How do early socioeconomic circumstances impact inflammatory trajectories? Findings from Generation XXI

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Highlights:

- Early socioeconomic circumstances impact inflammation trajectories in childhood
- Immediate impact of early socioeconomic circumstances on physiology dysregulation
- Low socioeconomic circumstances lead to increased inflammatory levels during childhood
- Social inequalities in population health have its onset at very early ages

Abstract

Background: The association between socioeconomic position and markers of inflammation in adults, including C-reactive protein (CRP), is well-established. We hypothesized that children from families of less-advantaged socioeconomic circumstances may be at higher inflammatory risk during childhood and, consequently, throughout their life course. Thus, we aimed to investigate whether early socioeconomic circumstances impact CRP trajectories using repeated measures of data from a population-based birth cohort.

Methods: Data from 2510 participants of Generation XXI, a prospective Portuguese population-based birth cohort, were included in this study. Early socioeconomic circumstances comprised maternal education and occupation, paternal education and occupation, and household income at the child's birth. Venous blood samples were collected from the children at ages four, seven, and ten years, and high-sensitivity CRP (Hs-CRP) was quantified. Hs-CRP trajectories were computed using a linear mixed-model approach.

Results: Participants from less-advantaged socioeconomic circumstances presented higher levels of Hs-CRP by age of ten years. The higher the mother´s education and disposable household income, the lower the minimum value of the log Hs-CRP observed throughout childhood. Further, the age at which that minimum log Hs-CRP value was reached occurs later, meaning that children born in more-advantaged socioeconomic circumstances had lower levels of log Hs-CRP compared with children from less-advantaged families.

Conclusions: Poor socioeconomic circumstances early in life are associated with increased inflammation levels throughout the first decade of life. This study demonstrates that social inequalities may impact population health beginning at very early ages.

Keywords: Socioeconomic circumstances; C-Reactive Protein; childhood; trajectories

Introduction

Social adversity during childhood is thought to become biologically embedded during sensitive periods of development, setting children on a trajectory of increased risk for chronic diseases in adulthood (Felitti et al., 1998; Miller et al., 2011; Taylor et al., 2011). Inflammatory processes have been suggested as a mechanism that explains the association between socioeconomic circumstances and later health outcomes (Allin and Nordestgaard, 2011; Reuben et al., 2002; Rutter, 2012). Life-course models hypothesize that exposure to social adversity is related to prolonged low-grade

activation of the immune system and, consequently, elevated levels of inflammatory markers (Galobardes et al., 2006b; Loucks et al., 2010). High-sensitivity (Hs) C-reactive protein (CRP) has been shown to be associated with future cardiovascular events, with both innate and adaptive immune responses leading to clinical manifestations of cardiovascular disease (Moriya, 2019).

There is evidence of the temporal dynamics through which socioeconomic status (SES) relates to physiological biomarkers of age-related health mechanisms at different phases of the life course (Yang et al., 2018). Literature shows that low childhood SES is associated with elevated concentrations of inflammatory markers, such as circulating levels of CRP and proinflammatory cytokines, in adulthood (Lawlor et al., 2005; Milaniak and Jaffee, 2019). Similarly, although scarce, evidence shows that adolescents from families with less-advantaged SES already have higher levels of inflammatory markers (Chiang et al., 2015; Dowd et al., 2010). To our knowledge, few studies have investigated the effect of socioeconomic circumstances on inflammatory markers during childhood. Nevertheless, cross-sectional studies have shown that children living in neighborhoods with high levels of poverty or crime had elevated CRP levels compared with children from other neighborhoods (Broyles et al., 2012), that children born to a parent with less than a high school degree have a higher CRP than those born to a parent with a college degree, and that children from low-income families also had higher CRP levels than those from a higher-income family (Schmeer and Yoon, 2016).

Thus, if social differences in inflammatory markers exist at early ages, then children born to families from less-advantaged socioeconomic circumstances may be on a trajectory toward higher inflammatory risk throughout childhood and, consequently, later in life.

Understanding the influence of socioeconomic circumstances in inflammatory markers during childhood may help identify social health inequalities early in life. Additionally, there are still gaps in our knowledge of inflammatory processes in childhood. Namely, few existing studies have prospectively examined childhood adversity and inflammation using repeated measures to study the impact of different socioeconomic measures that might capture different effects on children's care and, consequently, their health (Galobardes et al., 2006a). Furthermore, few studies have considered

the variation of CRP levels, in light of adiposity rebound, after which it is expected a consistent increase of these levels can be observed throughout life (Cook et al., 2000; Woloshin and Schwartz, 2005). Thus, our study aimed to add to the literature evidence of the impact of different SES measures in longitudinal Hs-CRP trajectories in the first ten years of life.

In this study, we investigated the impact of early socioeconomic circumstances on Hs-CRP trajectories over childhood, using repeated measures of data from a population-based birth cohort at ages four, seven, and ten years old.

2. Methods

2.1. Study design and participants

The study sample consisted of children who participated in Generation XXI, a prospective Portuguese population-based birth cohort. Briefly, recruitment occurred during 2005-2006 (Alves et al., 2012; Larsen et al., 2013), with mothers and children (n=8647) being recruited in public maternity units in Porto, Portugal. The entire cohort was invited to attend the second (2009-2011), third (2012-2014), and fourth (2016-2017) study waves, when children were aged four, seven, and ten years old, respectively. Anthropometric measures and blood samples were collected in all study waves, following the same standardized procedures. Data on demographic and socioeconomic characteristics, personal history of disease, and health-related behaviours were collected by trained interviewers through structured questionnaires.

