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Infections in early life and premature acute coronary syndrome: A case-control study

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Abstract

Background: Infections in young children may affect the vasculature and initiate early atherosclerosis. Whether infections experienced in childhood play a part in adult clinical cardiovascular disease remains unclear. We investigated the association between infections in early life and the occurrence of premature coronary heart disease.

Methods: We conducted a population-based case-control study of 153 patients with a first acute coronary syndrome before the age of 56 years and 153 age- and sex-matched controls. Any history of severe infections in childhood and adolescence was obtained, together with clinical and laboratory measurements and other cardiovascular risk factors. We developed an infection score for the overall burden of early life infections. Conditional logistic regression was used to assess the associations.

Results: Infections experienced in early life increased the risk of acute coronary syndrome at a young age with an odds ratio (OR) of 2.67 (95% confidence interval (CI) 1.47–4.83, $p = 0.001$). After adjustments for traditional risk factors, lifestyle, dietary patterns, socio-economic status and parental history of cardiovascular events, these associations remained significant and changed only slightly. There was an indication for an interaction between infections in early life and current cardiovascular risk (Framingham Risk Score (FRS); p-interaction $= 0.052$). Within participants with a low FRS (<10%), the OR of early life infection for acute coronary syndrome was 1.49 (95% CI 0.72–3.08, $p = 0.283$); within participants with an intermediate FRS (10–20%), the OR was 4.35 (95% CI 1.60–11.84, $p = 0.004$); and within participants with a high FRS (>20%), the OR 10.00 (95% CI 1.21–82.51, $p = 0.032$).

Conclusion: Infections in early life may partly explain premature coronary heart disease in adulthood and may potentiate traditional cardiovascular risk factor effects.

Keywords

Childhood infection, premature cardiovascular disease, cardiovascular risk factors

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Introduction

Cardiovascular disease (CVD) was responsible for 17.5 million deaths worldwide in 2012, representing almost 31% of all deaths.[1,2] Compared with high-income countries, many people with CVD in low and middle income countries are relatively young (<60 years).[1] As infectious diseases are highly prevalent in these low and middle income countries,[3] the emerging hypothesis on the possible relationships between infection and atherosclerotic CVD may be particularly relevant in these settings.

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Although clinically manifest in adulthood, the development of atherosclerosis, the underlying pathology of CVD, begins in early life[4–8] and chronic inflammation in response to injury of the arterial wall is central to the pathogenesis.[9–11] Many traditional CVD risk factors affect the vasculature in childhood,[9,12–15] but less is known about infections early life – a ubiquitous stimulus of host inflammation.[10,16] Infections in early life are pervasive and elicit repeated inflammatory responses from the developing immune system,[17] which may adversely affect the young vasculature.[9,16,18–21]

We investigated whether infections in early life are associated with early coronary heart disease in adulthood and if this association is modified by traditional risk factors. We conducted a population-based case-control study of incident patients with a first acute coronary syndrome (ACS) at a young age in the Makassar Cardiac Centre, Indonesia to determine the relationship between ACS and infections experienced in childhood and adolescence.

Methods

This study was conducted in Makassar Cardiac Centre, Wahidin Sudirohusodo Hospital, Indonesia between February 2013 and December 2014. Ethical approval was obtained from the Institutional Review Board of the Faculty of Medicine, University of Hasanuddin Makassar (letter no. 030/H4.8.4.5.31/PP 36-KOMETIK/2013).

Cases

The cases with premature ACS were defined as patients with an ACS event occurring before the age of 56 years. After obtaining written informed consent, we enrolled 153 consecutive new patients aged ≤ 55 years admitted to the cardiovascular care unit with a first ACS, a spectrum of clinical presentations consistent with acute cardiac ischaemia within 24 hours of hospital presentation, which ranged from unstable angina to non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction.[22,23]

Cardiologists made an initial diagnosis of ACS in patients presenting with acute cardiac chest pain based on clinical presentation, electrocardiography and changes in cardiac enzymes. Patients were diagnosed with ST-segment elevation myocardial infarction when they had new or presumed new ST-segment elevation ≥ 1 mm seen in any location, or new left bundle branch block on the index or any subsequent electrocardiogram, with at least one positive cardiac biochemical marker of necrosis.[24,25]

Unstable angina and non-ST-segment elevation myocardial infarction are closely related conditions; their clinical presentations are indistinguishable, but they differ in severity.[22,23] For a diagnosis of non-ST-segment elevation myocardial infarction, at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present.[23] Unstable angina was diagnosed when ischaemic chest pain lasted more than 20 minutes[23] with no evidence of myocardial necrosis or ST elevation.[24,25] Patients were excluded if they had a history of previous CVD or negative findings on coronary angiography.

