that low birthweight may have an adverse impact on microcirculatory structure,\(^13,14\) possibly initiating a cascade of arteriolar narrowing and vasoconstriction that ultimately leads to the development of hypertension. Clinical studies testing this hypothesis, however, are limited by the difficulty in assessing arteriolar structure in vivo.\(^15,14\) The retinal vasculature, which measures between 100 to 300 μm in diameter, can now be noninvasively imaged from retinal photographs, offering the unique opportunity for detailed examination of the microcirculation in vivo.\(^15-17\) In large prospective population-based studies, retinal arteriolar narrowing has consistently been shown to predict the onset of hypertension,\(^18-20\) as well as related conditions linked to low birthweight, such as diabetes,\(^21,22\) coronary heart disease,\(^23-25\) and stroke.\(^16,26\) These observations therefore suggest that retinal arteriolar narrowing may represent an early preclinical vascular change, possibly related to underlying endothelial dysfunction.\(^17\) Thus, we hypothesize that low birthweight may be associated with retinal arteriolar narrowing, and we test this hypothesis in a population-based study in middle-aged adults.

Methods

Study Population

The Atherosclerosis Risk In Communities (ARIC) study is a population-based study of middle-aged adults (45 to 64 years of age at recruitment in 1987 to 1989) randomly sampled from 4 US communities: Forsyth County, NC; Jackson, Miss; suburbs of...
Table 1. Characteristics of Participants, the Atherosclerosis Risk In Communities Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included in Analyses n=3800</th>
<th>Excluded From Analyses n=9087</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>58.8 (5.6)</td>
<td>60.5 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1455 (38.3)</td>
<td>4122 (45.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blacks, n (%)</td>
<td>490 (12.9)</td>
<td>2321 (25.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>211 (5.6)</td>
<td>57 (10.3)</td>
<td></td>
</tr>
<tr>
<td>2.5 to 3.0</td>
<td>675 (17.8)</td>
<td>95 (17.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;3.0 to 3.5</td>
<td>1394 (36.7)</td>
<td>200 (36.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;3.5 to 4.0</td>
<td>1029 (27.1)</td>
<td>144 (26.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;4.0 to 4.5</td>
<td>491 (12.9)</td>
<td>58 (10.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Retinal arteriolar caliber, μm (SD)</td>
<td>162.4 (17.0)</td>
<td>162.2 (16.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg (SD)</td>
<td>122.5 (17.9)</td>
<td>125.3 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg (SD)</td>
<td>71.5 (10.2)</td>
<td>71.8 (10.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>28.4 (5.5)</td>
<td>28.6 (5.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Adult height, cm (SD)</td>
<td>168.0 (9.4)</td>
<td>169.0 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive, n (%)</td>
<td>1349 (35.5)</td>
<td>3731 (41.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic, n (%)</td>
<td>454 (12.0)</td>
<td>1439 (15.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school education, n (%)</td>
<td>3319 (87.0)</td>
<td>6704 (73.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; BP, blood pressure.

Assessment of Birthweight
The birthweight data have been previously described by Tilling et al.28 In brief, participants were asked to report their birthweight in pounds and ounces, which we then converted to SI (System International) units. We examined the representativeness of our sample by comparing birthweight distributions with those recorded for 1950 by the US National Center for Health Statistics.29 The distribution of birthweight was broadly similar to 1950 population figure (when most participants were born), but participants appeared to have overreported birthweights >4.5 kg (9% versus 2%)—we hence excluded participants with birthweight >4.5 kg (n=248) and categorized the remaining participants into 5 ordered birthweight categories (<2.5 kg, 2.5 to 3.0 kg, >3.0 to 3.5 kg, >3.5 to 4.0 kg, and >4.0 to 4.5 kg). In the ARIC study, birthweight data followed expected patterns of associations with sex, height, weight, and body mass index (BMI).28

Measurement of Retinal Vascular Caliber
The retinal photography procedure and measurement of retinal vascular caliber has been described in detail elsewhere.15,23 Briefly, after 5 minutes of dark adaptation, we used an auto-focus camera to take a 45-degree photograph (centered on the region of the optic disc and the macula) of 1 randomly selected eye of each participant at the 3rd examination. We digitized the fundus photographs and used a validated computer-assisted method15 to measure the diameters of all arterioles and venules coursing through a prespecified region half to 1-disc diameter from the optic disc margin, from which we calculated a value representing the mean arteriolar and venular caliber.15 This method has high reproducibility (intra- and intergrader reliability coefficients of 0.84 and 0.79, respectively), and has been successfully used in several epidemiological surveys to investigate the relation of retinal vessel caliber to hypertension and cardiovascular disease.16,18–26