Generation XXI was approved by the National Data Protection Authority and by the ethics committee of São João Hospital. Data confidentiality and protection were guaranteed in all procedures according to the Declaration of Helsinki. Written informed consent was obtained for all participating children, signed by their legal guardian at every study wave (Alves et al., 2012).

A comparative analysis was conducted between the group of participants who met inclusion criteria and those who did not for the present study. Data indicated that participants who were not included in the study belonged to families with a lower monthly disposable household income (n = 1988, $p < 0.001$), whose mothers (n = 2783, $p < 0.001$) and fathers (n = 1314, $p < 0.001$) had lower levels of education, and whose mothers (n = 1179, $p < 0.001$) and fathers (n = 1050, $p < 0.001$) had lower occupational positions.

2.2. Measures

2.2.1. Early socioeconomic factors

Information on maternal and paternal education and occupation and disposable household income per month was provided by the mother at baseline.

Education was measured as the number of years of formal schooling successfully completed and classified according to the International Standard Classification of Education 2011 classes (UNESCO Institute of Statistics, 2012). The low educational level corresponded to 9 years or less of formal schooling; intermediate education to 12 years of formal education; and high education to more than 12 years of formal education.

Occupation was classified by major professional groups, according to the National Classification of Occupations (Instituto de Emprego e Formação Profissional, 2001), and grouped into three categories: low (blue collar: farmers, skilled and unskilled workers, craftsmen, machine operators, and assembly workers); intermediate (lower white collar: administrative and related workers, service and sales workers); and high (upper white collar: executive civil servants, industrial directors, scientists, middle management, and technicians) (Oakes and Kaufman, 2006).

Current disposable household income per month included salaries and other sources of income, such as financial assistance, rent, and monetary allowances for the whole household. It was collected using the following question*:* "Looking at this scale, choose from the following ranges or total the monthly net income (including earnings and other sources of income such as subsidies, agendas, monetary aids, food) of all the people living in your house". A low disposable household income was defined as 1000€ per month or less and in which both parents received at least the minimum national wage (374.70€ in 2005 and 385.90€ in 2006 [(PORDATA, 2019)]). The intermediate category was defined as between 1001€ and 2000€ per month, and the highest category was defined as higher than 2000€ per month.

2.2.2. Hs-CRP

Following an overnight fast, a venous blood sample was collected before 11 a.m. by trained nurses in our research center after applying a topical analgesic cream (EMLA cream). The samples were centrifuged at 3500 rpm for 10 minutes and plasma was aliquoted. Biomarkers were assayed in fresh

blood samples. Hs-CRP was assayed using CardioPhase hsCRP Flex and the Dimension Vista System from Siemens. Samples of 1.37µL were placed in the cuvette and used nondiluted. Reactant (27.3µL) was added and the processing of samples was conducted at 37ºC for 5 minutes and 50 seconds, at a wavelength of 840nm. During each test day, two separate analyses were performed with two test samples for each material tested for 20 days. Coefficient of variation for low control was 5.4% at a concentration of 0.06 mg/L and for high control was 4.4% at a concentration of 0.15 mg/L. All blood evaluations were performed at the Clinical Pathology Service, São João Hospital Center, Porto, Portugal.

Due to a highly skewed distribution, and for statistical purposes, Hs-CRP was log-transformed. The minimum detectable values were recoded as 0.2 mg/L for all study waves. Further, because high levels of Hs-CRP could represent an acute condition instead of a chronic inflammatory state (Wu et al., 2003), the analyses excluded participants with Hs-CRP levels higher than 10 mg/L to overcome this issue.

2.3. Covariates

In the models, we included body mass index (BMI) as a covariate. For children at four, seven, and ten years of age, trained researchers performed anthropometric measurements according to standardized procedures. In brief, weight and height were measured with the child in underwear and in bare feet. Weight was measured to the nearest one-tenth of a kilogram with the use of a digital scale (Tanita), and height was measured to the nearest one-tenth of a centimetre with the use of a wall stadiometer (seca®). BMI was calculated as the value of weight (kg) over squared height (m^2). For statistical purposes, BMI was computed as an age- and sex-specific BMI standard deviation (SD) score (*z* score), according to the World Health Organization Child Growth Standards (5-19 years) (WHO, 2018).

2.4. Data analysis

To evaluate the association between socioeconomic position and Hs-CRP levels, we used linear mixed-effects models (LMMs), calculating linear regression coefficients (β_2) and respective 95% confidence

intervals (CIs). The assessment of nadir (the lowest point in a curve) related to log Hs-CRP throughout childhood, together with the age at which it was observed, were assessed using trajectories of log Hs-CRP levels by socioeconomic circumstances. LMMs are frequently used to examine changes in human behaviour over time, are very flexible, and estimate model parameters (Kohli et al., 2015; Long and Pellegrini, 2003). To explain and interpret the values of β_2, Supplementary Figure 1 shows three simulated trajectories. Specifically, β_2, β_1, and β_0 represent the coefficients of equation $\beta_2*x^2 + \beta_1*x + \beta_0=0$. Focusing on the x-axis, h is the distance from the origin to the point x, where the curve reaches its minimum, that is, $h=-\beta_1/(2*\beta_2)$. Focusing on the y-axis, k is the distance from Y=0 to the point where the curve reaches its minimum, that is, $k= \beta_2*h^2 + \beta_1*h + \beta_0$. Then, curve 3 presents a higher value of h than curves 1 and 2 because the distance between the origin and the point at which the function reaches its minimum is larger than in the other curves. Additionally, curve 1 has the lowest value of k because the minimum point of this function is reached around 0.5. In contrast, the values of k for curves 2 and 3 are around 1.5 and 2.5, respectively.

