Infection-Related Hospitalization in Childhood and Adult Metabolic Outcomes

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abstract

BACKGROUND AND OBJECTIVES: Identifying childhood determinants of adult cardiometabolic disease would facilitate early-life interventions. There are few longitudinal data on the contribution of childhood infections. Therefore, we investigated whether hospitalization with childhood infection is associated with adult anthropometric and metabolic outcomes in a large, well-phenotyped longitudinal cohort.

METHODS: A total of 1376 subjects from the Cardiovascular Risk in Young Finns Study, aged 3 to 9 years at baseline (1980), who had lifetime data from birth onward on infection-related hospitalization (IRH) had repeated assessments through childhood and adolescence and at least once in adulthood (age 30–45 years in 2001–2011). Early childhood (<5 years), childhood/adolescence (5–18 years), adult (>18 years), and total lifetime IRHs were related to adiposity, BMI, and metabolic syndrome in adulthood. Analyses were adjusted for childhood and adulthood risk factors and potential confounders.

RESULTS: Early-childhood IRH correlated with adverse adult but not childhood metabolic variables: increased BMI (P = .02) and metabolic syndrome (risk ratio: 1.56; 95% confidence interval: 1.03–2.35; P = .03), adjusted for age, gender, birth weight, childhood BMI and other risk factors, and family income. The age at which differences in adult BMI became persistent was related to age of IRH in childhood. The greatest increase in adult BMI occurred in those with >1 childhood IRH.

CONCLUSIONS: Childhood IRH was independently associated with adverse adult metabolic variables. This finding suggests that infections and/or their treatment in childhood may contribute to causal pathways leading to adult cardiometabolic diseases.

WHAT’SN KNOWN ON THIS SUBJECT: Childhood inflammatory mediators are associated with adult obesity, but the stimuli that initiate and perpetuate chronic inflammation start in early life are largely unknown.

WHAT THIS STUDY ADDS: Childhood infection-related hospitalization was independently associated with adverse adult metabolic variables, which suggests that infections and/or their treatment in childhood may contribute to causal pathways leading to adult cardiometabolic diseases.
Cardiometabolic diseases are increasing rapidly in prevalence and will remain the leading causes of morbidity worldwide. Chronic inflammation is central to the pathogenesis and is associated with adverse outcomes in cardiovascular disease, metabolic syndrome, and type 2 diabetes and has considerable translational implications.

Childhood inflammatory mediators are associated with adult obesity, but the stimuli that initiate and perpetuate chronic inflammation start in early life are largely unknown. The burden of infectious diseases falls predominantly on young children, and the contribution of infection to the development of later cardiometabolic disease is of considerable interest. Data support both nonspecific cumulative proinflammatory effects of multiple infections and associations between specific pathogens and cardiometabolic intermediate phenotypes and outcomes.

Similarly, early-life infectious exposures have been implicated in the pathogenesis of obesity and metabolic dysfunction, both in a nonspecific manner and by pathogen-specific effects. Childhood infections are often treated empirically with antibiotics; the possible contribution of antibiotic-induced alterations to the intestinal microbiome during early life to later obesity has also been the subject of considerable recent interest.

Most data on childhood infection and later outcomes are derived from retrospective, cross-sectional, serologically based studies. Interpretation regarding causality (whether infection contributes to risk or whether those with adverse cardiometabolic status are more prone to infection [reverse causality]) has been largely impossible to date. Longitudinal analyses are therefore an important step to inferring causal mechanisms and developing preventative strategies.

In this study we analyzed the relationship between infection requiring hospitalization (infection-related hospitalization [IRH]) and adiposity and metabolic variables in both childhood and adulthood in longitudinal data from the Cardiovascular Risk in Young Finns Study.

METHODS
Participants
The sample included those participants from the Cardiovascular Risk in Young Finns Study whose entire lifetime hospitalization data were available from the national hospitalization database since 1969. The cohort comprised those 1376 individuals (76.2% of the total of 1806 Young Finns participants aged 3–9 years at baseline in 1980) who had (1) complete hospitalization data since birth, (2) cardiometabolic risk factor data from the baseline study assessment in 1980, and (3) at least 1 adult assessment performed in 2001, 2007, and/or 2011 (Supplemental Table 4). We have shown that baseline risk factors for those participating in follow-up are largely comparable to those for nonparticipants. The study had institutional ethical approvals, and written informed consent was obtained from participants.

