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Low birth weight and markers of inflammation and endothelial activation in adulthood: The ARIC study

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Abstract

Background—To investigate the hypothesis that intrauterine growth restriction might produce a longstanding pro-inflammatory tendency, we investigated the association of low birth weight with blood levels of markers of inflammation and endothelial activation in middle-aged adults.

Methods—The ARIC Study enrolled subjects aged 45–64 years sampled from four U.S. communities. An inflammation/endothelial activation score from 0 to 6 was created, one point being given for each above-median value of white blood cell count, fibrinogen, von Willebrand factor and Factor VIII, and for each below-median value of albumin and activated partial thromboplastin time.

Results—Of the 9809 individuals reporting birth weight and having all inflammation/endothelial markers and covariates, 349 (3.6%) reported low birth weight (LBW). The mean (standard deviation) score was 3.5 (1.5) for those with and 3.1 (1.6) for those without LBW ($p<0.001$). In robust poisson regression models adjusting for gender, ethnicity, age, study center, educational level, and current drinking and smoking status and amount, those with LBW were more likely to have a high score (≥4 points) (RR=1.16, 95% CI: 1.05–1.29).

Conclusion—In the ARIC Study, LBW predicted greater inflammation and endothelial activation, as indicated by the higher score of blood markers, consistent with the hypothesis that early life events may result in a hyper-responsive innate immune system. Such a pro-inflammatory

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tendency could help explain the association of low birth weight with elements of the metabolic syndrome and ischemic heart disease.

Keywords

Inflammation; Low birth weight; Leukocytes; Fibrinogen; Endothelial activation

1. Introduction

Intrauterine programming is hypothesized as a process through which a stimulus occurring during an intrauterine critical period of development leads to long-term alterations in genetic expression. Numerous cohort studies and experimental work in animals suggest that adverse conditions, such as undernutrition during fetal life, can lead to permanent adaptations in physiologic processes fundamental to future risk of coronary heart disease [1–4]. Atherosclerosis and other chronic diseases have thus been hypothesized to be “programmed” in utero [5,6]. However, the purported molecular and genetic mechanisms that link fetal adaptations to stressors such as undernutrition with disease in later life are not clearly understood.

Many studies suggest that inflammation plays an important role in the pathogenesis of atherothrombosis. Inflammatory cell infiltrates are common findings in chronic atherosclerosis, and evidence of immune activation in plaques has been shown [7]. Inflammation markers correlate with metabolic syndrome elements, and several causal mechanisms for inflammation in the pathogenesis of insulin resistance have been proposed [8–10]. Infection and other causes of environmental stress produce an activation of the innate immune system. If this activation occurs during a critical period for gene expression, it might produce a long-lasting or even permanent tendency for an increased pro-inflammatory state. To test the hypothesis that low birth weight, a surrogate of environmental stress during such a critical period, might produce such a longstanding pro-inflammatory tendency, we investigated whether low birth weight was associated with alteration in levels of markers of inflammation and endothelial activation in middle-aged adults.

2. Population and methods

The cohort component of the Atherosclerosis Risk in Communities (ARIC) Study is a prospective investigation of coronary heart disease (CHD) risk factors and the natural history of atherosclerosis. ARIC enrolled 15,792 white and African-American men and women ages 45–64 years selected by probability sampling from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) and interviewed them initially between 1987 and 1989, as has been described elsewhere [11].

The 11,656 patients who attended the fourth visit in 1996–1998 (when questions about birth weight were included) were eligible for the present study. We excluded 4 individuals with ages outside the stated range, 927 individuals missing information on the covariates studied and, due to small numbers, 69 participants from minority ethnic groups. We additionally

excluded 638 individuals who reported being born prematurely and 209 who reported being a twin or had incomplete information on this variable. Thus, 9809 participants were included in the final analysis.