Definition of Other Variables
Participants underwent standardized evaluations at each ARIC study examination.30 Blood pressures were taken with a random-zero sphygmomanometer, and the mean of the last 2 of 3 measurements was taken. We averaged blood pressure from the 1st, 2nd, and 3rd examinations to obtain 6-year average systolic and diastolic blood pressures. We used this variable to control for present and past blood pressure to examine the independent effect of birthweight on retinal vascular caliber. Hypertension, diabetes, cigarette smoking history, use of antihypertensive and diabetic medications, and highest educational level were ascertained from questionnaire and examination. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication during the previous 2 weeks. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL (≥7.0 mmol/L), or a nonfasting glucose ≥200 mg/dL (≥11.1 mmol/L), or a self-reported history of physician-diagnosed diabetes or pharmaceutical treatment for diabetes. Body mass index (BMI) was calculated from standing height and weight measured at the 3rd examination. Total plasma cholesterol and triglycerides were measured by enzymatic methods, and HDL cholesterol was measured after dextran-magnesium precipitation of the non-HDL lipoproteins. Education level was defined as: (1) grade school or 0 years education; (2) high school, but no degree; (3) high school graduate; (4) vocational school; (5) college; (6) graduate school or professional school. Data from the 3rd examination (except for birthweight [4th visit], blood pressure [1st to 3rd visits], and educational level [1st visit]) were used for analyses.

Statistical Methods
We modeled birthweight in categories (<2.5 kg, 2.5 to 3.0 kg, >3.0 to 3.5 kg, >3.5 to 4.0 kg, and >4.0 to 4.5 kg), and continuously, and examined associations with blood pressure and retinal vessel caliber. We constructed 3 multivariate models: model 1 adjusted for age (continuous), gender, race, and study center; model 2 adjusted for the variables in model 1 plus educational level (6 levels), BMI (continuous), height (continuous), present cigarette smoking (versus ex or never), present alcohol consumption (versus ex or never), total plasma cholesterol, high density cholesterol, triglycerides, fasting glucose (except for 89 participants who provided nonfasting glucose levels)—last 4 variables continuous; and model 3 adjusted for the variables in model 2 plus 6-year average systolic and diastolic blood.
pressure (continuous). We used analysis of covariance to estimate adjusted (model 2) systolic and diastolic blood pressure with birthweight categories and arteriolar caliber quintiles. Logistic regression was used to determine the odds ratio of hypertension with decreasing birthweight categories and increasing arteriolar caliber quintiles. Analysis of covariance was used to determine the relationship of birthweight categories with retinal arteriolar and venular caliber, and multiple regression to assess changes in arteriolar caliber per kg decrease in birthweight. We tested for interaction by including appropriate cross product terms in the full model and also performed subgroup analyses stratified by sex, race, hypertension, diabetes, and BMI (in tertiles). SAS version 9.1 (SAS Institute) was used for all analyses.

Results

In the study population, the mean birthweight was 3.34 (±0.52 SD) kg, mean retinal arteriolar caliber was 162.4 (±17.0) μm, and mean retinal venular caliber was 192.5 (±16.5) μm.

Table 2 shows the association of birthweight and retinal arteriolar caliber with blood pressure and hypertension. Both lower birthweight and narrower retinal arteriolar caliber were associated with higher systolic blood pressure, higher diastolic blood pressure, and higher odds of hypertension. The Figure shows the inverse relationship of systolic blood pressure with retinal arteriolar caliber.

Table 3 shows the association of birthweight and retinal arteriolar and venular caliber, adjusting for variables in models 1 to 3. Lower birthweight was consistently associated with narrower retinal arteriolar caliber in all 3 models. After adjustment for age, race, education level, BMI, adult height, and other variables in model 2, persons with birthweight in the <2.5 kg category had mean arteriolar caliber 3.3 μm narrower than persons in the >4.0 to 4.5 kg category (160.3 versus 163.6 μm respectively, \( P \) trend <0.0001). Additional adjustment for systolic and diastolic blood pressure averaged

