

# Size at birth, weight gain over the life course, and low-grade inflammation in young adulthood: northern Finland 1966 birth cohort study

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## Aims

Low-grade inflammation might mediate associations between size at birth, early life growth, excessive weight gain, and subsequent risk of cardiovascular disease in adult life. Our aim was to investigate relationships between fetal growth, weight over the life course, and low-grade inflammation measured by serum high sensitivity C-reactive protein (CRP) levels at 31 years.

## Methods and results

General population-based northern Finland 1966 Birth Cohort study of 5840 participants attending a clinical examination at 31 years, including measurement of CRP. Weight and height were assessed at birth, 12 months, and 14 and 31 years of age. CRP levels at 31 years were 16% [95% confidence interval (CI) 8, 23] higher per 1 kg lower birth weight, 21% (95% CI 2, 37) higher per 10 cm lower birth length, and 24% (95% CI 10, 36) higher per 1 kg/m<sup>3</sup> lower ponderal index, after adjustment for potential confounders. Participants with highest tertile body mass index (BMI) at 31 years and lowest tertile birth weight had the highest average CRP levels. Per unit increase in BMI from 14 to 31 years was associated with 16% (95% CI 14, 17) higher CRP levels; the association was larger for those in the top BMI tertile at age 14 years.

## Conclusion

Systemic low-grade inflammation may lie on the causal pathway that relates impaired fetal growth and weight gain from childhood to adulthood to adverse adult cardiovascular health. Lifestyle changes from early life might be an important step in reducing cardiovascular risk in adults.

## Keywords

Cardiovascular risk factors • C-reactive protein • Birth weight • Weight gain • Life course epidemiology

## Introduction

Environmental factors acting in early life may have an important influence on risk of adult disease.<sup>1</sup> People who had low birth weight/impaired fetal growth are at increased risk of developing coronary heart disease<sup>2–7</sup> and other cardiovascular and metabolic disorders including stroke, hypertension, and diabetes;<sup>8–10</sup> growth during childhood is also important for risk of future cardiovascular events.<sup>11</sup> While these epidemiological findings are strong and

consistent, an understanding of the underlying mechanisms—that may lead to identification of causal pathways, preventive measures, and targets for therapeutic interventions—is currently lacking.

A key role of low-grade inflammation has been postulated in the development and progression of atherosclerotic disease.<sup>12</sup> Observational studies have found associations between markers of systemic inflammation and the presence or progression of atherosclerosis as well as with the development of incident coronary heart disease, stroke, and peripheral arterial disease.<sup>13–16</sup> Of

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several inflammatory markers tested, an acute phase reactant secreted from the liver, C-reactive protein (CRP), is the most extensively studied. CRP has shown consistent associations with atherosclerosis and incident cardiovascular disease in several studies,<sup>17–22</sup> though its clinical application in cardiovascular risk prediction is open to question.<sup>23</sup>

Impaired fetal growth and growth during infancy or childhood may trigger inflammatory pathways leading to activated low-grade inflammation in adulthood; inflammation might be an intermediate factor linking impaired fetal growth and incident cardiovascular disease. We report here associations of adult CRP levels with small size at birth and weight gain in infancy, adolescence, and young adulthood, using data from the northern Finland 1966 Birth Cohort study, followed from the antenatal period to age 31 years.

## Methods

Recruitment and data collection methods in the northern Finland 1966 Birth Cohort study have been described.<sup>24</sup> Briefly, births with expected deliveries in 1966 in northern Finland were eligible ( $n = 12\,058$  live births, 96.3% of all births, 99% born in hospital). Follow-up in 1997–98 consisted of questionnaires ( $n = 11\,541$  alive and traced) and clinical examinations for those living in the original target or Helsinki area ( $n = 8463$  eligible).