Participants were asked to provide their birth weight in pounds and ounces. If the participant did not know his or her exact birth weight, she/he was asked to provide birth weight into one of three categories: low, medium or high. As only 4779 (48.7%) participants recalled an exact birth weight, these data, when reported, were converted to the metric system and categorized into three groups (<2.5 kg, 2.5–4 kg and >4 kg). Both qualitative and quantitative birth weight variables were combined in one single variable used in analysis.

All additional information analyzed was obtained during the 1987–89 baseline exam, during which health status, family medical history, cardiovascular risk factors, employment and education were queried, anthropometrics and blood pressure were obtained and blood sampled for lipid, hemostasis, hematology and chemistry measurements [12].

With the exception of white blood cell count, all analyses were determined in central laboratories following standardized procedures. Albumin was measured using Coulter's bromcresol green colorimetric assay [13]. Hemostasis variables were analyzed in citrated samples. Fibrinogen was measured by the thrombin time titration method, with reagents and calibration reference (Fibriquick) from General Diagnostics (Organon-Technika Co, Morris Plains, NJ). Factor VIII coagulant activity was measured by a one-stage assay using factor VIII deficient plasma (George King Biomedical, Overland Park, KS). Von Willebrand factor antigen was assayed by enzyme-linked immunosorbent assay (American Bioproducts Co., Parsipanny, NJ); and activated partial thromboplastin time (aPTT) on an automated coagulometer. The reference material for assays was the Universal Coagulation Reference Plasma (Thromboscreen, Pacific Hemostasis, Ventura, CA). The reliability coefficient, based on repeated testing of individuals over 1–2 weeks, was 0.72 for fibrinogen, 0.86 for factor VIII activity, 0.68 for von Willebrand factor and 0.92 for aPTT. Counts of leukocytes were determined locally using automated particle counters.

A inflammation/endothelial activation score was created from six factors measured at baseline: white blood cell count, albumin, fibrinogen, aPTT, von Willebrand factor and Factor VIII, assigning 1 point for each of white blood cell count, fibrinogen, von Willebrand factor and Factor VIII having a value above the sample median, and also 1 point for each of albumin and aPTT having values below the median. This score thus ranged from 0 to 6.

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist was measured at the umbilicus, hip circumference at its maximum, and waist–hip ratio (WHR) calculated as the ratio of the two. Systolic and diastolic blood pressure were determined as the mean of the second and third of three standardized measurements; hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg and/or current use of anti-hypertension medication. We defined diabetes as a fasting value of ≥126 mg/dL or a non fasting value ≥200 mg/dL, report of a physician diagnosis of diabetes, or use of anti-diabetes medications. Prevalent coronary heart disease was defined as a report of myocardial infarction, coronary bypass or balloon angioplasty, or a myocardial infarction detected on an adjudicated

baseline electrocardiogram. Educational level was categorized into 3 groups: advanced (attended or completed college, graduate or professional school); intermediate (completed high school); and basic (less than high school education). Participants were characterized as current, former or never drinkers, and current, former or never smokers. Cigarette years of smoking was estimated as the average number of cigarettes smoked per day times the number of years smoked.

Differences in levels of study factors between the three birth weight groups were compared using analysis of variance. Subsequently, since there were no significant differences between the high and medium birth weight groups, these two groups were merged, and reported analyses investigate differences between low vs. medium or high birth weight groups. Adjusted means were estimated as least-squares means of fixed effects using SAS PROC MIXED. Unadjusted differences were evaluated with *t*-tests. Chi-square testing was used to compare the distribution of inflammation/endothelial activation scores between those with low and those with medium or high birth weight.

We used multiple linear regression models to evaluate the adjusted association between categorical birth weight and each continuous markers of inflammation or endothelial activation. We then performed robust poisson regression to evaluate the adjusted association of low birth weight with having a high (≥4) number of above-median values for inflammation/endothelial activation markers [14]. In order to evaluate possible heterogeneity in associations, robust poisson regression models were performed separately in gender, ethnicity and disease (diabetes mellitus and prevalent ischemic heart disease) specific strata. All analyses were performed using SAS.