All coding was implemented using R language (R Core Team, 2017). Specifically, the analysis was conducted using the R package nlme (Pinheiro et al., 2019) uploaded in the Comprehensive R Archive Network (CRAN). Supplementary Figures 2a and 2b correspond to a preliminary analysis using local polynomial regression fitting methods. This allowed us to verify that the LMM approach used in this study fitted the data. Specifically, we applied the locally weighted scatter-plot smoother (LOWESS) from the ggplot2 (Wickham, 2016) R package. The LOWESS method provided a nonparametric estimation of the predicted trajectories, with the advantage of not having to assume a parametric model for the data. For all the socioeconomic indicators, the quadratic shape was generally similar for the three categories (low, intermediate, and high). Then, the LMM approach (considering a quadratic shape) was suitable for the data.

Thus, for the present analyses, we considered the role of BMI and underlying chronic conditions, such as asthma, because they may account for the studied association in children. Because this sample was not heterogeneous in terms of ethnicity, we were not able to consider this factor in the statistical models.

The interaction term between socioeconomic indicators and sex was fitted in the regression models, and no significant interaction was found (mother's education: $p > 0.764$; mother's occupation: $p > 0.980$; father's education: $p > 0.123$; father's occupation: $p > 0.910$; disposable household income: $p > 0.995$). However, to control for increased exposure to sex hormones, puberty-related shifts in body structure with significant changes in body composition—where girls tend to accumulate more fat than boys—and consequently Hs-CRP levels (Fonseca et al., 2019; Nemet et al., 2003) were stratified.

2.5. Sensitivity analysis

Information on disease history was obtained from caregivers. Although the prevalence of medical conditions is low in the study population, asthma is the most common chronic disease in children (Ferrante and La Grutta, 2018) and may play a role in the reported association between socioeconomic circumstances and Hs-CRP (Kony et al., 2004). Because asthma is an inflammatory disease, some patients with asthma have higher CRP levels than their healthy counterparts (Monadi et al., 2016; Navratil et al., 2009; Sigari and Ghasri, 2013). Furthermore, because formal analysis of interaction between socioeconomic indicators and asthma was found with paternal occupation ($p = 0.024$), a stratified analysis was performed to assess differences in log Hs-CRP trajectories in participants with and without an asthma diagnosis.

3. Results

3.1. General results description

Sample characteristics are shown in Table 1. At baseline, around 20% of mothers had a low occupational position, while almost 40% had less than nine years of formal education. Among fathers, almost 50% had a low level of formal education, and close to 40% had blue-collar occupations. For household income levels, the proportions were very similar for both girls and boys: less than 35% and around 50% of families had low and intermediate income, respectively.

Compared with children from families with more socioeconomic-advantaged circumstances, the median of the log Hs-CRP was higher among seven-year-old girls with fathers with a low occupational position and among seven-year-old boys with mothers with a low level of education and a low occupational position and from families with a low disposable household income. At the age of ten years, the median Hs-CRP was higher in girls and boys with mothers and fathers with a low level of formal education, and in girls with fathers with a low occupational level. Boys with mothers with a low occupational position and from families with a low disposable household income also had higher median Hs-CRP levels when compared with those from more socioeconomically advantaged families (Supplementary Table 1).

Figure 2 shows inflammation trajectories according to socioeconomic categories. In general, log Hs-CRP levels increased throughout childhood, and both girls and boys from less-advantaged socioeconomic circumstances presented high levels of Hs-CRP at the age of ten years. Table 2 includes the estimated results considering a linear mixed-effects model. Nadir and the age at which it occurs differs with socioeconomic circumstances. Specifically, log Hs-CRP levels were higher and nadir occurred earlier in participants from less-advantaged families.

3.2. Parental education

Girls whose mothers had high educational levels had a log Hs-CRP level 0.15 lower (95% CI: -0.27 to -0.03) than girls whose mothers had a low education level (Table 2). With regard to the age at which nadir occurred, among girls with highly educated mothers, nadir occurred 16.13 months later than in girls whose mothers had intermediate and low educational levels. Girls whose fathers had high educational levels had a log Hs-CRP level 0.21 lower (95% CI: -0.39 to -0.03) than girls whose fathers had a low education level (Table 2). Among girls with fathers with high educational levels, age at which nadir occurred was 8.43 months later than in girls with fathers with low educational levels.

In boys, the same tendency was observed. For instance, boys with mothers with intermediate and high educational levels had a log Hs-CRP level 0.14 and 0.08 lower, respectively, than boys with mothers with a low level of education. In regard to paternal education, boys with fathers with intermediate and high educational levels presented a log Hs-CRP level 0.05 and 0.14 lower, respectively, than boys with fathers with a low level of education. The same trend regarding age at nadir observed among girls was seen among boys. Boys with mothers with high levels of education had nadir 12.31 months later than boys with mothers with a low level of education. Boys with fathers with intermediate and high levels of education reached age at nadir 14.94 and 26.83 months later, respectively, than boys with fathers with a low level of education.

3.3. Parental occupation

Girls whose mothers were in the highest category of occupation had a log Hs-CRP level 0.02 lower (95% CI: -0.19 to -0.14) than girls whose mothers were in the lowest category (Table 2). It was observed that among girls with mothers in the highest category of occupation, age at nadir occurred 24.43 months later than in girls with mothers in the lowest category of occupation. Girls whose fathers had high occupational levels had a log Hs-CRP level 0.16 lower (95% CI: -0.29 to -0.04) than girls whose fathers had low occupational levels (Table 2). Age at which nadir occurred was 4.47 months later than among girls whose fathers had low occupational levels.