### Early life, birth, and infancy variables

Birth weight and birth length were measured using standardized methods. Ponderal index was calculated as the ratio of birth weight to birth length cubed. Gestational age was computed as number of completed weeks from date of mother's last menstrual period to delivery. Growth data were collected at 1 year from child welfare centres (91% attendance). For post-natal growth, participants were defined as 'changers', up or down, or 'non-changers' on the basis of sex and gestational age-adjusted standard deviation (SD) scores (calculated for entire cohort alive at birth/1 year) for weight at birth and 1 year. Change in weight SD scores  $>0.67$  (equivalent to one band on standard growth charts) were used to differentiate changers from non-changers. Family socioeconomic status (SES) at recruitment based on father's occupation (mother's if single) was classified I (high) to IV (low), and for farmers by farm size. Mothers were classified as light smokers if they smoked up to 10 cigarettes per day and as heavy smokers if they smoked more than 10 cigarettes per day after the second month of pregnancy.

### Variables at 14 and 31 years

At 14 years, data on the participant's own body weight and height were obtained by questionnaire (97% response). At 31 years, clinical examination included measurement of weight and height; systolic and diastolic blood pressure by trained nurses using a standard mercury sphygmomanometer after 15 min rest;<sup>10</sup> and blood samples drawn after overnight fasting. Samples were stored at  $-70^{\circ}\text{C}$  until analysed. Enzymatic assays of fasting serum total cholesterol and HDL cholesterol were measured using Hitachi 911 automatic analyzer and commercial reagents (Boehringer Mannheim, Germany) in the accredited laboratory of Oulu University Hospital. Serum CRP concentrations were determined by immunoenzymometric assay (Medix Biochemica, Espoo, Finland). The intra-assay (one sample 20 times in one run) and inter-assay (the same sample once in 20 or more repeated runs)

coefficients of variation (CV) were determined using human control samples. The inter-assay CV represents reproducibility over one to two month periods when the cohort samples were analysed. The intra- and inter-assay CV were 0.7 and 1.5% for total cholesterol (mean 4.86 mmol/L), 0.5 and 3.2% for HDL cholesterol (mean 1.38 mmol/L), and 4.2 and 5.2% for CRP (mean 3.0 mg/L). Serum insulin samples were stored at  $-20^{\circ}\text{C}$  and were analysed within 7 days of sampling by radioimmunoassay using commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden; sensitivity 2.4 mU/L, intra-assay CV 5.3%, inter-assay CV 7.6%, mean 20.1 mU/L).<sup>25</sup> Assay selection was based on the instruments and routine methods of Oulu University Hospital laboratory. Smoking from questionnaire was classified as ever (current and ex-smokers) and non-smokers. Participant's own SES was based on occupation and employment status from I (high) to IV (low).

### Statistical analysis

A total of 6033 individuals attended the clinical examination at age 31 years (71.3% of eligible) of whom 5840 participants (2808 males and 3032 females) had valid CRP measurements; they did not differ materially on birth and early life measures from the remaining 6218 births in the cohort (not shown). CRP and insulin levels were logarithmically transformed due to skewness. Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). BMI change from 14 to 31 years was calculated as BMI at 31 years minus BMI at 14 years. BMI and BMI change were divided into tertiles (three equal groups) and geometric mean CRP (antilogarithm of the arithmetic mean log values) was calculated in each tertile. Descriptive statistics are presented as means (SD) for continuous variables and percent for categorical variables. Multiple linear regression models were fitted to test associations between CRP and (i) birth weight, (ii) birth length, and (iii) ponderal index adjusted for sex without/with potential confounders at age 31 years (total/HDL cholesterol, smoking, systolic blood pressure, insulin, SES, and BMI) and at birth/early life (gestational age, maternal smoking, SES, parity). Interaction terms were tested between birth size measures and sex or BMI on CRP. Linear regression models were fitted to test associations between CRP and (i) weight at 12 months, (ii) BMI at 12 months and (iii) head circumference at 12 months adjusted for potential confounders at age 31 years (total/HDL cholesterol, smoking, systolic blood pressure, insulin, SES, and BMI). Potential confounders were selected based on previous evidence for associations between these variables and both CRP and birth size/early life growth.<sup>2–10,12–16</sup> Linear regression models were used to test associations between CRP levels and BMI/weight at 14 years or BMI/weight change between 14 and 31 years. Adjusted  $R^2$  was used to estimate the variance explained by each model. We used the formula  $(10^{(\text{regression coefficient})} - 1) * 100$  in order to represent percent differences in the logarithm of CRP per unit increase of the independent variable. Assumptions of the linear regression models were tested by evaluating plots of residuals vs. predicted values, reviewing scatterplot matrix showing all independent against all dependent variables and plots of the outcome variable (CRP) against tertiles and quartiles of independent variables (birth size). A two-sided  $P$ -value of  $<0.05$  was used to denote statistical significance. No adjustments were made for multiple tests since we have tested a set of predefined hypotheses. Data were analysed (by I.T.) using SPSS version 14 for Windows. Each participant gave written informed consent. The University of Oulu ethics committee approved the study.

