CHILDhood influences

Professor Malcolm Sears is working on elucidating the role and interplay of environmental and genetic risk factors in asthma and allergy. Here, he discusses his research interests and the Canadian Healthy Infant Longitudinal Development study which aims to elucidate childhood asthma and allergy

Firstly, could you provide a brief overview of your research interests?

My primary research interests are related to asthma, with particular focus on its development and natural history from childhood through to adulthood. I am involved in two longitudinal population-based cohort studies exploring risk factors for the development of asthma and potential for reduction of morbidity and even prevention. A parallel research interest is in optimum management of asthma.
I have been involved in the investigation of epidemics of asthma mortality which then led to studies of deleterious effects of short-acting beta-agonists. I am also involved in the debate over the safety of long-acting beta-agonists in asthma.

From what context did the Canadian Healthy Infant Longitudinal Development (CHILD) study evolve?

The CHILD study evolved from a confluence of interests. Firstly, in preparing data from the Dunedin Multidisciplinary Health and Development Research study, we identified, in those destined to have persistent asthma, a significant loss of lung function that had clearly occurred in early childhood before we first made measurements on nine year olds. Researchers here at McMaster University suggested a new study in collaboration with colleagues at the University of Toronto to assess development of infant lung function in relation to childhood asthma.

Secondly, I was involved in the early planning of what eventually became the Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence, a consortium of allergy-related researchers across Canada led by Dr Judah Denburg. We built the concept of a longitudinal birth cohort study into the infrastructure of the AllerGen Network.

Thirdly, there was increasing interest from Health Canada in environmental impacts on health, particularly in children, and advocacy to the Canadian Institutes of Health Research (CIHR) for the funding of a birth cohort study specifically looking at environmental and gene-environment effects in childhood asthma. CIHR partnered with AllerGen to support this initiative, each contributing CAD $6 million over six years, leading to an announcement of the Request for Application (RFA) entitled 'Indoor air exposures, genes and gene-environment interactions in the etiology of asthma and allergy in early childhood'. In collaboration with AllerGen, I put together a consortium of investigators from across Canada to respond to this RFA with an application which was internationally peer-reviewed and recommended for funding. To avoid selective recruitment of high-risk individuals, we wanted to avoid 'asthma' and 'allergy' in the name of the birth cohort, and emphasise its national nature; hence, the words 'Canadian' and 'healthy infant' which together with 'longitudinal development' become CHILD.

Which environmental determinants most affect the development of asthma?

To date, the major focus of our environmental determinants work has related to exposure to allergens, particularly house dust mite and

cats together with dampness, mould and air pollutants, particularly traffic-related air pollution. Environmental tobacco smoke exposure in early infancy and even *in utero* is now well-recognised as increasing the risk of childhood asthma.

Why did you decide to terminate recruitment after enrolling 3,600 families?

Recruitment was terminated after three years on the basis of prudent allocation of limited resources. Continuing recruitment was draining funding substantially, and with 3,600 families recruited we decided to focus our resources on maintaining in-depth follow up.

What have been the major strengths of this study?

The major strengths of the study are the multidisciplinary team, the excellent staff commitment to recruitment and following so many individuals with in-depth assessments and, finally, use of the latest technologies including infant pulmonary function testing. This is currently only performed in a few centres around the world, but one of them is the Hospital for Sick Children in Toronto. The increasing availability of sophisticated genetics and genomics techniques will provide new insights into the role of genetics in this gene-environment study. Other strengths include the development of novel dust retrieval systems eliminating potential contamination of dust by equipment-borne endotoxin, and spinoff effects of a study platform which allows the development of many other investigations within the realms of allergy, environmental assessments, and nutritional and physiological relationships with asthma.

Who will have access to the study's results?

In the first instance, the researchers primarily involved and invested in the study will access the data to test hypotheses and publish results, but in the long term we anticipate the results of this study will be disseminated widely.

Risk factors in asthma and allergy

A collaboration between the **Canadian Institutes of Health Research** and the **Allergy, Genes and Environment Network of Centres of Excellence** has provided a novel platform for future insights into complex diseases with multiple risk factors

ASTHMA AND ALLERGY are significant causes of morbidity and mortality, affecting one in three people in their lifetime: a rate on a par with diabetes, cancer and heart disease. In Canada alone, these conditions result in over 200 deaths each year. Asthma is the most common chronic disease amongst children and the rates of asthma and allergy diagnoses have increased substantially over recent decades.

Despite their prevalence, the causes of atopy – an immediate allergic reaction – and asthma are largely unknown. Indeed, a variety of environmental and genetic factors contributing in concert are thought to be involved, each triggering diverse effects depending on the developmental time period. Even genetic factors are elusive, and relatively little is understood about how genes contribute to asthma and allergy pathology.