Anthropometric and Clinical Assessment
Weight and height were measured to the nearest 0.1 kg and 1 cm, respectively. BMI was calculated by weight (kg)/height (m2). In adulthood, waist circumference was measured midway between the iliac crest and the lowest rib to the nearest 0.1 cm. In 1980, blood pressure in those aged 3 years was measured by using a ultrasound device; a standard mercury sphygmomanometer was used among 6- and 9-year-olds. In adulthood, a random zero sphygmomanometer was used. Venous blood samples in childhood and adulthood were drawn after a 12-hour fast. Standard enzymatic methods were used for serum lipids and plasma glucose. Serum insulin was measured by using a microparticle enzyme immunoassay kit. Childhood and adulthood highsensitivity C-reactive protein (CRP) levels were determined by an automated analyzer using a latex turbidimetric immunoassay. In childhood, questionnaires completed by the parents of the participant were used to obtain data on birth weight, physical activity, mother’s BMI, father’s BMI, family income, and parental smoking status. In adulthood, questionnaires were used to obtain data on participants’ education and alcohol consumption.

Classification of IRH
IRH was defined as a hospital discharge diagnosis that included at least 1 International Classification of Diseases infection-related code as either a primary or secondary code. In Finland, the hospital discharge register includes all hospitals with pediatric wards. We used both primary and secondary codes to ensure capture of all IRHs, an approach used previously. We selected infection-related International Classification of Diseases codes (versions 9 and 10) a priori on the basis of a modification of published, population-based epidemiologic studies of childhood IRH (Supplemental Table 5). Data on specific treatment received in hospital or in primary care, including antibiotic exposures, were not available.

Classification of Adult Metabolic Syndrome
Adult metabolic syndrome (MetS) was defined by the presence of ≥3 of the following criteria: waist circumference ≥102 cm in men or ≥88 cm in women, triglycerides ≥1.695 mmol/L (≥150 mg/dL or specific drug treatment of elevated triglycerides), HDL cholesterol...
Adulthood obesity. Moreover, we have shown to be main predictors of childhood BMI, and family income as covariates, because these factors have a history of hypertension, and/or fasting plasma glucose ≥5.6 mmol/L (≥100 mg/dL or specific drug treatment of elevated glucose).20

Analyses
To investigate the relationship between the age at which the first IRH occurred and metabolic outcomes, we analyzed IRH by predefined age strata (early childhood [<5 years of age], childhood/adolescence [5–18 years], and adult [≥18 years]) in addition to IRHs before and after 5 years and total lifetime IRHs. Among individuals participating in several adulthood follow-ups (2001, 2007, 2011), the data from the latest examination were used in the analyses. For continuous variables, we used regression models adjusted first for age and gender, and in further analyses also adjusted for available covariates. Because there were no age × early-childhood IRH or gender × early-childhood IRH interactions on adulthood outcomes, all analyses were performed in the entire cohort. Relative risks and 95% confidence intervals estimated by using Poisson regression were used to examine associations between IRH groups and adult MetS or its components. These multivariable analyses included age, gender, adulthood BMI, and family income as covariates, because these factors have been shown to be main predictors of adulthood obesity.6 Moreover, we performed additional regression analyses including other possible confounding factors (birth weight, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, insulin, CRP, physical activity, and parental smoking) in the models. Using multilevel mixed modeling with maximum-likelihood estimation, we compared the BMI trajectory as a function of age for 4 groups: those with an IRH at <5 years of age versus those without and those with an IRH at ≥5 years versus those without. This approach allows for missing data and takes into account correlations between repeated measures on the same individual. We fitted interaction terms between IRH group and time to compare the trajectory of BMI between IRH groups, allowing identification of the age at which differences in BMI become apparent. An unstructured covariance matrix was used in all models.

RESULTS
The study period was 1971–2011, representing the period from birth until the most recent assessment, which was performed at a mean age of 35.1 years. There was a slight predominance of women at the adult assessment (53% women), but they did not differ significantly from nonparticipants with respect to baseline childhood (1980) BMI, blood pressure, or lipid values (Supplemental Table 6).

