University of Southern Queensland

THE ECONOMICS OF CHILD AND ADOLESCENT HEALTH IN AUSTRALIA

A Thesis Submitted by

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ABSTRACT

Long-term medical conditions or disabilities, such as respiratory and allergic diseases, and obesity are the leading chronic conditions that affect children worldwide. This thesis examines the associations between maternal health and different childhood health outcomes, including wheezing, asthma, eczema and long-term medical conditions or disabilities. This thesis also identifies vulnerable clusters based on childhood wheezing, asthma or eczema morbidities and on the lifestyles and health behaviours of adolescents that contribute to obesity. Finally, this thesis examines the excess healthcare costs that are associated with children's asthma and any medical condition or disability that lasts six months or more. To accomplish the research objectives and make new contributions to the literature, this 'PhD by publication' thesis presents an accumulation of eight studies that use data from the Longitudinal Study of Australian Children (LSAC). The adapted developmental origins framework and the bio-ecological model of child development underpin this thesis, and the research relies on the applied quantitative approach for the empirical analyses. The spectrum of the study was enhanced by establishing data linkages between the Health CheckPoint survey, the Pharmaceutical Benefits Scheme and the Medicare Benefits Schedule data with the LSAC databases. The thesis follows a typical format: the eight research articles are bookended by rudimentary introduction and conclusion chapters. The research contents of this thesis are divided into the following four main parts:

i) prevalence and risk factor analyses of children's health
   a. in general
   b. based on leading chronic diseases – wheezing, asthma and eczema (Papers 1 and 2)

ii) survival analyses and risk factor assessments for long-term medical conditions or disabilities (Papers 3 and 4)

iii) identification of clusters of vulnerable children in relation to respiratory and allergic diseases and health-related behaviour or lifestyle characteristics (Papers 5 and 6)

iv) cost studies that assess the excess healthcare cost of children that are associated with asthma and long-term health conditions or disabilities (Papers 7 and 8)

Paper 1 utilised a cross-section analysis of infants' and adolescents' health status through the lens of the foetal origins hypothesis and analyses data from Wave 1 and Wave 7 of the LSAC surveys. The study found evidence that poor maternal physical health status and health-related behaviours during pregnancy or up to 15 months from childbirth adversely affected their children's health during infancy and adolescence in all three of the health dimensions examined; the poor general health, the chronic health conditions and lower physical health scores. Maternal psychological distress during pregnancy also increased the odds that their offspring would develop chronic health conditions and have lower physical health scores. Focusing again on the foetal origins framework and further strengthened by using longitudinal data from eight waves, Paper 2 reveals that maternal asthma, obesity, and smoking during pregnancy are strongly associated with an increased risk of offspring's wheezing and asthma. This study also reveals that the risk of contracting childhood eczema is mainly associated with maternal asthma during pregnancy. Paper 3 deployed a panel data survival analysis method to estimate the prevalence of long-term medical conditions or disabilities in Australian children. This study also examined the association of maternal health-related risk factors with chronic health conditions. Through an application of the same technique (survival analysis), Paper 4 reveals that low birth weight, receiving emergency hospital services just after birth, being male and being obese during childhood up to the age of 15 years are associated with an increased risk of having a long-term medical condition or disability. Both Papers 3 and 4 deployed a 'developmental origins' framework in forming the study questions and interpreting the findings.

This thesis implemented an unsupervised machine learning method known as latent class clustering to identify the vulnerable clusters of children who experience wheezing, asthma or eczema and vulnerable children with problematic lifestyles and health behaviours who are prone to be obese and have a lower quality of life (Paper 5 and 6, respectively). Finally, Papers 7 and 8 were conducted using a health economic approach to assess the direct costs of healthcare services. Paper 7 utilised an assessment of the national-level excess healthcare costs for Australian children that are associated with the burden of asthma morbidity. The estimated increased costs to the Australian healthcare system due to childhood asthma are A$190.6 million per year among children ages 2-3–to-18-19, based on the 2018 population data. Paper 8 reveals that at the population level, the estimated total excess Medicare costs associated with a medical condition or disability among children ages 0-1-to–16-17 is, on average, A$170.0 million per year. The evidence from this thesis should help health policymakers find ways to reduce and control asthma, obesity and long-term health conditions or disabilities and gain further insight into the associated excess healthcare costs of asthma and any childhood medical condition or disability.