3. Results

Our sample consisted of 1235 (13%) African-American women, 4268 (43%) white women, 642 (7%) African-American men and 3664 (37%) white men. Mean (standard deviation) age was 53.5 (5.62) years for women and 54.2 (5.72) years for men. There were 349 individuals (3.6%) in the low birth weight group and 9460 (96.4%) in the medium or high birth weight group. Table 1 presents the values for sociodemographic and clinical characteristics of the two groups adjusted for gender, race and age. Most reporting low birth weight were women. As adults, those with low birth weight were shorter, weighed less, drank less, showed higher levels of systolic blood pressure and had lower educational levels. African-Americans were more likely to report a low birth weight (4.5% vs. 3.3%). They also had higher values for vWF, VIII factor, fibrinogen and lower white blood count.

Table 2 shows the distribution of inflammation markers in the two birth weight groups by gender and adjusted for age and race. Both men and women with low birth weight had higher white cell counts. Women, additionally, presented higher fibrinogen and Factor VIII levels. Additionally, all other markers, with the exception of albumin, tended, though not statistically significantly so, toward a pro-inflammatory profile in the low birth weight group. Differences were larger in women.

Mean levels of inflammation markers by birth weight categories were further adjusted in linear regression models for gender, ethnicity, age, study center, educational level, current drinking and current smoking status and lifetime cumulative amount smoked. In these models, those with low birth weight had 273 more white blood cells/mm^3 (p=0.003) and 4.7% greater factor VIII activity (p=0.01). The values for fibrinogen were 0.12 μmol/L higher (p=0.20), for aPTT 0.29 s shorter (p=0.08) and for von Willebrand factor antigen 3.6% higher (p=0.12), although not statistically significantly so. Albumin levels did not differ between the groups (−0.004, p=0.78). Results were slightly stronger after further adjustment for BMI and WHR (data not shown). In models performed separately by gender, associations were similar, but tended to be somewhat stronger in women (data not shown).

As shown in Fig. 1, those with low birth weight had their distribution of inflammation/endothelial activation scores shifted towards higher values than those with medium or high birth weights (p<0.001).

Table 3 shows the risks of a high inflammation and endothelial activation score for those with low birth weight in robust poisson regression models adjusted for gender, ethnicity, age, study center and factors associated with low birth weight which could potentially confound the association — educational level, current drinking and smoking status and lifetime cumulative amount smoked. Those with low birth weight had an increased risk of a high inflammation/endothelial activation score (RR=1.16, 95% CI: 1.05–1.29) compared to those with medium or high birth weight. This association was stronger for men 1.21 (95% CI: 0.96–1.54) than women 1.15 (95% CI: 1.02–1.28). The relative risk for the overall association with additional adjustment for BMI and WHR was 1.18 (95% CI: 1.07–1.31).

Low birth weight did not predict a higher inflammation/endothelial activation score in African-Americans (RR=0.93, 95% CI: 0.75–1.16). For whites, the relative risk was 1.27 (95% CI: 1.13–1.41).

As misclassification of birth weight could occur in those who did not report exact weights, we reanalyzed the data including only the 4779 individuals who reported exact birth weights. This restriction yielded slightly stronger associations of low birth weight with a high inflammation/endothelial activation score, the relative risks being 1.22 (95% CI: 1.08–1.38) when adjusted for gender, ethnicity, age, study center, educational level, current drinking and smoking status and lifetime cumulative amount smoked, and 1.23 (95% CI: 1.09–1.40) with further adjustment for BMI and WHR.

African-Americans (35%) were less likely to recall an exact birth weight than whites (52%). However, we found no significant differences in the association between individuals reporting exact birth weight and those with qualitative data for either African-Americans or whites.

