Original Research Article

Life Course Weight Gain and C-Reactive Protein Levels in Young Adults: Findings from a Brazilian Birth Cohort

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ABSTRACT Rapid weight gain in childhood is associated with increased risk of chronic diseases in adults. C-reactive protein (CRP) is a mediator of atherosclerosis and chronically elevated levels predict cardiovascular outcomes. The effects of life course weight gain on CRP levels are not clear. The 1982 Pelotas (Brazil) birth cohort study (n = 5,914) has prospectively collected weight and health data at several follow-ups since birth. The most recent was in 2004–05, when 77.4% of the cohort was traced and CRP levels were measured in 89% of those interviewed (n = 3827). Geometric mean (SE) C-reactive protein levels were 0.89 mg/l (0.03) and 1.66 mg/l (0.04) in men and women, respectively. In analyses adjusted for confounding variables, weight gain in infancy showed a weak negative association among males, but from the second year onwards, weight gain was positively associated with CRP levels. In females, weight gain was associated with higher CRP at every period tested. The strongest associations were observed in the most recent (18–23 years) period; CRP ratios (95% CI) per z score increase in weight gain were 1.78 (1.57–2.00) and 1.52 (1.30–1.78) for men and women, respectively. Males who were stunted at 2 years and centrally obese at 23 years had the highest CRP levels (P = 0.002 for interaction). In summary, rapid weight gain throughout life predicted higher CRP levels. Public health efforts need to tackle chronic under-nutrition in infancy, together with rapid weight gain in later childhood and adolescence, especially in countries undergoing the nutritional transition. Am. J. Hum. Biol. 21:192–199, 2009. © 2008 Wiley-Liss, Inc.

Studies from developed countries showed that low birth weight is associated with cardiovascular risk in adult life though mechanisms remain largely speculatory (Barker, 1994). Early hypotheses centered on in-utero exposures but recently, rapid postnatal growth has also been implicated with increasing risk (Singhal and Lucas, 2004). Several recent studies have shown that growth in childhood, especially rapid weight gain, is associated with increased risk for overweight (Ekelund et al., 2006; Monteiro et al., 2003; Victora et al., 2007), elevated blood pressure (Horta et al., 2003), clustered metabolic risk (Ekelund et al., 2007), and coronary events (Barker et al., 2005). Data suggest that individuals who are small in the first years of life and subsequently put on weight rapidly present the greatest levels of risk (Adair and Cole, 2003; Barker et al., 2005; Bhargava et al., 2004; Eriksson et al., 2001).

C-reactive protein (CRP), an acute phase reactant used as a marker for systemic inflammation, is recognized as a potential mediator in the atherosclerotic process (Pepys and Hirschfield, 2003; Yeh 2004). Observational studies have shown that chronically elevated CRP levels predict coronary heart disease and related outcomes in adults, though most data are from high-income countries (Albert et al., 2002; Cesari et al., 2003; Ridker et al., 1998). The associations between early life variables and CRP levels have not been examined in depth. If life course weight gain, a modifiable factor, is a contributor to inflammatory mediators of disease, interventions beginning relatively early in life could be tailored to reduce long-term risk for coronary heart disease by keeping inflammatory levels in check long before conventional individual-level interventions normally begin.

Life course models are fundamental for the study of early risk for chronic disease in later life (Ben-Shlomo and Kuh, 2002; Kuh et al., 2003). However, literature from countries undergoing the epidemiological transition is sparse and few cohorts have adequate longitudinal data to explore these associations (Gillman and Kleinman, 2007). The 1982 Pelotas (Brazil) birth cohort study has prospectively collected data from participants at numerous follow-up visits, the most recent being in 2004–2005 when the cohort was aged 23 years. We used this data to examine weight gain throughout life in relation to levels of CRP levels in young adults.

METHODS

Study sample

The city of Pelotas in Southern Brazil has a population of ~350,000 (estimated, 2007). The 1982 Pelotas birth cohort began as a perinatal survey of all hospital births

The authors declare that they have no competing interests.