Keywords: Wheezing, Asthma, Obesity, Long-term medical condition, Disability, Health-related quality of life, Latent class analysis, Maternal health, Physical health index score, Healthcare costs, Medicare costs, PBS, MBS

CERTIFICATION OF THESIS

I Kabir Ahmad declare that the PhD Thesis entitled *The Economics of Child and Adolescent Health in Australia* is not more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, references, and footnotes.

This Thesis is the work of Kabir Ahmad except where otherwise acknowledged, with the majority of the contribution to the papers presented as a Thesis by Publication undertaken by the student. The work is original and has not previously been submitted for any other award, except where acknowledged.

Date: 22 July 2022

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Student and supervisors' signatures of endorsement are held at USQ.

STATEMENT OF CONTRIBUTIONS

This PhD thesis is drawn from the following published and submitted study papers in peer review journals. I am the lead author for all of the publications and manuscripts. I led the conceptual development, data extraction, analyses, interpretation, initial drafting and final revisions, and had final ownership of the submissions. I contributed entirely to the quantitative analyses and 65% to 75% of the overall contribution for each of the study. I gratefully acknowledge the guidance and contribution of my supervisors and other co-authors in the published and submitted studies contained in this thesis. The details of the scientific contribution of each researcher are provided below:

Study Paper I:

Ahmad K, Kabir E, Keramat SA, Khanam R: Maternal health and health-related behaviours and their associations with child health: Evidence from an Australian birth cohort. *PLoS One* 2021, 16(9):e0257188.

The overall contribution of Kabir Ahmad was 65% to this paper. Collectively Dr. Enamul Kabir, Dr. Sayed Afroz Keramat, and Professor Rasheda Khanam contribued the rest.

Study Paper II:

Ahmad K, Kabir E, Ormsby GM, Khanam R: Are wheezing, asthma and eczema in children associated with mother's health during pregnancy? Evidence from an Australian birth cohort. *Arch Public Health* 2021, 79(1):193.

The overall contribution of Kabir Ahmad was 75% to this paper. Collectively Dr. Enamul Kabir, Dr. Gail M. Ormsby, and Professor Rasheda Khanam contribued the rest.

Study Paper III:

Ahmad K, Ormsby GM, Kabir E, Khanam R: Association of maternal health characteristics with hazard of any medical condition or disability in Australian children. 2022. (under review in the SSM Population Health journal)

Kabir Ahmad contribtued 70% to this paper. Collectively Dr. Enamul Kabir, Dr. Gail M. Ormsby and Professor Rasheda Khanam contribued the rest.

Study Paper IV:

Ahmad, K., Keramat, S. A., Sathi, N. J., Kabir, E., & Khanam, R. (2022). Association of infant and child health characteristics with the hazard of any medical condition or disability in Australian children. *Arch Public Health, 80*(1), 158. doi:10.1186/s13690-022-00913-3

The overall conribution of Kabir Ahmad was 70% to this paper. Collectively Dr. Enamul Kabir, Dr. Sayed Afroz Keramat, Nusrat Jahan Sathi and Professor Rasheda Khanam contribued the rest.

Study Paper V:

Ahmad K, Kabir E, Ormsby GM, Khanam R: Clustering of asthma and related comorbidities and their association with maternal health during pregnancy: evidence from an Australian birth cohort. *BMC Public Health* 2021, 21(1):1952.

Kabir Ahmad contribtued 70% to this paper. Collectively Dr. Enamul Kabir, Dr. Gail M. Ormsby and Professor Rasheda Khanam contribued the rest.

Study Paper VI:

Ahmad K, Keramat SA, Ormsby GM, Kabir E, Khanam R: Clustering of lifestyle and health behaviours in Australian children and their relationship with obesity, self-rated health and quality of life. 2022. (Under 2nd review in the BMC Public Health journal)

Kabir Ahmad contribtued 75% to this paper. Collectively Dr. Enamul Kabir, Dr. Gail M. Ormsby and Professor Rasheda Khanam contribued the remainder.

