

## **TITLE**

Childhood infections, socio-economic status, and Adult Cardiometabolic Risk

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**Short Title**

Childhood infections, SES, and Adult Cardiometabolic Risk

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**Conflict of Interest Statement**

All authors have no conflicts of interest to disclose.

**Abbreviations List**

BMI: Body mass index; CVD: Cardiovascular disease; FIM: Finnish Marks; HDL: High-density lipoprotein; hsCRP: High sensitivity C-reactive protein; ICD: International classification of disease; LDL: Low-density lipoprotein; MET: Metabolic equivalent of task; SES: Socioeconomic status.

**What's Known on This Subject**

Cardiometabolic and infectious diseases share similar socioeconomic gradients. Acute and chronic infections may alter long-term host immune responses. Early life events may program a maladaptive immune response to vascular injury, and contribute to the socioeconomic inequalities in cardiometabolic disease.

**What This Study Adds**

Early life infection worsens adult cardiometabolic risk only in individuals whose socioeconomic position is below the median. Childhood infection may contribute to social gradients observed in adult cardiometabolic disease risk factors and non-communicable diseases.

## **CONTRIBUTORS' STATEMENT PAGE**

*Richard S Liu, David P Burgner:* Drs Liu, Burgner contributed to study conception and interpretation of results, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

*Markus Juonala:* Dr Juonala contributed to study conception and interpretation of results, performed the statistical analysis, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

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## **ABSTRACT**

### **Background and Objectives**

Socioeconomic disadvantage throughout the life-course is associated with increased risk of cardiometabolic diseases, but traditional risk factors do not fully account for the social gradient. We investigated the interactions between low socioeconomic status and infection in childhood, and adverse cardiometabolic parameters in adulthood.

### **Methods**

Participants from the Cardiovascular Risk in Young Finns Study, a cohort well-phenotyped for childhood and adulthood cardiometabolic risk factors and socioeconomic parameters, were linked to lifetime hospitalization data from birth onwards available from the Finnish National Hospital Registry. In those with complete data, we investigated relationships between infection-related hospitalization in childhood, socioeconomic status, and childhood and adult cardiometabolic parameters.

### **Results**

The study cohort consisted of 1015 individuals (age range 3-18 years at baseline and 30-45 years at follow-up). In adults who were raised in families with below median incomes, childhood infection-related hospitalizations (at age 0-5 years) were significantly associated with increased adult body mass index ( $\beta \pm \text{SE}$  comparing those with 0 vs 1 or more hospitalizations  $2.4 \pm 0.8 \text{ kg/m}^2$ ,  $P=0.008$ ), waist circumference ( $7.4 \pm 2.3 \text{ cm}$ ,  $P=0.004$ ), and reduced brachial flow-mediated dilatation ( $-2.7 \pm 0.9\%$ ,  $P=0.002$ ). No equivalent associations were observed in individuals from higher SES families.

### **Conclusions**

Infection was associated with worse cardiovascular risk factor profiles only in those from families of lower socioeconomic status. Childhood infection may contribute to social gradients observed in adult cardiometabolic disease risk factors. These findings suggest reducing childhood infections, especially in socioeconomic disadvantaged children, may reduce the cardiometabolic disease burden in adults.

## INTRODUCTION

Socioeconomic status (SES) is a strong predictor of cardiovascular disease (CVD, coronary heart, cerebrovascular and peripheral vascular disease), and of metabolic disease (obesity and type 2 diabetes mellitus).<sup>1-3</sup> Lower SES is associated with higher prevalence of traditional risk factors<sup>4</sup> and increased cardiometabolic disease prevalence and mortality.<sup>5</sup> The mechanisms by which early life and childhood social disadvantage lead to increased adult cardiometabolic diseases are multifactorial and are suggested to include biological, behavioral, psychological and social factors.<sup>5</sup> Overall, traditional risk factors do not fully account for the differences in attributable risk.<sup>1,6</sup>

Increased inflammation throughout the life course is associated with social disadvantage and adverse childhood experiences.<sup>7</sup> Chronic inflammation has a central pathogenic role in cardiometabolic diseases.<sup>8</sup> Both chronic infections<sup>9</sup> and general markers of inflammation<sup>10</sup> show a strong social gradient, and may contribute to the effect of SES on CVD<sup>11</sup> and type 2 diabetes.<sup>12</sup> SES alters innate immune<sup>13</sup> and cell mediated immune responses<sup>14</sup> – two examples out of many possible mechanisms by which infection could lead to chronic disease. To date, there are few longitudinal data from well-phenotyped cohorts on the relationships between standardized definitions of childhood infections, SES and cardiometabolic status in adulthood.