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TABLE 1. Comparison of demographic and socioeconomic characteristics of the cohort members located in each period

Year	1982	1983	1984	1986	1997	2000	2001	2004
N target	5,914	1,916	5,914	5,914	1,597	3,037	1,597	5,914
Variables[a]								
Sex								
Male	3,037	76.2%	87.1%	84.2%	73.1%	78.9%	71.0%	78.1%
Female	2,876	83.0%	87.3%	84.2%	70.4%	–	68.7%	76.6%
P-value		<0.001	0.8	1.0	0.02	–	0.05	0.2
Maternal skin color								
White	4,851	79.3%	87.0%	83.6%	73.3%	79.2%	71.2%	76.9%
Black/mixed	1,060	80.6%	88.3%	86.7%	64.9%	77.5%	63.9%	79.8%
P-value		0.3	0.3	0.01	<0.001	0.4	<0.001	0.04
Family income[b]								
≤1	1,288	67.5%	84.2%	80.7%	60.6%	72.7%	58.8%	74.7%
1.1–3	2,789	84.8%	89.1%	86.4%	72.4%	80.1%	71.0%	80.7%
>3	1,808	79.8%	86.7%	83.3%	79.0%	81.7%	76.4%	73.9%
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Maternal education, (years)								
0–4 years	1,960	75.5%	85.5%	83.1%	67.0%	76.2%	63.6%	78.4%
5–8 years	2,454	79.6%	89.0%	85.8%	73.0%	81.7%	72.1%	79.2%
9+ years	1,493	84.5%	86.7%	83.1%	75.9%	77.9%	74.4%	72.9%
P-value		<0.001	0.002	0.01	<0.001	0.004	<0.001	<0.001
Birth weight								
≥2500 g	5,375	79.6%	87.1%	84.1%	72.2%	79.1%	70.4%	77.3%
<2500 g	534	78.3%	89.1%	84.5%	67.5%	77.5%	65.4%	78.1%
P-value		0.5	0.2	0.9	0.02	0.6	0.02	0.7
N followed-up	5,914	1,523	5,161	4,979	1,146	2,393	1,102	4,579
N with complete data[c]	3,746	996	3,450	3,393	837	1,705	733	3,744
Mean age	0 m	11.3 m	19.4 m	43.1 m	14.7 y	18.2 y	18.9 y	22.8 y

Percentages refer to the follow-up rates of the original cohort or sample, including located individuals in each period and known deaths. *P*-values by χ^2 test for heterogeneity.
[a]All variables collected in 1982.
[b]Family income in minimum wages.
[c]Individuals with data on weight for respective follow-up, C-reactive protein in 2004, and other covariates (described in Methods).

taking place in the city that year (Victora and Barros, 2006). Over 99% of births (n = 5914) to mothers living in the urban area of the city were registered. In 1983, cohort members born from January to April were sought, resulting in 79% (n = 1457) of the sub-sample being examined. The 1984 and 1986 follow-ups began with city censuses in attempts to locate the entire cohort; 87% (n = 4934) and 84% (n = 4742) of the cohort were examined, respectively. Mean ages of the children were 11.3, 19.4, and 43.1 months at the 1983, 1984, and 1986 visits, respectively. In 1997, 27% of the city's census tracts were visited by systematic sampling in search of members of the cohort, resulting in a 72% follow-up rate (n = 1076) at a mean age of 14.7 years. Follow-up rates reported here include those known to have died.

The next examination took place in 2000, when cohort males were legally obligated to report to the army. Of the 3,037 cohort males, 2,250 were interviewed at a mean age of 18.2 years (79% follow-up rate). In 2001, the same 27% sub-sample as in 1997 was revisited and 1,031 cohort members were successfully examined and interviewed at a mean age of 18.9 years. In the current study, the 2000 and 2001 follow-ups were combined to include males and females, and mean age of this group was 18.4 years. The most recent cohort follow-up was conducted in 2004–2005. During this follow-up, 4,297 members of the cohort (mean age 22.8 years) were interviewed and examined, resulting in a follow-up rate of 77%.

Table 1 summarizes the follow-up periods and compares characteristics between individuals lost to follow-up and those successfully weighed and measured for the current analysis. A detailed analysis of these data in terms of the results obtained is presented in the Discussion section.