In boys, the same trend was observed. For instance, boys with mothers with intermediate and high occupational levels had a log Hs-CRP level 0.10 and 0.04 lower, respectively, than boys with fathers with a low level of occupation. Regarding paternal occupation, boys whose fathers had intermediate and high occupational levels had a log Hs-CRP level 0.03 and 0.09 lower, respectively, than boys whose fathers had a low level of occupation. The same trend regarding age at nadir observed among girls was also seen among boys. Boys whose mothers had high levels of occupation reached nadir 17.73 months later than boys whose mothers had a low level of occupation. Boys whose fathers had intermediate and high levels of occupation had age at nadir 0.87 and 7.17 months later, respectively, than boys with fathers with a low level of occupation.

3.4. Household income

Girls from families with a high disposable household income had a log Hs-CRP level 0.19 lower (95% CI: -0.34 to -0.03) than those from families with a low disposable household income (Table 2). Age at nadir occurred 5.33 and 12.82 months later in girls from families with an intermediate and high disposable household income, respectively, compared with girls from families with a low disposable household income (Table 2).

Among boys from families with intermediate and high disposable household income, the log Hs-CRP level was 0.04 and 0.12 lower, respectively, than for boys from families with low disposable household income. Boys from families with intermediate and high household disposable income reached age at nadir 2.11 and 10.28 months later, respectively, than boys from families with a low disposable household income.

3.5. Sensitivity analyses

A sensitivity analysis was conducted by adjusting for children's BMI, and a similar trend of the log Hs-CRP trajectories was found according to socioeconomic indicators, with nadir among participants from less-advantaged socioeconomic circumstances being higher than among more-advantaged participants. It also occurred earlier, as observed in the nonadjusted trajectories (Supplementary Table 2).

Stratified analysis was performed between participants with (5.3%) and without an asthma diagnosis. Children diagnosed with asthma presented a log Hs-CRP level at nadir lower than those without an asthma diagnosis (Supplementary Table 3a and 3b). The exception was found among boys when using the father´s occupation as the socioeconomic indicator ($p = 0.024$). Boys with asthma and whose father had a high occupational level had a log Hs-CRP level of -0.23 (95% CI: -0.83 to 0.36), while those without asthma had a log Hs-CRP level of -0.08 (95% CI: -0.18 to 0.01), which was very similar to the results found among the whole sample (log Hs-CRP level, -0.09 (95% CI: -0.20 to 0.02).

4. Discussion

The results of the present study show that children from less-advantaged socioeconomic circumstances had higher levels of Hs-CRP throughout childhood and began an increasing trajectory of Hs-CRP, after nadir, earlier than those from intermediate or high socioeconomic groups.

Inflammation is hypothesized to play a role in the link between socioeconomic circumstances and cardiometabolic health outcomes (Rutter, 2012) and cancer (Allin and Nordestgaard, 2011), as well as an increased risk of premature death (Reuben et al., 2002). The onset of this process of disease due to chronic low-grade inflammation seems to begin during childhood (Juonala et al., 2006; Slopen et al., 2012). In fact, cross-sectional studies have been reporting associations between lower socioeconomic position and low-grade inflammation already during childhood (Schmeer and Yoon, 2016). Thus, our results support the evidence that social differences may start early in life, with the potential to increase over the life course.

The pathways by which socioeconomic circumstances seem to impact inflammatory processes can occur via stress sensitization, by activation of the hypothalamic-pituitary-adrenal axis (McEwen, 2012), leading to altered insulin sensitivity, increased blood pressure, and inflated central adiposity, and consequently to elevated inflammation (McEwen, 2012; Miller et al., 2011). The adoption of harmful health habits, such as sedentary lifestyles, poor diet, and smoking (Strike and Steptoe, 2004), might also be mediating the association between low early socioeconomic circumstances and later disease development. In adult studies, health-related behaviours, such as smoking or sedentarism, may partly explain social differences in inflammation, with those from less-advantaged socioeconomic circumstances being more prone to engage in more unhealthy risk behaviours (Hosseinpoor et al., 2012; Stamatakis et al., 2014). In fact, it has been described that higher CRP levels are observed among participants from low SES when compared with participants in higher SES groups, after adjusting for health behaviours (Owen et al., 2003). Additionally, people living in poverty were more likely to be obese and less likely to exercise, contributing to a higher risk of very high CRP levels (Alley et al., 2006). Yet, the same study has shown that controlling for acute and chronic conditions

and health behaviors did not fully account for the effect of poverty on CRP levels (Alley et al., 2006). Another study showed that low parental socioeconomic position was associated with chronic low-grade inflammation in adolescence, after adjustment for sex, perinatal and physical environment factors, health-related behaviours, and health status (Fraga et al., 2020). Although we do not expect the same contribution of health-related behaviours in children, because they may not be fully established at these ages, they also seem to not fully explain the association between disadvantaged socioeconomic circumstances and elevated CRP levels. Thus, observing social differences in inflammatory markers in childhood leads us to hypothesize that exposure to adverse socioeconomic conditions during this sensitive developmental period may be explained by the stress pathway caused by deprivation, which may lead to chronic activation of the hypothalamic-pituitary-adrenocortical axis and, consequently, to the establishment of chronic low-grade inflammation (McEwen, 2012; Stringhini et al., 2010), in the first years of life.