We previously reported that childhood infection-related hospitalizations are associated with adverse cardiometabolic outcomes in early to mid-adulthood.<sup>15, 16</sup> Here we prospectively investigated the interaction between childhood SES and early life (age 0 – 5 years) infections on cardiometabolic risk markers in adulthood (age 30-36 years) among 1,015 individuals in the longitudinal Cardiovascular Risk in Young Finns Study.

## **PATIENTS AND METHODS**

### **Participants**

The Cardiovascular Risk in Young Finns Study is an ongoing prospective study of cardiovascular risk factors from childhood to adulthood. The baseline examination was in 1980, when participants were aged 3 – 18 years, with repeated follow-up assessments in 1983, 1986, 2001 and 2007.<sup>17</sup> The current sample included 1,015 individuals with entire lifetime hospitalization data extracted from the Finnish national hospitalization database (which commenced in 1969) and who had participated in the 27 year follow-up study in 2007. Baseline risk factors of those retained in follow-up are largely comparable to non-participants.<sup>18</sup> The study complies with the Declaration of Helsinki and has institutional ethics approval. Written informed consent was obtained from all participants.

### **Questionnaire Data**

In childhood, questionnaires completed by the parents of the participant were used to obtain data on physical activity, birth weight, prematurity, mother's body mass index (BMI), family income, parental years of education, fruit and vegetable consumption and parental smoking. Physical activity was assessed with questions concerning the frequency and intensity of physical activity and a physical activity index was calculated based on the variables as previously described.<sup>19</sup> There were two different kinds of physical activity questionnaires for the younger (three to six year olds, a parent completed questionnaire) and older children (nine to 18 year olds, self-completed questionnaire). The calculated physical activity indices were age- standardized to allow comparison across age groups. Annual family income strata at the time of enrollment was determined as follows: [category 1] <12500 Finnish markkas (FIM) (~5850 EUR); [2] 15001 - 25000 FIM; [3] 25001 - 35000 FIM; [4] 35001 - 45000 FIM; [5] 45001 - 55000 FIM; [6] 55001 - 75000 FIM; [7] 75001 - 100000 FIM; [8] > 100000 FIM). We also analyzed SES using parental years in education as a measure. In adulthood,

questionnaire data was used to gather information on annual income, smoking, diet and physical activity.

### **Definition of Infection-Related Hospitalization**

Infection-related hospitalization was defined as a hospital discharge diagnosis that included at least one International Classification of Disease (ICD) infection-related code as either a primary or secondary code. Hospitalization was defined as an admission that included at least one overnight stay. We used both primary and secondary codes to ensure capture of all infections, an approach we and others have used previously.<sup>16, 20</sup> We selected infection-related ICD codes (ICD versions 9 and 10) *a priori*, based on a modification of published population-based epidemiologic studies of childhood infection-related hospitalisation.<sup>15</sup> To investigate possible infection-specific effects, infection-related codes were grouped *a priori* into clinical diagnostic categories using a modification of methods described previously.<sup>20</sup> Early childhood was defined as birth to five years of age, when the infection burden is greatest.<sup>21</sup> Data on antibiotic usage either in hospital or in the community were not available.

### **Anthropometric and Clinical Assessment**

In all examinations, height and weight, rounded to the nearest 0.5 cm and 0.1 kg respectively, were measured at all time-points using standardized protocols and BMI was calculated as weight (kg) divided by height (m) squared.<sup>18</sup> Waist circumference (measured in duplicate at the level of the 12<sup>th</sup> rib or level with the umbilicus in thin subjects) was measured in adults. Enrolment blood pressure at three years of age was measured by ultrasound and at other childhood ages by a mercury sphygmomanometer. A random zero sphygmomanometer was used in adults. The first and fifth Korotkoff sounds were used to define systolic and diastolic blood pressures, which were averaged from three measurements. Blood samples were obtained following a 12-hour fast. Standard enzymatic methods were used for serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and plasma glucose. HDL

cholesterol was measured after dextran sulfate precipitation and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. High sensitivity C-reactive protein (hsCRP) was measured by an automated analyzer using a latex turbidimetric immunoassay. For hsCRP analyses, childhood serum samples were taken in 1980 and stored in -20°C. These samples were analyzed in 2005. During storage, the samples were not thawed or refrozen.

### **Ultrasound Imaging**

Common carotid and brachial artery ultrasound studies were performed using Sequoia512 ultrasound mainframes (Acuson, Mountain View, CA, USA) with 13.0 MHz linear array transducer in 2001 and 2007 follow-ups, as previously described.<sup>22</sup> The digitally stored scans were manually analyzed by a single observer blinded to subjects' details (MJ). To assess intra-individual reproducibility of ultrasound measurements, 57 subjects were re-examined three months after the initial visit (2.5% random sample).

### **Carotid Intima-Media Thickness (IMT)**

At least four measurements of the far wall of the left carotid artery were taken approximately ten mm proximal to the bifurcation to derive mean and maximum carotid IMT. The between-visit coefficient of variation of IMT measurements was 6.4%.