Study Paper VII:

Ahmad K, Khanam R, Kabir E, Juerges H: The healthcare costs of asthma in Australian children: A longitudinal population-based study. 2022. (Submitted to the Value in Health Journal)

The overall contribution of Kabir Ahmad was 70% to this paper. Collectively Professor Hendrik Juerges, Professor Rasheda Khanam and Dr. Enamul Kabir contribued the rest.

Study Paper VIII:

Ahmad K, Khanam R, Keramat SA, Hashmi R, Keating B, Kabir E, Juerges H,: Excess healthcare costs associated with children's long-term medical condition or disability: Estimates from the Longitudinal Study of Australian Children (ready for submission to a journal)

The overall contribution of Kabir Ahmad was 60% to this paper. Collectively Professor Rasheda Khanam , Professor Hendrik Juerges, Professor Byron Keating, Dr. Rubayyat Hashmi, Dr. Syed Afroz Keramat and Dr. Enamul Kabir contribued the remainder.

This PhD thesis has also contributed towards engagements in 2021 World Congress on Health Economics, organised by International Health Economic Association, held in July 12-15, 2021, virtually. I have participated in the conference on 14 July under the category of "Health Beyond Health Care Services: Non-Medical Production of Health and the Value of Health". The title of the session was "External Impacts and Shocks on Health and the presentation title was "Maternal Health and Health-Related Behaviour during Pregnancy and Their Association with Infant and Adolescent Health: Evidence from an Australian Birth Cohort". I have also attended a poster presentation session on 13 July and presented finding of Study Paper V; the title of the presentation was "A Cluster Analysis of Asthma and Asthma-Related Comorbidities and the Associations between Maternal Health Status during Pregnancy and the Cluster Memberships of Australian Children"

This thesis also got a media coverage from the findings of Study Paper I, published on September 14, 2021, in the Courier Mail. In the online edition of the newspaper, the news was published under the 'lifestyle' section, titled as "Stress in pregnancy could leave babies with chronic health problems". In the print edition, the title of the news was "Pregnant stress a problem for later". Both versions of the news was reported by Felicity Ripper. Images of the news are presented in Appendix D.

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I would like to start this acknowledgment with my utmost gratitude and thanks to the Almighty God who bestowed fortune upon me to start and finish this challenging work. My PhD journey has reached its endpoint with the financial, academic, and mental support of many. Without the financial support from the University of Southern Queensland (USQ), the International Stipend and Tuition Fees Scholarship through the Research Training Program (RTP), this thesis study would not have been started, let alone completed. USQ, you are the real hero of this project, and you will be in my memory forever.

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Most importantly, I want to thank my principal supervisor, Professor Rasheda Khanam and associate supervisor, Dr Enamul Kabir, for being an indispensable part of my PhD journey. They were devoted and caring mentors to enable me to gain success in the difficult pathway of achieving the milestones. Their profound support with moral encouragement always surprised me and helped me surpass any problem. I want to thank my other associate supervisor, Professor Hendrik Jeurges, for his state-of-the-art academic support and feedback from Germany.

I want to express my gratitude to Graduate Research School, USQ for providing the infrastructure, resources and support to work efficiently to finish the thesis. I would also like to acknowledge and thank the Department of Social Services (DSS), the Australian Institute of Family Studies (AIFS) and the Australian Bureau of Statistics (ABS) for providing the LSAC data set. I am incredibly grateful to Professor Peter Terry and

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With appreciation, I would like to acknowledge the co-authors of the journal articles for their input at various stages. A massive thank you should go to Dr Rubayyat Hashmi and Dr Syed Afroz Keramat who have been incredibly friendly and helped me throughout my PhD journey. My heartfelt thanks go to Dr Mohammad Mohsin and Dr Wahid Ferdous for all their support in many aspects. A special thanks to Dr Barbara Harmes and Dr Gail Ormsby for reading through and polishing my thesis. I would also like to thank my loving and supportive Bangladeshi fellow PhD students and seniors, Dr Rezwanul Hasan Rana, Dr Mohammad Afshar Ali, Dr Md. Irteja Islam, Dr Rashidul Alam Mahumud, and Bidhan Nath.

Thank you to my beautiful sons – Iftekhar Ahmad (Shian) and Ihtiram Ahmad (Shihab) – who have brought such joy to my life. You two have sacrificed more than anyone so that I may complete this journey.