Controls

We sampled young adult controls from the general population every weekend to obtain identical numbers to the cases. The controls were sampled from the same neighbourhood that the cases came from and were invited to visit a primary health care centre after matching for age (±3 years) and sex. To ensure a proper incidence-density sampling, every time a case was selected, a control was recruited within one week. Controls were excluded if they had any previous diagnosis of heart disease, presented current symptoms and signs of cardiovascular events, or were incapable of giving consent.

Measurements

A detailed questionnaire was developed and applied to all cases and controls. For all participants, we recorded data on socio-demographic characteristics such as age, sex, occupation, monthly income, educational level, dietary pattern, physical activity, smoking status, family history of heart disease, diabetes, and sudden cardiac death, as well as any known history of hypertension and diabetes. A positive family history of CVD was defined as ≥1 first-degree and/or ≥2 second degree family members with CVD before the age of 55 years in men and 65 years in women.[26–28]

Anthropometric measurements, including height, weight and waist circumference were collected. Two readings of blood pressure were recorded in a seated position with a mercury sphygmomanometer. Nurses were trained as research assistants and administered all measurements using standardized protocols. Fasting plasma glucose, lipid profiles, uric acid, and renal and liver functions were measured within 24 hours of hospital admission for all cases. We collected similar cross-sectional data from all controls at the primary health care centre.

For the overall burden of infections in early life, we developed an infection score based on the questionnaire data on the history of previous infections during four periods of life: infancy and pre-school (0–5 years),

elementary school (6–13 years), junior high school (14–17 years) and senior high school (18–21 years). All documented severe infections during a given time period were scored as 1 and were added to give a continuous infection score (minimum 0, maximum 4). We then dichotomized the score to either exposed to early life infections or unexposed (yes/no). Positive experienced early life infection was defined as an infection score ≥ 2 when the participants reported severe infections in at least in two periods early in life. Severe infection was defined as a fever for three or more days or hospitalization as a result of an infectious disease.

We asked the patients and close family members (parents, partner, siblings, aunts, uncles or others) accompanying them at the time of data collection in hospital to answer the interview questionnaire regarding the patient's history of diagnosed or experienced infections during childhood and adolescence. If the patients or family were in doubt, we cross-checked with other family members who were present during the patient's early life. We gathered this information for the controls with exactly the same questionnaire and interview methods as used for the cases while visiting their house to invite them to participate in this study and to obtain informed consent. To ensure there was no difference in recall or remembering of past events between cases and controls, we verified the answers of the cases and controls with their parents, siblings or closest family members before the cases were discharged from hospital and by telephone or home visit at the end of the study for the controls.

Using diagnostic test results in the cases and contemporary tests in controls, we calculated regular Framingham Risk Scores (FRSs) for all participants to arrive at a summary value. The FRS was calculated not for clinical purposes, but for the accurate ranking of traditional CVD risks for later analysis.

Statistical analysis

Comparisons of the general characteristics between the cases and controls were made first. Paired *t*-tests were performed with normal distributions and non-parametric Wilcoxon signed-rank tests for skewed distributions. McNemar's χ^2 tests were used for the categorical variables. Univariable and multivariable conditional logistic regression analyses were conducted for the early life infection variable to obtain unadjusted and adjusted odds ratios (OR) and their 95% confidence interval (CI), corresponding to two-sided $p < 0.05$.

We used four adjustment models for the multivariable logistic regression to show the respective influences of each model in modifying the OR for early life infection. Regarding sample size, we restricted the analyses to <15 variables in one model. Model 1 was adjusted for lifestyle and diet factors (current smoking, sedentary life, consumption of fatty foods, salty foods and monosodium glutamate, fried food and less fibre). Model 2 was adjusted for socio-economic status (monthly income and college education). Model 3 was adjusted for history of mother and father with CVD, history of parents with diabetes mellitus, maternal and paternal history of premature sudden cardiac death (at age < 60 years[29]). Model 4 was adjusted for traditional risk factors (hypertension, raised fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and obesity).