### **Carotid Distensibility**

Ultrasound loops of the carotid bifurcation and common carotid artery were acquired and stored in digital format, and the best quality cardiac cycle selected for subsequent offline analysis. The carotid diameter was measured at least twice (spatial measurements) in end-diastole and end-systole, respectively. Blood pressure was measured during the ultrasound study with an automated sphygmomanometer (Omron M4, Omron Matsusaka Co., Ltd, Japan). Ultrasound and concomitant brachial blood pressure measurements were used to calculate carotid distensibility by the following formula:



$$\frac{\left(\frac{D_s - D_d}{D_d}\right)}{P_s - P_d}$$

where  $D_d$  is the diastolic diameter;  $D_s$ , the systolic diameter;  $P_s$ , systolic blood pressure; and  $P_d$ , diastolic blood pressure. The between-visit coefficient of variation was 2.7% for diastolic diameter, and 16.3% for distensibility index.

### **Brachial Flow-Mediated Dilatation (FMD)**

The left brachial artery diameter was measured at rest and during reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by release. Three measurements of arterial diameter at a fixed distance from an anatomic marker were performed at end-diastole at rest and 40, 60, and 80 seconds after cuff release. The vessel diameters in scans after reactive hyperemia were expressed as the percentage relative to resting scan. The average of three measurements at each time point was used to derive the maximum FMD (the greatest value between 40 and 80 seconds post-cuff release). The between-visit correlation of variation was 3.2% for brachial diameter, and 26.0% for FMD.

### **Statistical Analyses**

Group comparisons were performed with t-tests and chi-square tests, as appropriate. To examine whether the association of early child infection-related hospitalizations with adult cardiometabolic outcomes differed by SES, we used logistic regression modeling. Family income, early child infection-related hospitalization, and family income\*early child infection-related hospitalization interaction terms were used in these models as explanatory variables. Thereafter, the effects of early child infection-related hospitalization on those outcomes with significant interaction were analyzed with linear regression models adjusted for age, sex and other childhood risk factors (BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic

blood pressure, fruit consumption, physical activity, maternal BMI, and parental smoking) separately among individuals with family income below or above median (Figure 1). In addition, we performed sensitivity analyses using i) a lowest quartile as a cut-point for lower SES and ii) using parental years of education as a socioeconomic measure.

In initial analyses, childhood SES significantly interacted with child infection-related hospitalization before age 5 years in predicting adult BMI. We therefore performed life-course analysis of BMI using multi-level mixed modelling with maximum likelihood estimation. Although a significant interaction between child infection-related hospitalization and SES was also demonstrated for adult waist circumference and brachial FMD in the above analyses, these data were only collected at two out of six data collection time-points so were not considered for life-course analyses. BMI trajectories were compared as a function of age for four groups: (1) not hospitalized for child infection before five years of age and above median family income in childhood; (2) not hospitalized for child infection before five years of age and below median family income in childhood; (3) hospitalized for child infection before five years of age and above median family income in childhood; and (4) child infection before five years of age and below median family income in childhood. All analyses were adjusted for sex and time (a categorical age variable). We fitted interaction terms between the infection-related hospitalization – SES groups and time that compares the trajectory of BMI between groups. These analyses allow the age at which any differences in BMI between the groups to be identified. Our models consider correlations between repeated measures on the same individual and allows for missing data. Statistical analyses were performed using SAS 9.3 or in the case of the life-course models, STATA 13.1.

## RESULTS

Characteristics of the study cohort are shown in Table 1. Rates of early childhood hospitalization with infection did not differ between those of high and low SES (11.6% vs 15.4% respectively,  $P=0.08$ ). Other childhood comorbidities did not differ significantly between groups (Supplemental Table I). In childhood, participants with family income below the median had lower HDL cholesterol, less fruit and vegetable consumption, and higher triglycerides levels; their mothers had higher BMI. In adulthood, these individuals had lower annual income, vegetable consumption and physical activity levels, higher BMI, systolic blood pressure, and rates of smoking.

Significant interactions between childhood family income and infection-related hospitalization were observed for adulthood BMI, waist circumference and brachial FMD (Table 2), but not for carotid IMT or distensibility. In analyses performed separately for those individuals with family income below or above median level within the cohort, early child infection-related hospitalizations were associated with higher adult BMI ( $\beta \pm SE$  comparing those never hospitalized with those with one or more hospitalizations  $2.4 \pm 0.8 \text{ kg/m}^2$ ,  $P=0.008$ ) (Figure 2) and waist circumference levels ( $7.4 \pm 2.3 \text{ cm}$ ,  $P=0.004$ ) (Figure 3), independent of age, sex and other childhood risk factors. This interaction was observed only in participants with lower than median family income. Similarly there was an inverse association between childhood infection-related hospitalization and reduced brachial FMD only among individuals with family income below cohort median level ( $-2.7 \pm 0.9\%$ ,  $P=0.002$ ) (Figure 4). Findings were similar in an analysis additionally adjusted for significant possible confounders, including adult BMI in the full cohort, and for birth weight and childhood hsCRP in a sub-cohort with complete data on these variables (all  $P$  values  $<0.005$  in analyses in those with family income below median and all  $P$  values  $>0.1$  in analyses in those with family income above median). In addition, sensitivity analyses using a cut-point of lowest quartile for family income (Supplemental

Figures I and II), or parental years of education as a proxy of SES (Supplemental Figures III and IV) gave similar findings to the primary analyses.