Measured variables

Newborns were weighed using calibrated pediatric scales sensitive to 100 g and mothers were interviewed on a number of sociodemographic and general health variables. Gestational age was estimated by mother's recall of last menstrual period, but about 20% of the sample had missing values. Maternal smoking was defined as smoking at least one cigarette per day. Height of the mother was taken using a portable stadiometer to the nearest millimeter. Maternal education was categorized by years of completed formal schooling. Family income was collected as a categorical variable representing less than 1, 1.1–3.0, 3.1–6.0, 6.1–10.0, and greater than 10 minimum wage units per month. Minimum wage in 1982 was equivalent to ~50 USD per month. Birth length was not measured.

Extensive questionnaires were applied and members were weighed and measured at each of the above follow-ups using methods previously described (Victora et al., 2003). In 2004–2005, a group of 25 trained interviewers applied questionnaires that included sections on health, behavior, and socioeconomic factors. Skin color was self-reported. Weight to the nearest 100 g was measured using the Seca (UNICEF) scale. Abdominal circumference was measured at the narrowest girth of the trunk or halfway between the costal margin and iliac crest. Central obesity was defined using cutoffs of ≥94 cm for men and ≥80 cm for women (WHO, 2006).

Current smoking was defined as smoking at least one cigarette every week. Fat and fiber intake were assessed using a modified Block method (Block et al., 1989). Fiber intake was dichotomized into "adequate/moderate" or

"low". Information on consumption of wine, beer, and liquor was used to calculate alcohol intake in grams and categorized as "non-drinker", "one drink per day" (equivalent to 350 ml beer, 150 ml wine or 30 ml liquor), or ">1 drink per day". Sedentary behavior (<150 min of moderate intensity per week of activity) was classified according to the long version of the International Physical Activity Questionnaire (www.ipaq.ki.se). Interviewers applied the Self-Reported Questionnaire-20, which has been validated in Brazil, to evaluate minor psychiatric disorder (Mari and Williams, 1986). Quality control procedures included standardization of interviewers prior to and during the study at regular intervals and re-evaluation of a sub-sample of the questionnaire of 10% of the interviewees by study supervisors; no irregularities were noted.

Nonfasting blood was collected from volunteers during the 2004–2005 follow-up. CRP measurements are not affected by fasting/nonfasting states (Pearson et al., 2003). Serum C-reactive protein was measured using the automated Immulite (Siemens) chemiluminescent immunoassay (Los Angeles, USA). The lower detection limit was 0.1 mg/l and measures below that value were converted to 0.05 mg/l for analysis. Detailed methods for the 2004–2005 follow-up visit and the high-sensitivity C-reactive protein assay are available (Nazmi et al., 2007).

Statistical analyses

Internal weight *z* scores were calculated using sex-specific distributions from all follow-up visits; 1982, 1983, 1984, 1986, 1997, 2000/2001 (combined), and 2004–05 at approximate ages of 1, 2, 4, 15, 18, and 23 years, respectively. Pregnant women in the 2001 and 2004–2005 were excluded from calculations to generate *z* scores (n = 46 and 103, respectively). Weight change in a given period was obtained by subtracting the initial from the final *z* score. Stunting at age 2 years was defined using the 2007 WHO growth standards for height-for-age *z* score (www.who.int/childgrowth/en/).

All analyses were adjusted for age in months at each visit, and stratified by sex. Analyses of weight gain in the first year of life were adjusted for gestational age. Results were virtually identical to the unadjusted values, and because 20% of the sample had no information on gestational age and had to be excluded from the adjusted analyses, only unadjusted values are presented.

Individuals with CRP >10 mg/l were excluded from the primary analyses. Linear regression was used to compare log-normalized CRP levels (mg/l) with age-adjusted internal weight gain *z* scores. Two further models were used: The first adjusted for weight at the beginning of the period being examined and was used to account for regression to the mean; a statistical phenomenon that is observed when measurements prone to random error are repeated over time (Barnett et al., 2005). Adjusting for baseline weight corrects for regression to the mean by estimating the true mean weight gain of the individual in each period. The final model was adjusted for age, weight at the beginning of the period, and potential confounders (skin color, maternal height, maternal smoking, family income at birth, maternal education, and parity in women). β Values and corresponding confidence intervals for CRP are shown in exponentiated form and may be interpreted as the multiplicative impact per *z* score increase of weight gain on CRP levels.