It is basically unknown whether an effect of childhood infections on vasculature, if any, would be direct or indirect through other CVD risk factors. Therefore we performed an interaction analysis using the interaction term experienced early life infection × FRS in multivariable modelling. For graphical evaluation of that interaction, we repeated both the crude and adjusted main analyses within the following strata of FRS: low risk, FRS < 10%; intermediate risk, FRS 10–20%; and high risk (FRS > 20%).[30] All analyses were performed using the IBM SPSS 22.0 statistical package.

Results

Table 1 shows the baseline characteristics of the cases and controls. Their mean ± SD age was 47 ± 6.3 years (range 28–55 years) and 81.7% were male. Compared with the controls, the cases had higher fasting plasma glucose, lower high-density lipoprotein cholesterol levels, lower low-density lipoprotein cholesterol levels and a higher serum creatinine level. The cases more often had a known history of hypertension, medication for hypertension, a history of diabetes and a higher education level (formal college education). Cases were more often current smokers, ate more fatty foods, more salt and more monosodium glutamate. Cases and controls had an approximately equal monthly income and a similar body mass index.

Table 2 shows that, in the univariable analysis, early life infection was associated with almost three-fold higher odds for acquiring premature ACS. None of the adjustments (models 1–4) materially changed these findings.

Considerable differences in the overall burden of infections were observed between cases and controls (Figure 1). In the entire study population, the most prevalent infectious diseases were varicella/chickenpox (28.1%), typhoid fever (23.9%), measles (21.6%), gastrointestinal infection/diarrhoea (11.8%), lower respiratory tract infections (5.6%), malaria (4.3%), dengue fever (3.9%), hepatitis A (2.6%) and tonsillitis (2.6%). The majority of the participants (80.7%) had at

Table 1. Comparison of baseline characteristics between cases and controls.

Variable	Case ($n=153$)	Control ($n=153$)	Total ($n=306$)	p
Male sex	125 (81.7)	125 (81.7)	250 (81.7)	1.000
Age (years)	47.1 ± 6.2	46.9 ± 6.4	47.0 ± 6.3	0.121
Systolic BP (mmHg)	120.7 ± 21.2	120.3 ± 21.6	120.5 ± 21.4	0.867
Diastolic BP (mmHg)	78.2 ± 13.7	80.2 ± 14.1	79.2 ± 13.9	0.221
Fasting plasma glucose (mmol/L)[a]	6.9 (5.7–9.6)	4.8 (4.3–5.6)	5.6 (4.7–7.5)	<0.001*
Raised plasma glucose[b]	103 (67.3)	25 (16.3)	129 (42.2)	<0.001*
Total cholesterol (mmol/L)[a]	5.1 (4.4–5.9)	5.3 (4.8–5.9)	5.2 (4.6–5.9)	0.541
Triglycerides (mmol/L)[a]	1.6 (1.1–2.4)	1.5 (1.2–2.3)	1.6 (1.2–2.3)	0.287
HDL-chol (mmol/L)	0.9 ± 0.2	1.2 ± 0.3	1.0 ± 0.3	<0.001*
LDL-chol (mmol/L)	3.5 ± 1.3	3.9 ± 0.9	3.7 ± 1.1	0.002*
Creatinine (μmol/L)[a]	88.4 (70.7–106.1)	81.3 (69.4–88.4)	82.2 (70.7–97.2)	<0.001*
BMI (kg/m^2)	24.4 ± 3.1	24.4 ± 4.1	24.4 ± 3.6	0.962
Obese (BMI ≥ 25)	55 (35.9)	62 (40.5)	117 (38.2)	0.494
Waist circumference (cm)	86.3 ± 7.8	88.7 ± 10.2	87.5 ± 9.1	0.013*
Metabolic syndrome	92 (60.1)	30 (19.6)	122 (39.9)	<0.001*
History of hypertension	99 (64.7)	60 (39.2)	159 (52.0)	<0.001*
Receiving medication for hypertension	57 (37.3)	38 (24.8)	95 (31.0)	0.020*
History of diabetes mellitus	44 (28.8)	17 (11.1)	61 (19.9)	<0.001*
Maternal history of CVD[c]	21 (13.7)	27 (17.6)	48 (15.7)	0.430
Paternal history of CVD[d]	22 (14.4)	25 (16.3)	47 (15.4)	0.755
Monthly income (≥Rp.1,810,000)[e]	82 (53.6)	68 (44.4)	150 (49.0)	0.146
College education	67 (43.8)	48 (31.4)	115 (37.6)	0.034*
Current smoker	70 (45.8)	49 (32.0)	119 (38.9)	0.015*
Ex-smoker	36 (23.5)	46 (30.1)	82 (26.8)	0.203
Sedentary life	101 (66.0)	117 (76.5)	218 (71.2)	0.060
Fatty food	31 (20.3)	9 (5.9)	40 (13.1)	<0.001*
Salty food and MSG	73 (47.7)	47 (30.7)	120 (39.2)	0.002*

