Atherosclerosis 239 (2015) 496–502

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Early childhood hospitalisation with infection and subclinical atherosclerosis in adulthood: The Cardiovascular Risk in Young Finns Study

David P. Burgner [a, b, c, **], Matthew A. Sabin [a, b], Costan G. Magnussen [d, f], Michael Cheung [a], Cong Sun [a], Mika Kähönen [g], Nina Hutri-Kähönen [h], Terho Lehtimäki [i, j], Eero Jokinen [k], Tomi Laitinen [l], Jorma S.A. Viikari [e, m], Olli T. Raitakari [d, m], Markus Juonala [a, e, m, *]

[a] Murdoch Childrens Research Institute, Royal Children's Hospital, 50 Flemington Road, Parkville 3052, Australia
[b] Department of Paediatrics, University of Melbourne, Grattan Street, Melbourne, Victoria 3010, Australia
[c] Department of Paediatrics, Monash University, 246 Clayton Road, Clayton, Victoria 3186, Australia
[d] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland
[e] Department of Medicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland
[f] Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia
[g] Department of Clinical Physiology, University of Tampere School of Medicine and Tampere University Hospital, Teiskontie 35, 33520 Tampere, Finland
[h] Department of Paediatrics, University of Tampere School of Medicine and Tampere University Hospital, Teiskontie 35, 33520 Tampere, Finland
[i] Department of Clinical Chemistry, University of Tampere School of Medicine and Tampere University Hospital, Teiskontie 35, 33520 Tampere, Finland
[j] Fimlab Laboratories, University of Tampere School of Medicine and Tampere University Hospital, Teiskontie 35, 33520 Tampere, Finland
[k] Hospital for Children and Adolescents, University of Helsinki, Stenböckinkatu 9, 00029 HUS Helsinki, Finland
[l] Department of Clinical Physiology, Kuopio University Hospital and University of Eastern Finland, Kotkankallionkatu 14, 70600 Kuopio, Finland
[m] Division of Medicine, Turku University Hospital, Kiinamyllynkatu 4-8, 20520 Turku, Finland

ARTICLE INFO

Article history:
Received 30 December 2014
Received in revised form
30 January 2015
Accepted 10 February 2015
Available online 16 February 2015

Keywords:
Child
Atherosclerosis
Infection
Asymmetric dimethylarginine

ABSTRACT

Objective: Most infections occur in pre-school children but the severity of the inflammatory response to common pathogens varies considerably. We examined the relationship between early childhood infections of sufficient severity to warrant hospitalisation, and markers of subclinical atherosclerosis in adulthood.

Methods: We investigated whether infection-related hospitalisation (IRH) in early childhood (0–5 years) was associated with adverse non-invasive phenotypes of atherosclerosis (carotid artery distensibility and intima-media thickness (IMT), and brachial artery flow-mediated dilation (FMD)) in adulthood in participants from the Cardiovascular Risk in Young Finns study. Analyses were adjusted for age, sex, and socioeconomic status and cardiovascular risk factors in childhood and adulthood. 1043 participants had lifetime IRH data with a mean age at adult follow-up of 33 years.

Results: Brachial FMD levels were significantly lower among individuals with early child IRH (mean ± SEM 8.15 ± 0.37 vs. 9.10 ± 0.16%, $p = 0.03$). These individuals had a 1.84% (95% CI 0.64–3.04, $p = 0.002$) greater decrease in FMD over a 6-year interval between two adult follow-ups at mean ages 27 and 33 years. Childhood IRH was associated with increased asymmetrical dimethylarginine (ADMA) in adulthood (0.62 ± 0.01 vs. 0.59 ± 0.01 μmol/l, $p = 0.04$), adjusted for age, sex, adult body mass index, and serum creatinine. Early childhood IRH was associated with lower carotid distensibility levels (1.95 ± 0.06 vs. 2.09 ± 0.02%/10 mmHg, $p = 0.02$), but not with carotid intima-media thickness (0.601 ± 0.006 vs. 0.596 ± 0.003 mm). All findings remained unchanged after adjustments for age, sex and conventional cardiovascular risk factors in childhood or adulthood.

