PHYSICAL ACTIVITY AND ASTHMA IN YOUTH: CAUSE OR CONSEQUENCE?

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Dedication

Submitted on her birthday, this thesis is dedicated to my darling *Poisson.*

Abstract

Asthma is the most common chronic disease in children, and often persists into and adulthood. Further, despite its known health benefits, it is estimated that more than 80% of the world's adolescents are insufficiently physically active. Since both asthma and physical inactivity are significant problems in child and adolescent populations, it is essential to focus research on these populations. The relationship between asthma and physical activity is complex and controversial, and the temporality of these associations remains unclear. My doctoral work attempted to tease out these relationships.

This work was divided into sections with distinct research questions, which together aimed to advance our current understanding of the relationship between asthma and physical activity in children and adolescents. Hence, this thesis contains two systematic reviews which were performed in order to understand the existing literature on the nature of the relationship between physical activity and asthma in children. These reviews are followed by three data analyses which employed a variety of statistical techniques to analyse data from questionnaires, accelerometry and clinical assessments collected by two well-established cohorts of Australian children: The Longitudinal Study of Australian Children (LSAC) and the HealthNuts study.

The first of the two systematic reviews found no evidence that children and adolescents with and without asthma participated in different amounts of objectively measured physical activity. The second review, which aimed to investigate the effect of physical activity on subsequent asthma outcomes, found insufficient evidence to determine the effect of physical activity on subsequent asthma and lung function outcomes. Hence, in the first data analysis, I aimed to elucidate the direction of the association by investigating the possibility of bidirectionality. However, there was no evidence of longitudinal associations in either direction. Next, I compared the amount of time spent in moderate to vigorous physical activity (MVPA) between children and adolescents with and without asthma at 5 different ages and again found no evidence that youth with and without asthma engaged in differential amounts of time in physical activity. Finally, I

investigated the effect of early wheeze and asthma on objectively measured physical activity in early childhood and again found no evidence that children who experience early life asthma and wheeze were less active at a later age.

Thus, my thesis presents sustained and compelling evidence of a lack of association between asthma and physical activity in youth – in either direction. A number of implications can be drawn from these findings. First, physical activity campaigns targeted at children need not focus specifically on children with asthma. Second, the effect of physical activity on future asthma outcomes remains unclear. However, even without evidence that physical activity is beneficial for future asthma outcomes, physical activity should be encouraged from a young age for its many other health benefits.

Declaration

This is to certify that:

I. the thesis comprises only my original work towards the PhD

II. due acknowledgement has been made in the text to all other materials used

III. the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies, and appendices.

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Candidate's signature

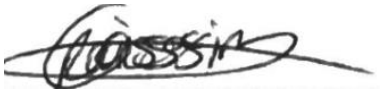
Raisa Cassim

Preface

My thesis contains five first author publications as thesis chapters. I additionally co-authored five publications whilst undertaking this PhD. Although these publications do not contribute to this thesis, they have been listed together with the first author publications which constitute thesis chapters presented below on page vii. I was invited to co-author these publications due to my knowledge and experience in undertaking systematic reviews and the specific data analyses they contained.

The first author publications were produced in collaboration with my supervisors and other researchers, whose valued contributions are duly noted. My supervisors were based at the University of Melbourne and the Murdoch Childrens' Research Institute, where I was also enrolled as a Doctoral Candidate and undertook research for this PhD thesis. For each publication, I lead the development of the paper, performed the literature searches, undertook the statistical analyses, and wrote and edited each draft. The listed co-authors aided with attaining data, analytical design and interpretation of results. Each listed co-author also provided feedback on the manuscripts prior to submission to the respective journals. In accordance with University guidelines, authorisation forms from each co-author of published manuscripts, and a declaration of collaborative work from my principal supervisor is provided. My PhD funding details are also listed below on page xi.

This thesis does not contain any material which has been accepted for the award of any other qualification in my name at any university or other tertiary institution. To the best of my knowledge, the thesis contains no material previously published or written by another person except where duly cited. All work presented in this thesis was conducted within the period of enrolment as a higher degree research student. Third party editorial assistance was not utilised in the preparation of this thesis.



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Candidate's signature

Raisa Cassim

Acknowledgments

It was an absolute privilege to have been offered the opportunity to undertake this PhD under the nurturing supervision of four exceptional and inspirational scientists. First, I would like to express my extreme gratitude to my primary supervisor Dr Melissa Russell for her patience, understanding, encouragement and support. I would also like to thank each of my co-authors: Professor Shyamali Dharmage who took the time to guide, encourage and mentor me, and who has given me the opportunity to develop my career by employing me as a research fellow to continue my work in this field; Dr Elasma Milanzi for her statistical advice, assistance and encouragement; Dr Jennifer Koplin for bridging the distance between The University of Melbourne and the Murdoch Childrens Research Institute. Each of my supervisors are experts in their respective fields, and I am grateful for the opportunity to have had their contributions and unwavering support throughout the duration of my candidature. Despite their busy schedules, they were always available to provide valuable feedback and advice at any hour of the day or night, and always warmly welcomed discussion. In addition, I would like to thank the Chair of my advisory panel, Professor Mark Jenkins, for his words of wisdom and support during the toughest times of my candidature.

I would also like to thank Dr Adrian Lowe, and the exceptional team of postgraduate students – past and present-, postdoctoral researchers and professional staff who constitute the Allergy and Lung Health Unit at the Melbourne School of Population and Global Health. It has been a pleasure to be part of this highly motivated and successful team, who were always helpful and informative.

Further, I extend my gratitude to Dr Francois Fraysse, Dr Dorothy Dumuid and Professor Tim Olds of the Alliance for Research in Exercise, Nutrition and Activity at the University of South Australia for their assistance with the accelerometry data processing and for their contribution to my final research paper. I would also like to thank Dr Dorothy Dumuid and Professor Tim Olds for their warm hospitality during my visits to Adelaide.

I would also like to acknowledge all the funders, investigators, researchers, staff, and participants of both the *Longitudinal Study of Australian Children* and *HealthNuts* studies. It is thanks to their continued hard work that these longitudinal studies endure, enabling research such as my own PhD. In addition, I would like to thank all the institutions who provided me with financial support: The National Health and Medical Research Council, the Murdoch Childrens Research Institute and The University of Melbourne's School of Population and Global Health.

On a personal note, I was fortunate to have had an excellent industry mentor in Kathryn Jowett during my candidature. In addition to assisting me in improving my employability skills, she has advised my career development and planning, while encouraging me through the PhD candidature. Although our formal mentoring arrangement ceased in 2018, Kathryn has continued to be an invaluable informal advisor and friend.

Lastly and most importantly, I would like to thank my wonderful family, without whom I would never have been able to complete this PhD. I am extremely grateful to my parents who have always inspired and encouraged me to achieve my goals, and always supported me in every way they could, without hesitation. I am also very appreciative of the unwavering support I received from my brother, my partner, and all of the friends who have accompanied me throughout this endeavour.

Publications, presentations, research supervision and grants

A list of publications, conference proceedings, seminars and grants produced during the course of this PhD is listed below:

First author peer-reviewed publications:

1. **Cassim R,** Koplin JJ, Dharmage SC, Senaratna BCV, Lodge CJ, Lowe AJ, Russell MA (2016) The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis. Journal of Asthma:00-00. doi:10.1080/02770903.2016.1175474

2. **Cassim R**, Dharmage SC, Koplin JJ, Milanzi E, Russell MA (2018) Suspected asthma status and time spent in physical activity across multiple childhood age groups. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 120 (2):219

3. **Cassim R**, Milanzi E, Koplin JJ, Dharmage SC, Russell MA (2018) Physical activity and asthma: cause or consequence? A bidirectional longitudinal analysis. Journal of epidemiology and community health: jech-2017-210287

4. **Cassim R**, Dharmage S, Koplin J, Milanzi E, Paro F, Russell M (2019) Does physical activity strengthen lungs and protect against asthma in childhood? A systematic review. Pediatric Allergy and Immunology

5. **Cassim R**, Dharmage SC, Peters RL, Koplin JJ, Allen KJ, LK Tang M, Lowe AJ, Olds TS, Fraysse F, Milanzi E, Russell MA (2020) Are young children with asthma more likely to be less physically active? Pediatric Allergy and Immunology

Co-authored peer-reviewed publications:

1. Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, **Cassim R**, Russell M, Burgess J, Hamilton GS, Dharmage SC (2017) Validity of the Berlin questionnaire in detecting obstructive sleep apnoea: A systematic review and meta-analysis. Sleep Medicine Reviews

2. Gasser CE, Mensah FK, Clifford SA, Kerr JA, **Cassim R**, Wake M (2018) Bidirectional associations between diet and body composition measures from 2–15 years: Longitudinal Study of Australian Children. British Journal of Nutrition:1-27

3. Wadhwa V, Lodge CJ, Dharmage SC, **Cassim R**, Slyx PD, Russell MA (2020) The association of early life viral respiratory illness and atopy on asthma in children: Systematic review and meta-analysis. The Journal of Allergy and Clinical Immunology: In Practice

4. Xu M, Lodge CJ, Lowe AJ, Dharmage SC, **Cassim R**, Tan D, Russell MA (2020) Are adults with asthma less physically active? A systematic review and meta-analysis. Journal of Asthma:1-18.

5. Bui DS, Faner R, Walters EH, Lodge CJ, Perret JL, Lowe AJ, Bowatte G, **Cassim R**, Hamilton GS, Frith P (2020) Can Circulating Biomarkers Identify Different FEV 1 Trajectories of COPD Patients? The Lancet Respiratory Medicine (accepted 04.08.2020)

Conference abstracts, symposia, and posters:

1. **Cassim R,** Milanzi E, Koplin JJ, Dharmage SC, Russell MA. Asthma and physical activity in childhood: Are they longitudinally related? Thoracic Society of Australia and New Zealand conference 2017, Canberra, Australia

2. **Cassim R,** Dharmage SC, Milanzi E, Fraysse F, Olds TS, Koplin JJ and Russell, MA on behalf of the HealthNuts investigators. Is asthma longitudinally related to physical activity in early childhood? Thoracic Society of Australia and New Zealand conference 2019, Gold Coast, Australia

3. **Cassim R**, Koplin JJ, Dharmage SC, Milanzi E, Olds TS, Fraysse F, and Russell MA on behalf of the HealthNuts investigators. Sex, BMI and the association between asthma and physical activity in childhood? Australasian Epidemiological Association conference 2019, Brisbane, Australia.

4. **Cassim R**, Dharmage SC, Milanzi E, Paro FM, Koplin JJ and Russell MA. Systematic review: Does physical activity improve lung function and prevent childhood asthma? Australasian Epidemiological Association conference 2019, Brisbane, Australia.

Presentations:

1. Oral presentation at the Allergy and Lung Health Unit "The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis" Melbourne, 14th October 2015.

2. Oral presentation at the Melbourne School of Population and Global Health Research Higher Degree conference: "The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis" Melbourne, 1st December 2015.

3. Oral presentation at the Allergy and Lung Health Unit: "Physical Activity and Asthma" Melbourne, 16th March 2016.

4. Confirmation oral presentation at the Melbourne School of Population and Global Health: "Physical Activity and Asthma: Cause or consequence?" Melbourne, 14th April 2016.

5. Oral presentation at the Allergy and Lung Health Unit: "Asthma and physical activity in childhood: Are they longitudinally related?" Melbourne, 14th March 2017.

6. Oral presentation at the Thoracic Society of Australia and New Zealand conference: "Asthma and physical activity in childhood: Are they longitudinally related?" Canberra, 27th March 2017.

7. Oral presentation at the Allergy and Lung Health Unit: "Predictors of Physical Activity in young children: an analysis of HealthNuts data" Melbourne, 23rd May 2018.

8. Oral presentation at the Allergy and Lung Health Unit: "Physical activity and asthma: cause or consequence?" Melbourne, 30th May 2019.

9. Poster presentation at the Thoracic Society of Australia and New Zealand conference: "Is asthma longitudinally related to physical activity in early childhood?" Gold Coast, 2nd April 2019.

10. Completion oral presentation at the Melbourne School of Population and Global Health: "Physical activity and asthma in youth: cause or consequence?" Melbourne, 18th July 2019.

Student supervision:

1. Supervised a Master of Public Health student for final year research project, The University of Melbourne (2018). Project title – "The Association between Levels of Physical Activity and Asthma Incidence: A Systematic Review and Meta-Analysis"

2. Supervised a Master of Public Health student for final year research project, The University of Melbourne (2016). Project title – "The difference in regular

physical activity performed by adults with and without asthma: A systematic review and meta-analysis"

Grants and Scholarships:

1. **Cassim R.** Murdoch Childrens Research Institute LifeCourse Scholarship (A$ 26,228 p/a), 2015-2016

2. **Cassim R.** Population Health Investing in Research Student Training (PHIRST) Grant (A$ 1,200), 2016

3. **Cassim R.** Australian Government National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (1133054) (A$ 36,173.75), 2016 – 2018

4. **Cassim R.** Melbourne Abroad Travelling Scholarship (MATS) (A$ 1,000), 2019

Abbreviations

ABS: Australian Bureau of Statistics

ACQ: Asthma Control Questionnaire

AIHW: Australian Institute of Health and Welfare

ATS: American Thoracic Society

aOR: adjusted Odds Ratio

BD: Bronchodilator

BMI: Body Mass Index

CAI: Computer-Assisted Interview

c-ACT: Childhood Asthma Control Test

CASI: Composite Asthma Severity Index

CI: Confidence Interval

CO: Carbon Monoxide

DAG: Directed Acyclic Graph

EIB: Exercise-Induced Bronchoconstriction

ERS: European Respiratory Society

FEV_1: Forced Expiratory Volume in 1 second

FEF: Forced Expiratory Flow

FVC: Forced Vital Capacity

GINA: Global Initiative for Asthma

GSEM: Generalised Structural Equational Modelling

HREC: Human Research Ethics Committee

ICS: Inhaled Corticosteroids

IPAQ: International Physical Activity Questionnaire

ISAAC: International Study of Asthma and Allergies in Childhood

LABA: Long-Acting Beta-Agonist

LRT: Likelihood Ratio Test

LSAC: *Growing Up in Australia*: Longitudinal Study of Australian Children

MAR: Missing At Random

MCAR: Missing Completely At Random

MCRI: Murdoch Childrens Research Institute

MET: Metabolic Equivalent

MNAR: Missing Not At Random

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

MVPA: Moderate to Vigorous Physical Activity

NACA: National Asthma Council of Australia

NAPLAN: National Assessment Program Literacy And Numeracy

NCD: Non-Communicable Disease

NHMRC: National Health and Medical Research Council

NO2: Nitrogen Dioxide

NSAID: Non-Steroidal Anti-Inflammatory Drug

PFT: Pulmonary Function Test

PM: Particulate Matter

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomised Controlled Trial

RTI: Respiratory Tract Infections

SABA: Short-Acting Beta-Agonist

SEIFA: Socio-Economic Indexes for Areas

SES: Socio-Economic Status

SO2: Sulphur Dioxide

TUD: Time Use Diary

UI: Uncertainty Interval

WHO: World Health Organization

Table of contents

List of tables

List of figures

CHAPTER EIGHT

CHAPTER ONE: Introduction

1.1 Overall aim of this research

The overall aim of this doctoral work was to investigate the *existence* and *direction* of the association between habitual physical activity and asthma development and persistence in youth (children and adolescents up to the age of 18 years). In a series of projects, this body of research collated evidence on the association between asthma and physical activity, and then attempted to establish whether asthma or physical activity was a causal antecedent of the other by analysing data from two longitudinal cohorts of Australian children.

1.2 Rationale for PhD

In recent years, an increase in the global prevalence of asthma (1) has been accompanied by a decrease in levels of physical activity (2). This observation has piqued the interest of researchers and led to escalating investigation of the relationship between these two important public health problems. To date, research has produced contentious and contradictory evidence for an association between asthma and physical activity, and the direction and temporality of the relationship between asthma and physical activity remain to be elucidated (3). Some studies have demonstrated the effect of physical activity on the development of asthma (2, 4) and, conversely, others have investigated the effect of asthma status on physical activity (5-14). These existing studies were heterogeneous in design, population, and size, and are limited by the lack of scientific consensus regarding the definition, measurement and classification of both asthma and physical activity.

Adding to the ambiguity that surrounds the relationship between asthma and physical activity are several other factors whose influence may confound, modify, or mediate the association. For example, sex may be an effect modifier, and socio-economic status a potential confounder of these associations. In addition, body mass index (BMI) may play an important role, as its effects have been investigated on both physical activity and asthma individually. However, these variables are

underrepresented in models, resulting in an inability to gain an appreciable understanding of the role that each one plays in the relationship between physical activity and asthma. The interconnectedness of these factors requires a more holistic investigation into the associations and confounding or modifying factors. To do so, longitudinal investigations are essential, but are scarce in the existing literature, particularly among child and adolescent populations.

While numerous studies have explored relationship between physical activity and asthma in adults (15), it is essential that these associations are investigated at the important developmental stages of childhood and adolescence, since there is evidence within the scientific literature that lifestyle and habits developed in youth persist into adulthood (16). It is hypothesised that a physically active childhood has an indirect, positive effect on health outcomes in adulthood. If so, it is both important and beneficial to address issues such as physical inactivity early in life, thereby promoting healthy lifestyles from a young age, and potentially preventing future adverse health outcomes and their consequences later in life. For this reason, my doctoral research focussed predominantly on youth, which I defined as child and adolescent populations up to the age of 18 years.

Conducting research in these populations presents some unique challenges. During these developmental years of life, numerous physical, psychological, and physiological changes occur. For example, priorities and daily routines change with age. Consequentially, physical activity profiles change over time, from erratic and unstructured play in pre-schoolers to more consistent and defined physical activity as school age children participate in school and after school sports. The contentious nature of measurement and classification schemes for physical activity, and the possibility of misdiagnosis of asthma in children before age five (17) add to the complexity of the research. Hence it is essential that these age groups are investigated, as the relationship between asthma and physical activity in youth could be entirely different than it is in adult populations.

1.3 My doctoral work

My doctoral work therefore aimed to address the aforementioned research gaps through a series of investigations of the directionality and temporality of the relationship between asthma and physical activity. This thesis is a compilation of the evidence produced on this topic and includes two systematic reviews of the existing evidence and three original analyses of data collected in two large cohorts of Australian children. Collectively, my work has produced valuable results which contribute to improving our understanding of whether physical activity is a cause or consequence of asthma in youth.

1.4 Research questions

The overarching aim of this doctoral work was to investigate the existence and direction of the relationship between asthma and physical activity in youth. This was addressed by the formulation and investigation of several research questions which constitute the chapters of this thesis. Individual research questions are as follows:

Research question 1: Does physical activity i) decrease the risk of developing asthma, ii) reduce asthma symptoms or iii) increase lung function in children and adolescents?

Research question 2: Does the existing evidence demonstrate that objectively measured physical activity in children and adolescents with asthma differs from those without asthma?

Research question 3: Is the relationship between physical activity and asthma in children and adolescents bidirectional?

Research question 4: Does the level of physical activity in Australian children and adolescents with asthma differ from their unaffected peers?

Research question 5: Is early life wheeze and suspected asthma (before five years of age) associated with less objectively measured physical activity at six years of age in Australian children?

1.5 Thesis statement

During the course of my PhD candidature, I produced several original research articles, including two systematic reviews and three data analyses, all of which have been peer reviewed and published in scientific journals. My research analysed longitudinal data from two large, established cohorts of Australian children and adolescents. Questionnaire data collected by the *Growing Up in Australia*: The Longitudinal Study of Australian Children (LSAC) was used to investigate whether Australian children and adolescents with asthma are as active as their peers, and also, importantly, to explore the possibility of bi-directional associations between asthma and physical activity. This was a novel analysis that had not previously been conducted in the examination of these relationships. In addition, both subjective and objective data collected within the HealthNuts study were used to evaluate the effect of early life wheeze and asthma on subsequent objectively measured physical activity in Australian children. The use of longitudinal data from large cohorts of child and adolescent populations is an important advantage of this work, which aimed to improve our understanding of the direction of the relationship between asthma and physical activity.

1.6 Thesis overview

Chapter 1 of this thesis provides a summary of the rationale behind this research, the overall and specific research questions, and an overview of the thesis.

Chapter 2 consists of a literature review of the background information on asthma and physical activity in child and adolescent populations.

Chapter 3 describes the methods used in this body of work.

Chapter 4 presents the first of two systematic reviews and includes the publication titled "Does physical activity strengthen lungs and protect against asthma in childhood? A systematic review".

Chapter 5 presents the second of two systematic reviews and includes the publication titled "The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis".

Chapter 6 presents the first in a series of three original data analyses and includes the publication titled "Physical activity and asthma: cause or consequence? A bidirectional longitudinal analysis".

Chapter 7 presents the second data analysis and includes a published Letter to the Editor titled "Suspected asthma status and time spent in physical activity across multiple childhood age groups".

Chapter 8 presents the final data analysis and includes the publication titled "Are young children with asthma more likely to be less physically active?"

Chapter 9 provides an overall discussion of the work including the strengths and limitations and places the findings of this research in the context of existing literature.

Chapter 10 concludes this thesis by describing the contributions and implications of this work and provides recommendations for future research based on the findings of this doctoral research.

CHAPTER TWO: Literature review

2.1 Chapter introduction

As described in the introduction to this thesis, this doctoral research focused on the association between asthma and physical activity in childhood and adolescence. In this chapter, I will provide an extensive and thorough review of the existing scientific literature in this field. In the first section of this literature review, I will describe the burden of asthma in children and over the life course, the phenotypes and pathophysiology of asthma and the physiology of the lung. I will then summarise the techniques for the measurement and diagnosis of asthma, including the widely used method of spirometric testing. Next, I will discuss some of the risk factors for development of this chronic condition and the triggers for attacks in child and adolescent asthma, including physical activity. The second part of the literature review will define physical activity and describe some of the techniques through which physical activity is quantified. In the final section, I will discuss the complex relationship between asthma and physical activity and highlight some of the gaps in the existing knowledge.

2.2 Asthma

Asthma is a chronic respiratory condition with a complex aetiology, characterised by narrowing of the airways and reversible airflow obstruction. As discussed in more detail below, this primarily occurs due to 1) inflammation of the bronchial epithelium, 2) increased secretion and accumulation of inflammatory materials (mucus) in the airway and 3) constriction of the airway smooth muscle (Figure 2.1) (18).

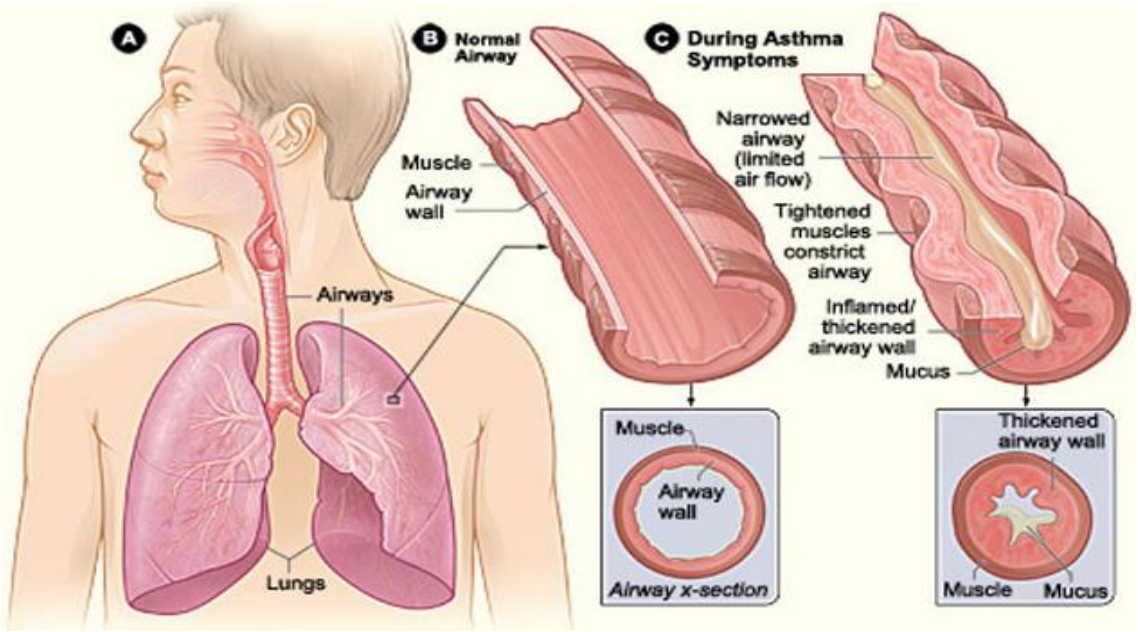

Figure 2.1: Diagram demonstrating the changes that asthma symptoms incur on normal airways. Source: The National Asthma Council Australia (2015).

Consequently, coughing, wheezing, breathlessness and a tightness of the chest are commonly experienced symptoms of the condition (19). Asthma symptoms tend to be episodic in nature, with exacerbations or "attacks" that vary in severity, duration and frequency (20).

In 2020, the Global Initiative for Asthma (GINA) updated the way in which asthma is defined. Asthma is now defined as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (21, 22).

2.2.1 Asthma burden of disease

Asthma is an important public health problem with a substantial burden of disease. In 2015, it was estimated that 0.4 (0.36-0.44) million people died from asthma (23) and in Australia in 2018, 389 deaths were attributed to asthma (24). On a societal scale, the economic cost of asthma is high as a result of absenteeism from work or school, combined with the financial burden of health care (25-27). Some research has been done in several high-income countries to quantify the financial costs of

asthma (28-30). These studies have produced estimates ranging from approximately 49 million USD in Singapore to 81.9 billion USD in the United States of America (USA) (28, 30). According to the Australian Institute of Health and Welfare (AIHW) Australia, the cost of asthma to the Australian health care system in 2015-2016 was estimated at $770 million (24).

Asthma is currently estimated to affect between 1 and 18% of the population, depending on the country (22), or as many as 334 million adults and children globally (28). The prevalence of asthma has increased in recent decades (31), and is expected to further increase with time. It is also expected that, as an increasing number of global communities move away from traditional and agricultural lifestyles to become more urbanised and adopt a more 'westernised' lifestyle, the prevalence of global asthma is expected to further increase (31, 32), so that approximately 400 million individuals will be affected by 2025 (32).

Although asthma affects people of all ages (Figure 2.2), it is the most common chronic, non-communicable condition among children and adolescents (7, 33, 34), and the increase in the global prevalence of asthma is especially apparent in children (35). The largest study of global childhood asthma prevalence data was collected by The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC is a large, multinational epidemiological study with 233 centres located in 98 countries, with approximately 1,200,000 children having participated in the ISAAC Phase Three prevalence survey (36-38). The ISAAC study estimated global prevalence of current asthma (defined as symptoms within the past 12 months) in children aged 6-7 years to be 11.7%, and 14% for adolescents aged 13 -14 years (36). Substantial variability in the prevalence and severity of asthma was observed between and within regions, countries, and cities. Australia ranks amongst the highest in the world in the prevalence of childhood asthma (28); higher indeed than many other high income countries (28, 39).

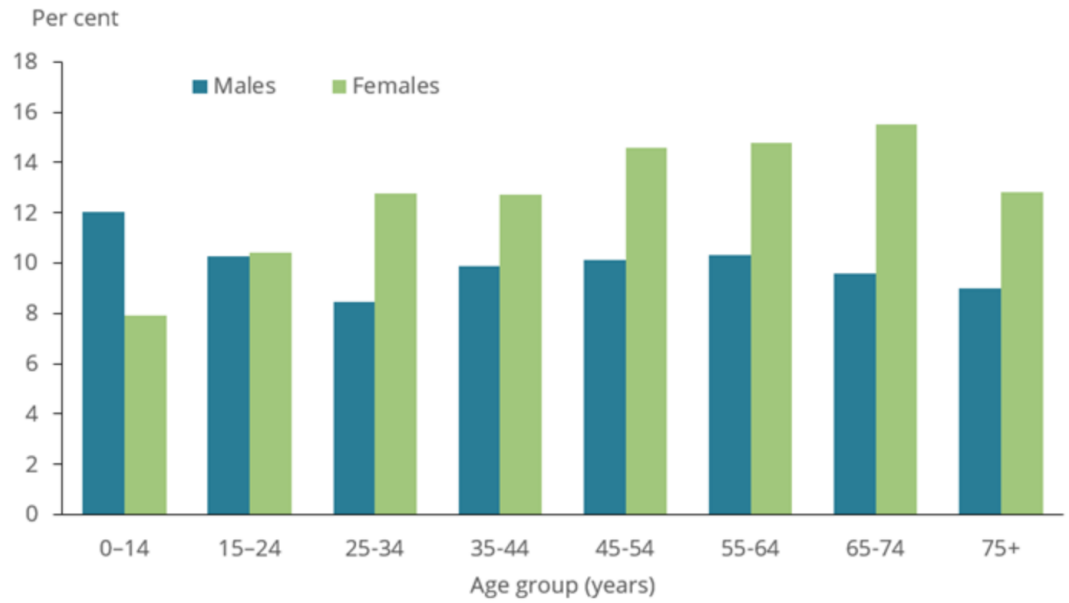

Figure 2.2: Prevalence of asthma by age group and sex in Australia 2017-2018. Source: Australian Institute of Health and Welfare (2020). Asthma was defined as self-report doctor or nurse diagnosis.

Whilst asthma can develop at any age, it often develops in childhood (28), and being a chronic condition, asthma has a potentially large burden on both an individual and societal scale. An individual with asthma faces potentially lifelong challenges with the condition. These challenges could include not only a substantial financial burden due to the continuing requirement of asthma medication, clinical assessments or even hospitalisation, but also a reduced quality of life, and even death (28). Studies have demonstrated that individuals with asthma often struggle with the symptoms of asthma that may affect their sleep and daily life (40-44). In addition, these individuals may make lifestyle decisions based on their asthma triggers, for example choosing not to own a cat if cat hair is a known trigger. Since there is no known cure for asthma, there remains a need to reduce the burden of the disease and mitigate its impact.

2.2.2 Asthma pathophysiology

The term “asthma” is an umbrella term that incorporates several asthma phenotypes (22). Each asthma phenotype is a set of recognisable demographic,

clinical and/or pathophysiological characteristics (21, 22). The most easily recognized asthma phenotype (21, 22) and the type primarily addressed within this thesis is allergic asthma. It is the principle phenotype of interest within this thesis as it is the type that frequently commences in childhood (21, 22). Allergic asthma is commonly associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, food or drug allergies and often involves eosinophilic airway inflammation (21). This asthma phenotype is usually quite responsive to inhaled corticosteroid (ICS) treatment (21). Some other common phenotypes are briefly described below (Table 2.1) (21, 45):

Table 2.1: Description of common asthma phenotypes

Asthma Phenotype	Description
Non-allergic asthma	Commonly experienced by adults and is not associated with allergy. Patients with non-allergic asthma often respond less well to ICS
Late-onset asthma	Developing in adulthood, and particularly in women, this phenotype is usually non-allergic, and often requires higher doses of ICS
Asthma with fixed airflow limitation	Observed in individuals with long-standing asthma, this phenotype is characterised by fixed airflow limitation that is thought to be due to the remodelling of airway walls
Asthma with obesity	This phenotype is observed in obese individuals, where respiratory symptoms are prominent but little eosinophilic airway inflammation is observed.
Exercise-induced 'sports' asthma	Respiratory symptoms and airway hyperresponsiveness induced by exercise without allergic features.

Regardless of asthma phenotype, there is a consensus that chronic inflammation of the airways is the underlying pathological mechanism (Figure 2.3) (46). The inflammatory mechanisms in play in allergic asthma have previously been described and discussed in detail (22). Briefly, studies in both animal and human models have shown that an asthmatic state appears to be the result of T-helper cell mediated

inflammation and that an imbalance of T-cell subtypes may be responsible for asthma (22). CD4+ T cells are divided into Th subtypes based on the cytokines they secrete (23). Th2 cells secrete interleukins which induce IgE and eosinophil production, regulate the functions of eosinophils and promote the growth of mast cells (23). Th1 cells delay hypersensitivity and inhibit Th2 processes (23). The anti-inflammatory interleukin-10 (IL-10) cytokine plays an important role. It inhibits mast cell and eosinophil function, and acts on macrophages to inhibit the production of pro-inflammatory cytokines and to inhibit the activation of Th2 cells (24). It has been shown that individuals who do not produce sufficient IL-10 suffer from more severe asthma (24).

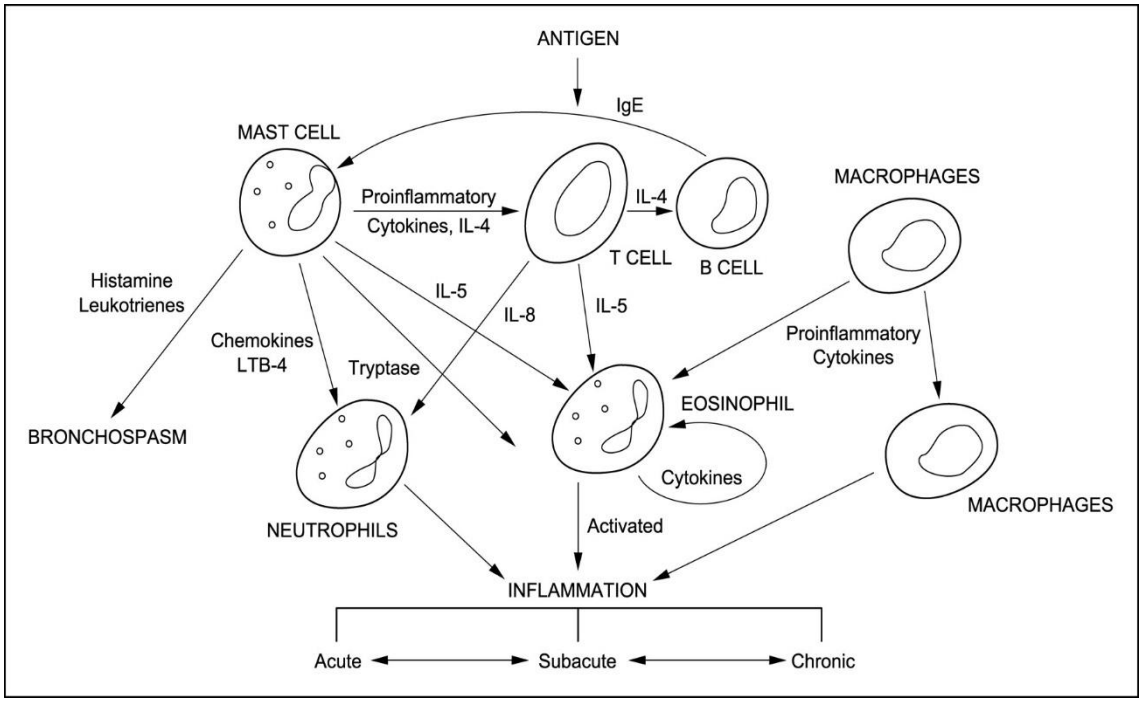

Figure 2.3: Inflammatory mechanisms involved in asthma. Source: Hill & Wood (2009) (47)

2.2.3 Asthma measurement

A detailed guide for the assessment and diagnosis of asthma is presented by the GINA (21, 22). Diagnosis of asthma is made based on history of characteristic patterns of respiratory symptoms, including wheezing, shortness of breath or coughing, as well as evidence of variable airflow limitation, as assessed by Pulmonary Function Testing (PFT) (22). PFT is used to clinically diagnose asthma,

to continue monitoring the disease once a diagnosis has been made (21), and also as a useful indicator of future risk (21). In their 2015 report, GINA recommends that lung function be recorded at diagnosis, 3–6 months after starting treatment, and periodically thereafter (21). A reduced FEV1/ FVC ratio is consistent with airflow obstruction and a diagnosis of asthma (8). Additionally, bronchial reversibility or bronchodilator (BD) responsiveness testing is useful in confirming the diagnosis of asthma (48). This is done by assessing lung function both before and after inhalation of a short-acting β_2-adrenergic agonist (SABA) such as albuterol (48). The clinical threshold for positive bronchial reversibility according to the ATS/ERS guidelines is a minimum of a 12% increase in FEV or FVC from baseline with a minimum increase in volume of 200mL (49). However, this method has recently been found to have low specificity for asthma in adults (50), and to poorly correspond to a clinical diagnosis of asthma in children (51). Therefore, these tests may be more valuable in the assessment of management strategies and progression of asthma than in asthma diagnosis (51).

2.2.3.1 Asthma measurement in young children

A clinical diagnosis of asthma in children 5 years and younger is particularly challenging, as transient wheeze and cough is common in children, especially before the age of 2 years. Recurrent wheeze associated with viral upper respiratory tract infections (RTI) may occur in young children as frequently as 6-8 times per year, thereby furthering hindering the identification of asthma (22). Additionally, the use of spirometry to assess airflow limitation or bronchodilator responsiveness in such young children is extraordinarily difficult due to the effort and coordination required for such testing to be performed. On the other hand, atopy, one of the most important risk factors for the development of asthma is present in the majority of children with asthma over the age of 3 years (22). The following symptoms may suggest the presence of asthma and may be used in the diagnosis of asthma in children aged 5 and under (22):

- Symptom patterns (e.g. Recurrent episodes of wheeze, cough, breathing difficulty, activity limitation, nocturnal symptoms)

- Presence of risk factors such as family history of atopy, allergic sensitisation, allergy, personal history of food allergy or atopic dermatitis
- Therapeutic response to treatment
- Exclusion of other potential diagnoses

2.2.3.1.1. Physiology of the lung

The lungs have a large, permeable epithelial surface, designed to optimise the exchange of respiratory gases with the circulatory system (52). They are divided into three lobes on the right and two of the left. Air is inhaled through the nose and mouth, passes through the larynx, trachea, and into the series of branching tubes known as bronchi and bronchioles, terminating in a conglomerate of alveolar sacs (52, 53). The lungs normally contain about 2.5L of air at end expiration and 6 L of air at full inspiration (52).

The development of the lungs begins in utero and continues into early adolescence (54, 55). Normal lung function values rapidly increase from birth through childhood and peak at the age of approximately 20 years (Figure 2.4). Lung function then plateaus for several years before gradually declining (54). Abnormal patterns of lung function growth, a low maximal lung function and early or rapid lung function decline are all indications of poor lung health, and are associated with the subsequent development of airflow obstruction (54, 56-58). Hence, studies that investigate early life lung function are useful for understanding and identifying the development of respiratory diseases such as asthma.

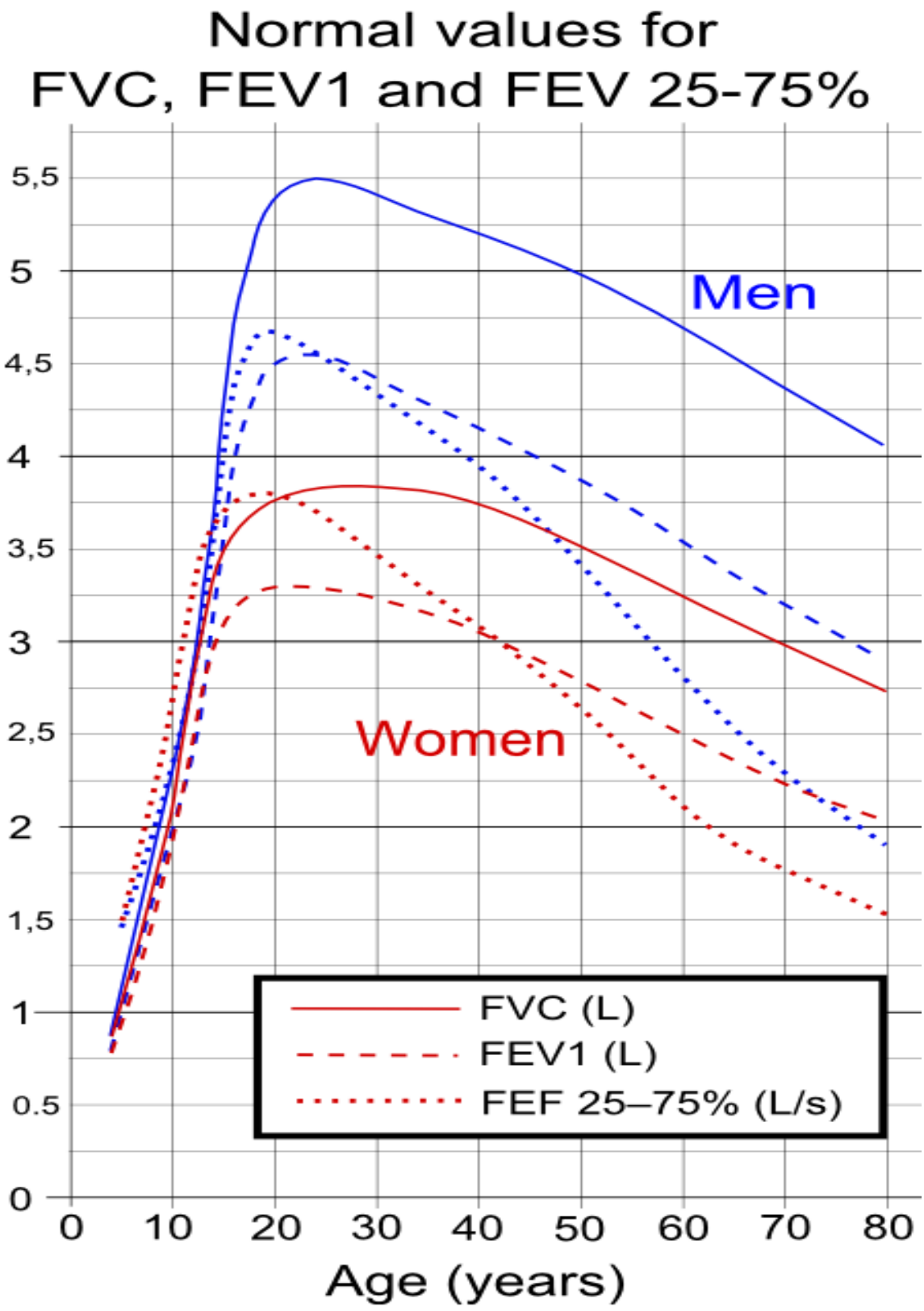

Figure 2.4: Normal values for Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 Second (FEV1) and Forced Expiratory Flow 25–75% (FEF25–75%). Y-axis is expressed in Litres for FVC and FEV1, and in Litres/second for FEF25–75%. Image by Mikael Häggström - Own work Made in Inkscape, Public Domain, https://commons.wikimedia.org/w/index.php?curid=9735199. Source: Stanojevic *et al.* 2010 (59)

2.2.3.1.2 Measurement of lung function

Several factors play a role in determining the size of the normal lung (60), which in turn affects lung function parameters. These factors include age, sex, body mass, ethnicity, posture, stature and daily activity pattern (60). As such, when measuring lung function, sex, height, and age at the time of measurement must minimally be taken into account. To further improve the accuracy of measurements, ethnicity and body composition should also be considered (53).

As an important indicator of respiratory health, the measurement of lung function is utilised in the diagnosis of asthma in children and adolescents who are old enough to participate in the test (usually aged over 5 or 6 years). Objective lung function data is routinely collected through PFT (48).

2.2.3.1.2.1 Spirometry

Spirometry is the gold standard and the most commonly performed method for lung function measurement in both adults and children (61). It is a technique for testing the physiological function of the lungs that involves the measurement of the flow and volume of air as a function of time (62, 63).

In 2005, a joint task force consisting of contributors from both the American Thoracic Society (ATS) and European Respiratory Society (ERS) published guidelines to ensure the standardisation of spirometry (62). The resulting document detailed the training required by personnel administering the test, equipment requirements and calibration, as well as instructions for the procedure (62). Briefly, the test begins with the participant breathing normally to record normal tidal breathing. Next, maximal inspiration is drawn, followed by maximal expiration of air into the device, and finally a return to normal tidal breathing (61). The manoeuvre is often repeated three times; however, this may increase depending on the acceptability of each blow (62). Test results are selected from the highest value of FEV1 and FVC from each of the three spirometric curves recorded (62). The

following parameters can be obtained or derived from spirometric testing (Table 2.2; Figure 2.5) (48, 60, 61, 63):

Table 2.2: Description of lung function parameters obtained or derived from spirometry

Parameter	Description
Tidal volume (V_T)	The volume of air that is inhaled and exhaled during a normal respiratory cycle.
Inspiratory capacity (IC)	The amount of air inspired from the resting expiratory level to full inflation.
Vital capacity (VC)	The maximum volume of air that can be exhaled.
Inspiratory vital capacity (IVC)	The maximum volume of air that can be inhaled after full expiration.
Residual volume (RV)	The volume of air remaining in the lungs after maximal expiratory effort.
Total lung capacity (TLC)	The maximal amount of air that can be contained in the lungs at the end of maximal inspiration. It is the sum of RV and VC.
Functional residual capacity (FRC)	The amount of air in the lungs at the end of normal tidal expiration.
Forced expiratory volume in 1 second (FEV_1)	The volume of air that is forcibly expelled in the first second of exhalation.
Forced vital capacity (FVC)	The volume of air that is forcibly expelled after a deep inhalation.
FEV_1/ FVC ratio	The ratio of FEV1 to FVC measurements that is often used in the definition of health.
Peak expiratory flow (PEF)	The average flow of air at the beginning of expiration.
Forced expiratory flow (FEF)	The average flow of air during the second half of expiration.

Spirometry results can also be easily compared to normal reference values which were developed by the Global Lung Function Initiative (GLI) in 2012 (64). The GLI used 97,759 records from healthy non-smokers of which approximately 55% were

female, who were aged between 2.5 and 95 years from 33 countries to develop reference values for lung function. Reference values were derived from the following equation which accounts for age (A, in years), sex, standing height (H, in centimetres) and ethnicity (a, b, c, d_1 and d_2 are coefficients which vary for each ethnic group):

$$Y = a + b \times H + c \times A + age\text{-}spline + d_1 \times group + d_2 \times group \times A$$

Where 'spline' is an age-specific contribution from the spline function and 'group' is a dummy variable with values of 0 or 1 indicating ethnicity, where Caucasians are the reference. The GLI has a calculator function for the easy conversion of raw lung function data available on the website (www.ers-education.org/guidelines/global-lung-function-initiative.aspx).

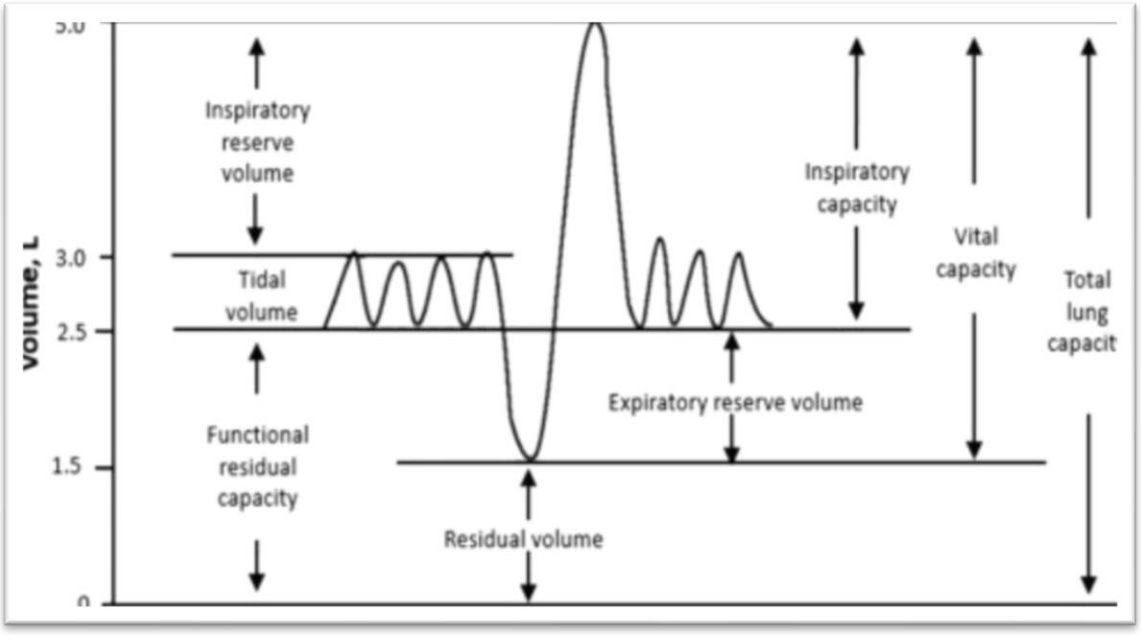

Figure 2.5: Schematic representation lung volume parameters including the typical range of values for a healthy adult subject. Source: Peters *et al.* 2018

2.2.3.1.2.2 Other methods

There are currently a number of other PFTs in existence for the objective measurement of lung function, with each method possessing its own set of advantages and limitations. These techniques include: body plethysmography, gas diffusion tests, and oscillometry (48, 61). However, these techniques will not be

discussed here in further detail, as they were not utilised during the course of this doctoral work.

2.2.3.1.3 Measurement of lung function in children

Measurement of lung function in children is often challenging due to their diminutive size and potential difficulty in following the test instructions (61). However, the assessment of lung function in children is essential for the evaluation and monitoring of the developing lung, as poor lung function in childhood may have effects in adulthood (61). Lung function testing should be performed by trained operators with equipment that is well-maintained and regularly calibrated in accordance with the ATS and ERS guidelines (21, 62, 65). In particular, when testing children, the equipment utilised should be capable of accurately measuring small volumes and low flows of air, and size of the mouthpiece should be adjusted (61). It has been observed that provided the appropriate encouragement and age-appropriate instruction, young children can voluntarily perform the manoeuvres from the age of 4 or 5 years (61, 62).

2.2.4 Asthma management

Whilst there are no known cures for the condition, the symptoms of asthma may be controlled and managed to minimise exacerbations, future risk of persistent airflow limitation and asthma-related mortality (22). These goals are addressed by avoiding known environmental triggers where possible, and through the use of pharmaceuticals (20, 66). Pharmacological options for the sustained treatment of asthma fall into three categories (22):

1. Controller medications reduce airflow inflammation and control symptoms.
2. Reliever/ rescue medications are provided to all patients for relief of exacerbations and for short-term prevention of exercise induced bronchoconstriction.

3. Additional therapies for severe asthma. These are considered in severe cases where symptoms and exacerbations persist despite treatment with high dose controller medications.

The most commonly used asthma medications are β2 agonists (reliever/ rescue medications) and corticosteroids (controller medications), which are commonly inhaled. Short-acting inhaled bronchodilators (SABA) such as salbutamol, act quickly to relax the smooth muscle of the airways, and are therefore used to relieve symptoms (67, 68). In contrast, long-acting β2 agonists (LABA) such as salmeterol are commonly combined with an inhaled corticosteroid to effectively control asthma (67, 68).

Asthma treatment is a continuous cycle of assessment, treatment and review of patient response (22). GINA recommends that treatment with ICS controllers commence as soon as possible after an asthma diagnoses is made (Table 2.3) (22). Recommended treatment types, dosages and combinations depend on the frequency and severity of symptoms (22). Treatment recommendations are also dependent on age.

Table 2.3: Recommended initial asthma treatment for children aged 6-11 years. Source: GINA 2020 (22)

Symptoms	Preferred treatment
Infrequent symptoms (e.g. less than twice a month) and no risk of exacerbations	SABA as needed
Asthma symptoms twice a month or more	Low does ICS with SABA as needed
Asthma symptoms most days; waking due to asthma once a week or more	Low dose ICS-LABA with SABA as needed or Medium does ICS with SABA as needed
Severely uncontrolled asthma or with acute exacerbation	Regular controller treatment with medium dose ICS-LABA with SABA as needed. Short course of oral corticosteroids as needed

Barriers such as inability to access asthma medications, improper use of inhalers and lack of asthma education contribute to the continuation of the burden of asthma (32, 69, 70). Hence, there remains a need for non-pharmaceutical methods that are both cost-effective and well-tolerated, to prevent and control for asthma.

2.2.5 Asthma control and severity

The terms "asthma control" and "asthma severity" are related (71), but should not be used interchangeably as they are distinct concepts (72). Asthma control refers to the extent to which the symptoms of asthma can be reduced or removed by the administration of treatment (21, 72). In contrast, the assessment of asthma severity is made retrospectively and is based on the level of treatment required to control asthma symptoms and exacerbations (21, 72). An individual's asthma control and severity is determined by the interplay between environment and genetics, underlying disease processes and the treatment taken, and psychosocial factors (21, 72). Asthma control is assessed based on symptoms, activity limitation and use of rescue medication (21). A number of tools have been developed to assist in the assessment of asthma control in children. These instruments assign a numerical score to indicate a level of control based on the responses to asthma questions, although most of these instruments do not incorporate a measure of lung function (71). These tools include the Asthma Control Questionnaire (ACQ) (73), the Childhood Asthma Control Test (c-ACT) (74) and the Composite Asthma Severity Index (CASI) (75).

2.2.6 Risk factors for development of asthma

Although the causes of asthma are not completely understood (20), a number of genetic and environmental risk factors for the condition have been identified (76). Risk factors may be roughly categorised as either unalterable (e.g. genetic composition) or modifiable (e.g. lifestyle factors). They can also be stratified according to their associations with the development of asthma in childhood or

adulthood. As this thesis focusses on childhood and adolescence, the risk factors for the development of adult asthma are not discussed in great depth here. However, several risk factors associated with childhood development of asthma have been explored:

- Asthma is often found in families, with maternal asthma increasing risk of asthma development in offspring (77). This familial aggregation of asthma indicates that the condition may have genetic component (78, 79), although heritability does not appear to follow Mendelian inheritance patterns (78). Instead, inheritance of the disease may be polygenic (more than one gene) or due to different combinations of genes (80). To date, genome wide association studies (GWAS) have identified multiple risk alleles and loci on many chromosomes (77-79).
- Due to the age-dependent nature of observed asthma incidence, it is hypothesised that sex hormones play a role in asthma development. Before puberty, asthma is more common in males than females, but this is reversed after puberty (77, 78).
- Personal history of atopy in the form of atopic dermatitis and/or allergic rhinitis (i.e. atopic sensitisation (77)) is associated with incident asthma. This is part of the sequential manifestation of atopic disease, typically from atopic dermatitis in infancy followed by allergic rhinitis and asthma, known as the 'atopic march' (81-83).
- Exposure to tobacco smoke is a known risk factor for asthma (77). Maternal smoking has long been known to increase incidence of asthma (84), while a recent study demonstrated that paternal smoking prior to conception was found to be associated with an increased risk of non-allergic asthma (85), indicating potential genetic or epigenetic mechanisms in the development of asthma. Tobacco smoke exposure also has a more direct effect on asthma, whereby in older children and adolescents, regular personal smoking is associated with increased risk of incident asthma (86).
- Other environmental risk factors and their effects on asthma incidence have also been investigated. Both indoor and outdoor air pollutants (77) including aeroallergens, particulate matter (PM), nitrogen dioxide (NO2), sulphur

dioxide (SO2), ozone and carbon monoxide (CO) have all been linked with development of asthma.

- In young children, lower respiratory tract infections have been shown to be associated with asthma development (87-90).
- Obesity and other early-life stressors (91) have also been found to play a role in asthma development.
- Epigenetic studies have shown that certain environmental factors (such as tobacco smoke exposure and air pollution) interact with genes in ways which may increase risk of asthma development (77, 79).

Additionally, a systematic review published in 2012 that concluded that increased levels of physical activity are associated with a reduced risk for asthma development (2). This is discussed further in section 2.4.2 Does physical activity affect asthma?

2.2.7 Risk factors for asthma exacerbations

A number of factors have been identified as triggers of acute symptom exacerbation in those individuals with existing asthma. Triggering factors and the National Asthma Council of Australia's (NACA) recommended management of such triggers are presented below (Table 2.4).

Each individual with asthma has their own specific set of asthma triggers, and asthma triggers may differ by age group. For example, viral respiratory infections may be a common trigger in childhood but less common in adulthood, while triggering by occupational irritants is not applicable in younger age groups. Importantly, poor asthma control is itself a risk factor for asthma exacerbations (22).

Notably, strenuous physical activity and exercise are known and important triggers for asthma exacerbations (22), causing increased bronchoconstriction and worsening symptoms in individuals with asthma. Currently, the underlying pathophysiological mechanism is thought to act through increased ventilation during exercise leading to increased water loss and dehydration and cooling of the airways resulting in airway smooth muscle contraction (92, 93). Increased water

loss alters the airway osmolarity and induces, among other effects, a release of inflammatory mediators from mast cells, eosinophils, neutrophils and other inflammatory cells (94). This inflammation of the airways as a result of repeated, high intensity physical activity, may be related to the `sports phenotype´ of asthma , which is defined by the presence of exercise-induced respiratory symptoms and bronchial hyperresponsiveness without allergic features (45). This area of research warrants further investigation but is beyond the scope of this thesis. Regardless, both NACA and GINA recommend that regular physical activity is encouraged in individuals with asthma (22, 95) and that certain accommodations may be made to facilitate physical activity, regardless of potential variability introduced by season and pollution levels. For example, it is recommended that symptoms are managed with the use of asthma medications (SABA or low dose ICS-formoterol) prior to or during exercise (22).

Table 2.4: Potential risk factors for asthma exacerbations and recommended management strategies

Potential trigger	**National Asthma Council of Australia's Recommendation (95)**
Tobacco smoke **(96)**	Always avoid
Allergens including: • house dust mite • cockroaches • animal allergens or pet dander **(20, 97)** • pollen • mould	Avoid or reduce where possible
Airborne and environmental irritants including: • strong scents such as deodorant, perfume or incense • woodfires and unflued gas heating • extreme weather e.g. bushfire and thunderstorm asthma (32-35) • indoor and outdoor air pollution	Avoid or reduce where possible
Certain dietary and medicinal triggers including: • Aspirin and NSAIDS • Bee products • Echinacea • Some food additives	Avoid or reduce where possible

Biologicals such as viral respiratory infections (87)	Manage
Comorbid medical conditions including: • Allergies • Upper airway disease • Obesity	Manage
Anxiety and other intense emotions (21, 32)	Manage
Strenuous activity and exercise **(20, 98)**	Do not avoid
Laughter	Do not avoid

Section Summary:

Asthma is a heterogeneous disorder characterised by inflammation of the airways. It is the most common chronic condition in children and has a significant burden. Asthma remains an enigmatic disease, as causes and cures have not yet been discovered. However, several risk factors for both the development of asthma, and for asthma attacks, have been identified. Physical activity has been implicated in both the development of asthma and as a trigger for asthma attacks. Hence, the following sections define physical activity, explain why it is considered a public health issue, and describe some of the techniques through which physical activity is measured.