Finally, thank you to my wonderful wife, Taslima Khanam. You have been my pacesetter through this marathon. I am truly blessed to have been able to share my research thoughts and challenges and have insightful 'pep talks' with the same person that I am building a life and family with.

DEDICATION

TO

MY PARENTS

I dedicate this thesis to the living memory of my father who breathed his last in 2007 and of my mother who breathed her last in 2008. My beloved parents, thank you very much for your relentless support, love, and compassion in supporting me to this stage.

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ABBREVIATIONS

ABS	Australian Bureau of Statistics
ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike's Information Criterion
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CI	Confidence Interval
HCP	Child Health CheckPoint
DF	Degrees of freedom
DOHaD	Developmental Origin of Health and Disease
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FOAD	Foetal Origin of Adult Disease
FVC	Forced vital capacity,
GINA	Global Initiative for Asthma
GLM	Generalised or Asthma
HR	Hazard Ratio
ICU	Intensive Care Unit
LL	Log-likelihood
LR	Likelihood-ratio
LSAC	Longitudinal Study of Australian Children
MBS	Medicare Benefit Schedule
MEF	Mid expiratory flow (FEF 25%–75%)
Npar	Number of parameters
PedQL	Paediatric Quality of Life
PBS	Pharmaceutical Benefits Scheme
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Context

Long-term medical conditions such as respiratory and allergic diseases, obesity are the leading chronic conditions for children worldwide, as well as in Australia. From 2017–2018, around 43% of children aged 0–14 had at least one long-term condition, while 20% had two or more long-term conditions (Australian Bureau of Statistics, 2018). According to the self-reported data from the ABS National Health Survey (2017–18), the leading chronic conditions for children aged 0–14 were diseases of the respiratory system, particularly asthma (Australian Institute of Health and Welfare, 2018). Furthermore, the same survey reveals that over 8% of children aged 2–17 was obese.

The importance of childhood health and foetal development in utero in determining the future health capital of children has received attention in the last three decades (Barker, 1997). Research in this area continues to evolve. The theory of 'foetal origins' developed from past studies in which Barker (1992) claimed that foetal conditions are responsible for emerging non-communicable diseases in a person's later life (Barker, 1992, Barker, 1997, Barker and Clark, 1997). Later, in subsequent studies by epidemiologists and economists, the 'foetal origins' theory evolved further with a domain of non-communicable diseases of mother and children, including asthma, obesity and disability (Giallo et al., 2015, Scholtens et al., 2010, Stokholm et al., 2014, Zetstra-van der Woude et al., 2014, Schendel and Bhasin, 2008, Schieve et al., 2016).

It has been observed from subsequent research studies, inspired by the foetal origins hypothesis, that environmental effects during infancy and early childhood also play an important role in shaping development

from childhood to adolescence and into adulthood. These findings led to the framework termed the Developmental Origin of Health and Disease (DOHaD) (Gluckman and Hanson, 2004). The DOHaD contends that health conditions during pregnancy and childhood and exposure to the environment influence the risks of a wide range of diseases and conditions such as asthma, eczema, obesity, diabetes, cardiovascular disease and mental disorders (Roura and Arulkumaran, 2015b). Many of these diseases are also associated with the modern lifestyle, suggesting that there are behavioural risk factors for these diseases. These include unhealthy dietary practices, reduced physical activity, tobacco smoking, the harmful use of alcohol and other adverse environmental factors.

Therefore, there is a need for a growing understanding of these disease patterns at the population level and their impact on the lives of children and adolescents in Australia. This thesis study attempts to assess the contemporary status of the foetal and developmental origins of childhood respiratory and allergic diseases (wheezing, asthma and eczema), childhood obesity and any health condition or disability that affects children and contributes to the childhood disease burden in Australia. In exploring these diseases, this thesis will contribute to the field of health economics as it relates to childhood and adolescent health. Through eight distinct studies, this thesis investigates the contemporary status of the main determinants of children's health, identifying the most vulnerable adolescent groups in terms of health capital and determining the direct excess healthcare costs derived from the studied diseases.