Data are presented as n (%) or mean ± SD values unless stated otherwise. Comparison of baseline characteristics between cases and controls was performed using a paired samples t-test for continuous variables and McNemar's χ^2 test for categorical variables.
BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; HDL-chol: high-density lipoprotein cholesterol; LDL-chol: low-density lipoprotein cholesterol; MSG: monosodium glutamate.
*$p < 0.05$.
[a]Data are presented as median (Q1–Q3) values. Comparison was performed using the Wilcoxon signed-rank test for paired samples.
[b]Defined as fasting plasma glucose ≥ 6.1 mmol/L.
[c]Maternal history of CVD defined as mother had CVD at age < 65 years.
[d]Paternal history of CVD defined as father had CVD at age < 55 years.
[e]US$ 1 = Rp.12,700 (Indonesian rupiah). This was the cut-off point based on the national average of proper life minimum income in 2015.

least one episode of acute upper respiratory tract infection in childhood and adolescence.

Table 3 shows the results of the analysis of the association between early life infections and premature ACS using the continuous score, which reflects the actual cumulative number of infectious diseases for each participant during their childhood and adolescence, irrespective of the severity of infection. The OR for premature ACS was significant for the total period of childhood and adolescence with OR 1.42 (95% CI 1.17–1.71, $p < 0.001$) and appeared to be stronger in early childhood (0–5 years), even after adjustments.

The adjusted model included the term early life infection × FRS indicated interaction ($p = 0.052$). Figure 2 shows how the overall association was modified by the predefined classes of FRS. Within the low risk group (FRS < 10%), the OR of early life infection for ACS was 1.49 (95% CI 0.72–3.08, $p = 0.283$); within the intermediate risk group (FRS 10–20%), OR = 4.35 (95% CI 1.60–11.84, $p = 0.004$); and within the high risk group (FRS > 20%), OR = 10.00 (95% CI 1.21–82.51, $p = 0.032$). After adjustment of these within-risk strata analyses for education, income, and paternal and maternal histories of CVD, these estimates were: low risk

Table 2. Odds ratios for severe infection in early life.

Infection experienced in early life	OR (95% CI)	*p*
Crude	2.67 (1.47–4.83)	0.001
Model 1	2.67 (1.39–5.10)	0.003
Model 2	2.57 (1.41–4.69)	0.002
Model 3	2.73 (1.50–4.98)	0.001
Model 4	3.88 (1.29–11.68)	0.016

Univariable and multivariable analyses were performed by conditional logistic regression for matched data.
Model 1 was adjusted for lifestyle and diet factors (current smoking, sedentary life, consumption of fatty food, salty food and monosodium glutamate, fried food and less fibre). Model 2 was adjusted for socio-economic status (monthly income and college education). Model 3 was adjusted for history of mother with cardiovascular disease at age < 65 years and father with cardiovascular disease at age < 55 years, history of parents with diabetes mellitus, maternal and paternal history of premature sudden cardiac death (at age < 60 years). Model 4 was adjusted for traditional risk factors (hypertension, raised fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and obesity).