The results were stratified by sex, but an overall Hs-CRP trajectory throughout childhood was added as supplementary material (Supplementary Figure 4). The rationale for stratifying is due to the biological differences found between girls and boys, and in accordance with published literature finding significantly greater mean CRP levels in women compared with men (Khera et al., 2005; Lakoski et al., 2006; Wong et al., 2001). Although published literature shows sex differences in adults, our results showed that these differences can be found in early ages, as levels of Hs-CRP are higher across all childhood in girls when compared with boys. However, although we observe some sex differences in childhood, this does not necessarily mean an increased risk of developing disease later in life. In fact, CRP has been shown to independently predict cardiovascular events in both men and women (Lakoski et al., 2006; Ridker et al., 2000). And although women have higher CRP levels, they are at lower risk for cardiovascular events compared with men (Pai et al., 2004), and some discussion has been raised on optimal sex-specific CRP cut-offs to be defined that most accurately predict cardiovascular risk (Lakoski et al., 2006). There are several factors that can potentially contribute to sex-differentiated trajectories of CRP. Among those, adiposity/obesity/BMI, which is one of the factors most strongly associated with CRP (Khera et al., 2005; Shanahan et al., 2013; Williams et al., 2004) (see

Supplementary Figure 3). Although CRP levels generally increase throughout childhood, as previously described (Cook et al., 2000), a decrease in the levels of Hs-CRP from the age of four years to the age of seven years was observed in the trajectories (nadir). This decline may be explained by the close association between CRP levels and BMI (Timpson et al., 2011). BMI rapidly increases during the first year of life, then subsequently declines and reaches a minimum at around the age of six years (as the adiposity rebound starts), before it begins to increase up to the end of adolescence (Rolland-Cachera et al., 1987; Rolland-Cachera et al., 1984). Thus, one may expect that Hs-CRP levels follow BMI patterns and shift from decreasing to increasing from late childhood until the end of the growth period. We conducted a sensitivity analysis adjusting for BMI and found similar trends in the Hs-CRP trajectories and age at nadir (Supplementary Table 2). Also, physical/sexual maturation might contribute to sex-differentiated trajectories of CRP by increasing exposure to sex hormones, with potentially different effects on girls and boys (Shanahan et al., 2013; Williams et al., 2004). Because some of these children are already in or at the onset of puberty, there is increased exposure to sex hormones and puberty-related shifts in body structure with significant changes in body composition, where girls tend to accumulate more fat than boys and consequently Hs-CRP levels (Fonseca et al., 2019; Nemet et al., 2003). This is supported by a previous study conducted in Generation XXI that showed that girls were more sexually mature than boys (Tanner≥2) and, independently of previous BMI, preteens with early puberty had more adiposity at the age of ten years (Fonseca et al., 2019).

In the present study, we found an association between early socioeconomic circumstances and higher levels of log Hs-CRP levels. We used three socioeconomic indicators to include different aspects of the early socioeconomic conditions that might influence educational and health-related choices regarding the child. However, different socioeconomic measures may capture different effects on the child's care and consequently on the child's health (Galobardes et al., 2006a). Knowledge and skills attained through formal education may affect a person's cognitive functioning (Galobardes et al., 2006a), with mother's education, in particular, contributing through factors more closely associated with mothers' literacy and consequently with mothers' care and choices regarding their children (Erola et al., 2016). Further, paternal occupation being more associated with financial availability and

material assets (Erola et al., 2016) may have a significant direct impact on children´s health (Pinilla et al., 2017). As easy and self-reported measures, both education and occupation are reliable sources of information about families' socioeconomic circumstances (Galobardes et al., 2006a). On the other hand, there is potential for underestimation in regard to income, with differences between reported income and tax-reported income, in particular, among the highest income participants. Although asking for family income might potentially lead to bias through underestimation (Moore et al., 2000), existence of bias would lead to an increasing of inequalities (Medeiros et al., 2015), therefore, not affecting our results. Nevertheless, the observed association between different indicators and low-grade inflammation during childhood emphasizes the role of early socioeconomic conditions on the onset and establishment of inflammatory processes during the first years of life.

4.1. Strengths and limitations

The main strength of this study lies in the use of longitudinal data from the well-established population-based birth cohort Generation XXI. The use of cohort data allowed us to observe and analyse different stages of children's growth and to establish a causal relationship between the exposure, family socioeconomic circumstances at birth, and the outcome of low-grade inflammation throughout childhood. Also, this study explored the onset of a trajectory of inflammation at very early ages. The assessment of three aspects of children's socioeconomic circumstances (parental education and occupation and household income), collected at the time of the children's birth, decreased the potential for recall bias. The collection of data about both parents also allowed us to have a more comprehensive assessment of the family´s socioeconomic circumstances. We used the above-mentioned measures of socioeconomic circumstances because we believe they allow us to characterize a family´s socioeconomic position. Socioeconomic circumstances were used as a proxy of exposure to adverse conditions because they have also been demonstrated to be significant predictors of health in adult life.