### Table 2. Birthweight, Retinal Arteriolar Caliber, and Blood Pressure

<table>
<thead>
<tr>
<th>Birthweight and Retinal Arteriolar Caliber Categories</th>
<th>Number</th>
<th>Mean Systolic BP, mm Hg (SD)*</th>
<th>Mean Diastolic BP, mm Hg (SD)*</th>
<th>OR (95% CI) of Hypertension*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>211</td>
<td>124.6 (18.0)</td>
<td>71.8 (10.0)</td>
<td>1.35 (0.93 to 1.96)</td>
</tr>
<tr>
<td>2.5 to 3.0</td>
<td>675</td>
<td>124.4 (19.2)</td>
<td>72.1 (10.0)</td>
<td>1.29 (0.98 to 1.70)</td>
</tr>
<tr>
<td>&gt;3.0 to 3.5</td>
<td>1394</td>
<td>122.8 (18.3)</td>
<td>71.7 (10.2)</td>
<td>1.12 (0.88 to 1.43)</td>
</tr>
<tr>
<td>&gt;3.5 to 4.0</td>
<td>1029</td>
<td>121.2 (17.1)</td>
<td>71.3 (10.0)</td>
<td>1.04 (0.82 to 1.34)</td>
</tr>
<tr>
<td>&gt;4.0 to 4.5</td>
<td>491</td>
<td>120.4 (16.8)</td>
<td>70.6 (10.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Retinal arteriolar caliber, (range in μm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narrowest quintile (84.2 to 148.5)</td>
<td>773</td>
<td>128.8 (18.3)</td>
<td>75.5 (10.4)</td>
<td>3.33 (2.61 to 4.24)</td>
</tr>
<tr>
<td>2nd quintile (148.6 to 158.3)</td>
<td>753</td>
<td>124.9 (17.6)</td>
<td>73.2 (10.3)</td>
<td>2.27 (1.77 to 2.90)</td>
</tr>
<tr>
<td>3rd quintile (158.4 to 166.1)</td>
<td>738</td>
<td>123.3 (17.1)</td>
<td>71.6 (9.4)</td>
<td>1.87 (1.46 to 2.40)</td>
</tr>
<tr>
<td>4th quintile (166.2 to 175.9)</td>
<td>770</td>
<td>120.1 (17.1)</td>
<td>70.3 (9.4)</td>
<td>1.46 (1.14 to 1.87)</td>
</tr>
<tr>
<td>Widest quintile (176.0 to 240.9)</td>
<td>766</td>
<td>115.4 (16.8)</td>
<td>67.1 (9.8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; BP, blood pressure.

*Mean systolic or diastolic BP, and odds ratio (OR) of hypertension comparing birthweight and retinal arteriolar caliber categories, adjusted for age, gender, race, center, educational level, body mass index, adult height, current cigarette smoking, current alcohol consumption, total cholesterol, high density lipoprotein cholesterol, triglycerides, fasting glucose level (Model 2).

†P value for linear trend across categories.

Figure. Systolic blood pressure and retinal arteriolar caliber. Data are mean (μm) and 95% confidence intervals.
over the past 6 years attenuated this association only slightly (161.0 versus 163.1 μm for <2.5 kg versus 4.0 to 4.5 kg categories respectively, \[P=0.005\]). Birthweight was not associated with venular caliber in models 1 to 3.

In Table 4, the same association of birthweight modeled continuously with arteriolar caliber was observed, with each kg decrease in birthweight associated with 2.4 μm (95% confidence intervals, 1.3 to 3.5, \[P<0.0001\]) narrower arterioles after multivariate adjustment in model 2. Additional adjustment for blood pressure averaged over the past 6 years and fasting glucose did not alter these findings, with each kg lower birthweight associated with a 1.7 μm (95% confidence intervals, 0.7 to 2.8, \[P<0.001\]) narrower retinal arteriolar caliber. The association persisted in persons without hypertension and in persons without diabetes and was of greatest magnitude in persons without either hypertension or diabetes. In persons without hypertension, diabetes, self-reported previous coronary heart disease, or stroke (\[n=2110\]), the same association was observed, with each kg decrease in birthweight associated with 1.7 μm (95% confidence interval 0.4 to 3.1, \[P=0.001\]) narrower retinal arterioles.

In analyses stratified by BMI tertiles and gender, we found the association between birthweight and narrower arterioles persisted in all 3 BMI tertiles, and in men and women (data not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown). We obtained similar results in analyses which not shown).

There were no significant interactions between birthweight (continuous) and sex, race, hypertension, diabetes, or BMI (continuous).