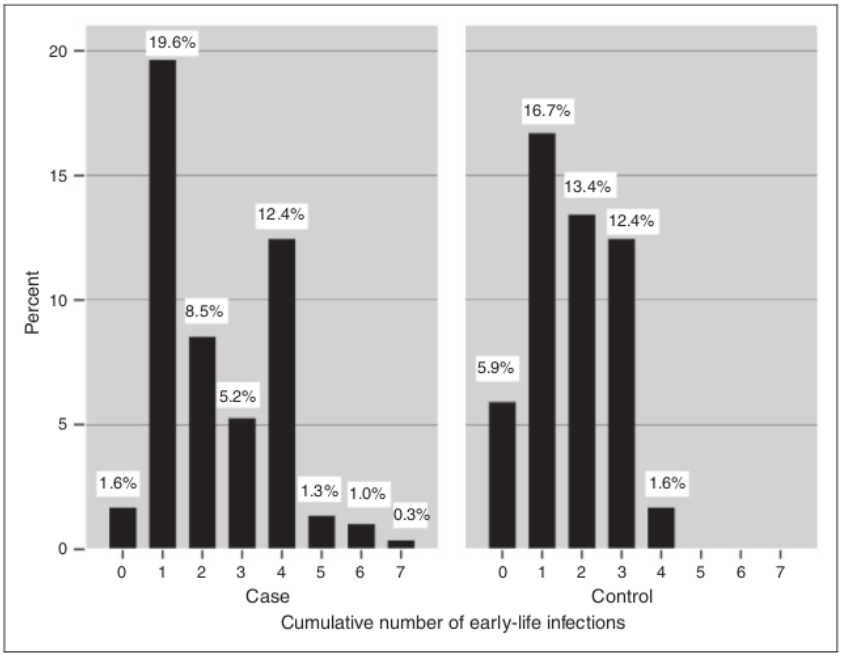

Figure 1. Number of overall infections during childhood and adulthood between cases and controls. Infectious diseases included in the score (the continuous score of overall infections based on the summation of each positive infectious disease, regardless of the severity; minimum = 0, maximum = 18) were: typhoid fever, measles, varicella (chickenpox), bronchitis, tuberculosis, pertussis, tonsillitis, acute upper respiratory tract infection, malaria, dengue fever, gastrointestinal infection (diarrhoea), febrile convulsions, hepatitis A, meningitis, dermatitis, oral infection, conjunctivitis and unknown fever ≥ 3 days.

(FRS < 10%), OR = 1.50 (95% CI 0.72–3.12, $p = 0.282$); intermediate risk (FRS 10–20%), OR = 5.29 (95% CI 1.79–15.62, $p = 0.003$); and high risk (FRS > 20%), OR = 12.58 (95% CI 1.18–134.31, $p = 0.036$).

Discussion

This study found that infection experienced during childhood and adolescence was associated with the higher occurrence of premature ACS later in life. There was an indication that this association became stronger with increasing levels of CVD risks.

To our knowledge, we are the first to report the relationship between early life infection and ACS at a young age in South-East Asians. We took some measures to ensure that our case-control findings could be validly interpreted as an incidence rate ratio from a cohort study. As an important part of our study

Table 3. Unadjusted and adjusted odds ratios for overall infection in early life.

Time period	Crude OR (95% CI)	p	Model 1 (95% CI)	p	Model 2 (95% CI)	p
Early childhood (0–5 years)	2.56 (1.66–3.96)	<0.001	2.68 (1.66–3.96)	<0.001	3.67 (1.87–7.22)	<0.001
Total period (0–21years)	1.42 (1.17–1.71)	<0.001	1.44 (1.15–1.79)	0.001	1.64 (1.21–2.23)	0.002

Univariable and multivariable analyses were performed by conditional logistic regression for matched data using the cumulative number of infectious episodes of each participant during childhood and adolescence.
CI: confidence interval; OR: odds ratio.
Model 1 was adjusted for history of mother and father with cardiovascular disease, socio-economic status (monthly income and college education), lifestyle and risk factors (current smoking, sedentary life, consumption of salty food and monosodium glutamate and less fibre). Model 2 was adjusted for traditional risk factors (hypertension, diabetes mellitus, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and obesity).