2.3 Physical Activity

Physical activity constitutes the movement of skeletal muscles that requires energy expenditure (99). Despite the known health benefits of physical activity (99, 100) and the introduction of physical activity guidelines for health (101), it is estimated that worldwide more than 80% of adolescents between the ages of 11 and 17 are still insufficiently physically active (99).

The problem of the rise of physical inactivity in youth has drawn many researchers to the topic in an effort to fully understand the motivations behind the decrease in children's activity, the acute impacts of an inactive life, whether this can be scientifically tracked to predict the activity patterns of adults, and the impacts that an inactive lifestyle may have on adult health. Associations between childhood

physical activity and adult health would further fuel the promotion of physical activity from a young age in order to prevent poor health in adulthood.

Research on physical inactivity has identified number of factors that influence physical activity. Large variations in physical activity are observed at every level, from an ecological scale to an individual level. At an individual level, gender appears to be an important determinant of physical activity, with females being less active than males in most age groups (99). Perhaps unsurprisingly, age also appears to have an effect on the amount of time spent in physical activity. As we age, we spend less time in physical activity as we are compelled by other commitments. In addition, the structures of physical activity profiles are altered as we are forced to schedule time for activity. For example, adults tend to engage in more structured and sustained activity when they attend the gym or schedule a time for running.

At this juncture, it is important to discuss the distinct yet related concepts of physical activity as described above, and exercise, defined as activities that are "planned, structured, and repetitive" where "the improvement or maintenance of physical fitness" is the objective (102, 103). Therefore, exercise is considered a subcategory of physical activity, and these concepts should not be used interchangeably (103). Reflecting on these definitions, we may consider physical education within school and extra-curricular sports participation as 'exercise'. A child's 'physical activity' on the other hand, will extend to the time spent in active play, active transport and so forth.

2.3.1 Physical activity as a public health problem

In 2010, the World Health Organization (WHO) identified physical inactivity as the fourth leading cause of global mortality; contributing to approximately 6% of global deaths (101). It is widely accepted that physical inactivity is a risk factor for a number of adverse health outcomes, including cardiovascular disease, diabetes and hypertension (104, 105). Physical activity is associated with many health benefits like improved mental health by reducing depression and dementia, and is believed to play a role in the prevention of obesity (106). As a leading and potentially

modifiable risk factor in the prevention of non-communicable diseases (NCDs), the WHO and several other health authorities embarked upon a mission to promote physical activity for its numerous health benefits (101, 107, 108). The WHO has since released a series of physical activity recommendations for the maintenance of good health, which are closely mirrored by the recommendations of other health authorities. In brief, the WHO recommendations are as follows (Table 2.5) (101):

Table 2.5: Physical activity recommendations by age group

Age group	WHO Recommendation
Children 5-17 years	Accumulate at least 60 minutes of moderate- to vigorous intensity physical activity daily. 2. Amounts of physical activity greater than 60 minutes provide additional health benefits. 3. Most of the daily physical activity should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.
Adults 18-64 years	1. Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. 2. Aerobic activity should be performed in bouts of at least 10 minutes duration. 3. For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. 4. Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.

Older adults 65+ years	1. Adults aged 65 years and above should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous intensity activity. 2. Aerobic activity should be performed in bouts of at least 10 minutes duration. 3. For additional health benefits, adults aged 65 years and above should increase their moderate intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous intensity aerobic physical activity per week, or an equivalent combination of moderate-and vigorous-intensity activity. 4. Adults of this age group, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week. 5. Muscle-strengthening activities should be done involving major muscle groups, on 2 or more days a week. 6. When adults of this age group cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow.

The recommendations further stipulate that physical activity at all ages should be mostly aerobic, but should also contain muscle and bone strengthening activities multiple times per week, and that activity that exceeds these recommendations provide additional health benefits (101).

Historically, the prevalence of physical inactivity has increased over the years since the industrial revolution, with the development of new technologies that reduced the need for physical labour (100). Prevalence of daily physical activity continues to decline globally, largely due to lifestyle changes that promote inactivity such as television and computers, and increased use of passive modes of transportation for example, driving in cars as opposed to walking or bicycling (99, 100). Additionally, a change toward more computer- and office-based employment signifies a shift from

highly physically intensive labour and physically active lifestyles toward more inactive and sedentary lifestyles.

Current research using data from 358 countries and including 1.9 million participants showed that in 2016, more than a quarter of the world's adults (27.5%, 95% Uncertainty Interval (UI): 25.0–32.2) were insufficiently active by the WHO standard (106). Prevalence of physical activity varied by country and region; insufficient physical activity was lowest in Oceania 16.3% (95% UI: 14.3–20.7) and highest in 39.1% (95% UI: 37.8–40.6) in Latin America and the Caribbean (106). The study further found that women were less active than men across all regions (Figures 2.6 and 2.7), with the exception of east and southeast Asia, and that prevalence of insufficient physical activity in high-income countries was more than double the prevalence in low-income countries (106).

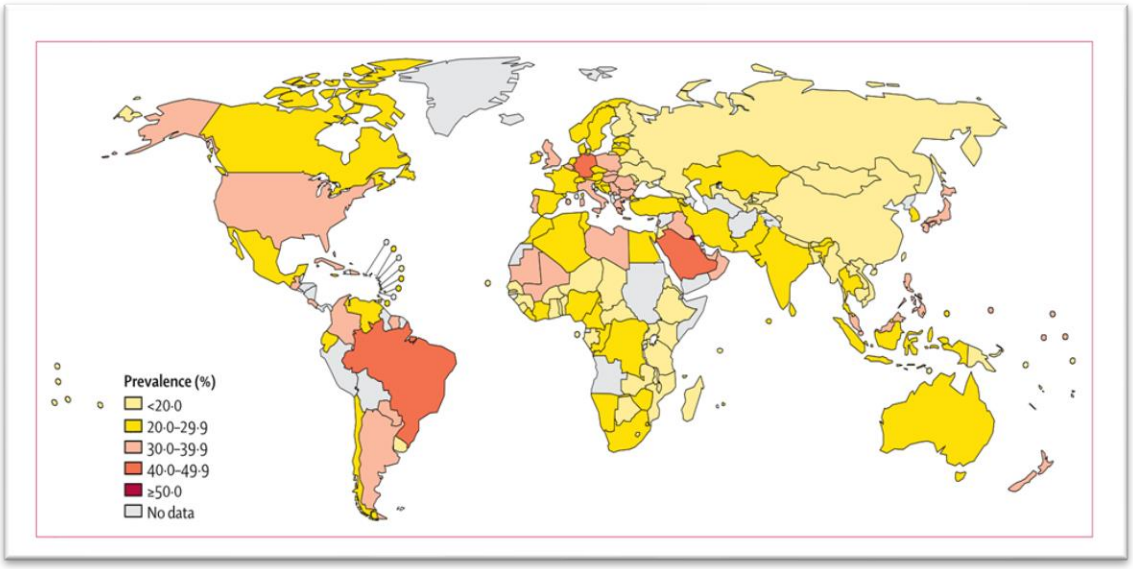

Figure 2.6: Country prevalence of insufficient physical activity in adult men (18 years and over) in 2016. Source: Guthold et al. 2018 (106)

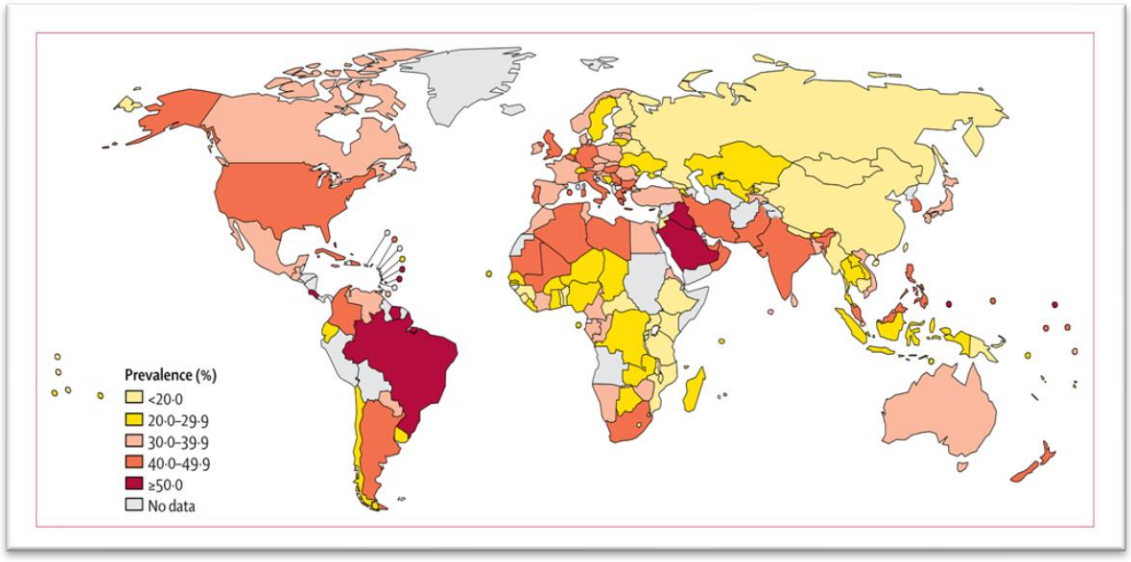

Figure 2.7: Country prevalence of insufficient physical activity in adult women (18 years and over) in 2016. Source: Guthold et al. 2018 (106)

An older study similarly described a similar variation between girls and boys, and also between countries (100). However, taking into account these variations, as well as the different recommended physical activity levels, this study produced high estimate for insufficient physical activity in adolescence. In this study, 80.3% (95% Confidence Interval (CI): 80.1–80.5) of 13–15-year-olds worldwide were found to be insufficiently physically active (100). As with adults, girls were found to be less active than boys (Figure 2.8) (100).

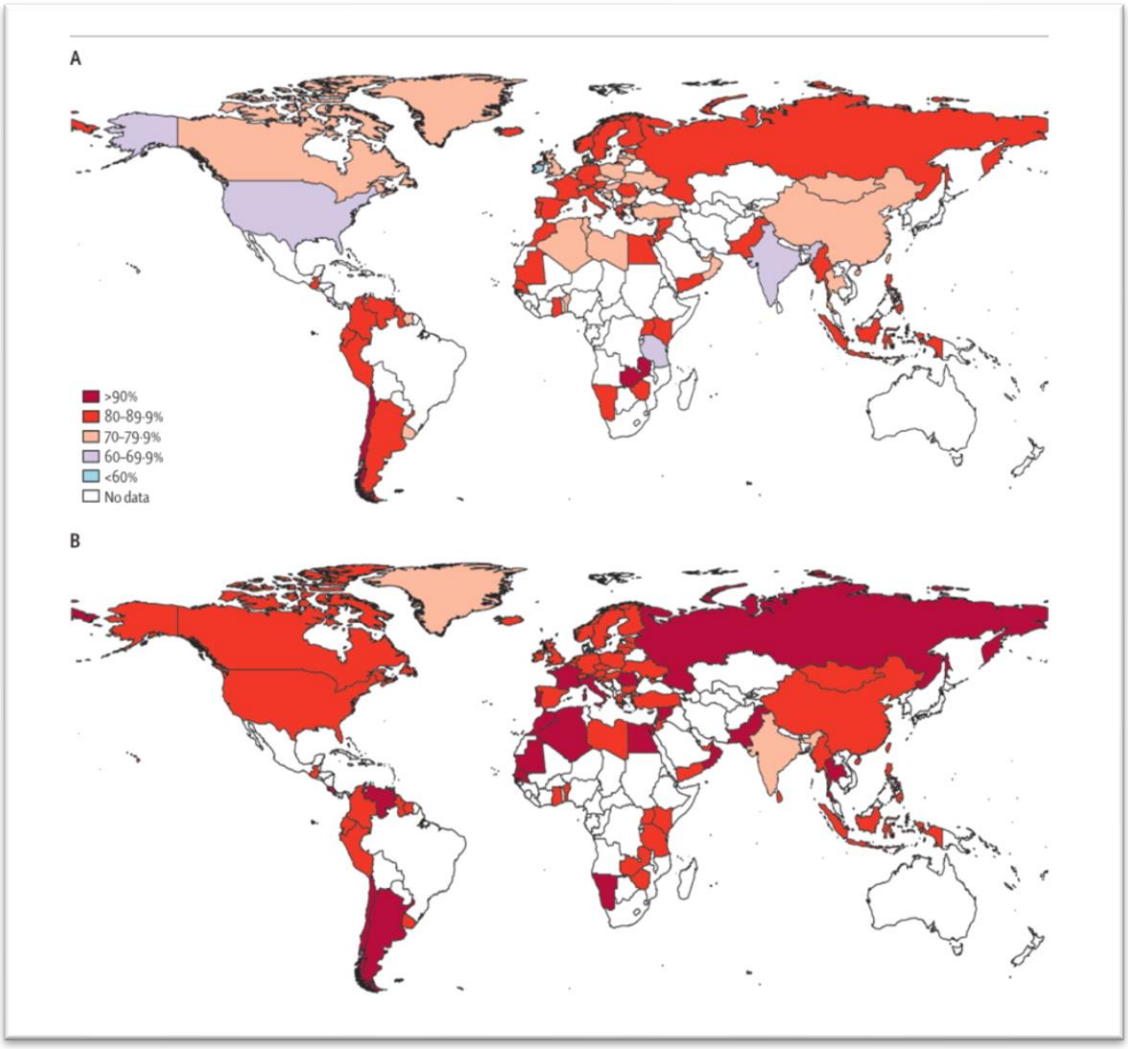

Figure 2.8: Proportion of 13–15-year-old boys (A) and girls (B) not achieving 60 min per day of moderate to vigorous physical activity. Source: Hallal et al. 2012 (100)

2.3.2 Physical activity in children

In 2010, the WHO released their guidelines for physical activity at each stage of life. Within the document, the WHO recommends that children and adolescents aged between 5 and 17 years accumulate at least 60 minutes of moderate to vigorous, preferably aerobic, physical activity daily in order to improve cardiorespiratory and muscular fitness, cardiovascular, metabolic and skeletal health (32).

A number of studies have since been conducted and published to describe the physical activity levels of children (109-113). In 2008, a systematic review of 39 studies in which the physical activity of preschool aged children was conducted, and

found that only 54% of all the study participants achieved the recommended 60 minutes per day (114).

2.3.2.1 Measurement of physical activity in children

Assessment of physical activity can be either subjective or objective. A variety of techniques including self-reporting, electronic or mechanical personal monitoring, direct observation, direct and indirect calorimetry and doubly labelled water have been developed for measuring physical activity (115, 116). There are advantages and limitations to each of these techniques.

Physical activity is notoriously difficult to measure in children, as their activity profiles tend to be unplanned, unstructured and tend to occur in brief and intermittent spurts of activity (116-118), for example jumping, running, and skipping. Such movement is difficult to accurately recall and quantify by observation (116-118). Especially when depending on the age of the participant of interest, a proxy such as a teacher, parent or carer is employed to report the child's activity (117). These proxies are expected to monitor the child and record their activity over a pre-specified period of time, but find it challenging to provide an accurate estimate of the child's activity (117) as they are rarely observing the child for the entire day, and can only provide an estimation of the child's activity rather than a detailed record of the intensity, frequency and duration of each burst of activity throughout the day. For this reason, the use of objective motion detectors that can be placed on a child is likely to provide a more reliable account of a child's physical activity. As such, the use of accelerometers in research is rapidly becoming a common means of obtaining an easier, accurate, reliable and more informative measure of physical activity, particularly in children (119).

2.3.2.1.1 Subjective measurement of physical activity

Self-reporting methods include the maintenance of an activity diary, or the completion of a questionnaire or interview. These methods are inexpensive,

unobtrusive and easily administered (115), and hence are often utilised in large population based studies. However, these subjective instruments may introduce measurement error in a number of ways. Human error in the form of overestimation of activity, lack of precision, varying interpretations of the questions may affect the measurement (115). Additionally, participants may not adhere to the rigorous reporting requirements of activity diaries (115). This is especially true for children and adolescents (115).

2.3.2.1.2 Objective measurement of physical activity

Of the objective measures, lab-based calorimetry and doubly labelled water methods are the most precise, however they are unsuited to large scale population studies due to the high cost, logistical difficulties involved with their application and substantial inconvenience to the participant (115). Consequently, self-reporting and the use of personal monitoring devices are attractive alternatives to lab based techniques as they are less costly and more easily applied to larger samples, although these instruments are less precise than the aforementioned methods (115).

Whilst objective measurements of physical activity through the use of personal monitoring devices do not eliminate bias altogether, they minimise measurement error and therefore provide more accurate measurements of physical activity than subjective methods.

Accelerometers are personal monitoring devices that are able to detect acceleration produced by the body when in motion (120). Depending on the number of piezoelectric sensors contained within, the accelerometer may detect movement in one, two or three planes (uniaxial, biaxial, triaxial accelerometers respectively) (120). Once an acceleration is detected by the sensor, a proportional voltage signal is generated and recorded as a "raw count" (120). The number of raw counts over a selected period of time (epoch length) are presented as physical activity counts (120). A major limitation is that activity counts are not clearly defined and are not standard across devices (117, 120), and thus standardised thresholds for the

categorisation of physical activity intensities have not been defined (117). Accelerometry is utilised in Chapter Eight of this thesis and is discussed in more detail in Chapter Three.

Section Summary:

Studies have shown declining prevalence of physical activity levels as technological advancements are made and populations gravitate toward western lifestyles. Insufficient physical activity has been identified as a risk factor for a number of non-communicable diseases, including asthma. It is postulated that the promotion of physically active lifestyles, particularly from a young age, may assist in reducing future adverse health effects.

2.4 Physical activity and its relationship with asthma

The concurrent increase in the global prevalence of asthma and decrease in the global prevalence of physical activity, has piqued the interest of many public health researchers. The relationship between physical activity and asthma remains unclear though, with research producing vastly varied results. Some studies suggest that physical activity has been identified as a factor that may potentially improve asthma symptoms and decrease risk of development, with a number of additional health benefits (2). However, other studies have shown that many asthmatics may avoid exercise due to fear of exacerbations, as exercise is a known trigger for symptoms (121). This is referred to as exercise-induced bronchoconstriction (EIB). EIB is an acute narrowing of the airways as a direct consequence of exercise, that is usually resolved approximately 60 minutes after exercise (93). It is thought to occur when increased ventilation during exercise causes loss of airway surface liquid and cooling resulting in the narrowing of the airways (92, 93). Importantly, it can occur regardless of asthma status (93, 122). The prevalence in children ranges between 3 and 35%, and is higher than in the general population, which is estimated to range between 5 and 20% (93). Children who compete in endurance sports may have even higher prevalence of EIB. Diagnosis is best made by measuring lung function before and after a standardised exercise test, such as running on a treadmill for 6-8 minutes. Management of exercise induced asthma may involve prophylactic

treatment and medication prior to physical activity. However, EIB is not considered in great depth in this thesis as exercise is a concept distinct from habitual physical activity (103). Regardless, an unhealthy sedentary lifestyle can be avoided in patients with asthma through effective use of preventative pharmaceutical medications prior to and during exercise, although inadequate education and inaccessibility of these medications are barriers against physical activity participation is individuals with asthma.

2.4.1 Biological plausibility

The mechanisms that link physical activity and asthma have only briefly been explored, and a considerate amount of work is still required in order to elucidate these underlying mechanisms. However, a few studies have attempted to describe the mechanisms at play in this relationship, and a few plausible processes have been proposed.

Several possible mechanistic scenarios have been observed which may describe the relationship between physical activity and asthma. First, physical activity is hypothesised to affect allergic asthma through an anti-inflammatory mechanism. In animal models physical activity was found to reduce eosinophil and lymphocyte levels and the Th2 response, thereby having a direct anti-inflammatory effect which may counteract the inflammatory response in asthma (123). Similar results were observed in humans with asthma. A systematic review of 16 randomised controlled trials and seven cohort studies found a reduction in total sputum cells, eosinophils and nitric oxide in individuals with asthma after training (124). Hence, there is some evidence for this pathophysiological mechanism, however, further longitudinal studies in this area would certainly help to improve our understanding of the underlying mechanisms that link these factors.

Other possible mechanisms act through adiposity. Physical activity is known to be associated with BMI (125, 126) and a high BMI (a proxy measure of adiposity), has been shown to be associated with asthma (127-130). Therefore, it is posited that BMI (or adiposity) plays a mediating role in the relationship between physical

activity and asthma. This may occur in number of ways. First, the accumulation of adipose tissue around the chest may be compressing the chest cavity and lungs, thereby physically restricting the expansion of the lungs and hence affecting the mechanics of respiration (131). Secondly, adiposity is associated with persistent low grade systematic inflammation (131). Adipose tissue secretes a number of pro-inflammatory cytokines including high-sensitivity C-reactive protein (hsCRP), tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-6 (131) which also circulate at elevated concentrations in asthma.

On the other hand, when the opposite relationship is examined, a number of potential ways in which asthma may affect physical activity are noted. Asthma may be a psychological barrier against physical activity (9, 13). The beliefs and perceptions of both the affected individual and their parents or caregivers may influence their physical activity participation (7, 132). With strenuous activity being a known risk factor for asthma exacerbations, individuals with asthma may actively avoid or reduce their physical activity in order to decrease the likelihood of experiencing an exacerbation of asthma symptoms. Further, individuals with asthma may believe that physical activity is not good for asthma (13) or that activity limitation is an inevitable consequence of their condition (7). Other studies have found that children may impose their own restrictions on physical activity, particularly at school, for fear of facing stigma and embarrassment at their need to medicate (133). Parents and caregivers may also intervene and restrict the physical activity participation of children with asthma for fear of inducing asthma symptoms (134).

A second barrier against physical activity relates to asthma medication. In resource poor settings, physical activity restriction could be due to logistical or financial issues limiting access to adequate health care and or appropriate medication. In well-resourced settings such as Australia, physical activity among those with asthma could be reduced due to non-adherence to asthma medication regimes (132). The incorrect or inappropriate use of asthma medication may ineffectively control symptoms during activity, and hence physical activities may simply be avoided as a potential solution.

2.4.2 Does physical activity affect asthma?

In part, this doctoral research sought to investigate of the effect of physical activity on asthma (see results Chapters Four and Six). A search of the literature showed that the effect of physical activity on asthma symptoms, control and quality of life remains unclear (135). Many of the studies that have been conducted were randomised controlled trials (RCT) and consisted of a physical activity or exercise intervention (121, 136). A systematic review of these randomised controlled trials conducted in children concluded that an exercise training program had positive effects on cardiorespiratory fitness outcomes and no apparent negative effects, but that there was limited evidence for the effect of training on asthma control, airway inflammation and bronchial hyper-responsiveness (136). The article reviewed included 29 studies of 1045 children aged 6 – 18 years. Training programs included in this review varied greatly in terms of exercise type, frequency, intensity, and durations of the training interventions. These differences prompted the review's authors to recommend that exercise training programs have at least 60 minutes of training twice a week for at least 3 months (136). However, training programs of this sort do not fulfil the WHO's activity recommendations for minimum physical activity levels in children, as described above. While a number of RCT's have since been published show a positive impact of physical training interventions on asthma (137-139), these short-term exercise interventions cannot be relied upon to reflect the benefits and effects of long-term, habitual physical activity, nor are they able to provide information about the effect of physical activity on asthma incidence. For these reasons RCT's were not considered to be the most appropriate study design to answer my research questions.

The existing scientific literature contains few studies that have investigated the effect of physical activity on asthma incidence (140-146). In their systematic review of 39 observational studies, Eijkemans *et al.* included a meta-analysis of five longitudinal studies (2). They concluded that higher levels of physical activity were associated with lower asthma incidence (odds ratio (OR): 0.88, 95%CI: 0.77-1.01), and hence may play a protective role against the development of asthma (2). However, this result was inconclusive due to the intersection of the confidence

interval with the null, and the fact that many of the studies did not sufficiently adjust for confounders. Furthermore, the results of this systematic review and meta-analysis did not differentiate between adult and child populations; of the five studies included in the meta-analysis (2), only one measured the association in adolescents less than 18 years of age (144). This Danish study used a population of twins aged between 12 and 41 years to investigate incident asthma at their 2002 follow up (144). Although they observed an association between physical activity and incident asthma, this result was not stratified by adult and child populations and therefore the results are unlikely to be true for child populations (144).

Hence, as part of this doctoral work, I conducted a systematic review of the relationship between habitual physical activity (as opposed to exercise and fitness interventions) and asthma outcomes specifically in child and adolescent populations. This systematic review is presented below in Chapter Four. The results of my systematic review were highly inconsistent, highlighting an unmet need for more longitudinal studies to observe the effect of habitual physical activity on the development and control of asthma symptoms, with a particular emphasis on child populations.

2.4.3 Does asthma hinder physical activity?

The second part of this doctoral work aimed to investigate the effect of asthma on physical activity (refer to results Chapters Five, Six, Seven and Eight). It is postulated that individuals with asthma may find it difficult to be as physically active as their peers, as their asthma symptoms or the fear associated with inducing an asthma attack may discourage them from participation. It is important to understand whether asthma does in fact, inhibit physical activity in affected individuals, as understanding the factors that dissuade activity will inform and enable public health specialists to provide recommendations for the encouragement and promotion of activity in this population.

Essentially, more longitudinal studies are needed to address the question of the effect of asthma status on physical activity, as this relationship is inconclusive within the literature (refer to the systematic review in Chapter Five).

A large proportion of studies that looked at this question were cross-sectional in nature, and therefore the inability to distinguish the temporality of this association was a major issue. Therefore, in my research, I sought to address this knowledge gap by using longitudinal data to observe whether asthma status has any effect on the amount of physical activity within child and adolescent populations.

2.5 Summary of knowledge gaps in the literature

Firstly, much of the existing literature on the relationship between asthma and physical activity involved the implementation of a fitness test or training program. Whilst such studies can give a strong indication of whether increasing physical activity levels can improve asthma outcomes, is not a true indication of the habitual physical activity performed in free-living situations, as such activity programs tend to stipulate the intensity, frequency, and duration of activity over a relatively short period of time. It is unlikely that an activity regime such as those implemented by trials are adhered to and continued over longer durations, and hence cannot accurately be used to describe habitual physical activity behaviours. Therefore, in my doctoral research, I restricted my research to observational studies.

Secondly, existing observational research was often conducted in adult populations. Since it is likely that healthy behaviours including physically active lifestyles in childhood extend into adulthood, research in young populations is warranted.

Thirdly, an examination of the available scientific evidence together with the systematic reviews conducted as part of this doctoral work (see results Chapters Four and Five) highlights a number of controversies regarding the existence and the nature of the relationship between physical activity and asthma. The systematic reviews conducted as part of this work have highlighted the substantial heterogeneity of research conducted in this field by presenting differing, and often, opposing results. Hence, further studies are required to determine whether a causal

relationship exists and the direction of the association. These questions can only be addressed through longitudinal investigations, but such studies are scarce in the existing literature.

Hence, my doctoral research aimed to address these gaps in the literature by employing and analysing longitudinal data from two large cohorts of Australian youth in order to investigate the directionality and temporality of the relationship between asthma and physical activity. In so doing, this doctoral work aimed to further improve our understanding of the causes and consequences of asthma.

Section Summary:

The relationship between physical activity and asthma is contentious; the existing literature is highly inconsistent, and several research gaps persist. For example, while the existence of a relationship between asthma and physical activity is debatable, the direction of the association also remains unknown. Furthermore, there is a scarcity of longitudinal data in cohorts of children and adolescents which impedes investigations of association and temporality in youth.

CHAPTER THREE: Research methodology

3.1 Chapter introduction

Chapter Three expatiates on the various styles of research methodologies used in this doctoral work. I begin by describing the design of the studies conducted within this thesis and explaining the underlying reasoning for my choice of the study design. Next, I present a detailed description of the longitudinal cohort studies from which data were sourced, and describe the variables used in my qualitative analyses. This chapter concludes with an overview of the statistical and analytical techniques employed within the various results chapters of this thesis.

3.2 Study design

Research questions in this thesis were addressed by analysing data from two population-based longitudinal cohort studies. Such studies tend to be representative of the general population, allowing for generalisability of conclusions from the study to the whole population from which the study sample was drawn. This is critical in translating research into public health policy. Further, longitudinal studies enable an investigation into the roles of risk factors in the natural progression from health to disease, and thus are fundamental in the assessment of research questions directed at elucidating temporality and causality. Considering that habitual physical activity, and health outcomes usually manifest over an extended period of time, data from cohort studies were considered the most suitable to address the outlined research questions. A trial is impractical, as it would require a large sample size and extensive funding to maintain the study over long periods of time. Additionally, the implementation of a short-term exercise intervention in a randomised controlled trial does not reflect the habitual physical activity patterns that I wish to investigate. Without nesting within a cohort study, case-control and cross-sectional designs are not appropriately suited for answering questions related to temporality. These designs are particularly susceptible to respondent errors such as inaccurate or poor recall bias or the deliberate over- or under-reporting of

desirable and undesirable factors as the exposures are not collected before the outcomes are assessed. Additionally, it is often difficult to select controls that are representative of a source population. Longitudinal study designs can overcome some of these issues. Baseline testing eliminates the need for recall and thereby minimises recall bias. Similarly, frequent reassessment of participants provides a more accurate overview of their risk profile and health status than measurements taken at a single timepoint.

3.3 Data sources

Two well-established cohorts of Australian children and adolescents were used to address the research questions presented in the introduction of this thesis. The first of these cohorts, *Growing Up in Australia*: Longitudinal Study of Australian Children (commonly simplified to Longitudinal Study of Australian Children or LSAC) is a national prospective study of children from all regions of Australia (147). The study is funded by the Australian Government Department of Family and Community Services and investigates all aspects of childhood development (147, 148). The second cohort is the HealthNuts study, a longitudinal study that spans from approximately the first to the tenth year of life. This ongoing study is run by the Murdoch Childrens Research Institute (MCRI) in Melbourne, Australia. These cohorts are described in greater detail below.

3.3.1 Longitudinal Study of Australian Children (LSAC)

Designed to investigate the impact of social, economic and environmental factors on the health, well-being and development of Australian children, LSAC is multiple cohort, cross-sequential design study, a design that combines longitudinal and cross-sectional data collection methods (149, 150). A sophisticated sampling strategy was employed to select a study sample that was representative of all Australian children (147). Recruitment of the two staggered cohorts from commenced in 2003 and 2004 (148). The first 'B' (baby) cohort recruited 5000

infants aged 0-1 years (148). These were babies born between March 2003 and February 2004 (151). The second cohort recruited also 5000 children aged 4-5 years (148). Children in this second "K" (Kindergarten) cohort were born between March 1999 and February 2000 (151). However, findings in this thesis are based on the K cohort only due to the fact that the first two waves of B cohort data would not meet the age inclusion criterion. For example, since a diagnosis of asthma before the age of 5 years is controversial, the first three of the six waves of B cohort data would have been excluded. By restricting my analyses to use of the K cohort only, I was able to analyse more waves of data and observe the relationships during the important transitional period from childhood to adolescence.

3.3.1.1 Data collection within the LSAC

The initial wave of data was collected in 2004, and subsequent waves were collected every two years. The study is ongoing, with wave 8 data collection in progress. However, when I commenced these analyses, the most recently released data were for wave 6, at which stage K cohort children were aged 14 - 15 years. As mentioned above, this PhD employed all available data from the K cohort, that is, data from waves 1 to 6 were included in these analyses. Data were collected from parents, teachers, and carers, as well as from the children themselves when they were old enough to provide responses, using a variety of data collection tools (148).

Sampling and recruitment methodology for the LSAC has previously been described in detail (147). Briefly, a nationally representative sample of 5000 children born between March 1999 and February 2000 (the "K" cohort; aged 4-5 years) were recruited in 2004. Follow ups occur every two years, where data is collected via interviews, questionnaires, time use diaries (TUDs) and through direct anthropometric measurements. At each wave, the LSAC team analyses and documents participation and non-response. These documents are readily available on the LSAC website, however, I have summarised participation at each wave in Table 3.1, to demonstrate the high rates of participation over time within the LSAC.

Table 3.1: Overview of LSAC data collection from wave 1 to 6.

	Wave 1 (2004)	Wave 2 (2006)	Wave 3 (2008)	Wave 4 (2010)	Wave 5 (2012)	Wave 6 (2014)
K cohort	4-5 years	6-7	8-9	10-11	12-13	14-15
Cross-sectional response	4983	4464	4331	4169	3956	3537
Longitudinal response	N/A	4464	4196	3940	3682	3276
Cross-sectional attrition rate (%)		10.4	13.1	16.3	20.6	29.0
Longitudinal attrition rate (%)		10.4	6.0	6.1	6.6	11.0
TUD completed n (%)	7449* (75)	6909* (77)	5924* (68)	3994 (96)	3649 (94)	3071 (91)

Cross-sectional response is number of children who responded to that particular wave, longitudinal response is number of children who responded up to that wave. * denotes the combined number of returned TUDs in the waves that requested the completion of two TUDs. % is the actual participation of those eligible. Source: LSAC technical paper (151).

3.3.1.2 Physical activity data within the LSAC

Physical activity data were measured indirectly through the completion of Time Use Diaries (TUDs). The LSAC has produced a number of documents that provide an intensive discussion of the development of the tools and the methodology of the TUD data collection (152-154). TUDs are often used as an effective means of collecting information on the way in which children spend their time (154). It is a validated measurement tool, however its utilization needs to be modified to be appropriate for the target age group (155). Hence, the TUDs used at waves 1-3 differ from those used at waves 4-6.

Examples of the diaries can be found in the appendices of this thesis. In earlier waves (wave 1 to 3), a 'light diary' was used (154). At the face to face interview, parents were shown how to complete the light TUD which divides the 24 hour day into 96 intervals of 15 minutes (152, 154). Parents were asked to complete the child's activity diary (by selecting from 26 pre-coded activities), indicating whom the child

was with, and the location of the activity for each 15 minute interval of the day, for one weekday and one weekend day (154, 155). From wave 4 onwards, children were asked to complete one TUD themselves by recording the activities they performed throughout the day, rather than selecting from pre-coded activities (154). At an interview with the study child, on the date after completion of the diary, data were entered in a computer-assisted interview (CAI). Free answer questions were later coded for analysis.

'Light diaries" were collected for both cohorts for waves 1 to 3. TUDs were completed by the K cohort study child in waves 4 to 6 (154). Response rates are presented below in Table 3.2:

Table 3.2: Response rates for the Time Use Diaries (TUDs) at each wave.

		Wave 1 (2004)	**Wave 2 (2006)**	**Wave 3 (2008)**	**Wave 4 (2010)**	**Wave 5 (2012)**	**Wave 6 (2014)**
K cohort		4-5 years	6-7	8-9	10-11	12-13	14-15
TUD 1	Eligible	4983	4464	4331	4169	3871	3387
	Actual	**3867**	**3446**	**2961**	**3994**	**3649**	**3071**
	%	78	77	68	96	94	91
TUD 2	Eligible	4983	4464	4331	N/A	N/A	N/A
	Actual	**3582**	**3460**	**2963**			
	%	72	78	68			

"Eligible" is the number of children who received the diary, and "Actual" is the number of diaries returned (156).

For this analysis, I used only those coded variables that directly correspond to physical activities and exercise, rather than work-related activities such as cleaning or tiding up. While this meant that the physical activity estimates I obtained were more conservative than the actual amount of physical activity performed, this restriction reduced the ambiguity related to certain coded activities. For example, "mowing the lawn" could either be done manually or could involve a ride on lawn mower, in which case would involve less energy expenditure. Similarly, "car washing" could be manual labour, or accompanying an adult to the car wash. Hence, to minimize the possibility of incorrect classification I restricted the activities of interest to structured or unstructured active play, organized sports/lessons/activities, riding bike/scooter/skateboard and walking/running skipping etc. Since the diary did not capture the level of intensity of each activity, I

will assume that all of the activities of interest were of moderate to vigorous intensity. That is, I assume that all of the included activities had a metabolic equivalent (MET) score of 3.0 or greater, as per the Compendium of Energy Expenditure for Youth (157).

For wave 3 diary data, I identified the variables that correspond to the total time spent in each coded physical activity. A continuous variable was created for minutes spent in physical activity. The total time spent in physical activity equated to the summation of the time spent in each coded physical activity. Next, a binary variable for activity was created using the WHO guidelines for recommended time spent in moderate to vigorous physical activity (MVPA) daily. Children who perform less than the recommended 60 minutes daily were classified as "insufficiently active" while those who engage in more than 60 minutes were categorized as "sufficiently active" (158).

For data collected at waves 4 to 6, I calculated the time in physical activity for each child by subtracting its start time from the start time of the next activity since the end time of each activity was not recorded. The total activity time was the sum of minutes spent on all physical activities. The continuous and binary physical activity variables were then created as described above.

3.3.1.3 Asthma data within the LSAC

Data regarding the respiratory health of these children and adolescents were collected through the study questionnaires. Respondents were asked several questions regarding the participant's history of wheezing and asthma diagnosis (Table 3.3). While the wording of some of the questions differed slightly depending on whether the responder was the study child or their parent, the constructs remained the same. The full questionnaires are available on the LSAC website. I have included a link to the website in the appendices of this thesis.

Table 3.3: Phrasing of the questions on asthma and wheeze used at different waves of the LSAC.

Survey Question	Waves where this question was asked
Has a doctor ever told you that the child has asthma?	2, 3, 4
In the last 12 months has the child taken any medication for asthma?	2, 3, 4, 5, 6
In the last 12 months, has the child had an illness with wheezing in the chest which lasted for a week or more? ('Wheezing' includes whistling or rattling noise)	2, 3, 4, 5, 6
Since the last interview, has a doctor told you that child has asthma?	5, 6

Participant responses to these questions were used to define current asthma as a parental report of doctor-diagnosed asthma and either wheeze and/or asthma medication use in the past 12 months (159). Similarly, current wheeze was defined as parental report of any wheezing in the last 12 months (160).

Analyses that utilized the LSAC data are presented in Chapters Six and Seven of this doctoral thesis.

3.3.1.4 Ethics of the LSAC

Ethical approval for the LSAC was granted by the Australian Institute of Family Studies Ethics Committee, which is a Human Research Ethics Committee (HREC) registered with the National Health and Medical Research Council (NHMRC). Consent for child participation was obtained from parents or carers. Furthermore, within each state and territory, education authorities granted approval to conduct research among teachers. Approval to access the de-identified data was granted on the 13th of January 2016 by the Australian Institute of Family Studies within the Commonwealth of Australia's Department of Social Services.

3.3.2 The HealthNuts Study

The HealthNuts study is a population-based longitudinal study that was primarily designed to investigate the aetiology, prevalence and burden of allergy (food allergy in particular) in early childhood (161). The sample was intended to be representative of children living within 70km of Melbourne's central business district (161).

Recruitment occurred between September 2007 and August 2011 (161). A total of 5,276 children were recruited into this longitudinal study at the age of twelve months as they presented for routine immunization at clinics in and around greater metropolitan Melbourne (161).

3.3.2.1 Data collection within the HealthNuts

The HealthNuts study consists of multiple waves of data collection. After recruitment at 1 year of age, the cohort has been followed up at the ages of 4 and 6 years (161). At each wave, data were collected via the administration of a questionnaire, as well as through clinical investigation of individuals with food allergies and food sensitisation at ages 1 and 4, and clinical investigation of the full cohort at age 6 years (Figure 3.1) (161). The clinical investigation at the 6-year follow up of the HealthNuts study included spirometry and skin prick testing (SPT), height, weight and body composition measurements, and the collection of both questionnaire and accelerometry data using GeneActiv accelerometers. The 10-year follow up of the HealthNuts study commenced in 2016.

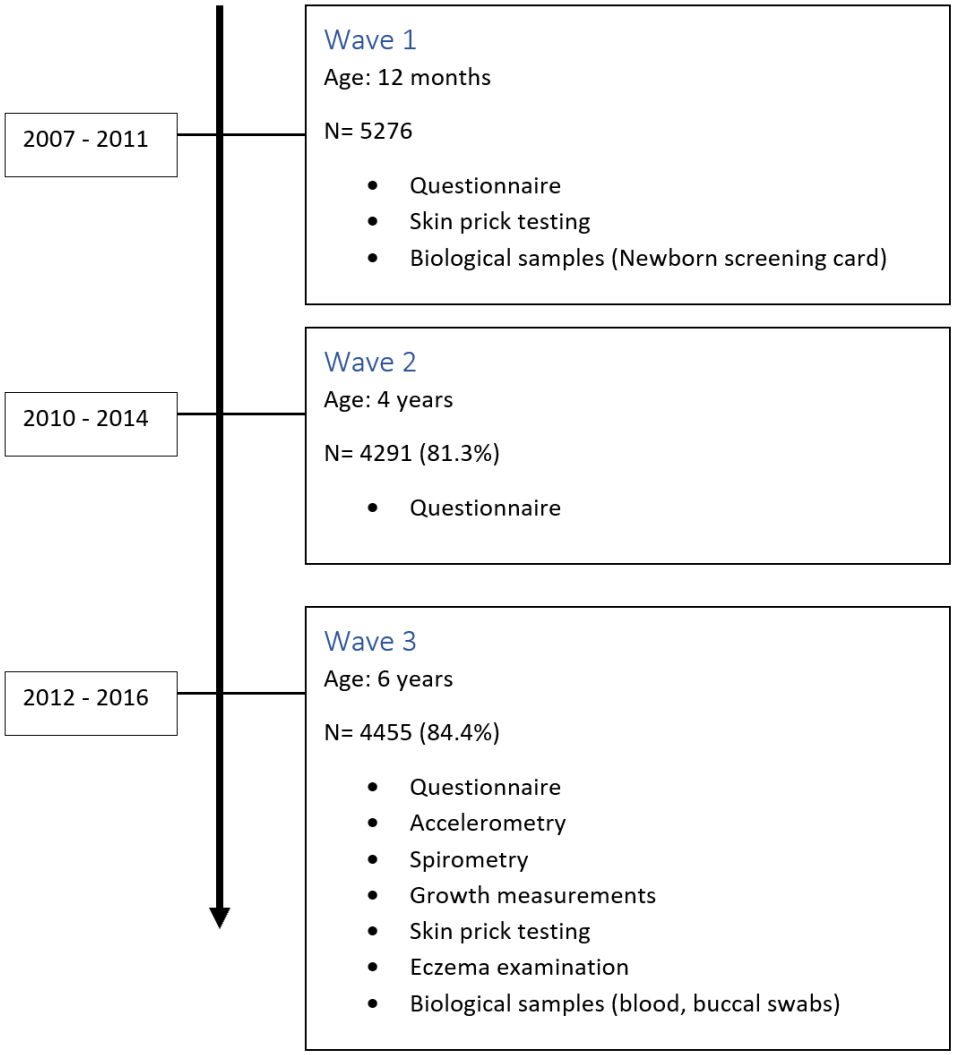

Figure 3.1: Schematic of the HealthNuts follow-ups with a summary of the data collected.

3.3.2.2 Asthma data within the HealthNuts

Although not specifically an asthma study, the HealthNuts data routinely collected asthma and allergy data. Each HealthNuts follow up included a questionnaire component which utilized standardized questions on asthma and allergy taken from the International Study of Asthma and Allergies in Childhood (ISAAC) (161-163). At both the 4 and 6-year follow ups parents or guardians were asked several questions based on the ISAAC regarding their child's history of wheezing and asthma diagnosis. For asthma, these questions included: "Were you told by a doctor that your child had asthma?" and either "In the last 12 months, has your child used any

medicines, pills, puffers or other medications for wheezing or asthma?" or "Has your child had wheezing or whistling in the chest in the last 12 months?" The questionnaires included the following questions for wheeze: "Has your child ever had wheezing or whistling in the chest at any time in the past?" and "Has your child had wheezing or whistling in the chest in the last 12 months?"

Responses to the questionnaires were used to define current asthma as a parental report of doctor-diagnosed asthma and either wheeze and/or asthma medication use in the past 12 months (159). Similarly, current wheeze was defined as parental report of any wheezing in the last 12 months (160). The study questionnaires are included in the appendices of this thesis.

3.3.2.3 Physical activity data within the HealthNuts Study

The 6-year data collection of the HealthNuts commenced in 2012 and terminated in 2016. Toward the latter part of the 6 year follow up testing, that is from 2015 onward, wrist-worn, waterproof GENEActiv (Gravity Estimator of Normal Everyday Activity, ActivInsights Ltd, Cambridgeshire, UK) triaxial accelerometers were dispensed at the 6 year follow up appointments, and parents were given instructions for the use of these devices. Children were required to wear the accelerometer watch on the left wrist 24 hours per day for 8 consecutive days, including during sleep, while swimming and at bath time. Parents were also asked to note the child's waking and bedtime and to briefly describe the child's activities per day on the paper log provided. Furthermore, they were asked to note times when the watch was removed and replaced, and the reasons for device removal.

At the end of 2017, I travelled to Adelaide, South Australia to process the HealthNuts accelerometry data. I did this with the invaluable advice and guidance of Dr Francois Fraysse and Professor Tim Olds at the University of South Australia (UNISA) and followed their reported technique (164). The processing is described in detail below.

3.3.2.3.1 Processing of the Accelerometry data

For this analysis, I sampled the activity at a frequency of 100 Hz and downloaded at 1 second epochs which were then collapsed into 60 second epochs for this analysis. This was done by summing the raw acceleration data over 60 second epochs and subtraction gravity to compute the signal vector magnitude (164):

$$SVM = \sum_{60s} \left| \sqrt{a_X^2 + a_Y^2 + a_Z^2} - g \right|$$

Where a_X, a_Y and a_Z are the three components of the acceleration and g is the acceleration of gravity (9.81 m/s^2) (164). Smaller epoch lengths are generally recommended for research in children as it increases the sensitivity to detect the brief bursts of activity (165). However, there is precedent for collapsing small epochs into larger ones (166) to minimize the misclassification of sedentary behaviour in children (165). I then imported the 60 second epoch data into the custom Matlab software *Cobra*, which was developed by the team at the UNISA. Cobra produces a graphical user report for the processing on accelerometry data. The software enables researchers to input the threshold values for their data, which the program uses to colour code physical activity intensities (Figure 3.2). Next, I manually inspected the data and compared them to the paper activity logs provided by the parents. I noted the sleep times, manually corrected for unreported periods of non-wear, and re-categorised documented non-wear time as time spent in MVPA where the paper logs indicated that the device had been removed for reasons pertaining to sport participation.

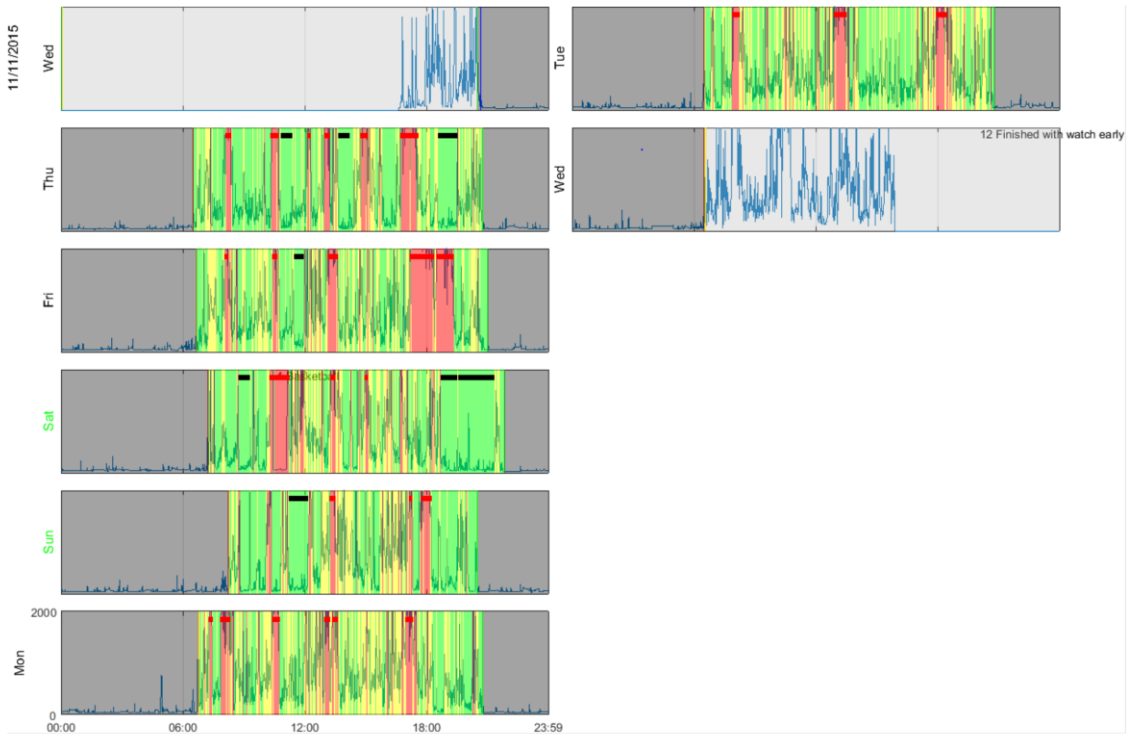

Figure 3.2: An example of the COBRA accelerometry output for the 8 days of accelerometry wear. MVPA in red, light intensity activity in yellow, sedentary activity in green and sleep time in dark grey. Black bars indicate bouts (of at least 10 minutes) of sedentary time, while red bars indicate bouts of MVPA.

Files were selected for the analyses if they fulfilled the following criteria. Individual days containing less than 16 hours of wear within a 24-hour period, or less than 10 hours of wake wear time were considered invalid (164, 167). A minimum of 4 valid days (164, 167) constituting 3 weekdays and 1 weekend day were required for inclusion in this analysis. Wake wear time was classified into sedentary time, light, moderate or vigorous intensity physical activity according to cut points defined by Phillips *et al.* (168) and proportionally adjusted to account for the different sampling frequency used (164). Cut points used to classify physical activity intensities are tabulated below (Table 3.4):

Table 3.4: Cut offs used to define physical activity intensities

Activity classification	Cut off
Sedentary	<488 g.min
Light intensity physical activity	<1575 g.min
Moderate to vigorous intensity physical activity	>4350 g.min

Processed accelerometry data were returned to the HealthNuts team at MCRI so that it may be used in other research; for example, a student recently used the accelerometry data in their Honours research project, which is expected to be submitted for publication.

The findings of the analyses completed using the accelerometery data and associated HealthNuts data are reported in Chapter Eight.

3.3.2.4 Ethics of the HealthNuts

Ethical approval for the HealthNuts at 1 year was obtained from the Victorian State Government Office for Children HREC (ref. no. CDF/07/492), the Victorian State Government Department of Human Services HREC (ref. no. 10/07), and the Royal Children's Hospital HREC (ref. no.27047). Ethical approval for the 6 year follow up, inclusive of this analysis and processing of the accelerometry data, was obtained from Royal Children's Hospital HREC (ref. no.32294). Written parental consent for child participation was obtained at recruitment.

3.4 Statistical and analytical techniques

A variety of approaches were employed to address the research questions within this thesis. The analytical techniques used varied throughout the thesis, as each technique was specifically selected to appropriately answer each individual research question, however a general description is provided below.

3.4.1 Systematic review

Each systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (169, 170) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (171) guidelines.

Where appropriate, data were meta-analysed using fixed- and random- effects models, producing a pooled estimate and pooled 95% confidence interval, and I^2 statistic to quantify the level of heterogeneity amongst the pooled articles.

3.4.2 Covariate identification

Potential confounding variables for the associations of interest within this thesis were identified from the literature and directed acyclic graphs (DAGs) were created using DAGitty software (172) to assist in the determination of confounders to be controlled for in the models. A DAG assists with the selection of potential confounders through the visualisation of theoretical relationships between variables. Confounding variables, common causes and various pathways can be identified, thereby minimising bias in study design and analysis (173).

The most important covariates considered were sex, socioeconomic status (SES) and body mass index (BMI). Each of my analyses included sex, which is a known modifier of the association between asthma and physical activity (174). Additionally, I accounted for SES, which is associated with both reduced physical activity (175) and increased asthma (176), and hence is a classic confounder.

However, the role of BMI in the relationship between asthma and physical activity is more complex. For example, a high BMI may act as a confounder of the relationship between physical activity and asthma, with overweight or obese people potentially undertaking less physical activity (177, 178) and also being at higher risk of incident asthma and asthma symptoms (129). Alternatively, a high BMI could act as a mediator of this relationship, where low physical activity leads to a high BMI and consequently increases risk of asthma incidence. However, to my knowledge, there have been no published studies that have formally investigated this.

BMI varies considerably with age in growing children as their bodies undergo a number of physiological changes and hence age should be accounted for in a calculation of BMI in children and adolescents (179, 180). In 2000, a collaborative effort between six large, nationally representative, cross sectional studies from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore and the USA enabled a

team of statisticians to develop centile curves for BMI in children aged 2 to 18 years (179). In doing so, they averaged the data from the aforementioned countries, and compiled international cut off points for overweight and obesity for children between the ages of 2 and 18 years (Figure 3.3). These international cut off points were defined to pass through BMI of 25 and 30kg/m^2 (the values which respectively represent the lower thresholds of overweight and obese in adults) at age 18 years (179). These thresholds were used my analyses. My data analyses investigated effect modification by BMI, and where no evidence for effect modification was found, I adjusted for it within the models.

	Body mass index 25 kg/m^2		Body mass index 30 kg/m^2	
Age (years)	Males	Females	Males	Females
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11
10.5	20.20	20.29	24.57	24.77
11	20.55	20.74	25.10	25.42
11.5	20.89	21.20	25.58	26.05
12	21.22	21.68	26.02	26.67
12.5	21.56	22.14	26.43	27.24
13	21.91	22.58	26.84	27.76
13.5	22.27	22.98	27.25	28.20
14	22.62	23.34	27.63	28.57
14.5	22.96	23.66	27.98	28.87
15	23.29	23.94	28.30	29.11
15.5	23.60	24.17	28.60	29.29
16	23.90	24.37	28.88	29.43
16.5	24.19	24.54	29.14	29.56
17	24.46	24.70	29.41	29.69
17.5	24.73	24.85	29.70	29.84
18	25	25	30	30

Figure 3.3: Table of international cut off points for overweight and obesity by gender in children and adolescents aged 2 to 18 years as developed by Cole *et al*. (179).

3.4.3 Statistical techniques

Statistical analyses were conducted using Stata statistical packages (181). The analytical techniques used in the different sections of this thesis are described within their respective chapters. However, in general, the qualitative analysis conducted in this doctoral work employed one or more of three statistical techniques: Linear regression, logistic regression, and generalised structural equational modelling (GSEM).

Linear regression is the widely used to express the relationship between a set of variables. The association between independent risk factors (x_n) and a continuous outcome variable (y) is quantified through the use of an elegant mathematical equation (182, 183):

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n$$

Regression coefficients (β_n) corresponding to risk factors are interpreted as the "change in the outcome per unit change of the risk factor". Zero change signifies no association.

Logistic regression varies from linear regression in that the outcome variable is a binary variable (i.e. takes the values of either 0 or 1). Logistic regression estimates the probability of the outcome of interest, *P* as follows:

$$P = \frac{e^{\beta_0 + \beta_1 X}}{1 + e^{\beta_0 + \beta_1 X}}$$

Where the regression coefficient $\beta_1$represents the multiplicative change in the odds of the outcome, when the risk factor *X* changes by one unit, commonly interpreted as the odds ratio. Similarly, no change signifies no association (184).

Generalised Structural Equational Modelling (GSEM) is a combination of factor analysis and regression (185). First, a relationship between variables is postulated and data is used to confirm whether the relationship holds. GSEM allows for analysis of different types of outcomes simultaneously, and an outcome variable in one relationship can be specified as a risk factor in another relationship. Relationships between variables of interest are represented by regression or path coefficients,

where zero coefficients imply no path or association. Using this modelling technique with data collected at multiple time points, allows testing of associations in both directions (186). Therefore, by enabling the assessment of whether the dependent variable is causal antecedent of the independent variable, or vice versa, we are able to examine bidirectionality of associations.

In general, the data analyses performed within this doctoral work utilised univariate and multivariate linear or logistic regression techniques, depending on whether the outcome variable was continuous (for example, where the outcome was minutes spent in MVPA) or categorical (for example, where the outcome was asthma status and could take the values of either yes or no) to produce estimates of association and 95% confidence intervals. Effect modification was investigated by comparing models with and without interaction terms using a likelihood ratio tests (LRT), small p values indicated effect modification.

Specifically, in Chapter Six, Generalised Structural Equational Modelling (GSEM) was used to investigate bidirectionality across several waves using the LSAC data. This approach involved formulation of linear and logistic regression models that looked at the relationship of asthma and physical activity in one direction and then in the other across multiple waves of data. The data is then fitted to the models to indicate which model best fits the data. In Chapter Seven, adjusted linear regression models were used to assess the associations between asthma and physical activity at five different ages in the LSAC cohort. Finally, adjusted linear regression models were used to assess the association between asthma, lung function and physical activity cross-sectionally and longitudinally in the HealthNuts children in Chapter Eight of this thesis.

3.4.4 Missing data

Missing and incomplete data is an important issue that can significantly affect the conclusions drawn from an analysis of the data (187). Missing data could potentially influence the representativeness of the study sample, thereby distorting the inferences made on a population level. Data may be incomplete or missing data for

a number of reasons related to either the participant or study design or the interaction between them (187). For example, a participant may overlook or refuse to answer a question, or may be lost to follow up, while researchers may be responsible for ambiguous questions, or errors in data collection or data entry that result in missing data. Missing data can be classified as follows (188):

- Missing completely at random (MCAR) – when missing data is completely independent of any variables of interest, in which case the analysis remains free from bias which may distort the results.
- Missing at random (MAR) – when missing data can be accounted for by the variables for which there is complete information.
- Missing not at random (MNAR) – where the value of the missing data is related to the reason it is missing. This type of missingness introduces a higher degree of bias than either of the other classifications, as the sample is disproportionately skewed.