We also performed additional analyses taking into account both childhood and adult SES. Among individuals with low SES in childhood and high SES in adulthood, those with early child IRHs had significantly higher BMI ( $28.4 \pm 1.2$  vs.  $25.8 \pm 0.5$  kg/m<sup>2</sup>, P=0.04). In this group there was no difference in FMD ( $7.9 \pm 0.9$  vs.  $8.8 \pm 0.4\%$ , P=0.64). Among those with low SES both in childhood and adulthood, early child IRHs were associated with decreased brachial FMD ( $7.0 \pm 0.7$  vs.  $10.1 \pm 0.3\%$ , P=0.002), but a significant difference was not observed in BMI ( $27.8 \pm 1.1$  vs.  $25.4 \pm 0.3$  kg/m<sup>2</sup>, P=0.12) (Supplemental Table II)

In Figure 5 life-course BMI levels are shown according to early child infection-related hospitalizations and family income in childhood. The most prominent differences became evident at the age of 24 years. At ages 24, 30 and 36 years individuals without early child infection-related hospitalizations and high family income had significantly lower BMI than the other three groups.

## DISCUSSION

This longitudinal follow-up of Finnish children and adolescents into adulthood suggests that childhood infection-related hospitalizations are a significant predictor of increased BMI, waist circumference, and reduced brachial flow mediated dilatation in adults raised in lower income families, but not in those raised in families with an income above the median. These findings were unchanged in sensitivity analyses using an alternative proxy of socioeconomic status (duration of parental education), and when comparing the lowest quartile of SES parameter with the remainder of the population. Differences in cardiometabolic risk become increasingly apparent over the life-course; sustained and significant differences in adulthood BMI were evident between groups defined by combined childhood exposures (SES and infection-related hospitalization).

Our data support previous findings related to socioeconomic inequalities in cardiometabolic disease.<sup>1,2</sup> The Whitehall II study showed that elevated levels of inflammatory markers account for part of the excess risk of type 2 diabetes associated with (retrospectively assessed) life-course socioeconomic disadvantage.<sup>12</sup> In the current study, we did not observe an association between childhood infection-related hospitalization, low SES and adult systemic inflammation.

Body mass index, waist circumference and brachial flow mediated dilatation are intermediate cardiometabolic risk phenotypes.<sup>23, 24</sup> Obesity, particularly in childhood and maintained into adulthood,<sup>18</sup> is a well-documented independent risk factor of later CVD.<sup>25</sup> Our data show an interaction between childhood infection and intermediate cardiometabolic risk phenotypes outcomes only in the context of low childhood SES. Low SES potentiates the effects of cardiovascular stress responses on the progression of carotid atherosclerosis,<sup>26</sup> and our results support the view that changes in vascular function, evidenced through brachial FMD, occur before evident vascular structural changes in intima media thickness.<sup>15</sup> In additional analyses we demonstrate that vascular changes are unlikely to be mediated by obesity alone, as

adjustment for adult BMI did not alter the interaction between childhood infection and brachial FMD significantly.

A plausible explanation for our findings is that there is a significantly better overall risk factor status among high SES individuals, who had better lipid and dietary profiles in childhood, as well as higher vegetable consumption and physical activity levels, lower BMI and systolic blood pressure levels, and lower smoking prevalence in adulthood. We adjusted for these factors and the interaction effect remained, but it is possible that residual confounding factors may still affect the relationship.

The strengths of this study include the completeness of the data and the depth of phenotyping for traditional risk factors throughout the life-course. We have standardized and complete statutory data on infection from birth onwards for almost 30 years. In the Finnish national database, ICD-based diagnoses are recorded for every hospitalization shortly after discharge by dedicated coders. Consequently the hospitalization diagnoses will be more reliable and much less prone to bias than retrospective diagnoses from hospital records. Additionally, there are multiple measures of SES during childhood. A significant interactive effect of parental education and infection-related hospitalization suggests that social determinants in addition to relative financial hardship may be involved.<sup>27</sup>

We have previously shown in an Australian population that childhood hospitalization with infection is associated in a dose-response manner with cardiovascular events in adulthood.<sup>28</sup>

While childhood infections, and associated inflammatory burden, are a potential mechanism through which childhood socioeconomic disadvantage increases cardiometabolic risk, the current study was not designed to investigate causal mechanisms. However, our interpretations can be partially informed by the data. For example, there were no significant differences in the frequency of childhood infection-related hospitalizations between above and below median

income level families. This suggests childhood SES is not a confounding factor in the association between childhood infection-related hospitalization and adult cardiometabolic risk factors. Instead infection-related hospitalization might lie on a pathophysiological pathway between SES and CVD. Further investigation is required to examine the long-term impact of serious childhood infections on clinical cardiovascular events and explore causal pathways for the present findings.

