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Infectious diseases are associated with carotid intima media thickness in adolescence☆

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ABSTRACT

Objective: Inflammatory risk factors in childhood, e.g. obesity, impact on carotid artery intima media thickness (CIMT), an early indicator of atherosclerosis. Little is known on potential infectious origins in childhood. We investigated the association between number of reported different childhood infectious diseases and CIMT in adolescence.

Study design: 288 SAPALDIA offspring (8–21years) underwent a clinical examination in 2010–2011: anthropometry, blood pressure, CIMT, blood draw (cardiovascular biomarkers, cotinine). Offspring and parents gave information on individuals' and family health, child's vaccination status, infectious diseases and other early life factors. Life-time prevalence of bronchitis, pneumonia, tonsillitis, otitis, mononucleosis, meningitis, appendicitis, and scarlet fever were investigated, separately, and as cumulative infectious disease score. Multilevel adjusted linear regression analysis on the association between subjects' CIMT average and infectious diseases score was performed, stratifying by sex.

Results: Youth (mean age 14.8 yrs; 53% female) reported on average 1.3 of the listed infectious diseases; 22% boys and 15% girls reported ≥3 infectious diseases ($p = 0.136$). Two-thirds were vaccinated according to recommendations (boys 56%, girls 61.5%, $p = 0.567$). Sex-stratified analyses yielded significantly increased CIMT in boys with ≥3 infectious diseases vs. none (0.046 mm, 95%CI 0.024; 0.068). In girls, the effect was of same direction but statistically non-significant (0.011 mm, 95%CI −0.015; 0.036).

Conclusion: The SAPALDIA Youth study complements current evidence on infectious origins of atherosclerosis in adults. The larger effects observed in boys may relate to a higher vulnerability of the vasculature and/or to infectious pathogens. Our data are suggestive of an early impact of childhood infectious diseases on vascular health.

Cardiovascular diseases remain the main cause of mortality and morbidity world-wide and early prevention is as relevant as ever [1]. Studies in children observed early vascular damage by measuring carotid artery intima media thickness (CIMT) already early in life, for example, in obese and diabetic children [2–5]. The relevance of childhood exposures for vascular health in adulthood [6–8] has been shown in various cohort studies. A key pathway to atherosclerosis is inflammation [9,10]. Inflammatory biomarkers per se [11–13], specific pro-inflammatory risk factors such as passive smoking [14–17], obesity [18–20], and chronic inflammatory diseases [21–25] have been associated with vascular health in children and adolescents. Evidence in human and animal studies is accumulating that infectious agents causing inflammatory

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responses induce the atherosclerotic process [26–29]. The current view is that multiple infectious organisms contribute to atherosclerosis via direct and indirect mechanisms [9]. While pathogen involvement has been observed in adult atherosclerosis [30], little is found on potential infectious origins in childhood or adolescence [31–34]. Exposure to pathogens is considered part of the early immune developmental process. However, children cope differently with pathogens and not all develop major infectious diseases, such as otitis, bronchitis, or meningitis. In the SAPALDIA Youth study, a cross-sectional population-based offspring study, we investigated the association between the number of different reported infectious diseases and CIMT in adolescence for both sexes, separately, and independent of chronic medical conditions.

1. Methods

1.1. Study design and study sample

The SAPALDIA Youth Study is a cross-sectional offspring study nested into the Swiss Study on Air Pollution And Lung and Heart Disease In Adults (SAPALDIA) [35]. Offspring born to participants between the first two surveys (1990–2001) and living in the German speaking study areas were considered eligible (N = 530). The overall participation rate was 67% (N = 356) and 288 participated in the clinical examinations (Supplemental Fig. 1). Based on the available parental data there is no evidence for non-participation bias [36]. High quality CIMT data were available in 281 youth. Data on vaccination status or infectious diseases were missing only for 4 youth. Children with known heart malformations (N = 5) or renal disease (N = 2) and with missing information on parental covariates (N = 13) were excluded from the analytic sample, resulting in 257 youth. Written informed consent was given by the parent, in case the youth was still a minor, or by offspring either globally for all examinations or separately for single assessments. Ethical clearance was obtained from the respective cantonal Ethical Review Boards.