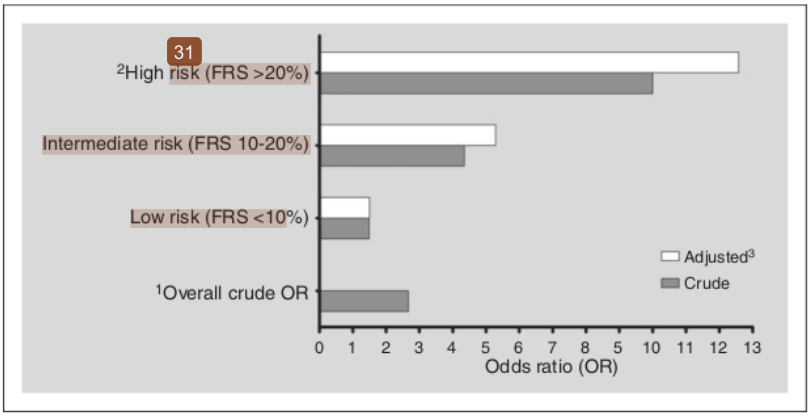

Figure 2. Odds ratios for early life infection (for acquiring premature ACS) among Framingham Risk Score classification groups.
[1]Univariable analysis was performed by conditional logistic regression to obtain the overall crude odds ratio (OR).
[2]Multivariable analyses were performed by logistic regression separately within the Framingham Risk Score (FRS) classification groups: low risk (FRS < 10%), intermediate risk (FRS 10–20%) and high risk (FRS > 20%).
[3]Models were adjusted for socio-economic status (formal education and monthly income) and family (maternal and paternal) histories of cardiovascular diseases.

design, we enrolled newly diagnosed patients or incident cases during the study period. One advantage of this is that the recall of past events in personal histories may be more accurate among new cases[31] and they are less likely to have changed their habits or exposures beneficial to acquiring the disease. Our method of randomly selecting age- and sex-matched controls from the residential neighbourhoods of the cases ensured that the controls came from the same source as the cases. To assure sampling from equal incidence-densities in cases and controls, we sampled controls every time the cases occurred.

There is consistent evidence that inflammation plays a substantial part in the pathogenesis of atherosclerosis.[6,32] It is increasingly recognized that both chronic low-grade inflammation[20] and bacterial and viral infections are associated with an increased risk of CVD.[33–35] There are a number of possible, non-exclusive mechanisms by which infection may act to potentiate the development of atherosclerosis. Individual or – more plausibly – multiple infectious agents may result in a local or systemic inflammatory response[11,32] or elicit an injury to the vascular endothelium that affects both the arterial structure and function.[10] Pessi et al.[36] identified bacterial material from coronary arteries and thrombus aspirates, whereas Ott et al.[37] demonstrated the presence of widely varied bacterial DNA in atherosclerotic coronary plaques.

Infection may also potentiate traditional risk factors such as dyslipidaemia. Liuba[19] reported that acute infections in young children were accompanied by increased oxidized low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol and followed by carotid intima-media thickening. Notably in young people, these changes might accumulate over time and increase the vulnerability of vessels to early atherosclerosis.

Most studies on infections and CVD have been carried out in adults, whereas atherosclerosis begins to develop in early life.[4–10] Research has shown that severe childhood infection is independently associated with hospitalization for CVD,[38] subclinical atherosclerosis[17] and adverse metabolic profiles in adulthood.[39]

Our findings are in line with the most recent Cardiovascular Risk in Young Finns Study[17] and the SAPALDIA Youth Study,[9] which provided further evidence of the association between childhood infections and adult atherosclerosis. Although Burgner et al.[17] used records of admission to hospital as a measure of the more severe infections in the first five years of life, we collected the history of various infectious diseases regardless of severity over childhood and adolescence, an approach also used in the SAPALDIA Youth Study.[9] The SAPALDIA childhood infection score summarized the cumulative number of specific types of infections, although the precise age of onset was not given.[9] In our study, we used age categories based on school years to facilitate parental and participant recall of infections. We primarily analysed severe and systemic infections with a history of fever ≥ 3 days or that resulted in admission to hospital, on the assumption that these reflected a more severe inflammatory response and were more likely to be recalled by families.