## Results

### Descriptive statistics

Mean values of various measures of growth, and weight and BMI are given in *Table 1* for all 5840 participants. Mean (SD) birth weight was 3.50 (0.52) kg, birth length 50.3 (2.14) cm, and ponderal index 2.73 (0.24) kg/m<sup>3</sup>; birth weight was highly correlated with both birth length and ponderal index, Pearson  $r = 0.80$  and  $r = 0.55$ , respectively. Females were lighter at birth, 12 months, and 14 and 31 years than males (not shown). At 31 years, geometric mean [95% confidence interval (CI)] serum CRP was 0.72 mg/L (0.70, 0.75); 17% of the population had CRP >3 mg/L.<sup>26</sup> Mean (SD) systolic blood pressure was 124.9 (13.5) mmHg; mean (SD) total and HDL cholesterol were 5.08 (1.00) and 1.56 (0.38) mmol/L, and geometric mean (95% CI) serum insulin was 7.8 (7.7, 7.9) mmol/L. Fifty-five percent was classified as SES I or II and 63% were ever smokers (current and ex-smokers).

### Multiple regression analyses

With adjustment for sex, 1 kg lower birth weight was associated with 12% higher CRP levels, whereas 10 cm lower length at birth or 1 kg/m<sup>3</sup> lower ponderal index were associated with 20 and 19% higher CRP in adulthood ( $P < 0.05$  to  $P < 0.001$ , *Table 2*). Associations with CRP persisted after adjustment for other potential confounding factors added separately to the model, including total/HDL cholesterol ratio, smoking, systolic blood pressure, and SES. However, associations between CRP and

measures of birth size became statistically non-significant after adjustment for insulin, while adjustment for BMI at age 31 strengthened the associations in all models. The interaction terms between birth weight and BMI in adulthood or between birth weight and sex in association with CRP levels were not significant. Sensitivity analysis of 5712 singletons (2741 males and 2971 females) resulted in similar estimates (*Table 2*).

With adjustment for sex, neither weight nor BMI at 12 months were significantly associated with CRP levels in adulthood: CRP was estimated to be 3 and 1% higher per one unit lower weight or BMI, respectively (see Supplementary material online, *Table S1*). One centimetre smaller head circumference at 12 months was associated with 3% higher CRP levels measured 30 years later. These associations were strengthened (all statistically significant) when BMI at age 31 was added to the model. Post-natal growth and mean weight SD score change from birth to 12 months was not significantly associated with higher levels of CRP in any of the models examined.

At 14 years, 1 kg/m<sup>2</sup> higher BMI was associated with 7% (95% CI 5, 9) higher CRP levels at 31 years of age. Those who had lowest tertile birth weight and highest tertile BMI at either 14 or 31 years had the highest average CRP plasma levels in adulthood (*Figure 1*). Mean (SD) change in BMI in the study population from 14 to 31 years was 5.3 (3.4) kg/m<sup>2</sup>. One kg/m<sup>2</sup> increase in BMI from 14 to 31 years was associated with 16% (95% CI 14, 17) higher CRP at 31 years; BMI change (14 to 31 years) explained 11% of the variance in CRP compared with 2% explained by BMI at 14 years alone.

Increase in BMI for those in the top BMI tertile at 14 years was associated with higher CRP levels and explained a higher proportion of variance ( $R^2 = 18\%$ ) in CRP than increase in BMI for those in the middle ( $R^2 = 11\%$ ) and bottom ( $R^2 = 9\%$ ) BMI tertiles at 14 years (*Figure 2*). Weight change explained less of the variance in CRP at age 31 than BMI change (data not shown).