Five hundred ninety-seven (of 1376; 911; data not shown) individuals with complete data on these variables (N = 911; data not shown). Comparison of life-course BMI trajectory from 3 to 39 years of age in those with and without early-childhood IRH indicated that BMI increased significantly in early adulthood (from ~24 years of age) in those who had early childhood IRH (before 5 years of age) and remained significantly increased thereafter (Fig 1A). In those with an IRH only after 5 years of age, a significant increase in adult BMI was also observed, with differences between those with and without later childhood/adolescent IRH apparent from later in adulthood (~27 years) (Fig 1B). In addition, in those with both early-childhood and later childhood/adolescent IRH (ie, IRH both before age 5 years and at ages 5–18 years), adult BMI was significantly increased (Fig 1C).

IRHs and MetS
The prevalence of MetS and its components is shown in Supplemental Table 7. Early-childhood IRH was associated with increased risk of adult MetS, after
adjustment for age, gender, childhood BMI, and family income (Table 3).
With respect to the different components of MetS, both early-childhood and lifetime IRHs were associated with higher risk of increased adult waist circumference. All of these results remained similar in analyses additionally adjusted for birth weight, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, insulin, CRP, physical activity, and parental smoking in childhood among individuals with complete data on these variables (N = 911; data not shown).

### DISCUSSION

This longitudinal study indicates that IRH in childhood is significantly associated with increased BMI and MetS in adulthood. The association was independent of age, gender, socioeconomic status, childhood BMI, and other traditional cardiometabolic risk factors. The relationship between IRH and adult adiposity–related risk factors was largely driven by IRH in preschool-aged children.

A recent Danish study showed that among 17 456 males who underwent mandatory army fitness examinations, IRH before 5 years of age was associated with obesity at 19 years of age.\(^2^1\) Our findings are consistent with these results. Our longitudinal data additionally show that the association is not due to excess adiposity in childhood and that persistent differences in metabolic risk factors in those who had early-childhood IRH become evident by

### TABLE 1 Childhood and Adulthood Characteristics in Relation to Timing of IRH

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Early-Childhood IRH (&lt;5 Years)</th>
<th>Lifetime IRH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>6.2 ± 2.4</td>
<td>5.9 ± 2.5</td>
</tr>
<tr>
<td>Male gender, %</td>
<td></td>
<td>46.1</td>
<td>53.0</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td></td>
<td>3.58 ± 0.8</td>
<td>3.53 ± 0.79</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td></td>
<td>1.58 ± 0.31</td>
<td>1.56 ± 0.30</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td></td>
<td>0.60 ± 0.26</td>
<td>0.59 ± 0.24</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>15.9 ± 1.7</td>
<td>16.1 ± 2.1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td></td>
<td>107 ± 10</td>
<td>107 ± 11</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td></td>
<td>67 ± 9</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td></td>
<td>1.0 ± 2.9</td>
<td>1.5 ± 3.8</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td></td>
<td>6.4 ± 3.9</td>
<td>6.4 ± 4.4</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td></td>
<td>3.51 ± 0.52</td>
<td>3.48 ± 0.64</td>
</tr>
<tr>
<td>Physical activity, z score</td>
<td>1228</td>
<td>0.02 ± 1.00</td>
<td>−0.09 ± 1.00</td>
</tr>
<tr>
<td>Mother’s BMI, kg/m²</td>
<td></td>
<td>23.0 ± 3.7</td>
<td>23.0 ± 4.4</td>
</tr>
<tr>
<td>Father’s BMI, kg/m²</td>
<td></td>
<td>23.8 ± 5.1</td>
<td>23.4 ± 6.0</td>
</tr>
<tr>
<td>Parental smoking, %</td>
<td></td>
<td>48.9</td>
<td>54.9</td>
</tr>
<tr>
<td>Family incomea</td>
<td></td>
<td>26.4 ± 13.2</td>
<td>23.9 ± 13.0</td>
</tr>
</tbody>
</table>

### Table 2 Multivariable Associations Between IRH In Early Childhood and Lifetime With Adult BMI and Waist Circumference

<table>
<thead>
<tr>
<th></th>
<th>BMI, kg/m²</th>
<th>Waist Circumference, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B ± SE</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>B ± SE</td>
<td>P</td>
</tr>
<tr>
<td>Early-childhood IRH (&lt;5 years)</td>
<td>0.85 ± 0.36</td>
<td>.02</td>
</tr>
<tr>
<td>Lifetime IRH</td>
<td>0.62 ± 0.25</td>
<td>.02</td>
</tr>
</tbody>
</table>

N = 1325. All analyses were adjusted for age, gender, childhood BMI, and childhood family income.
early adulthood. Importantly, early-childhood IRH was also associated with a 60% increased risk of MetS in adulthood.