The observed association between early life infections and early atherosclerotic CVD could be of major importance for future prevention strategies to reduce the CVD burden. This may be especially relevant in South-East Asia, where infectious diseases continue to be highly prevalent among a young and rapidly increasing population.[40] Therefore we consider our findings to be an aetiologically important signal that early life infections could play a part in the high incidence of premature coronary heart disease in South-East Asia.

Numerous studies have suggested that infection in childhood may affect the vasculature.[9,16–19,38] The precise mechanisms by which infection, alone or in combination with traditional risk factors, may contribute to atherosclerosis remains unclear.[10] We assessed whether early life infection modified the effect of traditional CVD risk factors by applying the FRS to our study group. FRS measures the absolute CVD risk burden continuously and therefore provides a more precise and accurate score. Instead of estimating the 10-year risk of developing CHD in each individual participant, we used the FRS to rank all participants based on their traditional risks burden. We classified them as low, intermediate and high risk classes. From the analyses, we then attained appreciable differences in the ORs of early life infection between the low, intermediate and high risk classes.

Limitations

This study has some potential limitations. First, as a result of the unavailability of registry data on infection-related admission to hospital and exposure to antibiotics, we relied on participant and parental recall of infection. Therefore the possibility of recall bias and differential recall of past infections as a result of current disease status is acknowledged. To minimize recall bias, we verified the infection data from the cases and controls with first-degree family members. In addition, questionnaires about early life exposures collected other data unrelated to infection and the participants were not aware of the main research question. Second, the lack of specificity of infections observed in this study limited the conclusions that can be drawn regarding potential mechanisms that may act in the inflammatory process; however, no consensus exists on which infectious diseases are most relevant for CVD. Third, the absence of serological data limited our ability to validate the exposure to specific infectious agents, although this approach has inherent limitations as it is not informative about clinical symptoms or severity.[21] Fourth, we excluded fatal cases of ACS, which may introduce a bias in the assessment of the association between early life infection and premature ACS if the association differed with CVD mortality. However, we speculate that the association is more likely to be stronger in patients with ACS who died (as they may have had more severe CVD) and therefore the strength of the association may be underestimated.

Conclusion

This study confirms that infection experienced in early life is associated with early coronary heart disease in adulthood and may potentiate the effects of traditional CVD risk factors.