We acknowledge some limitations. Given the relative young age of the cohort, we can only assess intermediate cardiometabolic phenotypes rather than disease outcomes. However these phenotypes track from childhood into adulthood, where they are known to be strongly predictive of later disease.<sup>29</sup> We are unable to assess whether infection-related hospitalization reflect community or nosocomial infections, although in childhood, infections are largely acquired outside hospital. Length of hospitalization is also not available from the data. The sample size did not permit meaningful analyses by different clinical groupings of infection. We cannot comment on total infection burden in the cohort; most infections, including those implicated in cardiometabolic diseases, do not usually result in hospitalization. Other data on childhood infections, including primary care, emergency department and parental data were not available. In addition, we cannot discount social disadvantage, rather than clinical severity, as a possible contributory factor to the decision to hospitalize some children with infection. Socially disadvantaged children may seek clinical care later and therefore some infections may be more severe by presentation, necessitating hospitalization.

We are unable to ascribe causation and it is possible that increased infectious burden represents a poorer overall childhood environment, leading to other adverse exposures that impact on future cardiometabolic risk. We should also consider important unmeasured confounders, particularly antibiotic exposures early in life, which may be of considerable biological relevance. There is growing evidence for the role of an altered microbiome in the pathogenesis

of obesity in mice and humans.<sup>30</sup> Antibiotics can modify the microbiome,<sup>31</sup> especially in the context of serious infections that require hospitalization, where use of broad spectrum antibiotics is common. Detailed prospective studies that capture total infection burden and antibiotic use are needed to address this issue.



## **CONCLUSION**

We report prospective data showing that early infectious exposures may contribute to social gradients in adult cardiometabolic risk. Replication of these findings in other populations and further mechanistic studies are warranted to facilitate novel interventions aimed at reducing the growing burden of adult cardiometabolic diseases.

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## FIGURE LEGENDS

### Figure 1

Schematic diagram of participant timelines and groupings throughout the study. IRH: infection-related hospitalization.

### Figure 2

Difference in adult BMI between individuals without and with early child infection-related hospitalizations according to family income in childhood.

Values and analyses are adjusted for age, sex, and childhood BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, fruit consumption, physical activity, maternal BMI and parental smoking. BMI: body mass index, HDL: high-density lipoprotein, IRH: infection-related hospitalization, LDL: low-density lipoprotein.

### Figure 3

Difference in adult waist circumference between individuals without and with early child infection-related hospitalizations according to family income in childhood.

Values and analyses are adjusted for age, sex, and childhood BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, fruit consumption, physical activity, maternal BMI and parental smoking. BMI: body mass index, HDL: high-density lipoprotein, IRH: infection-related hospitalization, LDL: low-density lipoprotein.

### Figure 4

Difference in adult brachial flow mediated dilatation between individuals without and with early child infection-related hospitalizations according to family income in childhood.

Values and analyses are adjusted for age, sex, and childhood BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, fruit consumption, physical activity, maternal BMI and parental smoking. BMI: body mass index, FMD: flow mediated dilatation, HDL: high-density lipoprotein, IRH: infection-related hospitalization, LDL: low-density lipoprotein.

### Figure 5

Mean BMI trajectories across the early life – course according to childhood infection-related hospitalizations before age 5 and family income at baseline (1980) as a marker of SES.

White circles indicate not hospitalized for child infection before age 5 years and above median family income (high SES) in childhood; light – grey circles indicate not hospitalized for child infection before age 5 years and below median family income (low SES) in childhood; dark – grey circles indicate hospitalized for child infection before age 5 years and above median family income (high SES) in childhood; black circles indicate hospitalized for child infection before age 5 years and below median family income (low SES) in childhood. Data are adjusted for sex. 95% confidence intervals are not shown to aid graphical interpretation. \* $P < 0.05$  for comparison between child infection (-), high SES and each of the three other groups. BMI: body mass index, SES: socioeconomic status.

## TEXT TABLES

**Table 1**

Characteristics of the study cohort according to annual family income\* in 1980.