* Corresponding author. Department of Medicine, University of Turku, Kiinamyllynkatu 4-8, 20520 Turku, Finland.
** Corresponding author. Murdoch Childrens Research Institute, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria 3052, Australia.
E-mail addresses: david.burgner@mcri.edu.au (D.P. Burgner), mataju@utu.fi (M. Juonala).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.024

Conclusion: Infection-related hospitalisation in the pre-school period was associated with adverse adult atherosclerotic phenotypes and increased ADMA. Infection may contribute to causal pathways leading to the development of endothelial dysfunction and early atherosclerosis.

Atherosclerotic cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide [1]. Clinically manifest in adulthood, the chronic inflammatory pathogenesis of atherosclerosis begins in early childhood [2]. Conventional risk factors, including dyslipidaemia, hypertension, diabetes, and obesity account only part of the total attributable risk of CVD [3]. There is therefore considerable interest in novel determinants, especially those that operate early in the life course, as modification of childhood risk trajectories may have considerable impact on the burden of CVD in adulthood.

Infectious diseases are ubiquitous in early life and elicit repeated inflammatory responses from the developing immune system. Children vary considerably in the extent of the inflammatory response, and in the frequency and severity of clinical infection [4]. In adults there is a clear temporal association between acute infections and atherosclerotic plaque instability and acute myocardial infarction and stroke [5]. In addition, bacterial material has been identified from coronary arteries and thrombus aspirates [6,7]. Investigation of the contribution of childhood infection to early atherosclerosis development and CVD risk is more difficult. Most data are from retrospective case–control studies of adults with established CVD and provide serological evidence of previous exposure to a limited selection of putative pro-atherogenic pathogens, but limited information regarding the timing and severity of the host response. There are few datasets that allow longitudinal analysis of childhood infection and cardiovascular risk in adulthood in the same individuals.

Here we report findings using longitudinal data from the Cardiovascular Risk in Young Finns Study to investigate the relationship between severe clinical infection in early childhood and validated, predictive cardiovascular risk phenotypes in the same individuals approximately three decades later. The non-invasive measures of arterial health included distensibility, flow-mediated dilatation (FMD), and carotid intima-media thickness (IMT) which are recognised early markers of atherosclerosis burden and adverse CVD risk [8].

1. Methods

1.1. Participants

The Cardiovascular Risk in Young Finns Study is an ongoing prospective study of cardiovascular risk factors from childhood onwards. The study commenced in 1980, when participants were aged 3–9 years, with repeated follow-up assessments [9]. The current sample included 1043 individuals with entire lifetime hospitalisation data extracted from the Finnish national hospitalisation database, which commenced in 1969. Main outcome measures included carotid/brachial artery ultrasound data from 2001 (age 24–30 years) and 2007 (age 30–36 years). Baseline risk factors of those retained in follow-up are largely comparable to non-participants [10]. The study complies with the Declaration of Helsinki and has institutional ethics approval. Written informed consent was obtained from all participants.

1.2. Questionnaire data

In childhood, questionnaires completed by the parents of the participant were used to obtain data on birth weight, mother's body mass index (BMI), father's BMI, family income, fruit and vegetable consumption and parental smoking. Family income at the time of enrolment was used as a measure of the child's household socio-economic status, previously shown that it is independently predictive of adult cardiometabolic risk in this population [11]. In adulthood, questionnaires were used to obtain data on the participant's smoking status, physical activity, years in education and diet.

1.3. Anthropometric and clinical assessment

Height and weight were measured at all time-points using a similar protocol and BMI was calculated by weight (kg)/height $(m)^2$. Enrolment blood pressure in those aged 3 years 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-h 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 sulphate precipitation and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. High-sensitivity C-reactive protein (hsCRP) was measured by an automated analyser using a latex turbidimetric immunoassay. Serum creatinine was determined spectrophotometrically with the Jaffe' method (picric acid; Olympus Diagnostica GmbH, Hamburg). Asymmetrical dimethylarginine (ADMA) was measured in samples collected in 2001 (when individuals were aged 24–30 years) by a modified isocratic high-pressure liquid chromatographic [12].

1.4. Classification of infection-related hospitalisation

Infection-related hospitalisation (IRH) 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. We used both primary and secondary codes to ensure capture of all infections, an approach we and others have used previously [13]. 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 IRH [13]. To investigate possible infection-specific effects, the infection-related codes were grouped *a priori* into clinical diagnostic categories (lower respiratory tract, upper respiratory tract, gastrointestinal, viral, skin and soft tissue and invasive bacterial infections), using a modification of methods described previously [13]. Early childhood was defined as birth to 5 years of age (i.e. pre-school), when the infection burden is greatest [14].