This introductory chapter provides the following: the background of the research, a discussion of the factors influencing childhood health and well-being, a literature review and a description of the research gaps, the thesis' research objectives, an overview of the research methods (including research questions), a conceptual framework and a brief outline of the thesis structure.

1.2 Background and rationale

1.2.1 Respiratory and allergic diseases

Childhood respiratory and allergic diseases - wheezing, asthma, and eczema, are leading causes of global morbidity (Mallol et al., 2013). The 2000–2003 International Study of Asthma and Allergies in Children found that 14.1% and 7.3% of children aged 13–14 years suffered from asthma or eczema, respectively (Mallol et al., 2013). A 2018 Australian health survey revealed that among children aged 5–14 years, 11% reported current asthma, making asthma the leading health burden in that age group (Australian Institute of Health and Welfare). A longitudinal study conducted in 2009 found that 16.9% of Australian children born in 2004 experienced wheezing or asthma within the first three years of life (Australian Centre for Asthma Monitoring, 2009). Wheezing, asthma and eczema pose significant long-term health burdens to children (Gray et al., 2019), such as poor lung function or the development of persistent asthma in later life (Asher and Pearce, 2014, McGeachie et al., 2016, Stern et al., 2007, Kusel et al., 2007). Furthermore, the incidences of wheezing, asthma or eczema are influenced by maternal health and environmental conditions (Watson and McDonald, 2014, Lebold et al., 2020, Andersen et al., 2012) which include maternal exposure to asthma or obesity, antibiotic or antidepressant medication use, or smoking during pregnancy (Kusel et al., 2007, Harvey et al., 2020, Gray et al., 2019, Ekstrom et al., 2015, Chen et al., 2020a, Mulder et al., 2016, Liu et al., 2015). Therefore, comprehensive research to determine the longitudinal prevalence of wheezing, asthma and eczema among children, while taking maternal health during pregnancy into account, should be a public health priority.

1.2.2 Prevalence of asthma by age and sex

Based on the 2017–18 National Health Survey of Australia, asthma was more common among boys than girls in the 0–14 age group. On the

contrary, among those aged 25–34 and those 45 and over, asthma was more common among women than men. Prevalence was similar among males and females aged 15–24 and 35–44. This change in prevalence for men and women in adulthood is likely due to a complex interaction between changing airway size and hormonal changes that occur during adolescent development, as well as differences in environmental exposures (Almqvist et al., 2008).

1.2.3 Obesity

Excess weight and obesity are global public health problems, and their prevalence has tripled since 1975. In 2016, 39% of adults (1.9 billion) aged 18 years and over were overweight, and 13% (650 million) were obese. Over 340 million children and adolescents aged 5–19 were overweight or obese in 2016, even though this condition is preventable (WHO 2020: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). The prevalence of excess weight and obesity among children and adolescents aged 5–19 has risen dramatically, from just 4% in 1975 to just over 18% in 2016. According to the data for 2017–18, nearly two-thirds of Australian adults were either overweight or obese, and 1 in 3 adults was obese (Australian Bureau of Statistics 2018). Among Australian children and adolescents aged 2–17, an average of 1 in 4 (25%) were overweight or obese, and 1 in 12 (8.2%) were obese. While the prevalence of excess weight and obesity increased for those aged 5–17 between the data for 1995 (20%) and the 2007–2008 data (25%), since then, it has remained relatively stable over the last decade (Australian Bureau of Statistics 2018).

1.2.4 Any health condition or disability

Medical conditions or disabilities generate a disease burden for children worldwide. The term ‘medical condition or disability’ refers to any disability or related medical condition that affects adults and children, for example, sight, hearing and speech problems; blackouts; chronic pain;

nervousness; head injuries; difficulty breathing; learning difficulties; limited use of arms, fingers, legs or feet; gripping problems; or other physical long-term health conditions (CDC, 2020, CDC, 2021). The Global Burden of Disease study in 2004 estimated that a total of 5.1% (93 million) children aged 14 or under lived with moderate or severe disability, and approximately 0.7% (13 million) lived with severe medical conditions (World Health Organization, 2008). In addition, approximately 150 million children aged 18 years or under have a medical condition or disability, and most of them live with the reality of exclusion in the world (UNICEF, 2006). A similar picture has been observed in Australia. In 2018, nearly 7.7% of children (357,500) under the age of 15 years had experienced a medical condition or disability, of which 4.5% and 1.6% had severe and moderate/mild conditions, respectively (Australian Bureau of Statistics, 2018). In addition, the proportion of children with disabilities has increased from 6.9% (295,900) in 2012 (Australian Bureau of Statistics, 2018).