Whilst prevention of missing data would always be ideal, it is not always possible, particularly in the context of longitudinal studies where the time between follow ups may be lengthy or in circumstances where secondary analyses of data are conducted (187). There are several statistical techniques for dealing with missing data:

- Imputation – where missing values are filled
- Omission – where samples with missing values are omitted from the analysis resulting in a smaller dataset with no missing data. This is also referred to as complete case analysis.
- Analysis – where methods are not affected by missing data are applied

The data analyses within this thesis primarily employed complete case analysis of the data, as missingness was assumed to be missing completely at random and missing data were generally minimal.

CHAPTER FOUR: Summary of the evidence on the effect of physical activity on asthma

4.1 Chapter introduction

This chapter contains one of two published systematic reviews undertaken as part of this doctoral work. This review synthesised the evidence on the relationship between physical activity with subsequent asthma outcomes in children and adolescents. Although this review was published later, it was conceptualised early in the PhD to complement the first published review (see Chapter Five). The reviews were designed to complement each other by investigating the evidence for the relationship between physical activity on asthma, and the relationship between asthma and physical activity.

4.2 Research question

Does physical activity i) decrease the risk of developing asthma, ii) reduce asthma symptoms or iii) increase lung function in children and adolescents?

4.3 Synopsis of the review

The causes of asthma are unknown; however, the condition appears to have both genetic and environmental foundations (189). Since genetics cannot be controlled, the identification of environmental and lifestyle factors that may alter the risk of asthma development and control has been the focus of much research (78, 190). Physical activity has been identified as one such potentially modifiable risk factor. Prior to my systematic review, two systematic reviews on the relationship of physical activity and asthma had been published (2, 191). Both systematic reviews concluded that low physical activity increased risk of incident asthma but these did not restrict to longitudinal cohort studies (2, 191) and one based their conclusion on the few longitudinal studies conducted in adult populations, as compared to

paediatric populations (2). Further, neither review investigated lung function outcomes. Finally, as these reviews were published in 2012 (2) and 2016 (191), there was an opportunity to update these systematic reviews with new information.

Therefore, there remained a need for investigation into whether physical activity is associated with the development and symptoms of asthma in youth. This review, therefore, aimed to explore and collate the available evidence on the influence of physical activity as a risk factor for asthma incidence, prognosis and lung function outcomes in children and adolescents.

English language studies that measured physical activity as the exposure and asthma development, persistence or lung function parameters were measured subsequently in children and adolescents up to the age of 18 years were included in this systematic review. The review consisted of a search of PubMed and EMBASE databases from which 2298 articles were retrieved, and 739 duplicates were deleted. The remaining items were screened by title and abstract. Following the examination of 63 full texts, nine studies met the inclusion and exclusion criteria. Six of these investigated the effect of physical activity on asthma outcomes and three investigated lung function outcomes. Risk of bias was explored, and the studies generally exhibited low to moderate risk of bias. Due to the substantial heterogeneity in the populations included, the methods of exposure and outcome assessment, and the small number of studies within categories, a meta-analysis could not be performed.

The substantial review highlighted several gaps in the literature. First, despite the increased interest in physical activity as a potentially modifiable risk factor in asthma, there is a scarcity of longitudinal studies that have investigated this association in children and adolescents. Further, there was only one study that employed accelerometers to measure physical activity; most physical activity data were collected subjectively. Secondly, although most research was conducted in high income settings, there were no Australian data. Limited clinical recommendations could be made from this review due to the startling lack of consistency across the study methodologies and results.

4.4 Publication

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ORIGINAL ARTICLE

WILEY

Does physical activity strengthen lungs and protect against asthma in childhood? A systematic review

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Abstract

Background: Physical activity may be a potentially modifiable risk factor for asthma and driver of lung function development. This systematic review aimed to summarize the available evidence concerning the longitudinal effect of physical activity on the development of asthma, the persistence of asthma symptoms and lung function outcomes in children and adolescents.

Methods: PubMed and Embase electronic databases were searched for all original articles that investigated the longitudinal association between physical activity and asthma outcomes or lung function outcomes in children and adolescents. The search and data extraction were conducted by two independent researchers. The methodological quality of the included studies was assessed using two critical assessment tools.

Results: The literature search retrieved 2298 publications from the electronic databases. All articles were screened, and 2289 were subsequently excluded, resulting in nine longitudinal studies eligible for inclusion in this review. Two studies found no association with incident wheeze, and two of four found no association with various asthma outcomes. Three studies investigated the effect on lung function: one observed an association in boys only, one observed an association in girls only, and one found no associations.

Conclusion: The evidence was highly inconsistent for the relationship between physical activity and asthma and lung function outcomes. Hence, we conclude that there is insufficient evidence to suggest that physical activity has a long-term effect on the risk of asthma development in youth. Furthermore, there is insufficient evidence to determine the longitudinal effects of physical activity on lung function in children.

KEYWORDS

adolescents, asthma, children, lung function, physical activity, systematic review

1 | INTRODUCTION

Asthma affects approximately 339 million people worldwide[1] and is the most common chronic condition affecting children. It is characterized as chronic inflammation of the airways[2] associated with reversible airway obstruction and bronchial hyperresponsiveness,[3] leading to symptoms of coughing, wheezing and shortness of breath. Additionally, lung function (LF) impairment in childhood leads to abnormal patterns of LF growth and decline in adulthood.[4]

Recent efforts have focussed on identifying potentially modifiable targets for asthma prevention.[3,5] One such factor is physical activity (PA); which is thought to potentially play a protective role against asthma through its known anti-inflammatory effects.[6] For this reason, several international health authorities, including the World Health Organization (WHO), endorse PA participation for variety of health benefits.[7-9] Currently, a minimum of 60 minutes of moderate-to-vigorous physical activity per day is recommended for children and adolescents between the ages of 5 and 17 years.[7-9] However in 2010, the WHO estimated that globally 81% of adolescents aged between 11 and 17 years were insufficiently active.[10,11]

Two systematic reviews investigating the effects of PA on asthma incidence and prevalence have previously been published.[12,13] However, the first review was published seven years ago and did not restrict to child populations.[13] The second, more recent review seemed to have overlooked several cohort studies,[14-19] including all of those included in the present review, and furthermore did not consider the effect of PA on asthma symptoms.[12] Neither review restricted their inclusion to cohort designs, nor did they investigate the effect of PA on LF in children.[12,13]

The present review, therefore, intends to collate the literature regarding the longitudinal effect of PA on asthma incidence, on the persistence of asthma symptoms and on LF outcomes, focussing specifically on youth. This review will also be the first to synthesize the available evidence on the relationship between PA and LF outcomes in youth. Specifically, this systematic review aims to address the following research questions:

1. Do children and adolescents who engage in increased PA experience (a) decreased risk of developing asthma or (b) reduced asthma symptoms among asthmatics, compared to their less active peers?
2. Are higher levels of PA associated with increased LF in children and adolescents (a) with asthma and (b) without asthma?

Key Message

This is the first systematic review to investigate the evidence for the longitudinal effect of physical activity on asthma incidence, symptoms and lung function in children and adolescents. The review found that the literature contained highly inconsistent results and identified several methodological limitations within the field, which led to the conclusion that there was insufficient evidence to determine the effect of physical activity on asthma and lung function in children and adolescents.

2 | METHODS

This systematic review was registered with Prospero, the international prospective register of systematic reviews (registration number: CRD42018098833), and the reporting of this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

2.1 | Search strategy

A systematic search was conducted for publications in the PubMed and Embase electronic databases to obtain all articles that investigated the relationship between PA and asthma or lung function. Key terms were identified for each construct and combined using the Boolean operators 'OR' within the construct and 'AND' between constructs. Medical subject (MeSH) terms were included in the PubMed search as appropriate. The complete search strategies are appended below (Appendix S1). Furthermore, reference lists were manually checked to identify any articles that may have been missed by the search. The search was conducted independently by two researchers (RC and FMP), and any discrepancies were resolved by a third (MAR). A final search was conducted on 18 March 2019.

2.2 | Eligibility criteria

Studies where PA was measured as the exposure variable and asthma status or LF was measured subsequently in children and adolescents up to the age of 18 years were included in this review. Cross-sectional, case-control studies and intervention studies in which children underwent exercise programmes or fitness training were excluded, as this review was primarily interested in the longitudinal effect of habitual PA. Studies where sedentary behaviour was the exposure of interest were excluded, since PA and sedentary behaviour are considered to be distinct behaviours.[21] Additionally, animal and in vitro studies, those conducted in special populations (eg, athletes), non-English language articles, conference abstracts and letters or reviews that did not present original data were excluded. There were no restrictions on date of publication. Inclusion and exclusion criteria were assessed independently by two researchers (RC and FMP), and any discrepancies were resolved by a third (MR).

2.3 | Data extraction

The following information was extracted from each eligible article: author, date of publication, location of study, the study population, study design, measurement tools and timing of exposure and outcome measurements, all confounding variables that were adjusted for in the analysis, unadjusted and adjusted (where both were available) reported measures of association, and the author's conclusions. In an attempt to include all eligible articles, one author was contacted, and clarification of the results of their paper was obtained.[22] Data were tabulated separately according to the outcome measured.

2.4 | Critical appraisal

The quality of eligible articles was assessed using two critical appraisal tools. Firstly, articles were assessed using the preliminary version of the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E;

available online at http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/). This tool assessed bias in several aspects of a study: bias due to confounding, participant selection, exposure classification, departures from intended exposure, missing data, outcome measurement and selection of the reported result. Each study was then given an overall bias score. In addition, articles were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Each article was awarded a score out of four for selection bias, two for comparability and three for bias in the outcome assessment, with a maximum total score of nine points. An a priori decision was taken to exclude articles that scored poorly (defined as an overall NOS score <5 and an overall ROBINS-E score greater than moderate) on both tools.

3 | RESULTS

3.1 | Literature search

The search identified a total of 2298 articles. Of these, 739 duplicates were removed, and a further 1496 were excluded after screening of titles and abstracts. The remaining 63 articles were assessed in detail, and 53 publications were subsequently excluded as they did not meet the inclusion criteria (Figure 1). Finally, the paper by Twisk et al[22] was excluded as the longitudinal analysis included outcomes measured beyond the age of 18 years. The process resulted in nine articles eligible for inclusion in this review. Included studies were stratified by outcome (Tables 1 and 2).

3.2 | Critical appraisal

Using the ROBINS-E tool, included studies were found to contain low[14,17,18,23]-to-moderate[15,16,19,24,25] levels of overall bias. Additionally, studies scored five,[16] six,[15,19,25] seven[14,18,23] or eight[17,24] out of nine points on the NOS, indicating moderate-to-high quality; hence, all studies were included in this review. Individual quality assessment scores are presented in Table 3.

3.3 | PA and asthma outcomes

Six studies assessed the relationship between PA and asthma-related outcomes[14-19] (Table 1). All of these studies were conducted

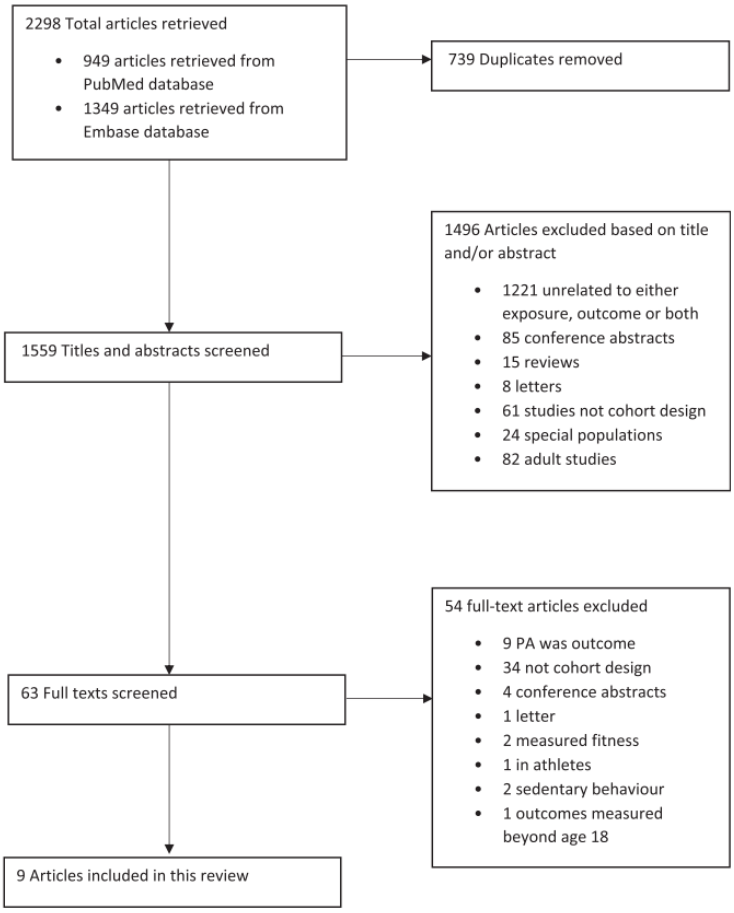

FIGURE 1 Flow diagram of studies from search to inclusion in the systematic review

TABLE 1 Details of six included articles that investigated the effect of physical activity on asthma outcomes

Author, date, location	Sample size and participant age	Physical activity measurement	Asthma outcome measurement	Main effects	Covariates included	Author's conclusions
General population studies						
Byberg, 2016[17] Norway; 'the Stavanger study'	617 children followed from birth. At first follow-up, girls were 10.8 y and boys were 11.8 y old. At the second follow-up, both sexes were aged 12.8 y	Maternal reports of child's physical activity at age 3-6 and ages 6-10 y using the 'Stanford Brief Activity Survey', a questionnaire validated for adults. Activity was categorized as low = passive and/or not so active, normal = active, high activity = very active	Parental reports of doctor's diagnosis of asthma ever were evaluated at the first follow-up. At the second follow-up, children responded to the ISAAC questionnaire and current asthma (defined as ever asthma and asthma symptoms or the use of asthma medications in the last 12 mo) was evaluated	(a) Asthma ever by first follow-up: PA at 3-6 y, n = 454 (LR-*P* = .014); OR (95% CI) Normal PA, n = 275 (ref); Low PA, n = 57 3.61 (1.56, 8.36) High PA, n = 122; 1.34 (0.61, 2.97) PA at 6-10 y, n = 558 (LR-*P* = .038); OR (95% CI) Normal PA, n = 351 (ref) Low PA, n = 92; OR = 2.52 (1.24, 5.12) High PA, n = 115; 1.02 (0.46, 2.28) (b) Current asthma at second follow-up: PA at 3-6 y, n = 361 (LR-*P* = .475); OR (95% CI) Normal PA, n = 220 (ref) Low PA, n = 48; OR = 1.92 (0.66, 5.59) High PA, n = 93; 1.40 (0.55, 3.55) PA at 6-10 y, n = 426 (LR-*P* = .177) Normal PA, n = 274 (ref.) Low PA, n = 69; 1.98 (0.80, 4.85) High PA, n = 83; 1.97 (0.83, 4.67)	(a) Asthma ever at first follow-up: sex, gestational age, mother's pre-eclampsia and mother's asthma. (b) Current asthma at second follow-up: sex, mother's pre-eclampsia and mother's asthma	Physical activity in early childhood is associated with asthma later in childhood
Protudjer, 2012[15] Canada '1995 Manitoba Prospective Cohort Study'	489 children aged 8-9 (mean 8.6 ± 0.5) years at baseline followed up at 12-14 (mean 12.6 ± 0.5) years	Parental reports of physical activity and screen time through adapted questionnaire at 8-10 y. Physical activity was binary (active or inactive) to represent whether children were achieved ≥ 60 min of activity daily. Screen time treated as binary outcome with a threshold of screen time above or below 1 h daily	Asthma status ascertained by paediatric allergist assessment at baseline and follow-up according to the Canadian Asthma Consensus Guidelines and based on semi-structured asthma history from children and parents and physical examination	All participants: (a) Asthma at 8-10 y; Model 1a 0.93 (0.76-1.15), *P* = .50; Model 2b 0.91 (0.73-1.15), *P* = .44; (b) Asthma at 12-13 y; Model 1a 1.07 (0.82-1.39), *P* = .64; Model 2b 1.03 (0.78-1.37), *P* = .83	Model (a) adjusted for region of residence and ethnicity. Model (b) adjusted for region of residence, ethnicity, parental income and education	'Physical activity frequency was not associated with asthma… results fell short of demonstrating a prospective association between physical activity and asthma'

(Continues)

TABLE 1 (Continued)

Author, date, location	Sample size and participant age	Physical activity measurement	Asthma outcome measurement	Main effects	Covariates included	Author's conclusions
Asthma-free population studies						
Driessen, 2014[18] The Netherlands; 'The Generation R study'	347 children followed from birth. Mean ages at follow-ups were 2, 3 and 4 y	At age 2 y, an ActiGraph accelerometer worn for at least 400 min on 2 d (1 weekend, 1 weekday). Epoch length = 15 s. Physical activity was categorized as light (302-614 counts/15 s), moderate (615-1230 counts/15 s) or vigorous activity (≥1231 counts/15 s). Data were adjusted for accelerometer wear time by calculating the mean percentage of physical activity per day relative to the number of min per day of wearing the accelerometer	Parental reports of wheeze and shortness of breath, assessed by the ISAAC questionnaire at 2, 3 and 4 y. Current wheeze and shortness of breath were defined as at least one episode of wheeze or shortness of breath in the third and fourth year, respectively. Data at age 2 were not used as an outcome	(a) Wheeze at age 3: univariate model, OR (95% CI): LPA 0.97 (0.86-1.08), *P* = .56; MVPA 1.01 (0.89-1.15), *P* = .86; multivariate model, OR (95% CI): LPA 0.94 (0.83-1.06), *P* = 32, MVPA 1.00 (0.88-1.15), *P* = .7. (b) Wheeze at age 4 y: univariate model, OR (95% CI): LPA 0.99 (0.89-1.11), *P* = .87; MVPA 1.01 (0.88-1.16), *P* = .92; multivariate model, OR (95% CI): LPA 0.95 (0.84-1.08), *P* = .43; MVPA 1.00 (0.85-1.18), *P* = .96 (c) Shortness of breath at age 3: univariate model, OR (95% CI); multivariate model, OR (95% CI): LPA 0.95 (0.85-1.06), *P* = .35; MVPA 1.00 (0.88-1.13), *P* = .96. (d) Shortness of breath at age 4: univariate model, OR (95% CI): LPA 1.09 (0.96-1.22), *P* = .19; MVPA 1.09 (0.95-1.26) 0.23; multivariate model, OR (95% CI) LPA 1.04 (0.91-1.19), *P* = .54, MVPA 1.08 (0.93-1.25), *P* = .33	Maternal BMI, maternal age, maternal educational level, household income, infant's consumption of vegetables and salty snacks in second year of life, infant's gender, day care attendance in second year of life and infant's motor function	'Physical activity may not play an important role in the development of respiratory symptoms in pre-school children'
Vogelberg, 2007[14] Germany; 'Study on Occupational Allergy Risks (SOLAR)'	2910 children aged 9-11 y (wheeze-free) at baseline followed up at 15-17 y	Leisure-time activity assessed via questionnaire, categorized into (1) four categories of sport frequency between not more than once per month and 3 times per week; (2) computer work and TV watching ≥ 1 h per day; and (3) visiting a discotheque (yes or no)	Incident wheeze identified by questionnaire	Adjusted OR for incident wheeze OR (95% CI): Sport > 3 times per week vs ≤ once per month 0.8 (0.5-1.3); Computer work > 1 h/d vs ≤ 1 h/d 1.1 (0.8-1.5); TV watching > 1 h/d vs ≤ 1 h/d 1.1 (0.9-1.5); Visiting discotheques yes vs no 1.0 (0.8-1.3). When stratifying the analysis for smokers and non-smokers, no significant association was found between leisure-time activity and wheeze	SES, BMI, sex, passive and active smoking	A 'significantly negative association was found between wheeze and increasing frequency of sport' in the crude analysis, but 'The association between physical activity and new onset of wheeze disappeared when active smoking was taken into account'

(Continues)

TABLE 1 (Continued)

Author, date, location	Sample size and participant age	Physical activity measurement	Asthma outcome measurement	Main effects	Covariates included	Author's conclusions
Asthma populations						
Nnodum, 2017[16] United States of America; 'Asthma-DIET study'	147 children aged 5-12 y with physician-diagnosed asthma assessed daily for three 8-d periods. Followed up after 3 and 6 mo	Physical activity was self-reported at the end of each 8-d monitoring period using the Physical Activity Questionnaire for Children which has been validated for children	Questionnaires assessed asthma medication use and asthma severity based on NAEPP guidelines, pre- and post-bronchodilator spirometry at baseline. Asthma symptoms assessed using the paediatric asthma diary, a validated questionnaire, completed twice daily for 8 d by child and their parent/caregiver during each of the monitoring periods	Adjusted OR/RR (95% CI) primary outcomes: (a) Daytime asthma symptom diary scale 1.04 (1.00-1.09), *P* = .04; (b) Nocturnal asthma symptom diary scale 1.03 (1.00-1.06), *P* = .01; (c) Daily puffs of albuterol inhaler used 1.13 (0.81-1.58) *P* = .4; (d) Absent from school due to asthma 0.97 (0.54-1.74), *P* = .91; (e) Doctor's visit due to asthma 1.09 (0.58-2.02), *P* = .79; (f) Trouble breathing 1.05 (1.00-1.10), *P* = .02; (g) Bother due to asthma 1.04 (1.00-1.09), *P* = .04; (h) Activity limitation due to asthma 1.04 (1.00-1.09), *P* = .06	Baseline age, gender, race, baseline BMI, caregiver's education, baseline asthma severity, inhaled corticosteroid use and season	'Physically active children with asthma were more likely to report daytime asthma symptoms, nocturnal awakenings due to asthma, and being bothered by asthma symptoms'
Tiggelman, 2014[19] The Netherlands	260 adolescents with asthma aged 10-14 y at baseline, followed up after 1 y (T2) and 2 y (T3 – mean age 13.9 y). Only used data from T2 and T3	Self-reported physical activity at T2. Activities were given a MET score based on the Compendium of Physical Activities, and MET scores were then multiplied by the minutes that the adolescents spent on participating in these activities every week. These scores were combined to produce a total PA score	ACQ at T2 and T3. The items were measured on a 7-point scale ranging from 0 (complete control) to 6 (very little control). Scores were then reversed, with higher scores on ACQ, reflecting better asthma control. Lung function assessed by Spida5 to complement the ACQ but was not analysed separately	Correlations between the model variables: (a) Asthma control T2 and PA = −0.17; (b) Asthma control T2 and PA = −0.13	BMI, gender and age	'Path analyses in the total group showed that habitual PA did not predict changes in psychosocial outcomes or asthma control over time'

Abbreviations: ACQ, Asthma Control Questionnaire; BMI, body mass index; ISAAC, International Study of Asthma and Allergies in Childhood; LPA, light physical activity; LR, likelihood ratio; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity; NAEPP, National Asthma Education and Prevention Program; OR, odds ratio; PA, physical activity; SES, socioeconomic status.

in high-income countries, namely Norway,[17] the Netherlands,[18,19] Germany,[14] USA[16] and Canada.[15] All studies adjusted for one or more potential covariates; importantly, five of the six studies adjusted for sex[14,16-19] and three adjusted for body mass index (BMI).[14,16,19] Four studies accounted for socioeconomic status (SES), or parental or caregiver education.[14-16,18]

3.3.1 | General population studies

Two studies included children with and without asthma at baseline.[15,17] Protudjer *et al* analysed data from 489 children who were 8-9 years old at baseline and followed up at 12-14 years of age.[15] Although their study was conducted in a birth cohort, Byberg et al[17] analysed data from 617 children who were asked about their PA between the ages of 3-6 and 6-10 years at the first follow-up (when girls were 10.8 years and boys were 11.8 years old). Asthma outcomes were assessed at a second follow-up when children of both sexes were aged 12.8 years.

Protudjer et al[15] employed a paediatric allergist to ascertain asthma status, while in the Byberg study, maternal reports of ever or current asthma, wheeze and shortness of breath were assessed using the ISAAC questionnaire.[17]

Physical activity data were measured subjectively via parental reports in both studies. Based on the Stanford Brief Activity Survey, Byberg et al[17] asked parents to recall their child's activity levels when they were 3-6 years old. Protudjer et al[15] assessed frequency of PA from a close-ended response to the question: 'In the last 12 months, how many times a week does your child engage in vigorous or competitive PA long enough to make him/her breathe hard?'.

The two studies produced inconsistent results. Protudjer et al[15] found no association between low levels of PA at age 9 years and paediatric allergist-defined asthma at age 13, while Byberg et al[17] found low levels of PA between the ages of 3 and 6 years to be positively associated with ever asthma at age 10.8 in girls and at age 11.8 in boys.

3.3.2 | Asthma-free population studies

Participants were free of asthma or wheeze at baseline in two of the six studies.[14,18] The study populations consisted of 347 young children[18] and 2910 adolescents,[14] respectively. Driessen et al[18] were the one team to investigate this relationship in early life, measuring PA by accelerometery at age 2 years and measuring wheeze at 4 years of age. In contrast, the large German study by Vogelberg et al[14] followed children for approximately 6 years from the baseline PA measurement at 9-11 years, until the adolescents were 15-17 years old.

Driessen et al[18] used the ISAAC questionnaire to measure ever or current asthma, wheeze and shortness of breath based on parental report, while Vogelberg et al[14] used their own study questionnaire to identify their primary outcome—incident wheeze. Similarly, Vogelberg et al[14] used their own study questionnaire to collect PA data, while Driessen et al[18] employed accelerometery.

Driessen et al[18] found that PA measured by accelerometery in the second year of life was not associated with wheeze at ages 3 and 4 years. In their unadjusted analysis, Vogelberg[14] found that increasing PA was significantly associated with decreasing prevalence of wheeze in older adolescents; however, when they adjusted for active smoking, the association was no longer observed.

3.3.3 | Asthma population studies

Two studies were conducted in children with asthma.[16,19] These studies analysed 147 children aged 5-12 years[16] and 260 adolescents aged 10-14 years[19] at baseline. In their study, Nnodum et al[16] collected data on asthma symptoms using a paediatric asthma diary (PAD) completed twice daily by child and parent/caregiver for a period of 3-6 months. The PAD assessed a number of daytime and night-time symptoms on 6- and 4-point Likert scales, respectively.[16] In contrast, Tiggelman et al[19] used the Asthma Control Questionnaire to measure asthma control with a follow-up period of one year.

In both studies, PA data were collected subjectively via self-report.[16,19] Nnodum et al[16] used the Physical Activity Questionnaire for Children (PAQ-C), while Tiggelman et al[19] did not specify which questionnaire was used.

The studies reported inconsistent results. Nnodum et al[16] concluded that more PA was longitudinally associated with more reported asthma symptoms, while Tiggelman et al[19] concluded that habitual PA was not longitudinally associated with asthma control.

3.4 | PA and LF outcomes

Three of the nine eligible studies used spirometry to collect forced expiratory volume (FEV) and forced vital capacity (FVC) as outcome data[23-25] (Table 2). All three studies adjusted for BMI, height, maternal education and parental smoking. Only Ji *et al* adjusted for earlier LF indices in their longitudinal data analyses.[24] All studies presented results stratified by sex.[23-25] No studies were found that investigated the association in children with asthma.

3.4.1 | General population studies

Two large Brazilian studies analysed data from the same birth cohort whose participants were followed up and spirometric measurements collected at the ages of 11, 15 and 18 years.[23,25] The earlier study by Menezes et al[25] examined the relationship between the change in leisure-time PA status between the ages of 11 and 15 and LF parameters measured at age 15, while the more recent study by da Silva and colleagues in 2016 used PA exposure data at ages 11 and 15 and spirometry outcome data from the cohort at 15 and 18 years.[23]

Both analyses collected information on PA through self-report questionnaires, but neither specified which PA questionnaire was used. In addition, PA was categorized using different thresholds. Menezes et al[25] defined being active as 300 minutes of PA per week, while da Silva et al[23] categorized being active as either

TABLE 2 Details of three included articles that investigated the effect of physical activity on lung functions outcomes

Author, date, location	Sample size and participant age	Physical activity measurement	Lung function outcome measurement	Main effect	Covariates included	Author's conclusions
General population studies						
da Silva, 2016[23] Brazil; '1993 Pelotas Birth Cohort Study'	3571 children followed from birth. Mean ages at follow-ups were 11, 15 and 18 y	Physical activity was self-reported through questionnaires at ages 11 and 15 y. Classified based on the Compendium of Physical Activity where thresholds of 150 min of moderate physical activity and 75 min of vigorous-intensity physical activity per week were used to classify individuals as active or inactive	Pre- and post-bronchodilator spirometry performed on all participants at ages 15 and 18 y. Pre-bronchodilator spirometry used for this study	Boys' FEV1 gain (*z*-score), adjusted β (95% CI): Leisure-time PA: (a) Never active: Ref; (b) Active once: 0.095 (−0.009, 0.199); (c) Always active: 0.177 (0.063, 0.290). Total PA: (a) Never active: Ref; (b) Active once: 0.057 (−0.062, 0.175); (c) Always active: 0.137 (0.017, 0.258). FVC gain (*z*-score): Leisure-time PA: (a) Never active: Ref; (b) Active once: 0.072 (−0.011, 0.156); (c) Always active: 0.146 (0.054, 0.237); Total PA: (a) Never active: Ref (b) Active once: 0.051 (−0.044, 0.147) (c) Always active: 0.113 (0.016, 0.210). Girls' FEV1 gain (*z*-score), adjusted β (95% CI): Leisure-time PA: (a) Never active: Ref (b) Active once: −0.006 (−0.064, 0.053) (c) Always active: 0.030 (−0.079, 0.138) Total PA: Never active: Ref Active once: 0.044 (−0.016, 0.105) Always active: 0.018 (−0.063, 0.098) FVC gain (*z*-score): Leisure-time PA: Never active: Ref Active once: 0.015 (−0.045, 0.075) Always active: −0.054 (−0.164, 0.056) Total PA: Never active: Ref Active once: 0.020 (−0.041, 0.082) Always active: −0.005 (−0.087, 0.077)	Skin colour, family income at birth, maternal schooling at birth, birth weight, smoking during pregnancy, mother's height at birth, BMI at 11 y, BMI at 15 y, height at 15 y, wheezing in the previous year at 15 y, smoking at 15 y and Tanner stage at 15 y	Physical activity in early adolescence is associated with gains in pulmonary function by the end of adolescence in boys. No significant associations were found among girls

(Continues)

TABLE 2 (Continued)

Author, date, location	Sample size and participant age	Physical activity measurement	Lung function outcome measurement	Main effect	Covariates included	Author's conclusions
Menezes, 2012[25] Brazil; '1993 Pelotas Birth Cohort Study'	4010 children followed since birth. Mean ages at follow-up were 11 and 15 y	Physical activity was self-reported through questionnaires at ages 11 and 15 y. Classified as active if they reached 300 min per week of physical activity. Change in physical activity were categorized as inactive-inactive (did not reach the 300 min/wk cut-off point at age 11 or 15 y); inactive-active (reached the threshold at the age 15-year visit only); active-inactive (reached the threshold at the age 11-year visit only); or active-active (reached the threshold in both visits)	Pre- and post-bronchodilator spirometry performed at age 15 y	Boys' adjusted β (95% CI) FEV1: Changes of leisure-time PA (11-15y) Inactive-inactive: (ref) Inactive-active: 0.204 (−1.339, 1.747), p-.796 Active-inactive: −1.223 (−2.886, 0.439), *P* = .149 Active-active: −0.912 (−2.436, 0.613), *P* = .241 FVC: Inactive-inactive: (ref) Inactive-active: 1.269 (−0.381, 2.919), *P* = .132 Active-inactive: −0.635 (−2.413, 1.142), *P* = .484 Active-active: −0.395 (−2.025, 1.235), *P* = .635 Girls' adjusted β (95% CI) FEV1: Changes in leisure-time PA (11-15 y) Inactive-inactive: (ref) Inactive-active: 0.960 (−0.748, 2.669), *P* = .270 Active-inactive: 0.704 (−0.823, 2.231) *P* = .366 Active-active: 2.172 (−0.202, 4.546), *P* = .073 FVC: Inactive-inactive: (ref) Inactive-active: 0.754 (−1.087, 2.595), *P* = .422 Active-inactive: 0.435 (−1.210, 2.080), *P* = .604 Active-active: 3.573 (1.015, 6.130), *P* = .006	Family income at birth, maternal schooling at birth, birthweight, smoking during pregnancy, mother's height at birth, height at 15 y, wheezing in past year, BMI, allergy status and asthma medication	'Self-reported leisure-time physical activity was associated with better effort-dependent lung function parameters, particularly among girls'
Asthma-free population studies						
Ji, 2013[24] China	1713 children aged 9-11 y followed up for 18 mo	Physical activity was self-reported through questionnaire in classroom with guidance of trained investigators. Classified as inactive or active, where active was defined as at least 30 min of sport of vigorous activity 3 times a week	Spirometry performed at baseline and at follow-up	FVC; mean (SE) difference per year in litres (dpy, l) Boys: Active (n = 535): 0.29 (.01) Inactive (n = 323): 0.29 (.01) Girls: Active (n = 452): 0.28 (.01) Inactive (n = 403): 0.27 (.01) FEV1; mean (SE) difference per year in litres (dpy, l) Boys: Active (n = 535): 0.24 (.01) Inactive (n = 323): 0.25 (.01) Girls: Active (n = 452): 0.27 (.01) Inactive (n = 403): 0.25 (.01)	District, age, height, BMI, passive smoking and maternal education	'Physical activity is positively associated with lung function growth among Chinese school-aged girls'. However, 'the deficits in lung function growth for inactive girls were observed only in FEF but not FEV1 and FVC'

Abbreviations: BMI, body mass index; DPY, difference per year; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PA, physical activity; ref, reference; SE, standard error

TABLE 3 The ROBINS-E and NOS quality assessment scores for each of the nine included studies

Study	Newcastle-Ottawa Scale				Risk of bias in non-randomized studies-E (ROBINS-E)							Overall bias
	Selection	Comparability	Outcome	Total score	Confounding	Participant selection	Exposure classification	Departures from intend-edexposure	Missing data	Outcome measurement	Selection of the reported result	
Byberg (2016)[17]	4	2	2	8/9	Moderate	Low	Moderate	Low	Low	Low	Low	Low
da Silva (2016)[23]	2	2	3	7/9	Low	Low	Low	Low	Moderate	Low	Low	Low
Driessen (2014)[18]	4	2	1	7/9	Low	Low	Low	Low	Low	Low	Low	Low
Ji (2013)[24]	3	2	3	8/9	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Menezes (2012)[25]	2	2	2	6/9	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Nnodum (2017)[16]	1	2	2	5/9	Low	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Protudjer (2012)[15]	2	1	3	6/9	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Tiggelman (2014)[19]	2	2	2	6/9	Low	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Vogelberg (2007)[14]	3	2	2	7/9	Low	Low	Moderate	Low	Low	Moderate	Low	Low

150 minutes of moderate PA or 75 minutes of vigorous-intensity PA per week.

Both studies measured FEV_1 and FVC, although their aims differed. In their study, da Silva et al[23] focussed on gains in pulmonary function from age 15 to 18 years, while Menezes et al[25] aimed to assess the effect of change in PA on LF at 15 years. Results were stratified by gender.

Reported results were highly inconsistent. da Silva et al[23] found PA at 11 and 15 years to be longitudinally associated with larger gains in FEV_1 and FVC between the ages of 15 and 18 in boys. The authors noted that boys who became active from age 11 to age 15 did not benefit from the increased gains in pulmonary function; hence, they emphasized the importance of PA in early adolescence. No significant associations between PA and pulmonary function gain in girls were observed. In contrast, Menezes et al found that girls who were physically active during their leisure time at age 11 and 15 years had higher per cent predicted FVC (3.573 [1.015, 6.130], $P = .006$) at age 15 years compared to girls who were inactive in their leisure time at both ages. There were no significant associations with FEV_1 in girls, and no associations were found in boys. The authors did not observe any associations between total PA—as opposed to leisure-time PA—and LF.

3.4.2 | Asthma-free population studies

One study excluded children with asthma at baseline. The large Chinese study analysed data from 1713 asthma- free children aged between 9 and 11 years and followed them up for 18 months.[24]

Physical activity data were collected through self-report questionnaires with the 'guidance of trained investigators', but the authors did not state which PA questionnaire was used. Children were considered physically active if they participated in at least 30 minutes of sport and/or vigorous free play at least 3 times per week.

Ji et al[24] investigated the effect of PA on LF growth and found no statistically significant associations between FEV_1 and FVC in either boys or girls. The mean [standard error] FEV_1 and FVC values for boys who were active at one or both surveys were 0.24 [.01] and 0.29 [.01], respectively, compared to FEV_1 and FVC values of 0.25 [.01] and 0.29 [.01] in boys who were inactive at both time points. Similarly, the mean [standard error] growth in FEV_1 and FVC girls who were active at one or both time points was 0.27 [.01] and 0.28 [.01], respectively, compared to 0.25 [.01] and 0.27 [.01] for girls who were inactive at both time points.[24]

4 | DISCUSSION

4.1 | Summary

The present systematic review attempted to determine the longitudinal effect of PA on the development of asthma and the persistence of asthma symptoms in youth. It is also the first to review the evidence of the relationship between PA and subsequent LF outcomes.

The results of these studies were highly inconsistent and did not produce any clear evidence for the effects of PA. Briefly, two studies reported a positive association between low levels of PA and asthma symptoms,[16] and ever asthma.[17] No associations were observed between PA and incident wheeze in two studies[14,18] nor with asthma control,[19] nor with paediatric allergist-defined asthma.[15] Of the three LF studies, one observed an association in girls only,[25] one observed an association in boys only,[23] and one found no associations in either boys or girls.[24] The differential results for effect on LF by sex may be due to the ages at which measurements were taken, since girls experience growth-related changes at earlier ages compared to boys, who experience a period of rapid growth between the ages of 15 and 18 years.[23,26] This is consistent with the findings of the studies, where the study that measured LF outcomes at 15 found an association in girls only,[25] while when LF was measured at 18 years, an association was observed in boys only.[23] Additionally, no associations were found in pre-adolescent children,[24] who had not yet experienced growth-related changes. Despite the inability to meta-analyse results, it is apparent that most studies found little evidence of relationship between PA and various respiratory outcomes.

Interestingly, a recent publication found that increases in aerobic fitness during childhood and adolescence were longitudinally associated with higher lung function parameters.[27] While this study differs from the present one in that the exposure investigated was fitness measured using cycle ergometer tests rather than habitual physical activity, the positive finding reported by Hancox and Rasmussen[27] adds another dimension to the complexity of the evidence. There were some similarities in their reported results, compared to the studies contained within this review. Specifically, in their article, Hancox and Rasmussen reported associations with FEV1 and FVC, but not with FEV1/FVC ratio, which they propose indicates an association with lung size rather than an association with the quality of the airways.[27] They further stated that their associations were stronger in boys, which again may be due to the older developmental age of participants at time of measurement.[27]

The present findings are discordant with those of the two existing systematic reviews, which found PA to play a protective role against the incidence of asthma in both adults and children.[12,13] This is likely due to important differences between those reviews and the present one. Firstly, the Eijkemans[13] review did not restrict by population age nor study design. Due to the nature of their design, longitudinal studies provide stronger evidence for temporality than cross-sectional studies; hence, the present review restricted to cohort studies. In their meta-analysis of five longitudinal studies (I^2 = 45%), Eijkemans et al[13] concluded that higher levels of PA were associated with lower incidence of asthma (odds ratio 0.88 (95% CI: 0.77-1.01)). However, all of the studies conducted in children were cross-sectional in nature; hence, they did not have the longitudinal evidence to support this conclusion in child populations.[13] On the other hand, the Lochte et al[12] review did restrict their population age but did not restrict to longitudinal study design. Although the I^2 values obtained were moderate (60.6% for both fixed and random effects), the articles included in the meta-analysis had varying definitions of PA.[12] For example, one study measured television viewing time,[28] and this was included as a proxy measure for low levels of PA despite some research, suggesting that there is a distinction between low PA and sedentary behaviours.[29,30] As a result, the articles included in the Lochte et al[12] review did not correspond with those contained within the present review, since the present review elected to exclude sedentary behaviours.

The true relationship between PA and subsequent asthma or LF may still be masked by several analytical issues. Firstly, the definitions and categorizations of PA used varied greatly between the included studies, an issue not unique to this paper. There remains a critical lack of standardized protocols for the measurement, processing and categorization of PA within the scientific community. This presents an important barrier against comparing and collating PA studies. Future studies will need to address these challenges in order to improve the generalizability of PA research. Furthermore, the included studies adjusted for a variety of potentially confounding variables. Although most accounted for sex through either adjustment or stratification, many, including one of the studies that reported a positive association, did not adjust for other potentially important factors such as BMI, SES, passive smoking or ethnicity. Overall, however, there was no consistency between the variables included for adjustment and the associations found. Future studies should include participants who are asthma-free at baseline to investigate whether PA affects asthma development and LF growth, and participants with varying asthma severity to assess the impact of PA on asthma symptoms and control and LF growth. When designing and conducting further research in this area, it may also be beneficial to consider the length of follow-up time required to observe an effect. For example, when measuring the effect on lung function or asthma incidence, it is necessary to study the effect over multiple years.

4.2 | Strengths

This review was systematically and thoroughly conducted by two independent researchers in order to identify and include all relevant data on this topic. Searches were performed in two distinct databases and included a manual search of reference lists in order to ensure that relevant articles were not overlooked. Furthermore, the quality assessment of included articles was conducted using two critical appraisal tools—the ROBINS-E and the NOS, the results of which appeared to be largely congruous for each included article. Finally, the included articles were of moderate-to-high quality.

4.3 | Limitations

In contrast, this review had several limitations. Firstly, substantial variation in the methodologies of the included studies prevented the intended meta-analysis of the data. The included studies varied greatly not only in the outcomes measured, but also in their

specific exposure and outcome measurement techniques, the thresholds and definitions used, the range of participant ages and duration of follow-up periods, and the reporting of their results. Secondly, although critical appraisal of the studies was conducted, the review is limited by the critical appraisal tools available. The NOS has drawn some criticism for its potential to produce arbitrary results.[31] Similarly, the more detailed ROBINS-E tool has been criticized for being time-consuming, for confusing, and for failing to assess some sources of bias.[32] Additionally, the small number of included studies meant that further analyses to investigate effect potential modification by factors such as age bracket and asthma status could not be performed.

5 | CONCLUSIONS

In conclusion, due to the highly inconsistent results of the included studies, this systematic review has found that there is insufficient evidence to determine the longitudinal effect of PA on subsequent asthma and LF outcomes in children and adolescents. A robust tool for the measurement of PA in children and adolescents is lacking, as is a standardized analytical methodology. These issues must be circumvented for further longitudinal research to meaningfully assess these relationships.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

RC, EM, JK, SD, MR and FP each contributed to the conception and design, acquisition of data, or analysis and interpretation of data. RC produced the first draft. EM, JK, SD, MR and FP edited and revised it critically for important intellectual content. RC, EM, JK, SD, MR and FP reviewed and approved the final version of the manuscript and accept accountability for the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CHAPTER FIVE: Summary of the evidence on the effect of asthma on physical activity

5.1 Chapter introduction

This chapter consists of a published systematic review and meta-analysis that synthesised the existing scientific literature on whether physical activity is reduced in children and adolescents with asthma, compared to their unaffected peers. This systematic review was the first publication I authored during the course of this PhD and served as the foundation upon which the subsequent research questions were based. By summarising the available evidence for the opposite relationship to the one reported in Chapter Four, the two complementary systematic reviews provide an overview of the complex relationship between asthma and physical activity.

5.2 Research question

Does the existing evidence demonstrate that children and adolescents with asthma are less physically active than those without asthma, when measured objectively through accelerometry?

5.3 Synopsis of the review

Since physical activity is a known trigger for asthma symptoms, qualitative studies have investigated the affect that asthma status has on physical activity in children and adolescents with asthma (6, 8-13). Some of these studies found that children and adolescents with asthma may avoid physical activity in an attempt to prevent the exacerbation of their asthma symptoms (8-10, 13). For this reason, children and adolescents with asthma are believed to partake in less physical activity than their non-afflicted peers (5-7). However, several observational studies have disputed this claim (11, 12).

Since these studies provide contradictory results, there remains a need for investigation into whether children and adolescents with asthma do in fact perform less physical activity than those without asthma. Hence, my systematic review elected to include only those studies where physical activity was measured objectively, as the use of accelerometers provide a more accurate and reliable assessment of habitual physical activity in children (125). An exploration of the existing literature indicated that there were a sufficient number of studies measuring physical activity through accelerometry. The knowledge gained from this systematic review may advise as to whether health policies and campaigns that specifically target children and adolescents with asthma in their promotion of physical activity are required.

Studies were included if they measured physical activity objectively in children and adolescents up to the age of 18 years with and without asthma. My review systematically searched the PubMed, EMBASE and Medline databases. Together, the three searches retrieved over 20 000 articles, of which 15 270 duplicates were deleted. The remaining items were screened by title and abstract. Following the examination of the full texts, twelve studies met the inclusion and exclusion criteria. Of the 12 observational accelerometry studies, nine were included in a meta-analysis. Results of the meta-analysis showed no significant difference in the mean amount of physical activity level performed by children with and without asthma (both the fixed and random effect estimate = 0.01 activity counts per minute 95% CI: -0.09, 0.11, p = 0.50, I^2= 0.0%).

Whilst undertaking this systematic review and meta-analysis, several gaps in the literature became apparent. Firstly, there was a distinct lack of standardisation between accelerometer outputs and for categorisation of physical activity that needs to be addressed. Secondly, studies rarely accounted for important confounding or moderating variables such as BMI or considered the level of asthma control or severity among the children with asthma and the effect this had on physical activity levels. Finally, there were no data from any Australian cohorts. The latter points led to the formation of the second research question of this PhD, in which I attempted to address these gaps in the literature and investigate whether asthma is a barrier against physical activity in the Australian context.

5.4 Publication

Cassim R, Koplin JJ, Dharmage SC, Senaratna BC, Lodge CJ, Lowe AJ, Russell MA (2016) The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis. Journal of Asthma 53 (9):882-892

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REVIEW

The difference in amount of physical activity performed by children with and without asthma: A systematic review and meta-analysis

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Abstract

Objective: Despite the benefits of a physically active lifestyle, some studies suggest fear of exacerbations by both children and their parents limit physical activity in children with asthma. We undertook a systematic review to quantify the difference in objectively measured physical activity levels of children and adolescents with and without asthma. *Data Sources*: MEDLINE, PubMed and EMBASE. *Study Selection*: English language observational studies of children and adolescents to the age of 18 that compared objectively measured physical activity (accelerometer or pedometer devices) between those with asthma and without asthma. *Results*: Overall 22,285 articles were retrieved with 12 studies being included in the review: 1 cohort, 1 case-control and 10 cross-sectional. A meta-analysis of accelerometry data from the single cohort study and 8 cross-sectional studies produced an overall mean difference of 0.01 (95% CI: −0.09–0.11) activity counts per minute in children and adolescents without asthma compared to those with asthma. *Conclusion*: We did not find any evidence that children and adolescents with and without asthma engaged in different amounts of physical activity when measured objectively by accelerometers. Children and adolescents with asthma may not require differentially targeted policies to encourage more physical activity, however further longitudinal studies are needed.

Keywords

Physical activity, asthma, systematic review, child

History

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Introduction

Regular physical activity has substantial short- and long- term physical and mental health benefits for all age groups [1]. In children and adolescents, these benefits can endure into adulthood [1]. As a result, the World Health Organisation (WHO) and national health departments recommend that children and adolescents aged between 5 and 17 years should engage in at least 60 minutes of moderate- to vigorous- physical activity daily [2, 3]. However, globally many children and adolescents fail to reach these targets [4].

Whilst there are currently no guidelines for physical activity specifically for children with asthma, a recent update published by the Global Initiative for Asthma (GINA) recommends that children with controlled asthma should be encouraged to exercise [5, 6] because regular aerobic exercise improves the management of asthma symptoms [7, 8] and lung function (peak expiratory flow in one second (PEF), forced expiratory volume in one second (FEV_1), and forced expiratory flow (FEF_{25})) [9], as well as incurring other health benefits including improvement of cardiovascular and bone health and reducing the risk of diabetes, stroke and depression [10].

In enacting these recommendations, it is important to know whether physical activity levels are actually lower in children and adolescents with asthma compared to those without asthma. Some qualitative studies suggest that fear of exacerbations by both children and their parents may limit the duration, frequency and intensity of physical activity in children with asthma [6, 7, 9, 11–13], however the results of these qualitative studies are inconsistent [12, 14–18]. A review published by Williams *et al.* in 2008 also concluded that children with asthma find it difficult to be as physically active as children without asthma [19]. However this review was a narrative rather than systematic review and did not include studies with objective measures of physical activity [19].

To determine the impacts and effects of physical activity on health outcomes, it is necessary to obtain an accurate and reliable assessment of habitual physical activity [20]. Measuring physical activity objectively is important to overcome potential reporting and recall biases associated with subjective measurements such as questionnaires, particularly in children. Physical activity in children tends to occur in brief and intermittent bouts of activity which can be difficult to accurately recall

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and quantify [21–23]. Furthermore a proxy reporter such as a parent or teacher is often called upon in questionnaires to provide an estimate of the child's activity, however, these proxies are unlikely to be able to accurately describe a child's activity profile throughout the whole day [22]. The use of accelerometers can help to overcome some of these pitfalls, and provide a more accurate measure of habitual physical activity in children.

Accelerometers are devices able to detect acceleration produced by the body when in motion [24]. Once an acceleration is detected by a sensor, a proportional voltage signal is generated and recorded as a "raw count" [24]. Several studies have investigated the validity of accelerometers in children, and have found them to be valid against energy expenditure [25–27]. However, whilst they do not eliminate all measurement bias, accelerometers appear to be the best choice for objective measurement of physical activity in epidemiological studies of children [28].

To our knowledge there have been no systematic reviews that have investigated the difference in objectively measured physical activity in children or adolescents with and without asthma. Therefore, in this systematic review we aimed to identify and collate the available scientific evidence of objectively measured physical activity to investigate whether children and adolescents with asthma are less physically active than their peers. If there is evidence that children with asthma engage in less physical activity, there may be a need for specific physical activity recommendations to counter barriers to exercise in this group of children and adolescents.

Methods

Search strategy

We conducted an electronic search for publications in 3 databases (MEDLINE, PubMed and EMBASE) to obtain all articles that investigated the relationship between physical activity and asthma from inception to 5th August 2015 for PubMed and Medline, and from inception to 18th August 2015 for EMBASE. A final search of the 3 databases was conducted on 19th December 2015. The key terms employed in the searches were "physical activity", "physical training", "exercise", "sedentary", "asthma", "early life wheeze" and "transient wheeze", and appropriate MeSH terms. Terms were combined using the Boolean operators "OR" and "AND" (see appendix for full details). Reference lists of published articles were checked to ensure that all relevant articles were included.

Screening of articles

Articles were first screened using the inclusion and exclusion criteria specified below by title and abstract. Finally, the full texts of manuscripts were reviewed and excluded if they failed to meet the inclusion criteria. Titles, abstracts and data extraction of the retrieved articles were independently screened by two investigators (RC and BCVS). Disagreements were resolved by a third investigator (MR).

Exclusion and inclusion criteria

We included observational studies where the exposure variable was the presence or absence of asthma, and the outcome was physical activity. We limited the review to include only those studies which measured physical activity objectively by use of an accelerometer or pedometer. Only English language studies that reported associations in children or adolescents with and without asthma between birth and 18 years of age were selected for inclusion in this review. Letters or reviews that did not present original data, and animal and *in vitro* studies were excluded.. There were no restrictions on date of publication.

Confounding variables

Several variables were identified as *a priori* potential confounders of the relationship between asthma and physical activity. The included studies were checked for adjustment for these variables: gender, age, socioeconomic status, parental asthma, number of siblings and pet ownership.

Data extraction

The following information was extracted from each included article: author, date of publication, location of study, the study population age and gender, whether cross-sectional, case-control or cohort design, length of follow up if longitudinal design, definition of the exposure and tool used to measure the exposure, type of accelerometer used to measure the outcome, length of time the accelerometer was worn, measurement units and cut off points for the categorisation of physical activity, level of asthma control, the confounding variables considered in the analysis, the unadjusted and adjusted results, and the author's conclusions. The authors of ten articles were contacted to request mean and standard deviation activity data for children with and without asthma for inclusion in this analysis [14, 29–37]. Four authors responded and provided the requested data [14, 29, 31, 32]. However 2 of these articles [29, 31] used data from a previously identified study [38], hence we only included the primary article that focused on the difference in physical activity between adolescents with and without asthma [38].

Quality assessment

Included papers were assessed using the Newcastle-Ottawa Scale (NOS) [39]. The NOS is a tool to assess the methodological quality of cohort and case-control study designs. The NOS rates studies on several design-specific criteria, including: the definition of the exposed and unexposed groups, selection and representativeness of exposed and unexposed groups, comparability, and assessment of both the exposure and outcome variables of interest. Cohort and case-control studies could be awarded a maximum of nine points. A modified version of the NOS that has been used in other publications [40–42] was then used to assess the cross-sectional studies. Using our modified NOS scale for cross-sectional studies, studies could be awarded a maximum of 8 points.

Meta-analysis

Mean and standard deviation of the mean raw physical activity counts as measured by accelerometer for both children with and without asthma were compared. Where articles presented confidence intervals of the mean, data were transformed into mean and standard deviation. Data were pooled with a both

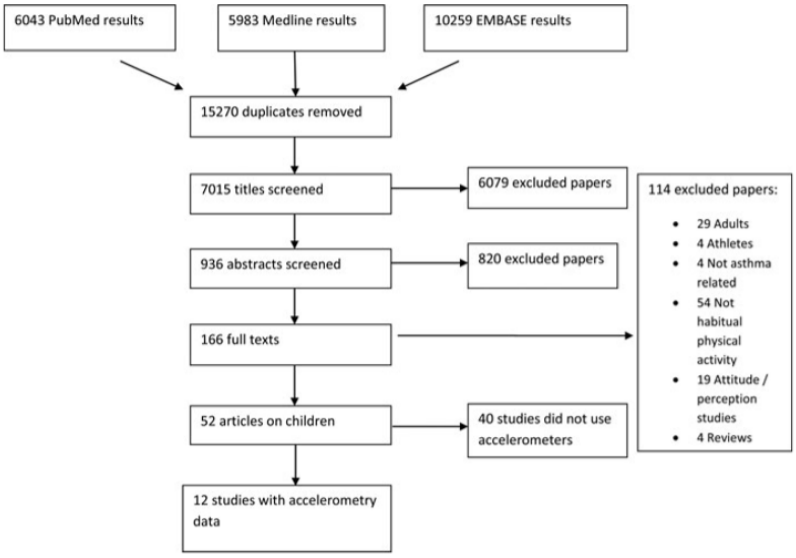

Figure 1. Flow chart of articles through the search process.

fixed and random effect models. An I^2 value of 70% or greater was chosen to indicate a substantial amount of heterogeneity. A meta-regression was not performed due to insufficient number of included studies [43]. A funnel plot was used to investigate potential publication bias. Stata 12 (StataCorp, College Station Texas) statistical package was used for all analyses.

Results

Search results

The 3 databases searched retrieved 22,285 results of which 15,270 duplicates were deleted. Of the 116 full text articles examined, 52 studies were conducted in child or adolescent populations. Ultimately, 12 manuscripts measured physical activity objectively through the use of an accelerometer were included for analysis in this review [14, 30, 32–34, 37, 38, 44–48] (Figure 1).

Description of included studies

Study design

The extracted information from the 12 included articles were collated (Table 1). Ten manuscripts were cross-sectional studies [30, 33, 34, 36–38, 44–47], 1 was a case-control [32] and 1 was a cohort study [14]. This review presents data collected from a total of 5797 children and adolescents between the ages of 2 and 14. Sample sizes ranged from 1614 children in a population based cross-sectional study by van Gent et al. [33] to 2 cross-sectional analyses with 54 children each [30, 49].

Participants

The case-control study [32] and seven of the ten cross-sectional studies were conducted in children and adolescents aged between six and 14 years [33, 34, 36, 38, 45–47]. Three cross-sectional studies were conducted in children between the ages of 3 and 5 years [30, 37, 44]. The cohort study followed children from birth until the age of 5 years [14].

Populations

The included studies were conducted in Brazil [32], Cyprus [47], the Netherlands [14, 33], Denmark [37, 46], Norway [38] and the United States America [30, 34, 36, 44–46]. The cohort study was drawn from a larger, population-based, birth cohort study – the KOALA study- in which information about wheeze and doctor's diagnosis of asthma was collected through questionnaires at the age of seven months, then again at the ages of 1, 2, 4 and 5 years. Accelerometry data were then collected from 305 children at the age of 4 or 5 [14]. The case-control study recruited children who presented with asthma from a hospital as cases, and children of the hospital employees were recruited as healthy controls [32].

Three of the 10 included cross-sectional studies were conducted in subsets of the population: females [34], children with obesity [36] and children with maternal asthma [37]. The remaining cross-sectional studies were conducted on population-based samples [30, 33, 38, 44–47].

Physical activity assessment

Physical activity data were collected by accelerometry in all studies except one, which used a pedometer [34]. The most widely reported outcome measure was raw activity counts [14, 30, 32, 33, 37, 38, 44–47], produced when accelerometers convert accelerations into "counts" and add them over a selected time interval [21]. Other studies transformed accelerometer activity counts into metabolic equivalent values (METs) through the use of regression equations [50] and reported these as well [14, 30, 33, 38, 44–47]. Cut-off points for sedentary activity, light, moderate, vigorous and moderate-to-vigorous levels of physical activity varied greatly between studies (Table 2).

Asthma assessment

Three studies looked and "asthma ever" [30, 37, 48] and 5 looked at "current asthma", usually within the last 12 months

Table 1. Summary of studies that contained accelerometry data for physical activity in asthmatic and control children.

