RACP Foundation Research Awards

FINAL REPORT

Project Title	A mechanistic investigation of the adverse effects of acute childhood infections on cardiovascular risk: The VASCFIND study
Name	Prof David Burgner
Award Received	2017 Career Development Fellowship Award
Report Date	1 March 2018
Chief Investigator / Supervisor	Prof David Burgner
Administering Institution	Murdoch Children's Research Institute
Funding Period — Start Date:	1 January 2017
Funding Period — Finish Date:	31 December 2017

PROJECT SUMMARY

Cardiovascular disease (CVD, heart attack, stroke and heart failure) is a leading cause of death and illness in Australia and globally. CVD kills an Australian every 12 minutes and is the most expensive disease group. The underlying cause of CVD, atherosclerosis (hardening of the arteries) is a process that starts in childhood, a period that is largely overlooked in terms of prevention.

Atherosclerosis is a chronic inflammatory condition. There is good evidence that infection, which is common in childhood and causes inflammation, is associated with CVD, but the mechanisms are poorly understood.

The VASCFIND (Vascular Changes Following Infectious Diseases) study aims to fill this knowledge gap and is the first study of its kind. We are recruiting children with well-characterised and common infections that are severe enough to present to a children's hospital and measuring their vascular health at 2 weeks, 2 months and 6 months later, as well as collecting blood and other samples.

Our goal is to characterise how infections affect the cardiovascular system, which types of infection have the worst effects and whether the effects persist. The findings are of both scientific and clinical interest; ultimately we would like to intervene to reduce any adverse effects of infection on later cardiovascular health.

PROJECT AIMS / OBJECTIVES

OVERALL AIM:

To prospectively investigate markers indicative of early atherosclerosis and inflammation, following well-defined, acute childhood infections.

SPECIFIC AIMS AND HYPOTHESES:

Aim 1: To investigate CV intermediate risk phenotypes at defined time points in children following acute severe bacterial or viral infection

Hypothesis 1: All infections will be associated with subsequent adverse CV risk phenotypes (increased aorta and carotid artery intima-media thickness [aIMT and cIMT]), decreased arterial distensibility, increased pulse-wave velocity [PWV] and blood pressure [BP]). The most significant and pervasive effects will follow Gram negative bacterial infections, which are more proinflammatory and are treated with antibiotics that particularly disrupt the microbiome.

Aim 2: To investigate cardiometabolic and inflammatory biomarkers at these defined time points.

Hypothesis 2: The greatest and most pervasive pro-atherogenic lipid profile and increased inflammation will follow Gram negative bacterial infections

We are currently meeting all these aims. Recruitment is steady and consistent. We have recruited ~60 participants with ~90% follow up to the third (6 month visit) and ~95% full sample collection at each time-point. We have excellent buy-in from relevant clinical departments at RCH (e.g. dentistry, emergency, general medicine and surgery), which is facilitating patient recruitment. Recruitment will be complete within the next 12-18 months. We have secured additional funding for research staff and other costs to complete the study. Recruitment is greatly facilitated by the recent introduction of EMR at RCH.

SIGNIFICANCE AND OUTCOMES

This is potentially transformative research. The study has provoked considerable positive interest during discussions with inter/national colleagues from diverse relevant fields, including adult cardiology. The findings will provide: (i) important new scientific knowledge regarding the mechanisms by which childhood infection affects CV risk phenotypes and key biomarkers; and (ii) a platform for translation, facilitating the development of biologically-based, simple and acceptable childhood interventions that can be targeted at those with greatest risk.

We are incorporating similar methodological approaches with granular infection-related data and cardiovascular phenotyping to a raft of cohort studies and also overseas (e.g. China, South Africa). VASCFIND data are a major component of our NHMRC CRE application in the 2018/9 funding round (CIA Burgner).

PUBLICATIONS / PRESENTATIONS

We are not able to undertake detailed analyses of the phenotypic or laboratory data until recruitment is fully complete. However CI Burgner continue to publish related papers and give invited presentations including:

Miller JE, Wu C, Pedersen LH, de Klerk N, Olsen J, Burgner DP Maternal antibiotic exposure during pregnancy and hospitalization with infection in offspring: a population-based cohort study. Int J Epidemiol. 2018 Apr 1;47(2):561-571.

Leentjens J, Bekkering S, Joosten LAB, Netea MG, Burgner DP, Riksen NP Trained Innate Immunity as a Novel Mechanism Linking Infection and the Development of Atherosclerosis. Circ Res. 2018 Mar 2;122(5):664-669.

Qanitha A, de Mol BAJM, Burgner DP, Kabo P, Pabittei DR, Yusuf I, Uiterwaal CSPM.Pregnancy-related conditions and premature coronary heart disease in adult offspring. Heart Asia. 2017 May 24;9(1):90-95.

Liu RS, Aiello AE, Mensah FK, Gasser CE, Rueb K, Cordell B, Juonala M, Wake M, Burgner DP Socioeconomic status in childhood and C reactive protein in adulthood: a systematic review and meta-analysis. J Epidemiol Community Health. 2017 Aug;71(8):817-826

Recent invited / selected presentations include:

University of British Columbia, Vancouver, Canada 2018

NZ Paediatric Society Meeting 2018

Liggins Institute 2018

ANZ DOHAD meeting 2018

ANZPID / ECDMID Perinatal infection meeting 2018