1.2. Childhood exposures and infectious diseases

The participants were sent questionnaires by post, one addressed to the offspring and one addressed to the parents. The offspring were free to fill in their questionnaire either alone (N = 80, mean age 17.5) or together with a parent (N = 192, mean age 14). The youth questionnaire covered different topics such as early life factors, life style, current health, physical development, and Tanner puberty stages (Supplemental Table 1) [37]. Among the health questions, children were asked if they suffered from one of the chronic disease and if a doctor had diagnosed the disease (Asthma, hypertension, dislipidemia, renal disease, heart malformations, diabetes). Parents were asked to fill in a questionnaire on pregnancy, birth outcomes and medical history of offspring and their grand-parents, including vaccination status of their child according to Swiss recommendations. Parental health and socio-economic data were available from the previous and current SAPALDIA surveys.

The **exposure to infectious diseases** in childhood is based on parental report. Parents were asked: “Did your child ever have one of following diseases?” Among the listed medical conditions were: bronchitis, pneumonia, tonsillitis, otitis, mononucleosis, meningitis, appendicitis, salmonellosis, and scarlet fever. These infectious diseases were used in the calculation of the infectious disease score. Infectious diseases which are essentially preventable by vaccination (measles, mumps, whooping cough, rubella) were also listed in the questionnaire, but given the high vaccination coverage in this population, were not included into the score.

Childhood infectious disease score: all reported childhood infections were given the value 1 and were added up to a continuous exposure variable (min 0 – max 9), as well as a categorical variable (none, one, two, three infectious or more diseases reported).

Trained SAPALDIA field workers examined the youth at the study centers following standard operating procedures described in detail elsewhere [36]. In short, anthropometric measurements (height, weight and waist hip ratio) were taken with the child dressed in light clothing without shoes; non-fasting blood samples were drawn for analyses of cardio-metabolic (glucose, HbA1c, total cholesterol, HDL-cholesterol) and inflammatory biomarkers (hsCRP), systolic and diastolic blood pressure was measured twice with an oscillograph after sitting quietly for at least 10 min. The mean of both systolic and diastolic measures was used in further analyses.

1.3. Carotid intima media thickness

The outcome, CIMT, was bilaterally examined by trained and certified field workers using carotid ultrasound. Duplicate CIMT exams were performed in 202 participants of the SAPALDIA 3 cohort within 2 weeks of the first exam. The between-visit coefficient of variation for average CIMT was 3.98% (3.52–4.44). All instruments were equipped with a SAPALDIA-specific instrument application protocol, jointly developed and validated by the investigators (Swiss TPH, AMC, DSBG) and Fukuda Denshi R&D (Basel, CH), and a vascular linear array transducer (FUT-LA385-12LA, 38 mm, 5–12 MHz). According to a validated imaging protocol, field workers visualized the common carotid in two angles (longitudinal and ear-to ear) during 3 complete separate cardiac cycles and images were stored digitally. An automatic contour detection of CIMT was applied in the ultrasound image and CIMT was measured over a 1 cm segment proximal to the carotid bulb across several heart cycles. We used the measures of both angles of both the right and left common carotid artery to calculate the individual's enddiastolic average and maximum CIMT.

1.4. Statistical analyses

Descriptive statistics of the study population (Table 1) and comparative analyses of SAPALDIA Youth participants with and without CIMT measures were performed (chi2 test). P-values<0.05 were considered as statistically significant. Given the complexity of the potential confounding factors we constructed a directed acyclic graph (DAG) based on prior knowledge and hypotheses to guide us in the initial covariate selection. Three potential confounder groups were identified: 1. Birth and pregnancy related outcomes: pre- and in-pregnancy smoking, birth weight, pregnancy complications, birth complications; 2. Adolescent lifestyle: smoking, nutrition, BMI, physical activity, parental education and 3. Other early childhood inflammatory exposures (parental smoking, environmental tobacco smoke), vaccination and chronic disease (doctor-diagnosed diabetes, dyslipidemia, arterial hypertension, asthma and allergies or biomarkers: IgE, HDL, LDL, HbA1C). IgE, HDL, LDL, HbA1C were dichotomized in below and above cut-offs based on the laboratory reference values and pediatric guidelines [36, 38]. Various additional inflammatory exposures or proxies were considered in extended models as effect modifiers: hsCRP, reported vaccination and asthma status, total IgE as well as other infectious disease preventable by vaccination. Vaccination status was categorized by number of reported recommended vaccinations: <2, 2–5, >5. Sex, age and tanner puberty stages were considered *à priori* covariates. Covariates included in the final model were kept based on a respective p-level of ≤0.20: height percentiles, term birth, maternal