In addition, there is a dearth of detailed information regarding illness progression in relation to potential risk factors. Longitudinal data of this kind could provide insights into development of illness, paving the way for better treatments, diagnosis, preventative strategies, and eventually lead to a significant reduction in the number of people developing asthma or allergies. This would not only improve the quality of life of those affected and prevent untimely deaths, but it would save millions of dollars on visits to the emergency department alone.

CHILD

Professor Malcolm Sears at McMaster University is working to understand this problem, acquiring novel datasets of the required depth and complexity necessary to investigate the impact of genetic and environmental factors in relation to the expression of asthma and allergies. This work is supported by the Canadian Institutes of Health Research (CIHR) in partnership with the Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence (NCE) and was allocated an inital budget of CAD $12 million.

Sears' initiative, called the Canadian Healthy Infant Longitudinal Development (CHILD) study, aims to simultaneously record relevant biological, environmental and clinical data regarding possible risk factors that contribute to asthma and allergic reactions. CHILD aims to improve our understanding of the complex interrelationships between genetic and environmental factors involved in the development of allergy and asthma through a combination of expertise in epidemiology, paediatrics, immunology, infant pulmonary function, genetics, epigenetics, nutrition, and psychosocial and environmental sciences.

Over 25 genes have been consistently identified to be associated with atopy and asthma development, and numerous environmental exposures require investigation. Relatively little is known in terms of how they interact or contribute to pathology. It is hoped that CHILD will help uncover hidden relationships between these factors by enabling analysis of different risk factor combinations in relation to detailed clinical information. The number of possible combinations to be tested is substantial, and the datasets will serve as a long-term resource for multiple hypotheses to be studied.

In addition, the data will also be used in the analysis of other chronic noncommunicable diseases potentially established during early life, including diabetes, obesity, hypertension and cardiovascular disease. CHILD is a longitudinal study, which means that information is collected across multiple time points: a necessity since risk factors may affect atopy and asthma differently depending on the stage of growth and development.

THE DATA

Sears' team has completed recruitment of an ethnically, environmentally, culturally and socioeconomically diverse sample of over 3,600 families from the general Canadian population in Vancouver, Edmonton, Manitoba and Toronto. Most mothers are in their second trimester at the time of recruitment, and are monitored throughout the remainder of pregnancy. Their children are clinically assessed at three months, and at ages one, three and five. An impressive range of biological samples are collected at varying time points, including genetic material of both parents and child, cord blood, breast milk, meconium, viral swabs, urine and stool samples and infant peripheral blood. To date, over 300,000 aliquots of biological samples have been stored for future analyses and successful acquisition of multiple biological samples in infancy exceeds 90 per cent.

Environmental factors are assessed through repeated questionnaires completed by the mother during pregnancy up until her child reaches five years of age. Data on pre- and postnatal nutrition, health status and medication are also collected in this way. The home environment is assessed by the researchers three months after birth, where they collect dust to measure levels of common allergens, endotoxin

CANADIAN HEALTHY INFANT LONGITUDINAL DEVELOPMENT (CHILD) STUDY

OBJECTIVES

To better understand key relationships and interactions among the many genetic determinants and environmental exposures associated with the development of asthma and allergies, and to use this understanding to reduce or even prevent these conditions and improve their management.

KEY COLLABORATORS

McMaster University, Canada: **Sonia Anand**; **Judah Denburg**; **Joseph Macri** • Hospital for Sick Children, Toronto, Canada: **Padmaja Subbarao** co-Principal Investigator (co-PI) and site leader; **Felix Ratjen**; **Sanja Stanojevic**; **Theo Moraes** • University of Manitoba, Canada: **Allan Becker**, co-PI and site leader; **Kent HayGlass** • University of Alberta, Canada: **Piush Mandhane**, co-PI and site leader; **Anita Kozyrskyj**; **Dean Befus** • University of British Columbia, Canada: **Stuart Turvey**, co-PI and site leader; **Andrew Sandford**; **Michael Brauer**; **Michael Kobor**; **Tobias Kollmann** • Northwestern University, USA: **Gregory Miller** • Simon Fraser University, Canada: **Timothy Takaro** • Environment Canada: **Jeffrey Brook** • University of Toronto, Canada: **James Scott**; **Richard Hegele**; **Wendy Lou** • University of Waterloo, Canada: **Susan Elliott** • Université du Québec à Chicoutimi, Canada: **Catherine Laprise**