1.2.5 The burden of direct healthcare costs in the healthcare systems

Studies of the costs of illness in the context of children and adolescents in Australia remain limited. The cost of illness for children's medical condition or disability could be determined using the economic assessment approach, which includes two aspects: healthcare (direct cost) and societal (indirect cost). The direct cost comprises the assessment of the cost of patient care, whereas the indirect cost includes the cost of non-patient costs, such as loss of productivity (Van den Hout, 2010). The Australian healthcare system is ideal for analysing the direct healthcare costs since the system is very comprehensive and more than 99% of the population has full Medicare support. However, studies of the direct and indirect costs of asthma morbidities and long-term health conditions or disabilities among children or adolescents are scarce. Vu et al. (2020) estimate the costs of disability in Australia by using the Standard of Living and a dynamic model approach, but for adults in

Australia. There are few studies evaluating the healthcare costs from Medicare data on obesity, ADHD, mental health, and sleep problems in Australia (Au, 2013; Sciberras et al., 2013, Clifford et al., 2015, Lucas et al., 2013; Quanch et al. 2013, Vu et al., 2020). Furthermore, the Longitudinal Study of Australian Children (LSAC) provides linked Medicare data and also about the morbidities of asthma, and long-term medical condition or disability. Hence, these datasets could be utilised to evaluate the healthcare costs of asthma and long-term medical condition or disability among Australian children.

1.3 Factors influencing childhood health and well-being

Some general perceptions of the causes of diseases often only recognise the nature of biological and psychological factors. However, there is increasing evidence that a complex interaction between factors (e.g. genetic, environmental, behavioural and societal) contribute to the health and disease of children, adolescents and adults. Key factors that contribute to a child developing any health or well-being issue are displayed in Figure 1. The figure shows that broad social and environmental factors, as well as factors related to socioeconomic status, knowledge, attitude, beliefs, health behaviours, psychology, safety and biology, can directly or indirectly influence a person's health. Many of these factors may contribute individually or in combination in causing children to develop a disease; however, some components have a higher direct impact on a particular disease than others. For example, the health behaviour of using tobacco has a greater effect on asthma than it has on obesity. Further, socioeconomic characteristics affect common risk factors such as dietary patterns, exercise and obesogenic environments that aggravate the causal relationship between obesity and several other diseases. The detailed theoretical frameworks linked to this framework for determinants of health are discussed in Section 1.9 of this chapter (Australian Institute of Health and Welfare, 2020).