TABLE 2. Weight gain from birth to age 23 years in cohort males and females, in kg

Weight gain	Males		Females	
	Mean (SD)	*N*	Mean (SD)	*N*
Birth to 1 year	6.33 (1.12)	714	5.88 (1.11)	742
1 to 2 years	2.55 (0.88)	653	2.70 (0.87)	683
2 to 4 years	4.33 (1.39)	2,291	4.46 (1.47)	2,185
4 to 15 years	41.86 (11.40)	517	39.51 (9.51)	480
15 to 18 years	9.50 (7.06)	536	3.16 (5.95)	470
18 to 23 years	5.04 (6.52)	1,982	3.03 (6.18)	772

Excluding pregnant women at ages 18 and 23 years.
$P < 0.001$ for all differences in weight gain between males and females.

Pregnant women (n = 103) and women using oral contraceptives (n = 479) were excluded from all analyses involving CRP, as were those with acute-level CRP (> 10 mg/l). CRP was dichotomized in some analyses, using a cut-off of 3 mg/l to indicate elevated levels (Pearson and others 2003).

The Federal University of Pelotas Ethical Committee approved all phases of the 1982 Pelotas birth cohort study. Verbal informed consent was obtained until 1986 and written informed consent thereafter.

RESULTS

Follow-up rates were generally high; 79% (1983), 87% (1984), 84% (1986), 72% (1997), 79% (2000), 69% (2001), and 77% (2004). These rates include those known to have died. Table 1 compares demographic and socioeconomic characteristics between cohort members located in each period of follow-up and the entire cohort. Individuals successfully followed-up were born to families with higher income and mothers with more education than those lost to follow-up. Distribution of other factors such as maternal skin color and birth weight did not consistently differ throughout the follow-up periods.

Table 2 describes weight gain (in kg) between follow-up periods from birth to age 23 years. Males tend to gain more weight in every period except from 1–2 years and 2–4 years, whereas females gained more. Weight gain was significantly different between males and females in every period.

Mean (SD) birth weight was 3.25 kg (0.56) and 3.13 kg (0.55) for cohort males (n = 3,035) and females (n = 2,873), respectively. At the 2004–2005 follow-up, when the cohort was aged 23 years, respective mean (SD) weights were 71.9 kg (14.0) and 60.9 kg (12.7). Table 3 describes these and other characteristics at birth and at the 2004–2005 follow-up.

Using serum from the 2004–2005 follow-up, 1,919 men and 1,908 women had CRP levels evaluated. Excluding 93 pregnant women and 445 women using oral contraceptives at the time of the blood draw, geometric mean (SE) levels of CRP in men and women were 0.89 mg/l (0.03) and 1.66 mg/l (0.04), respectively (P < 0.001). Subjects with CRP levels above 3 mg/l included 16.8% of the males and 40.5% of the females, whereas 4.1% and 10.2% of male and females, respectively, had CRP above 10 mg/l. The latter (CRP > 10 mg/l) were excluded from the main analyses because of possible acute inflammatory conditions.

Table 4 shows associations between weight change *z* scores and CRP levels using three different levels of

adjustment. Beta coefficients are interpretable as the multiplicative impact on CRP levels per standard deviation increase of weight gain during that period; greater than 1.0 indicates a positive association.

Age-adjusted weight gain models (Model 1) are presented first. In men, weight gain in the first year of life showed a nonsignificant, inverse association with CRP levels. Beginning from age 1 year, there were strong positive associations with CRP levels in all periods, with a borderline association at 4–15 years. Weight change in adolescence and early adulthood were more powerfully associated than in earlier periods, with a 35% (95% CI 11–66) and 53% (95% CI 36–71) increase in CRP levels for every z-score increment of weight gain between 15–18 and 18–23 years, respectively. Accounting for regression to the mean (Model 2), all positive effects were strengthened. Further adjustment for confounders did not have a marked effect on the coefficients, and weight gain from 2 years and above maintained strong positive associations, with a weaker association in the 4–15 year period. The nonsignificant inverse association with weight gain in infancy observed in the crude analyses was maintained. Associations in the latter periods (15–18 and 18–23 years) increased in magnitude by 31% and 32% in the final model when compared with the first model.

Weight gain in women showed slightly different patterns of association. In fully adjusted analyses, weight gains in all periods showed positive associations with CRP. Weight gain in the 1–2 year period was positively associated with CRP at the borderline level of significance, likely because of the smaller *N* associated with that period. Magnitudes of association in women in the 1–2 and 2–4 years periods were comparable with those in men, whereas women showed stronger associations from 4–15 years and men showed stronger associations in the last two periods tested. As in men, the strongest associations were observed in the 18–23 years age range.