	Family income below median	Family income above median	P-value
N	396	619	
<b>Childhood (in 1980)</b>			
Annual family income (thousand euros) †	14.1±4.6	34.6±10.5	
Parental years of study	9.7±2.4	11.7±3.4	<0.001
Males (%)	45.5	46.7	0.70
Age (years)	5.9±2.4	6.2±2.5	0.07
≥1 infection-related hospitalization, <5 years old (%)	15.4	11.6	0.08
BMI (kg/m <sup>2</sup> )	15.9±1.8	15.9±1.8	0.47
LDL cholesterol (mmol/l)	3.65±0.80	3.55±0.81	0.08
HDL cholesterol (mmol/l)	1.53±0.28	1.61±0.31	0.002
Triglycerides (mmol/l)	0.64±0.27	0.58±0.24	0.004
Systolic blood pressure (mmHg)	107±11	108±11	0.14
hsCRP (mg/l, N=784)	1.1±3.3	1.0±2.5	0.47
Birth weight (kg, N=970)	3.50±0.57	3.53±0.54	0.36
Premature birth (% , N=970)‡	9.9	8.6	0.49
Fruit consumption (servings/week)	7.1±2.7	7.8±2.3	<0.001
Vegetable consumption (servings/week)	6.3±2.8	7.1±2.6	<0.001
Physical activity (z-score)	0.02±0.95	0.01±0.99	0.82
Mother's BMI (kg/m <sup>2</sup> )	23.5±3.9	22.9±3.3	0.004
Parental smoking (%)	52.7	46.5	0.06
<b>Adulthood (in 2007)</b>			
Age (years)	32.9±2.4	33.2±2.5	0.07
Annual income (thousand euros)	26.4±12.9	31.7±16.8	<0.0001

Individuals with lifetime infection-related hospitalization (%)	41.9	41.5	0.89
Number of lifetime infection-related hospitalization	0.78±1.37	0.69±1.14	0.30
BMI (kg/m <sup>2</sup> )	25.9±5.2	25.2±4.4	0.02
LDL cholesterol (mmol/l)	3.00±0.74	2.94±0.75	0.18
HDL cholesterol (mmol/l)	1.32±0.34	1.35±0.34	0.26
Triglycerides (mmol/l)	1.40±0.90	1.31±0.80	0.10
Systolic blood pressure (mmHg)	120±13	118±13	0.01
hsCRP (mg/l)	2.0±4.1	1.7±3.0	0.23
Glucose	5.23±0.57	5.25±1.10	0.74
Fruit consumption (g/day)	197±202	209±187	0.34
Vegetable consumption (g/day)	239±155	271±163	0.004
Physical activity (MET index)	17.5±21.4	20.6±20.2	0.03
Smoking (%)	22.9	16.5	0.01

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\* Family income is an 8 step variable (1-8) with a median split between 4 and 5

† Finnish currency in 1980 is converted to thousand euros and the levels adjusted to correspond to 2007 levels

‡ Born at gestational week 37 or earlier

P-values from t-tests or chi-square tests. BMI: body mass index, FMD: flow mediated dilatation, HDL: high-density lipoprotein, hsCRP: high sensitivity C-reactive protein, IMT: intima media thickness, LDL: low-density lipoprotein, MET: metabolic equivalent of task

