Inverse Association Between Birth Weight and C-Reactive Protein Concentrations in the MIDSPAN Family Study

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Objective—Inflammation markers and low birth weight each predict elevated risk of cardiovascular events and type 2 diabetes. However, potential associations between the low-grade inflammatory response as represented by C-reactive protein (CRP) concentrations and low birth weight have been sparsely examined.

Methods and results—In the MIDSPAN Family Study, 1663 individuals had birth weight data and CRP concentrations measured as adults (age 30 to 59). The relationship between these parameters was examined after adjusting for factors known to influence CRP concentrations inclusive of age, body mass index, smoking, socio-economic deprivation, and hormone use in women. After adjusting for potential confounders, there was a negative association between birth weight and CRP, whereby a 1-kg increase in birth weight is associated with a 10.7% decrease in CRP (95% CI: 3.0% to 17.8% decrease). There was no strong evidence that the effects differed in men and women (P=0.32).

Conclusion—Low birth weight contributes to elevated CRP concentration in adult life. Future studies are required to determine to what extent this association reflects catch-up centile crossing, in utero programming, or genetic factors.

Key Words: inflammation ■ fetal programming ■ obesity ■ birth weight ■ C-reactive protein

Epidemiological studies using old birth records demonstrate associations between low birth weight and increased adult risk for coronary heart disease (CHD), stroke, and type 2 diabetes.1,2 Mortality from vascular disease approximately doubles from the highest to the lowest extremes of birth weight.1,2 However, low birth weight at best only modestly explains adult levels of several classical risk factors, including blood pressure, cholesterol, and glucose, and insulin concentrations.3–5

In recent years, low-grade inflammation, as depicted by elevated C-reactive protein (CRP) concentrations in the range traditionally accepted as “normal,” ie, <6 mg/L, has emerged as a strong independent risk factor for CHD and type 2 diabetes.6–8 Men and women with CRP concentrations in the top tertiles of the population have on average a 2-fold risk of myocardial infarction or type 2 diabetes compared with those in the bottom tertile after adjustment.6,7 Moreover, therapeutic modalities proven to reduce vascular and metabolic risk, such as statins, ACE inhibitors, or the thiazolidinedione class of drugs, all appear to possess potent anti-inflammatory properties.9–11 The strength of the association between CRP and cardiovascular disease is sufficiently consistent that a recent joint American Heart Association/Center for Disease Control statement6 produced guidelines for its potential incorporation into future risk factor stratification.

Currently, data examining the association of birth weight with CRP concentration in adults are lacking. In light of the foregoing observations, we hypothesized that low birth weight may be an additional factor contributing toward elevated CRP concentration in adults.

Methods

Sample
Data from the MIDSPAN Family Study12 were used to examine our hypothesis. The Family Study involved 2338 individuals who completed a questionnaire (covering socio-demographic details, personal and family medical history, risk behaviors, and health beliefs) underwent a physical examination (including body size, blood pressure, lung function, and ECG) and submitted (non-fasting) blood samples for subsequent analysis. The study participants were the adult offspring (age 30 to 59) of married couples who were screened in 1972 to 1976 as part of the Renfrew-Paisley (MIDSPAN) Study13 and were living in the central belt of Scotland when invited to participate in 1996.

Data
When the sample was provided, participants were asked if they had a cough, cold or flu, sore throat, diarrhea, or had received an antibiotic during the past 7 days. For 676 participants, hospital records were used to obtain documented birth weight information;14 a further 1188 participants provided questionnaire responses regarding their birth weight. Questionnaires also provided information...
regarding age, smoking habit, and (for women) current hormone use (either hormone replacement therapy or oral contraceptives). Body mass index (BMI) was calculated as weight (kg)/height (m)^2. Socio-economic status was derived from postcode data. After exclusions for missing data, there were 1663 individuals (716 men and 947 women) available for analysis.

**Laboratory Analyses**
CRP was measured as described previously using a sensitive double-antibody sandwich ELISA with rabbit antihuman CRP and peroxidase conjugated rabbit anti-human CRP. The assay was linear up to 5 mg/L and logarithmic thereafter. The inter-assay and intra-assay coefficients of variation were <10% across the range of measured results.

**Statistical Methods**
Birth weight data were available from hospital records and subject reports. Using data from individuals with both sources of information, the reporting bias was determined and an adjustment was made to the reported birth weights of those without documented birth weight.