IRH was common; one-third of children in our cohort had an IRH by age 5 years and >40% by early middle age. Early-childhood IRH was not associated with an increased risk of infection beyond age 5 years of age. Similar rates of IRH have been reported in other industrialized settings. In a populationwide study in Australian children >10 years old, nearly 1 in 5 non-Aboriginal children had at least 1 IRH by 2 years of age and hospitalizations were commoner in boys. In a national US study, 1 in 14 infants (<1 year of age) had an IRH.

The mechanisms underlying the association between childhood IRH and later metabolic risk may reflect the infectious pathogen itself, the host inflammatory response, and/or antibiotic alteration to the microbiome; antibiotics are often given empirically to an unwell febrile child and have been associated with later obesity. Specific pathogens may contribute to the association between infection and adiposity, although infection with these putative etiologic pathogens generally do not warrant hospitalization. Several studies reported a correlation between adenovirus 36 and obesity. Animal data suggest that adenovirus 36 induces early adipocyte inflammation via monocyte chemoattractant protein-1 (MCP-1), which promotes obesity and MetS. However, cross-sectional serologic analyses do not indicate the age at which infection occurred nor the clinical severity, and a causal relationship remains unproven. Other specific pathogens, including those implicated in cardiovascular disease, have also been associated with obesity. Infection with a variety of pathogens (the “pathogen burden”) may also have a nonspecific effect on cardiometabolic outcomes. Studies of
pathogen burden rely on serologic evidence of exposure to a handful of microbes that have been implicated in cardiometabolic pathogenesis. Overall pathogen burden has previously been associated with fat mass,20 insulin resistance in middle-aged men,29 and cardiovascular disease morbidity and mortality.30,31 Our IRH data reflect exposure and severe clinical disease to a greater array of pathogens, with similar associations.

IRH may be indicative of infection severity, which may reflect the extent of pathogen-induced host inflammation more broadly. All children are repeatedly exposed to the pathogens, but severe infection occurs only in a minority. This variation in clinical severity partly reflects differences in the host inflammatory response.32 Children who have infections severe enough to warrant hospitalization may have a generic proinflammatory response to all infectious stimuli, including those managed outside of the hospital. Thus, hospitalization with infection may be a marker of a greater and more persistent nonspecific inflammatory response to the numerous infectious insults in early life. The resulting chronic inflammatory state may contribute to the development of obesity and MetS over the lifetime course.

Acute infection may lead to persistent chronic inflammation by a number of mechanisms. Viral infections may result in increased circulating endotoxin despite viruses lacking a cell wall.33 Endotoxin induces the expression of Toll-like receptor 4 (TLR4) by various cell types, including adipocytes, and TLR4 expression is predictive of obesity, diabetes, and MetS.34 In animal models, human viral pathogens act synergistically with lipopolysaccharide to increase inflammation.35 Infection also increases the expression of high mobility group box 1 (HMGB1), a nuclear protein released by damaged cells. HMGB1 has been shown to enhance chronic inflammation in adipose tissue.36 Once inflammation is established, it may perpetuate the chronic inflammatory state that is well recognized in obesity and MetS.37 Infection-activated monocyte/macrophages may migrate into adipose tissue and establish a chronic inflammatory milieu that promotes obesity and insulin resistance.27,38 The significant association between adverse metabolic variables in adulthood and early-life gastrointestinal IRH also raises the possibility that infection-related alteration of the intestinal microbiome might influence later metabolic risk. Children hospitalized with infection are likely to receive empirical parenteral antibiotics, even for viral infections, because distinguishing bacterial from viral infection clinically is often difficult. Antibiotics may have marked effects on the microbiome,22 and early-life antibiotic exposure is associated with subsequently increased BMI.39 Reduced microbiome diversity is implicated in the development of obesity and MetS.23,24 Childhood antibiotic data were not available in the current study, because the collection of statutory pharmaceutical data only commenced in Finland when the study cohort was in adulthood. Prospective investigation of total infection burden and early-life antibiotic exposures and their effects on the microbiome and later metabolic risk is warranted.