**Table 2**

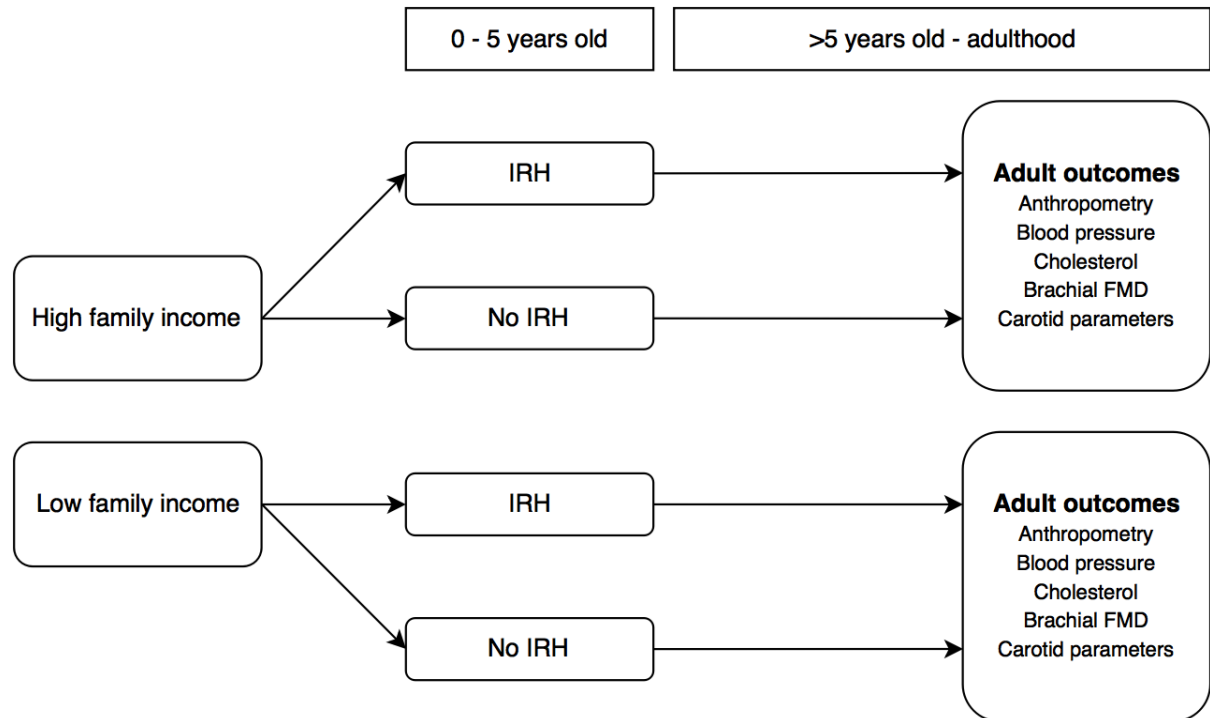
## Interaction analyses

Adult outcome	P-value for child socioeconomic status*child infection-related hospitalization
BMI	0.02
Waist circumference	0.009
Systolic blood pressure	0.54
LDL cholesterol	0.28
HDL cholesterol	0.21
Triglycerides	0.96
Glucose	0.39
Brachial FMD	0.01
Carotid IMT	0.24
Carotid distensibility	0.85

P-values from logistic regression analyses adjusted with age and sex testing the interaction of childhood family income\*infection-related hospitalization variables on adult outcomes. BMI: body mass index, FMD: flow mediated dilatation, HDL: high-density lipoprotein, IMT: intima media thickness, LDL: low-density lipoprotein