Variables are summarized for men and women as mean and standard deviation (SD) for age, birth weight, and BMI; geometric mean and 1 SD range (calculated as mean±SD on a logarithmic scale, then transformed back to the original scale) for CRP; or number and percentage for smoking variables (never, former, or current), recent infection (self-report of cough, cold or flu, sore throat, diarrhea, or use of antibiotic in past week), current use of aspirin, statin, or ACE inhibitor, and current use of HRT or oral contraceptives.

Geometric mean CRP was calculated for individuals categorized by quartiles of birth weight and BMI. Raw CRP trends across birth weight and BMI were compared with trends in CRP after direct standardization to a uniform distribution in the other variable (e.g., trend in CRP across quartiles of birth weight, assuming that within each quartile of birth weight, 25% of individuals are in each quartile of BMI).

Regression models were fitted with the logarithm of CRP as the dependent variable to determine the association between birth weight and CRP. The initial model adjusted for age, sex, and hormone use (HRT or oral contraceptives), with sex and hormone use included as a 3-level categorical variable (male or female not using hormones/female using hormones), and with age-sex-hormone use interactions included regardless of statistical significance. The second model contained the same terms as the first, but also adjusted for smoking (never, former, or current), recent infection, drug use (aspirin, statin, and/or ACE inhibitor), and for socio-economic deprivation using Carstairs deprivation categories (classified as: affluent, categories 1 and 2; intermediate, categories 3 and 4; or deprived, categories 5 to 7). The final model also adjusted for BMI as a linear continuous effect. Under each model, the effect of birth weight is reported as the percentage increase in CRP associated with a 1-kg increase in birth weight, with a 95% confidence interval (CI) and corresponding P value. Effect estimates are reported from models that assume equal birth weight effects in men and women and from models that allow different effects in men and women by including birth weight by sex interactions. Probability values are given for the tests of effect heterogeneity.

To test for heterogeneity of birth weight effects dependent on levels of BMI, a model was fitted allowing for separate birth weight effects in each quartile of BMI while controlling for the effects of other variables in the analysis, and compared with the model with the same birth weight effect for all levels of BMI using an F test for improvement in model fit. An analogous method was used to test for heterogeneity of BMI effects dependent on birth weight.

Each model was fitted using the generalized estimating equations approach to allow for clustering of CRP values within families, using the statistical software package S-Plus for Windows v4.5.

**Results**
In the 465 individuals with reported and documented birth weight, reporting bias was not seen to be associated with age, sex, adult BMI, or documented birth weight but had a mean value of −1.84 ounces (SE = 0.54 ounces [≈15.3 g]). The correlation between self-reported and hospital birth weight was 0.84. Reported birth weight of those without documented values were adjusted accordingly for use in the remainder of the analysis.

Table 1 shows summaries of all variables used in this analysis for men and women. Men had higher birth weights and BMI and were slightly younger than women participants, were more likely to be using aspirin, statin, or an ACE inhibitor, and were more likely to have smoked, although the proportion of who currently smoked were similar.

Table 2 shows the association of the factors listed in Table 1 with CRP. Note that CRP increased with increasing age and BMI but that height was inversely related to CRP. CRP was also increased by smoking in men, by deprivation and recent infection in both sexes, and by hormonal use in woman.

Table 3 shows the distribution of CRP (for men and women combined) according to quartiles of birth weight and BMI. There was a positive association between birth weight and BMI, and the association between CRP and BMI was
apparent at every level of birth weight, as it is overall, with similar trends seen using raw data and after standardization to a uniform birth weight distribution.

There was no discernible trend in CRP across quartiles of birth weight when using raw data, but a trend was seen in the fourth quartile of BMI, in which individuals with larger birth weights have lower CRP. After standardization to a uniform BMI distribution in each quartile of birth weight, a negative trend in CRP values emerged.

Table 4 reports the associations between birth weight and CRP, as determined by regression modeling. Controlling for age, sex, and hormone use, there was no significant association between birth weight and CRP in either men or women. The same was true after controlling for smoking, recent infections, deprivation category, and current medications. However, after controlling for BMI, there was a negative association between birth weight and CRP, whereby a 1-kg increase in birth weight was associated with a 10.7% decrease.
in CRP (95% CI: 3.0% to 17.8% decrease). There was no strong evidence that the effects differed in men and women (P=0.32). Moreover, although not shown in this Table, there was no evidence that birth weight effects differ between quartiles of BMI (P=0.90) or vice versa (P=0.44).

A significant birth weight–CRP association was maintained when we adjusted for obesity (BMI >30 kg/m²) rather than BMI (−8.7% in CRP decrease for every 1-kg increase in birth weight; 95% CI: −16.2, −0.4; P=0.040) or added height to the model (P=0.045, data not shown). Finally, we examined the CRP–birth weight association after removing subjects with a history of CHD or stroke from the analyses. In this case, the CRP–birth weight association, although attenuated by ≈10%, also remained significant (P=0.013, data not shown).