### Discussion

Hypertension affects an estimated one billion persons worldwide, and up to 7.1 million deaths a year may be attributable to hypertension.\(^1\) Numerous studies in the past decade have shown that persons born with lower birthweight have higher blood pressure in both childhood and adulthood.\(^2\)–\(^5\) However, despite a significant amount of epidemiological data, the vascular mechanisms underlying this relationship are not known.\(^12\),\(^31\)

In this population-based study in middle-aged adults, we tested and confirmed the hypothesis that persons born with lower birthweight have narrower retinal arterioles, a structural vascular marker of hypertension, and related cardiovascular disease. There are a few small clinic-based studies that support our premise that structural changes in the retinal arterioles are associated with low birthweight.\(^13\),\(^32\) A study in 100 men reported low birthweight was associated with narrower retinal arteriolar bifurcation angles,\(^13\) whereas another in 44 men and women\(^14\) found that individuals who were small for gestational age were more likely to have longer retinal arterioles and less vascular branch points. Another large population-based study,

### Table 3. Birthweight and Retinal Vascular Caliber

<table>
<thead>
<tr>
<th>Birthweight (kg)</th>
<th>Retinal Arteriolar Caliber (μm)*</th>
<th>Retinal Venular Caliber (μm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>160.8</td>
<td>160.3</td>
</tr>
<tr>
<td>2.5 to 3.0</td>
<td>161.1</td>
<td>160.8</td>
</tr>
<tr>
<td>&gt;3.0 to 3.5</td>
<td>161.6</td>
<td>161.7</td>
</tr>
<tr>
<td>&gt;3.5 to 4.0</td>
<td>163.8</td>
<td>164.1</td>
</tr>
<tr>
<td>&gt;4.0 to 4.5</td>
<td>163.7</td>
<td>163.6</td>
</tr>
</tbody>
</table>

*Retinal arteriolar and venular caliber adjusted for variables in Models 1 to 3.

Model 1: adjusted for age (continuous), gender, race, and center.

Model 2: adjusted for variables in model 1 plus education level, body mass index, adult height, current cigarette smoking, current alcohol consumption, total cholesterol, high density lipoprotein cholesterol, triglycerides, and fasting glucose level.

Model 3: adjusted for variables in model 2 plus 6-year average systolic and diastolic blood pressures.

\[\text{P trend}\] value for trend across birthweight categories.

### Table 4. Decrease in Retinal Arteriolar Caliber per kg Decrease in Birthweight, by Hypertension and Diabetes Status

<table>
<thead>
<tr>
<th>Models</th>
<th>All Persons</th>
<th>No Hypertension</th>
<th>No Diabetes</th>
<th>No Hypertension or Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=3800</td>
<td></td>
<td>n=2451</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>2.0 (1.0 to 3.1)</td>
<td>&lt;0.001</td>
<td>2.4 (1.0 to 3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.4 (1.3 to 3.5)</td>
<td>&lt;0.001</td>
<td>2.6 (1.3 to 4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.7 (0.7 to 2.8)</td>
<td>&lt;0.001</td>
<td>2.1 (0.8 to 3.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Mean (95% confidence intervals) decrease in retinal arteriolar caliber, adjusted for variables in Models 1 to 3.

Model 1: adjusted for age (continuous), gender, race, center.

Model 2: additionally adjusted for educational level (6 levels), body mass index, adult height, current cigarette smoking, current alcohol consumption, total cholesterol, high density lipoprotein cholesterol, triglycerides, and fasting glucose level.

Model 3: adjusted for variables in model 2 plus 6-year average systolic and diastolic blood pressures.

\[\text{P value}\] for linear association between birthweight and arteriolar caliber (both modeled continuously).
the Sydney Myopia Study, examined this in 6-year old children (n=1369) and found the same results. In fact, that study found the same magnitude of effect of low birthweight on narrower retinal arterioles in childhood, (2.3 μm [95% CI, 0.6 to 3.9] P=0.01) even in the absence of adult cardiovascular risk factors (Paul Mitchell, unpublished data, 2007), further substantiating our findings.

Although our results do not imply that low birthweight itself causes vascular changes, they do support the idea that intrauterine influences such as nutritional restriction, of which low birthweight is a consequence, may result in structural circulatory changes, which are adaptive in fetal life but maladaptive in adulthood, and subsequently predispose individuals to cardiovascular disease. An alternative interpretation is that common genes or socioeconomic factors influence both birthweight and arteriolar caliber, although recent data indicate that these potential confounders are unlikely to be important.