## Discussion

We used the birth cohort approach to investigate relationships of size at birth and weight gain over the life course with low-grade inflammation in adulthood. Serum CRP levels were on average higher at 31 years for men and women with lower birth weight, ponderal index, and smaller birth length; for those with lower tertile birth weight and upper tertile BMI during adolescence or adulthood, and those with the greatest weight gain from adolescence to young adulthood. We conclude that small size at birth and excessive weight gain during adolescence and young adulthood may predispose to low-grade inflammation—which in turn is associated with increased risk of developing cardiovascular disease.<sup>27</sup>

Though an inverse association of CRP with birth weight has been reported,<sup>28</sup> no previous study has reported associations of CRP with other growth measures including ponderal index and post-natal growth. Weight change between birth and 12 months was not associated with adult CRP levels, suggesting the importance of fetal as compared with post-natal growth on low-grade inflammation in adulthood. Associations of birth size with adult CRP levels were confounded to some extent by adult insulin

**Table 1** Measures of growth at birth and 1 year and weight and body mass index at ages 14 and 31 years

	All	
	n	Mean (SD)/percent
Males	2808	48.1%
Birth weight (kg)	5840	3.50 (0.52)
Birth length (cm)	5789	50.30 (2.14)
Ponderal index (kg/m <sup>3</sup> )	5789	2.73 (0.24)
Gestational age (weeks)	5640	40.0 (1.9)
Birth weight relative to gestational age (kg)	5640	50.32 (28.53)
Weight at 12 months (kg)	5180	10.21 (1.20)
BMI at 12 months (kg/m <sup>2</sup> )	5049	17.89 (1.65)
Head circumference at 12 months	5242	46.71 (1.48)
Post-natal growth (0–12 months) <sup>a</sup>		
Change down	1313	21.9%
No change	2621	43.6%
Change up	1152	19.2%
BMI at 14 years (kg/m <sup>2</sup> )	5329	19.4 (325)
Weight at 14 years (kg)	5398	51.67 (8.80)
BMI at 31 years (kg/m <sup>2</sup> )	5796	24.7 (4.2)
Weight at 31 years (kg)	5815	72.60 (14.81)

CRP: high sensitivity C-reactive protein, BMI: body mass index.

<sup>a</sup>Change in weight SD score between 0 and 12 months (see Methods).

**Table 2** Percent difference (95% CI) in C-reactive protein at 31 years associated with unit increase in birth size measurements ( $n = 5840$ - $5356$ ); adjusted for sex, plus adult or birth/early life factors, and all factors

Adjusted:	Birth weight (per kg)	P-value	Birth length (per 10 cm)	P-value	Ponderal index (per kg/m <sup>3</sup> )	P-value
Sex	-12.4 (-18.9, -5.3)	0.0008	-20.2 (-34.2, -3.3)	0.02	-18.6 (-31.0, -3.9)	0.02
Sex plus adult factors (age 31)						
Total/HDL cholesterol	-11.0 (-17.5, -3.9)	0.003	-18.1 (-32.2, -1.1)	0.04	-16.9 (-29.4, -2.1)	0.03
Smoking	-12.1 (-18.7, -4.9)	0.001	-19.5 (-33.7, -2.3)	0.03	-18.8 (-31.2, -4.0)	0.02
Systolic blood pressure	-11.1 (-17.7, -4.0)	0.003	-17.9 (-32.3, -0.6)	0.04	-16.7 (-29.4, -1.8)	0.03
Insulin (log)	-7.2 (-14.1, 0.2)	0.06	-11.3 (-26.6, 7.3)	0.22	-13.0 (-26.2, 2.5)	0.10
Socioeconomic status	-11.2 (-17.9, -4.1)	0.003	-18.2 (-32.5, -0.7)	0.04	-17.6 (-30.2, -2.7)	0.02
BMI	-16.4 (-22.3, -10.0)	<0.0001	-22.0 (-35.0, -6.4)	0.007	-29.7 (-39.9, -17.8)	<0.0001
All above (without BMI)	-6.4 (-13.4, 1.1)	0.09	-10.2 (-25.9, 8.7)	0.27	-12.1 (-25.5, 3.8)	0.13
All above (with BMI)	-13.1 (-19.4, -6.2)	0.0003	-17.8 (-31.8, -0.8)	0.04	-24.9 (-36.1, 11.6)	0.0006
Sex plus Birth/early life factors						
Gestational age	-11.9 (-18.6, -4.7)	0.0008	-19.3 (-33.5, -2.1)	0.02	-18.0 (-30.6, -3.1)	0.04
Maternal smoking	-13.7 (-20.3, -6.6)	0.0003	-22.4 (-35.4, -4.7)	0.01	-20.7 (-33.2, -5.9)	0.007
Socioeconomic status	-12.2 (-18.8, -5.1)	0.001	-20.8 (-35.0, -3.4)	0.02	-17.8 (-30.6, -2.5)	0.02
Parity	-11.7 (-18.4, -4.4)	0.0021	-19.2 (-33.4, -1.9)	0.03	-16.9 (-29.7, -1.7)	0.03
All factors <sup>a</sup>	-15.7 (-22.9, -7.8)	0.0002	-21.3 (-36.7, -2.2)	0.03	-23.7 (-35.6, -9.5)	0.002
All above (singletons only) ( $n = 4491$ - 4949)	-16.0 (-23.3, -7.9)	0.0002	-22.2 (-37.8, -2.7)	0.03	-22.8 (-35.0, -8.2)	0.003