Nevertheless, this study also has potential limitations. The association between increasing inflammatory levels with low parental socioeconomic circumstances throughout childhood may be

explained by the fact that these children may be more exposed to environmental and physical risk factors, and thus be more susceptible to infections (Dowd et al., 2010). Trying to minimize the effect of acute infections, we excluded participants with Hs-CRP levels higher than 10 mg/L (Wu et al., 2003) from the analysis. However, the number of exclusions was low and thus not having an impact in the trajectory definition (Supplementary Table 4). Moreover, this study only comprised one measure of inflammation, but several population studies, also using CRP levels, have been successful in establishing an association between being born in less-advantaged socioeconomic circumstances with prolonged low-grade activation of the immune system and consequently higher inflammatory levels (Chiang et al., 2015; Van Dyke et al., 2017). Other studies have shown an inverse association of basal circulating levels of interleukin (IL)-6 with indicators of parental SES during the first two years of life, but not later in childhood. These associations were independent of adult SES, suggesting that SES in early childhood has a unique role in adult inflammation (Lockwood et al., 2018). Also, in general, behavioural and psychosocial health risk factors, such as smoking, lower physical fitness, poorer sleep quality, lower self-compassion, and loneliness, are associated with larger increases in circulating IL-6 (Marsland et al., 2017). Although data on IL-6 could possibly reinforce our results, we only have information on this biomarker for a subsample of participants at the age of ten years and, while CRP is broadly known as a marker of chronic inflammation (Pepys and Hirschfield, 2003), IL-6 is mainly an acute-phase protein, synthesized in a local lesion in the initial stage of inflammation (Tanaka et al., 2014). Additionally, we did not expect behavioural risks to be present during the first years of life and we would not expect to observe a perceptible impact on this biomarker.

The use of Generation XXI cohort data allowed us to observe and analyse levels of Hs-CRP across the first ten years of life. However, because it is common in prospective birth cohorts, there has been attrition over time, leading to a reduction in the sample size and a more socioeconomically advantaged group of participants throughout childhood. Nevertheless, we believe that the inclusion of the more-disadvantaged group would have widened the differences found in the inflammatory profile, which may be underestimating the effect of socioeconomic circumstances on children's CRP levels.

Research indicates that family structure at birth seems to influence children's health outcomes, with children raised in stable married families presenting better overall health (Manning, 2015). Also, children living in single-parent households may be affected from not having both parents living in the same house, thus relying on the parent that is more present in all life stages and having fewer resources available at home to face expenses. Even a single parent supporting the family with an above-average salary may increase the burden and impact a child's health. However, by using different socioeconomic indicators we believe that we overcame this issue.

Despite these limitations, these results show a relevant role of early socioeconomic circumstances shaping inflammatory processes over the period of early to late childhood. These results also increase our understanding of socioeconomic circumstances as an aspect of children's family contexts that may induce inflammation related to chronic stress exposure.

5. Conclusion

Our results suggest that socioeconomic circumstances at birth are associated with increased inflammation levels throughout the first decade of life. This study demonstrates that the impact of social inequalities in population health seems to have its onset at very early ages. We hypothesize that early childhood may be a sensitive developmental period that reflects the embodiment of family socioeconomic characteristics. This might be reflecting a pathway for the onset of low-grade inflammation, rather than the accumulation of risk that will only be more evident in later stages of life, such as the end of adolescence and during adult life. Interventions in early childhood and strategies for ensuring that every child has an optimal start in life are crucial to reducing the burden of inflammation and, consequently, health inequalities.

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Figure 1 shows the participation attrition of cohort participants. The present study uses data from participants with complete information on Hs-CRP levels for at least two of the three included study waves. Thus, the analyses were based on data from 2510 participants (1174 girls and 1336 boys), and the sample characteristics are presented in Table 1.