Author, Date, Country	Population	Physical Activity	Asthma Measurement	Confounders	Results	Author's Conclusions
			Population-based cohort studies			
Eijkemans (2008), The Netherlands [14]	305 children followed from birth to age 5 yrs	Actigraph (Actigraph, FL) Accelerometer worn for 5 days Questionnaire	Reported doctor's diagnosis and use of asthma medications and symptoms (asthma ever and last 12 months)	Gender, parental asthma, mother's education, others	Total activity (counts/min) Boys recent wheeze GMR: 1.02 (0.90–1.14) Boys past wheeze GMR: 1.11 (1.02–1.20) Boys never wheeze GMR: reference; Girls recent wheeze GMR: 0.98 (0.85–1.13) Girls past wheeze GMR: 1.00 (0.92–1.09) Girls never wheeze GMR: reference	No evidence that wheezing children are less physically active.
			Hospital-based case-control studies			
Sousa (2014), Brazil [32]	121 children aged 7–12 yrs	Power Walker (PowerWalker, Yamax, Japan) Accelerometer worn for 6 days	Doctor's diagnosis (last 6 months)	Matched for age, others	Mean (sd) total activity counts/min: Asthmatics: 6171 (2574), Controls: 5700(1865)	Children with good asthma control had DPA levels similar to children without asthma. More asthmatic children were overweight if sedentary as compared to physically active asthmatic children.
			Population-based cross-sectional studies			
Berntsen (2009), Norway [38]	174 adolescents 13–14 yrs	SenseWear Armband (Bodymedia Inc., Pittsburgh, PA) in Accelerometer worn for 4 days and questionnaire	Reported doctor's diagnosis, use of asthma medication or symptoms (current asthma)	Age, gender, others	MPA (mean, 95% CI): Asthma: 39736 (35828–43643), Controls: 35245 (32543–37947); VPA (mean, 95% CI): Asthma: 16351 (13380–19321), Controls: 14291 (12380–16201)	Hours spent in moderate to vigorous physical activity were similar in asthmatics and non-asthmatics.
Brasholt (2010), Denmark [37]	253 children 5 yrs	Actical (Philips Respironics, Murraysville, Pa) Accelerometer worn for 4 weeks	Doctor's diagnosis (asthma ever)	Age, mother's education, others	Boys ARR: 0.88 (0.79–0.97); Girls ARR: 0.9 (0.85–0.97); Non-asthmatics ARR: 0.9 (0.82–0.98)	No association between physical activity and asthma diagnosis.
Fedele (2014), USA [36]	248 obese children 7–12 yrs	Sensewear Armband (Bodymedia Inc., Pittsburgh, PA) in Accelerometer worn for 7 days	Reported doctor's diagnosis (asthma ever)	Age, gender	Time spent in activity, Mean (SD): Obesity only (controls): 117.91 (75.41) Asthma and obesity: 94.98 (47.98)	Children with both asthma and obesity engaged in less physical activity than children with obesity only (though this was not statistically significant).

(*Continued on next page*)

Table 1. (Continued)

Author, Date, Country	Population	Physical Activity	Asthma Measurement	Confounders	Results	Author's Conclusions
Firrincieli (2005), USA [30]	54 children 3–5 yrs	Actiwatch (Mini Mitter Co., Bend, OR) Accelerometer worn for 6–7 days	Reported asthma diagnosis, medication use and symptoms (asthma ever)	None stated	Data not presented (means)	Children with history of wheezing were significantly less active than non-wheezing children.
Rundle (2009), USA [44]	437 children age 4 yrs	Actiwatch (Mini Mitter Co., Bend, OR) Accelerometer worn for 6 days	Reported doctor's diagnosis or wheeze or use of asthma medications (last 12 months)	Age, gender, others	Mean (sd) Total activity counts/min: Asthma: 686.4 (147.5) Controls: 683.4 (151.8)	Asthma symptoms were not associated with physical activity.
Tsai (2012), USA [49]	54 children 9–11 yrs	Actigraph (Actigraph, FL) Accelerometer worn for 7 days	Reported doctor's diagnosis and medication. (unclear)	Gender, others	Mean (sd) total activity counts/ min: Asthma: 650 (202), Controls: 752 (260)	Children with asthma have similar levels of activity as non-asthmatic children.
van Gent (2007), The Netherlands [33]	1614 children 7–10 yrs	PAM (PAM B.V. The Netherlands) Accelerometer and Questionnaire worn for 5 days	Reported doctor's diagnosis, and FEV variability (last 12 months)	None stated	Mean (95%) MPA: Undiagnosed asthma: 86 (76–95), Diagnosed asthma: 78 (66–90), Controls: 78 (71–85); Mean (95%) VPA: Undiagnosed asthma: 22 (15–25), Diagnosed asthma: 21 (14–28), Controls: 20 (14–21)	No difference in daily physical activity or intensity of physical activity between children with diagnosed asthma, undiagnosed asthma or healthy controls.
Vangeepuram (2014), USA [34]	1182 girls 6–8 yrs	Pedometer worn and Questionnaire answered for 7 days (minimum 4 days)	Reported doctor's diagnosis, asthma symptoms or medication. (asthma ever and last 12 months)	Age, level of caregiver education, others	Pedometer steps (mean, sd): Asthma: 9590 (4348) Control: 10359 (4161)	Did not find strong associations between asthma diagnosis and physical activity.
Vahlkvist (2009), Denmark [46]	214 children 6–14 yrs	RT3 (Stayhealthy, Monrovia, CA) Accelerometer worn for 4 weeks	Reported asthma symptoms, and FEV variability (current asthma)	Matched on age, gender	Total PA counts/min (mean, CI): Asthma 348.3 9325.1–371.5) Control: 362.6 (350.5–374.8)	No statistically significant differences between asthmatics and non-asthmatics in overall daily activity, time spent in high or vigorous activity.
Yiallouros (2015), Cyprus [47]	203 children 8–9yrs	Actigraph (Actigraph, FL) Accelerometer worn for 6 days	Reported doctor's diagnosis (asthma ever and in last 12 months)	Gender, parental education, others	Total PA counts/min (means, 95% CI): Control: 509.5 (497.8–521.2) Inactive asthma: 493.6 (478.6–508.7) Active asthma: 500.2 (476.4–524.0)	No difference in sedentary and physical activity levels in asthmatic and non-asthmatic boys. Girls with active asthma are less active than healthy peers.

PA = Physical activity, MPA = moderate physical activity, VPA = vigorous physical activity, MVPA = moderate-to-vigorous physical activity, BMI = body mass index, GMR = geometric mean ratio.

Table 2. Definitions for sedentary, light, moderate, vigorous and moderate to vigorous physical activity levels used by the studies included in this review.

Study	Sedentary	Light Physical Activity (LPA)	Moderate Physical Activity (MPA)	Vigorous Physical Activity (VPA)	Moderate-Vigorous Physical Activity (MVPA)
Berntsen (2009) [38]			Not defined		
Brasholt (2010) [37]			Not defined		
Eijkemans (2008) [14]	0 – 363 counts/15sec	364 – 811 counts/15sec	812 – 1234 counts/15sec	>1234 counts/15sec	ND
Fedele (2014) [36]	ND	ND	ND	ND	≥ 3 METs
Firrincieli (2005) [30]	ND	ND	ND	>2000 activity units	ND
Rundle (2009) [44]	≤598 counts/min	599 – 685 counts/min	686 – 773.5 counts/min	>773.5 counts/min	ND
Sousa (2014) [32]	ND	Boys: >15000 steps/day Girls: >12000 steps/day	ND	ND	ND
Tsai (2012) [45]	0 – 49 counts/min	50 – 699 counts/min	700 – 2499 counts/min	>2500 counts/min	ND
Vahlkvist (2009) [46]	ND	ND	3 – 5 METs	≥6 METs	ND
Vangeepuram (2014) [34]	ND	ND	ND	ND	>4.5 MET-hours
van Gent (2007) [33]	ND	ND	3 – 6 METs	>6 METs	ND
Yiallouros (2015) [47]	0 – 99counts/sec	100 – 3200counts/sec	ND	ND	>3200 counts/sec

ND = not defined; METs = metabolic equivalent values.

[32, 33, 38, 44, 46]. Three of these studies looked at both asthma ever and current asthma [14, 34, 47]. With the exception of 2 studies in which physicians diagnosed asthma in participants 37], other included studies relied on parental/child reports of a doctor's asthma diagnosis in conjunction with reports of asthma symptoms and/or use of asthma medication [14, 32, 30, 38, 44, 45, 47]. Two studies measured Forced Expiratory Volume (FEV) variability in addition to reported doctor's diagnosis and reported asthma symptoms [33, 46].

Asthma control

Nine of the 12 included studies mentioned asthma control or severity in their study populations [32–34, 30, 37, 38, 45–47]. Four studies reported good asthma control: two had a range of disease severities but good control [32, 37], one study reported good or partially controlled asthma [45], and one reported good asthma control but did not discuss asthma severity [38]. One study used the ISAAC questionnaire to look at asthma severity [30]. Two studies stratified by diagnosed and undiagnosed asthma [33] or stratified by active and inactive asthma [47] but did not discuss this in terms of asthma severity or control. One study reported the use of asthma controller medications, but did not describe the level of asthma control or severity in their population [34]. One study used the childhood asthma control test (C-ACT) and reported that asthma was not optimally controlled in the study population [46]. Two studies had no discussion of asthma control or severity [14, 44], and one was unable to assess asthma severity [36]. We were unable to perform a meta-analysis that stratified by asthma control due to the high degree of heterogeneity between studies.

Confounding variables

Seven of the included studies adjusted or matched for age [32, 34, 36–38, 44, 46] and gender [14, 36, 38, 44–47]. Four studies adjusted for parent or caregiver education as a proxy for socioeconomic status [14, 34, 37, 47]. One study adjusted for parental asthma [14]. None of the included studies adjusted for number of siblings or pet ownership. Two studies did not report adjustment for any covariates [30, 33].

Findings of the studies included in the systematic review but not the meta-analysis

Three cross-sectional studies could not be included in the meta-analysis as they did not present information regarding the number of children with and without accelerometry data, the mean and standard deviation or confidence interval of the mean [30, 34, 36]. Two of these 3 cross-sectional studies found that children with asthma or wheeze were less active than those without asthma or wheeze [30, 36]. This result was significant in the study by Firrincieli et al. [30] but was not statistically significant in the study by Fedele et al. [36]. Both of these studies were conducted in the United States. The study conducted by Firrincieli et al. had a small sample size of 54 children aged between 3 and 5 years [30], while Fedele et al. had a sample size of 248 children with obesity aged 7 to 12 years [36]. The third study was an analysis of 558 female children conducted in the United States, which found no association between asthma diagnosis and physical activity [34].

Quality assessment of included studies

The cohort [14] scored 8 out of 9 and the case-control [32] scored 7 out of 9 using the NOS. Study scores for the cross-sectional designs ranged from 4 [30] to 8 [47] out of 8 points. Four studies scored 7 [34, 37, 38] or above [47] out of 8, again indicating acceptable quality. The 3 studies that could not be included in the meta-analysis scored 4 [30], 6 [36] and 7 [34] out of 8 points. This suggests that with the exception of Firrincieli et al. [30], 2 of the 3 studies excluded from meta-analysis were of reasonable quality. Table 3 presents the NOS point allocation for each of the included studies.

Results of meta-analysis

Nine studies (8 cross-sectional and 1 cohort) presented mean and standard deviation data (or data from which these measures could be derived) for the amount of physical activity performed by children with and without asthma, as measured by accelerometer and were pooled in a meta-analysis [14, 32, 33, 37, 38, 44–47] (Figure 2). There was no significant difference in mean physical activity level between children with and without asthma (both the fixed and random effect estimate =

Table 3. Presentation of the allocation of Newcastle-Ottawa Scale (NOS) points for each study.

Study, >Design	Berntsen (2009), Cross-sectional [38]	Brasholt (2010), Cross-sectional [37]	Fedele (2014), Cross-sectional [36]	Firrincieli (2005), Cross-sectional [30]	Rundle (2009), Cross-sectional [44]	Tsai (2012), Cross-sectional [45]	Vahlkvist (2009), Cross-sectional [46]	Vangeepuram (2014), Cross-sectional [34]	van Gent (2007), Cross-sectional [33]	Yiallouros (2015), Cross-sectional [47]	Sousa (2014), Case-control [57]	Eijkemans (2008), Cohort [14]
Points	7/8	7/8	6/8	4/8	6/8	6/8	6/8	7/8	5/8	8/8	7/9	8/9
Representativeness	1	1	1	1	1	1	0	1	1	1	1	1
Sample size	0	0	0	0	0	0	0	0	0	1	N/A	N/A
Comparability	2	2	2	0	2	2	2	2	0	2	2	2
Statistical Test	1	1	1	0	0	1	1	1	1	1	N/A	N/A
Non-response rate	1	1	0	1	1	0	1	1	1	1	0	N/A
Ascertainment of outcome	2	2	2	2	2	2	2	2	2	2	N/A	1
Selection of controls/ non-exposed cohort	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	1
Ascertainment of exposure	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	0
Definition of controls	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
Same method of ascertainment for both cases and controls	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
Case definition	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A
Outcome not present at start of study	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0
Adequate follow up time	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1
Adequacy of follow up of cohort	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1

N/A (not applicable) was allocated when the scale did not include that criterion for a specific study design.

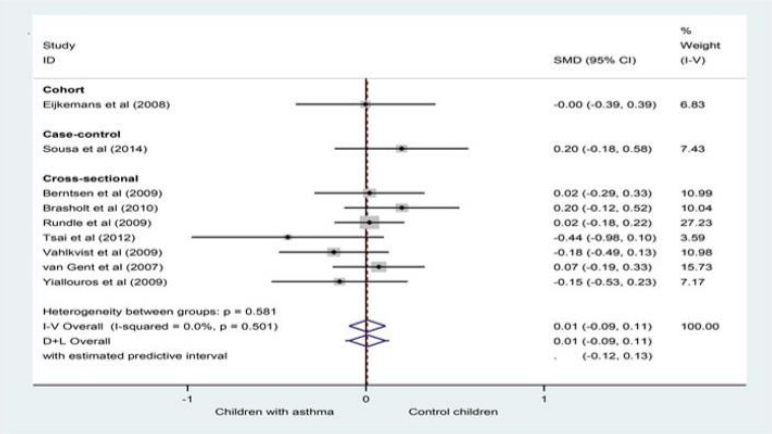

Figure 2. Meta-analysis of mean difference (SMD) in physical activity between children with and without asthma, as measured by accelerometer. SD = standard deviation of the mean.

0.01 activity counts per minute 95% CI: −0.09, 0.11, $p = 0.50$, $I^2 = 0.0\%$). There was no overt evidence of small study bias as demonstrated by the funnel plot (Figure 3).

Discussion

This is the first systematic review and meta-analysis of evidence surrounding objectively measured physical activity level of children with asthma and without asthma. The meta-analysis of 9 studies including 3375 children showed no significant difference in physical activity level between children with asthma and those without the condition [14, 32, 33, 37, 38, 44–47]. This result was supported by 1 of the 3 studies that were not included in the meta-analysis [34]. The remaining two studies that were not included in the meta-analysis had contradictory findings, concluding that children with asthma were less active than their peers [30, 36].

It is unlikely that the 3 studies that did not provide estimates for inclusion in the meta-analysis would have greatly affected the result of this analysis, despite 2 of these concluding that children with wheeze or asthma were less active. The first study had a small sample size and therefore is unlikely to have had sufficient power to influence the estimate [30]. Despite the relatively large sample size of the second article, they reported that

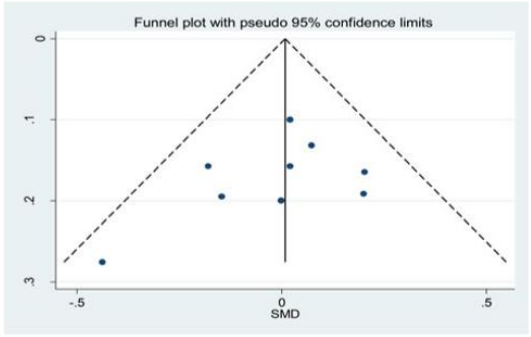

Figure 3. A funnel plot of included studies.

the trend for less activity in children with asthma was not statistically significant [36]. In addition, this study was conducted in a population of obese children with and without asthma [36]. The co-morbidity of obesity may have altered the difference in amount of activity performed between those with and without asthma, therefore the implications of this finding to the wider population (including non-obese children) are not clear.

Our results are discordant with the previous review by Williams et al. who concluded that individuals with asthma are less likely to participate in physical activity than individuals without asthma [19]. The conflicting conclusions may be due to several fundamental differences. The present review included only studies that measured physical activity with accelerometry, thereby excluding more subjective measurements. In contrast, Williams et al. did not include any studies that measured physical activity objectively through accelerometry [19]. Second, the review by Williams et al. was a narrative review rather than a systematic review.

A major strength of this review is that only studies that objectively measured physical activity through an accelerometer were included, as these measures of physical activity are more reliable and accurate than self-reporting, or parental reports of frequency and intensity of physical activity, particularly in children [22, 51]. However, it is difficult to establish standard thresholds for categories of physical activity [22]. This is evident in the varied cut-off points for low, moderate and vigorous physical activity used by the included studies.

A limitation of this review is participant behaviour modification within the included studies. Participant behaviour modification due to the knowledge of their participation could influence the study results (the Hawthorne effect). However, this potential behaviour modification is unlikely to alter the behaviour of children or adolescents if the activity is tracked for more than 1 day [22] and all the studies in this review all measured physical activity for more than a single day. A second issue with accelerometry is the potential underestimation of physical activity data due to the removal of the device for water-based activities where the devices are not water resistant. The removal of the accelerometer for water based activity

could potentially bias the results if children with asthma perform more water-based activity than children without asthma; however there is insufficient evidence to demonstrate that this is true.

We were unable to perform subgroup analyses to investigate the effects of asthma control or severity on the relationship between asthma and physical activity. This was due to the limited number of articles that accounted for or stratified by level of asthma control or severity in their studies. Future studies should also investigate the role of body mass index (BMI) in their analyses, since BMI is a potentially important variable that could act as either a confounder, mediator or as an effect modifier in the relationships between asthma and physical activity. BMI was not included in this review as few articles included it as a confounder in their analyses. For this reason we were unable to meta-analyse or stratify the results by BMI.

It is conceivable that these results present similar levels of physical activity for children with and without asthma since the included studies stem primarily from countries such as the United States, the Netherlands and Norway, which share similar and sophisticated asthma management programs. In fact, many of the included articles reported good asthma control in their study populations [32, 37, 38, 45]. For this reason, the results of this review may not be applicable to populations in which asthma medication and education is inaccessible or inadequate. In future, stratification by level of asthma control or severity may add valuable insight into the effect of poor asthma control on children's physical activity, with implications for the improvement of asthma programs to encourage more active lifestyles.

Cross-sectional studies cannot be relied upon to determine temporality of the association, and introduce the possibility of reverse causation. Therefore, longitudinal studies that objectively measure sustained and habitual physical activities over time, as well as symptoms of wheeze and asthma, are required to investigate causality and the temporal relationship between asthma and physical activity. That is, to distinguish whether physical inactivity leads to the development of asthma, or whether asthmatics are more prone to a sedentary lifestyle due to fear of asthma exacerbations or a reduced capacity for physical activity. In this review, the included cohort study did not find differences between the levels of physical activity attained by children with and without asthma. However further longitudinal studies are required to investigate these intricacies.

As recommended [52], we performed an evaluation of included studies through the use of the Newcastle-Ottawa Scale (NOS) [39]. Despite the availability of other tools, there is not yet any single tool that is an obviously better option than the others [53]. Use of the NOS scale, however, remains controversial, as critical reviews of the scale itself found that it has low inter-rater reliability [54], questionable validity [55] and low agreement between reviewers and authors [56]. For this reason, we did not attribute much weight to the NOS tool ratings; we merely used the ratings as an indication of study quality and to highlight areas that future research studies should focus on to improve quality.

Based on the available evidence using objective measurements of physical activity, there appears to be no need for physical activity programs to specifically target children and adolescents with asthma in countries with developed asthma care systems. However, these results may not apply to countries with less developed asthma management programs. Efforts should continue to promote habitual physical activity in children in accordance with World Health Organisation guidelines.

Conclusion

This systematic review and meta-analysis did not find evidence that children and adolescents with asthma engaged in less physical activity, when measured objectively, than their peers without asthma. Therefore, public health policies that encourage children and adolescents to increase their level of physical activity do not need to differentially target children with asthma in settings where effective asthma campaigns have been established.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

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Appendix

Search strategy

Medline: "physical activity."af., "physical activity."sh., "physical training."af., "physical training."sh., exercise.af., exercise .sh., sedentary.af., sedentary.sh., asthma.af., asthma.sh., "early life wheeze."af., "early life wheeze."sh., "transient wheeze."af., "transient wheeze."sh

PubMed: ((((“physical activity”[All Fields] OR “exercise”[All Fields]) OR “exercise”[MeSH Terms]) OR “physical training”[All Fields]) OR “sedentary”[All Fields]) AND (“asthma”[MeSH Terms] OR “asthma”[All Fields] OR “early life wheeze”[MeSH Terms] OR “early life wheeze”[All Fields] OR “transient wheeze”[MeSH Terms] OR “transient wheeze”[All Fields])

Embase: (“physical activity.”mp. or exp exercise/ or exp physical activity/) or (“physical training.”mp. or exp training/) or (exp exercise/ or exercise.mp.) or (exp exercise/ or exp sedentary lifestyle/ or sedentary.mp. or exp physical activity/) and (exp asthma/ or asthma.mp.) – excluding Medline journals.

CHAPTER SIX: Investigation of a bi-directional relationship between asthma and physical activity

6.1 Chapter introduction

This chapter contains a data analysis of the *Growing Up in Australia*: Longitudinal Study of Australian Children (LSAC) cohort. This data analysis aimed to investigate the possibility of a bi-directional association between asthma status and physical activity in youth. The publication that resulted from this data analysis was the third publication that I authored during the course of this PhD.

6.2 Research question

Is the association between physical activity and asthma bi-directional? In other words, this data analysis aimed to investigate whether there is an association between i) asthma status and subsequent PA level, and ii) PA level and subsequent asthma status, simultaneously in a single statistical model.

6.3 Chapter synopsis

My published systematic reviews (Chapters Four and Five) highlighted the inconsistency of results for the relationship between asthma and physical activity in children in the scientific literature, with published articles providing evidence both for and against the effect of physical activity on asthma and vice versa. However, many of these studies have been cross-sectional in nature and so the issue of reverse causality has prohibited the ascertainment of the direction and temporality of the association.

To address the problem of temporality, data from multiple waves of the LSAC's K cohort were employed. The data spanned a total of 8 years, from when the LSAC children were 6 to 14 years of age. Information on asthma status and level of physical activity was collected at each wave. Using structural equational modelling techniques, I explored whether amount of time spent doing physical activity at a given time influenced asthma status later in life and similarly whether asthma status at a given time affected the amount

of time spent doing physical activity. The LSAC with its multiple waves of data collection, enabled these bidirectional associations to be investigated. This data analysis and the resulting publication was the first article to examine the relationships between asthma and physical activity in this manner.

Physical activity data were collected through Time Use Diaries (see Chapter Three for the detailed methodology) and a continuous variable for total time spent in moderate-to-vigorous physical activity for each child was created by summing the time in minutes spent in all coded physical activities for the day the data were collected. Asthma data were collected via parental- or self- administered questionnaire and were defined as either incident or current asthma. Covariates were selected based on existing literature, and the DAG presented below.

A linear regression was fitted for investigating the relationship between asthma status and subsequent amount of time spent doing physical activity while a logistic regression was used to investigate association between amount spent doing physical activity and subsequent asthma status.

This analysis found no evidence of associations between physical activity and subsequent asthma nor between asthma and subsequent physical activity. However, it was noted that measures of asthma and physical activity used could be improved and reproducing this study with objective measures was recommended.

6.4 Directed acyclic graphs (DAGs)

The following DAGs were created to assist in the understanding of the relationships between the variables or interest. By definition DAGs should be acyclic, that is, the "flow" of association can only be in a single direction and feedback loops are not permitted (192, 193). Since a DAG could not be created to demonstrate bidirectionality, two separate DAGs were developed in order to show the assumed causal relationship in each direction. These are presented below (Figures 6.1, 6.2, 6.3).

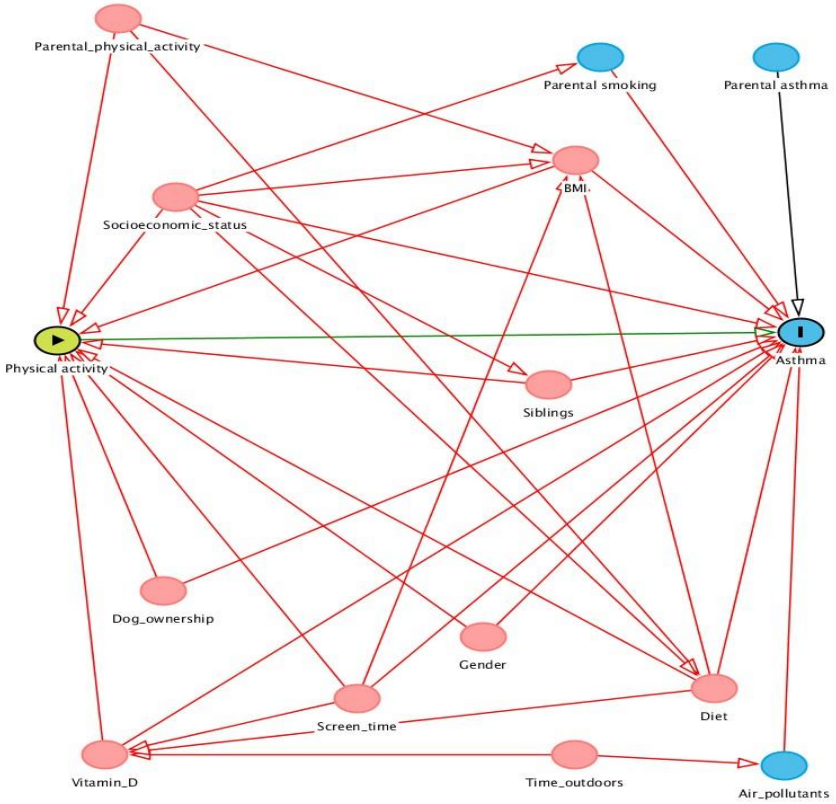

Figure 6.1: First attempt at a directed acyclic graph (DAG) of the relationships between physical activity and subsequent asthma and the potential covariates. Created with Daggity software.

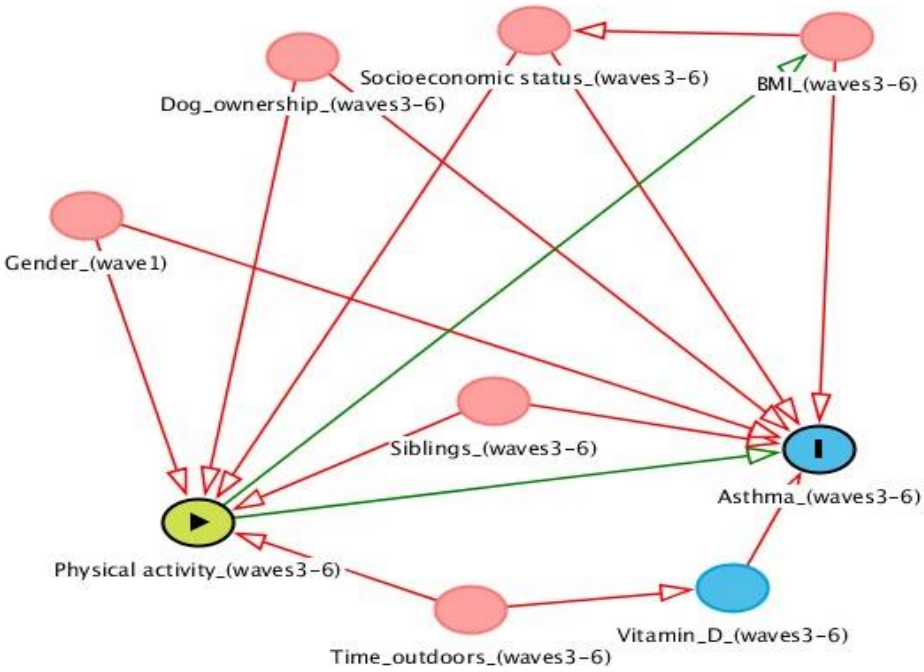

Figure 6.2: A revised and simplified outlining the association between physical activity and subsequent asthma, with timepoints of measured variables Created with Daggity software.

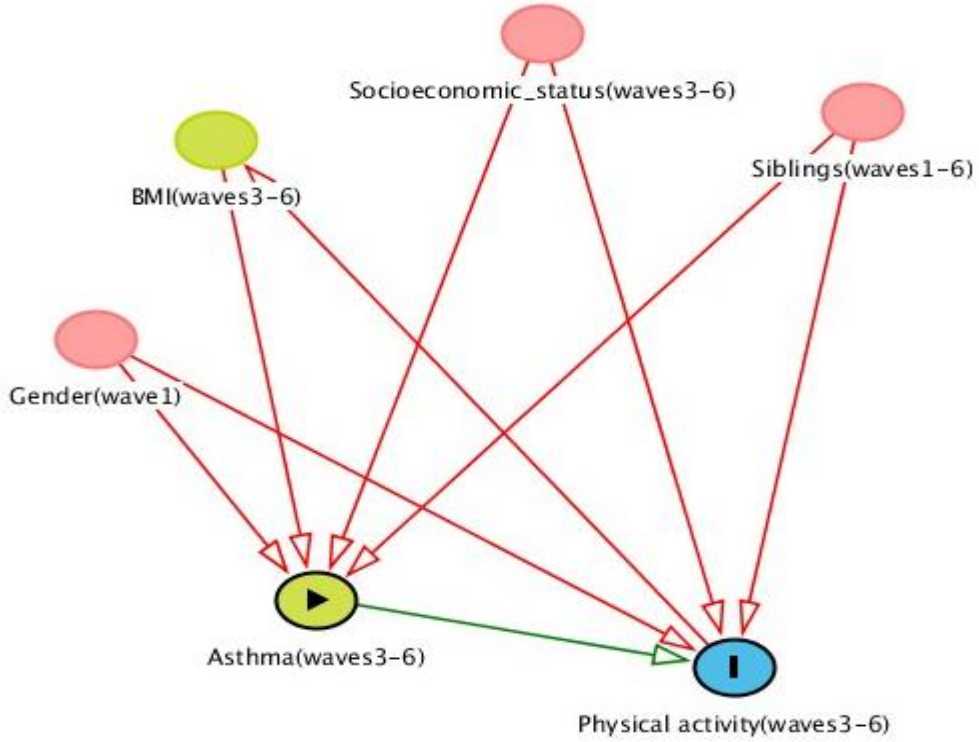

Figure 6.3: A revised and simplified DAG outlining the association between asthma and subsequent physical activity, with timepoints of measured variables. Created with Daggity software.

6.5 Publication

Cassim R, Milanzi E, Koplin JJ, Dharmage SC, Russell MA (2018) Physical activity and asthma: cause or consequence? A bidirectional longitudinal analysis. Journal of epidemiology and community health: jech-2017-210287

Physical activity and asthma: cause or consequence? A bidirectional longitudinal analysis

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ABSTRACT

Background There is increasing interest in the role physical activity (PA) can play in the development and management of asthma. Understanding whether PA can have a positive effect is hindered by the potential influence of asthma on PA and a lack of relevant longitudinal data, leading to a debate on the existence and direction of these links. The aim of this study was to explore whether having asthma results in lower PA levels, and/or whether lower PA levels lead to more asthma in children and adolescents.

Methods In a population-based study of 4983 children, data on asthma and PA were collected via questionnaires and time use diaries biennially, between the ages of 6 and 14. Current asthma was defined as use of asthma medications or wheeze in the past year, and incident asthma was defined as doctor's diagnosis since the previous wave. PA was time spent doing moderate-to-vigorous physical activities in a day. Bidirectionality of this relationship was investigated using cross-lagged structural equational models.

Results PA was not longitudinally associated with incident or current asthma. Similarly, there was no evidence that incident or current asthma predicted PA at any of the ages.

Conclusions Using a novel strategy to investigate bidirectionality between PA and asthma, our results suggest that asthma and PA participation are not longitudinally associated in either direction. Our findings suggest that PA does not play an important role in the development or persistence of asthma.

INTRODUCTION

While the increase in the prevalence of asthma appears to have plateaued in recent years, it remains high globally,[1] especially in children and adolescents.[2] The reason for this high prevalence is multifactorial; however, several lifestyle factors, including increased screen time and decreased physical activity (PA), have been identified as possible contributors to the perpetuation of asthma as an important public health problem.[3] It is estimated that globally, a large proportion of children and adolescents do not attain the recommended 60 min of moderate-to-vigorous PA (MVPA) per day,[4] and there are concerns that an even smaller proportion of children and adolescents with asthma meet these recommendations.[2]

The relationship between PA and asthma is complex and may in fact be bidirectional. Some previous research has investigated the effect of PA on asthma in children, and this research was collated in a systematic review published in 2016 by Lochte *et al*.[5] Their meta-analysis of three longitudinal studies concluded that lower levels of PA were associated with a 35% increased risk of new-onset asthma and wheeze in children (fixed-effect pooled OR 1.35; 95%CI 1.13 to 1.62; I^2=60.6%).[5] However, these studies varied in their assessment and definition of the exposure; while one looked at sedentary time,[6] the second and third questioned the amount of time spent in sports.[7 8] In addition to this, the scarcity of longitudinal studies in child and adolescent populations means that further studies are warranted.

On the other hand, an asthmatic state has been found to reduce levels of PA in affected individuals,[9–11] probably through self-imposed or parentally imposed behavioural changes.[2 12] Since strenuous exercise is a known trigger for asthma, studies have shown that individuals with the condition tend to refrain from participation in strenuous activity to avoid triggering an asthma attack.[10] Despite this, several large international studies found no evidence that children with asthma participate in less PA than children without asthma.[13–16] Similarly, our recent systematic review and meta-analysis concluded that children with and without asthma engaged in equivalent amounts of objectively measured PA.[17] However, the majority of the studies included in the review were cross-sectional, with only one longitudinal study. Further longitudinal research would clarify the extent of any effect of childhood asthma on PA levels over time.

In summary, although the relationship between PA and asthma has been reviewed and documented in the literature,[5 17] the temporality of the association has not yet been elucidated. There is both evidence for and against the effect of PA on asthma and the effect of asthma on PA. Inference on causality and direction of the relationships between asthma and PA are inhibited primarily by limited numbers of longitudinal studies in children and the potential for reverse causality. Importantly, to date, there have been no studies that have investigated these links between PA and asthma while taking into account the possibility of the bidirectionality.

Therefore, this study aimed to investigate the possibility of a reciprocal relationship between asthma and PA in children and adolescents in a longitudinal manner using a novel analytical approach. That is, this analysis aimed to investigate (i) the effect of asthma status at an earlier age on PA level at a later age and (ii) the effect of PA level at

an earlier age on asthma status at a later age. We hypothesised that there would be evidence of associations in both directions.

METHODOLOGY

Longitudinal Study of Australian Children (LSAC)

This study used longitudinal data from the *Growing Up in Australia: Longitudinal Study of Australian Children (LSAC)* whose sampling and recruitment methodology has previously been described[18 19] and is accessible on the LSAC website (www.growingupinaustralia.gov.au). The present analysis was conducted in one of the two nationally representative LSAC cohorts, namely the 'K' cohort which consisted of 5000 children aged 4–5 years at recruitment (wave 1). Participants were followed up biennially, and data have been collected via interviews, questionnaires, time use diaries (TUDs) and direct anthropometric measurements. This study used the data collected at waves 2 to 6 (ages 6 to 14) for the exposure and outcome variables; since asthma diagnosis in children is contentious before the age of 5 years,[20] wave 1 (age 4) data were included for analytic adjustment purposes only.

Physical activity

PA data were extrapolated from the completion of TUDs. The use of TUDs in LSAC has previously been published in detail,[21] but their use for this analysis is described below. The TUDs used at waves 1–3 differ from those used at waves 4–6. In earlier waves,[22] at the face-to-face interview, parents were shown how to complete the TUD which divides the 24-hour day into 15 min intervals.[22] Parents were asked to complete the child's activity diary (by selecting from 26 precoded activities, presented in online appendix 1), indicating location and with whom the activity was performed for each 15 min interval of the day, for 1 weekday and 1 weekend day.[22 23] From wave 4 onwards, children were asked to complete a single TUD themselves by recording the activities they performed throughout the day on any 1 day.[22]

For waves 2 and 3 where two TUDs were completed, we randomly selected one TUD per participant for analysis to ensure consistency across all waves. Since the TUDs did not capture the intensity of PA, the following coded activities within the TUDs were considered MVPA (with a metabolic equivalent score of 3.0 or greater) based on the Compendium of Energy Expenditure for Youth categorisations[24]: structured or unstructured active play, organised sports/lessons/activities, riding bike/scooter/skateboard and walking/running skipping. For each wave, a continuous variable for total time spent in MVPA for each child was created by summing the time in minutes spent in all coded physical activities for the day the data were collected.

Asthma measurement

The present analysis investigated two asthma outcomes:

a. *incident asthma* since the last wave was defined as present if the response was 'yes' to the question 'Has a doctor ever told you that child has asthma?' at waves 1 to 4 (when the answer had been 'no' in previous waves) or 'Since the last interview, has a doctor told you that study child has asthma?' at waves 5 and 6;
b. *current asthma* was considered to be present if there was an affirmative response to either 'In the last 12 months, has child taken any medication for asthma?' or "In the last 12 months, has the child had an illness with wheezing in the chest which lasted for a week or more?'.[25]

Covariates

Three time-varying covariates, resident older siblings,[26 27] socioeconomic position (SEP)[28 29] and body mass index (BMI),[30] and one non-time varying covariate, gender,[30] were selected based on the literature and availability of data. Gender and the presence of one or more older siblings residing in the home with the study child were collected in the questionnaires and analysed as binary variables. SEP ranked each LSAC family based on parental income, education and occupation and was included in the models as a z-score. The development of this variable has been described extensively in a paper published by LSAC.[31]. Height was measured using an Invicta stadiometer in waves 2 and 3, and in waves 4, 5 and 6, a laser stadiometer was used.[32] Weight was measured using HoMedics digital BMI bathroom scales in waves 2 and 3, and Tanita body fat scales were used in waves 4 to 6.[32] BMI at each wave was categorised as 'underweight', 'normal weight' or 'overweight' based on the age appropriate cut-offs proposed by Cole *et al*.[33]

Statistical methodology

Stata/MP (StataCorp LLC) statistical software was used for all analyses. Initially, descriptive analyses of participant characteristics were undertaken by calculating frequency and percentages for categorical variables and means and SD for continuous variables. Time spent in MVPA was converted to hours for reporting purposes.

To examine the bidirectionality of the association between asthma and PA, we looked at three models using generalised structural equational modelling (GSEM) for both incident asthma and current asthma. GSEM is a statistical modelling technique used to analyse structural relationships between multiple variables. It works by first postulating what we believe to be the relationship between several variables, this can be based on expert knowledge input or literature review. The data are then used to confirm the postulated relationship. We used both linear and logistic regressions as appropriate. GSEM intrinsically accounts for missing and incomplete data using maximum likelihood estimation which assumes missingness at random. More details can be found in the reference.[34]

Our first model estimated the lagged effects of PA at each wave on asthma at the next wave using logistic regression and will be referred to as Model 1x ('a' for incident asthma, 'b' for current asthma). Through this model, we postulated that PA at a previous wave affects asthma at the current wave. For the second model, the lagged effects of asthma at each wave on PA at the next wave were investigated with linear regression in GSEM (Model 2x). In this model, we implied that incident asthma status at a previous wave influences the amount of time spent doing physical activities. The final model estimated the cross-lagged effects of asthma on PA and PA on asthma simultaneously (Model 3x). The model assumed that PA and asthma status have simultaneous causal effects on each other, that is, PA at a previous wave causes asthma at the current wave, and asthma status at a previous wave has a causal effect on PA (figure 1).

Models 1 and 2 were compared with the cross-lagged model (Model 3x) using the likelihood ratio test (LRT) to determine if one of the parsimonious models was adequate. This test served two purposes. The first was to check if the two models are equally likely. The second was to test if the effect was evident in one direction only; that is, if either Model 1x or 2x was better than the cross-lagged model (Model 3x). Small p values from the LRT would favour the more complex model.

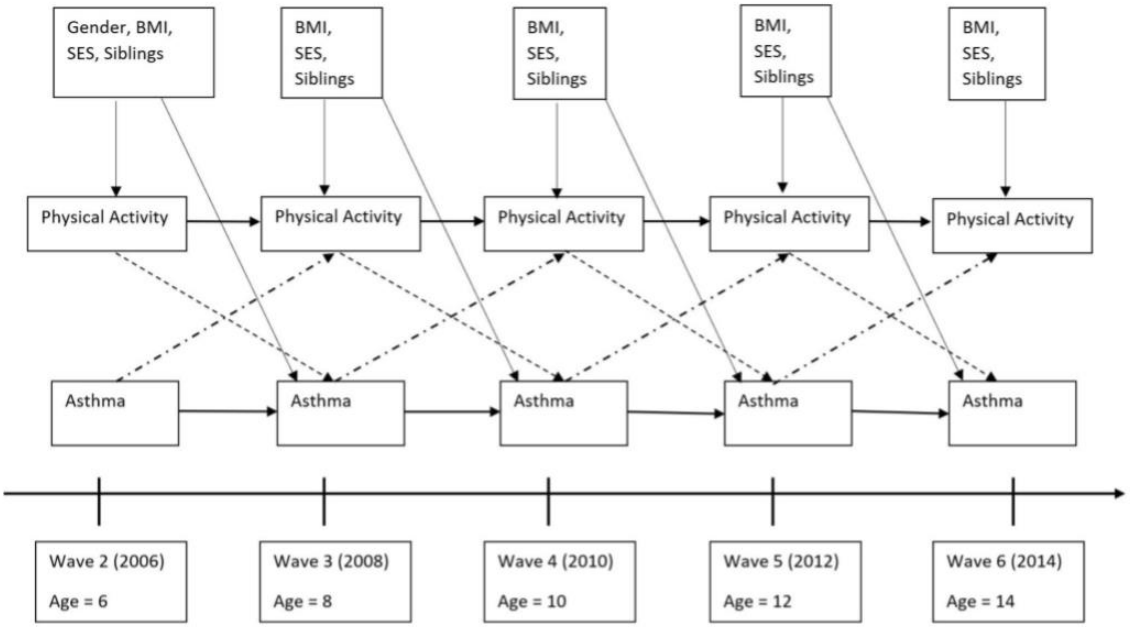

Figure 1 Schematic representation of the cross-lagged GSEM model (Model 3x). BMI, body mass index; GSEM, generalised structural equational modelling; SES, socioeconomic status.

Further estimation to compare models was performed using Akaike's Information Criterion (AIC), where lower AIC scores indicated a better fit than higher scores.[35]

For GSEM Model 1b (current asthma) only, an interaction term was fitted to investigate whether the association between PA and odds of subsequent current asthma differentially varied depending on the presence or absence of current asthma at a younger age.

RESULTS

Descriptive analyses

Of the 4983 children initially recruited, 4464, 4332, 4169, 3956 and 3537 children participated at waves 2 through 6, respectively. Documents detailing non-response at each wave are available online (www.growingupinaustralia.gov.au). Female participants constituted 49% of the study sample at each wave (table 1). The percentage of children who experienced incident asthma and current asthma at each wave decreased over time. For all children, the mean time spent in MVPA increased from ages 6 to 8 years, then decreased over time. The largest reduction in time spent in PA was observed between ages 8 and 10 (waves 3 and 4).

Investigation of bidirectionality

Results of LRT comparing the single direction GSEM Models 1 and 2 to the cross-lagged GSEM Model 3 indicated that neither model was clearly better than the others for both current and incident asthma (table 2). Similarly, the AIC confirmed this result, showing little difference between models. Hence, each of the single-directional models was the most parsimonious models and was used to estimate the individual effects. GSEM Model 3 results are presented in online supplementary table 1.

Individual effect estimates

Effect of PA on subsequent asthma

The adjusted logistic regression GSEM Model 1a indicated a minimal effect from PA on risk of incident asthma for ages 8–12 years (table 3). There was moderate evidence (p=0.08) of association between PA and asthma at age 10 where a 1-hour increase in PA reduced the odds of incident asthma by 10% (95% CI 0.81 to 1.01). At age 12, increasing PA increased the odds of incident asthma at age 14. However, the associated 95% CIs for each age group traversed the null value, and p values larger than 0.05 suggested that there was little evidence of association. Similarly, although PA decreased the odds of current asthma at 8, 12 and 14 years, there was little evidence of association.

The p values associated with the fitted interaction term at each age (p=0.1, 0.5, 0.1 and 0.3 at ages 8 to 14, respectively) indicated that having previous asthma symptoms did not modify the association between PA and current asthma. When the mean time spent in PA at each age was stratified by the presence and absence of current asthma symptoms at the previous wave, it could be seen that that previous asthma symptoms had a minimal differential impact on future time spent in PA (data not shown).

Effect of asthma on subsequent PA

Results of the adjusted GSEM Model 2a suggested that incident asthma had little effect on the average time spent doing MVPA at ages 8, 10 and 14 (table 4). There was weak evidence (p=0.14) of an association at age 12, although again the associated 95% CI traversed the null. Similarly, there was moderate evidence (p=0.09 and 0.06) for the GSEM Model 2b at ages 8 and 10, respectively, but there was no evidence to suggest that current asthma at ages 10 and 12 affects subsequent PA at ages 12 and 14, respectively.

Table 1 An overview of data collection and participant characteristics across waves

	Wave 2 (2006)	Wave 3 (2008)	Wave 4 (2010)	Wave 5 (2012)	Wave 6 (2014)
Participants, n	4464	4332	4169	3956	3537
Age, mean (SD)	6.3 (0.5)	8.3 (0.4)	10.3 (0.8)	12.4 (0.5)	14.4 (0.5)
Male gender, n (%)	2276 (51)	2212 (51)	2132 (51)	2020 (51)	1798 (51)
BMI, kg/m^2 mean (SD)	16.5 (2.1)	17.6 (2.8)	19.0 (3.8)	20.5 (3.9)	21.9 (4.1)
Older sibling(s) present in the home, n (%)	2563 (57)	2464 (57)	2297 (55)	2076 (52)	1722 (49)
Incident asthma, n (%)	295 (8.39)	129 (4.26)	96 (3.53)	51 (2.02)	40 (1.79)
Current asthma, n (%)	995 (22.3)	872 (20.1)	814 (19.5)	734 (18.6)	581 (16.4)
Wheeze, n (%)	697 (15.6)	527 (12.2)	468 (11.2)	380 (9.6)	295 (8.3)
Asthma medication use, n (%)	685 (15.3)	667 (15.4)	637 (15.3)	592 (15.0)	469 (13.3)
Both wheeze and medication use, n (%)	387 (8.7)	322 (7.4)	291 (7.0)	238 (6.0)	183 (5.2)
Wheeze without medication, n (%)	310 (6.9)	205 (4.7)	177 (4.3)	142 (3.6)	112 (3.2)
TUD completed, n (%)	3385 (53)	2911 (67)	3483 (84)	2896 (73)	2157 (61)
Day of the week					
Monday, n (%)	306 (9.0)	242 (8.3)	563 (16.2)	518 (17.9)	354 (16.4)
Tuesday, n (%)	320 (9.5)	307 (10.6)	635 (18.2)	504 (17.4)	384 (17.8)
Wednesday, n (%)	351 (10.4)	290 (10.0)	587 (17.1)	470 (16.2)	367 (17.0)
Thursday, n (%)	379 (11.2)	319 (11.0)	524 (15.0)	430 (14.8)	293 (13.6)
Friday, n (%)	364 (10.8)	294 (10.1)	495 (14.2)	393 (13.6)	312 (14.5)
Saturday, n (%)	798 (23.6)	726 (24.9)	147 (4.2)	138 (4.8)	102 (4.7)
Sunday, n (%)	855 (25.3)	732 (25.1)	522 (15.0)	443 (15.3)	345 (16.0)
Hours spent in MVPA per day*, mean (SD)					
All participants	3.3 (2.6)	3.4 (2.7)	2.3 (1.6)	1.9 (1.6)	1.8 (1.6)
Participants with current asthma	3.2 (2.6)	3.3 (2.7)	2.2 (1.6)	1.9 (1.5)	1.8 (1.5)
Participants without current asthma	3.4 (2.6)	3.4 (2.7)	2.3 (1.6)	1.9 (1.6)	1.8 (1.6)

*This does not distinguish between weekday and weekend day, since one diary was randomly selected for children who completed two TUDs at earlier waves.
BMI, body mass index; MVPA, moderate-to-vigorous physical activity; TUD, time use diary.

DISCUSSION

This present study is the first to investigate bidirectionality of the association between asthma and PA. In a large cohort of children and adolescents aged 6 to 14 years, this study found no evidence that current asthma influenced time spent in PA nor was any effect seen from incident asthma. In addition, there was no evidence to suggest that PA longitudinally affected either incident or current asthma at any age.

Influence of PA on asthma

Contrary to the findings by Lochte *et al*,[5] our analysis found no evidence that PA influences either current or incident asthma. The inconsistency between our results and those of the systematic review[5] may be due to fundamental differences in the exposure and outcome definitions and measurement techniques employed by our team as compared with those within the systematic review. For example, while our study looked at time spent in PA, the studies contained within the review used number of team sports played,[8] sports participation frequency[7] and duration of tv viewing[6] as their PA exposure. Additionally, these studies differed in the definition of the outcome. Two looked at doctor-diagnosed new-onset asthma,[6 8] and the third investigated new-onset wheeze.[7] On the other hand, a recently published Norwegian cohort study produced similar results to our own. They too concluded that low PA level at ages 3–6 and 6–10 years was not longitudinally associated with current

Table 2 Comparison of three GSEM models using the AIC results comparing each model and LRT results comparing each single directional model to the cross-lagged model

		AIC		LRT		
GSEM model		AIC	Df	Df	X^2	P values
Incident asthma	1a	29549.07	63	4	2.98	0.56
	2a	29550.95	63	4	4.86	0.30
	3a	29554.08	67			
Current asthma	1b	43990.11	67	4	6.99	0.14
	2b	43986.38	67	4	3.26	0.52
	3b	43991.12	71			

AIC, Akaike's Information Criterion; GSEM, generalised structural equational model; LRT, likelihood ratio test.

Table 3 Logistic regression coefficients in ORs for the GSEM Model 1 (a—incident asthma; b—current asthma) investigating the lagged effects of physical activity at each wave on incident and current asthma at the next wave as the outcome

Asthma outcome at	Incident asthma outcome GSEM Model 1a		Current asthma outcome GSEM Model 1b*	
	aOR (95% CI)	P values	aOR (95% CI)	P values
Age 8	0.98 (0.93 to 1.03)	0.42	0.99 (0.96 to 1.03)	0.82
Age 10	0.90 (0.81 to 1.01)	0.08	1.00 (0.96 to 1.04)	0.88
Age 12	0.93 (0.77 to 1.13)	0.50	0.95 (0.89 to 1.02)	0.18
Age 14	1.06 (0.86 to 1.32)	0.54	0.95 (0.87 to 1.04)	0.25

Models were adjusted for SEP, gender, BMI and presence of one or more older siblings in the home.
*Model additionally adjusted for current asthma at an earlier wave.
aOR, adjusted OR; BMI, body mass index; GSEM, generalised structural equational modelling; SEP, socioeconomic position.

Table 4 Linear regression coefficients for the GSEM Model 2 (a—incident asthma; b—current asthma) investigating the lagged effects of asthma at each wave on physical activity at the next wave as the outcome

Physical activity outcome at	Incident asthma exposure GSEM Model 2a		Current asthma exposure GSEM Model 2b*	
	β coefficient (95% CI)	P values	β coefficient (95% CI)	P values
Age 8	0.02 (–0.40 to 0.44)	0.93	–0.22 (–0.47 to 0.03)	0.09
Age 10	0.12 (–0.14 to 0.38)	0.36	–0.14 (–0.29 to 0.01)	0.06
Age 12	–0.29 (–0.69 to 0.10)	0.14	0.01 (–0.16 to 0.18)	0.94
Age 14	0.00 (–0.62 to 0.62)	0.99	–0.08 (–0.27 to 0.11)	0.41

Models adjusted for SEP, gender, BMI and presence of one or more older siblings in the home.
*Additionally adjusted for physical activity at an earlier wave.
BMI, body mass index; GSEM, generalised structural equational modelling; SEP, socioeconomic position.

asthma at age 13.[36] Despite emerging evidence that PA may have an anti-inflammatory effect on airways,[37] more evidence regarding the long-term longitudinal effect of PA in epidemiological studies is required.

Furthermore, we also found no evidence of interaction between PA and current asthma symptoms on time spent in future PA. That is, PA does not appear to differentially modify the odds of asthma in children with and without current asthma at an earlier age.

Influence of asthma on PA

We found no evidence that children with current or incident asthma participate in less PA than their peers. Despite indications by previous studies, self-imposed or parentally imposed restraints against PA involvement as a means of avoiding exacerbations[2 12] are not being applied in these children, suggesting that these children and their caregivers do not perceive asthma alone to be a barrier against PA. This could be attributed to a good understanding of an individual's specific triggers and adequate management and control of asthma symptoms, although asthma control could not be measured in the present study due to a lack of relevant data. Appropriate control of asthma symptoms, through the strategic administration of asthma medication, enables children with asthma to attain similar levels of PA as their unaffected peers.[38] This is evident in our results and in the results of other international studies,[13–16] many of which measured PA through accelerometry.[13–16] On the contrary, many studies which reported an association collected PA information via questionnaire.[9–11]

Strengths and limitations

This analysis had several important strengths and limitations. Use of the data collected by the LSAC was a major strength of this study, as the repeated, cross-sectional structure of the LSAC data is particularly conducive to the cross-lagged analytical method used to investigate bidirectionality; bidirectional investigations such as this are only possible in longitudinal studies with repeated measurements of both exposure and outcome variables, and hence previous studies have conducted similar statistical analyses using data from LSAC with different outcomes.[39 40] A second strength was the large sample size of the LSAC which powers the associations observed, despite incomplete data and the inevitable attrition over time.

An important limitation of this study is the use of subjective data collection techniques, such as questionnaires and TUDs. Although commonly used in research, the imprecision of these methods of measurement exposes the analysis to a substantial amount of misclassification of both the exposure and outcome variables. For example, the LSAC instrument did not capture details about the formulation, dosage and frequency of asthma medications used, thus inhibiting an investigation of the effect of asthma severity or level of asthma control. Additionally, there are limitations in extrapolating the results to habitual PA as the measurements were collected on a single day, and the intensity of the PA was not formally recorded. Coded variables that directly correspond to physical activities and exercise, rather than work-related activities such as cleaning or tiding up, were included. While this means that the estimated amount of PA is more conservative than the actual amount of PA performed, this restriction reduced the ambiguity related to certain coded activities. Hence, to minimise the possibility of incorrect classification, we restricted the activities of interest to those listed above. Finally, we were unable to adjust for familial history of asthma and atopy.

CONCLUSIONS

Our novel analysis found that in childhood and adolescence, neither current nor incident asthma was longitudinally associated with reduced reported PA. Similarly, we found little evidence to suggest that PA has a longitudinal effect on asthma development or symptoms, although more longitudinal research with objective PA measurement is warranted.

What is already known on this subject

- Previous research investigating the effect of either asthma on physical activity (PA) or PA on asthma has yielded inconsistent results. However, the possibility of a reciprocal relationship has not yet been explored.

What this study adds

- This study uses a novel technique to investigate the possibility of bidirectionality between asthma and PA in children and adolescents. The results imply that a physically active lifestyle should be encouraged in all children, as it does not appear to have any effect on asthma. Similarly, asthma does not appear to be a hindrance to PA in children.

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Contributors All authors contributed to the conception or design of the work; data acquisition, analysis and interpretation of data; drafting and critical revision of the paper; checking it for important intellectual content; approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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6.6 Supplementary material to the publication

Appendix 1: List of pre-coded activities used in the Light Time Use Diaries (waves 1 to 3 only) from Baxter 2007(152) and Mullen 2014(154).

1. School or nonparental care:
    - Day care centre, playgroup
    - School, after/before school care
    - Homework

2. Necessary activities:
   Sleeping

    - Sleeping, napping
    - Awake in bed/cot

   Eating

    - Breastfeeding
    - Eating, drinking, being fed
    - Eating and drinking

   Personal care

    - Bathe/nappy change, dress/hair care
    - Personal care, health care
    - Bathing, dressing, toileting, teeth brushing, hair care
    - Dentist, doctor, chiropractor, physiotherapist, optometrist

3. Leisure:
   TV and music

    - Watching TV, a video or a DVD
    - Listening to tapes, CDs, radio, music

   Computers

    - Using a computer/computer game
    - Computer games—internet; computer games—not internet; Xbox, Playstation, Nintendo, Wii; internet not covered elsewhere

Reading

- Read a story, talked/sung to, sing/talk
- Reading or looking at book by self
- Reading/being read to

Doing nothing

- Looking around/doing nothing
- Do nothing, bored/restless
- Doing nothing

Organised activities/ lessons/sport

- Organised activities/playgroup
- Organised lessons/activities
- Organised sport/physical activity (e.g. swim/dance/Auskick)
- Organised team sports and training: football, basketball, netball, cricket
- Organised individual sports and training: swimming, dancing, tennis, martial arts, gymnastics
- Other organised lesson/activity (e.g. music, drama)
- Non-active club activities: chess club, art/craft groups
- Private music, language or religion lessons, tutoring
- Scouts, girl guides, cadets, youth groups

Other physical activity

- Crawl, climb, swing arms or legs 16
- Active free play (e.g. running, climbing, ball game)
- Other exercise: swim/dance/run about
- Ball games, riding bike/scooter/skateboard, skipping, running, chasing

Other play/leisure

- Colour/draw, look at book, puzzles
- Colour/draw, look at book, puzzles, educational games
- Other play, other activities
- Quiet free play (e.g. board games, craft, dress-ups)
- Quiet free play (e.g. jigsaw, craft, dress-ups)
- Board/card games, puzzles, toys, art and craft

Other non– home leisure time

- Taken places with adult (e.g. shopping)
- Visiting people, special event, party
- Shopping
- Going to church, museums, cultural events, fairs, community events
- Cinema
- Going to live sporting events

4. Travel:
    - Taken out in pram or bicycle seat
    - Travel in car/other household vehicle
    - Travel on public transport, ferry, plane
    - Walking (for travel or fun)
    - Ride bicycle, trike, etc. (for travel or fun)
    - Travel by foot
    - Travel by bike/scooter/skateboard

5. Other activities:
   Behaviour

    - Crying, upset
    - Crying, upset, tantrum
    - Arguing, fighting
    - Destroy things, create mess
    - Arguing, fighting, destroy things
    - Being reprimanded, corrected
    - Held, cuddled, hugged, comforted, soothed

   Chores/housework

    - Being taught to do chores, read, etc.
    - Helping with chores, jobs
    - Making own bed, tidying own room; making/preparing own food; getting self ready, packing/unpacking own school/sports bag; cleaning, tidying other rooms; cooking, meal preparation, making lunch, setting table for others; washing dishes, stacking, emptying

dishwater; gardening, putting out bin; taking care of siblings, other children; taking care of pets; taking pets for a walk

Missing, other

- Not sure what child was doing
- Missing
- Other

Supplementary Table 6.S1: Results of the cross-lagged GSEM models for both incident and current asthma.