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References

1. World Health Organization. Cardiovascular diseases (CVDs), http://www.who.int/research/en/ (2015, accessed 25 March 2015).
2. Hong Y. Burden of cardiovascular disease in Asia: big challenges and ample opportunities for action and making a difference. *Clinchem* 2009; 55: 1450–1452.
3. World Health Organization (WHO). *The global burden of disease: 2004 update*. Geneva: WHO, 2004.
4. Skilton MR, Evans N, Griffiths KA, et al. Aortic wall thickness in newborns with intrauterine growth restriction. *Lancet* 2005; 365: 1484–1486.
5. Sun C, Burgner DP, Ponsonby AL, et al. Effects of early-life environment and epigenetics on cardiovascular disease risk in children: highlighting the role of twin studies. *Pediatr Res* 2013; 73: 523–530.
6. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
7. Nakashima Y, Wight TN and Sueishi K. Early atherosclerosis in humans: role of diffuse intimal thickening and extracellular matrix proteoglycans. *Cardiovasc Res* 2008; 79: 14–23.
8. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* 1998; 338: 1650–1656.
9. Dratva J, Caviezel S, Schaffner E, et al. Infectious diseases are associated with carotid intima media thickness in adolescence. *Atherosclerosis* 2015; 243: 609–615.
10. Liuba P and Pesonen E. Infection and early atherosclerosis: does the evidence support causation? *Acta Paediatr* 2005; 94: 643–651.
11. Rosenfeld ME and Campbell LA. Pathogens and atherosclerosis: update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. *Thromb Haemost* 2011; 106: 858–867.
12. Laitinen TT, Pahkala K, Venn A, et al. Childhood lifestyle and clinical determinants of adult ideal cardiovascular health: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Princeton Follow-Up Study. *Int J Cardiol* 2013; 169: 126–132.
13. Berenson GS. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease: The Bogalusa Heart Study. *Am J Cardiol* 2002; 90(Suppl.): 3L–7L.
14. Geerts CC, Evelein AM, Bots ML, et al. Body fat distribution and early arterial changes in healthy 5-year-old children. *Ann Med* 2012; 44: 350–359.
15. Huang RC, Burke V, Newnham JP, et al. Perinatal and childhood origins of cardiovascular disease. *Int J Obes* 2007; 31: 236–244.
16. Charakida M, Donald AE, Terese M, et al. Endothelial dysfunction in childhood infection. *Circulation* 2005; 111: 1660–1665.
17. Burgner DP, Sabin MA, Magnussen CG, et al. Early childhood hospitalisation with infection and subclinical atherosclerosis in adulthood: the Cardiovascular Risk in Young Finns Study. *Atherosclerosis* 2015; 239: 496–502.
18. Pesonen E, Paakkari I and Rapola J. Infection-associated intimal thickening in the coronary arteries of children. *Atherosclerosis* 1999; 142: 425–429.
19. Liuba P. Acute infections in children are accompanied by oxidative modification of LDL and decrease of HDL cholesterol, and are followed by thickening of carotid intima–media. *Eur Heart J* 2003; 24: 515–521.
20. Evelein AM, Visseren FL, van der Ent CK, et al. Allergies are associated with arterial changes in young children. *Eur J Prev Cardiol* 2015; 22: 1480–1487.
21. Burgner D, Liu R, Wake M, et al. Do childhood infections contribute to adult cardiometabolic diseases? *Pediatr Infect Dis J* 2015; 34: 1253–1255.
22. Kumar A and Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin* 2009; 84: 917–938.
23. Grech ED and Ramsdale DR. Acute coronary syndrome: unstable angina and non-ST segment elevation myocardial infarction. *BMJ* 2003; 326: 1259–1261.
24. Pieper KS, Gore JM, FitzGerald G, et al. Validity of a risk-prediction tool for hospital mortality: the Global Registry of Acute Coronary Events. *Am Heart J* 2009; 157: 1097–1105.
25. Tang EW, Wong CK and Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *Am Heart J* 2007; 153: 29–35.
26. Mulders TA, Meyer Z, van der Donk C, et al. Patients with premature cardiovascular disease and a positive family history for cardiovascular disease are prone to recurrent events. *Int J Cardiol* 2011; 153: 64–67.
27. Lloyd-Jones DM, Nam B, D'Agostino RB, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004; 291: 2204–2211.
28. Nasir K, Budoff MJ, Wong ND, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007; 116: 619–626.
29. Ranthe MF, Carstensen L, Oyen N, et al. Family history of premature death and risk of early onset cardiovascular disease. *J Am Coll Cardiol* 2012; 60: 814–821.
30. Bosomworth NJ. Practical use of the Framingham risk score in primary prevention. *Can Fam Physician* 2011; 57: 417–423.
31. Grobbee DE and Hoes AW. Case-control studies. In. *Clinical epidemiology – principles, methods, and applications for clinical research*. Burlington, MA: Jones and Bartlett, 2009, pp. 226–269.

32. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on progression of carotid atherosclerosis. *Stroke* 2002; 33: 2581–2586.
33. Zhu J, Nieto FJ and Horne BD. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation* 2001; 103: 45–51.
34. Maniar A, Ellis C, Asmuth D, et al. HIV infection and atherosclerosis: evaluating the drivers of inflammation. *Eur J Prev Cardiol* 2013; 20: 720–728.
35. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. *Circulation* 2001; 103: 1064–1070.
36. Pessi T, Karhunen V, Karjalainen PP, et al. Bacterial signatures in thrombus aspirates of patients with myocardial infarction. *Circulation* 2013; 127: 1219–1228.
37. Ott SJ, El Mokhtari NE, Musfeldt M, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. *Circulation* 2006; 113: 929–937.
38. Burgner DP, Cooper MN, Moore HC, et al. Childhood hospitalisation with infection and cardiovascular disease in early-mid adulthood: a longitudinal population-based study. *PLoS One* 2015; 10: e0125342.
39. Burgner DP, Sabin MA, Magnussen CG, et al. Infection-related hospitalisation in childhood and adult metabolic outcomes. *Pediatrics* 2015; 136: e554–e562.
40. World Health Organization (WHO). *Health situation in the south-east region 2001–2007*. New Delhi: WHO Regional Office for South-East Asia, 2008.

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Publication

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