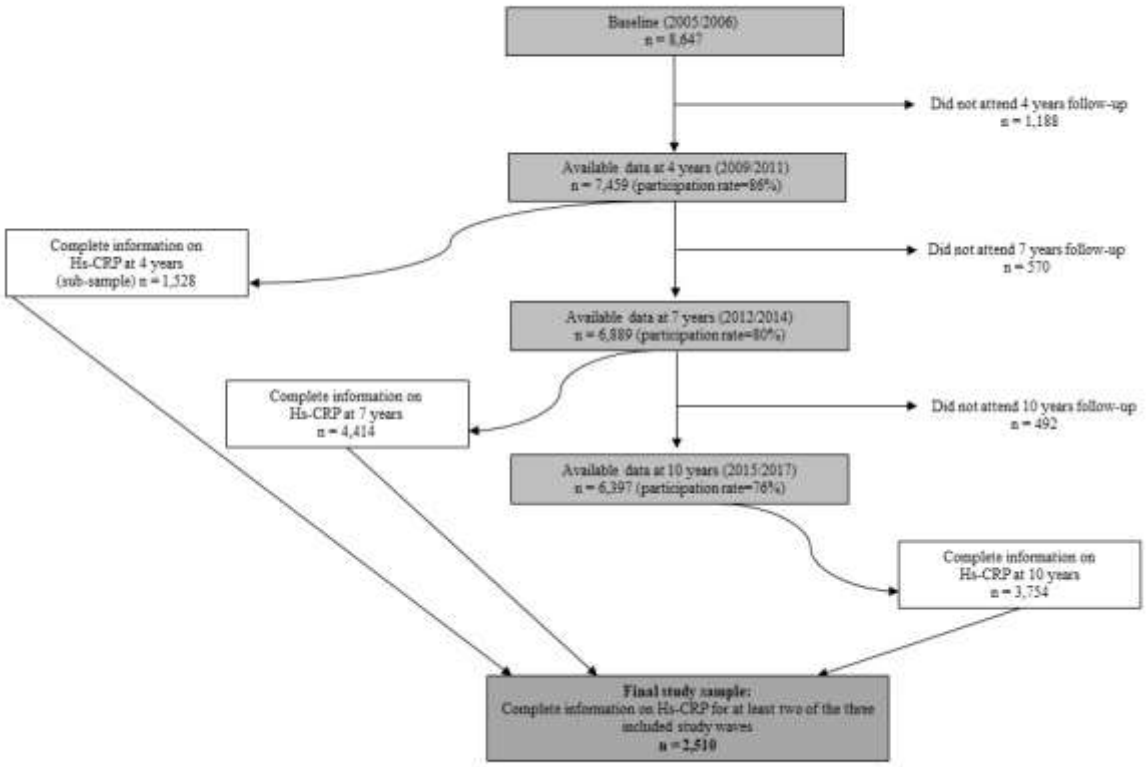
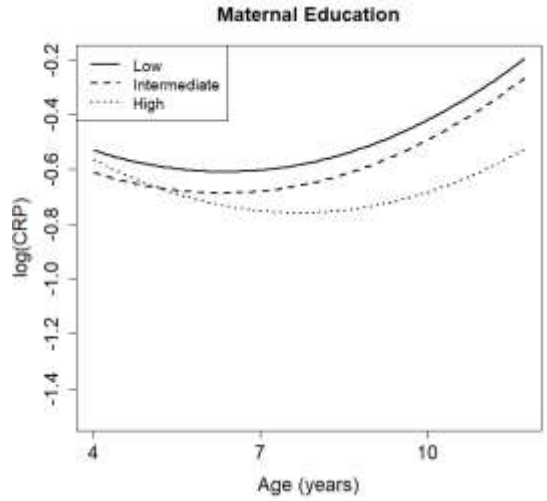
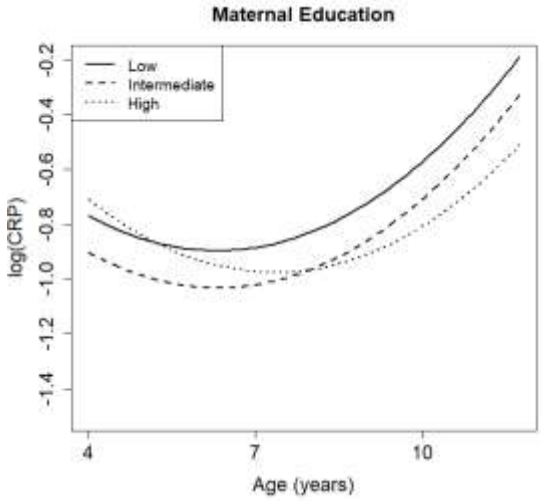
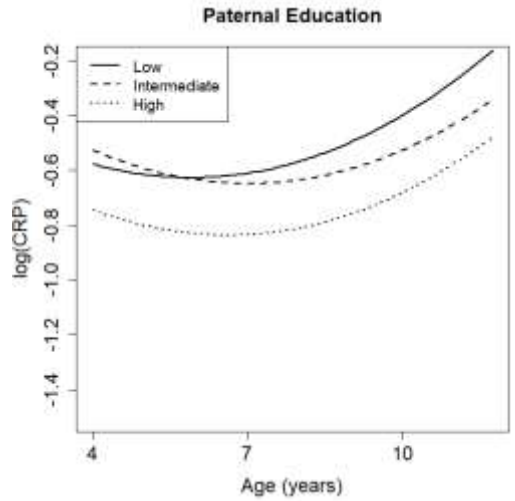
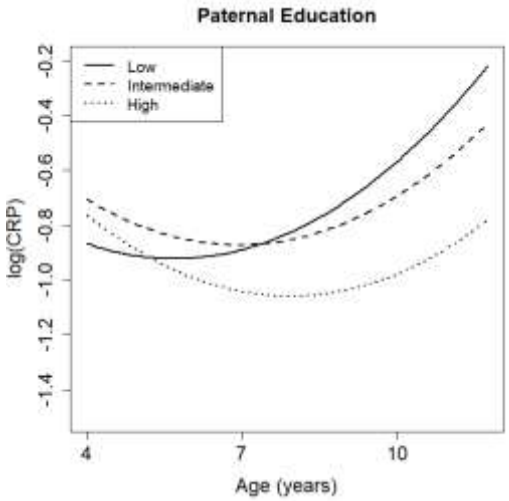


Figure 2. Predicted fixed effects of log Hs-CRP and child age by socioeconomic indicators among girls and boys.

Girls	Boys
 Maternal Education Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)	 Maternal Education Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)
 Maternal Occupation Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)	 Maternal Occupation Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)
 Paternal Education Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)	 Paternal Education Low Intermediate High log(CRP) -0.2 -0.4 -0.6 -0.8 -1.0 -1.2 -1.4 4 7 10 Age (years)

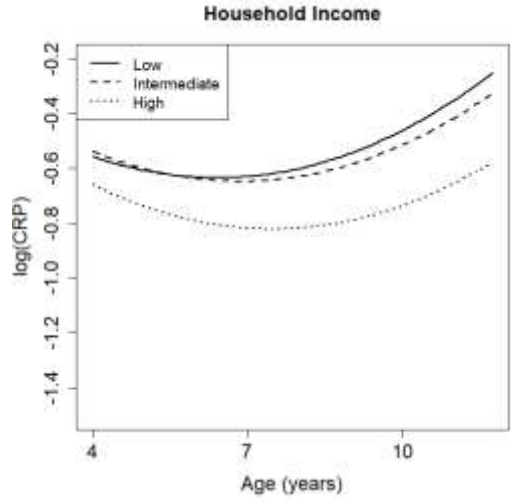
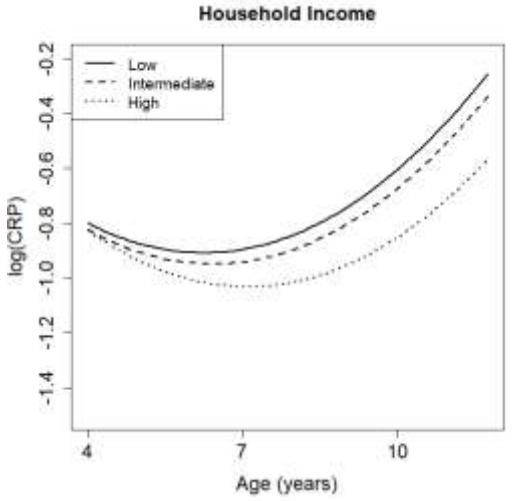
Girls	Boys
	