	Incident asthma		Current asthma	
Asthma outcome	**EE (95% CI)**	**P value**	**EE (95% CI)**	**P value**
Wave 3	0.96 (0.91, 1.02)	0.202	1.02 (0.98, 1.05)	0.405
Wave 4	0.96 (0.86, 1.06)	0.470	1.03 (0.98, 1.07)	0.220
Wave 5	0.94 (0.77, 1.14)	0.502	0.96 (0.90, 1.03)	0.301
Wave 6	1.07 (0.864, 1.03)	0.540	0.95 (0.87, 1.04)	0.247
Physical activity outcome				
Wave 3	-0.20 (-0.59, 0.20)	0.332	-0.18 (-0.43, 0.06)	0.139
Wave 4	0.10 (-0.15, 0.37)	0.432	-0.14 (-0.29, 0.01)	0.064
Wave 5	-0.30 (-0.69, 0.10)	0.142	0.01 (-0.17, 0.17)	0.951
Wave 6	0.00 (-0.62, 0.62)	0.993	-0.08 (-0.27, 0.11)	0.403

Adjusted effect estimates (EE) are presented as the odds of asthma where physical activity at the previous wave is the exposure and as regression coefficients (in hours of MVPA) where asthma at the previous wave is the exposure.

CHAPTER SEVEN: Investigation of the effect of asthma on physical activity in children and adolescents

7.1 Chapter introduction

This chapter contains a second data analysis of the LSAC K cohort data, wherein the association between asthma status and physical activity was investigated across a range of ages spanning childhood and adolescence. The article was initially authored as an original research piece, then later revised, and submitted as a Letter to the Editor, the format in which it was accepted and published. The original research piece is included below, after the published letter.

7.2 Research question

Are children and adolescents with asthma consistently less active than their non-asthmatic peers at all ages? Does gender, BMI or SES modify this association?

7.3 Chapter synopsis

Asthma has inconsistently been found to be a risk factor for physical inactivity in children. Whether asthma does in fact hinder physical activity in youth poses an important public health problem, as physical inactivity has been linked to multiple adverse health outcomes. Therefore, in this chapter, I aimed to investigate whether asthma was associated with physical activity at any stage in childhood.

To address this research question, I again employed data from five waves of the K cohort of the LSAC. Asthma and physical activity data were collected from the LSAC children biennially between the ages of 6 and 14 years of age, and the cross-sectional relationship between asthma and physical activity at each age was investigated using multivariate linear regression. I also examined whether gender, BMI or SES modified the association between asthma and physical activity.

This study found that asthma status was not associated with physical activity at any of the multiple ages investigated. There was no evidence of a modifying effect from any of the factors investigated This supported the finding of my previously conducted systematic review that concluded that children with asthma were not more inactive than their unaffected peers (see Chapter Five).

7.4 Directed acyclic graph

The following DAG (Figure 7.1) was created as part of the analytical plan for this work, to help identify the potential relationships between variables of interest within this analysis.

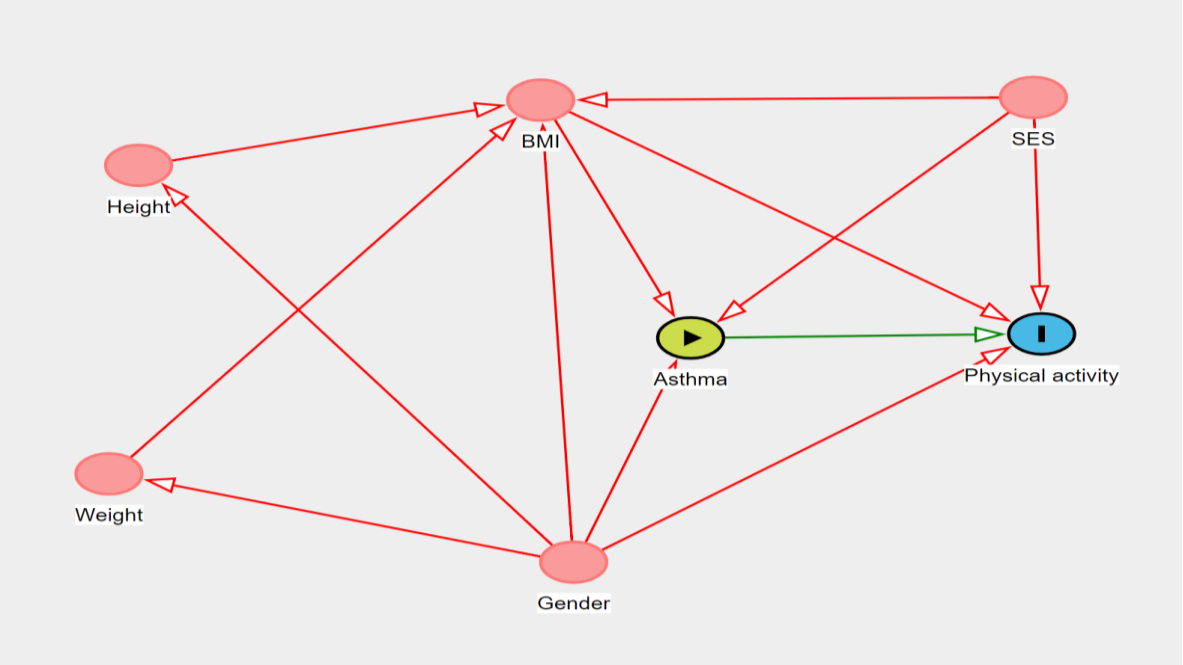

Figure 7.1: Directed acyclic graph (DAG) of the relationships between asthma, physical activity, and the potential covariates. Created with Daggity software.

7.5 Publication

Cassim R, Dharmage SC, Koplin JJ, Milanzi E, Russell MA (2018) Suspected asthma status and time spent in physical activity across multiple childhood age groups. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 120 (2):219

Suspected asthma status and time spent in physical activity across multiple childhood age groups

Asthma is the most common chronic condition in children worldwide; however, rates of overdiagnosis are high, particularly when the case definition is not confirmed by spirometric assessment.[1] However, it is important to encourage physical activity (PA) in children and adolescents across age groups regardless of asthma status because a physically active lifestyle is associated with many beneficial health outcomes.[2]

Several studies have investigated whether PA is reduced in children with asthma, but the results of these studies have been inconsistent. Some found that children with asthma ranging between the ages of 5 and 12 years were less active than their peers,[3,4] whereas others, including one study that confirmed asthma diagnosis through spirometric testing,[5] concluded there was no difference between children with and without asthma within the age range of 5 to 18 years.[5–7] Our objective was to compare the amount of time spent in moderate to vigorous PA (MVPA) between children and adolescents with and without suspected asthma at 5 different ages that span the important transitory phases of childhood and adolescence.

We used data collected from the Growing Up in Australia: Longitudinal Study of Australian Children (LSAC), whose sampling and recruitment methods have previously been described.[8] Briefly, the cohort has been followed up biennially since the initial wave of data collection in 2004 at the ages of 6, 8, 10, 12, and 14 years (waves 2, 3, 4, 5, and 6, respectively). We defined current suspected asthma status at each age as follows: (1) parental report of physician's diagnosis of asthma and (2) current wheeze and/or (3) use of asthma medications in the previous 12 months. PA was measured through the completion of a single time use diary (TUD), which indicated what the study child was doing and with whom for every 15-minute interval of a 24-hour period.[8] For this analysis, the activities within the TUDs were graded as MVPA based on the Compendium of Energy Expenditure for Youth categorizations.[9]

Time spent in MVPA was the dependent variable, which was log transformed for linear regression analyses because of its right-skewed distribution. Univariate and multivariate analyses were undertaken, with the covariates of socioeconomic status (SES) *z* score, sex, and categorical body mass index (BMI) added to the models in the multivariate analyses. Interactions between sex and suspected asthma, SES z score and suspected asthma, and BMI and suspected asthma were investigated by fitting an interaction term into the adjusted linear regression model where appropriate. To accommodate for attrition from wave 1, each model was weighted using the cross-sectional sampling weights provided for the cohort. Results of the regression model were back transformed and are presented as geometric means and 95% confidence intervals (CIs).

Of the 4,983 children initially recruited, 4464, 4332, 4169, 3956, and 3537 children participated at ages 6, 8, 10, 12, and 14 years, respectively. Female participants made up 49% of the study sample at each wave. The prevalence of suspected asthma was 16% at each follow-up between the ages of 6 and 12 years and decreased to 14% at age 14 years (Table 1). Multiple regression found no evidence of a difference in time spent in MVPA at any age between children with and without suspected asthma, after adjusting for categorical BMI, SES *z* score, and sex. Adjusted linear regression coefficients were 1.01 (95% CI, 0.93–1.09) at 6 years of age, 0.98 (95% CI, 0.89–1.07) at 8 years of age, 0.94 (95% CI, 0.86–1.03) at 10 years of age, 1.01 (95% CI, 0.91–1.12) at 12 years of age, and 1.04 (95% CI, 0.91–1.18) at 14 years of age. There was no evidence of effect modification by sex, BMI, or SES *z* score at any wave.

This large study compares PA levels across many ages for children with and without suspected asthma. Overall, we found that asthma status was not associated with time spent in MVPA at any age. These results concur with the findings of previous Brazilian and US studies in which no difference was found between children with and without asthma in the time spent in PA.[6,7] The fact that children with suspected asthma were not less active than those without suspected asthma in our study may be related to an inaccurate asthma diagnosis, disease severity, and/or symptom control. Well-controlled suspected asthma may enable individuals to be more physically active. Hence, the lack of difference observed between children with and without suspected asthma in our analysis may be attributable to a good level of suspected asthma control within this study population or a high level of asthma overdiagnosis.

This study had several strengths, including use of the LSAC population, whose large sample size improved the statistical power of the analysis. In addition, the collection of multiple waves of data enabled us to observe the trends and changes that occur during the important transitional phase between childhood and adolescence. Conversely, this analysis had several limitations, the greatest being the lack of confirmation of the asthma diagnosis by documenting reversible airflow obstruction or methacholine hyperreactivity. Other limitations were the lack of data on asthma severity and control and loss to follow-up. To account for loss to follow-up from the initial recruitment, this analysis included a weighting variable at each wave. Another limitation is that the TUD collection of a single 24-hour TUD is limiting and may not accurately represent a child's habitual PA. However, the TUD is a validated and accepted technique that gives an indication of the amount of time spent in various activities.[10]

Disclosures: Authors have nothing to disclose.

Table 1
Participant Characteristics at Each Wave[a]

Characteristic	Wave 2 (2006)	Wave 3 (2008)	Wave 4 (2010)	Wave 5 (2012)	Wave 6 (2014)
Participants, No. (%)	4464 (90)	4332 (88)	4169 (84)	3956 (79)	3537 (71)
Age, mean (SD), y	6.3 (0.5)	8.3 (0.4)	10.3 (0.8)	12.4 (0.5)	14.4 (0.5)
Male sex, No. (%)	2,276 (51)	2,212 (51)	2,132 (51)	2,020 (51)	1,798 (51)
BMI, No. (%)					
Underweight	224 (5)	233 (5)	235 (6)	260 (7)	207 (6)
Normal weight	3,373 (76)	3,044 (71)	2,720 (68)	2,549 (67)	2,194 (67)
Overweight	826 (19)	1012 (24)	1063 (26)	994 (26)	875 (27)
Has current asthma, No. (%)	721 (16)	713 (16)	681 (16)	624 (16)	500 (14)
Time spent in MVPA, median (IQR)	165 (75–300)	165 (90–300)	115 (65–187)	95 (47–164)	85 (35–150)

Abbreviations: BMI, body mass index; IQR, interquartile range; MVPA, moderate to vigorous physical activity.
[a]Linear regression model adjusted for sex, socioeconomic status *z* score, and categorical BMI.

In summary, there was no evidence that children and adolescents with suspected asthma at the ages of 6, 8, 10, 12, and 14 years spent less time in MVPA. Combinations of high BMI and suspected asthma, SES *z* score and suspected asthma, or sex and suspected asthma did not appear to be detrimental for PA participation. These results suggest that children with suspected asthma across different age groups do not require more extensive targeting to promote PA because there is no evidence they are less active than their peers.

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7.6 Full length article

Title: **The effect of asthma status on the amount of time children and adolescents spend in moderate to vigorous physical activity**

Abstract:

BACKGROUND: Several studies have reported on the effect of asthma status on physical activity participation, however the results of these studies have been inconsistent. Hence, we aimed to examine the effect of asthma status on amount of time spent in physical activity over a range of ages.

METHOD: Data were from 4983 children who participated in the Longitudinal Study of Australian Children (LSAC). Asthma and anthropometric data were collected via questionnaire and interview, and physical activity data were collected through Time Use Diaries at the ages of 6, 8, 10, 12 and 14 years. Time spent in moderate to vigorous physical activity (MVPA) per day was compared between asthmatic and non-asthmatic children using linear regression models, adjusted for gender, socioeconomic status, and body mass index (BMI).

RESULTS: There was no difference in time spent in MVPA between children with and without asthma at any of the ages investigated; adjusted regression coefficients (95% CI) for this association were 1.01 (0.93, 1.09) at 6 years, 0.98 (0.89, 1.07) at 8 years, 0.94 (0.86, 1.03) at 10 years, 1.01 (0.91, 1.12) at 12 and 1.04 (0.91, 1.18) at 14 years. The majority of asthmatic children met WHO recommendations for daily MVPA, however the proportion meeting these recommendations decreased with age from 84% at age 6 years to 65% at 14 years.

CONCLUSIONS: There was no evidence that asthma was associated with the amount of time spent in MVPA between the ages of 6 and 14. Older children and adolescents with asthma were less likely to meet daily physical activity recommendations, regardless of their asthma status.

Introduction:

Asthma is the most common chronic condition in children worldwide (7, 33); the burden of which extends beyond the direct economic costs of medication (32). Personal costs in the form of absence from school, lower self-confidence and social alienation due to non-participation in activities that may exacerbate asthma symptoms, further reduce the quality of life of individuals with asthma (96, 194). It is important however, to encourage physical activity in children and adolescents regardless of asthma status (13, 32), as a physically active lifestyle is associated with many beneficial health outcomes (13).

Several studies have investigated whether physical activity is reduced in children with asthma, but the results of these studies have been inconsistent. Studies in the United States of America and the United Kingdom found that children with asthma were less active than their peers (9, 195), while in Norway and Taiwan studies concluded that children with asthma were equally as active as their peers (11, 14). These differences may be due to variations in physical activity measurement techniques and asthma definitions. Additionally, access and availability of asthma medication and healthcare influences the level of asthma control in various study settings (5), and hence is likely to also contribute to the disparity in the results of published studies.

This study aimed to compare the amount of time spent in physical activity between children and adolescents with and without asthma at five different age groups that span the important transitory phases of childhood and adolescence. Further, the proportion of children with and without asthma who met the World Health Organization (WHO) cut-off of 60 minutes of daily MVPA was investigated to assess whether children and adolescents with asthma meet current WHO physical activity guidelines (99), or whether they require further targeting and encouragement to partake in physical activity.

Methods:

Participants:

The research questions were addressed using data collected from *Growing Up in Australia*: Longitudinal Study of Australian Children (LSAC). The LSAC is a government funded longitudinal study of the health and development of Australian children (148). The LSAC sampling and recruitment methodology has previously been described (147). At the initial wave of data collection in 2004, 4983 children aged 4 years participated. The cohort has since been followed up every two years at the ages of 6, 8, 10, 12 and 14 years (waves 2, 3, 4, 5 and 6, respectively). Data is collected via interviews, questionnaires, time use diaries (TUDs) and through direct anthropometric measurements (147).

Asthma measurement:

Asthma data were collected via questionnaire at each follow up. Current asthma status at each age was defined as: 1) parental report of doctor's diagnosis of asthma and either 2) current wheeze in the previous 12 months and/or 3) use of asthma medications in the previous 12 months (159). Age 4 (wave 1) data were not included in this analysis because asthma diagnosis in children is contentious before the age of 5 years (196).

Physical activity measurement:

Physical activity was measured through the completion of a single Time Use Diary (TUD) by a parent when the children were 6 and 8 years old (in waves 2 and 3), and by the study child when they were 10 years and older (in wave 4 and beyond). The TUD journal requires the participant to indicate what they were doing and with whom for every 15-minute interval of a 24-hour period. For this analysis, the activities within the time use diaries graded as moderate-to-vigorous physical activity (MVPA) were: structured or

unstructured active play, organized sports/lessons/activities, riding bike/scooter/skateboard and walking/running skipping. This categorisation was made based on the Compendium of Energy Expenditure for Youth categorisations (157). Total time spent in MVPA for each child was calculated by the summation of minutes spent in each activity for the day the diary was recorded. Children who engaged in 60 minutes or more MVPA were categorised as "sufficiently active" based on the WHO recommendation (99).

Covariates:

Based on the existing literature, the variables socioeconomic status (SES), gender and body mass index (BMI) were selected as *a priori* confounders or potential effect modifiers. Height was measured using an Invicta stadiometer from Modern Teaching Aids in waves 2 and 3, and in waves 4, 5 and 6 a laser stadiometer was used (197). Weight was measured using HoMedics digital BMI bathroom scales in waves 2 and 3, and Tanita body fat scales were used in waves 4 to 6 (197). BMI at each wave was categorised as "underweight", "normal weight" or "overweight" based on the age appropriate cut-offs proposed by Cole *et al.* (179).

Statistical analyses:

At each age, the descriptive characteristics of respondents are presented as mean values and standard deviations from the mean (SD) unless otherwise stated. The mean time spent in MVPA was stratified by gender and asthma status at each age and tabulated.

Current asthma status at each age was the independent variable of interest. Time spent in MVPA was the dependent variable and log transformed for linear regression analyses due to its right-skewed distribution. Univariate and then multivariate analyses were

undertaken, with the covariates of socioeconomic z-score, gender and categorical BMI added to the models in the multivariate analyses. Interactions between gender and asthma, SES z-score and asthma, and BMI and asthma were investigated, and an interaction term was fitted into the adjusted linear regression model where appropriate. To accommodate for attrition from wave 1, each model was weighted using the cross-sectional sampling weights provided for the cohort (197). Results of the regression model were back transformed and are presented as geometric means and 95% confidence intervals. Analyses were conducted using Stata statistical software (181).

Results:

Of the 4983 children initially recruited, 4464, 4332, 4169, 3956 and 3537 children participated at ages 6 through to 14, respectively (Table 7.E1). Female participants made up 49% of the study sample at each wave, and the prevalence of asthma was 16% in each follow up between ages 6 to 12 years, and 14% at age 14 years. At wave 2, 83.7% of the 6 year old children met the WHO recommendation of 60 minutes of MPVA per day (99). At subsequent follow ups the percentages were 84.3%, 79.2%, 69.9% and 64.6% at age 8, 10, 12 and age 14 years, respectively (Table 7.E2). At every age, the proportion of children with asthma who were sufficiently physically active was greater than the proportion of children with asthma who were insufficiently active. At 6 years, 84.3% of children with asthma were sufficiently active, 81.6% at age 8; 78.9%, 70.8% and 65.4% at 10, 12 and 14 years, respectively (Table 7.E2).

Time spent in MVPA decreased with age for both boys and girls, with the greatest reduction in time spent in MVPA observed between the ages of 8 and 10 years for both girls and boys (Table 7.E3). Regardless of asthma status, boys tended to be more active than girls at all ages with a single exception. At 8 years of age, girls with asthma were

more active than their male counterparts. This was also the age at which time spent in physical activity peaked for girls with asthma (Table 7.E3).

Multiple regression found no evidence of a difference in time spent in MVPA at any age between children with and without asthma, after adjusting for categorical BMI, SES and gender (Table 7.E4). Adjusted regression coefficients (and 95% confidence intervals) were 1.01 (0.93, 1.09) at 6 years, 0.98 (0.89, 1.07) at age 8 years, 0.94 (0.86, 1.03) at 10 years, 1.01 (0.91, 1.12) at age 12 and 1.04 (0.91, 1.18) at 14 years of age. There was no evidence of effect modification by either gender, BMI or SES at any wave.

Discussion:

This cross-sectional analysis of the LSAC cohort study found that asthma status was not associated with time spent in moderate-to-vigorous physical activity in children and adolescents aged 6 to 14 years. Furthermore, these associations were not significantly modified by BMI, gender, or SES at any of the ages investigated.

The results of this study concur with the findings of previous Norwegian and Taiwanese studies in which no difference was found between children with and without asthma in the time spent in physical activity (11, 14). The fact that children with asthma were not less active than those without asthma in our study may be related to disease severity and symptom control. Lang *et al.* previously reported that asthma severity predicted activity level in children, with greater severity associated with less physical activity (195). Hence the lack of difference observed between children with and without asthma in our analysis may be due to a good level of asthma control within this study population.

This analysis also found that the majority of children and adolescents met the WHO levels of recommended physical activity, regardless of asthma status. The proportion of children and adolescents engaged in the recommended 60 minutes of MVPA per day in this analysis was higher than the proportion stated in a recent Australian Bureau of Statistics (ABS) publication where only 60% of children and adolescents aged 5-17 years were found to meet the recommendation (198). The discrepancy in proportions of sufficiently active children and adolescents may be due to the difference in data collection mode, and different age groups in this analysis compared to the ABS survey. The ABS collected 8 days of physical activity data through pedometers in participants between the ages of 5 and 17 years (198). Both the ABS survey and this study showed that time spent in physical activity decreases with age, and hence the inclusion of older adolescents in

the ABS survey, namely 15-17 year old adolescents, may contribute to the lower percentage of active participants overall observed in that survey (198).

When compared to international populations, the proportion of active children in this study exceeded the proportions reported in a study of approximately 6500 UK children wherein 50.8% of 7 year-olds met the recommended quota (199), and a recent Irish study of 826 primary school children aged 8 to 11 years where 22.1% (95%CI: 19.3 – 25.0%) were sufficiently active (200). These proportions were also substantially higher than the proportions reported for South Korean middle (6.9%) and high (4.9%) school children (201). Again, the discrepancy could be due to the method of physical activity collection, since both the UK and Irish studies collected accelerometry data (199, 200), although there is evidence that physical activity engagement varies greatly between countries and populations (100, 202).

This study had several strengths, including use of the LSAC study population whose large sample size improved the statistical power of the analysis. An additional strength was the collection of multiple waves of data within this cohort, which enabled us to observe the trends and changes that occur during the important transitional phase between childhood and adolescence. Conversely, this analysis had several limitations. One such limitation was loss to follow up or missing data. To account for loss to follow up from the initial recruitment, this analysis included a weighting variable at each wave. A second important limitation of this study is the inaccurate and unspecific measurements for both the exposure and outcome. Although the LSAC collects data on both physical activity and asthma in children, the study was not designed to address this question. Hence the questionnaire contained general asthma questions such as “In the last 12 months has study child taken any medication for asthma?”, but failed to collect data on formulation,

dosage and frequency of medication, which effectively inhibited stratification of physical activity by asthma severity. While objective measurements such as pulmonary function testing (PFT) for the definition of asthma would have greatly improved the accuracy and quality of the data, it would also have greatly reduced the sample size as funding and access to such testing is restrictive. Similarly, whilst the TUD is a validated and accepted technique that gives an indication of the amount of time spent in various activities (203), the collection of a single 24-hour TUD is limiting, and may not be an accurate representation of a child's habitual physical activity over time. Additionally, the TUD's do not capture the intensity of the activity performed. Hence, we used the Compendium of Energy Expenditure in Youth to estimate the intensity of each activity listed in the TUD's. This may have led to an over-estimation of children's physical activity; however, this misclassification is likely to be non-differential. Some of these issues could have been overcome using accelerometry as the measurement tool for physical activity, although the use of accelerometers for such a large sample size located over a vast geographical range would be economically and logistically challenging.

The implication of these results, therefore, is that between the ages of 6 and 14 years, the level of control of asthma symptoms appears to be adequate so that having asthma poses no barrier to physical activity. In addition, these results indicate that overweight children with asthma do not require further targeting to promote physical activity as they are equally as active as their peers.

Conclusion:

In summary, this analysis suggests that the majority of children and adolescents with asthma meet the recommended physical activity levels in childhood. There was no statistically significant difference in the amount of time spent moderate to vigorous

physical activity between children and adolescents with and without asthma at the ages of 6, 8, 10, 12 and 14, and the combinations of high BMI and asthma, SES and asthma, or gender and asthma did not appear to be detrimental for physical activity participation in children and adolescents.

Tables:

Table 7.E1: Table of participant demographics.

	Wave 2 (2006)	Wave 3 (2008)	Wave 4 (2010)	Wave 5 (2012)	Wave 6 (2014)
Number of participants (% of wave 1)	4464 (90)	4332 (88)	4169 (84)	3956 (79)	3537 (71)
Mean age (SD)	6.3 (0.5)	8.3 (0.4)	10.3 (0.8)	12.4 (0.5)	14.4 (0.5)
Male gender (%)	2276 (51)	2212 (51)	2132 (51)	2020 (51)	1798 (51)
BMI					
Underweight (%)	224 (5)	233 (5)	235 (6)	260 (7)	207 (6)
Normal weight (%)	3373 (76)	3044 (71)	2720 (68)	2549 (67)	2194 (67)
Overweight (%)	826 (19)	1012 (24)	1063 (26)	994 (26)	875 (27)
Has current asthma (%)	721 (16)	713 (16)	681 (16)	624 (16)	500 (14)
Median (IQR) time spent in MVPA	165 (75-300)	165 (90-300)	115 (65-187)	95 (47-164)	85 (35-150)

SD: Standard Deviation IQR: Interquartile range

Table 7.E2: Number (percentage) of children who met the WHO recommendation of 60 minutes of MVPA, stratified by asthma status at each age.

	n	No asthma	Asthma	All Children
Age 6	3385	2374 (83.62)	460 (84.25)	2834 (83.72)
Age 8	2911	2067 (84.78)	386 (81.61)	2453 (84.27)
Age 10	3483	2322 (79.30)	438 (78.92)	2760 (79.24)
Age 12	2896	1695 (69.72)	329 (70.75)	2024 (69.89)
Age 14	2157	1182 (64.48)	212 (65.43)	1394 (64.63)

Table 7.E3: Number of observations, arithmetic mean (standard deviation) of time spent in MVPA at each wave stratified by gender and asthma status.

	Boys			Girls		
	No asthma	Asthma	Total	No asthma	Asthma	Total
Age 6	1422 202.32 (154.79)	334 205.82 (161.97)	1756 202.98 (156.14)	1417 198.95 (160.48)	212 193.44 (150.95)	1629 198.23 (159.24)
Age 8	1197 201.67 (161.71)	292 190.17 (164.52)	1489 199.41 (162.28)	1241 197.64 (156.11)	181 195.50 (161.87)	1422 197.36 (161.53)
Age 10	1476 142.86 (96.64)	336 139.55 (102.09)	1812 142.25 (97.65)	1452 129.72 (92.21)	219 119.51 (82.89)	1671 128.38 (91.09)
Age 12	1245 130.34 (97.62)	281 127.84 (98.42)	1526 129.88 (97.74)	1186 103.78 (87.30)	184 98.48 (87.11)	1370 103.07 (87.26)
Age 14	921 114.20 (96.09)	191 124.74 (101.38)	1112 116.01 (97.05)	912 102.15 (94.17)	133 90.23 (72.13)	1045 100.64 (91.72)

Table 7.E4: Coefficients (95% confidence intervals) of the linear regression model for time spent in moderate to vigorous physical activity (results have been back-transformed from the log-scale).

	Age 6	Age 8	Age 10	Age 12	Age 14
Unadjusted Model					
Current asthma	1.01 (0.93, 1.09)	0.97 (0.89, 1.07)	0.95 (0.87, 1.04)	1.03 (0.93, 1.14)	1.02 (0.89, 1.16)
Adjusted Model					
Current asthma	1.01 (0.93, 1.09)	0.98 (0.89, 1.07)	0.94 (0.86, 1.03)	1.01 (0.91, 1.12)	1.04 (0.91, 1.18)
Gender	0.94 (0.89, 1.00) *	0.97 (0.91, 1.05)	0.89 (0.84,0.95) **	0.72 (0.67, 0.78) **	0.82 (0.74, 0.91) **
SES z-score	1.09 (1.06, 1.13) **	1.06 (1.03, 1.10) **	0.98 (0.95, 1.00)	1.01 (0.97, 1.05)	0.98 (0.93, 1.03)
BMI					
Underweight	1.01 (0.89, 1.16)	0.92 (0.80,1.05)	1.00 (0.88,1.15)	0.91 (0.79,1.06)	1.05 (0.88, 1.27)
Normal weight	Reference	Reference	Reference	Reference	Reference
Overweight	0.91 (0.84, 0.99)	0.88 (0.81,0.96)	0.90 (0.83, 0.97)	0.88 (0.80,0.97)	0.89 (0.79. 1.01)

* indicates p value < 0.05 and ** indicates p-value <0.001.

CHAPTER EIGHT: Investigation of the relationship between asthma and objectively measured physical activity in young children

8.1 Chapter introduction

This chapter contains the final of three data analyses conducted as part of this PhD. The analysis presented within this chapter used information from the HealthNuts Study to investigate whether asthma and wheeze at the age of 4 years was longitudinally associated with objectively measured physical activity at age 6 years. Cross-sectional associations between asthma, early life wheeze and physical activity were additionally examined as this study further sought to corroborate the evidence from the earlier work and to examine whether the conclusions drawn were upheld in a younger population, and when physical activity was measured objectively.

8.2 Research question

Is early life wheeze and suspected asthma (before five years of age) associated with less objectively measured physical activity at six years of age in Australian children?

8.3 Chapter synopsis

There is evidence that physical activity in childhood has a positive effect on adult health outcomes, and it is hypothesised that the lifestyle and habits developed in youth persist into adulthood (16). However, to date, there have been no studies where accelerometry has been used to measure and compare physical activity in young children with and without wheeze or asthma. Hence, to address this research gap, I utilised accelerometry data collected at the 6 year follow up of the HealthNuts study to longitudinally and cross-sectionally compare the time spent in moderate to vigorous physical activity at age 6 between children who experienced early life wheeze and/ or asthma and those who had

not. Furthermore, this analytical model included several additional variables to investigate whether they modified the associations.

The results of this study inform physical activity policymakers and health campaigners as to whether parents of Australian children with early life wheeze or asthma require additional targeting and education to ensure that these children continue to be physically active as they age. The findings suggest that this may not be necessary, as children with asthma and wheeze appeared to engage in a similar amount of time in MVPA as their unaffected counterparts. This implies that physical activity is not restricted among these young children with asthma, and that Australian asthma management and education strategies are effectively eliminating asthma as a barrier against physical activity.

8.4 Directed acyclic graph

The following DAG (Figure 8.1) was created prior to analysis, to help identify potentially important confounding variables to be accounted for in the statistical models.

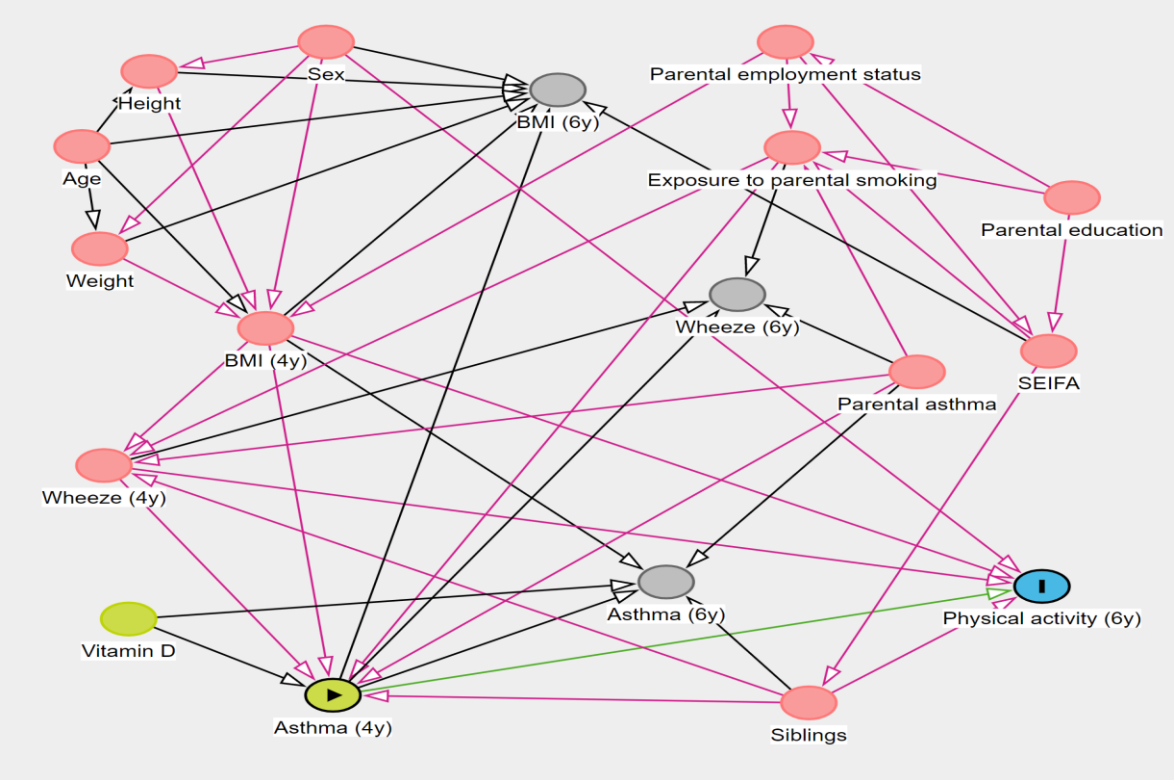

Figure 8.1: Directed acyclic graph (DAG) of the relationships between asthma, physical activity, and potential covariates in the HealthNuts Study. Created with Daggity software.

8.5 Publication

Cassim R, Dharmage SC, Peters RL, Koplin JJ, Allen KJ, LK Tang M, Lowe AJ, Olds TS, Fraysse F, Milanzi E, Russell MA (2020) Are young children with asthma more likely to be less physically active? Pediatric Allergy and Immunology

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ORIGINAL ARTICLE

WILEY

Are young children with asthma more likely to be less physically active?

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Abstract

Background: Previous research suggests that children who experience asthma may be less physically active; however, results have been inconclusive. This study aimed to investigate whether the presence of asthma or wheeze is associated with lower physical activity levels in children, and whether sex, body mass index or earlier asthma or wheeze status modifies the association.

Methods: This study was conducted in 391 HealthNuts participants in Melbourne, Australia. Asthma and wheeze data were collected via questionnaire at age 4 and 6, and physical activity was measured through accelerometry. Using adjusted linear regression models, the cross-sectional and longitudinal associations were investigated.

Results: There was no evidence of a difference in time spent in moderate-to-vigorous physical activity (MVPA) at age 6 years between children with and without asthma at age 4; children with asthma spent 8.3 minutes more time physically active per day (95% CI: −5.6, 22.1, $P = .24$) than children without asthma. Similar results were seen for children with current wheeze (5.8 minutes per day more, 95% CI: −5.9, 17.5, $P = .33$) or ever wheeze or asthma (7.7 minutes per day more, 95% CI: −4.8, 20.2, $P = .23$) at age 4 years. Comparable null results were observed in the cross-sectional analyses. Interaction with BMI could not be assessed; however, previous asthma or wheeze status and sex were not found to modify these associations.

Conclusion: This analysis found no evidence of asthma hindering physical activity in these young children. These results are encouraging, as they indicate that the Australian asthma and physical activity public health campaigns are being effectively communicated and adopted by the public.

KEYWORDS
accelerometry, asthma, children, cohort, physical activity, wheeze

1 | INTRODUCTION

Physical inactivity is a leading risk factor for the development of a variety of non-communicable diseases. Since physical activity tracks moderately through life, the promotion of a physically active lifestyle from a young age may be important and beneficial for future health.[1] For this reason, the World Health Organization (WHO) and other national health guidelines currently recommend that children and adolescents between the ages of 5 and 17 years engage in a minimum of 60 minutes of moderate-to-vigorous physical activity (MVPA) daily.[2,3] However, numerous international studies have demonstrated that large proportions of children and adolescents fail to meet the current physical activity recommendations.[4,5] It is believed that physical activity engagement decreases with age and that subgroups of children are more likely to be insufficiently active than others.

Some studies have found that children who experience asthma may lead less physically active lives[6]; however, these results are inconsistent.[7] Globally, asthma is the most common chronic condition in childhood, adversely affecting quality of life and constituting an important global health problem in childhood.[8] Despite asthma guidelines encouraging physical activity as a non-pharmaceutical intervention for asthma, strenuous physical activity is a known trigger for asthma exacerbations.[8] As such, some studies have found that children with asthma avoid physical activity for fear of triggering their asthma symptoms, or due to a fear of being mocked or stigmatized for these symptoms.[9] Another study found that parents may impose physical activity restrictions on children with asthma.[10]

Our recent systematic review concluded that children with asthma were equally as physically active as their unaffected peers.[7] This finding was based mainly on cross-sectional studies as only one cohort study to date had been published.[11] Therefore, the present study aimed to investigate the longitudinal relationship between asthma and wheeze at age 4 and objectively measured physical activity in children aged 6 years. The cross-sectional relationship at the age of 6 years was also examined, and whether a change in asthma status from age 4 to 6 is associated with physical activity. Finally, we explored whether BMI and sex modified the association between asthma and physical activity.

Key Message

This prospective study investigates the association between asthma at 4 years and physical activity at 6 years. It provides evidence that asthma does not hinder subsequent moderate-to-vigorous physical activity in these young, Australian children. It provides evidence of a successful management model used in Australia that can and should be adopted by other settings wishing to address the issue of insufficient physical activity in children with asthma.

2 | METHODOLOGY

The HealthNuts study is a population-based study of allergic disease burden in over 5000 children.[12] Between September 2007 and August 2011, children aged between 11 and 15 months who presented for routine 12-month vaccinations at immunization clinics within a 70-km radius of the Melbourne central business district were approached to participate.[13] The cohort has been followed up twice, first between 2010 and 2014 and then between 2012 and 2016, when the children were aged 4 and 6, respectively. At each follow-up, caregivers were invited to complete the study questionnaire, and at age 6, they were invited for a clinical assessment.[13] Ethical approval was obtained from the Human Research Ethics Committee (HREC) of the Office for Children, Government of Victoria (ref. no. CDF/07/492), Department of Human Services, Government of Victoria (ref. no. 10/07), and the Royal Children's Hospital HREC (ref. no. 27047 and ref. no.32294).

Exposure variables were taken from the 4- and 6-year follow-ups of the HealthNuts questionnaire. Standardized questions on asthma and wheeze from the validated International Study of Asthma and Allergies in Childhood (ISAAC) were used.[13,14] For this analysis, current asthma was defined as parental report of ever having doctor-diagnosed asthma and at least one of parent-reported wheeze or use of asthma medication in the past 12 months.[14] Current wheeze was defined as parental report of any wheezing in the last 12 months.[15] Ever wheeze or asthma was defined as a parental report of ever having had doctor-diagnosed asthma or wheeze at 4 and/or 6 years.

Participants who attended the 6-year follow-up clinical appointment from March 2015 onwards were asked to wear the waterproof GENEActiv (Gravity Estimator of Normal Everyday Activity, ActivInsights Ltd, Cambridgeshire, UK) triaxial accelerometer watch on the wrist of their non-dominant hand 24 hours per day for 8 consecutive days, including during sleep, while swimming and at bath time. Parents were given instructions for the use of these devices and were asked to note the child's waking and bedtime and to briefly describe the child's activities per day on the paper log provided. Furthermore, they were asked to note times when the watch was removed and replaced, and the reasons for device removal.

For this analysis, activity was sampled at 100 Hz, then collapsed into 60-second epochs. Participant accelerometry files and paper log were combined, and activity cut-points were applied using custom MATLAB software. Data were then manually inspected, correcting for unreported periods of non-wear and re-categorizing documented non-wear as time spent in MVPA where the physical activity logs indicated that the device was removed for reasons pertaining to sport participation. Individual days containing <16 hours of wear within a 24-hour period, or <10 hours of wake wear time were excluded from analysis. Participants with <4 valid days, or with no weekend days of valid accelerometry, were excluded from analysis. Further detail of the accelerometry processing methodology is reported elsewhere.[16]

The primary outcome of this analysis was daily minutes spent in MVPA, as measured by accelerometry at age 6 years, where

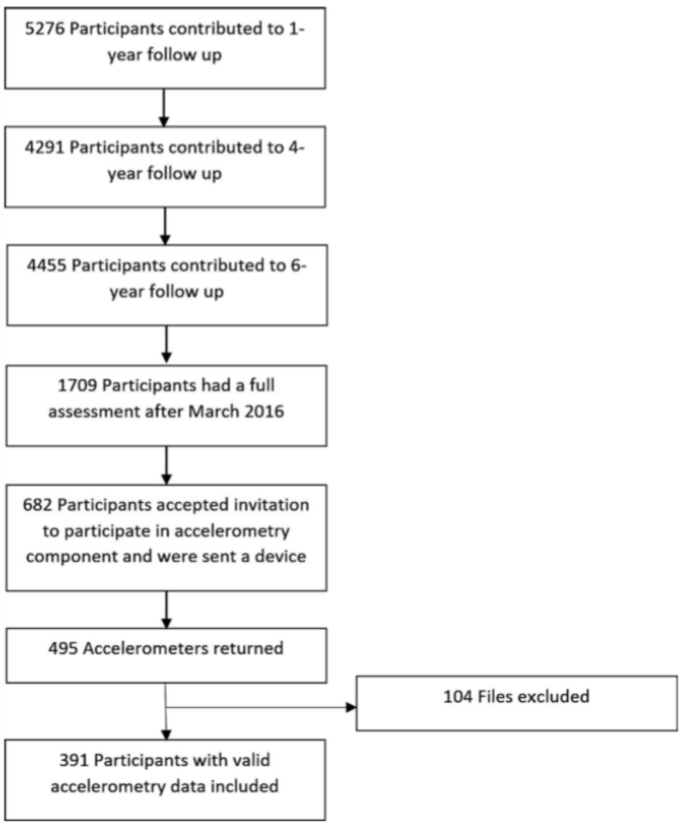

FIGURE 1 Flow chart of participants through the HealthNuts study

MVPA was defined as >4350 g/min, as per the cut-offs presented by Phillips et al[17]

Potential confounders were identified from the existing scientific literature and selected for inclusion in these analyses based on a directed acyclic graph (DAG; Figure S1). Sex, BMI, the presence of older siblings and familial history of allergy and asthma data were collected via questionnaire at the HealthNuts follow-ups (ie ages 1 and 4 years). The Socio-Economic Indexes for Areas (SEIFA) was used as a proxy for socio-economic status. Based on home postcode, each participant is allocated a SEIFA Index of Relative Socio-Economic Advantage and Disadvantage, derived from the 2006 Australian census data.[18] Participant BMI at age 4 was calculated from parent-reported height and weight and then categorized as 'underweight', 'normal weight' or 'overweight' based on age-appropriate cut-offs.[19]

2.1 | Statistical analysis

All statistical analyses were performed using Stata/MP 15.1 (StataCorp LLC, College Station, TX, USA). Descriptive statistics of the study sample are presented. Associations between individual exposures and MVPA were analysed in univariate linear regression models first, and then in multivariate linear regression models with adjustment for the confounders selected based on the DAG.

Prior to an investigation of effect modification by sex, BMI, or asthma or wheeze at age 4, the number of individuals within each stratum was considered. Where small numbers were found within strata, the investigation was not further pursued; however, where numbers permitted, potential effect modification was assessed by fitting individual interaction terms in the multivariate regression models and comparing models using likelihood-ratio tests. Stratified results were presented if the *P* value for interaction was ≤.05.

3 | RESULTS

Of those children who attended the 6-year clinical follow-up, 1709 children had a full assessment after March 2015 and were invited to participate in the accelerometry testing. Accelerometers were sent to 682 (40%) of these children, and data were returned for

495 participants. Of these, 104 files were excluded because they did not contain sufficient valid data or were corrupted. Hence, this study analysed valid data from a sample of 391 children (Figure 1).

In this study sample, 50.6% of children were male and 48.3% were female (Table 1). The proportion of children who experienced wheeze was 12.8% at age 4 years and 17.4% at age 6 years. The proportion of children with current asthma was 8.7% at age 4 and 12.5% at 6 years. At age 6, the mean [standard deviation] time spent in MVPA for all HealthNuts children was 98 [35] minutes per day, and on average, boys spent more time in MVPA than girls (111 [35] vs 85 [30] minutes per day, respectively). Overall, 88.5% (82% girls and 95% of boys) of the study children met the WHO recommendation of 60 minutes of MVPA per day.

3.1 | Association between exposures at age 4 and physical activity at age 6

Children with current asthma at age 4 participated in an average of 8.3 (95% confidence interval (CI): −5.6, 22.1, $P = .24$) minutes more MVPA per day at age 6 than children without asthma (Table 2). Similarly, there were no associations seen for current wheeze (5.8 minutes 95% CI: −5.9, 17.5, $P = .33$) or ever wheeze or asthma at age 4 years (7.7 minutes 95% CI: −4.8, 20.2, $P = .23$) for time spent in MVPA at 6 years.

3.2 | Association between exposures at age 6 and physical activity at age 6

Children who experienced current asthma at age 6 years participated in an average of 2.9 minutes more MVPA per day (95% CI: −12.8, 18.6) than those who did not experience current asthma (Table 2). Similarly, children who experienced current wheeze at 6 years spent an average of 1.3 (95% CI: −13.2, 10.6) minutes less in MVPA than those without current wheeze and children with a history of asthma or wheeze spent an average of 5.3 (95% CI: −7.4, 17.9) more minutes in MVPA than their peers, with no evidence of a difference between these groups ($P = .72$, $P = .83$ and $P = .41$, respectively).

3.3 | Investigation of effect modification

The small number of observations within some strata prohibited the investigation of effect modification by BMI at both ages (Tables S1-S3). However, likelihood-ratio test for interaction found no evidence of effect modification by sex for any of the asthma/wheeze variables at 4 or 6 years, on time spent in MVPA (all P values for interaction >0.3) (Table 2). Similarly, there was no evidence of effect modification between exposure status at age 4 and either current asthma ($P = .17$), current wheeze ($P = .59$), or ever asthma or wheeze ($P = .70$).

TABLE 1 Comparison of descriptive characteristics of children with accelerometry data at age 6

Characteristic	N (%) or mean [SD]
Measured at 1 y	
Sex,	
Male	198 (50.7)
Female	189 (48.3)
Missing	4 (1.0)
Maternal asthma,	
Yes	65 (16.6)
No	326 (83.4)
Missing	0
Paternal asthma,	
Yes	55 (14.1)
No	336 (85.9)
Missing	0
Older siblings, n (%)	
Yes	185 (47.3)
No	204 (52.2)
Missing	2 (0.5)
SEIFA index,	
1 (most disadvantaged)	74 (18.9)
2	71 (18.2)
3	95 (24.3)
4	76 (19.4)
5 (least disadvantaged)	75 (19.2)
Measured at 4 y	
BMI,	
Underweight	36 (9.2)
Normal weight	179 (45.8)
Overweight	34 (8.7)
Missing	142 (36.3)
Current asthma,	
Yes	34 (8.7)
No	258 (66)
Missing	99 (25.3)
Current wheeze,	
Yes	50 (12.8)
No	238 (60.9)
Missing	103 (26.3)
Ever asthma or ever wheeze,	
Yes	57 (14.6)
No	304 (77.8)
Missing	30 (7.7)
Measured at 6 y	
BMI, n (%)	
Underweight	80 (20.5)

(Continues)

TABLE 1 (Continued)

Characteristic	N (%) or mean [SD]
Normal weight	265 (67.8)
Overweight	41 (10.5)
Missing	5 (1.3)
Maternal education, n (%)	
High school	49 (12.5)
Technical or trade qualification	86 (22)
University qualification	237 (60.6)
Missing	19 (4.9)
Paternal education, n (%)	
High school	45 (11.5)
Technical or trade qualification	116 (29.7)
University qualification	200 (51.1)
Missing	30 (7.7)
Current asthma, n (%)	
Yes	49 (12.5)
No	337 (86.2)
Missing	5 (1.3)
Current wheeze, n (%)	
Yes	68 (17.4)
No	305 (78.0)
Missing	18 (4.6)
Ever asthma or ever wheeze, n (%)	
Yes	57 (14.6)
No	332 (84.9)
Missing	2 (0.5)
Minutes spent in MVPA,	
Total	97.9 [35.1]
Boys	110.7 [35]
Girls	84.8 [30.3]
Met WHO recommendation for MVPA,	
Total	346 (88.5)
Boys	188 (94.9)
Girls	154 (81.5)

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; SEIFA, Socio-Economic Indexes for Areas.

4 | DISCUSSION

This study is among the first to look at the longitudinal relationship between asthma and wheeze and objectively measured MVPA in a population of young children. We found no evidence of associations between current asthma, current wheeze, or a history of ever having asthma and wheeze at 4 or 6 years and MVPA as measured by accelerometer at 6 years of age. Statistical tests for interaction also found no evidence for effect modification by either sex, or asthma or wheeze status at 4 years. We were unable to explore effect modification by BMI due to insufficient power. Within this sample, the majority (88.5%) of children met the WHO recommendation of 60 minutes of MVPA per day. A greater proportion of boys (95%) than girls (82%) achieved this recommended amount. The mean time spent in MVPA in this study was 98 [35] minutes per day. This suggests that the cohort was highly active, contrary to reports of inadequate physical activity on other studies of this age group.[20,21]

The null results obtained in the present study are concordant with the other longitudinal study of the association between wheeze and physical activity in young children,[11] and with the few additional studies that have found no longitudinal association between asthma and physical activity in youth.[22,23] Further, this result supports the finding of our previously published systematic review[7] and multiple studies that have found no cross-sectional associations.[24,25] These null results are a positive indication that, at least within Australia, these young children with asthma are not restricting their physical activity engagement on account of their asthma. Of course, these results are likely to be age-dependent, with older children and adolescents partaking in less physical activity. However, these results suggest that the current asthma guidelines and public health messaging on the importance of physical activity in childhood are being effectively disseminated to, and well adopted by parents. Additionally, it signifies that general practitioners are providing children with asthma and their parents or caregivers with appropriate and effective management plans and knowledge, thus adequately controlling asthma symptoms and allowing these children to participate in physical activity without fear. These results and their implications may not be generalizable to other settings around the world, where a variety of different social, health care and economic factors may influence the relationship between asthma and physical activity.

A major strength of this analysis is the use of robust tools for the outcome measurement of MVPA. The present study is one of few that has used accelerometers to measure physical activity in children as young as 6 years. The use of the validated ISAAC questionnaire,[26] together with objective accelerometry measurements, inspires confidence in the data. The use of an objective measurement technique is particularly important for the collection of physical activity data in children of this age, since subjective measurements of physical activity in young children may be over- or underestimated.[27] Measurements by proxies such as parents or caregivers may be inaccurate, since young children tend to have brief bursts of activity that can be difficult to quantify through observation.[28] An additional strength is the data drawn from a prospective, population-based cohort of young children, which enables the assessment of data in a longitudinal manner to account for the temporality of the association, unlike previous studies that have been cross-sectional in nature.[25,29]

This study also had several shortcomings. First, the high proportion of HealthNuts children who met the WHO's physical activity recommendations may be due to potential selective participation for children who were more active. Children from higher socio-economic status have higher levels of physical activity,[30] this may be reflected in the current results, where families with a higher SEIFA index were found to be more likely to participate in the HealthNuts study.[12] This

TABLE 2 Table of adjusted regression coefficients, 95% confidence intervals for cross-sectional and longitudinal models and *P* values for the likelihood-ratio tests for interaction

	Current asthma Coefficient (95% CI)	*P* value	Current wheeze Coefficient (95% CI)	*P* value	Ever wheeze or asthma Coefficient (95% CI)	*P* value
Longitudinal (exposure at 4 y)	8.3 (−5.6, 22.1)	.24	5.8 (−5.9, 17.5)	.33	7.7 (−4.8, 20.2)	.23
Interaction with sex		.41		.51		.89
Cross-sectional (exposure at 6 y)	2.9 (−12.8, 18.6)	.72	−1.3 (−13.2, 10.6)	.83	5.3 (−7.4, 17.9)	.41
Interaction with sex		.44		.39		.31
Interaction with exposure status at age 4		.17		.59		.70

Note: Longitudinal models adjusted for sex, SEIFA, older siblings, maternal and paternal asthma and BMI at 4 y. Cross-sectional models adjusted for sex, SEIFA, older siblings, maternal and paternal asthma, BMI at 6 y and the respective exposure status at 4 y.

limits the external generalizability of these results. Further, major limitations with accelerometry persist through the lack of an agreed and standardized processing, analysing and reporting method.[31] For example, the threshold used to define moderate-to-vigorous physical activity can vary widely, resulting in substantially different results and conclusions.[31] However, as our study focused on comparative differences in MVPA, the choice of cut-point should have no effect on the findings. Secondly, when the accelerometer was removed for sport, we replaced the entire non-wear period with MVPA. This likely results in an overestimation of MVPA for these periods, since the removal period may also include time to get changed, shower, etc As a result, this could create misclassification if some participants reported significantly more sport non-wear than others. This issue is discussed in greater detail elsewhere[16]; however, any misclassification is likely to be non-differential across categories of children with and without asthma as their reporting of physical activity was independent of their knowledge of this study's research questions and exposures of interest. Finally, a substantial amount of missing data at the 4-year follow-up meant there was insufficient power to present reliable results for interaction between BMI and asthma. Future longitudinal studies with greater statistical power should explore the signal for asthma and BMI in more depth.

5 | CONCLUSION

We found no evidence of either longitudinal or cross-sectional associations between current asthma, current wheeze or a history of ever having had asthma or wheeze and the amount of time spent in objectively measured moderate-to vigorous physical activity at 6 years of age. These results suggest that in this Australian setting, asthma guidelines and management strategies seem to be working effectively, so that physical activity is not restricted in young children with asthma.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

Raisa Cassim: Conceptualization (equal); Formal analysis (lead); Investigation (lead); Methodology (supporting); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Shyamali C Dharmage:** Conceptualization (equal); Funding acquisition (equal); Supervision (equal); Writing-review & editing (equal). **Rachel Louise Peters:** Investigation (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Jennifer Julia Koplin:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Katrina J Allen:** Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Writing-review & editing (equal). **Mimi Tang:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Project administration (equal); Writing-review & editing (equal). **Adrian J Lowe:** Conceptualization (equal); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Timothy S Olds:** Data curation (supporting); Methodology (supporting); Software (supporting); Writing-review & editing (supporting). **Francois Fraysse:** Data curation (supporting); Investigation (supporting); Methodology (supporting); Software

(supporting); Writing-review & editing (supporting). **Elasma Milanzi:** Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Melissa A Russell:** Conceptualization (equal); Investigation (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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8.6 Supplementary material to the publication

Supplementary Table 8.S1: The distribution of exposures by category of BMI.

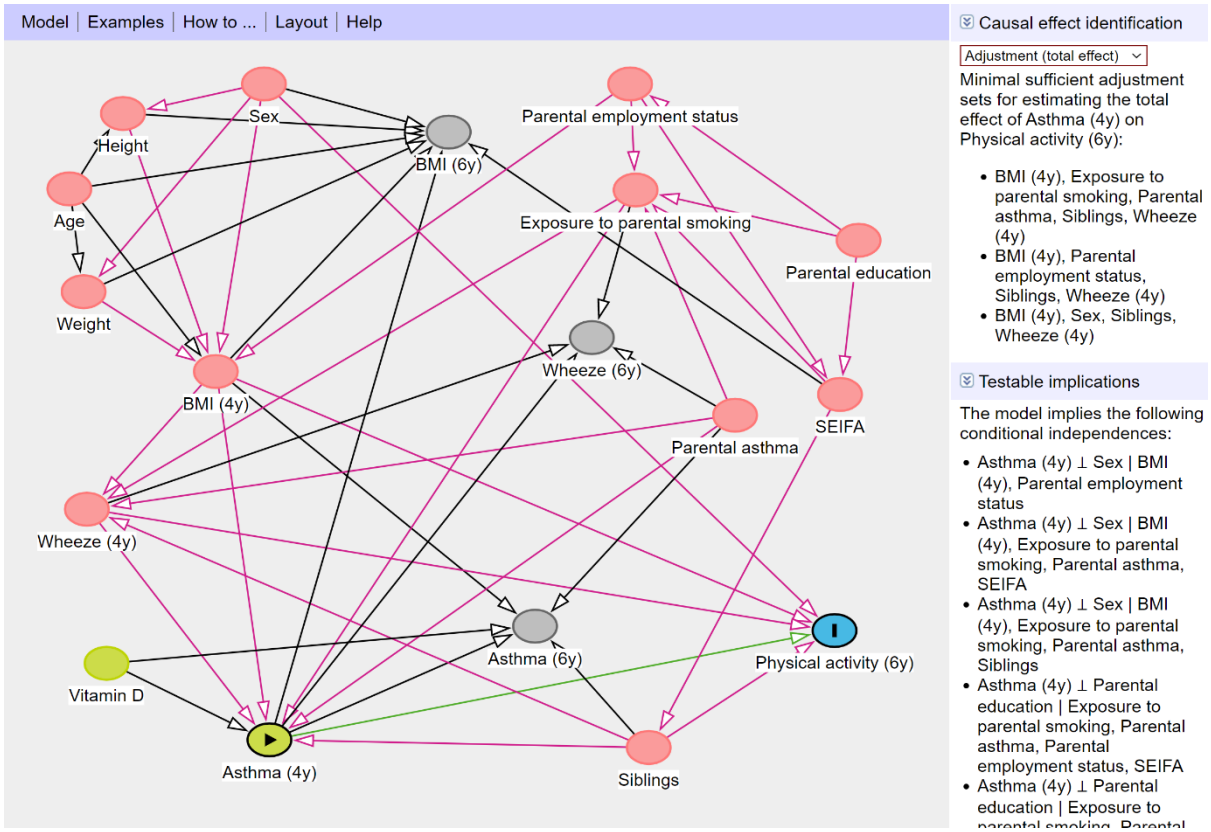
		BMI AT 4 YEARS			
		UNDERWEIGHT **(N=36)**	NORMAL WEIGHT **(N=179)**	OVERWEIGHT **(N=34)**	MISSING **(N=142)**
EXPOSURE AT 4 YEARS	NO ASTHMA **(N=258)**	30	162	31	35
	ASTHMA **(N=34)**	6	13	3	12
	MISSING **(N=99)**	0	4	0	95
	NO WHEEZE **(N=238)**	29	148	32	29
	WHEEZE **(N=50)**	6	25	2	17
	MISSING **(N=103)**	1	179	34	142
	NO HISTORY OF ASTHMA OR WHEEZE **(N=304)**	28	161	31	84
	HISTORY OF ASTHMA OR WHEEZE **(N=57)**	8	18	3	28
	MISSING **(N=30)**	0	0	0	30
		BMI AT AGE 6 years			
EXPOSURE AT 6 YEARS		UNDERWEIGHT **(N=80)**	NORMAL WEIGHT **(N=265)**	OVERWEIGHT **(N=41)**	MISSING **(N=5)**
	NO ASTHMA **(N=337)**	70	227	36	4
	ASTHMA **(N=49)**	10	35	4	0
	MISSING **(N=5)**	0	3	1	1
	NO WHEEZE **(N=305)**	67	200	34	4
	WHEEZE **(N=68)**	10	53	5	0
	MISSING **(N=18)**	3	12	2	1
	NO HISTORY OF ASTHMA OR WHEEZE **(N=304)**	69	222	37	4
	HISTORY OF ASTHMA OR WHEEZE **(N=57)**	11	42	4	0
	MISSING **(N=30)**	0	1	0	1

Supplementary Table 8.S2: The distribution of exposures at ages 4 and 6 by sex.