BMI, body mass index; HDL, high density lipoprotein.

<sup>a</sup>All adult and early life factors are entered in this model except for socioeconomic status at birth which was not entered due to high correlation with socioeconomic status at 31 years.

levels, reflecting well-established associations between insulin and CRP<sup>29</sup> and between birth size and insulin in adulthood.<sup>30</sup>

Adult as well as early life factors are important in development of low-grade inflammation. As in other studies,<sup>31,32</sup> adjustment for adult BMI strengthened associations of weight as well as length or thinness (ponderal index) at birth or at 12 months with CRP in our study, whereas excessive weight gain and increase in BMI from age 14 to 31 years were associated with higher CRP levels at 31 years. This is consistent with results of the Coronary Artery Risk Development in Young Adults (CARDYA) study showing worsening of components of metabolic syndrome with weight gain over a 15-year period.<sup>33</sup> Taken together, our study and CARDYA indicate the importance of weight gain in development of an adverse cardiovascular health profile in young adulthood.

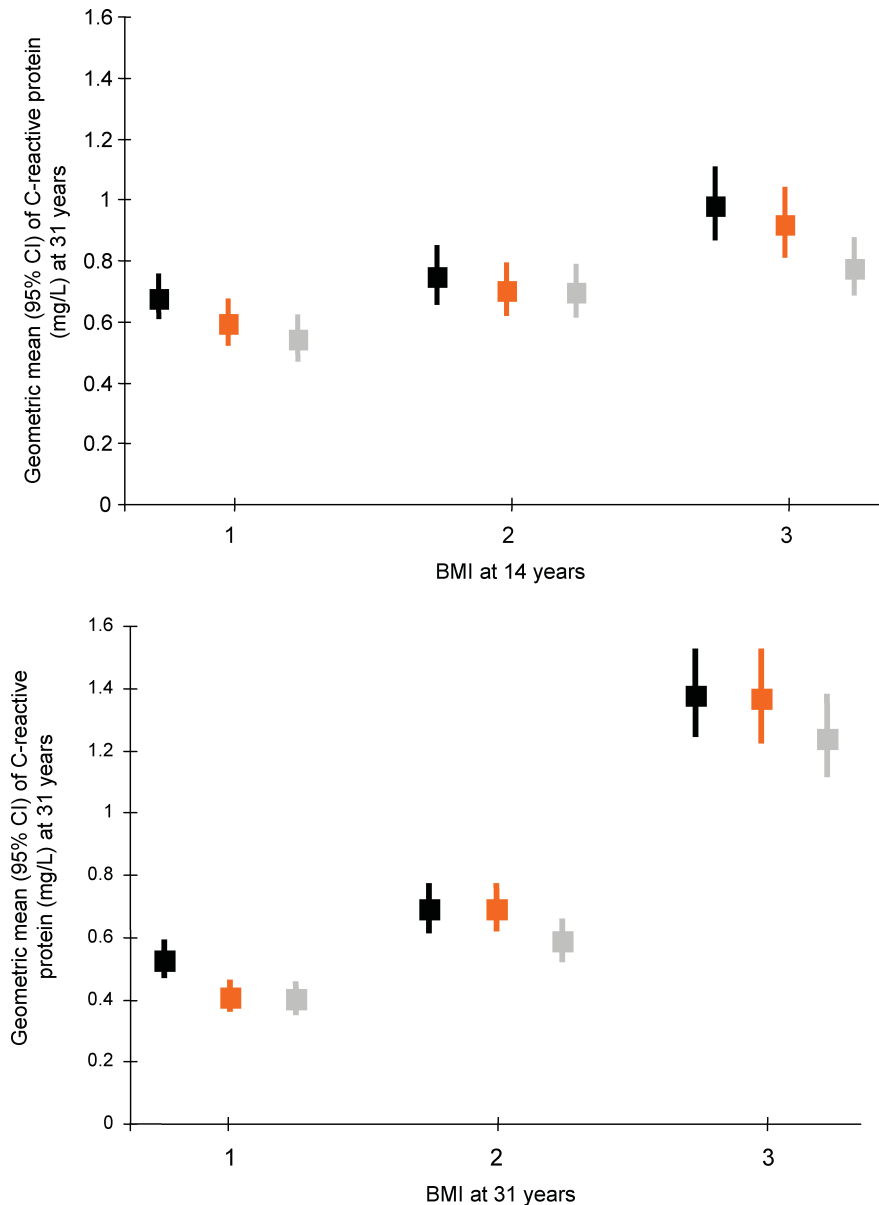
## Potential mechanisms

Several mechanisms might explain the relationships of small size at birth with chronic inflammation in adulthood. Barker et al.<sup>34</sup> reported that birth weight was related to fibrinogen levels measured in men aged 59–70 years. Fibrinogen and CRP are both acute phase reactants secreted by the liver and both are up-regulated by interleukin-6 (IL-6), a cytokine cleared principally via the kidneys. Animal models have shown that restricted overall growth is related to organ growth.<sup>35,36</sup> Thus, increased adult plasma levels of these inflammatory markers associated with reduced infant growth may reflect a persisting response to impaired liver or kidney development during a critical early phase. In addition, low birth weight has been associated with