4. Discussion

In this population-based study of middle-aged individuals, an aggregate of markers of inflammation and endothelial activation, and, among them, most notably white cell count and factor VIII, were higher in those with low reported birth weight. The few studies that

have investigated the association between low birth weight and subsequent levels of inflammation markers had contradictory findings. However, most of these studies were small. A study with 77 pairs of twins failed to demonstrate an association of birth weight with fibrinogen and albumin excretion rate [15], and one study in 641 children aged 10–11 years reported the lack of association between birth weight and fibrinogen [16] and C-reactive protein (CRP) levels [17].

In adults, the report of Martyn et al. is consistent with our findings, showing that plasma concentrations of fibrinogen increased in men by 0.12 g/L (95% CI: 0.05–0.19) for each pound decrease in birth weight, but not in women [18]. In the MIDSPAN Family Study, which included 1663 adults with ages from 30 to 59, there was a negative association between birth weight and CRP: the authors reported a 10.7% increase in CRP for each 1 kg decrease in birth weight, both in men and women [19].

None of these studies attempted, as we have done, to combine a series of markers of inflammation or endothelial activation to obtain a more complete picture. The relatively weak correlations that exist between different inflammatory markers, and the weaker associations found with individual markers when compared to the highly significant ones found with the score, emphasize the difficulty of characterizing the state of systemic inflammation and endothelial activation with individual markers.

The choice of these markers was governed chiefly by their availability in the ARIC cohort. Most are well described as measures of either inflammation or endothelial activation. Two of the markers, albumin and aPTT, both of which were less clearly associated with birth weight, were maintained in the score as having been selected *a priori*. Albumin is a negative acute phase reactant, as its production decreases during the acute phase reaction. Little has been published concerning a shortened aPTT as a marker of subclinical inflammation/endothelial activation. A quicker aPTT represents a tendency toward hypercoagulability via the intrinsic pathway [20], which has been described as occurring, in part, due to endothelial cell activation [21] Many of these markers and a similar score were predictors of incident diabetes in the ARIC cohort [22–24].

A large body of evidence has accumulated in recent years relating atherosclerosis to inflammatory pathogenic mechanisms. Markers of inflammation are important correlates of the metabolic syndrome [25–27] and predictors of the risk of diabetes, weight gain in middle-age, hypertension and cardiovascular events [8,28,29]. Low birth weight has also been linked to impaired endothelial function in children [30] and, although not always consistently, to numerous chronic conditions in adulthood, including fatal and non-fatal CHD and stroke, hypertension, hypertriglyceridemia and low HDL-C, diabetes mellitus, and obesity [31–38].

The mechanisms through which the fetal environment may increase cardiovascular risk are still under debate. We hypothesize that one possible mechanism is a programming of the innate immune system. Long-term effects of early life deprivation on immune functioning have been previously reported. In adolescents, low birth weight has been associated with a less intense immune response to typhoid immunization [39]. In regions of rural Africa with

significant seasonal disparities in food availability, the season of birth is a strong predictor of adult fatal infections and death. In one report, individuals born during the hungry season (as compared to those born during harvest season) had a 10 fold increased risk of death after 25 years of age [40,41].

Programming of the immune system could result in a longstanding up regulation of pro-inflammatory gene expression. Gene expression is increasingly being shown to be a very dynamic phenomenon, involving qualitative and quantitative alterations to promote functional adaptation to environmental changes [42–44]. For example, the expression of numerous clusters of genes is altered in different phases of atherosclerotic plaque formation and macrophage migration, in what has been described as an “endothelial cell pro-inflammatory phenotype” [42].

Our results thus present evidence consistent with the hypothesis that undernutrition and other stressors during fetal development cause alterations of gene expression, which leads to a chronic, low grade state of inflammation that could predispose to the development of the metabolic syndrome, diabetes and CHD. An alternative hypothesis might be that linked genes affect both birth weight and inflammation, but low birth weight does not directly affect inflammation.