	MALE (N=198)	FEMALE (N=189)	MISSING (N=4)
EXPOSURES AT AGE 4			
NO ASTHMA (N=258)	129	127	2
ASTHMA (N=34)	23	10	1
MISSING (N=99)	46	52	1
NO WHEEZE (N=238)	118	118	2
WHEEZE (N=50)	32	17	1
MISSING (N=103)	48	54	1
NO HISTORY OF ASTHMA OR WHEEZE (N=304)	145	156	3
HISTORY OF ASTHMA OR WHEEZE (N=57)	38	18	1
MISSING (N=30)	15	15	0
EXPOSURES AT AGE 6			
NO ASTHMA (N=337)	162	172	3
ASTHMA (N=49)	33	15	1
MISSING (N=5)	3	2	0
NO WHEEZE (N=305)	147	156	2
WHEEZE (N=68)	43	24	1
MISSING (N=18)	8	9	1
NO HISTORY OF ASTHMA OR WHEEZE (N=332)	155	174	3
HISTORY OF ASTHMA OR WHEEZE (N=57)	42	14	1
MISSING (N=2)	1	1	0

Supplementary Table 8.S3: The distribution of exposure status at age 6 by previous exposure status at 4 years.

		EXPOSURE AT AGE 6		
EXPOSURE AT AGE 4		NO ASTHMA **(N=337)**	ASTHMA **(N=49)**	MISSING **(N=5)**
	NO ASTHMA **(N=258)**	246	10	2
	ASTHMA **(N=34)**	9	25	0
	MISSING **(N=99)**	82	14	3
		NO WHEEZE (N=305)	**WHEEZE** (N=68)	**MISSING** (N=18)
	NO WHEEZE **(N=238)**	213	18	7
	WHEEZE **(N=50)**	19	27	4
	MISSING **(N=103)**	73	23	7
		NO HISTORY OF ASTHMA OR WHEEZE (N=332)	**HISTORY OF ASTHMA OR WHEEZE** (N=57)	**MISSING** (N=2)
	NO HISTORY OF ASTHMA OR WHEEZE **(N=304)**	287	15	2
	HISTORY OF ASTHMA OR WHEEZE **(N=57)**	18	39	0
	MISSING **(N=30)**	27	3	0



Supplementary Figure 8.S1: Directed Acyclic Graph (DAG) showing the potential relationships between asthma and physical activity. Created with Daggity 3.0 software.

CHAPTER NINE: Discussion

9.1 Chapter introduction

This discussion chapter aims to contextualise this doctoral work by considering how the key findings and methodological approaches relate to the existing literature and theoretical epidemiological concepts. The chapter begins with a succinct summary of my thesis, followed by a discussion of my key findings in the context of other research in this area. Subsequently, I will expand upon methodological issues encountered within this thesis and how they may have influenced my doctoral findings. I will also discuss the epidemiological concepts involved in assessing the causation of an association, which I have attempted to address within this body of work. The implications of these findings and the recommendations for clinicians, public health policy makers and researchers are outlined in the next and final chapter of this thesis (Chapter Ten).

9.2 Thesis Summary

My doctoral work investigated the relationship between physical activity and asthma in five research projects. Each project investigated one of the following three assertions in children and adolescents:

1. Increased physical activity has a beneficial or protective effect on subsequent asthma
2. Experiencing asthma negatively affects the amount of physical activity performed
3. A bidirectional association exists between physical activity and asthma

Evidence on the first two assertions were synthesised using the systematic review methodology, and one qualitatively collated the evidence through a metanalysis. These systematic reviews highlighted the lack of evidence in the above statements. Therefore, all three assertions were tested through the statistical analyses of data collected in children and adolescents up to the age of 18 years across two cohorts. In these cohorts, asthma and physical activity data were collected using a variety of tools, including

questionnaires, diaries, and accelerometers. A variety of statistical techniques were employed for the analyses of these associations. These included linear and logistic regression, and generalised structural equational modelling.

The first of two systematic reviews included in this thesis investigated the association between physical activity and subsequent asthma and lung function outcomes in children and adolescents (Chapter Four). I searched the PubMed and EMBASE databases for longitudinal investigations of these associations. Of the nine articles eligible for inclusion on this systematic review, two studies found no association with incident wheeze, two of four found no association with various asthma outcomes. Three of these nine studies investigated the effect on lung function, with one observing an association in boys only, one in girls only, and one found no associations. This systematic review concluded that there was insufficient evidence to determine the role of physical activity on asthma and lung function. This systematic review was published in 2019 in the Journal of Pediatric Allergy and Immunology (204).

The second systematic review (Chapter Five) investigated the association between asthma status and objectively measured physical activity in children and adolescents. Three databases (MEDLINE, PubMed and EMBASE) were searched for articles that measured physical activity in children and adolescents up to the age of 18 years. I restricted my review to objective measurements of physical activity in an attempt to minimise measurement error. Twelve studies, comprising of 1 cohort and 8 cross-sectional studies were included in my systematic review. The meta-analysis of data from the single cohort study and 8 cross-sectional studies found little difference between the amount of physical activity performed by children with and without asthma (overall mean difference 0.01 (95%CI:−0.09–0.11) activity counts per minute). This systematic review and meta-analysis was published in 2016 in the Journal of Asthma (205).

The data analyses within this thesis were designed to address the knowledge gaps detected within the systematic reviews by quantitatively investigating associations between asthma and physical activity in two longitudinal cohorts of Australian children. That is, I endeavoured to use standardised and robust measurement and analytical tools, and to explore the relationships in different age groups.

The first of three data analyses used repeated data collection from the LSAC to investigate the possibility of a bidirectional relationship between asthma and physical activity in children and adolescents (Chapter Six). I used asthma and physical activity data that the LSAC collected at five timepoints and analysed them using generalised structural equational modelling (GSEM). The study found no evidence of associations between physical activity and subsequent asthma nor between asthma and subsequent physical activity. I concluded that the results of this analysis should be confirmed with objective measures of physical activity. This paper was published in 2018 in the Journal of Epidemiology and Community Health (206).

The second data analysis again used LSAC data to investigate whether individuals with asthma are less active than their peers at several ages that spanned the important developmental transition from childhood to adolescence. This analysis found there was no difference in the amount of activity performed by those with compared to those without asthma (Chapter Seven) at any of the ages investigated. This analysis was published in 2018 in the Journal of Annals of Allergy, Asthma & Immunology (207).

The final results chapter (Chapter Eight) analysed data from the HealthNuts cohort of children. This study investigated the effect of asthma status at age 4 on time spent in objectively measured MVPA at age 6 and tested for interactions by sex, categorical BMI, and earlier exposure status. This analysis again found no association between asthma or wheeze and subsequent time spent in physical activity, and that these associations were not modified by either sex, BMI, or previous exposure status in this cohort of preschool aged children. This final analysis was recently published in the Journal of Pediatric Allergy and Immunology (208).

Hence, in this doctoral work, I consistently found no evidence of associations between physical activity and asthma, irrespective of participant age, whether physical activity was measured subjectively or objectively, follow up time, or direction of association. Hasty floccinaucinihilipilification of these null findings would be erroneous; contrarily, these null results are valuable and inspiring, as they convey a positive message of Australian success in the establishment of:

1. Adequate and appropriate asthma management by healthcare providers
2. Effective physical activity promotion by public health bodies

3. Positive attitudes toward physical activity in children with asthma and their parents and caregivers.

9.3 Contextualising these findings

In the following sections, I will discuss the findings of my thesis in the context of existing research.

9.3.1 Effect of asthma on physical activity

The systematic review and data analyses conducted within this body of work consistently produced evidence to suggest that there is no association between asthma and reduced physical activity in children and adolescents either cross-sectionally or longitudinally. This result endured within the data analyses conducted for this thesis, despite alterations in the sample population tested and the measurement tools employed to collect data. This conclusion is concordant with findings of previous cross-sectional studies in which no difference was found between children and adolescents with and without asthma in the time spent in physical activity (11, 14, 209-213) as well as with the few studies that have found no longitudinal association between the presence of asthma and physical activity in youth (210, 214). These studies include children and adolescents of various ages. Additionally, much of the previously conducted research has been in carried out in countries such as Norway and the UK which share similar sociodemographic properties as Australia (see section 9.6 External validity of this research program), but similar results have also been seen in Brazilian children (212).

Contrastingly, the conclusions of this doctoral research are discordant with a previous review by Williams *et al* who concluded that individuals with asthma are less likely to participate in physical activity than individuals without asthma (7). While this review restricted their population to children and adolescents, they did not include any studies that measured physical activity objectively through accelerometry (7).

It is worth noting that many studies that reported an association collected physical activity information via questionnaire (6, 9, 215, 216), whilst those that did not find an

association between asthma and physical activity measured physical activity through accelerometry (12, 214, 217, 218). This suggests that there is a risk of systematic measurement error in the reporting of physical activity based on asthma diagnosis, which may lead to differential misclassification bias.

The evidence produced by the work in this thesis, together with existing literature, therefore, appears to support the assertion that asthma does not adversely affect the amount of physical activity that an affected child performs.

9.3.2 Effect of physical activity on asthma

The findings produced in this thesis further suggested that there is no evidence that physical activity longitudinally affects subsequent asthma development or symptoms. This is in direct contrast to earlier reviews by Lochte *et al.* (191) and Eijkemans *et al.* (2), both of whom found physical activity to play a protective role against the incidence of asthma in children (191) and adults (2). Whilst Eijkemans *et al.* concluded that higher levels of physical activity were associated with lower incidence of asthma (OR 0.88 (95% CI: 0.77–1.01), their conclusions were based on their meta-analysis of five longitudinal studies (I^2= 45%) conducted primarily in adult populations (2). The authors did not have the longitudinal evidence to support this conclusion in child populations, as all included studies that were conducted in child populations were cross-sectional (2). However, the same authors recently published results of a prospective analysis of 1838 children from the KOALA birth cohort study (219). This study concluded that physical activity was not associated with future asthma development in children (219); a result which corresponds with the findings of this thesis. A further longitudinal study of objectively measured physical activity and subsequent wheeze in 347 young children similarly concluded that physical activity was not associated with subsequent wheezing or shortness of breath (220).

On the other hand, the Lochte *et al.* review that did restrict their research to children and adolescents, meta-analysed 3 cohort studies which led to the conclusion that low levels of physical activity were associated with increased odds of new-onset asthma (OR [95 % CI] 1.32 [0.95; 1.84] [random effects] and 1.35 [1.13; 1.62] [fixed effects]) (191). Within

this review, there were substantial differences in definitions of physical activity used in the meta-analysis, resulting in moderate levels heterogeneity (I^2 = 60.6%) (191). The definitions of physical activity incorporated within this review were also very different from the ones I employed in my own review, meaning that there was no overlap in the studies included in the two reviews. For example, while my own review considered sedentary behaviour to be a distinct concept from physical activity (221), Lochte *et al*. included sedentary activities such as TV viewing as a proxy measure for low physical activity (191). I expect that these methodological differences are at the root of the opposing conclusions drawn by Lochte *et al.*'s review and that of my own systematic review.

While the role of physical activity on lung function has recently been investigated in adults (222), my second systematic review highlighted a paucity of longitudinal studies that investigated the role of physical activity on asthma persistence or lung function in youth (204). This shortage of studies and the heterogeneity amongst them impeded any pooling of results. Thus, there was insufficient evidence available to draw conclusions regarding the role of physical activity on asthma persistence or lung function. Some RCT's have investigated the effect of exercise training interventions on aerobic fitness, lung function, asthma control and quality of life and have found their interventions to have a positive impact (137, 138), and a systematic review is underway (223). However, these results cannot be used to infer associations in free living conditions over extended periods of time. Similarly, results from the adult study which found evidence of positive associations between physical activity and lung function (in both directions) (222), cannot be extrapolated to younger populations.

Hence, evidence on for a role of physical activity on asthma in children and adolescents is still relatively scant, and further longitudinal investigations are essential. Existing research suggests that there is little evidence that physical activity plays a beneficial role by reducing the development of asthma in childhood and adolescence, while evidence for the role of physical activity on asthma persistence or lung function is both inadequate and inconsistent.

9.4 Overall methodological strengths and limitations

As with any research, this doctoral work possesses both strengths and limitations. In the following sections, I will comment on the both the strengths and limitations of the overall methodology used in this doctoral work. In this section, I appraise the truth and trustworthiness of my findings, by examining various potentially influential factors within the methodology of the research and the applicability of the findings to the other settings (internal and external validity, respectively).

9.4.1 Study designs employed

In this doctoral work, I attempted to investigate the association between physical activity and asthma and identify which was the ancestral variable in the association. Hence, longitudinal studies were favoured in this thesis as they are the most appropriate design to investigate the issues of temporality within associations (224).

Although a randomised controlled trial to investigate the effect of physical activity on asthma incidence may enable researchers to control the physical activity exposure and confounding variables among groups of children, such a study is not feasible. The cost of such a trial would be substantial, and the sample size and length of time required for follow up also make this study design impractical, unethical, and wholly unsuitable for the research questions under examination. Additionally, an RCT to investigate the relationship between asthma and physical activity is implausible and nonsensical, as asthma cannot be randomly assigned to participants.

Case-control study designs are also not suitable to address these research questions, as the retrospective collection of exposure data that occurs in case-control studies subjects the study to further bias: recall bias inherent in case-control studies, and social desirability bias. Social desirability bias is where participants aware of the associations under investigation, provide responses considered socially desirable rather than those that reflect the truth (225). Furthermore, in case-control studies, the selection of controls should be representative of the source population. This can be quite challenging and, if done incorrectly, can result in selection bias.

Further, case-control studies, as with cross-sectional designs, raise the issue of reverse causation, thus inhibiting any investigation of temporality and causal associations. Hence, this doctoral work utilised data from longitudinal studies that both consisted of measurements taken at multiple time points: The Longitudinal Study of Australian Children (LSAC) and the HealthNuts study. The chosen study design was the best and most appropriate approach to address my research questions.

9.4.2 Bias

9.4.2.1 Selection bias

Selection bias is a consequence of the selection of participants into a study and factors that influence study participation (226). It may arise at various stages of a study through the way in which individuals are selected into an analysis of a study. Selection bias incorporates biases arising from the inappropriate selection of controls in case-control studies, differential loss to follow up (attrition), nonresponse (missing data) or selection of participants from volunteers (volunteer bias) or other driven groups (e.g. the healthy-worker bias) (193, 227). It may lead to an over or under-estimation of the true association. For example, inappropriate sample selection may not reflect the true population effect if the selected sample is not representative of the source population. Another example is where unequal loss to follow-up amongst either the exposed or unexposed group results in differential misclassification (227). Selection bias can be minimised by designing a study well, ensuring high participation and retention, and by minimising missing data where possible.

Within this doctoral work, data were drawn from two longitudinal cohort studies. The LSAC participants were drawn from a nationally representative population-based sample of children, so selection bias arising from participant selection and recruitment is likely to be minimal. The HealthNuts sample, however, was drawn from a smaller geographical range, making them less representative of children nationally. Selective participation for higher SEIFA index and older mothers was observed and documented for this study (228). It is possible that this resulted in a sample that was more likely to be more active,

as higher SES has been linked to higher levels of physical activity (229). This may have artificially increased the physical activity level and decreased the representativeness of our study sample compared to the general population. Neither of these cohorts were intentionally recruited or selected based on their asthma or physical activity status, hence it is unlikely that the selection of participants into this doctoral work has markedly biased my results.

Loss to follow up is an inevitable element of longitudinal studies. As both the LSAC and HealthNuts studies are longitudinal cohort designs, they are subject to attrition over time as participants withdraw or are unable to be traced. While both of these cohort studies were subject to loss to follow up over time, it is unlikely that the reason for loss to follow up in either of these studies are due to both the exposures and outcomes of my doctoral research. Hence, it is unlikely that attrition has been a source of bias in my doctoral work.

Missing data were a potential problem within this thesis. Missing data were assumed missing at random and complete case models were used in the final analyses. It is again highly unlikely that data were missing differentially based on a participants' exposure or outcome status.

9.4.2.2 Information bias

Information bias occurs as a result of measurement error. Within association studies, it arises due to error in the measurement of exposure or outcome. Measurement error can arise in several ways:

- Tools and instruments employed by researchers, e.g. questionnaires
- Respondent error, e.g. through misunderstanding of a question
- Observer or interviewer error, e.g. nonspecific wording of a question
- Data processing error, e.g. accidentally incorrect data entry or coding
- Underlying variability within the construct of interest, e.g. blood pressure

Measurement error can be differential, or non-differential. Measurement error is referred to as differential misclassification if the error within the measurement of the exposure differs depending on the status of the outcome. Differential misclassification may

strengthen or attenuate an association. Non-differential misclassification occurs when error within the measurement of the exposure does not differ depending on the status of the outcome. Non-differential misclassification predictably attenuates associations.

Potential measurement error within this doctoral work is explored below in depth, however, since measurement of the exposures and outcomes of this doctoral research occurred without prior knowledge of the research questions specific to this doctoral work, the likelihood of misclassification of exposures and outcomes is minimal, and any misclassification encountered is likely non-differential in the context of this thesis.

9.4.3 Variable definitions and assessment

The way in which variables are defined can have a significant impact on the interpretation of the results. The definitions used for the collection and analyses of data also affects the comparability of the findings to other research. Hence, in this work, I used definitions for asthma and physical activity that largely adhered to definitions used in previous research, whilst capturing the concepts of interest. Furthermore, while details of each variable assessment and use are described in full within each chapter, in this section, I discuss some of the methodological issues and their potential effects on the results obtained.

9.4.3.1 Asthma definitions

Asthma is an umbrella term for a number of heterogenous, chronic respiratory conditions. Thus, definitions used vary greatly in the existing literature and there is no single operational definition currently in use for epidemiological research (230, 231). Presently, the gold standard definition for current asthma used in epidemiological studies involves a combination of a reported medical diagnosis of asthma together with reported asthma symptoms over the past 12 months and/or at least a 12% and over 200 mL increase in FEV_1 after bronchodilation (230). A recent report found this definition to be inadequate, and proposed that a standardised definition 'should include a composite score based on questionnaire-driven responses and airway reversibility as these measures probably address different expressions of the disease' (230). However, lung

function testing is not routinely performed in child populations (230), and may not be viable for sizeable epidemiological studies with large sample sizes.

Since lung function data were not available for use within this thesis, with the exception of systematic reviews, the following asthma definitions were used in the data analyses (Table 9.1):

Table 9.1: Asthma definitions used in this thesis

Variable	Definition	Thesis chapter(s) where definition was used
Incident asthma	This first report of a doctor's diagnosis of asthma when a diagnosis of asthma had not previously been reported (232).	Six
Current asthma	Parental report of doctor's diagnosis of asthma and either current wheeze in the previous 12 months and/or use of asthma medications in the previous 12 months (159).	Six, Seven, Eight
Current wheeze	Parental report of any wheezing in the last 12 months (160).	Eight
Ever wheeze or asthma	Parental report of ever having had asthma or wheeze.	Eight

These definitions are commonly used in large epidemiological research studies around the world, when lung function parameters cannot be obtained.

9.4.3.2 Asthma assessment

The studies employed in this doctoral work assessed asthma in two ways. Firstly, the LSAC study collected asthma data via their study questionnaires (see Appendices). Similarly, the HealthNuts used standardised questions on asthma and wheeze taken from the International Study of Asthma and Allergies in Childhood (ISAAC) (161, 162) (see Appendices). While the use of questionnaires to collect information is a commonly employed epidemiological tool, this method of subjectively collecting data is inherently open to measurement error and social desirability bias. With regard to asthma, non-differential measurement error may arise as parents or participants may struggle to accurately recall exact symptoms, their frequency and timing. However, any biases introduced by the method of data collection is unlikely to vary between classes of physical activity, as these data were collected independently, and participants and parents were unaware of the research questions for this thesis. Hence, overall, while the method for the assessment of asthma may be inaccurate, any potential biases are unlikely to have been differential, and as such, would have attenuated the results toward the null.

9.4.3.3 Physical activity definition

The accepted definition for physical activity is "any bodily movement produced by skeletal muscles that requires energy expenditure" (101). This definition encapsulates all forms of activity, including walking (for transport of leisure), sport and recreation (e.g. yoga or dance), and even domestic activities (e.g. gardening). Therefore, this definition is used to determine *habitual* physical activity levels as opposed to time spent *specifically* in formal physical activity or exercise programs which tend to be 'planned, structured and repetitive movements' (e.g. at the gym) (102). Hence, when using this definition, we are able to gain insight into the overall activity levels of individuals. This is important, as children and adolescents who may not specifically make time for formal physical activity programs, may still be active in their other daily activities, for example by taking active transport to and from school or through active play. The current WHO recommendations for physical activity by age group are:

- Children and adolescents between the ages of 5 and 17 years should accumulate at least 60 minutes of MVPA daily.
- Adults aged 18 to 64 years are recommended to engage in a minimum of 150 minutes of MPA, or 75 minutes of VPA, or an equivalent combination of MVPA in bouts of at least 10 minutes duration, throughout the week.
- Older adults aged 65 and over should similarly engage in at least 150 minutes of MPA, or 75 minutes of VPA or an equivalent combination of MVPA in bouts of at least 10 minutes duration, throughout the week.

Whilst the WHO guidelines are clear in terms of duration and frequency of physical activity, measurement, and definition of different intensities of physical activity are remain a challenge. These are discussed in further details below in section 9.4.3.4 Physical activity assessment.

In this thesis, where TUD's were analysed to obtain physical activity estimates (Chapters Six and Seven), the reported time spent in each activity was summated to provide a continuous measure of time spent in physical activity.

For accelerometers, calibration studies have been conducted to determine appropriate cut off points for distinguishing between light, moderate and vigorous intensity physical activities. These usually involve comparing accelerometer activity counts with measures of oxygen uptake (i.e. indirect calorimetry) (233). However, different studies have recommended different cut offs thresholds to define physical activity intensities, as demonstrated below in Table 9.2. This variability between thresholds used for analysing data adds uncertainty to estimates and reduces the comparability of results between studies (234).

Table 9.2: Physical activity intensity cut offs used in different studies

Source	Participant age	Epoch length	SB	LPA	MPA	VPA
Evenson (233)	5-9	15	0 – 25	26 - 573	574 - 1002	≥ 1003
Treuth (235)	13-15	30	0 – 50	51 - 1499	1500 – 2600	≥ 2601

Puyau (236)	6-16	60	0 – 799	800 - 3199	3200 – 8199	≥ 8200
Mattocks (237)	12	60	0 – 3580		3581 – 6129	≥ 6130
Romanzini (238)	10-15	15	0 – 180	181 - 756	757 - 1111	≥ 1112
Phillips (168)	8 - 14	1	0 - 487	488 - 1575	≥ 4350	

9.4.3.4 Physical activity assessment

Methods of physical activity assessment used for the data analyses within this thesis are summarised below in Table 9.3. The studies which provided data for analyses in this doctoral work assessed physical activity subjectively and objectively.

Table 9.3: Physical activity assessment methods used in this thesis

Assessment method	**Thesis chapter(s) where assessment method was used**
Time Use Diary (TUD) completed for a single day by either parents or participant depending on age of participant.	Six, Seven
GENEActiv Accelerometer worn for 8 consecutive days to collect minimally 4 days' worth of valid data.	Eight
Paper activity logs completed by parent; used to corroborate accelerometry data.	Eight

Firstly, as mentioned earlier in this thesis, the LSAC measured physical activity subjectively through the completion of Time Use Diaries (TUDs). The methodology has been described in depth in Chapters Three, Six and Seven, however, the potential effects of this assessment method are discussed below.

Briefly, TUDs were completed by parents in waves 1-3, when children were too young to complete the diaries themselves. Completion of the child's diary involved selection of

activity from a list of 26 pre-coded activities, indicating whom the child was with, and the location of the activity for each 15 minute interval of a 24 hour day, for one weekday and one weekend day (154, 155). From wave 4 onwards, children were asked to complete a TUD themselves by recording the activities they performed throughout the day on any one day (154). At an interview with the study child, on the date after completion of the diary, data were entered in a computer-assisted interview (CAI). This method of data collection leaves much room for error. Parents completing a diary at the end of the day may over or underestimate time spent in various activities, or may have had incomplete data, for example while the child was at day care, or with family or friends. While self-report may minimise some of the inaccuracies introduced by third-party reporting, entrusting children, and adolescents to accurately report their own activities is similarly not infallible. As with all subjective measures, self-administered diaries may have been subject to non-differential measurement bias. A particular issue in self-reporting physical activity is systematic error, where social desirability bias may lead to participants' overestimating physical activity levels (239, 240).

In my analyses, where two TUDs were completed (waves 2 and 3), I randomly selected one TUD per participant for analysis to ensure consistency across all waves. This resulted in analysis of only one diary per participant at each time point, which greatly expanded the variation within the tool, as some participant data would have been estimated from a weekday diary, while others may have been a weekend diary. Furthermore, the use of a single diary is an inaccurate measure of estimate habitual physical activity. Despite this, the error resulting from this imprecise representation of habitual activity would not differentially affect the measurement taken for children with and without asthma.

Since the TUDs did not capture the intensity of physical activity, the following coded activities within the time use diaries were considered moderate-to-vigorous physical activity (with a metabolic equivalent (MET) score of 3.0 or greater) based on the Compendium of Energy Expenditure for Youth categorisations (157): structured or unstructured active play, organized sports/lessons/activities, riding bike/scooter/skateboard and walking/running skipping. For each wave, a continuous variable for total time spent in moderate-to-vigorous physical activity for each child was created by summing the time in minutes spent in all coded physical activities for the day the data were collected.

Time Use Diaries were originally used in the field of sociology, but have recently been explored for their potential to surveil physical activity levels and sedentary behaviour in populations (203). They have been found to provide valid and reliable estimates of time expenditure (155, 203), with similar test-retest reliability to other commonly used physical activity questionnaires such as the US Behavioral Risk Factor Surveillance System physical activity questionnaire, the International Physical Activity Questionnaire (IPAQ) or the Global Physical Activity Questionnaire (203). They are also thought to be less susceptible to reporting error and social desirability bias than the other tools as they were found to fare better than these questionnaires when compared with an accelerometer (203). Despite this, TUD's possess some limitations. Firstly, while they are able to collect detailed information over a range of domains, they are unable to accurately assess the intensity of physical activities, so researchers are often left to assume the intensity of a reported activity. This of course, introduces the possibility of misclassification of an activity which may either over- or under-estimate an individual's physical activity. Regardless, TUD's have been and continue to be used as a tool for the assessment of time use in general, and physical activity in particular. For example, a recently published study also used the LSAC TUD's to investigate participation within various physical activity domains (organised and non-organised physical activity, active transport and active chores) between childhood and adolescence (241).

In my final data analysis, I used data from The HealthNuts Study which collected physical activity data using accelerometers. Accelerometry is the most widely used method for objectively measuring free-living physical activity in youth (119), as it eliminates biases related to subjective recall and social desirability, eliminates the need for third party observation and reporting, and negates any participant language and literacy requirements (233). Accelerometry studies may, however, be subject to the Hawthorne Effect, i.e. where participants consciously alter their behaviour due to their awareness of being under observation. The magnitude of bias introduced by the Hawthorne Effect cannot be definitively estimated (242), however, the young age of the HealthNuts participants may minimise the Hawthorne Effect as young children are unlikely to understand the significance between monitoring their physical activity and their health. Further, any excessive activity due to initial excitement of receiving the device is unlikely to be sustained for the entire period of observation.

Before data collected by accelerometers can be used in an analysis, a series of decisions regarding the methodology needs to be made (Table 9.4):

Table 9.4: Decisions about accelerometry in studies and their potential impacts

Decision	Potential impact
The type of accelerometer to be used	Bi or triaxial devices measure activity in either two or three planes, leading to under- or over-estimation of physical activity
The wear site (e.g. wrist or hip)	Different acceptability, and range of motion detected
A time frame for recording data	Longer recording time collects more data
Data sampling frequency	Activity data may be over or under-estimated leading to an imprecise measurement
Epoch length for recording data	Activity data may be over or under-estimated leading to an imprecise measurement
Definition of "valid" data (e.g. a certain number of hours per day)	Activity data may be over or under-estimated depending on age or day of the week, leading to an imprecise measurement.
Selection of a time frame for analysis (e.g. weekdays or weekends or both)	Activity type and duration may differ according to the day of the week
Cut off points used to distinguish between activity intensities	Activity may be misclassified leading to over or underestimation of total activity

Each of these methodological decisions has the potential to influence the way the data is interpreted, and comparability between studies (243, 244), and therefore researchers are urged to clearly state their methodological decisions when reporting their research (245). Many researchers have called for standardisation of accelerometry processing techniques (119, 243, 245-247), however to date, there remains little consensus amongst researchers regarding the optimal type of monitor, the most appropriate wear site, and the best processing and analytical methods (243, 244). This lack of consensus prevents the accurate and meaningful comparison of research results (119). It is essential that standardised techniques are devised for research in this field to truly advance.

While each of the aforementioned points may have introduced some element of error in the physical activity readings, again, this is unlikely to be differential misclassification by asthma status. Hence, again, this error would have resulted in an attenuation of the results so that null results were obtained. This reflects the results observed.

9.4.4 Confounding

Potentially confounding factors were identified from the existing scientific literature. At the commencement of each analysis, I produced directed acyclic graphs (DAGs) in order to identify which of potential confounding variables needed to be accounted for within my models. The DAGs often underwent several iterations. Whilst each individual analysis adjusted for the confounding variables deemed to be important and for which data were available, it is possible that one or more known, unknown, or latent variables have not been accounted for in these analyses. The underlying residual confounding from these unknown variables may also have influenced the results. Similarly, there were several occasions where potential covariates were identified by the DAG, but these data were not measured. Therefore, the effect of these variables on our associations of interest could not be determined.

9.4.5 Chance, random error, and sampling error

Chance, or random error, is another potential explanatory element for observed findings, and should be explored prior to a discussion of the implications of this research. Chance may result in sampling error or variability; whereby different samples produce different results (248). Such sampling error may distort the conclusions drawn from these results in one of two ways:

- Type 1 error (α) – where the null hypothesis is rejected, although it is true. This is often referred to as a "false positive" result.
- Type 2 error (β) – where the null hypothesis is erroneously accepted, although it is false. This is known as a "false negative" result.

Sampling error cannot be entirely eliminated, but may be minimised through careful study design, such as ensuring and appropriate sample size (248). Sampling error can be measured by the standard error, which in turn can be used in the calculation of confidence intervals using the following formula:

$$95\%\ CI\ =\ 1.96\ x\ SE\ \pm\ \mu$$

Where μ is the sample mean. The confidence interval provides a set of limits which may contain the population mean to a degree of certainty.

In this thesis, my conclusions were based largely upon whether clinically important point estimates and confidence intervals were observed, as there has been much debate in the scientific community and a concerted effort to move away from the use of p-values and "statistical significance" when drawing conclusions (249). For the analyses within this research, the confidence intervals spanned a range of estimates that may have indicated both positive or negative associations, however, in general, the point estimates obtained were not clinically significant, and the range of estimates within the corresponding confidence intervals did not follow a specific pattern of association. Specifically, within the LSAC analyses, the sample size was large and confidence intervals were small, indicating quite precise estimates, while within the HealthNuts study the sample size was relatively smaller and confidence intervals were larger. Regardless, both studies suggested that there was little evidence for either positive or negative associations, suggesting that sampling error is unlikely to be influencing the conclusions drawn from this research.

9.5 Association and causation

Association does not imply causation; however, an association must be present for a relationship to be causal. This doctoral work investigated the associations between physical and activity in an attempt to identify the which variable was a causal antecedent of the other. However, the findings of this research have produced little evidence to support an association between physical activity and asthma in either direction. Consequently, much of the research undertaken in this doctoral work leads to the

conclusion that there is no association between asthma and physical activity in either direction, and therefore that the relationship between these factors are not causal.

Regardless, as this work attempted to elucidate the causal antecedent between physical activity and asthma, an exploration of the evidence as it applies to the epidemiological concept of causation has been included below.

9.5.1 The Bradford Hill Criteria

As this thesis is composed and submitted in the field of epidemiology, a consideration of the theoretical principles for exploration of a causal relationship must be included. In epidemiological studies, investigation of a causal relationship between a potential agent and an observed effect involves the consideration of the Bradford Hill criteria. These consist of nine assertions first proposed by the English epidemiologist and statistician Sir Austin Bradford Hill in 1965 that, when met, provide strong evidence for causation (250). Bradford Hill's nine principles are briefly paraphrased below and are accompanied by a discussion of how each of Hill's specified criterion may be applied to this doctoral work. It is important to remember that there were no observable associations found within this doctoral work, and that the following discussion approaches the Bradford Hill criteria with this in mind. Furthermore, it should be noted that the Bradford Hill principles are a tool for critical evaluation rather than a definitive 'checklist for causation'.

1. **Strength** (or effect size): Bradford Hill asserted that larger associations between a potential causal agent and an observed effect are more likely to be causal than smaller ones, although a small association does not necessarily mean that an effect is not causal.

   The investigations conducted as part of this thesis found weak evidence to support an association between physical activity and asthma, and similarly, there was no evidence of an association between asthma and physical activity. Consequently, this criterion provides evidence against causal relationships in either direction.

2. **Consistency** (or reproducibility): An association is consistently observed between the potential causal agent and an observed effect when a study is replicated in various settings and by different researchers.

   This criterion was sufficiently met within this doctoral research, as the investigations conducted within this thesis consistently produced null results for an association between both asthma and physical activity and physical activity. The findings of this research program were consistent, regardless of the dataset used, the age of the included participants and the measurement techniques used. Hence, there was strong evidence to support the conclusions drawn.

3. **Specificity**: The probability of a causal relationship between a potential causal agent and an observed effect increases with the specificity of the relationship, that is, if there are few other likely explanations available for the observed effect.

   The relationships investigated within this doctoral work were complicated. Asthma is undeniably a multifactorial condition, so physical activity may, at best, be a contributing factor as opposed to a singular cause. Similarly, many variables may affect the amount of physical activity performed by any given individual. Physical activity may also be associated with many other healthy behaviours, for example, diet. Therefore, unraveling confounding factors can be challenging, and the specificity for these associations is low.

4. **Temporality**: Exposure to a potential causal agent must occur at some point in time before the effect is observed.

   In this doctoral work, I looked at two associations. First, the relationship between asthma as an exposure and physical activity as an outcome. Second, where physical activity was the exposure and asthma the outcome variable. In both cases, I endeavoured to use longitudinal data to ensure that the temporality aspect was met, that is to say, that the exposure always preceded the outcome. These data were considered to have greater weight in the assessment of results, and in the formulation of interpretations and conclusions. However, due to the nature of

each of these factors, the timeframe surrounding the use of each of these factors as exposure variables was not distinct. For example, asthma is a chronic disease, and physical activity is always performed, albeit the level of activity may vary with time. I attempted to control for this in the selection of variable definitions, so that asthma was defined as 'current asthma' by restricting to individuals who experienced symptoms in the past year. Similarly, physical activity habits were assumed based on data collected over a defined period of time.

5. **Biological gradient** (or the dose-response relationship): A relationship is observed between the magnitude of the potential causal agent and the magnitude of the effect produced. This relationship may be directly or indirectly proportional, or may be more complex, for example, parametric in shape.

   Research into the effect of the type and amount of physical activity needed for good health suggests that moderate-to-vigorous intensity physical activity is the most beneficial. As such, many national and international health recommendations and guidelines are often framed according to time spent in moderate-to-vigorous intensity physical activity. However, a dose-response curve between physical activity and asthma has been recorded and is thought to be U-shaped. That is, both low and extremely high levels of physical activity are thought to be association with increased asthma symptoms. Conversely, individuals who suffer from more severe asthma symptoms may have more activity restriction (209). This effect was not observed in this study.

6. **Plausibility**: A (biologically) plausible mechanism of action exists between the potential causal agent and the observed effect. This criterion is useful, although in his article, Bradford Hill conceded that knowledge of any specific mechanism may be limited.

   A few biological and behavioural mechanisms have been proposed to link asthma and physical activity. First, increased levels of physical activity are thought to reduce immunological inflammation observed in asthma through its anti-inflammatory properties (251). Second, physical activity may be acting through a

reduction in adiposity to reduced strain placed on the cardiovascular system, thereby permitting easier flow of air through the airways. Conversely, asthma is thought to effect physical activity through psychological, rather than biological mechanisms. Studies have suggested that individuals with asthma impose restrictions on physical activity as a means of avoiding exercise-induced symptom exacerbation (9). Hence, plausible explanations that link asthma and physical activity have been proposed.

7. **Coherence**: An epidemiological interpretation of a relationship between a potential causal agent and an observed effect should agree with known natural history and biology of the disease. That is, agreement between laboratory and epidemiological tests increase the evidence for causation, however lack of laboratory evidence does not nullify the epidemiological evidence.

   Although this doctoral work did not include any laboratory testing, my literature searches uncovered studies in both animal and human models that showed that an asthmatic state to be the result of T-helper cell mediated inflammation and that an imbalance of T-cell subtypes may be responsible for asthma (123, 251). A systematic review of 16 randomised controlled trials and seven cohort studies observed a reduction in total sputum cells, eosinophils and nitric oxide in individuals with asthma after training (124). Hence, there appears to be coherence between laboratory and epidemiological studies.

8. **Experiment**: Where possible, experimental evidence of a causal relationship can be sought. A demonstrated relationship between the potential causal agent and observed effect provides strong evidence for causality.

   This thesis was based on qualitative, epidemiological data collected in child populations. Since habitual physical activity undertaken in free-living conditions were the variable of interest in this work, physical activity regimes were not imposed on children in order to obtain these data. However, trials have been conducted wherein participants are provided an activity regime and are monitored over a specified period of time. Many of these studies were randomised

controlled trials (RCT) with a physical activity or exercise intervention (121, 136). A systematic review of twenty-nine randomised controlled trials conducted in children between the ages of 6 and 18 years was conducted (136). Training programs included in this review varied greatly in terms of exercise type, frequency, intensity, and durations of the training interventions. This systematic review concluded that an exercise training program had positive effects on cardiorespiratory fitness outcomes and no apparent negative effects (136). Interventional experimentation cannot be performed to test the opposite association as asthma cannot be randomly assigned.

9. **Analogy**: At times, analogies, or similarities between the association under investigation and other known associations may be used to make assumptions regarding the relationship between causal agent and effect. Whilst sometimes analogies may prompt empirical research, this criterion is considered to be less important.

   This thesis is based on epidemiological data. However, there are many analogies regarding the effect of asthma on physical activity and of physical activity on asthma. In fact, it is common to hear individuals relate personal experiences about how swimming in particular 'cured' their asthma; or alternatively, that they experience asthma exacerbations during or after exercise.

It is essential to note that the criteria described by Bradford Hill are useful guidelines for assessing the evidence for causation, but all items are not essential when making a decision regarding causality. For example, 'temporality' is a key criterion that must be met in the assessment of a causal relationship, while 'plausibility' would strengthen the argument for causality and 'analogy' may or may not be useful. More recently, an American psychologist Dr Herman Staudenmayer proposed the addition of a tenth consideration: 'reversibility' (252). Reversibility posits that removal of the causal agent deletes the observed effect (252). Reversibility in this context may not be as straightforward as removing the exposure to remove the outcome. In fact, research conducted as part of this doctoral work explored the possibility of bidirectionality of this

relationship, as the predicting factor in this relationship is unclear. If it were possible, simply 'removing' asthma may not be sufficient to increase physical activity, and this is evident in that children with and without asthma appear to have similar levels of physical activity (205, 207, 209, 210). Similarly, exclusion of physical activity is unlikely to eliminate, or lead to a significant increase in asthma because of its multifactorial aetiology and various phenotypes.

9.6 External validity of this research program

This body of work analysed data collected from two population-based Australian cohorts of children and adolescents. Due to the LSAC's nationally representative sampling strategy of the LSAC, results from the LSAC data analyses may be extrapolated to the broader population of Australian children and adolescents. While the HealthNuts study was similarly a population-based cohort, the results may not be readily translatable to children living in rural or remote regions, those coming from a low socio-economic background, or international cohorts.

Australia enjoys certain social, political, and environmental advantages that impacts life and health. These sociodemographic properties limit the generalisability of the conclusions of this research to geographical regions with similar properties. Hence, while it may be reasonable to compare these findings to countries with similar socio-economic settings such as the UK, Europe or Norway, the results cannot be extrapolated to other regions of the world. Large areas of the globe are under-represented in research, and there remains a need to study these under-represented populations as diverse settings and other factors unique to the location may influence these associations.

CHAPTER TEN: Conclusion

10.1 Chapter introduction

In the concluding chapter of this thesis, I will reiterate the key findings of my doctoral work and demonstrate how my research has contributed to the fields of asthma and physical activity by filling pertinent knowledge gaps. I will also discuss the clinical and public health implications of this work and provide recommendations for future epidemiological research which may use this doctoral work as a foundation. Finally, I will close this thesis with some concluding remarks.

10.2 Chapter summaries and their contributions to the field

My thesis has contributed to the scientific fields of child and adolescent asthma and physical activity through the peer-reviewed publication of two systematic reviews, one meta-analysis and three original data analyses. These important contributions are summarised individually below.

10.2.1 Summary of the evidence on the effect of physical activity on asthma

10.2.1.1 Main finding and contribution to the field

This systematic review concluded that the evidence for the relationship between physical activity and asthma and lung function outcomes was highly inconsistent. There was insufficient evidence to suggest that physical activity has a long-term effect on the risk of asthma development in youth, and insufficient evidence to determine the longitudinal effects of physical activity on lung function in children.

This work emphasised a need for further high-quality, longitudinal studies to thoroughly explore these associations in youth, as an investigation of physical activity as a modifiable risk factor for asthma has the potential to be extremely important in the efforts to reduce the burden of asthma. However, a lack of research persists in this area, and particularly

in younger populations. Recent research has since endeavoured to address this gap in the literature (219), however it may be many years until more and improved evidence on this relationship is published.

10.2.2 Summary of the evidence on the effect of asthma on physical activity

10.2.2.1 Main finding and Contribution to the field

This systematic review collated evidence on the relationship between children and adolescents up to the age of 18 years with and without asthma, and investigated whether those with asthma were less likely to be physically active (as measured objectively) than their unaffected peers. The meta-analysis produced an overall mean difference of 0.01 (95%CI: −0.09–0.11) activity counts per minute. Therefore, I concluded that there was no evidence that children and adolescents with asthma engaged in different amounts of physical activity compared to those without asthma.

This systematic review and meta-analysis was the first to synthesise and quantify the evidence of the association between asthma and objectively measured physical activity in children and adolescents. Previous systematic reviews did not or were unable to stratify by age, resulting meta-analyses not specific to young populations. Further, other reviews did not focus on objective measures. My review found that asthma did not have an effect on physical activity in youth and again highlighted the scarcity of longitudinal cohort studies investigating the relationship between physical activity and asthma. In so doing, this systematic review formed the foundation for the data analyses within my doctoral work. This systematic review also instigated further research into these complex associations and has been referenced in numerous research papers and theses (210, 219, 253-264).

10.2.3 Summary of the evidence for a bi-directional relationship between asthma and physical activity

10.2.3.1 Main finding and contribution to the field

Having reviewed the existing literature of the relationship between asthma and physical activity, the question of bidirectionality of the associations persisted. Thus, within this research project, I used a novel strategy to investigate the possibility of bidirectionality between physical activity and the development and persistence of asthma in childhood and adolescence. The analysis used data collected from multiple waves of the LSAC study, when participants were between 6 and 14 years of age. I employed generalised structural equational modelling (GSEM) techniques in an attempt to elucidate whether asthma or physical activity was the causal antecedent of the other. The results of this analysis suggested that physical activity does not play an important role in the development or persistence of asthma. Equally, asthma was not found to have a longitudinal effect on physical activity.

Prior to my study, the possibility of bidirectionality in the relationship between asthma and physical activity had never been considered. Previous studies had only investigated the association in a single direction and were precluded from this type of cross-lagged analysis primarily by a lack of repeated data collection over time within a longitudinal study. Therefore, my analysis and the subsequent publication have contributed to the advancement of the field by analysing the relationship in an original and novel manner. This research further stressed the need for replication of these results using more robust data measurement, such as accelerometry. This study has been cited in other publications (219, 265).

10.2.4 Summary of the evidence on the effect of asthma on physical activity in children and adolescents

10.2.4.1 Main finding and contribution to the field

Using data from multiple waves of a nationally representative sample of children and adolescents, I investigated whether children and adolescents with asthma were less physically active than their unaffected peers at a number of important ages during the important transitional phase between childhood and adolescence. This analysis used

linear regression to investigate whether asthma was associated with reduced physical activity at 6, 8, 10, 12 or 14 years of age. While there was evidence that the amount of time spent in physical activity decreased with increasing age, I found no evidence that children and adolescents with asthma were less physically active than their unaffected peers at any of the ages examined.

Few epidemiological studies have investigated the association between asthma and physical activity at multiple timepoints throughout the important developmental stages from childhood to adolescence. The LSAC captured this data, enabling me to examine the physical activity engagement of children and adolescents with asthma compared to their unaffected peers. My study was the first to do this in a population of Australian children and adolescents. The primary contribution of this paper was that it examined multiple time points to identify if and when children and adolescents with asthma become less physically active than their unaffected peers. Previous studies have been limited in their ability to do so by a lack of repeated data collection over time. The findings of this paper provided epidemiological evidence that, while the average time spent in physical activity decreases with age, Australian children with asthma do not appear to be less physically active than their unaffected peers at any age throughout childhood and adolescence. This may indicate that, in Australia, children with asthma are well managed. However, this study collected physical activity data through parental and self-reporting, and therefore could be improved by using accelerometry as a tool for the measurement of physical activity.

10.2.5 Summary of the evidence for the relationship between asthma, and objectively measured physical activity in children

10.2.5.1 Main finding and contribution to the field

Drawing from the lessons and limitations of the LSAC analyses, this final data analysis utilised accelerometry as a means of physical activity data collection in the 6-year-old participants of the HealthNuts study. Accelerometry was used to overcome the problem of potential measurement error introduced through parental and self-reporting. In this

final analysis of 391 young children I found no evidence that having asthma or wheeze at age 4 reduced the amount of time spent in physical activity at 6 years of age.

This research project was original as it was one of the first epidemiological studies to examine the relationship between asthma and subsequent objectively measured physical activity in children as young as 6 years of age. Despite the young age of the participants and the objective collection of physical activity data, this study confirmed the results of my previous systematic review and data analyses; asthma and wheeze was not found to be associated with time spent in physical activity, either cross-sectionally or longitudinally. Thus, this study again provided encouraging evidence that, at least within this Australian setting and this age group, the policies and strategies currently in place to control and manage asthma are successfully diminishing the impact of asthma on physical activity.

10.3 Implications and recommendations

The findings and conclusions drawn from my doctoral research appear to deviate from the widely accepted belief that an association between asthma and physical activity exists. Alternative explanations for these null results are scrutinised in the Discussion chapter of this thesis (see Chapter Nine), however, this critique demonstrated that these conclusions are less likely a result of bias, confounding or chance. Rather, the consistency of the null results, despite variations in the age groups examined, and definitions and methods used for the assessment of exposures and outcomes, provides strong evidence that these findings may in fact reflect truth. As such, the significance of this work and its impact on recommendations for future research are exceptional, yet equally valid.

10.3.1 Significance for clinicians and policy

Despite these results indicating that there is no association between asthma and time spent in physical activity or physical activity and the development or persistence of asthma, this research has significant implications for clinicians and developers of public health policy. In the first instance, the lack of evidence for an adverse association between

asthma and physical activity should be celebrated. Although this doctoral work was unable to investigate asthma control and severity, the findings suggests that clinicians are adequately and appropriately managing asthma in this population, allowing children and adolescents with asthma to engage in physical activities to the same extent as their unaffected peers. Consequently, there is no need for public health policy and promotion to further target youth with asthma in Australia.

Then again, I also found that physical activity was not associated with the development or persistence of asthma. Whilst having identified an association would have indicated that physical activity may be a modifiable risk factor for the development or persistence of asthma, this was not found to be the case in children and adolescents in Australia. So although there is insufficient evidence to suggest that clinicians should recommend physical activity as a means of prevention or management of asthma specifically, the lack of evidence to suggest that an asthma diagnosis is a barrier against physical activity means that clinicians should continue to encourage physical activity in children with asthma for its other health benefits.

10.3.2 Future research recommendations

This doctoral work investigated whether asthma was a causal antecedent of low physical activity and whether low physical activity was a causal antecedent of asthma development or persistence and lower lung function in youth.

The evidence for physical activity as a modifiable risk factor for the development or persistence of asthma was inconclusive within this doctoral work. However, my research has emphasised the need for more longitudinal studies to examine this association using more robust measurements and taking into account other potentially confounding, mediating or modifying variables. Specifically, the role of BMI, diet and sedentary time should be thoroughly examined. Evidence for a positive association between physical activity and the development of asthma has important implications and it is therefore critical that this association is further explored. Further longitudinal research should also take into account the potential effect of physical activity on asthma control, severity, and lung function in individuals with asthma. For example, future research may investigate

whether higher levels of physical activity improve lung function over time, thereby strengthening the lungs and reducing the severity of asthma symptoms. Alternatively, it may also be important to investigate whether increased levels of physical activity agitate the airways leading to an increased requirement for asthma medications.

This doctoral work also reviewed the evidence for the relationship between asthma and physical activity, both cross sectionally and longitudinally. I repeatedly obtained results that indicated asthma was not a factor resulting in lower levels of physical activity. Should asthma act as a barrier to physical activity as was previously hypothesised, a greater public health response would be required in order to promote the benefits of physical activity in youths with asthma. In addition, it is critical that future studies examine the effect of BMI in more detail. The treatment of BMI as either a confounding or modifying variable may have an important influence on the results obtained in an analysis. In future studies, BMI should be considered as either an effect modifier or a mediator. BMI appears to interact with asthma to have a detrimental effect on physical activity. Thus, a public health response is required to address the disparities in physical activity in overweight children with asthma and encourage increased engagement in this group of children.

Further, the possibility of a bidirectional association between physical activity and asthma warrants additional investigation. Although my study was the first of its kind to investigate this possibility due to the structure of the LSAC data collection, future studies should aim to replicate this analysis with a robust methodology, repeated longitudinal data collection, and valid, reliable assessment techniques. Additionally, a replication study should consider including BMI as an effect modifier or mediator in these models. Again, obtaining results that indicate a bidirectional relationship between physical activity and asthma would have far-reaching implications. Public health policy makers and clinicians would need to re-evaluate the physical activity recommendations in the context of safety and acceptability for individuals with asthma.

To summarise, based on the findings of my doctoral work, it is my recommendation that future epidemiological studies endeavour to utilise standardised, objective measurements and improved analytical models to confirm of the null results seen in many of my studies and further advance this area of research.

10.4 Conclusion

I commenced this doctoral work with the aim of investigating the existence and direction of the relationship between asthma and physical activity in youth. The body of work I undertook produced a systematic review and meta-analysis of the evidence for the association between asthma and physical activity in childhood and adolescence, followed by a second systematic review in which I synthesised the evidence for an association between physical activity and subsequent asthma and lung function outcomes in childhood and adolescence. Subsequently, I undertook multiple data analyses using data from two prospective cohorts of Australian children: The Longitudinal Study of Australian Children (LSAC) and the HealthNuts study. The key findings of this body of research can be summarised as follows:

- The relationship between asthma and physical activity in youth does not appear to be bidirectional.
- There is strong evidence to suggest that asthma does not have a detrimental effect on physical activity at any age in childhood or adolescence in Australia.
- Physical activity is not associated with the development or persistence of asthma in children and adolescents.

In conclusion, my doctoral research has produced evidence which has filled some important gaps in our understanding of the relationship between asthma and physical activity in children and adolescent populations. My work has also emphasised the need for more longitudinal studies with objective measures that conform to standardised collection, analytical and interpretative guidelines. Additionally, more careful investigation of other potentially modifying factors, such as BMI and asthma severity are required to enhance our understanding of these relationships. In future, research should overcome these challenges in order to extensively explore the complex, interrelated relationship between asthma, physical activity and other factors. Such research will have great public health benefit by informing recommendations for physical activity and asthma, thereby reducing the burden of these conditions.

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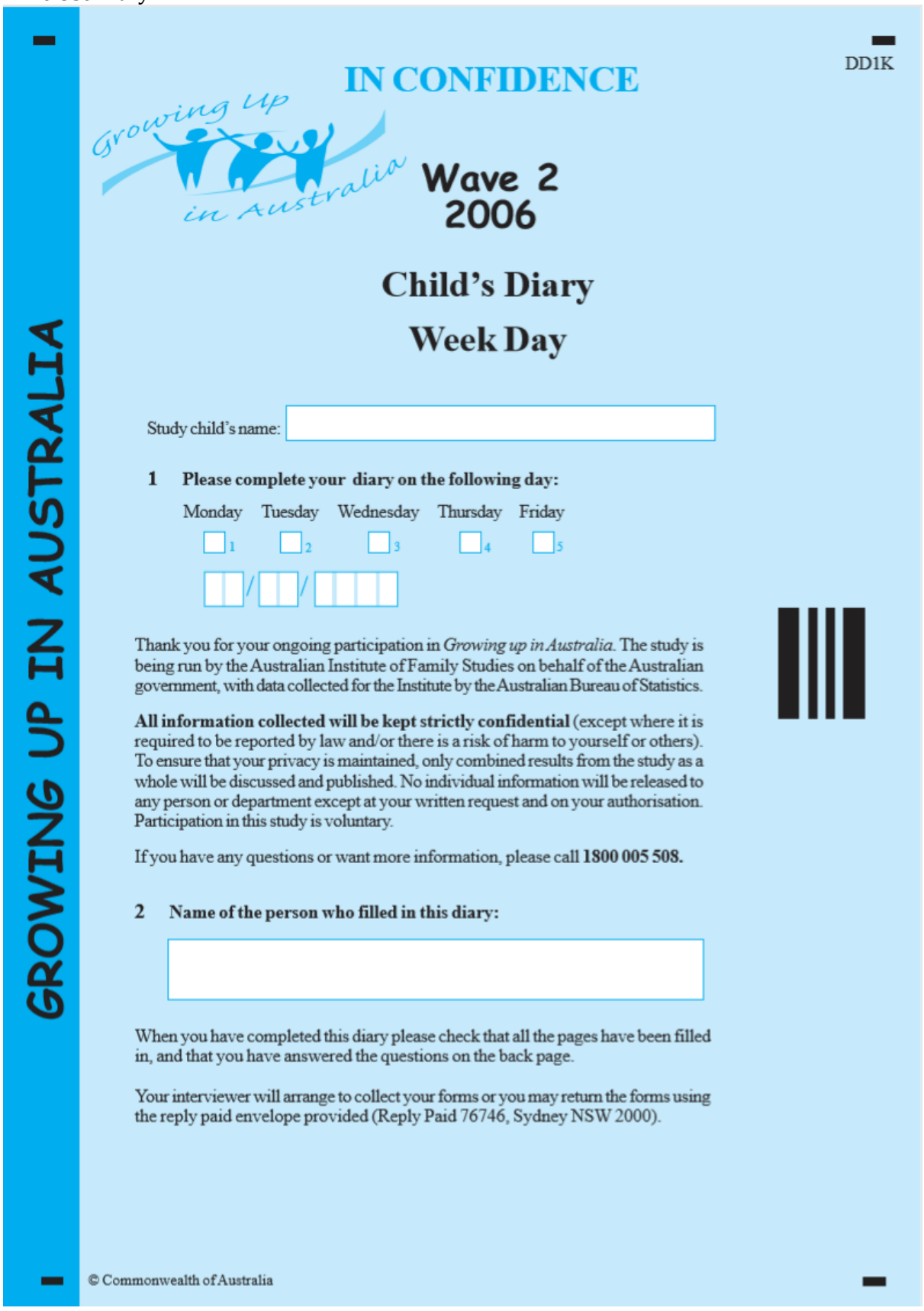
Appendices

Appendix 1: *Growing Up in Australia*: The Longitudinal Study of Australian Children Questionnaires

The length of the LSAC questionnaires made them unfeasible for reproduction in the appendices of this thesis. All LSAC data collection instruments are available on the LSAC website. A link to the study documentation is included:

https://growingupinaustralia.gov.au/data-and-documentation/study-questionnaires/downloads

Appendix 2: *Growing Up in Australia*: The Longitudinal Study of Australian Children Wave 2 Time Use Diary



GROWING UP IN AUSTRALIA

DD1K

IN CONFIDENCE

Growing up in Australia

Wave 2
2006

Child's Diary
Week Day

Study child's name:

1 Please complete your diary on the following day:

Monday ☐1 Tuesday ☐2 Wednesday ☐3 Thursday ☐4 Friday ☐5

☐☐/☐☐/☐☐☐☐

Thank you for your ongoing participation in *Growing up in Australia*. The study is being run by the Australian Institute of Family Studies on behalf of the Australian government, with data collected for the Institute by the Australian Bureau of Statistics.