	

Table 1. Descriptive statistics of selected sociodemographic characteristics and anthropometric measures in the Generation XXI cohort

	Girls	**Boys**
Children´s current characteristics		
Age, months (median [25th-75 percentile])		
2nd wave	50.0 (48.0-53.0)	50.0 (48.0-53.0)
3rd wave	85.0 (84.0-85.0)	85.0 (84.0-85.0)
4th wave	123.1 (122.0-124.2)	123.1 (122.2-124.1)

Body Mass Index		
2nd wave (4 years)		
Underweight/normal	712 (65.8)	889 (72.0)
Overweight	246 (22.7)	249 (20.2)
Obese	124 (11.5)	97 (7.8)
3rd wave (7 years)		
Underweight/normal	737 (62.8)	878 (65.7)
Overweight	262 (22.3)	278 (20.8)
Obese	175 (14.9)	180 (13.5)
4th wave (10 years)		
Underweight/normal	650 (57.5)	740 (57.4)
Overweight	307 (27.1)	327 (25.4)
Obese	174 (15.4)	221 (17.2)
Family´s characteristics at baseline		
Maternal education		
Low	446 (38.2)	499 (37.6)
Intermediate	358 (30.6)	417 (31.3)
High	365 (31.2)	414 (31.1)
Maternal occupation		
Low	230 (20.9)	260 (20.4)
Intermediate	531 (48.3)	622 (48.9)
High	339 (30.8)	390 (30.7)
Paternal education		
Low	315 (49.5)	370 (47.9)
Intermediate	165 (25.9)	226 (29.3)
High	157 (24.6)	176 (22.8)
Paternal occupation		
Low	387 (37.0)	460 (38.5)
Intermediate	219 (21.0)	245 (20.6)
High	439 (42.0)	489 (40.9)
Household income		
Low	361 (34.8)	389 (32.6)
Intermediate	492 (47.5)	596 (50.0)
High	183 (17.7)	207 (17.4)

Table 2. Predicted values of minimum log Hs-CRP (nadir) and calendar age at nadir (months), by socioeconomic indicators using a mixed-effects model, in girls and boys.

		Girls				Boys			
Socioeconomic indicator		**β_2[a]**	**Nadir (95% CI)[b]**	***p***	**Age at nadir (months) (95% CI)**	***p***	**β_2[a]**	**Nadir (95% CI)[b]**	***p***	**Age at nadir (months) (95% CI)**	***p***
Maternal Education	Low	0.0001	Reference		Reference		0.0002	Reference		Reference	
	Intermediate		-0.08 (-0.21; 0.06)	0.259	-0.56 (-16.65; 15.52)	0.945		-0.14 (0.25; -0.02)	0.027	0.12 (-8.37; 8.61)	0.978
	High		-0.15 (-0.27; -0.03)	0.017	16.13 (-2.28; 34.53)	0.086		-0.08 (-0.19; 0.03)	0.169	12.31 (2.96; 21.66)	0.010
Maternal Occupation	Low	0.0001	Reference		Reference		0.0002	Reference		Reference	
	Intermediate		-0.08 (-0.08; 0.24)	0.338	11.30 (-7.38; 29.99)	0.236		-0.10 (-0.24; 0.04)	0.153	2.93 (-7.14; 13.00)	0.569
	High		-0.02 (-0.19; -0.14)	0.770	24.43 (-0.61; 48.24)	0.045		-0.04 (-0.18; -0.11)	0.616	17.73 (5.35; 30.11)	0.005
Paternal Education	Low	0.0001	Reference		Reference		0.0001	Reference		Reference	
	Intermediate		-0.02 (-0.19; 0.15)	0.813	13.14 (-11.66; 37.95)	0.300		-0.05 (-0.11; -0.21)	0.526	14.94 (0.03; 29.86)	0.050
	High		-0.21 (-0.39; -0.03)	0.023	8.43 (-15.34; 32.20)	0.488		-0.14 (-0.30; 0.02)	0.096	26.83 (7.78; 45.88)	0.006
Paternal Occupation	Low	0.0001	Reference		Reference		0.0002	Reference		Reference	
	Intermediate		-0.09 (-0.23; 0.06)	0.246	8.29 (-10.58; 27.15)	0.390		-0.03 (-0.11; 0.17)	0.644	0.87 (-9.00; 10.74)	0.864
	High		-0.16 (-0.29; -0.04)	0.010	4.47 (-10.77; 19.72)	0.566		-0.09 (-0.20; 0.02)	0.128	7.17 (-1.18; 15.53)	0.093
Household Income	Low	0.0001	Reference		Reference		0.0001	Reference		Reference	
	Intermediate		-0.01 (-0.14; 0.11)	0.844	5.33 (-11.82; 22.47)	0.543		-0.04 (-0.16; 0.08)	0.499	2.11 (-7.25; 11.47)	0.659
	High		-0.19 (-0.34; -0.03)	0.020	12.82 (-10.32; 35.95)	0.278		-0.12 (-0.27; 0.02)	0.096	10.28 (-2.45; 23.01)	0.114

[a] β_2: linear regression coefficient.
[b] Nadir: minimum value of log Hs-CRP throughout childhood.