depressed immune function and propensity for infections, including hospitalizations, during childhood.<sup>37,38</sup> During infection, pathogenic microbes induce the inflammatory response; recurrent or persistent infections in early life may result in activation of a chronic inflammatory response which might later predispose individuals to increased risk of developing cardiovascular disease.

An alternative mechanism involves an activated inflammatory response as a result of stress response programming during pregnancy or early life. Maternal stressors such as diet, physiological stress, physical environment, ergonomical challenges (and others) might affect the fetus by the *trans*-placental passage of maternal hormones including cortisol. This might lead to persistent glucocorticoid signalling, disrupt the potentially adaptive response to stress,<sup>39,40</sup> and favour a persistent inflammatory response that results in adverse effects on adult health. Epidemiological evidence in support of this hypothesis comes from studies of maltreated children exposed to early life stress.<sup>41</sup> These children showed increased levels of CRP, fibrinogen, and white blood cell count at 32 years of age.

As found in our study, weight gain and obesity correlate with low-grade inflammation. Adipose tissue produces ~25% of the body's circulating IL-6, the main stimulus of CRP production;<sup>42–44</sup> therefore weight gain might contribute to low-grade inflammation through excess adipose tissue and elevated cytokine production. However, elevated levels of inflammatory markers (fibrinogen and CRP) have been reported to predate weight gain<sup>45,46</sup> which makes it difficult to infer the direction of association between obesity and inflammation. Our data favour the hypothesis