All information collected will be kept strictly confidential (except where it is required to be reported by law and/or there is a risk of harm to yourself or others). To ensure that your privacy is maintained, only combined results from the study as a whole will be discussed and published. No individual information will be released to any person or department except at your written request and on your authorisation. Participation in this study is voluntary.

If you have any questions or want more information, please call **1800 005 508.**

2 Name of the person who filled in this diary:

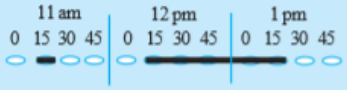
When you have completed this diary please check that all the pages have been filled in, and that you have answered the questions on the back page.

Your interviewer will arrange to collect your forms or you may return the forms using the reply paid envelope provided (Reply Paid 76746, Sydney NSW 2000).

INSTRUCTIONS

This diary covers what **your child has been doing** over the 24 hours that started at 4 AM today and ends at 4 AM tomorrow.

Each oval in the diary grid represents 15 minutes. In the example below, the activity occurred between 11:15 and 11:30, and then again between 12:15 and 1:30.



For each 15 minutes, please draw a line across the ovals that show:

- what your child was doing, including any travel involved (**white rows**)
- where he or she was (**light shaded section**)
- who else was present (**medium shaded section**)
- whether an activity was part of the child's homework (**dark shaded section**)

Mark at least one row in each of the white, light shaded and medium shaded sections for each quarter hour.

The **white rows** show what your child was doing, as well as any travel involved. Most parents mark only 1 or 2 activities per time slot, but you can mark other rows if your child did more than one thing during the 15 minutes. Please do not mark more than four categories for any one quarter hour. Remember to also mark the Travel section if there was any travel involved.

For example:

- Reading a book in bed is both 'Awake in bed' and 'Reading or looking at book by self'
- Sleeping in the car is both 'Sleeping, napping' and 'Travel in car'

The **light shaded section** shows where your child was. If your child moved from one place to another during a 15 minute time slot, please mark both locations.

The **medium shaded section** at the bottom of the page shows who was in the same room, or who was near the child if the child was outside. If your child was with more than one person, please mark all that apply.

The **dark shaded section** at the bottom of the page shows whether an activity was done for, or as part of, the child's homework.

You can choose to fill in the diary:

- 2 or 3 times a day **or**
- all at once when your child goes to bed **or**
- in the morning after the diary day.

Important

Please mark like this only: **or**

- This form will be read using electronic equipment.
- If you make a mistake, please erase the pencil mark fully.
- Use **black pencil** only when completing this form - do not use ballpoint or felt tip pen.

When you have filled in the diary, please complete the questions on the back page.

EXAMPLE

Below is an example of how the diary would be filled in for a child's morning.

Joshua woke at 6.30am and dressed himself. He then watched the morning news with his father. At 7.00am he had breakfast with his parents and baby brother. After breakfast he helped his mother clear the breakfast dishes from the table and at 7:45am went outside to play with the family dog. At 8.15am his father went outside to tell Joshua it was time to leave for school. Joshua became upset because he didn't want to stop playing with the dog. His father calmed him down and they left home at 8.30am to drive to school. During the drive to school Joshua read out loud to his father from a book he had brought home from school the previous day. His father dropped him off at school ten minutes later and gave him a hug goodbye before going on to work.

		Night		Morning			
		4 am	5 am	6 am	7 am	8 am	9 am
		0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45
What was the child doing?	Not sure what child was doing					●	●
	Sleeping, napping	●	●	●			
	Awake in bed						
	Eating and drinking				●		
	Bathing, dressing, hair care, health care			●			
	Doing nothing, bored/restless						
	Crying, upset, tantrum					●	
	Arguing, fighting, destroying things						
	Being held, cuddled, comforted, soothed						
	Being reprimanded, corrected						
	Watching TV, video, DVD, movie			●			
	Listening to tapes, CDs, radio, music						
	Using computer/computer game						
	Being read to, told a story, or sung to						
	Reading or looking at book by self					●	
	Quiet free play (e.g. board game, craft, dress-ups)						
	Active free play (e.g. running, climbing, ball game)				●		
	Helping with chores, jobs				●		
	Visiting people, special event, outing						
	Organised sport/physical activity (e.g. swim, dance, Auskick)						
	Other organised lesson/activity (e.g. music, drama)						
Travel	Walking (for travel or fun)						
	Riding bicycle, scooter, roller blades etc. (for travel or fun)						
	Travel in car					●	
	Travel on public transport						
	Being taken places with adult (e.g. shopping)						
		4 am	5 am	6 am	7 am	8 am	9 am
		0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45	0 15 30 45
Where was the child?	Own home, indoors	●	●	●	●		
	Own home, outdoors				●	●	
	School, after/before school care						●
	Other, indoors						
	Other, outdoors					●	
In the same room, nearby if outside	Alone	●	●	●			
	Mother, step mother				●		
	Father, step father				●	●	
	Grandparent(s)/other adult relative(s)						
	Brother(s), sister(s), other children				●		●
	Other adult(s)						●
	Dog, cat or other pet (not fish)					●	
	Was this activity done for or as part of homework					●	

K2D?!

!= 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

		Night				Morning											
		4 am				5 am				6 am				7 am			
		0	15	30	45	0	15	30	45	0	15	30	45	0	15	30	45
What was the child doing?	Not sure what child was doing	?=A01															
	Sleeping, napping	A02															
	Awake in bed	A03															
	Eating and drinking	A04															
	Bathing, dressing, hair care, health care	A05															
	Doing nothing, bored/restless	A06															
	Crying, upset, tantrum	A07															
	Arguing, fighting, destroying things	A08															
	Being held, cuddled, comforted, soothed	A09															
	Being reprimanded, corrected	A10															
	Watching TV, video, DVD, movie	A11															
	Listening to tapes, CDs, radio, music	A12															
	Using computer/computer game	A13															
	Being read to, told a story, or sung to	A14															
	Reading or looking at book by self	A15															
	Quiet free play (e.g. board game, craft, dress-ups)	A16															
	Active free play (e.g. running, climbing, ball game)	A17															
	Helping with chores, jobs	A18															
	Visiting people, special event, outing	A19															
	Organised sport/physical activity (e.g. swim, dance, Auskick)	A20															
	Other organised lesson/activity (e.g. music, drama)	A21															
Travel	Walking (for travel or fun)	B01															
	Riding bicycle, scooter, roller blades etc. (for travel or fun)	B02															
	Travel in car	B03															
	Travel on public transport	B04															
	Being taken places with adult (e.g. shopping)	B05															
		4 am				5 am				6 am				7 am			
		0	15	30	45	0	15	30	45	0	15	30	45	0	15	30	45
Where was the child?	Own home, indoors	C01															
	Own home, outdoors	C02															
	School, after/before school care	C03															
	Other, indoors	C04															
	Other, outdoors	C05															
In the same room, nearby if outside	Alone	D01															
	Mother, step mother	D02															
	Father, step father	D03															
	Grandparent(s)/other adult relative(s)	D04															
	Brother(s), sister(s), other children	D05															
	Other adult(s)	D06															
	Dog, cat or other pet (not fish)	D07															
	Was this activity done for or as part of homework	E01															

!=25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48

Afternoon

10 am 0 15 30 45	11 am 0 15 30 45	12 pm 0 15 30 45	1 pm 0 15 30 45	2 pm 0 15 30 45	3 pm 0 15 30 45		
○○○○	○○○○	○○○○	○○○○	○○○○	○	?=A01	Not sure what child was doing	What was the child doing?
○○○○	○○○○	○○○○	○○○○	○○○○	○	A02	Sleeping, napping	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A03	Awake in bed	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A04	Eating and drinking	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A05	Bathing, dressing, hair care, health care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A06	Doing nothing, bored/restless	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A07	Crying, upset, tantrum	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A08	Arguing, fighting, destroying things	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A09	Being held, cuddled, comforted, soothed	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A10	Being reprimanded, corrected	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A11	Watching TV, video, DVD, movie	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A12	Listening to tapes, CDs, radio, music	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A13	Using computer/computer game	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A14	Being read to, told a story, or sung to	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A15	Reading or looking at book by self	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A16	Quiet free play (e.g. board game, craft, dress-ups)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A17	Active free play (e.g. running, climbing, ball game)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A18	Helping with chores, jobs	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A19	Visiting people, special event, outing	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A20	Organised sport/physical activity (e.g. swim, dance, Auskick)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A21	Other organised lesson/activity (e.g. music, drama)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B01	Walking (for travel or fun)	Travel
○○○○	○○○○	○○○○	○○○○	○○○○	○	B02	Riding bicycle, scooter, roller blades etc. (for travel or fun)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B03	Travel in car	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B04	Travel on public transport	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B05	Being taken places with adult (e.g. shopping)	
10 am 0 15 30 45	11 am 0 15 30 45	12 pm 0 15 30 45	1 pm 0 15 30 45	2 pm 0 15 30 45	3 pm 0 15 30 45			
○○○○	○○○○	○○○○	○○○○	○○○○	○	C01	Own home, indoors	Where was the child?
○○○○	○○○○	○○○○	○○○○	○○○○	○	C02	Own home, outdoors	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C03	School, after/before school care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C04	Other, indoors	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C05	Other, outdoors	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D01	Alone	In the same room, nearby if outside
○○○○	○○○○	○○○○	○○○○	○○○○	○	D02	Mother, step mother	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D03	Father, step father	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D04	Grandparent(s)/other adult relative(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D05	Brother(s), sister(s), other children	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D06	Other adult(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D07	Dog, cat or other pet (not fish)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	E01	Was this activity done for or as part of homework	

K2D?!

!= 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72

		Afternoon				Evening											
		4 pm				5 pm				6 pm				7 pm			
		0	15	30	45	0	15	30	45	0	15	30	45	0	15	30	45
What was the child doing?	Not sure what child was doing	?=A01															
	Sleeping, napping	A02															
	Awake in bed	A03															
	Eating and drinking	A04															
	Bathing, dressing, hair care, health care	A05															
	Doing nothing, bored/restless	A06															
	Crying, upset, tantrum	A07															
	Arguing, fighting, destroying things	A08															
	Being held, cuddled, comforted, soothed	A09															
	Being reprimanded, corrected	A10															
	Watching TV, video, DVD, movie	A11															
	Listening to tapes, CDs, radio, music	A12															
	Using computer/computer game	A13															
	Being read to, told a story, or sung to	A14															
	Reading or looking at book by self	A15															
	Quiet free play (e.g. board game, craft, dress-ups)	A16															
	Active free play (e.g. running, climbing, ball game)	A17															
	Helping with chores, jobs	A18															
	Visiting people, special event, outing	A19															
	Organised sport/physical activity (e.g. swim, dance, Auskick)	A20															
	Other organised lesson/activity (e.g. music, drama)	A21															
Travel	Walking (for travel or fun)	B01															
	Riding bicycle, scooter, roller blades etc. (for travel or fun)	B02															
	Travel in car	B03															
	Travel on public transport	B04															
	Being taken places with adult (e.g. shopping)	B05															
		4 pm				5 pm				6 pm				7 pm			
		0	15	30	45	0	15	30	45	0	15	30	45	0	15	30	45
Where was the child?	Own home, indoors	C01															
	Own home, outdoors	C02															
	School, after/before school care	C03															
	Other, indoors	C04															
	Other, outdoors	C05															
In the same room, nearby if outside	Alone	D01															
	Mother, step mother	D02															
	Father, step father	D03															
	Grandparent(s)/other adult relative(s)	D04															
	Brother(s), sister(s), other children	D05															
	Other adult(s)	D06															
	Dog, cat or other pet (not fish)	D07															
	Was this activity done for or as part of homework	E01															

!= 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96

Night								
10 pm 0 15 30 45	11 pm 0 15 30 45	12 am 0 15 30 45	1 am 0 15 30 45	2 am 0 15 30 45	3 am 0 15 30 45			
						?=A01	Not sure what child was doing	What was the child doing?
						A02	Sleeping, napping	
						A03	Awake in bed	
						A04	Eating and drinking	
						A05	Bathing, dressing, hair care, health care	
						A06	Doing nothing, bored/restless	
						A07	Crying, upset, tantrum	
						A08	Arguing, fighting, destroying things	
						A09	Being held, cuddled, comforted, soothed	
						A10	Being reprimanded, corrected	
						A11	Watching TV, video, DVD, movie	
						A12	Listening to tapes, CDs, radio, music	
						A13	Using computer/computer game	
						A14	Being read to, told a story, or sung to	
						A15	Reading or looking at book by self	
						A16	Quiet free play (e.g. board game, craft, dress-ups)	
						A17	Active free play (e.g. running, climbing, ball game)	
						A18	Helping with chores, jobs	
						A19	Visiting people, special event, outing	
						A20	Organised sport/physical activity (e.g. swim, dance, Auskick)	
						A21	Other organised lesson/activity (e.g. music, drama)	
						B01	Walking (for travel or fun)	Travel
						B02	Riding bicycle, scooter, roller blades etc. (for travel or fun)	
						B03	Travel in car	
						B04	Travel on public transport	
						B05	Being taken places with adult (e.g. shopping)	
10 pm 0 15 30 45	11 pm 0 15 30 45	12 am 0 15 30 45	1 am 0 15 30 45	2 am 0 15 30 45	3 am 0 15 30 45			
						C01	Own home, indoors	Where was the child?
						C02	Own home, outdoors	
						C03	School, after/before school care	
						C04	Other, indoors	
						C05	Other, outdoors	
						D01	Alone	In the same room, nearby if outside
						D02	Mother, step mother	
						D03	Father, step father	
						D04	Grandparent(s)/other adult relative(s)	
						D05	Brother(s), sister(s), other children	
						D06	Other adult(s)	
						D07	Dog, cat or other pet (not fish)	
						E01	Was this activity done for or as part of homework	

3 For the day described in this diary, how often did this child eat or drink the following?
(Tick one box per row only)

		Not at all	Once	Twice	Three times	Four or more times	Don't know
K2DBP301	Fresh fruit	1	2	3	4	5	-2
K2DBP302	Fruit juice	1	2	3	4	5	-2
K2DBP303	Cooked vegetables	1	2	3	4	5	-2
K2DBP304	Raw vegetables or salad	1	2	3	4	5	-2
K2DBP305	Meat pie, hamburger, hot dog, sausage or sausage roll	1	2	3	4	5	-2
K2DBP306	Hot chips or french fries	1	2	3	4	5	-2
K2DBP307	Potato chips or savoury snacks such as 'Twisties'	1	2	3	4	5	-2
K2DBP308	Biscuits, doughnuts, cake, pie or chocolate	1	2	3	4	5	-2
K2DBP309	Bread	1	2	3	4	5	-2
K2DBP310	Full cream milk or full cream milk products	1	2	3	4	5	-2
K2DBP311	Skim milk or skim milk products	1	2	3	4	5	-2
K2DBP312	Water	1	2	3	4	5	-2
K2DBP313	Soft drink or cordial, not diet	1	2	3	4	5	-2
K2DBP314	Diet soft drink or cordial	1	2	3	4	5	-2
K2DBP315	Breakfast	1	2	3	4	5	-2

4 What is your relationship to the study child?

K2DBP4

- Mother 1
- Father 2
- Grandmother 3
- Other relative 4
- Carer/babysitter 5
- Other 6

5 When did you fill in this diary?

K2DBP5

- More than 3 times a day 1
- 2 to 3 times a day 2
- Once, when the child went to bed 3
- Once, the next morning 4
- At a later time 5

6 If you did not fill in the diary for the day allocated, what day does the diary relate to?

K2DBP6 ☐☐/☐☐/☐☐☐☐

7 What day of the week does the diary relate to?

K2DBP7

Monday 1 | Tuesday 2 | Wednesday 3 | Thursday 4 | Friday 5

8 How many hours of paid work did you do on this day?

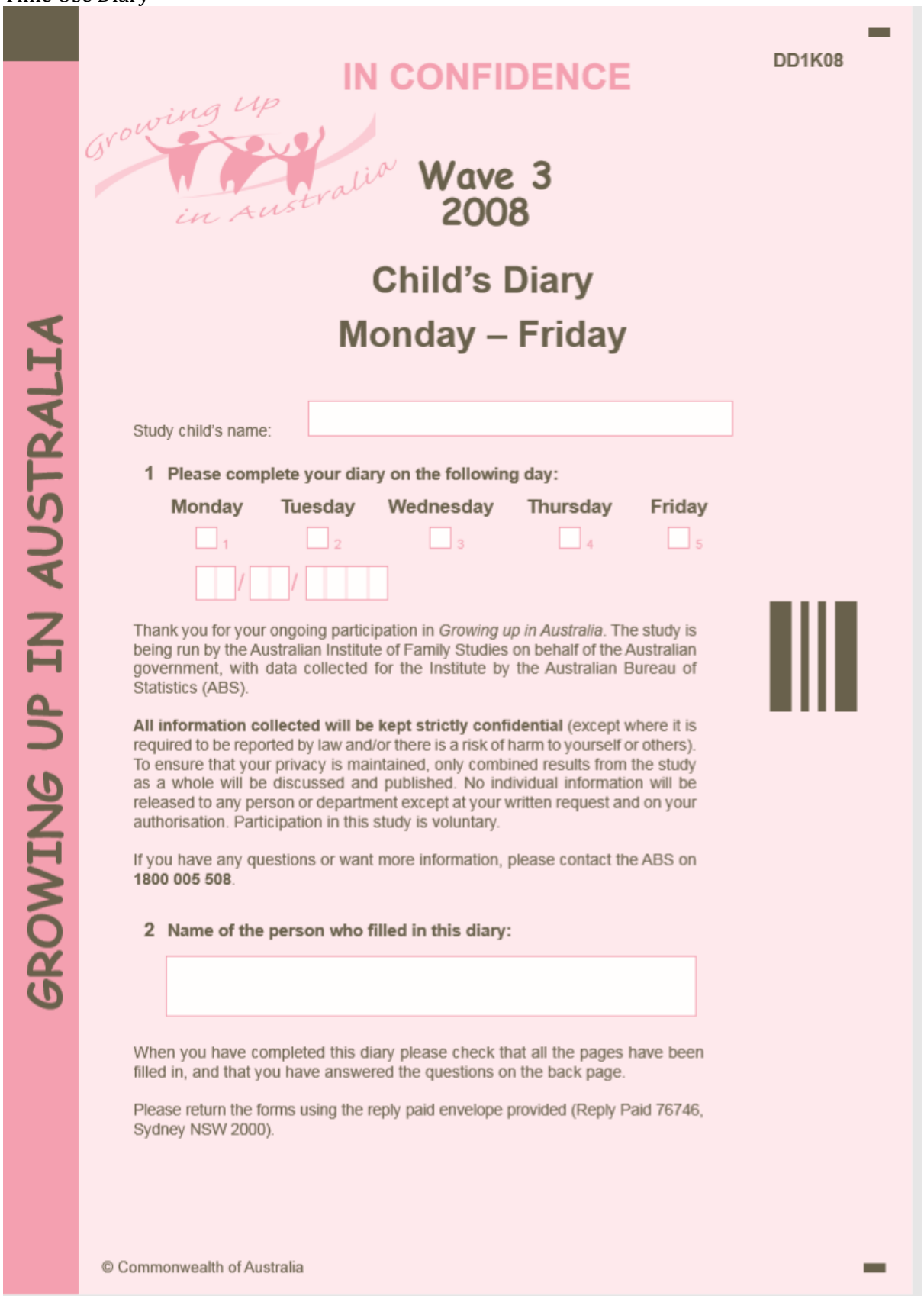
K2DBP8 ☐☐

9 What kind of day is described in this diary?

Tick all that apply

- K2DBP901 An ordinary day ☐
- K2DBP902 A holiday or a family celebration ☐
- K2DBP903 A school holiday ☐
- K2DBP904 A parent took time off work ☐
- K2DBP905 Our family dealt with a crisis ☐
- K2DBP906 We had guests staying with us ☐
- K2DBP907 A family member was away ☐
- K2DBP908 I was ill ☐
- K2DBP909 This child was ill ☐
- K2DBP910 This child was a great deal more stressed than normal ☐
- K2DBP911 An unusual day for another reason ☐

Appendix 3: *Growing Up in Australia:* The Longitudinal Study of Australian Children Wave 3 Time Use Diary



GROWING UP IN AUSTRALIA

DD1K08

IN CONFIDENCE

Growing up in Australia

Wave 3
2008

Child's Diary
Monday – Friday

Study child's name:

1 Please complete your diary on the following day:

Monday	Tuesday	Wednesday	Thursday	Friday
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

☐☐ / ☐☐ / ☐☐☐☐

Thank you for your ongoing participation in *Growing up in Australia*. The study is being run by the Australian Institute of Family Studies on behalf of the Australian government, with data collected for the Institute by the Australian Bureau of Statistics (ABS).

All information collected will be kept strictly confidential (except where it is required to be reported by law and/or there is a risk of harm to yourself or others). To ensure that your privacy is maintained, only combined results from the study as a whole will be discussed and published. No individual information will be released to any person or department except at your written request and on your authorisation. Participation in this study is voluntary.

If you have any questions or want more information, please contact the ABS on **1800 005 508**.

2 Name of the person who filled in this diary:

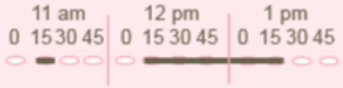
When you have completed this diary please check that all the pages have been filled in, and that you have answered the questions on the back page.

Please return the forms using the reply paid envelope provided (Reply Paid 76746, Sydney NSW 2000).

INSTRUCTIONS

This diary covers what **your child has been doing** over the 24 hours that started at 4am today and ends at 4am tomorrow.

Each oval in the diary grid represents 15 minutes. In the example (right), the activity occurred between 11:15am and 11:30am, and then again between 12:15pm and 1:30pm.



For each 15 minutes, please draw a line across the ovals that show:

- **What your child was doing, including any travel involved (white section)**
  Most parents mark only 1 or 2 activities per time slot, but you can mark other rows if your child did more than one thing during the 15 minutes. Please do not mark more than four categories for any one quarter hour. Remember to also mark the Travel section if there was any travel involved.

  For example:
  - Reading a book in bed would be marked as 'Awake in bed' and 'Reading or looking at book by self'.
  - Sleeping in the car would be marked as 'Sleeping, napping' and 'Travel in car'.

- **Where your child was (light shaded section)**
  This section shows where your child was. If your child moved from one place to another during a 15 minute time slot, please mark both locations. If the child was travelling for an entire 15 minute time slot, there is no need to mark where they were during this period.

- **Who else was present with your child (medium shaded section)**
  This section shows who was in the same room, or who was near the child if the child was outside. If your child was with more than one person, please mark all that apply.

- **Whether an activity was part of the child's homework (dark shaded section)**
  This section shows whether an activity was done for, or as part of, the child's homework.

Mark at least one row in each of the white, light shaded and medium shaded sections for each quarter hour.

You may wish to involve your child when completing this diary. Talking to your child about what he/she has been doing during the 24 hour period may help you to record the activities that occurred when you were not nearby (e.g. when your child was at a friend's house). On the last page, you can indicate if your child was involved in completing the diary.

If you are unsure about what your child was doing at times during the nominated day, please mark the 'Not sure what child was doing' category at the top of the diary page.

If you are not sure what your child was doing for the entire 24 hour period (i.e. he/she was being cared for by someone else), please fill in the diary on the same day of the following week. For example, if it is not possible to complete the diary for a Monday, please do the diary on the next Monday.

You can choose to fill in the diary:
- 2 or 3 times a day **or**
- all at once at the end of the day **or**
- in the morning after the diary day.

Important

Please mark like this only:

or

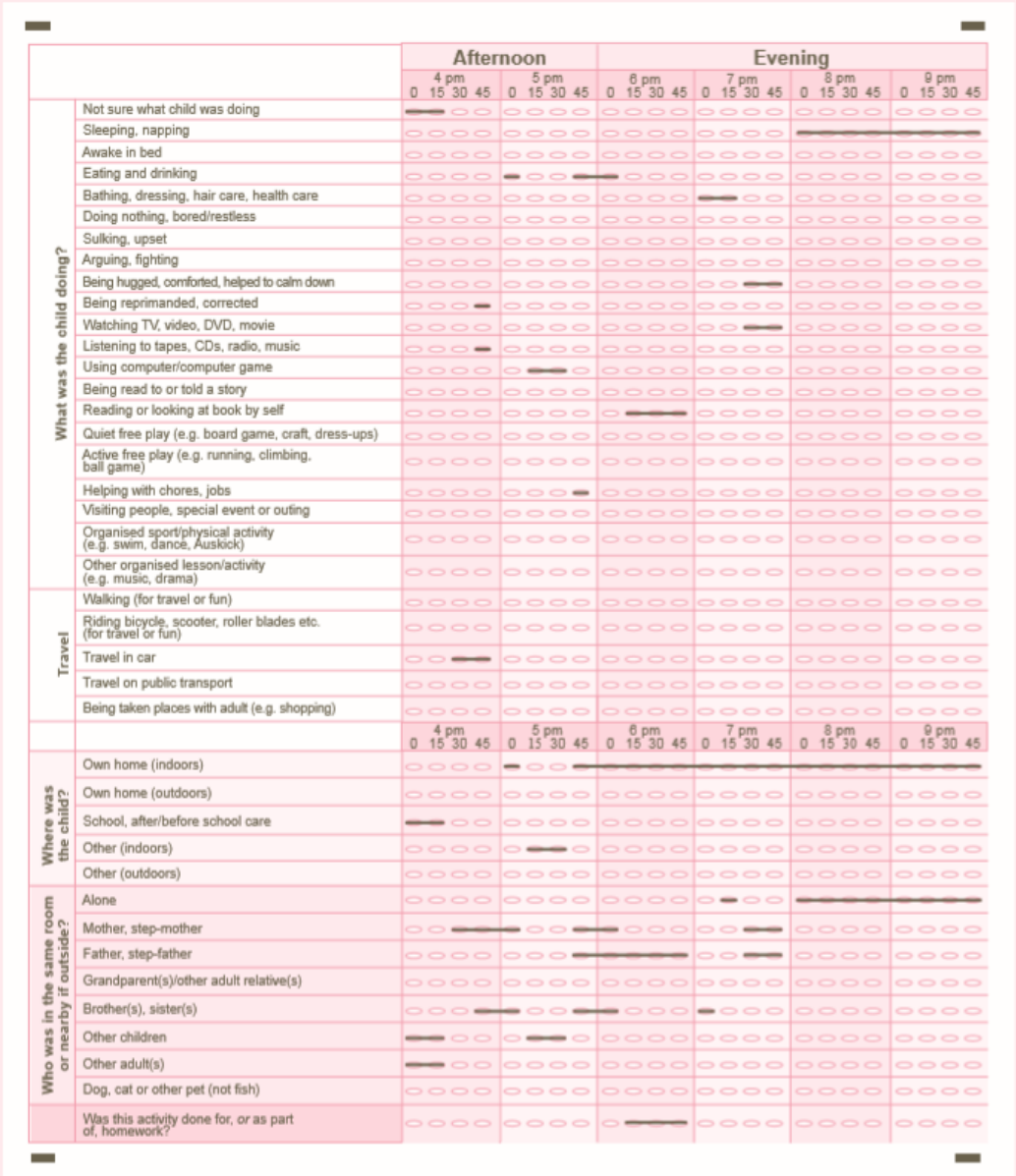
- This form will be read using electronic equipment.
- Use **black pencil** only when completing this form - do not use ballpoint or felt tip pen.
- If you make a mistake, please erase the pencil mark fully.

When you have filled in the diary, please complete the questions on the back page.

EXAMPLE

Below is an example of how the diary would be filled in for a child's afternoon.

Tamika attended after school care until her mother picked her up at 4.30pm (Tamika could not remember what she had done at after school care). Tamika and her mother drove to pick up her baby brother from child care at about 4.45pm. On the way home, Tamika turned up the radio, waking her brother who had fallen asleep in the back seat. He began to cry. Tamika's mother turned the radio down and talked with Tamika about the need to be mindful of noise when her brother is sleeping. They got home at 5pm and, after having a quick snack, Tamika went next door at 5.15pm to play with her friend (Tamika later recalled that they played on the computer) until her father called her home at 5.45pm to have dinner. Tamika set the table and the family ate dinner until 6.15pm. Tamika spent the next 45 minutes completing homework and reading to herself, with her father cleaning up nearby and her mother preparing her brother for bed. Tamika said goodnight to her brother at 7.00pm, then had a shower, cleaned her teeth and changed into her pyjamas. Tamika snuggled up on the couch with her mother and father at 7.30pm to watch her favourite television program and went to bed at 8.00pm.



K3D?!

!= 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

		Night		Morning			
		4 am 0 15 30 45	5 am 0 15 30 45	6 am 0 15 30 45	7 am 0 15 30 45	8 am 0 15 30 45	9 am 0 15 30 45
What was the child doing?	Not sure what child was doing	?=A01					
	Sleeping, napping	A02					
	Awake in bed	A03					
	Eating and drinking	A04					
	Bathing, dressing, hair care, health care	A05					
	Doing nothing, bored/restless	A06					
	Sulking, upset	A07					
	Arguing, fighting	A08					
	Being hugged, comforted, helped to calm down	A09					
	Being reprimanded, corrected	A10					
	Watching TV, video, DVD, movie	A11					
	Listening to tapes, CDs, radio, music	A12					
	Using computer/computer game	A13					
	Being read to or told a story	A14					
	Reading or looking at book by self	A15					
	Quiet free play (e.g. board game, craft, dress-ups)	A16					
	Active free play (e.g. running, climbing, ball game)	A17					
	Helping with chores, jobs	A18					
	Visiting people, special event or outing	A19					
	Organised sport/physical activity (e.g. swim, dance, Auskick)	A20					
	Other organised lesson/activity (e.g. music, drama)	A21					
Travel	Walking (for travel or fun)	B01					
	Riding bicycle, scooter, roller blades etc. (for travel or fun)	B02					
	Travel in car	B03					
	Travel on public transport	B04					
	Being taken places with adult (e.g. shopping)	B05					
		4 am 0 15 30 45	5 am 0 15 30 45	6 am 0 15 30 45	7 am 0 15 30 45	8 am 0 15 30 45	9 am 0 15 30 45
Where was the child?	Own home (indoors)	C01					
	Own home (outdoors)	C02					
	School, after/before school care	C03					
	Other (indoors)	C04					
	Other (outdoors)	C05					
Who was in the same room or nearby if outside?	Alone	D01					
	Mother, step-mother	D02					
	Father, step-father	D03					
	Grandparent(s)/other adult relative(s)	D04					
	Brother(s), sister(s)	D05					
	Other children	D06					
	Other adult(s)	D07					
	Dog, cat or other pet (not fish)	D08					
	Was this activity done for, *or* as part of, homework?	E01					

!=25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48

DD1K08

Afternoon

10 am 0 15 30 45	11 am 0 15 30 45	12 pm 0 15 30 45	1 pm 0 15 30 45	2 pm 0 15 30 45	3 pm 0 15 30 45		
○○○○	○○○○	○○○○	○○○○	○○○○	○	?=A01	Not sure what child was doing	What was the child doing?
○○○○	○○○○	○○○○	○○○○	○○○○	○	A02	Sleeping, napping	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A03	Awake in bed	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A04	Eating and drinking	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A05	Bathing, dressing, hair care, health care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A06	Doing nothing, bored/restless	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A07	Sulking, upset	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A08	Arguing, fighting	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A09	Being hugged, comforted, helped to calm down	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A10	Being reprimanded, corrected	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A11	Watching TV, video, DVD, movie	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A12	Listening to tapes, CDs, radio, music	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A13	Using computer/computer game	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A14	Being read to or told a story	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A15	Reading or looking at book by self	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A16	Quiet free play (e.g. board game, craft, dress-ups)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A17	Active free play (e.g. running, climbing, ball game)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A18	Helping with chores, jobs	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A19	Visiting people, special event or outing	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A20	Organised sport/physical activity (e.g. swim, dance, Auskick)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A21	Other organised lesson/activity (e.g. music, drama)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B01	Walking (for travel or fun)	Travel
○○○○	○○○○	○○○○	○○○○	○○○○	○	B02	Riding bicycle, scooter, roller blades etc. (for travel or fun)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B03	Travel in car	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B04	Travel on public transport	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B05	Being taken places with adult (e.g. shopping)	
10 am 0 15 30 45	11 am 0 15 30 45	12 pm 0 15 30 45	1 pm 0 15 30 45	2 pm 0 15 30 45	3 pm 0 15 30 45			
○○○○	○○○○	○○○○	○○○○	○○○○	○	C01	Own home (indoors)	Where was the child?
○○○○	○○○○	○○○○	○○○○	○○○○	○	C02	Own home (outdoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C03	School, after/before school care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C04	Other (indoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C05	Other (outdoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D01	Alone	Who was in the same room or nearby if outside?
○○○○	○○○○	○○○○	○○○○	○○○○	○	D02	Mother, step-mother	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D03	Father, step-father	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D04	Grandparent(s)/other adult relative(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D05	Brother(s), sister(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D06	Other children	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D07	Other adult(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D08	Dog, cat or other pet (not fish)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	E01	Was this activity done for, *or* as part of, homework?	

K3D?!

!= 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

		Afternoon		Evening			
		4 pm 0 15 30 45	5 pm 0 15 30 45	6 pm 0 15 30 45	7 pm 0 15 30 45	8 pm 0 15 30 45	9 pm 0 15 30 45
What was the child doing?	Not sure what child was doing	?=A01					
	Sleeping, napping	A02					
	Awake in bed	A03					
	Eating and drinking	A04					
	Bathing, dressing, hair care, health care	A05					
	Doing nothing, bored/restless	A06					
	Sulking, upset	A07					
	Arguing, fighting	A08					
	Being hugged, comforted, helped to calm down	A09					
	Being reprimanded, corrected	A10					
	Watching TV, video, DVD, movie	A11					
	Listening to tapes, CDs, radio, music	A12					
	Using computer/computer game	A13					
	Being read to or told a story	A14					
	Reading or looking at book by self	A15					
	Quiet free play (e.g. board game, craft, dress-ups)	A16					
	Active free play (e.g. running, climbing, ball game)	A17					
	Helping with chores, jobs	A18					
	Visiting people, special event or outing	A19					
	Organised sport/physical activity (e.g. swim, dance, Auskick)	A20					
	Other organised lesson/activity (e.g. music, drama)	A21					
Travel	Walking (for travel or fun)	B01					
	Riding bicycle, scooter, roller blades etc. (for travel or fun)	B02					
	Travel in car	B03					
	Travel on public transport	B04					
	Being taken places with adult (e.g. shopping)	B05					
		4 pm 0 15 30 45	5 pm 0 15 30 45	6 pm 0 15 30 45	7 pm 0 15 30 45	8 pm 0 15 30 45	9 pm 0 15 30 45
Where was the child?	Own home (indoors)	C01					
	Own home (outdoors)	C02					
	School, after/before school care	C03					
	Other (indoors)	C04					
	Other (outdoors)	C05					
Who was in the same room or nearby if outside?	Alone	D01					
	Mother, step-mother	D02					
	Father, step-father	D03					
	Grandparent(s)/other adult relative(s)	D04					
	Brother(s), sister(s)	D05					
	Other children	D06					
	Other adult(s)	D07					
	Dog, cat or other pet (not fish)	D08					
	Was this activity done for, *or* as part of, homework?	E01					

Night								
10 pm 0 15 30 45	11 pm 0 15 30 45	12 am 0 15 30 45	1 am 0 15 30 45	2 am 0 15 30 45	3 am 0 15 30 45			
○○○○	○○○○	○○○○	○○○○	○○○○	○	?=A01	Not sure what child was doing	What was the child doing?
○○○○	○○○○	○○○○	○○○○	○○○○	○	A02	Sleeping, napping	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A03	Awake in bed	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A04	Eating and drinking	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A05	Bathing, dressing, hair care, health care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A06	Doing nothing, bored/restless	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A07	Sulking, upset	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A08	Arguing, fighting	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A09	Being hugged, comforted, helped to calm down	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A10	Being reprimanded, corrected	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A11	Watching TV, video, DVD, movie	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A12	Listening to tapes, CDs, radio, music	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A13	Using computer/computer game	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A14	Being read to or told a story	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A15	Reading or looking at book by self	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A16	Quiet free play (e.g. board game, craft, dress-ups)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A17	Active free play (e.g. running, climbing, ball game)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A18	Helping with chores, jobs	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A19	Visiting people, special event or outing	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A20	Organised sport/physical activity (e.g. swim, dance, Auskick)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	A21	Other organised lesson/activity (e.g. music, drama)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B01	Walking (for travel or fun)	Travel
○○○○	○○○○	○○○○	○○○○	○○○○	○	B02	Riding bicycle, scooter, roller blades etc. (for travel or fun)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B03	Travel in car	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B04	Travel on public transport	
○○○○	○○○○	○○○○	○○○○	○○○○	○	B05	Being taken places with adult (e.g. shopping)	
10 pm 0 15 30 45	11 pm 0 15 30 45	12 am 0 15 30 45	1 am 0 15 30 45	2 am 0 15 30 45	3 am 0 15 30 45			
○○○○	○○○○	○○○○	○○○○	○○○○	○	C01	Own home (indoors)	Where was the child?
○○○○	○○○○	○○○○	○○○○	○○○○	○	C02	Own home (outdoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C03	School, after/before school care	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C04	Other (indoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	C05	Other (outdoors)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D01	Alone	Who was in the same room or nearby if outside?
○○○○	○○○○	○○○○	○○○○	○○○○	○	D02	Mother, step-mother	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D03	Father, step-father	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D04	Grandparent(s)/other adult relative(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D05	Brother(s), sister(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D06	Other children	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D07	Other adult(s)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	D08	Dog, cat or other pet (not fish)	
○○○○	○○○○	○○○○	○○○○	○○○○	○	E01	Was this activity done for, *or* as part of, homework?	

3 For the day described in this diary, how often did this child eat or drink the following?
(Tick one box per row only)

		Not at all	Once	Twice	Three times	Four or more times	Don't know
K3DBP301	Fresh fruit	1	2	3	4	5	6
K3DBP302	Fruit juice	1	2	3	4	5	6
K3DBP303	Cooked vegetables	1	2	3	4	5	6
K3DBP304	Raw vegetables or salad	1	2	3	4	5	6
K3DBP305	Meat pie, hamburger, hot dog, sausage or sausage roll	1	2	3	4	5	6
K3DBP306	Hot chips or french fries	1	2	3	4	5	6
K3DBP307	Potato chips or savoury snacks such as 'Twisties'	1	2	3	4	5	6
K3DBP308	Biscuits, doughnuts, cake, pie or chocolate	1	2	3	4	5	6
K2DBP309	Bread	1	2	3	4	5	6
K3DBP310	Full cream milk or full cream milk products	1	2	3	4	5	6
K3DBP311	Skim milk or skim milk products	1	2	3	4	5	6
K3DBP312	Water	1	2	3	4	5	6
K3DBP313	Soft drink or cordial, not diet	1	2	3	4	5	6
K3DBP314	Diet soft drink or cordial	1	2	3	4	5	6
K3DBP315	Breakfast	1	2	3	4	5	6

4 What is your relationship to the study child?

K3DBP4
- 1 Mother
- 2 Father
- 3 Grandmother
- 4 Other relative
- 5 Carer/babysitter
- 6 Other

5 When did you fill in this diary?

K3DBP5
- 1 More than 3 times a day
- 2 2 to 3 times a day
- 3 Once at the end of the day
- 4 Once, the next morning
- 5 At a later time

6 If you did not fill in the diary for the day allocated, what day does the diary relate to?

K3DBP6 ___ / ___ / ___

7 Did the study child participate in completing this diary?

K3DBP7
- 1 Yes
- 2 No

8 What day of the week does the diary relate to?

K3DBP8
- 1 Monday
- 2 Tuesday
- 3 Wednesday
- 4 Thursday
- 5 Friday

9 How many hours of paid work did you do on this day?

K3DBP9 ___

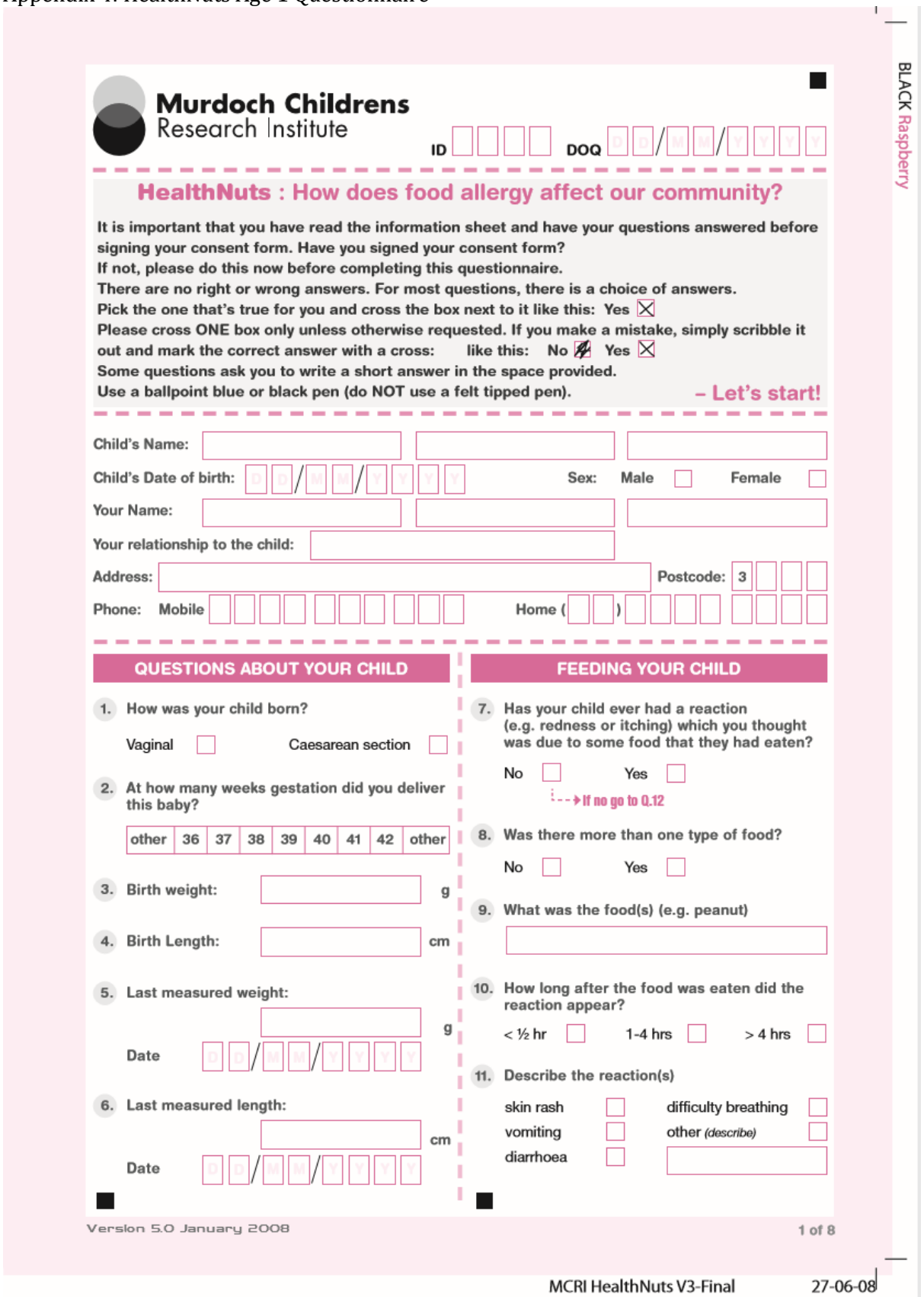
10 What kind of day is described in this diary?
(Tick all that apply)

- K3DBP101 1 An ordinary day
- K3DBP102 2 A holiday or a family celebration
- K3DBP103 3 A school day
- K3DBP104 4 A school holiday
- K3DBP105 5 A parent took time off work
- K3DBP106 6 Our family dealt with a crisis
- K3DBP107 7 We had guests staying with us
- K3DBP108 8 A family member was away
- K3DBP109 9 I was ill
- K3DBP110 10 This child was ill
- K3DBP111 11 This child was a great deal more stressed than normal
- K3DBP112 12 An unusual day for another reason

11 Was the weather good enough for outdoor activities?

K3DBP11
- 1 Yes
- 2 No

Appendix 4: HealthNuts Age 1 Questionnaire



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ID ☐☐☐☐ DOQ D D/M M/Y Y Y Y

HealthNuts : How does food allergy affect our community?

It is important that you have read the information sheet and have your questions answered before signing your consent form. Have you signed your consent form?
If not, please do this now before completing this questionnaire.
There are no right or wrong answers. For most questions, there is a choice of answers.
Pick the one that's true for you and cross the box next to it like this: Yes ☒
Please cross ONE box only unless otherwise requested. If you make a mistake, simply scribble it out and mark the correct answer with a cross: like this: No ☒ Yes ☒
Some questions ask you to write a short answer in the space provided.
Use a ballpoint blue or black pen (do NOT use a felt tipped pen).

– Let's start!

Child's Name: ☐ ☐ ☐

Child's Date of birth: D D/M M/Y Y Y Y Sex: Male ☐ Female ☐

Your Name: ☐ ☐ ☐

Your relationship to the child: ☐

Address: ☐ Postcode: 3 ☐☐☐

Phone: Mobile ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ Home (☐☐) ☐☐☐☐ ☐☐☐☐

QUESTIONS ABOUT YOUR CHILD

1. How was your child born?
   Vaginal ☐ Caesarean section ☐
2. At how many weeks gestation did you deliver this baby?

other	36	37	38	39	40	41	42	other

3. Birth weight: ☐ g
4. Birth Length: ☐ cm
5. Last measured weight: ☐ g
   Date D D/M M/Y Y Y Y
6. Last measured length: ☐ cm
   Date D D/M M/Y Y Y Y

FEEDING YOUR CHILD

7. Has your child ever had a reaction (e.g. redness or itching) which you thought was due to some food that they had eaten?
   No ☐ Yes ☐
   → If no go to Q.12
8. Was there more than one type of food?
   No ☐ Yes ☐
9. What was the food(s) (e.g. peanut) ☐
10. How long after the food was eaten did the reaction appear?
    < ½ hr ☐ 1-4 hrs ☐ > 4 hrs ☐
11. Describe the reaction(s)
    skin rash ☐ difficulty breathing ☐
    vomiting ☐ other *(describe)* ☐
    diarrhoea ☐ ☐

Version 5.0 January 2008 1 of 8

MCRI HealthNuts V3-Final 27-06-08

BLACK Raspberry

BLACK Raspberry

We are now going to ask you questions on the introduction of food to your child's diet.
(please circle **weeks** *or* **months** *)*

12. Age started breastfeeding (include colostrum in the first few days after birth)

Age ☐ in days

Not sure ☐
Not started ☐

13. Still breastfed

No ☐ Yes ☐

14. Age breastfeeding stopped

Age ☐ weeks / months

Not sure ☐
Not started ☐

15. Age infant formula bottle feeding started

Age ☐
weeks / months

Not sure ☐
Not started ☐

16. Age infant formula bottle feeding stopped

Age ☐ weeks / months

Not sure ☐
Not started ☐

17. When was solid food first introduced

Age ☐ weeks / months

Not sure ☐
Not started ☐

18. Age of change from formula to cow's milk

Age ☐ weeks / months

Not sure ☐
Not started ☐

19. Brand(s) of formula used and age introduced (See flash card of labels in folder)

Brand ☐
Age ☐ months

Brand ☐
Age ☐ months

20. Has your child eaten.....Nuts?

	No	Don't know	Yes
Peanut butter	☐	☐	☐
Peanut oil	☐	☐	☐
Other nuts (e.g. cashews, mixed nuts) *(please specify)*	☐	☐	☐

☐

21. Has your child consumed.....Eggs?

	No	Don't know	Yes
Soft boiled / scrambled egg	☐	☐	☐
Hard boiled egg	☐	☐	☐
Meringue	☐	☐	☐
Cakes	☐	☐	☐
Biscuits	☐	☐	☐
Other form *(Please Specify)*	☐	☐	☐

☐

22. Has your child consumed.....Other foods?

	No	Don't know	Yes
Sesame product	☐	☐	☐
Tahini	☐	☐	☐
Sesame seeds on bread	☐	☐	☐
Fish	☐	☐	☐
Shellfish *(Please Specify)*	☐	☐	☐

☐

23. Has your child consumed.....Soy (not including formula)?

	No	Don't know	Yes
Soy milk or soy products *(Please Specify)*	☐	☐	☐

☐

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YOUR CHILD'S RASHES

24. Has you child at any time had an itchy rash other than nappy rash?

No ☐ Yes ☐

→ If no go to Q.29

25. Did you use medication to treat it?

Never ☐
Used in the past ☐
Used now ☐
Not sure ☐

26. Creams or moisturizers?

No ☐ Yes ☐ Not sure ☐

Name _____

27. Topical Steroids (e.g. cortisone)

No ☐ Yes ☐ Not sure ☐

Name _____

28. Did you use steroids for more than 10 days in a row?

No ☐ Yes ☐ Not sure ☐

29. Has your child ever been diagnosed with eczema?

No ☐ Yes ☐ Not sure ☐

30. Age when eczema was first diagnosed?

_____ months old

31. Has your child ever wheezed?

No ☐ Yes ☐ Not sure ☐

32. Number of episodes of wheeze?

_____

33. Has your child ever had bronchiolitis (bron-key-o-litus)

No ☐ Yes ☐ Not sure ☐

34. Was your child hospitalised with bronchiolitis?

No ☐ Yes ☐ Not sure ☐

If yes, age _____ in months

35. Has your child ever had antibiotics?

No ☐ Yes ☐ Not sure ☐

If yes, age _____ in months

Reason (e.g. ear infection) _____

36. Type of antibiotic (if known)

_____

37. If more than one course of antibiotic, how many?

_____ number

_____ number

_____ number

38. Does your child attend childcare / daycare?

No ☐ Yes ☐

→ Does your child attend family care?

No ☐ Yes ☐

→ How many days per week?

1	2	3	4	5	6	7

→ How many hours per session?

1	2	3	4	5	6	7	8	9	10	11	12

→ At what age did they begin (months old)?

1	2	3	4	5	6	7	8	9	10	11	12

39. In general, would you say your child's health is *(please **cross** one box)*...

Excellent ☐
Very good ☐
Good ☐
Fair ☐
Poor ☐

BLACK Raspberry

40. Compared to other babies, I think my baby is *(please **cross** one box)*:

- Much easier than average ☐
- Easier than average ☐
- Average ☐
- More difficult than average ☐
- Cannot say ☐

41. Do you believe your child has a food allergy?

No ☐ Yes ☐ Not sure ☐

42. Do you believe your child is at risk of food allergy?

No ☐ Yes ☐ Not sure ☐

43. Has your child ever had colic?

No ☐ Yes ☐ Not sure ☐

→ If no go to Q.44

If yes, how old was the child when it started?

☐ weeks / months

→ **How many hours per day on average did they have colic?**

☐

→ **How long did it last?**

☐ days / weeks / months

→ **Did you consult a doctor?**

No ☐ Yes ☐ Not sure ☐

→ **Did you change your child's formula?**

No ☐ Yes ☐ Not sure ☐

→ **Was your child hospitalised?**

No ☐ Yes ☐ Not sure ☐

44. Did your child ever have reflux?

No ☐ Yes ☐ Not sure ☐

→ If no go to Q.45

If yes, how old was the child when it started?

☐ weeks / months

→ **How long did it last?**

☐ days / weeks / months

→ **Did you consult a doctor?**

No ☐ Yes ☐ Not sure ☐

→ **Did you change your child's formula?**

No ☐ Yes ☐ Not sure ☐

→ **Was your child hospitalised?**

No ☐ Yes ☐ Not sure ☐

→ **Was your child prescribed medication?**

No ☐ Yes ☐ Not sure ☐

→ **Which medication?**

☐

45. Did your child ever suffer from bouts of vomiting?

No ☐ Yes ☐ Not sure ☐

→ If no go to Q.46

If yes, how old was the child when it started?

☐ weeks / months

→ **How long did it last?**

☐ days / weeks / months

→ **Did you consult a doctor?**

No ☐ Yes ☐ Not sure ☐

→ **Did you change your child's formula?**

No ☐ Yes ☐ Not sure ☐

→ **Was your child hospitalised?**

No ☐ Yes ☐ Not sure ☐

46. Did your child ever suffer from diarrhoea?

No ☐ Yes ☐ Not sure ☐

→ If no go to Q.47

If yes, how old was the child when it started?

☐ weeks / months

→ **How long did it last?**

☐ days / weeks / months

→ **Did you consult a doctor?**

No ☐ Yes ☐ Not sure ☐

→ **Did you change your child's formula?**

No ☐ Yes ☐ Not sure ☐

→ **Was your child hospitalised?**

No ☐ Yes ☐ Not sure ☐

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47. Cross the foods that the child's **mother** has eaten.....

Which food?	When? (you can cross more than one)				How often?		
	Never eat food	Ate food during pregnancy	Ate food while breastfeeding	Not sure	Less than once a week	At least once a week	Daily
Nuts							
Peanut (e.g roasted, peanut butter, cakes)	☐	☐	☐	☐	☐	☐	☐
Any other nuts e.g. cashews, walnuts *(please specify)*	☐	☐	☐	☐	☐	☐	☐
Other foods							
Sesame products	☐	☐	☐	☐	☐	☐	☐
Shellfish	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐
Soy or soy products	☐	☐	☐	☐	☐	☐	☐

48. Have you had any supplements or drugs during your pregnancy?

	No	Yes	Not sure
Iron	☐	☐	☐
Folate	☐	☐	☐
Multivitamin	☐	☐	☐
Fish Oil	☐	☐	☐
Calcium	☐	☐	☐
Probiotics	☐	☐	☐
Alternative medicine supplement *(please describe)*	☐	☐	☐
Other *(please describe)*	☐	☐	☐
Drug Treatments (please describe)	☐	☐	☐

BLACK Raspberry

QUESTIONS ABOUT YOUR FAMILY

49. Does your 12 month old have other brothers and sisters?

No ☐ Yes ☐

	Date of birth
Brother 1	D D / M M / Y Y Y Y
Brother 2	D D / M M / Y Y Y Y
Sister 1	D D / M M / Y Y Y Y
Sister 2	D D / M M / Y Y Y Y
other siblings	D D / M M / Y Y Y Y

50. Mother's date of birth

D D / M M / Y Y Y Y

51. Father's date of birth

D D / M M / Y Y Y Y

52. The following people live with my child in our house (for at least half the week) the child's.....?

- Father ☐
- Mother ☐
- Siblings (as described above) ☐
- Other relatives(describe e.g. uncles, grandmother) ☐
- Other people (describe eg, friend of family, lodger) ☐

53. In what country was the child's mother born?

Australia ☐

Other *(please list)* ☐

54. In what country was the child's father born?

Australia ☐

Other *(please list)*

55. What is the main language spoken at home?

- English ☐
- Italian ☐
- Greek ☐
- Vietnamese ☐
- Arabic ☐
- Turkish ☐
- Chinese ☐
- Other *(please list)* ☐

56. Have you moved to Australia from another country in the last 5 years.

No ☐ ------→ If no go to Q.59

Yes ☐ ------→ Which country?