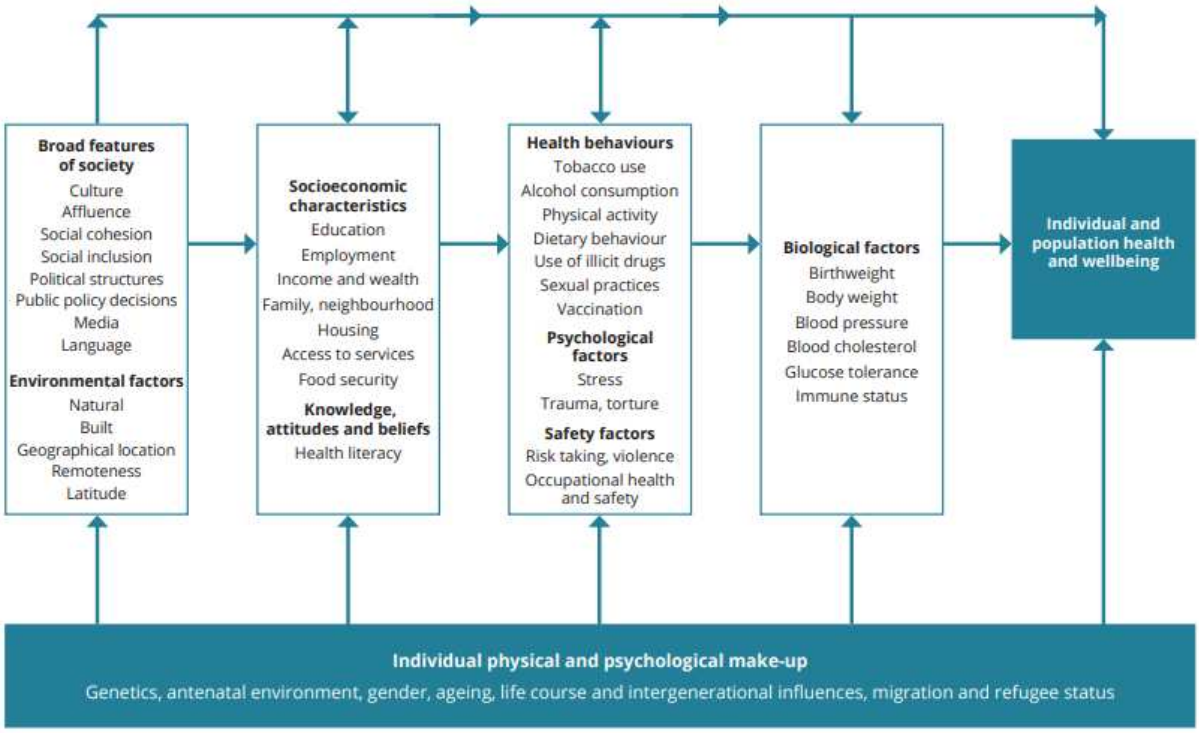

Figure 1: Framework for determinants of health

Source: Australian Institute for Health and Welfare 2020

1.4 The importance of addressing the issues of childhood health and well-being

Health professionals and policymakers are increasingly providing evidence that investing in children's health is a sound economic decision for governments. Though there are calls on moral and public health grounds that emphasise the benefits of further research and additional interventions, health economists are also explaining the potentially vast economic advantages that may result from these investments. For example, Belli et al. (2005) conducted a review of the existing literature and demonstrated that there are potential short-term, intermediate channels through which improvements in children's health can create an economic impact (Belli et al., 2005). Figure 2 presents the channels that connect improvements in health with better economic performance. It also describes the circular relationship between health and growth. This thesis study intends to contribute to understanding the childhood health

determinants that support decision-making in the priority areas of childhood health investments for policymakers.

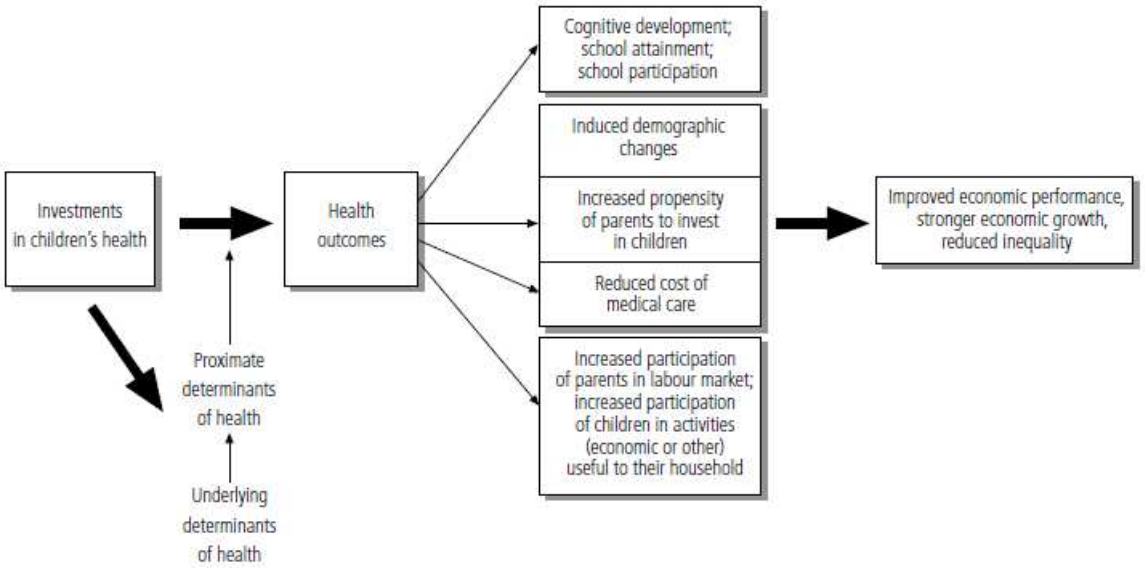

Figure 2: Channels through which childhood health interventions benefit the economy