Longitudinal analysis of a population-representative cohort over 4 decades is the key strength of this study. Differences in BMI between those with and without early-childhood IRH became apparent in early adulthood, indicating that childhood may be optimal for interventions aimed at reversing or reducing later metabolic risk. The association between early-childhood infection and adult increased BMI and MetS is more informative than retrospective cross-sectional studies in high-risk adults, which are subject to ascertainment bias and rely on serologic data rather than clinical infection. The use of hospitalization as a standardized measure of clinically significant infection is less susceptible to differences in socioeconomic status and health-seeking behavior than emergency department or primary care attendances40 and to physician-related variation in diagnosis.

We acknowledge some unavoidable limitations in the study. IRH data do not capture milder; often chronic infections (such as those caused by chlamydophilia, Helicobacter; and chronic viral infections), commonly implicated in adverse cardiometabolic outcomes. A more complete prospective ascertainment of total infection burden is necessary.

### Table 3: Multivariable Associations Between IRHs in Early Childhood or During Lifetime With Adult MetS and Its Components

<table>
<thead>
<tr>
<th></th>
<th>High WC</th>
<th>High BP</th>
<th>Low HDL-C</th>
<th>High Triglycerides</th>
<th>High Glucose</th>
<th>MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early childhood IRH</td>
<td>1.12 (1.01–1.24)</td>
<td>.04</td>
<td>1.05 (0.95–1.12)</td>
<td>.51</td>
<td>1.13 (0.94–1.36)</td>
<td>20</td>
</tr>
<tr>
<td>Lifetime infection</td>
<td>1.09 (1.02–1.16)</td>
<td>.02</td>
<td>0.98 (0.93–1.04)</td>
<td>.53</td>
<td>1.11 (0.98–1.25)</td>
<td>10</td>
</tr>
</tbody>
</table>

N = 1325. All analyses were adjusted for age, gender, childhood BMI, and childhood family income. BP, blood pressure; CI, confidence interval; HDL-C, HDL cholesterol; RR, risk ratio; WC, waist circumference.
to establish whether childhood infection is causally related to adverse metabolic status in adulthood and to investigate underlying mechanisms. The number of individuals in each specific infection group is relatively low, and these analyses should be interpreted with some caution. We were unable to distinguish between community-acquired and nosocomial IRHs, but the latter do not contribute a large proportion of the total infection burden in early childhood, when we saw the strongest relationships.8 Because our age cohorts were 3, 6, and 9 years old at baseline, the 2 oldest cohorts were >5 years of age at baseline assessment. However, there were no differences according to early-childhood IRHs (at ages 0–5 years) in adiposity or metabolic markers at baseline, suggesting that this finding did not affect the results. Data on immunizations and childhood antibiotic exposures (which occur largely outside of the hospital) were not available. The association between early-childhood IRH and increased adult BMI and MetS was independent of known risk variables, but we are unable to exclude completely residual confounding by shared, unidentified determinants of both early-life infection and later metabolic risk. However, the Cardiovascular Risk in Young Finns cohort is well phenotyped for risk factors, including those that may influence both infection risk and adverse cardiometabolic status (eg, parental smoking, parental BMI, birth weight, and childhood BMI). The findings are therefore unlikely to reflect major missed confounding factors.

CONCLUSIONS
We report a temporal association between childhood IRH and increased BMI and MetS in adulthood. The timing of childhood IRH was related to the age at which adult BMI became significantly increased. Those who had IRH both before and after age 5 years had the most marked increase in BMI as adults. The findings suggest that childhood infections are associated with increased metabolic risk variables in adulthood. Children hospitalized with infection may represent an at-risk group for later noncommunicable disease. Prospective studies are required to identify causal and mechanistic pathways necessary for the development of therapeutic interventions.

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ABBREVIATIONS
CRP: C-reactive protein
IRH: infection-related hospitalization
MetS: metabolic syndrome

Drs Burgner and Sabin conceptualized and designed the study and drafted the initial manuscript; Drs Cheung and Dwyer conceptualized and designed the study and critically reviewed the manuscript; Drs Kähönen, Lehtimäki, Hutri-Kähönen, Jokinen, Laatikainen, and Taittonen coordinated and supervised data collection at study sites and critically reviewed the manuscript; Drs Viikari and Raitakari designed and coordinated the data collection and critically reviewed the manuscript; Drs Magnussen and Juonala conceptualized the study, carried out the initial analyses, and critically reviewed the manuscript, and all authors approved the final manuscript as submitted.

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