57. Has your diet changed significantly since moving to Australia?

- Strongly agree ☐
- Agree ☐
- Not sure ☐
- Disagree ☐
- Strongly Disagree ☐

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Version 5.0 January 2008

MCRI HealthNuts V3-Final 27-06-08

58. **Which ONE or MORE of the following statement best applies to your diet since moving to Australia?**

- My diet is much the same now as before the move ☐
- I eat MORE processed food now than before (eg foods that are bought in a packet) ☐
- I eat LESS processed food now than before (eg foods that are bought in a packet) ☐
- I eat MORE take-away food and restaurant food now than before (eg hamburgers, fish and chips) ☐
- I eat LESS take-away food and restaurant food now than before (eg hamburgers, fish and chips) ☐

59. **Does anyone smoke inside the home?**

No ☐ Yes ☐

Who? _____ Number _____ cigs/day

60. **Does anyone smoke outside the home (e.g. in the garden)?**

No ☐ Yes ☐

Who? _____ Number _____ cigs/day

61. **Did the mother smoke in pregnancy?**

No ☐ Yes ☐

Number _____ cigs/day

62. **Did the mother smoke in the past?**

No ☐ Yes ☐

How long _____ yrs Number _____ cigs/day

63. **Did the father smoke in the past?**

No ☐ Yes ☐

How long _____ yrs Number _____ cigs/day

BLACK Raspberry

64. Does anyone in your family suffer.....*(please cross)*?

	1 year old	Mother	Father	Brother 1	Brother 2	Sister 1	Sister 2	Other bro	Other sis
Asthma	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dermatitis	☐	☐	☐	☐	☐	☐	☐	☐	☐
Eczema	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hay fever	☐	☐	☐	☐	☐	☐	☐	☐	☐
Seasonal allergies	☐	☐	☐	☐	☐	☐	☐	☐	☐
Year round allergies	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sinus problems	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lupus	☐	☐	☐	☐	☐	☐	☐	☐	☐
Arthritis	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other allergies :									
Bee sting / ants	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drug	☐	☐	☐	☐	☐	☐	☐	☐	☐
Food *(please specify)*	☐	☐	☐	☐	☐	☐	☐	☐	☐
Latex	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nickel jewellery	☐	☐	☐	☐	☐	☐	☐	☐	☐

65. Could you please give an indication of your combined household income (yearly)?

Our household income is

$ ☐

or

- 0-25,000 ☐
- 25,000-50,000 ☐
- 50,000-75,000 ☐
- 75,000-100,000 ☐
- More than 100,000 ☐
- Don't know ☐
- Don't wish to answer question ☐

66. Do you have pets at home?

	Inside	Outside	Both
Cat	☐	☐	☐
Dog	☐	☐	☐
Bird	☐	☐	☐
Other *(please describe)*	☐	☐	☐

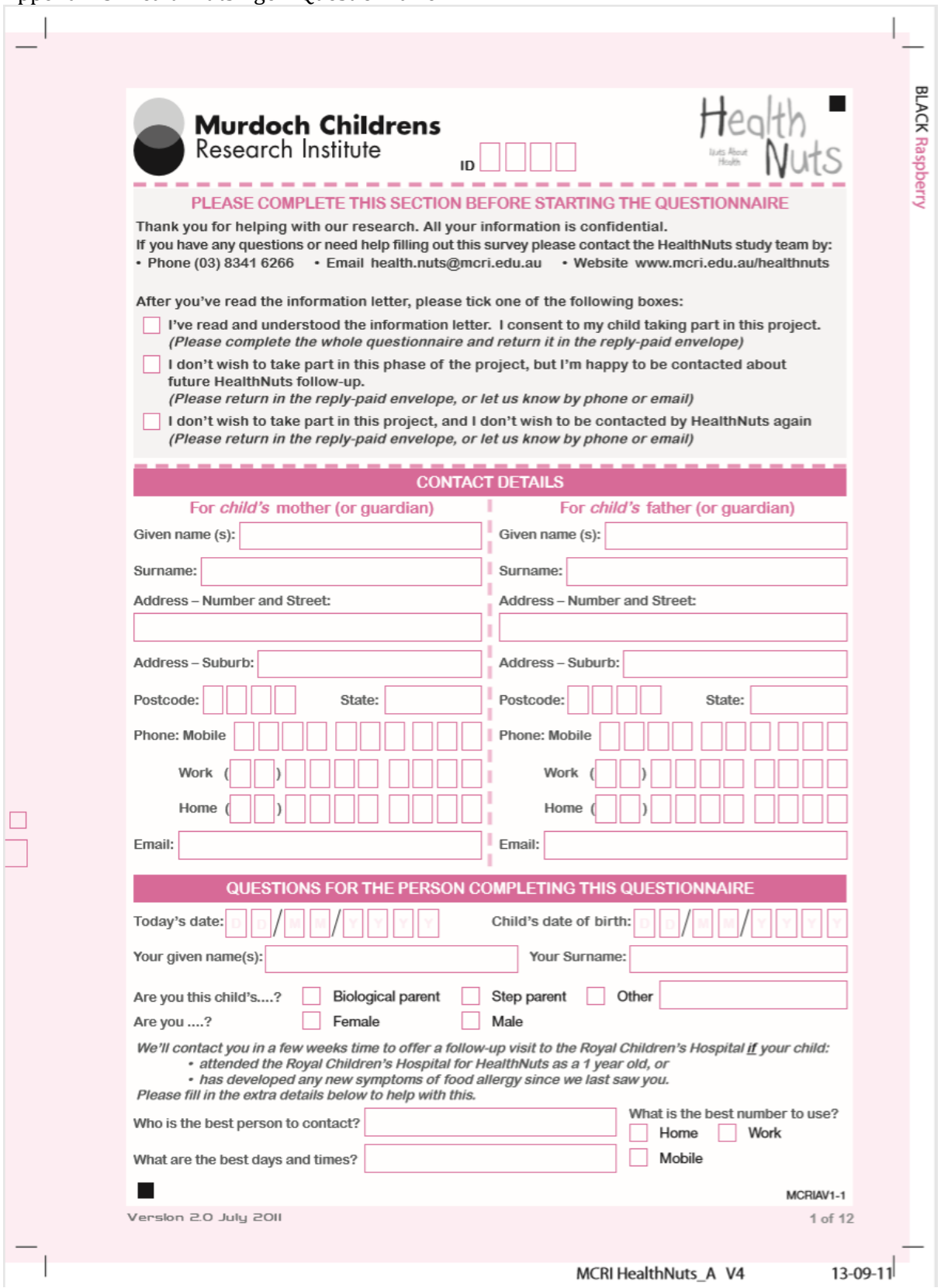
67. Do you live on a farm with animals?

No ☐ Yes ☐

Thank you for participating in our study.
Please let the researcher know you have finished filling out the questionnaire and they will help you with the rest of the allergy test.
HealthNuts – Nuts about health

Murdoch Childrens Research Institute

Appendix 5: HealthNuts Age 4 Questionnaire



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ID

HealthNuts

PLEASE COMPLETE THIS SECTION BEFORE STARTING THE QUESTIONNAIRE

Thank you for helping with our research. All your information is confidential.
If you have any questions or need help filling out this survey please contact the HealthNuts study team by:
• Phone (03) 8341 6266 • Email health.nuts@mcri.edu.au • Website www.mcri.edu.au/healthnuts

After you've read the information letter, please tick one of the following boxes:

- ☐ I've read and understood the information letter. I consent to my child taking part in this project. *(Please complete the whole questionnaire and return it in the reply-paid envelope)*
- ☐ I don't wish to take part in this phase of the project, but I'm happy to be contacted about future HealthNuts follow-up. *(Please return in the reply-paid envelope, or let us know by phone or email)*
- ☐ I don't wish to take part in this project, and I don't wish to be contacted by HealthNuts again *(Please return in the reply-paid envelope, or let us know by phone or email)*

CONTACT DETAILS

For *child's* mother (or guardian)	For *child's* father (or guardian)
Given name (s):	Given name (s):
Surname:	Surname:
Address – Number and Street:	Address – Number and Street:
Address – Suburb:	Address – Suburb:
Postcode: State:	Postcode: State:
Phone: Mobile	Phone: Mobile
Work ( )	Work ( )
Home ( )	Home ( )
Email:	Email:

QUESTIONS FOR THE PERSON COMPLETING THIS QUESTIONNAIRE

Today's date: D D / M M / Y Y Y Y Child's date of birth: D D / M M / Y Y Y Y

Your given name(s): Your Surname:

Are you this child's....? ☐ Biological parent ☐ Step parent ☐ Other

Are you ....? ☐ Female ☐ Male

We'll contact you in a few weeks time to offer a follow-up visit to the Royal Children's Hospital if your child:
- *attended the Royal Children's Hospital for HealthNuts as a 1 year old, or*
- *has developed any new symptoms of food allergy since we last saw you.*

Please fill in the extra details below to help with this.

Who is the best person to contact?

What are the best days and times?

What is the best number to use?
☐ Home ☐ Work ☐ Mobile

MCRIAV1-1

Version 2.0 July 2011

1 of 12

BLACK Raspberry

MCRI HealthNuts_A V4 13-09-11

BLACK Raspberry

MCRIAV1-2

1. FEEDING YOUR CHILD

We last saw you when your child was 12 months old. We want to know what new foods you've introduced into your child's diet since that time. Since age 12 months, has your child eaten the following foods? (tick one box on each line)

	No	Eaten 3 times or less	Eaten more than 3 times
1.1 Peanut butter	☐	☐	☐
1.2 Peanuts	☐	☐	☐
1.3 Pistachios	☐	☐	☐
1.4 Cashews	☐	☐	☐
1.5 Almonds	☐	☐	☐
1.6 Hazelnuts (including Nutella)	☐	☐	☐
1.7 Pine nuts	☐	☐	☐
1.8 Other nuts *(please specify)*	☐	☐	☐
1.9 Tahini (or hummus)	☐	☐	☐
1.10 Sesame seeds on foods (eg. bread, sesame snaps)	☐	☐	☐
1.11 Semi-cooked (runny) egg (eg. scrambled, soft boiled, fried, poached)	☐	☐	☐
1.12 Completely cooked (hard) egg (eg. hard boiled, fried, poached)	☐	☐	☐
1.13 Meringue, pavlova or macaroons	☐	☐	☐
1.14 Cakes containing egg	☐	☐	☐
1.15 Biscuits containing egg (eg teddy bear biscuits)	☐	☐	☐
1.16 Other foods containing egg *(please specify)*	☐	☐	☐
1.17 Fish	☐	☐	☐
1.18 Shellfish *(please specify)*	☐	☐	☐
1.19 Soy milk or other soy products *(please specify)*	☐	☐	☐
1.20 Cow's milk (including on cereal)	☐	☐	☐
1.21 Cow's milk in baked products (eg. cakes, muffins)	☐	☐	☐
1.22 Other dairy products (e.g. cheese, yoghurt, cream, ice cream) *(please specify)*	☐	☐	☐
1.23 Other types of milk e.g. goat's milk *(please specify)*	☐	☐	☐
1.24 Wheat (e.g. bread, cakes, biscuits)	☐	☐	☐

1.25 Do you restrict any particular foods in your child's diet? ☐ No ☐ Yes

If yes, (a) which foods does your child avoid?

(b) why are these foods avoided?

1.26 At what age did this child stop breastfeeding? _____ months (write N/A if never breastfed)

Murdoch Childrens Research Institute

Version 2.0 July 2011

MCRI HealthNuts_A V4 13-09-11

2. FOOD ALLERGIES AND INTOLERANCES

2.1 Since we last saw you has your child had a reaction which you thought was due to some food they had **eaten**?

☐ No ---→ **go to Question 2.2**

☐ Yes *(answer questions below)*....

To which food(s)	How old were they?		What was the reaction (please tick all that apply)?								How long after food eaten was the reaction?		
	years	OR months	hives/ urticaria/ wheals	facial swelling	vomiting	diarrhoea	breathing problems (eg: cough, wheeze, shortness of breath)	eczema flare	other reaction *(please specify)*:	less than 1 hr	1-4 hrs	more than 4 hrs
EXAMPLE: *peanut*	Years 3	Months	☑	☐	☑	☐	☐	☑	*redness on face*	☑	☐	☐
a	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
b	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
c	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
d	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
e	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
f	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐
g	Years	Months	☐	☐	☐	☐	☐	☐		☐	☐	☐

2.2 Have you ever consulted any health professionals about your child's food reactions?

No ☐ ---→ If no, go to Question 3.1

a.	Doctor - general practitioner (GP)	☐ How many times did you see a GP?	
b.	Paediatrician	☐ How many times did you see a paediatrician?	
c.	Allergist	☐ How many times did you see an allergist?	
d.	Other health professional *(please specify)*	☐ How many times did you see this health professional?	
e.	Complementary medicine practitioner *(please specify)*	☐ How many times did you see a complementary medicine practitioner?	

2.3 Does your child currently have an EpiPen/Anapen for food allergy? ☐ No ☐ Yes

3. RASHES, CHEST SYMPTOMS, RUNNY NOSE

3.1 In general, would you say your child's health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

Rashes

3.2 Has your child ever had an itchy rash which was coming and going for at least six months?

☐ No ---→ go to Question 3.3 ☐ Yes ☐ Don't know

If yes...

a. Has your child had this itchy rash at any time in the last 12 months?

☐ No ☐ Yes ☐ Don't know

b. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

☐ No ☐ Yes ☐ Don't know

c. At what age did this itchy rash first occur?

☐ Under 2 years ☐ Age 2-4 years

d. Has this rash cleared completely at any time in the last 12 months?

☐ No ☐ Yes ☐ Don't know

e. In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?

☐ Never in the last 12 months
☐ Less than one night per week
☐ One or more nights per week

BLACK Raspberry

3.3 Has your child been diagnosed with eczema?

☐ No ☐ Yes ---→ a. Age when symptoms started ☐ months old

3.4 In the last 12 months, has your child suffered from dry skin in general?

☐ No ☐ Yes

3.5 Did you use medication to treat your child's eczema, itchy rash or dry skin? (You can tick more than one box if necessary)

☐ Never ---→ go to Question 3.6 ☐ Used in the past ☐ Use now

If you have ever used medication for your child's eczema or itchy rash

a. Have you used moisturisers?

☐ No ☐ Yes Name ☐ Don't know

b. Have you used topical steroid creams or ointments (e.g. sigmacort, celestone, elocon, cortic, hydrocortisone, advantan fatty ointment)?

☐ No ☐ Yes Name ☐ Don't know

c. Did you use steroid creams for more than 10 days in a row?

☐ No ☐ Yes ☐ Don't know

3.6 Have you ever consulted any health professionals about your child's eczema or dry skin?

No ☐ ---→ If no, go to Question 3.7

a.	Doctor - general practitioner (GP)	☐ How many times did you see a GP?	☐
b.	Paediatrician	☐ How many times did you see a paediatrician?	☐
c.	Allergist	☐ How many times did you see an allergist?	☐
d.	Other health professional *(please specify)* ☐	☐ How many times did you see this health professional?	☐
e.	Complementary medicine practitioner *(please specify)* ☐	☐ How many times did you see a complementary medicine practitioner?	☐

Wheezing and coughing

3.7 Has your child ever had wheezing or whistling in the chest at any time in the past?

☐ No ---→ go to Question 3.8 ☐ Yes ☐ Don't know

If yes...

a. At what age did the symptoms first start? ☐ year(s) old

b. Has your child had wheezing or whistling in the chest in the last 12 months?

☐ No ---→ go to Question 3.8 ☐ Yes

c. How many attacks of wheezing has your child had in the last 12 months?

☐ None ☐ 1 to 3 ☐ 4 to 12 ☐ More than 12

d. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

- ☐ Never woken with wheezing
- ☐ Less than one night per week
- ☐ One or more nights per week

e. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

- ☐ No
- ☐ Yes

3.8 Has your child ever had asthma?

- ☐ No
- ☐ Yes ---→ a) Were you told by a doctor that your child had asthma? ☐ No ☐ Yes
  b) Age when symptoms started ☐ years old

3.9 In the last 12 months has your child used any medicines, pills, puffers or other medications for wheezing or asthma?

☐ No ---→ go to Question 3.10 ☐ Yes ☐ Not sure

If yes, please list the medications and when they were used.

	a. Name of 'Western' medicine	When wheezy	Regularly (every day for at least 2 months)
		☐	☐
		☐	☐
		☐	☐
	b. Name of 'Alternative' medicine		
		☐	☐
		☐	☐

3.10 Have you ever consulted any health professionals about your child's wheezing or asthma?

☐ No ---→ If no, go to Question 3.11

a.	Doctor - general practitioner (GP)	☐	How many times did you see a GP? ☐
b.	Paediatrician	☐	How many times did you see a paediatrician? ☐
c.	Allergist	☐	How many times did you see an allergist? ☐
d.	Other health professional *(please specify)* ☐	☐	How many times did you see this health professional? ☐
e.	Complementary medicine practitioner *(please specify)* ☐	☐	How many times did you see a complementary medicine practitioner? ☐

BLACK Raspberry

Hay fever

*All questions are about problems which occur when your child **DOES NOT** have a cold or the flu.*

3.11 Has your child ever had sneezing or a runny or blocked nose, when he/she **did not** have a cold or the flu?

☐ No ---→ go to Question 3.12 ☐ Yes ☐ Don't know

If yes...

a. At what age did the symptoms first start? ☐ year(s) old

b. In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she DID NOT have a cold or the flu?

☐ No ---→ go to Question 3.12 ☐ Yes ☐ Don't know

c. In the past 12 months, has this problem been accompanied by itchy-watery eyes?

☐ No ☐ Yes ☐ Don't know

d. In the past 12 months, how much did this nose problem interfere with your child's activities?

☐ Not at all ☐ A little ☐ A moderate amount ☐ A lot

e. In which of the past 12 months did nose problems occur?
(tick all that apply)

☐ January	☐ April	☐ July	☐ October
☐ February	☐ May	☐ August	☐ November
☐ March	☐ June	☐ September	☐ December

3.12 Has your child ever had hay fever?

☐ No ---→ go to Question 4.1

☐ Yes ---→ a. Were you told by a doctor that your child had hay fever? ☐ No ☐ Yes

b. Age when symptoms started ☐ years old

3.13 Have you ever consulted any health professionals about your child's hay fever?

☐ No ---→ If no, go to Question 4.1

a.	Doctor - general practitioner (GP)	☐ How many times did you see a GP?	☐
b.	Paediatrician	☐ How many times did you see a paediatrician?	☐
c.	Allergist	☐ How many times did you see an allergist?	☐
d.	Other health professional *(please specify)* ☐	☐ How many times did you see this health professional?	☐
e.	Complementary medicine practitioner *(please specify)* ☐	☐ How many times did you see a complementary medicine practitioner?	☐

MCRIAV1-8

4. OTHER QUESTIONS ABOUT YOUR CHILD

4.1 Does your child regularly receive childcare or go to kindergarten or preschool?

☐ No ---→ go to Question 4.2

☐ Yes ---→ a. On average, how many hours does your child spend there every week?

☐ hrs /week

b. At what age did your child start childcare? ☐ months

c. At what age did your child start kindergarten/preschool? ☐ months

d. How many children does your child have contact with at childcare, kindergarten or preschool?

☐ 1-5 ☐ 5-9 ☐ 10-15 ☐ more than 15

4.2 Has your child ever had a gastrointestinal worm infection (e.g. Threadworms or Pinworms)

☐ No ---→ go to Question 4.3

☐ Yes ---→ a. How old was your child when they first had worms?

☐ Less than 1 year ☐ 1 to 3 years ☐ At least 3 years

b. How many times have they had worms? ☐

4.3 During the last year, how much time did your child spend in the sun?

	Summer	<1 hr a day	1 to 2 hrs per day	2 to 3 hrs per day	3 to 4 hrs per day	≥ 4 hrs a day
a.	on weekdays	☐	☐	☐	☐	☐
b.	on weekends	☐	☐	☐	☐	☐
	Winter					
c.	on weekdays	☐	☐	☐	☐	☐
d.	on weekends	☐	☐	☐	☐	☐

4.4 a. What was your child's last measured **weight**? ☐☐.☐ kg

b. Date recorded ☐☐/☐☐/☐☐

4.5 a. What was your child's last measured **height**? ☐☐☐ cm

b. Date recorded ☐☐/☐☐/☐☐

4.6 Does your child have **younger** brothers and sisters? (we already know about older siblings from our previous questionnaire)

☐ No younger siblings ☐ Yes *(please give details below)*

Younger sisters	Date of birth	Younger brothers	Date of birth
a. Sister 1	D D/M M/Y Y	b. Brother 1	D D/M M/Y Y
c. Sister 2	D D/M M/Y Y	d. Brother 2	D D/M M/Y Y
e. Sister 3	D D/M M/Y Y	f. Brother 3	D D/M M/Y Y

4.7 Below is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child in the past ONE month.

	Physical functioning (problems with...)	Never	Almost Never	Some-times	Often	Almost Always
a.	Walking	☐	☐	☐	☐	☐
b.	Running	☐	☐	☐	☐	☐
c.	Participating in active play or exercise	☐	☐	☐	☐	☐
d.	Lifting something heavy	☐	☐	☐	☐	☐
e.	Bathing	☐	☐	☐	☐	☐
f.	Helping to pick up his or her toys	☐	☐	☐	☐	☐
g.	Having hurts or aches	☐	☐	☐	☐	☐
h.	Low energy levels	☐	☐	☐	☐	☐
	Emotional functioning (problems with...)					
i.	Feeling afraid or scared	☐	☐	☐	☐	☐
j.	Feeling sad or blue	☐	☐	☐	☐	☐
k.	Feeling angry	☐	☐	☐	☐	☐
l.	Trouble sleeping	☐	☐	☐	☐	☐
m.	Worrying	☐	☐	☐	☐	☐
	Social functioning (problems with...)					
n.	Playing with other children	☐	☐	☐	☐	☐
o.	Other kids not wanting to play with him or her	☐	☐	☐	☐	☐
p.	Getting teased by other children	☐	☐	☐	☐	☐
q.	Not able to do things that other children his or her age can do	☐	☐	☐	☐	☐
r.	Keeping up when playing with other children	☐	☐	☐	☐	☐
	Day-care functioning – please complete this section if your child attends day-care (problems with...)					
s.	Doing the same day-care activities as peers	☐	☐	☐	☐	☐
t.	Missing day-care because of not feeling well	☐	☐	☐	☐	☐
u.	Missing day-care to go to the doctor	☐	☐	☐	☐	☐

4.8 The next questions are about your child's emotional well-being and behaviour. These can be big issues for 4-year-olds. It would help us if you answered the items as best you can even if you are not absolutely certain. Please give your answers on the basis of the child's behaviour over the last 6 months.

		Not True	Somewhat True	Certainly True
a.	considerate of other people's feelings	☐	☐	☐
b.	restless, overactive, cannot stay still for long	☐	☐	☐
c.	often complains of headaches, stomach-aches or sickness	☐	☐	☐
d.	shares readily with other children, for example toys, treats, pencils	☐	☐	☐
e.	often loses temper	☐	☐	☐
f.	rather solitary, prefers to play alone	☐	☐	☐
g.	generally well behaved, usually does what adults request	☐	☐	☐
h.	many worries or often seems worried	☐	☐	☐
i.	helpful if someone is hurt, upset or feeling ill	☐	☐	☐
j.	constantly fidgeting or squirming	☐	☐	☐
k.	has at least one good friend	☐	☐	☐
l.	often fights with other children or bullies them	☐	☐	☐
m.	often unhappy, depressed or tearful	☐	☐	☐
n.	generally liked by other children	☐	☐	☐
o.	easily distracted, concentration wanders	☐	☐	☐
p.	nervous or clingy in new situations, easily loses confidence	☐	☐	☐
q.	kind to younger children	☐	☐	☐
r.	often lies or cheats	☐	☐	☐
s.	picked on or bullied by other children	☐	☐	☐
t.	often volunteers to help others (parents, teachers, other children)	☐	☐	☐
u.	thinks things out before acting	☐	☐	☐
v.	steals from home, school or elsewhere	☐	☐	☐
w.	gets along better with adults than with other children	☐	☐	☐
x.	many fears, easily scared	☐	☐	☐
y.	good attention span, sees tasks through to an end	☐	☐	☐

4.9 At what time does your child usually go to bed at night? ☐ pm

4.10 What is their usual wake-up time in the morning? ☐ am

BLACK Raspberry

5. QUESTIONS ABOUT YOUR FAMILY

5.1 Since we first saw you when your child was 1 year old, has anyone in your immediate family developed any new symptoms of .....

		No one	4 year old child	Child's mother	Child's father	Child's brother 1	Child's brother 2	Child's sister 1	Child's sister 2	other sibling
a.	Asthma	☐	☐	☐	☐	☐	☐	☐	☐	☐
b.	Eczema	☐	☐	☐	☐	☐	☐	☐	☐	☐
c.	Hay fever	☐	☐	☐	☐	☐	☐	☐	☐	☐
d.	Latex allergy	☐	☐	☐	☐	☐	☐	☐	☐	☐
e.	Insect allergy which insect:	☐	☐	☐	☐	☐	☐	☐	☐	☐
f.	Food allergy which foods:	☐	☐	☐	☐	☐	☐	☐	☐	☐

5.2 Do you currently have pets at home?

☐ No ----→ go to Question 5.3 ☐ Yes

If yes,

			Inside and outside	Outside only	Inside only
a.	Number of cats:		☐	☐	☐
b.	Number of dogs:		☐	☐	☐
c.	Number of birds:		☐	☐	☐
d.	Other pet *(please specify)*		☐	☐	☐

5.3 Does your household currently keep your pets outside or avoid having pets at home because of allergy?

☐ No ☐ Yes, avoid cats only ☐ Yes, avoid dogs only ☐ Yes, avoid both cats and dogs

5.4 How many people in your household regularly smoke (most days of the week)? ☐

5.5 What is the total number of cigarettes smoked by all residents **outside** your home?

☐ per week

5.6 What is the total number of cigarettes smoked by all residents **inside** your home?

☐ per week

5.7 Does anyone smoke in the same room as the child?

☐ Never ☐ Sometimes ☐ Usually

MCRIAV1-B

5.8 What is the highest education or vocational qualification completed by the child's....

	a. mother	b. father
year 10 or less	☐	☐
year 11	☐	☐
year 12	☐	☐
trade apprenticeship	☐	☐
technical diploma/certificate	☐	☐
university degree	☐	☐
postgraduate university degree	☐	☐
Other *(please specify)*	☐	☐

5.9 a. Is the child's **mother** currently in paid work? ☐ No ☐ Part-time ☐ Full-time

b. Is the child's **father** currently in paid work? ☐ No ☐ Part-time ☐ Full-time

Thank you for completing this questionnaire.
Please check that you've answered all the questions, on both sides of each page and filled in the date on Page 1.
Please return it to us in the reply paid envelope.
For queries, contact the HealthNuts team
on (03) 8341 6266 or health.nuts@mcri.edu.au.

We'll contact you again when your child turns 6 years old to ask about their food allergy, eczema, asthma and hay fever once they are at school. Just in case your address or phone number changes, is there a friend or relative (such as a grandparent or aunt/uncle) we could contact?

Given name(s):

Surname:

Relationship to the child:

Address – Number and Street:

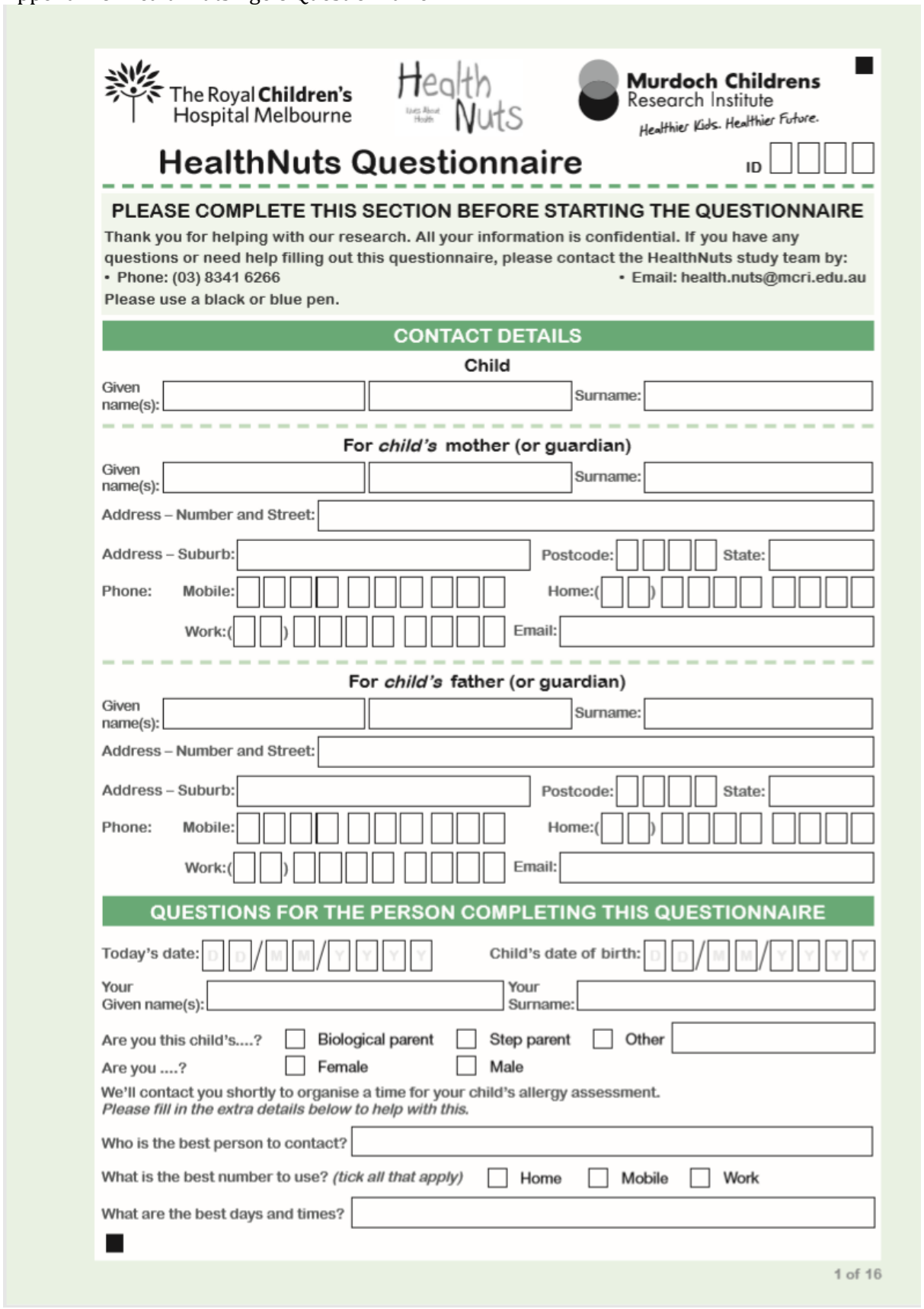
Address – Suburb: Postcode:

Phone: Mobile Home ( )

Email:

Murdoch Childrens Research Institute

Appendix 6: HealthNuts Age 6 Questionnaire



The Royal Children's Hospital Melbourne

Health Nuts

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

HealthNuts Questionnaire

ID

PLEASE COMPLETE THIS SECTION BEFORE STARTING THE QUESTIONNAIRE

Thank you for helping with our research. All your information is confidential. If you have any questions or need help filling out this questionnaire, please contact the HealthNuts study team by:

- Phone: (03) 8341 6266
- Email: health.nuts@mcri.edu.au

Please use a black or blue pen.

CONTACT DETAILS

Child

Given name(s): Surname:

For *child's* mother (or guardian)

Given name(s): Surname:

Address – Number and Street:

Address – Suburb: Postcode: State:

Phone: Mobile: Home:( )

Work:( ) Email:

For *child's* father (or guardian)

Given name(s): Surname:

Address – Number and Street:

Address – Suburb: Postcode: State:

Phone: Mobile: Home:( )

Work:( ) Email:

QUESTIONS FOR THE PERSON COMPLETING THIS QUESTIONNAIRE

Today's date: D D/M M/Y Y Y Y Child's date of birth: D D/M M/Y Y Y Y

Your Given name(s): Your Surname:

Are you this child's....? ☐ Biological parent ☐ Step parent ☐ Other

Are you ....? ☐ Female ☐ Male

We'll contact you shortly to organise a time for your child's allergy assessment.
Please fill in the extra details below to help with this.

Who is the best person to contact?

What is the best number to use? *(tick all that apply)* ☐ Home ☐ Mobile ☐ Work

What are the best days and times?

1 of 16

1. FEEDING YOUR CHILD

We last were in contact with you when your child was 4 years old. We want to know what new foods you've introduced into your child's diet since that time. Since age 4, has your child eaten the following foods? *(tick one box on each line)*

	Never in child's life	Yes, but not in the last 2 years	Yes, eaten 1-3 times in the last 2 years	Yes, eaten more than 3 times in the last 2 years
1.1 Peanut butter	☐ 1	☐ 2	☐ 3	☐ 4
1.2 Peanuts	☐ 1	☐ 2	☐ 3	☐ 4
1.3 Pistachios	☐ 1	☐ 2	☐ 3	☐ 4
1.4 Cashews	☐ 1	☐ 2	☐ 3	☐ 4
1.5 Almonds	☐ 1	☐ 2	☐ 3	☐ 4
1.6 Hazelnuts (including Nutella)	☐ 1	☐ 2	☐ 3	☐ 4
1.7 Pine nuts	☐ 1	☐ 2	☐ 3	☐ 4
1.8 Other nuts *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.9 Tahini (or hummus)	☐ 1	☐ 2	☐ 3	☐ 4
1.10 Sesame seeds on foods (e.g. bread, sesame snaps)	☐ 1	☐ 2	☐ 3	☐ 4
1.11 Semi-cooked (runny) egg (e.g. scrambled, soft boiled, fried, poached)	☐ 1	☐ 2	☐ 3	☐ 4
1.12 Completely cooked (hard) egg (e.g. hard boiled, fried, poached)	☐ 1	☐ 2	☐ 3	☐ 4
1.13 Meringue, pavlova or macaroons	☐ 1	☐ 2	☐ 3	☐ 4
1.14 Cakes containing egg	☐ 1	☐ 2	☐ 3	☐ 4
1.15 Biscuits containing egg (e.g. teddy bear biscuits)	☐ 1	☐ 2	☐ 3	☐ 4
1.16 Other foods containing egg *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.17 Fish	☐ 1	☐ 2	☐ 3	☐ 4
1.18 Shellfish *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.19 Soy milk or other soy products *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.20 Cow's milk (including on cereal)	☐ 1	☐ 2	☐ 3	☐ 4
1.21 Cow's milk in baked products (e.g. cakes, muffins)	☐ 1	☐ 2	☐ 3	☐ 4
1.22 Other dairy products (e.g. cheese, yoghurt, cream, ice cream) *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.23 Other types of milk (e.g. goat's milk) *(please specify)*	☐ 1	☐ 2	☐ 3	☐ 4
1.24 Wheat (e.g. bread, cakes, biscuits)	☐ 1	☐ 2	☐ 3	☐ 4

1.25 Do you restrict any particular foods in your child's diet? ☐ 1 No ☐ 2 Yes

If yes, (a) which foods does your child avoid?

(b) why are these foods avoided?

1.26 In the past 12 months, how often, on average, did your child eat or drink the following?
(Please leave blank if you do not know what a food is) (tick one box on each line)

		Never or occasionally	Once or twice per week	Three or more times a week
a)	Meat (e.g. beef, lamb, chicken, pork)	☐ 1	☐ 2	☐ 3
b)	Seafood (including fish)	☐ 1	☐ 2	☐ 3
c)	Oily fish (e.g. salmon, fresh tuna, trout, mackerel, sardines)	☐ 1	☐ 2	☐ 3
d)	Fruit	☐ 1	☐ 2	☐ 3
e)	Vegetables (green and root)	☐ 1	☐ 2	☐ 3
f)	Pulses (peas, beans, lentils)	☐ 1	☐ 2	☐ 3
g)	Cereal (including bread)	☐ 1	☐ 2	☐ 3
h)	Pasta	☐ 1	☐ 2	☐ 3
i)	Rice	☐ 1	☐ 2	☐ 3
j)	Butter	☐ 1	☐ 2	☐ 3
k)	Margarine	☐ 1	☐ 2	☐ 3
l)	Nuts	☐ 1	☐ 2	☐ 3
m)	Potatoes	☐ 1	☐ 2	☐ 3
n)	Cow's milk *Please specify type (e.g. full fat, low fat etc)*	☐ 1	☐ 2	☐ 3
o)	Other types of milk *Please specify type (e.g. soy, almond etc)*	☐ 1	☐ 2	☐ 3
p)	Eggs	☐ 1	☐ 2	☐ 3
q)	Fast food / takeaway	☐ 1	☐ 2	☐ 3
r)	Soft drink	☐ 1	☐ 2	☐ 3
s)	Cordial	☐ 1	☐ 2	☐ 3
t)	Fruit juice	☐ 1	☐ 2	☐ 3
u)	Powdered nutritional supplements *(e.g. Sustagen)*	☐ 1	☐ 2	☐ 3

1.27 Has your child ever been fed toddler formula or follow-on formula (e.g. Karicare Toddler or Heinz Nurture Follow-on)?

☐ 1 No → go to Question 2.1

☐ 2 Yes → a. At what age did they start? ☐☐ year(s) **or** ☐☐ months

b. At what age did they stop? ☐☐ year(s) **or** ☐☐ months

c. What was the name/s of the formula/s?

2. FOOD ALLERGIES AND INTOLERANCES

2.1 Since we last were in contact with you (child age 4), has your child had a reaction which you thought was due to some food they had **eaten**?

☐₁ No ---→ **go to Question 2.2** ☐₂ Yes *(answer questions below)....*

To which food(s)?	How old were they?		What was the reaction? *(please tick all that apply)*							How long after food eaten was the reaction?		
	years & months		hives/ urticaria/ wheals	facial swelling	vomiting	diarrhoea	breathing problems (e.g. cough, wheeze, shortness of breath)	eczema flare	other reaction *(please specify)*:	less than 1 hr	1-4 hrs	more than 4 hrs
EXAMPLE:	**Years**	**Months**										
peanut	Y 5	M 3	☑	☐	☑	☐	☐	☑	redness on face	☑	☐	☐
a	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
b	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
c	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
d	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
e	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
f	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃
g	Y Y	M M	☐	☐	☐	☐	☐	☐		☐₁	☐₂	☐₃

2.2 Since age 4, have you consulted any health professionals about your child's food reactions?

No ☐ ---→ If no, go to Question 3.1

a. Doctor - general practitioner (GP) ☐ How many times did you see a GP? ☐

b. Paediatrician ☐ How many times did you see a paediatrician? ☐

c. Allergist ☐ How many times did you see an allergist? ☐

d. Other health professional *(please specify)* ☐ How many times did you see this health professional? ☐

e. Complementary medicine practitioner *(please specify)* ☐ How many times did you see a complementary medicine practitioner? ☐

2.3 Does your child currently have an EpiPen/Anapen for food allergy? ☐$_1$ No ☐$_2$ Yes

3. RASHES, CHEST SYMPTOMS, RUNNY NOSE

Rashes

3.1 Has your child ever had an itchy rash which was coming and going for at least six months?

☐$_1$ No ---→ go to Question 3.2 ☐$_2$ Yes ☐$_3$ Don't know

If yes...

a. Has your child had this itchy rash at any time in the last 12 months?
☐$_1$ No ☐$_2$ Yes ☐$_3$ Don't know

b. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?
☐$_1$ No ☐$_2$ Yes ☐$_3$ Don't know

c. At what age did this itchy rash first occur?
☐$_1$ Under 2 years ☐$_2$ Age 2-4 years ☐$_3$ Age 5-6 years

d. Has this rash cleared completely at any time in the last 12 months?
☐$_1$ No ☐$_2$ Yes ☐$_3$ Don't know

e. In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?
☐$_1$ Never in the last 12 months
☐$_2$ Less than one night per week
☐$_3$ One or more nights per week

3.2 Has your child been diagnosed with eczema?

☐$_1$ No ☐$_2$ Yes ---→ a. Age when symptoms started ☐ year(s) **or** ☐ months old

3.3 In the last 12 months, has your child suffered from dry skin in general?

☐ 1 No ☐ 2 Yes

3.4 Have you ever used medication to treat your child's eczema, itchy rash or dry skin?
(You can tick more than one box if necessary)

☐ Never had eczema, itchy rash or dry skin ---→ go to Question 3.5
☐ Had/have eczema, itchy rash or dry skin but never used ---→ go to Question 3.5
☐ Used in the past
☐ Use now

If you have ever used medication for your child's eczema, itchy rash or dry skin

a. Have you used moisturisers?
☐ 1 No ☐ 2 Yes Name ☐ 3 Don't know

b. Have you used topical steroid creams or ointments (e.g. sigmacort, celestone, elocon, cortic, hydrocortisone, advantan fatty ointment)?
☐ 1 No ☐ 2 Yes Name ☐ 3 Don't know

c. Did you use steroid creams for more than 10 days in a row?
☐ 1 No ☐ 2 Yes ☐ 3 Don't know

3.5 In the past **12 MONTHS**, how many days (or part days) of school has your child missed because of an itchy skin rash or eczema?

☐ 1 None
☐ 2 1 to 5
☐ 3 6 to 10
☐ 4 More than 10

3.6 Since age 4, have you consulted any health professionals about your child's eczema or dry skin?

No ☐ ---→ If no, go to Question 3.7

a.	Doctor - general practitioner (GP)	☐ How many times did you see a GP?	
b.	Paediatrician	☐ How many times did you see a paediatrician?	
c.	Allergist	☐ How many times did you see an allergist?	
d.	Dermatologist	☐ How many times did you see a dermatologist?	
e.	Other health professional *(please specify)*	☐ How many times did you see this health professional?	
f.	Complementary medicine practitioner *(please specify)*	☐ How many times did you see a complementary medicine practitioner?	

Wheezing and coughing

3.7 Has your child **ever** had wheezing or whistling in the chest at any time in the past?

☐ 1 No ---→ go to Question 3.8 ☐ 2 Yes ☐ 3 Don't know

If yes...

a. At what age did the symptoms first start? ☐ year(s) old

b. Has your child had wheezing or whistling in the chest in the last 12 months?

☐ 1 No ---→ go to Question 3.8 ☐ 2 Yes

c. How many attacks of wheezing has your child had in the last 12 months?

☐ 1 None ☐ 2 1 to 3 ☐ 3 4 to 12 ☐ 4 More than 12

d. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

☐ 1 Never woken with wheezing
☐ 2 Less than one night per week
☐ 3 One or more nights per week

e. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

☐ 1 No ☐ 2 Yes

3.8 Has your child ever had asthma?

☐ 1 No
☐ 2 Yes ---→ a) Were you told by a doctor that your child had asthma? ☐ 1 No ☐ 2 Yes

b) Age when symptoms started ☐ year(s) old

c) Do you have a written asthma action plan which tells you how to look after your child's asthma?

☐ 1 No ☐ 2 Yes ☐ 3 Don't know

3.9 In the last 12 months, has your child used any medicines, pills, puffers or other medications for wheezing or asthma?

☐ 1 No ---→ go to Question 3.10 ☐ 2 Yes ☐ 3 Not sure

If yes, please list the medications and when they were used.	When wheezy	Regularly (every day for at least 2 months)
	(tick one box for each line)	
a. Name of 'Western' medicine		
☐	☐ 1	☐ 2
☐	☐ 1	☐ 2
☐	☐ 1	☐ 2
b. Name of 'Alternative' medicine		
☐	☐ 1	☐ 2
☐	☐ 1	☐ 2

3.10 Since age 4, have you consulted any health professionals about your child's wheezing or asthma?

No ☐ ---→ If no, go to Question 3.11

a.	Doctor - general practitioner (GP)	☐ How many times did you see a GP?	
b.	Paediatrician	☐ How many times did you see a paediatrician?	
c.	Allergist	☐ How many times did you see an allergist?	
d.	Other health professional *(please specify)*	☐ How many times did you see this health professional?	
e.	Complementary medicine practitioner *(please specify)*	☐ How many times did you see a complementary medicine practitioner?	

3.11 In the past **12 MONTHS**, how many times has your child been admitted to the hospital because of wheezing or asthma?

☐ 1 None	☐ 4 3 to 5
☐ 2 1	☐ 5 6 to 10
☐ 3 2	☐ 6 More than 10

3.12 In the past **12 MONTHS**, how many days (or part days) of school has your child missed because of wheezing or asthma?

☐ 1 None	☐ 3 6 to 10
☐ 2 1 to 5	☐ 4 More than 10

Hay fever

*All questions are about problems which occur when your child **DOES NOT** have a cold or the flu.*

3.13 Has your child ever had sneezing or a runny or blocked nose, when he/she **did not** have a cold or the flu?

☐ 1 No ---→ go to Question 3.14 ☐ 2 Yes ☐ 3 Don't know

If yes...

a. At what age did the symptoms first start? ☐ year(s) old

b. In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she DID NOT have a cold or the flu?

☐ 1 No ---→ go to Question 3.14 ☐ 2 Yes ☐ 3 Don't know

c. In the past 12 months, has this problem been accompanied by itchy-watery eyes?

☐ 1 No ☐ 2 Yes ☐ 3 Don't know

d. In the past 12 months, how much did this nose problem interfere with your child's activities?

☐ 1 Not at all ☐ 2 A little ☐ 3 A moderate amount ☐ 4 A lot

e. In which of the past 12 months did nose problems occur? *(tick all that apply)*

☐ January	☐ April	☐ July	☐ October
☐ February	☐ May	☐ August	☐ November
☐ March	☐ June	☐ September	☐ December

3.14 Has your child ever had hay fever?

☐ 1 No ---→ go to Question 3.16

☐ 2 Yes ---→ a. Were you told by a doctor that your child had hay fever? ☐ 1 No ☐ 2 Yes

b. Age when symptoms started ☐☐ year(s) old

3.15 Since age 4, have you consulted any health professionals about your child's hay fever?

No ☐ ---→ If no, go to Question 3.16

a.	Doctor - general practitioner (GP)	☐	How many times did you see a GP? ☐☐
b.	Paediatrician	☐	How many times did you see a paediatrician? ☐☐
c.	Allergist	☐	How many times did you see an allergist? ☐☐
d.	Other health professional *(please specify)* ☐☐☐☐☐☐☐☐☐☐	☐	How many times did you see this health professional? ☐☐
e.	Complementary medicine practitioner *(please specify)* ☐☐☐☐☐☐☐☐☐☐	☐	How many times did you see a complementary medicine practitioner? ☐☐

3.16 In the past **12 MONTHS**, how much did any nose problem interfere with your child's daily activities?

☐ 1 Not at all ☐ 3 A moderate amount

☐ 2 A little ☐ 4 A lot

3.17 In the past **12 MONTHS**, has your child used any medicines, pills, nose sprays or other medication for hay fever or nose problems?

☐ 1 No ☐ 2 Yes ☐ 3 Don't know

3.18 In the past **12 MONTHS**, how many days (or part days) of school has your child missed because of hay fever or nose problems?

☐ 1 None ☐ 3 6 to 10

☐ 2 1 to 5 ☐ 4 More than 10

4. OTHER QUESTIONS ABOUT YOUR CHILD

4.1 In general, would you say your child's health is:

☐ 1 Excellent ☐ 2 Very good ☐ 3 Good ☐ 4 Fair ☐ 5 Poor

4.2 Has your child ever had a gastrointestinal worm infection (e.g. Threadworms or Pinworms)?

☐ 1 No ---→ go to Question 4.3

☐ 2 Yes ---→ a. How old was he/she when they first had worms?

☐ 1 Less than 1 year ☐ 2 1 to 3 years ☐ 3 4 to 6 years

b. How many times has he/she had worms? ☐☐

4.3 During the last year, how much time did your child spend in the sun?

	Summer	<1 hr a day	1 to 2 hrs per day	2 to 3 hrs per day	3 to 4 hrs per day	≥ 4 hrs a day
a.	on weekdays	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b.	on weekends	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Winter					
c.	on weekdays	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d.	on weekends	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4.4 a. What was your child's last measured **weight**? ☐☐.☐ kg

b. Date recorded D D/M M/Y Y

4.5 a. What was your child's last measured **height**? ☐☐☐ cm

b. Date recorded D D/M M/Y Y

4.6 Does your child have any brothers or sisters (including half siblings)?

☐ 1 No ---→ go to Question 4.7 ☐ 2 Yes - *Please provide details about the child's siblings, starting from oldest to youngest*

Number	Date of birth	Relation	Sibling type	Do they live more than ½ the time in the child's household?
1	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes
2	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes
3	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes
4	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes
5	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes
6	D D/M M/Y Y	☐ 1 Sister ☐ 2 Brother	☐ 1 Full ☐ 3 Half, father common ☐ 2 Half, mother common ☐ 4 Other	☐ 1 No ☐ 2 Yes

Please list any other siblings and answer questions above:

4.7 Below is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child in the past ONE month.

		Never	Almost Never	Some-times	Often	Almost Always
	Physical Functioning (problems with...)					
a.	Walking more than one block	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b.	Running	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c.	Participating in sports activity or exercise	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d.	Lifting something heavy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e.	Taking a bath or shower by him or herself	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f.	Doing chores, like picking up his or her toys	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g.	Having hurts or aches	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h.	Low energy level	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Emotional Functioning (problems with...)					
i.	Feeling afraid or scared	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j.	Feeling sad or blue	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k.	Feeling angry	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l.	Trouble sleeping	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m.	Worrying about what will happen to him or her	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Social Functioning (problems with...)					
n.	Getting along with other children	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
o.	Other kids not wanting to be his or her friend	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
p.	Getting teased by other children	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
q.	Not able to do things that other children his or her age can do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
r.	Keeping up when playing with other children	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	School Functioning (problems with...)					
s.	Pay attention in class	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
t.	Forgetting things	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
u.	Keeping up with school activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
v.	Missing school because of not feeling well	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
w.	Missing school to go to doctor or hospital	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4.8 The next questions are about your child's emotional well-being and behaviour. These can be big issues for 6-year-olds. It would help us if you answered the items as best you can even if you are not absolutely certain. Please give your answers on the basis of the child's behaviour over the last 6 months.

		Not True	Somewhat True	Certainly True
a.	Considerate of other people's feelings	☐ 1	☐ 2	☐ 3
b.	Restless, overactive, cannot stay still for long	☐ 1	☐ 2	☐ 3
c.	Often complains of headaches, stomach-aches or sickness	☐ 1	☐ 2	☐ 3
d.	Shares readily with other children, for example toys, treats, pencils	☐ 1	☐ 2	☐ 3
e.	Often loses temper	☐ 1	☐ 2	☐ 3
f.	Rather solitary, prefers to play alone	☐ 1	☐ 2	☐ 3
g.	Generally well behaved, usually does what adults request	☐ 1	☐ 2	☐ 3
h.	Many worries or often seems worried	☐ 1	☐ 2	☐ 3
i.	Helpful if someone is hurt, upset or feeling ill	☐ 1	☐ 2	☐ 3
j.	Constantly fidgeting or squirming	☐ 1	☐ 2	☐ 3
k.	Has at least one good friend	☐ 1	☐ 2	☐ 3
l.	Often fights with other children or bullies them	☐ 1	☐ 2	☐ 3
m.	Often unhappy, depressed or tearful	☐ 1	☐ 2	☐ 3
n.	Generally liked by other children	☐ 1	☐ 2	☐ 3
o.	Easily distracted, concentration wanders	☐ 1	☐ 2	☐ 3
p.	Nervous or clingy in new situations, easily loses confidence	☐ 1	☐ 2	☐ 3
q.	Kind to younger children	☐ 1	☐ 2	☐ 3
r.	Often lies or cheats	☐ 1	☐ 2	☐ 3
s.	Picked on or bullied by other children	☐ 1	☐ 2	☐ 3
t.	Often volunteers to help others (parents, teachers, other children)	☐ 1	☐ 2	☐ 3
u.	Thinks things out before acting	☐ 1	☐ 2	☐ 3
v.	Steals from home, school or elsewhere	☐ 1	☐ 2	☐ 3
w.	Gets along better with adults than with other children	☐ 1	☐ 2	☐ 3
x.	Many fears, easily scared	☐ 1	☐ 2	☐ 3
y.	Good attention span, sees tasks through to the end	☐ 1	☐ 2	☐ 3

4.9 At what time does your child usually go to bed at night? ☐ pm

4.10 What is their usual wake-up time in the morning? ☐ am

5. QUESTIONS ABOUT YOUR FAMILY

5.1 Since we last were in contact with you when your child was 4 years, has anyone in your immediate family developed any new symptoms or diagnoses of .....

		No one	Child's mother	Child's father	Child's brother 1	Child's brother 2	Child's sister 1	Child's sister 2	Other sibling
a.	Asthma	☐	☐	☐	☐	☐	☐	☐	☐
b.	Eczema	☐	☐	☐	☐	☐	☐	☐	☐
c.	Hay fever	☐	☐	☐	☐	☐	☐	☐	☐
d.	Latex allergy	☐	☐	☐	☐	☐	☐	☐	☐
e.	Insect allergy *(specify insect)*	☐	☐	☐	☐	☐	☐	☐	☐
f.	Food allergy *(specify food)*	☐	☐	☐	☐	☐	☐	☐	☐

5.2 Do you currently have pets at home?

☐1 No ---→ go to Question 5.4 ☐2 Yes

If yes,

			Inside and outside	Outside only	Inside only
a.	Number of cats:	☐	☐1	☐2	☐3
b.	Number of dogs:	☐	☐1	☐2	☐3
c.	Number of birds:	☐	☐1	☐2	☐3
d.	Other pet *(please specify)*	☐	☐1	☐2	☐3

5.3 Does your household currently keep your pets outside or avoid having pets at home because of allergy?

☐1 No ☐2 Yes, avoid cats only ☐3 Yes, avoid dogs only ☐4 Yes, avoid both cats and dogs

☐5 Yes, avoids other pets *(please specify)*

5.4 Do you live on a farm or property with any animals (livestock)? ☐1 No ☐2 Yes

5.5 How many people in your household regularly smoke (most days of the week)? ☐

5.6 What is the total number of cigarettes smoked by all residents **outside** your home?

☐ per week

5.7 What is the total number of cigarettes smoked by all residents **inside** your home?

☐ per week

5.8 Does anyone smoke in the same room as the child?

☐ 1 Never ☐ 2 Sometimes ☐ 3 Usually

5.9 What is the highest education or vocational qualification completed by the child's....

	Mother	Father
Year 10 or less	☐ 1	☐ 2
Year 11	☐ 1	☐ 2
Year 12	☐ 1	☐ 2
Trade apprenticeship	☐ 1	☐ 2
Technical diploma/certificate	☐ 1	☐ 2
University degree	☐ 1	☐ 2
Postgraduate university degree	☐ 1	☐ 2
Other *(please specify)*	☐ 1	☐ 2

☐

5.10 a. Is the child's **mother** currently in paid work? ☐ 1 No ☐ 2 Part-time ☐ 3 Full-time

b. Is the child's **father** currently in paid work? ☐ 1 No ☐ 2 Part-time ☐ 3 Full-time

5.11 a. Child's **mother's** current weight
(if currently or recently pregnant, record pre-pregnancy weight): ☐☐☐.☐ kg

b. Child's mother's height: ☐☐☐ cm

c. Child's mother's date of birth: D D/M M/Y Y

5.12 a. Child's **father's** current weight: ☐☐☐.☐ kg

b. Child's father's height: ☐☐☐ cm

c. Child's father's date of birth: D D/M M/Y Y

5.13 In which country/region was your child born?

☐ 1 Australia / New Zealand	☐ 6 America
☐ 2 Europe	☐ 7 Asia (e.g. Singapore, Malaysia, Vietnam)
☐ 3 India / Pakistan / Bangladesh	☐ 8 Middle East (e.g. Egypt, Syria)
☐ 4 Africa	☐ 9 Other ☐
☐ 5 United Kingdom	

☐

5.14 Child's **mother's** ethnicity?

- ☐ 1 Caucasian
- ☐ 2 Asian
- ☐ 3 African
- ☐ 4 Aboriginal or Torres Strait Islander
- ☐ 5 Middle Eastern
- ☐ 6 Other *(please specify)*

5.15 Child's **father's** ethnicity?

- ☐ 1 Caucasian
- ☐ 2 Asian
- ☐ 3 African
- ☐ 4 Aboriginal or Torres Strait Islander
- ☐ 5 Middle Eastern
- ☐ 6 Other *(please specify)*

5.16 What is the ethnicity of your child's natural GRANDPARENTS? (i.e., their ethnic origin)

Mother's Parents:		Father's Parents:	
Mother *(tick one box)*	Father *(tick one box)*	Mother *(tick one box)*	Father *(tick one box)*
☐ 1 Caucasian	☐ 1 Caucasian	☐ 1 Caucasian	☐ 1 Caucasian
☐ 2 Asian	☐ 2 Asian	☐ 2 Asian	☐ 2 Asian
☐ 3 African	☐ 3 African	☐ 3 African	☐ 3 African
☐ 4 Aboriginal or Torres Strait Islander	☐ 4 Aboriginal or Torres Strait Islander	☐ 4 Aboriginal or Torres Strait Islander	☐ 4 Aboriginal or Torres Strait Islander
☐ 5 Middle Eastern	☐ 5 Middle Eastern	☐ 5 Middle Eastern	☐ 5 Middle Eastern
☐ 6 Other *(please specify)*	☐ 6 Other *(please specify)*	☐ 6 Other *(please specify)*	☐ 6 Other *(please specify)*

Thank you for completing this questionnaire.
Please check that you've answered all the questions, on both sides of each page and filled in the date on Page 1.
Please return it to us in the reply paid envelope.
For queries, contact the HealthNuts team on (03) 8341 6266 or health.nuts@mcri.edu.au

Just in case your address or phone number changes, is there a friend or relative (such as a grandparent or aunt/uncle) we could contact?

Given name(s):

Surname:

Relationship to the child:

Address – Number and Street:

Address – Suburb: Postcode: State:

Phone: Mobile: Home: ( )

Email:

Appendix 7: HealthNuts Age 6 Paper Activity Log

Health Nuts
Nuts About Health

*Please remember to start to fill out diary for the day after the monitor is put on & describe each day.

Activity Monitor Diary

Monitor number: _____
ID: _____

Child name:

- This **accelerometer** starts recording on: _____ ___ / ___ / ___ at ___ am/pm
- Please remove the **accelerometer** on: _____ ___ / ___ / ___ at ___ am/pm

What kind of day was it today? Please describe your child's day and let us know if it was unusual in any way. For example, you might write 'school day', 'weekend', 'holidays', 'sick' or 'sports carnival'. *Day 1 is the day AFTER your HealthNuts assessment (the day after the monitor is put on).

	Day of week	Wake up time	Bed time	Description of child's day
0	[eg Mon 8 June]	[eg 7:30am]	[eg 8:00pm]	[eg Took part in the HealthNuts allergy health check!]
1		*am/pm*	*am/pm*	
2		*am/pm*	*am/pm*	
3		*am/pm*	*am/pm*	
4		*am/pm*	*am/pm*	
5		*am/pm*	*am/pm*	
6		*am/pm*	*am/pm*	
7		*am/pm*	*am/pm*	
8		*am/pm*	*am/pm*	

The accelerometer is waterproof! Your child doesn't need to take it off for swimming or showering/bathing. But, if your child does take it off at any time, please write down the time it was taken off, the time it was put it back on, and why it was taken off.

Day	Date	Time off	Time on	Reason taken off
	__/__/__	*am/pm*	*am/pm*	
	__/__/__	*am/pm*	*am/pm*	
	__/__/__	*am/pm*	*am/pm*	
	__/__/__	*am/pm*	*am/pm*	

Wearing and returning the Accelerometer

- The accelerometer records your child's movement every 15-30 seconds, day and night
- Your child wears it on their *non-dominant* **wrist** (**not** the hand he/she writes with), just like a watch
- **It is worn for 8 days** – keep it on your child all the time
- Leave it on over night! It should not disturb your child's sleep
- The accelerometer is **waterproof!** It doesn't need to be taken off for swimming or having a bath or shower

Important! If your child does need to take the accelerometer off:

- **Write down when and why** on the front of this sheet
- **Put it back on your child as soon as you can** (on the *non-dominant* wrist)

When the 8 days are up:

- Mail the accelerometer with this Sheet back to us using the package we gave you
- Please post the package in an Australia Post mailbox **as soon as possible**

Do you have any comments about your child wearing the accelerometer?

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Thank you for your help!

The HealthNuts Study team

Any questions?

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murdoch children's research institute