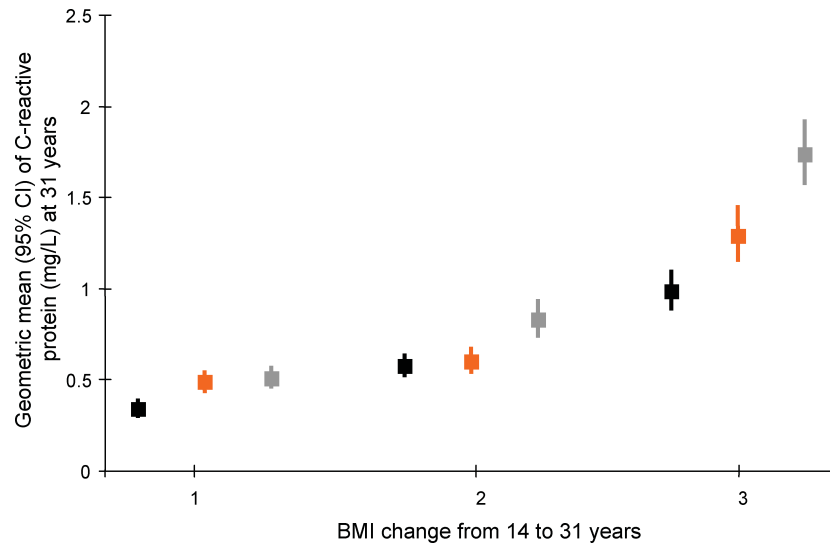
**Figure 1** Geometric mean C-reactive protein per tertile of birth weight and body mass index at ages 14 and 31 years. Bars represent 95% confidence intervals of the geometric mean. Sex-specific cut-points for body mass index tertiles were 18.26 and 19.89 kg/m<sup>2</sup> for males and 18.29 and 20.13 kg/m<sup>2</sup> for females at 14 years and 23.5 and 26.3 kg/m<sup>2</sup> for males and 21.8 and 24.8 kg/m<sup>2</sup> for females at 31 years. For birth weight cut-points were 3.35 and 3.78 kg for males and 3.25 and 3.64 kg for females (black square, bottom; red square, middle; grey square, top tertile). For body mass index 1: bottom, 2: middle, 3: top tertile.

that increase in body weight or BMI precedes the production of a low-grade inflammatory response.

### Limitations

Some study limitations need to be addressed. Clinical examination at age 31 was restricted to those still living in the original study area or in the capital city area, which comprised the largest migrated group. Although this, together with non-responders (30%), introduces possible bias, demographic factors were similar among those attending clinical examination and included in present analyses, and the

remainder alive. Misclassification may have occurred with self-reported weight at age 14 (and thus weight change to age 31, when weight was measured at the clinical examination) and in the assessment of CRP, which was measured once only—though intra-individual variation in CRP would tend to result in underestimation of true associations. Finally, due to the young age of this cohort there are only a few cardiovascular events to date; continued follow-up over the next 20+ years will allow associations between small size at birth, weight gain, low-grade inflammation, and incident cardiovascular events to be explored within the same cohort.



**Figure 2** Geometric mean C-reactive protein per tertile of body mass index (BMI) change between 14 and 31 years according to tertiles of BMI at 14 years. Bars represent 95% confidence intervals of the geometric mean. Sex specific cut-points for body mass index tertiles were 18.26 and 19.89 kg/m<sup>2</sup> for males and 18.29 and 20.13 kg/m<sup>2</sup> for females at 14 years and 4.54 and 6.92 kg/m<sup>2</sup> for males and 2.86 and 5.45 kg/m<sup>2</sup> for females for body mass index change at 31 years. For body mass index change 1: bottom, 2: middle, 3: top tertile. For body mass index at 14 years black square, bottom; red square, middle; grey square, top tertile.

## Conclusions

We found associations between lower birth weight and weight gain between 14 and 31 years of age with low-grade inflammation in adulthood. Given the emerging role of inflammation in cardiovascular disease, our results add important information on the relationship between small size at birth, weight gain, and adult cardiovascular health. A better understanding of the mechanisms that underlie these associations is essential to inform preventive measures—from the fetal period through childhood, adolescence, and young adulthood. The finding that weight gain from adolescence to young adulthood appears to play a greater role in low-grade inflammation than weight in adolescence *per se*, could have important implications for the primordial prevention of cardiovascular disease. Promoting healthier lifestyle in childhood and adolescence leading to weight stabilization<sup>26</sup> might be a crucial step in establishing a low cardiovascular risk profile in young adults.

## Supplementary material

Supplementary material is available at European Heart Journal online.

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**Conflict of interest:** none declared.

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