A fourth model (not shown) was fitted, which also included mediators known to influence CRP levels: current smoking, fat and fiber intake, alcohol consumption, sedentary lifestyle, and minor psychiatric disorder measured at age 23 years. The results were very similar to those presented in Model 3 of Table 4.

Figure 1 plots the average weight trajectories of subjects according to CRP levels above or below/equal to 3 mg/l. Although those with high CRP were slightly heavier throughout their lives—except for males at 15 years—the differences only become marked at the age of 18 years for men and 15 years for women.

To test the hypothesis that early growth restriction coupled with later life obesity is associated with excess risk, we evaluated the combined effects of stunting (length-for-age) at age 2 years and central obesity at age 23 years in relation to CRP levels (see Fig. 2). Males who were stunted and subsequently became centrally obese had nearly six times higher CRP levels than those who were stunted and did not become obese (ratio 5.98; 95% CI 3.23–11.06) and more than twice as high (ratio 2.48; 95% CI 1.42–4.34) as those who were not stunted and subsequently became centrally obese. The interaction between stunting and central obesity was statistically significant ($P = 0.002$). A similar but not as marked pattern was observed among women, among whom the interaction was not significant ($P = 0.3$). Interactions between early stunting and BMI levels were positive but not significant; 1.25 (0.87–1.79) in men and 1.02 (0.68–1.53) in women.

TABLE 3. Descriptive characteristics at birth and at age 23 years in the 1982 Pelotas birth cohort study

	Mean (SD) or (%)
At birth	
Birthweight, g	3187 (565)
Gestational age, w	39.3 (1.9)
% Female	48.6
Maternal age, y	25.8 (6.1)
Maternal height, m	1.6 (0.1)
Maternal education, y	6.5 (4.2)
Family income, minimum wages	
<1	21.9
1–3	47.4
3.1–6.0	18.5
6.1–10	6.5
10+	5.7
% Maternal smoking	35.6
N, 1982	5,914
At age 23 years	
% White, self-reported	75.4
Education, y	9.4 (3.1)
Family income, minimum wages	
<1	5.7
1–3	32.3
3.1–6.0	33.6
6.1–10	15.2
10+	13.3
Weight, kg	66.6 (14.5)
Abdominal circumference, cm	78.3 (10.9)
% Smoker	25.7
% High or very high fat intake	64.0
% Low fiber intake	69.1
% >1 alcoholic drink per day	23.0
% Sedentary at leisure time	64.4
CRP, mg/l[a]	1.45 (1.02)
N, 2004	4,297

[a]CRP shown as geometric mean (SE).

DISCUSSION

This is the first study to examine associations between weight gain trajectories and an inflammatory marker outside high-income countries. Serum CRP levels in the current sample were similar to those from population-based studies of similar age samples in the USA but slightly lower than those from a New Zealand cohort (Ford et al., 2003, 2004; Williams et al., 2004).

In our sample, those born lighter gained more weight in the first year of life, showing catch up growth (data not shown) (Tanner, 1989). Earlier analyses of the 1982 and 1993 Pelotas cohorts suggest that early weight gain is associated with accumulation of a greater proportion of lean body mass (Victora et al., 2007; Wells et al., 2005), while also being protective against early life morbidity and mortality. Weight gain later in childhood, however, has been associated with deposition of fat mass (Wells et al., 2005).

Two other studies, both from high-income countries, analyzed early anthropometric indices in relation to CRP levels in later life. Sattar et al. (2004) showed an inverse association between birth weight and CRP levels among adult men and women from the MIDSPAN (UK) family study, but they did not have information on weight gain and relied mostly on birth weight by recall (Sattar et al., 2004). A recent Finnish study also found inverse associa-

TABLE 4. Associations between C-reactive protein (CRP) levels[a] and weight change z-score in 3 linear regression models