Limitations of our study merit discussion. Being observational in nature, residual confounding, especially by socioeconomic status, cannot be ruled out as an explanation for the findings. The proportion of individuals not knowing their birth weight suggests that misclassification is possible. In fact, in related work based on this cohort, the categorized exact birth weight in ARIC corresponded more closely to distributions found in national vital statistics than did the qualitative birth weight [45]. Also, those who recalled exact birth weight were more likely to be white, female, and to have higher levels of education than those who provided qualitative birth weight [37]. However, the fact that similar results were obtained when only those reporting an exact weight were analyzed is reassuring. It is quite possible that given misclassification of birth weight, true associations may be larger than those that we report, as associations were somewhat stronger in analyses including only those who reported their exact birth weight. Furthermore, some authors suggest that maternal malnutrition during gestation may result in specific alterations of body proportions, permanently affect adult health without affecting significantly the size of the baby at birth [46]. This implies that the long-term consequences of a stressful uterine environment will be underestimated if these are solely based on the size at birth, although birth weight is the most practical and, in many studies, the only feasible, measure of fetal growth [47]. Residual confounding due to subclinical disease is another possibility. However, this appears unlikely to have occurred, since the association between birth weight and the score increased after adjustment for overall and central obesity, conditions associated with a chronic inflammatory state.

The lack of association between birth weight and the inflammatory/endothelial activation score in African-Americans could be due to insufficient statistical power, given the small numbers of African-American individuals in our study, or to greater birth weight misclassification in this group. Nevertheless, it is important to consider the possibility that

programming of genes responsible for inflammatory and endothelial activation in response to intrauterine environmental stress may vary according to ethnicity. Differences between whites and African-Americans in terms of inflammation and related chronic disease have been reported. For example, African-Americans showed a significantly higher inflammatory/endothelial activation score in ARIC, and are known to have a different composition of the metabolic syndrome elements than whites [48]. In the ARIC cohort, the association of inflammation markers with incident diabetes was present in whites, but not in African-Americans [22].

In conclusion, low birth weight predicted a greater systemic inflammation and endothelial activation in middle-aged adults, permitting speculation that fetal stressors may result in altered gene expression (fetal programming) producing a hyper-responsive innate immune system. This state may help explain reported association of low birth weight with insulin resistance, elements of the metabolic syndrome and ischemic heart disease, all known today as conditions having important inflammatory components.

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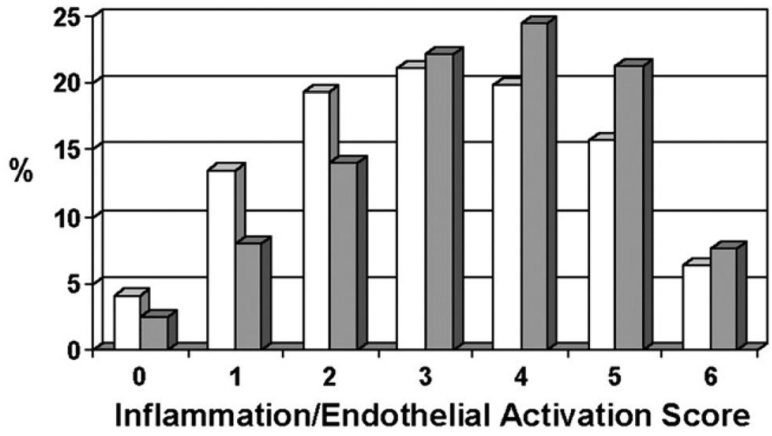

Fig. 1.

Frequency of scores of inflammation and endothelial activation according to low (grey columns) and medium/high (white columns) birth weight.

Table 1

Distribution of sociodemographic characteristics and cardiovascular risk factors by birth weight as a dichotomous variable, adjusted by gender, race and age.