These findings provide further evidence to address an important gap in the literature regarding the influence of fetal growth restriction on the vasculature. Low birthweight is known to be associated with narrower aortic, common carotid, and coronary arteries. Our study now shows that low birthweight is also associated with narrower resistance arterioles in addition to arteries. Importantly, we have previously demonstrated that retinal arteriolar narrowing is linked to a number of hypertension-related genes, and prospectively predicts the development of hypertension and cardiovascular events such as coronary heart disease and stroke.

Low birthweight may thus be associated with structural narrowing and altered arteriolar resistance in utero that persists into childhood and may thus be associated with structural narrowing and altered tension. We observed the same association of low birthweight with the subsequent risk of hypertension and associated cardiovascular disease. Such resistance changes are seen in the preglomerular vasculature and may initiate renovascular hypertension. We observed the same association of low birthweight and narrower arterioles in persons without hypertension, diabetes, previous coronary heart disease, and stroke. These findings suggest that our results are not confounded by these conditions, and that narrower arterioles secondary to low birthweight alone may not be sufficient to influence the onset of clinical cardiovascular disease. However, other influences may be necessary to trigger the progression from arteriolar narrowing to clinical cardiovascular disease. Such triggers may include volume overload from reduced nephron number, which has been associated with low birthweight. Unfortunately, we do not have these data to test this hypothesis.

We note that differences in arteriolar caliber between birthweight categories were small (3 to 4 μm difference between persons with birth weight <2.5 kg and 4.0 to 4.5kg). Our data therefore do not imply that changes in arteriolar caliber of this magnitude are responsible for the increased vascular resistance observed in hypertension. However, a difference of 3 to 4 μm in retinal vessel diameter corresponds to a difference in resistance of 13% to 17% according to the Poiseuille equation whereby resistance varies by the inverse of the fourth power of the diameter. This change in resistance corresponds to an increase in pressure of 13% to 17%. We have also previously shown that changes of this magnitude predict the incidence of hypertension and coronary heart disease, and other researchers have found even smaller decreases in retinal arteriolar caliber are associated with significant increase in systolic blood pressure (eg, a 1.1-μm reduction in arteriolar caliber is associated with a 10-mm Hg increase in systolic blood pressure).

Our finding of a lack of influence of birthweight on retinal venular caliber is important, as it is consistent with previous studies of the lack of association between venular caliber and hypertension. This suggests that the effect of low birthweight on vascular structure is specific for arterioles and is not confounded by unexplained ocular factors (eg, refraction), which should be common to both arterioles and venules.

A few limitations deserve further mention. Firstly, we used self-reported birthweight which is less precise than birthweight records. Nonetheless, it has been found to have moderate to high correlation with actual birthweight (0.86) and is often the only practical means of obtaining birthweight information. Previous investigators have found that self reported birthweight in the ARIC population follow expected patterns of association when used in analyses. Self reported birthweight is also reported to underestimate, rather than bias, associations between birthweight and adult outcomes. Secondly, only 30% of our sample reported birthweight and were included in the analyses. This could have introduced selection bias, although the similarity in retinal arteriolar calibers of included and excluded participants suggests this bias is likely nondifferential and would only attenuate our findings. Third, in model 3 we controlled for blood pressure to determine whether the association was independent of blood pressure. This may be an overadjustment, and the findings from this model should be interpreted with caution. However, the consistency of association from all 3 models suggests that the results are unlikely to be attributable to confounding. Finally, because these data are cross-sectional, our study cannot provide definitive “cause and effect” evidence. However, the most likely direction of the association is that low birthweight is related to changes in retinal microvascular structure, because the reverse direction of effect (microvascular alterations leading to low birthweight) is unlikely.

**Perspectives**

This study in a large middle-aged population demonstrates that low birthweight is associated with narrower retinal arterioles, independent of age, gender, race, height, diabetes, and other factors. These findings provide the first line of evidence that structural alterations in the arteriolar microvasculature may be a potential mechanism underlying the association of low birthweight with the subsequent risk of hypertension and associated cardiovascular conditions. We thus suggest that arteriolar narrowing may be one of several mechanisms linking low birthweight and elevated blood pressure. Low birthweight may also be associated with other abnormalities, such as reduced nephron number, which may predispose to developing hypertension. The relative contributions of arteriolar narrowing and other mechanisms underlying the link between low birthweight and hypertension warrant further investigation.

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Disclosures
None.

References
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