Weight change z score	*N*	β coefficients (95% confidence intervals) in 3 linear regression models		
		Adjusted for age at both follow-ups	Adjusted for age and initial weight	Adjusted for age, initial weight, and confounders[b]
Males				
Birth to 1 year	467	0.93 (0.83–1.04)	0.94 (0.83–1.07)	0.90 (0.78–1.03)
1 to 2 years	442	**1.26 (1.03–1.54)**	**1.30 (1.05–1.61)**	1.19 (0.95–1.07)
2 to 4 years	1,587	**1.15 (1.04–1.27)**	**1.20 (1.08–1.33)**	**1.18 (1.06–1.32)**
4 to 15 years	379	1.16 (0.99–1.35)	**1.18 (1.00–1.40)**	1.15 (0.97–1.37)
15 to 18 years	398	**1.35 (1.11–1.66)**	**1.49 (1.21–1.84)**	**1.51 (1.21–1.88)**
18 to 23 years	1,671	**1.53 (1.36–1.71)**	**1.80 (1.61–2.03)**	**1.78 (1.57–2.00)**
Females[c]				
Birth to 1 year	323	1.11 (0.97–1.26)	**1.22 (1.06–1.42)**	**1.30 (1.11–1.52)**
1 to 2 years	308	0.94 (0.73–1.21)	1.15 (0.88–1.50)	1.29 (0.98–1.72)
2 to 4 years	1,088	1.10 (0.98–1.25)	**1.13 (1.00–1.27)**	**1.16 (1.02–1.31)**
4 to 15 years	269	**1.17 (1.00–1.38)**	**1.30 (1.09–1.56)**	**1.31 (1.09–1.58)**
15 to 18 years	268	1.10 (0.93–1.30)	**1.19 (1.00–1.42)**	**1.19 (1.00–1.42)**
18 to 23 years	487	**1.20 (1.04–1.38)**	**1.53 (1.31–1.78)**	**1.52 (1.30–1.78)**

Coefficients are interpretable as multiplicative impact on CRP levels. Significant coefficients in bold.
[a]Excludes individuals with CRP> 10 mg/l.
[b]Skin color, maternal height, maternal smoking, family income at birth, years of maternal education and parity at age 23 years for women.
[c]Excluding pregnant women at ages 18 and 23 years and those using oral contraceptives at age 23 years.

tions between birth weight and CRP levels, but showed that weight gain in the first year of life did not have positive effects (Tzoulaki et al., 2008). Weight gain between 14 and 31 years, however, was strongly associated with risk for higher CRP levels at age 31.

Our finding that weight gain in the first year of life in men is not associated with higher adult CRP levels, whereas weight gain after 2 years leads to increased levels, supports the hypothesis that rapid weight gain in the first year does not incur higher risk. Weight gain in men after 2 years, however, was consistently associated with higher CRP levels, indicating increased risk beginning in later childhood.

In women, weight gain in the first year was significantly associated with increased CRP levels, contrasting with the results in men. Similar to men, however, weight gain from the second year onwards was associated positively with CRP levels. In both sexes, the strongest magnitudes of association were in the most recent period measured, suggesting that while weight gain throughout the life course does impact inflammatory levels, excess weight gained after adolescence may play a more important role.

Rapid weight gain was associated with elevated CRP levels (>3 mg/L) after the second year in males, and after the fourth year in females (see Fig. 1). These effects also became more pronounced in the periods following adolescence. These findings highlight the risks associated with sustained rapid weight gain beginning in late childhood (Eriksson et al., 2001; Victora et al., 2007). Given that adipose tissue is a strong mediator of inflammation (Yudkin et al., 1999), it is plausible that sustained weight gain over greater periods of time leads to higher inflammatory levels via the mediating effects of an ever-increasing adipose burden (Chu et al., 2003; Cook et al., 2000). This could also partially explain the powerful associations seen in both sexes with the most recent periods of weight gain.

Behavioral factors such as smoking, fat and fiber intake, alcohol consumption, physical activity, and stress have also been shown to have independent associations with CRP levels (de Maat and Kluft, 2001). These lifestyle factors may also partially explain differences in outcome measures between the sexes. In the current study, including these variables in our analyses did not affect the conclusions in either sex.