FUNDING

Canadian Institutes of Health Research

AllerGen Network of Centres of Excellence

CONTACT

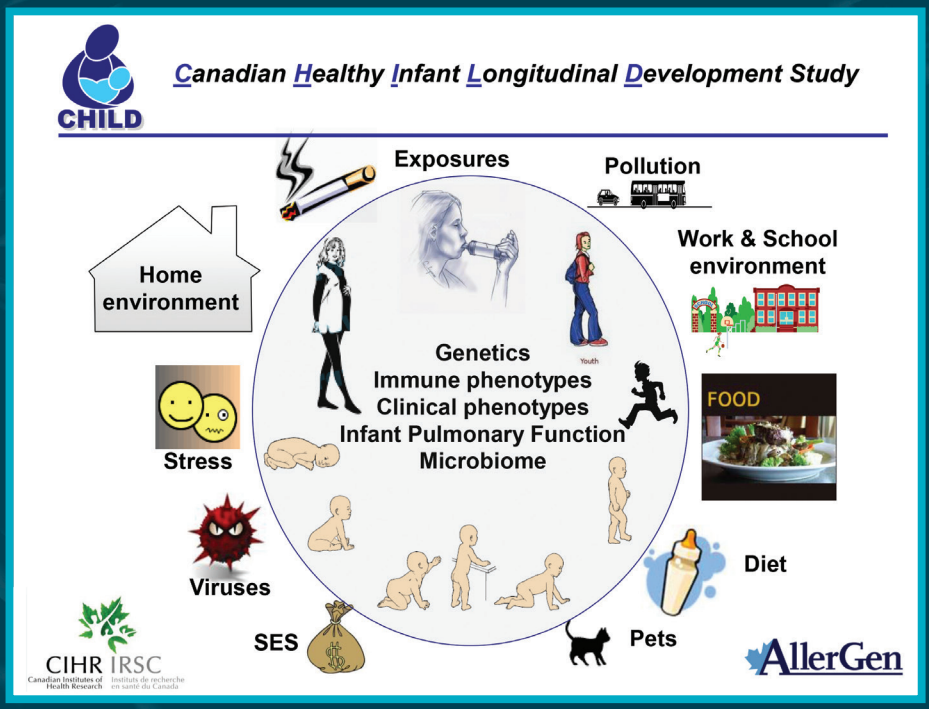
Professor Malcolm Sears
Astra Zeneca Chair in Respiratory Epidemiology

Division of Respirology, Department of Medicine
St Joseph's Healthcare
McMaster University
50 Charlton Avenue East
Hamilton, Ontario L8N 4A6, Canada

T +1 905 522 1155 x 33286
E searsm@mcmaster.ca

www.fhs.mcmaster.ca/medicine/respirology

DR MALCOLM SEARS graduated from the University of Otago, Dunedin, New Zealand, progressing to faculty. He later took on the roles of Director of the Firestone Regional Chest and Allergy Unit, Director of Respiratory Medicine at St Joseph's Healthcare and Professor in the Department of Medicine at McMaster University in Canada. He has published over 200 peer-reviewed papers and book chapters, together with numerous abstracts. He lectures frequently at national and international scientific meetings, and serves on many asthma advisory boards. Sears became the first holder of an endowed AstraZeneca Chair in Respiratory Epidemiology at McMaster University.



Schematic of the multiple areas of investigation in the CHILD study and the sequential time points for assessments from pregnancy to age five years.

and ß-glucan. Anthropometric measures, pulmonary function and viral infections are also recorded.

Data regarding illness onset and progression are logged by objective assessment in conjunction with further questionnaires. Genetics, allergy skin testing and spirometry are used to identify and characterise food allergy, atopic dermatitis, recurrent wheezing and asthma. Lung physiology is also assessed using a multiple breath washout protocol and spirometry.

> CHILD is a powerful tool that will influence understandings of complex illnesses

RESULTS SO FAR

Since data are still being obtained, there are no definitive results as of yet; however, preliminary findings are already sufficiently diverse to reach the desired statistical power to achieve the goal of the study and facilitate multiple analyses. For example, mould was present in 40 per cent of homes examined. Urine analyses indicated exposure to phthalate attributable to household substances. By one year, more than 10 per cent of children had experienced recurrent wheezing; 16 per cent had positive skin allergy tests; 14 per cent had atopic dermatitis; and 6 per cent reported a food allergy. The breadth of information available will facilitate the study of a wide range of hypotheses.

WIDER IMPLICATIONS

Once the required amount of data has been collected, Sears and his colleagues aim to investigate multiple hypotheses. It is also expected that CHILD will trigger a multitude of future projects that build upon these data. Many hypotheses have already been put forward that take advantage of the abundance of immunological, physiological and genetic data accumulated by this study. These projects will cover diverse subjects including the effects of immunity, nutrition, psychosocial environment and epigenetics on asthma and allergy development. The data will also shed light on other chronic childhood illnesses.

CHILD is a powerful tool that will influence understandings of complex illnesses, and aid the discovery of new therapeutic and preventative strategies. Looking to the future, it will also help to train the next generation of scientists, through mentoring young investigators, providing rich datasets and biological samples that will facilitate multiple analyses and publications, and nurturing their research interests in allergy and asthma.