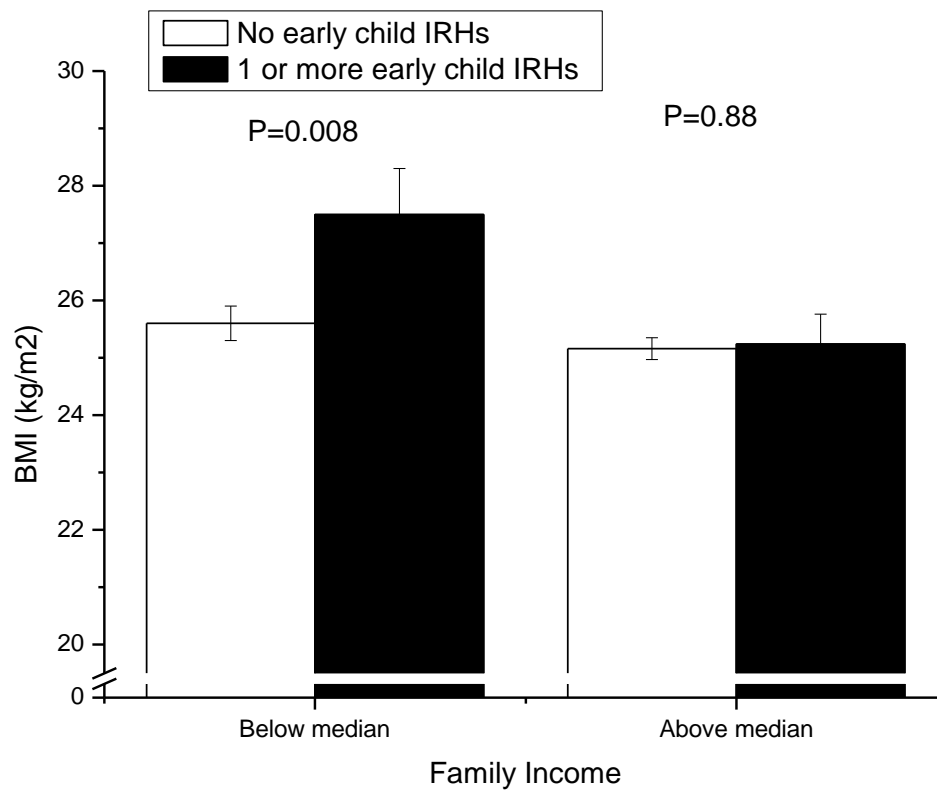
# FIGURES

Figure 1

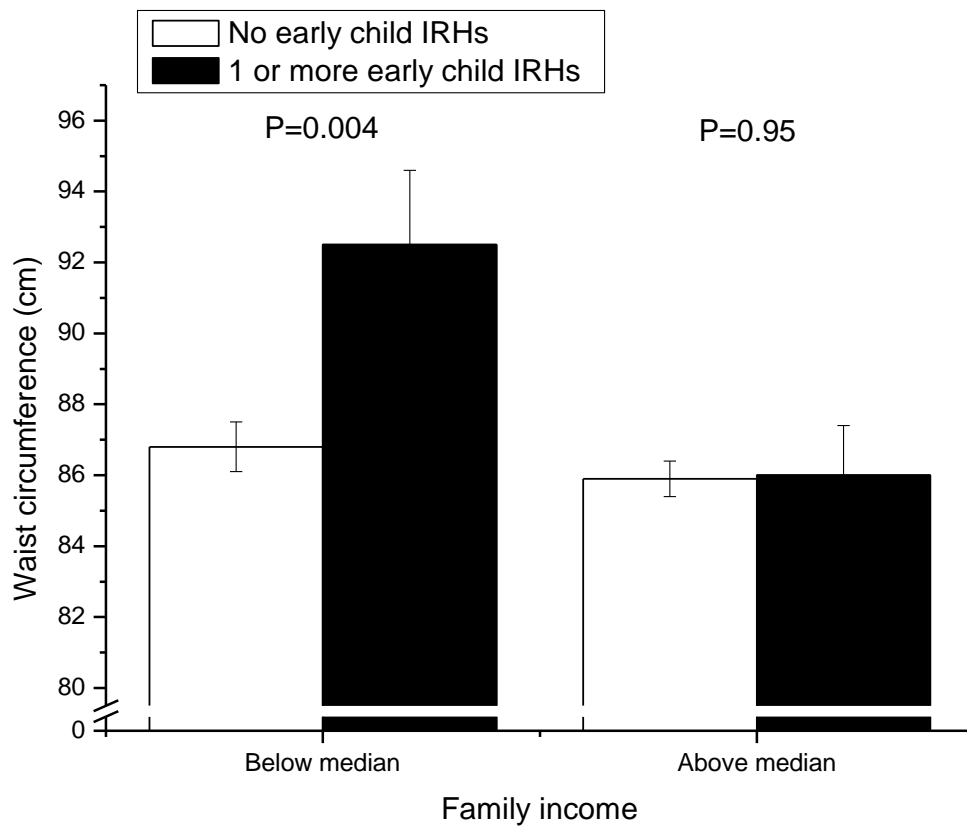




**Figure 2**



**Figure 3**



**Figure 4**

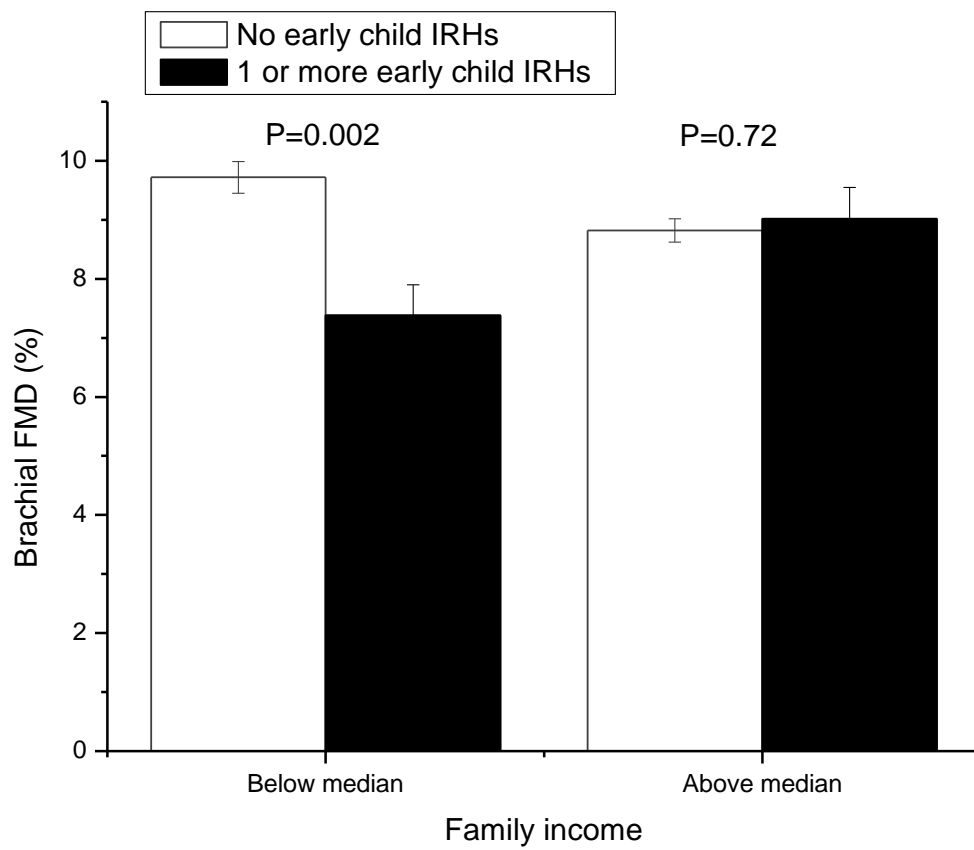


Figure 5