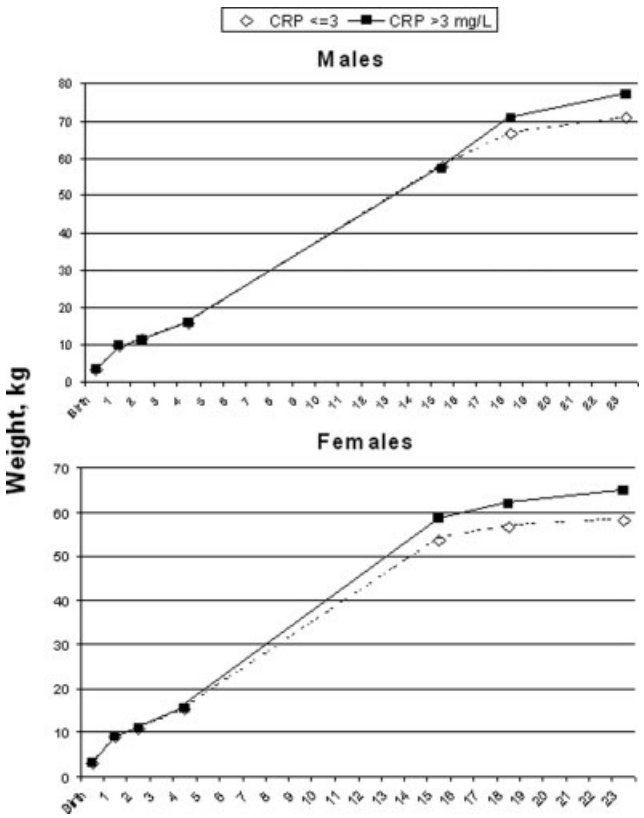

Fig. 1. Lifecourse weight trajectories of cohort males and females with and without elevated C-reactive protein levels (> 3 mg/l) at age 23 years. Cohort members were weighed at birth, 1, 2, 4, 15, 18, and 23 years of age. Lines connecting points are used for illustrative purposes.

The high risk associated with being undernourished in the first few years of life and then gaining weight rapidly

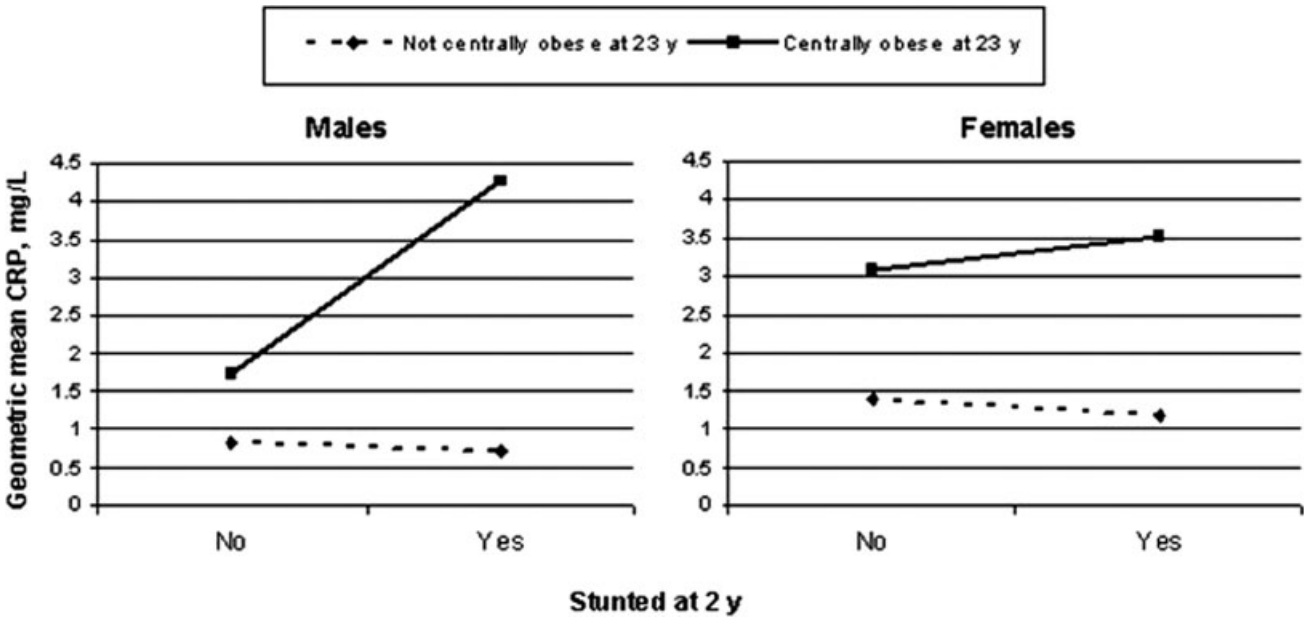

Fig. 2. Combined effects of stunting at 2 years with central obesity at 23 years on C-reactive protein levels. *P*-values for interaction: 0.002 for males and 0.3 for females.