Discussion

To our knowledge, these are the first data in adults to relate sensitive CRP concentration to birth weight in a large population of middle-aged men and women with comprehensive information on other potential predictors of CRP. The data demonstrate that higher birth weight is related to a lower inflammatory burden, as measured by CRP, in adult life. Indeed, CRP decreased by nearly 11% for every 1-kg increase in birth weight. The data indicate that part of the association of low birth weight with elevated risk for vascular and metabolic disease in later life could be mediated by inflammatory pathway perturbation.

Two previous studies in children failed to find a significant association between CRP and birth weight, but it is notable that both studies were much smaller in size than this present study. Moreover, the former study was severely limited by the use of CRP assay with low sensitivity: measurable CRPs were available in only 110 children. It is also possible than because CRP levels and associated metabolic changes increase with age, there may have been an improved potential to demonstrate an association of CRP with birth weight caused by magnified differences over time.

If the relationship between CRP and birth weight is confirmed, then potential mechanisms underlying programming of inflammatory pathways in utero need to be examined. Cytokines such as IL-6 and TNF-α are synthesized and released by inflammatory cells such as monocytes, but additional sources such as adipocytes and endothelial cells are pertinent to the heightened low-grade inflammatory response predictive of CHD and type 2 diabetes. Cytokine clearance occurs principally via kidneys, and hepatic CRP synthesis is principally IL-6–mediated. Hence, programming of any of these tissues may be relevant to inflammatory status in adults.

It is also relevant that pregnancy is associated with an increase in circulating cytokine and CRP concentrations and that the increase in TNF-α appears to strongly correlate to the decrease in insulin sensitivity in pregnancy. In addition, a recent study in rats demonstrates that prenatal exposure to cytokines (IL-6, and TNF-α) leads to marked increase in adipose tissue mass in male and female offspring. The metabolic consequences of this excess abdominal fat mass were reduced insulin sensitivity in male offspring and hyperandrogenism in female offspring. Hence, pregnancy-induced elevations in cytokines may be relevant to fetal programming; therefore, it is not inconceivable that CRP levels in adult offspring may be influenced by this route.

That the relationship between CRP and birth weight is seen after adjustment for BMI is not surprising, because obesity is known to be a major factor determining the inflammatory response in otherwise healthy individuals. The obesity–CRP association also makes biological sense because adipocytes produce a plethora of inflammatory mediators, including IL-6, TNF-α, and other cytokine-like molecules such as adiponectin and leptin. Clearly, the greater effect of current obesity on CRP levels than of birth weight, as noted in Table 2 (≈4-fold elevation in CRP from first to fourth quartiles of BMI), suggests that tallking obesity in adult life would have a greater influence on inflammatory status than modifying prenatal environment. Physical activity is also important; for example, we recently showed the extent to which CRP concentrations can be reduced to in men who undertook ultramarathons, whereas others have shown that even modest regular physical activity is associated with lower CRP levels.

Although, as discussed, our results are potentially consistent with in utero programming of inflammatory pathways, other mechanisms such as centile crossing may be equally or more important. For example, we did not collect information about weight in infancy or later during childhood, and it is possible that the relevant exposure involving change in weight between birth and later life, rather than birth weight per se, is relevant to our finding. Clearly, only longitudinal analyses can help dissect out potential mechanisms. Another possibility is common genetic factors leading to low birth weight and elevated CRP.
Whatever the mechanism, chronically elevated higher levels of CRP, or its precursor cytokines (eg, IL-6), in the circulation are potentially damaging via several mechanisms that collectively combine to accelerate atherosogenesis.6,27 For example, high CRP levels are independently linked to endothelial dysfunction, dyslipidemia, insulin resistance, and elevated blood pressure.6 In line with these associations, elevated CRP levels are seen in association with the metabolic syndrome and predict incident diabetes.28,29 While the observational evidence on markers of inflammation and CHD risk is well established, the causal nature of these associations is difficult to judge given that atheroma may itself lead to an increase in such markers and that many confounding factors are related to inflammatory markers and CHD risk. Approaches using “Mendelian randomization”30 offer an attractive way of obtaining evidence on causality.

In conclusion, we have shown that birth weight is inversely related to CRP concentration in adult life after adjusting for its other known determinants. Therefore, part of the association of low birth weight with future risk of CHD and diabetes may be mediated via a perturbation in inflammatory pathways.

References

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