	Birth weight		*P* value
	Low (*n* = 349)	**Medium or high (*n* = 9460)**	
Age — years	54.1±0.30	53.8±0.06	0.42
Gender — female	278 (79.4)	5225 (55.2)	<0.001
Ethnicity — African-American	85 (22.7)	1792 (19.0)	0.09
Height — cm	165.5±0.33	168.7±0.06	<0.001
Weight — kg	74.2±0.79	78.4±0.15	<0.001
BMI — kg/m^2	27.0±0.27	27.5±0.05	0.06
WHR	0.93±0.004	0.92±0.001	0.34
Systolic BP — mm Hg	122.2±0.88	119.1±0.17	<0.001
Diastolic BP — mm Hg	73.3±0.53	73.0±0.10	0.52
Cigarette years of smoking	283.2±20.44	279.6±3.91	0.79
Current smoker	80 (23.2)	1982 (0.9)	0.33
Usual ethanol intake — g/week	36.3±4.58	41.7±0.88	0.23
Current drinker Education level	166 (51.6)	5692 (60.0)	0.003
Advanced[a]	96 (29.4)	3806 (40.2)	<0.001
Intermediate[b]	170 (47.4)	4001 (42.3)	0.07
Basic[c]	83 (23.1)	1651 (17.5)	0.01
Hypertension	127 (35.6)	2826(29.9)	0.03
Prevalent CHD	6 (2.7)	314 (3.4)	0.57
Diabetes	35 (9.8)	812 (8.6)	0.43
Fasting glucose — mg/dL	107.3±1.62	104.8±0.31	0.12
Insulin[d] — μU/mL	10.8±0.44	10.5±0.08	0.50
Physical activity at work — points	2.15±0.05	2.21±0.01	0.21
Leisure time physical activity — points	2.39±0.03	2.42±0.01	0.29

BMI = body mass index, WHR = waist to hip ratio, BP = blood pressure CHD = coronary heart disease.

Variables expressed as mean±Standard Error of Mean or *N* (%).

[a] College, graduate or professional school.

[b] High school graduate.

[c] Basic education.

[d] Excluding those with diabetes.

Table 2

Inflammation markers according to birth weight categories for men and women, adjusted for age and race.

Marker	Birth weight									
	Men					Women				
	Low		Medium–high		*p*	Low		Medium–high		*p*
	Mean	SEM	Mean	SEM		Mean	SEM	Mean	SEM	
aPTT (s)	29.5	0.37	29.6	0.05	0.84	28.5	0.18	28.9	0.04	0.08
Factor VIII (%)	128.5	3.95	123.4	0.51	0.20	135.8	2.12	130.4	0.49	0.01
VWF (%)	119.2	5.07	113.4	0.66	0.25	118.2	2.60	114.0	0.60	0.11
Fibrinogen (μmol/L)	8.60	0.20	8.56	0.02	0.83	9.05	0.10	8.84	0.02	0.05
Albumin (g/L)	39.0	0.3	39.0	0.04	0.50	38.0	0.2	38.0	0.03	0.76
WBC (1000/mm^3)	6.6	0.22	6.1	0.03	0.03	6.1	0.11	5.9	0.02	0.01

p value for difference in means between low and medium–high birth weight.

SEM = standard error of mean, aPTT = activated partial thromboplastin time, vWF = von Willebrand factor, WBC = white blood cell.

Table 3

Risks of a high inflammation and endothelial activation score for those with low birth weight.

Model	RR	95% IC
Overall		
Model 1[a]	1.16	1.05–1.29
Model 2[b]	1.18	1.07–1.31
Stratified by gender		
Men[c]	1.21	0.96–1.54
Women[c]	1.15	1.02–1.28
Stratified by ethnicity		
African-Americans[d]	0.93	0.75–1.16
Whites[d]	1.27	1.13–1.41

[a] Adjusted through robust poisson regression for gender, ethnicity, age, study center, educational level, drinking and smoking status, and amount smoked.

[b] Adjusted additionally for BMI and WHR.

[c] Adjusted as in model 1, except not for gender.

[d] Adjusted as in overall, except not for ethnicity.