later in childhood has been described with respect to diabetes-related disorders (Bhargava et al., 2004; Newsome et al., 2003), increased blood pressure (Adair and Cole, 2003), coronary events (Barker et al., 2005), and mortality (Eriksson et al., 1999). This may result from metabolic programming following early exposure to under-nutrition (Bogin et al., 2007; Gluckman et al., 2007), which becomes maladaptive in populations undergoing nutritional transition, leading to excess risk for chronic disease. Mechanisms that have been proposed to explain this increased risk include compromised pancreatic β cell formation and altered metabolic parameters (Barker, 1994). Our results support this hypothesis. We found that being stunted at 2 years (a marker for chronic under-nutrition) coupled with central obesity at age 23 years was associated with a marked increase in the risk for inflammation, particularly for males (see Fig. 2). The immune system is sensitive to in-utero and early life exposures, that may have permanent effects on postnatal immune response (Dietert et al., 2000; Holladay and Smialowicz, 2000). Also, greater levels of inflammation may be associated with the endocrine role of excess fat tissue in individuals who became centrally obese after being undernourished in childhood (Mohamed-Ali et al., 1998). Further research is needed to elucidate which pathways are affected and how early programming, especially vis-à-vis central adiposity, impacts the chronic inflammatory response.

The sampling strategies for these analyses deserve mention (Table 1). There were high overall follow-up rates for target populations in each period, ranging from 69% to 87%. Table 1 compares potential confounding variables of cohort members based on their follow-up status at each visit. Individuals not followed-up from 1982 to 2004 were generally poorer at birth and born to mothers with less education, whereas mother's skin color did not consistently vary (Barros et al., 1990). These findings are not surprising; loss to follow-up in poorer and less educated sub-groups is a well characterized phenomenon in longitudinal studies (Graaf et al., 2000; Siddiqui et al., 1996). The potential impact of these losses on our results is difficult to assess. We used regression models using only those cohort members with data from all periods to assess differences. Although *N* was very limited, at 99 for men and 66 for women leading to wide confidence intervals, the directions of effect and model dynamics were similar to those shown in Table 3 (results not shown).

Other limitations of this study should be considered. CRP was evaluated on a single occasion so we cannot draw inferences as to chronic inflammatory states. Similarly, these cross-sectional analyses of CRP at age 23 years preclude implications of causality. This study did not exclude individuals with clinical inflammatory conditions at the time of the blood draw, however given the young age of the participants, it is unlikely that this affected our analyses. Likewise, data on concurrent acute infections was not collected. To address these potential shortcomings, our main analyses excluded individuals with CRP >10 mg/l. Further, we did not have information on weight within the first year of life, a period that has been described as having important effects on later risk (Ekelund et al., 2007; Singhal et al., 2004). On the other hand, we were able to examine the cohort at numerous follow-ups, allowing for a life course perspective. Lastly, estimates of gestational age were limited to the subset of mothers who could recall the date of their last menstrual period ($\sim$80%), but *N* limitations of this covariate likely did not impact our results.

In summary, rapid weight gain throughout life positively impacted CRP levels in both sexes, but the effects varied slightly by sex. In males, risk increased markedly

with rapid weight gain, starting around the age of 2 years. In females, rapid gain in the first year of life was already associated with higher risk, as was rapid gain after 2 years. In both sexes, rapid weight gain in the most recent period (18–23 years) was associated with the highest risk for elevated CRP levels. A significant additional risk was observed among individuals who were stunted at age 2 years then subsequently became obese adults, particularly for males.

Our results suggest that interventions designed to promote healthy weight gain beginning early, and continuing throughout life, may help to reduce risk for elevated inflammation and its associated sequelae later in life. Public health efforts tackling chronic under-nutrition in infancy, together with rapid weight gain in later childhood and adolescence may confer greater population benefit than focusing on specific age groups, especially in countries undergoing the nutritional transition.

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