(Source: Belli et al., 2005)

1.5 Objectives of the study

This research ventures to fill gaps in the extant literature by providing new evidence and a critical assessment of the foetal and developmental origins of childhood health outcomes and well-being in the context of Australia through the use of longitudinal data. In the context of the prevailing gaps in the existing research, the overall goal of this thesis is to untangle the determinants of children and adolescents' health and evaluate the associated costs of illness for the selected morbidities using LSAC data. Specifically, the research objectives for each of the studies are divided into four main research themes:

(i) Assessing the prevalence and identifying the risk factors of infant and adolescent's general health, any health condition and physical health index score, and childhood wheezing, asthma and eczema to extend the understanding of foetal origins of childhood health.

(ii) Evaluating the prevalence and risk factors of any medical condition or disability through the survival analysis of time-to-event data.

(iii) Classifying adolescents and identifying vulnerable groups through the use of the LCA, a machine learning-based structural modelling strategy based on health morbidities and health-related characteristics.

(iv) Investigating the cost of illness in the context of direct healthcare costs associated with asthma and any long-term medical condition or disability.

1.6 Overview of methods

This thesis includes eight studies based upon secondary sources of data from the LSAC and Health CheckPoint surveys. A summary of the data sources used for this thesis has been presented below. This section also provides a synopsis of the study designs and methods that were followed to address the research questions.

1.6.1 Data sources

Data from the LSAC have been utilised to investigate the hypotheses regarding the impact of maternal and infant health conditions on the health outcomes of the study child in their infancy or adolescence or longitudinally during childhood. The LSAC study, also popularly known as Growing Up in Australia, is conducted in partnership with the Department of Social Services, the AIFS and the Australian Bureau of Statistics. The LSAC recruited two cohorts of children, identified as the B cohort ('birth' at Wave 1) and the K cohort ('kindergarten' at Wave 1). This thesis utilised the B-cohort data across all the studies under the thesis. The LSAC captures information on multiple dimensions of children's development, health and well-being, following them until 2020 in nine consecutive waves, which added valuable information on the B-cohort children, who were born between March 2003 and February 2004.

As part of the main focus of the LSAC, a wide spectrum of family information for each study child has been collected: for example, parental physical and mental health, parenting style (warmth, discipline), health-related behaviours (smoking, alcohol consumption, etc.) and information on the economic resources of the household (income, employment, housing conditions, and neighbourhood) for each wave. Most of the data are collected in face-to-face interviews with the primary carer and self-completion questionnaires, including computer-assisted instruments in more recent waves. The datasets of the LSAC have enabled this study project to investigate the influence of family characteristics, including mothers' physical and mental health, on children's physical health and their health-related quality of life outcomes.

This study project also used data obtained from the specialised one-off physical health assessment of the LSAC study children, termed the Health CheckPoint (HCP) survey. This data enabled us to learn about the spirometry health outcome differences (lung function) as a biomarker of the health status of the study children during adolescence (age 12–13), among the distinct clusters of adolescents based on asthma and related morbidities. Further, the LSAC has linked datasets for the healthcare costs of the study participants, which were obtained from the Medicare database of the Australian government through its universal healthcare system. Costs included the subsidies for healthcare services/attendances (Medicare Benefits Schedule [MBS]) and prescription medications (Pharmaceutical Benefits Scheme [PBS]). In order to conduct two healthcare cost studies, this thesis study utilised these datasets obtained from the Medicare database.

1.6.2 Study design

The papers included in this thesis were both cross-sectional and longitudinal in design. As they evolved based on the aims of the thesis, all the eight papers utilised a wide range of health economic and

epidemiological methods to attempt to answer the relevant research questions. Paper 1 used the cross-sectional datasets of Wave 1 and Wave 7 and applied the incidence-based approach to devise the logistic regression models for measuring determinants of infant and adolescent health from the B cohort of the LSAC participants. Papers 2–4 used a longitudinal study design. Paper 2 used logistic regression models to measure the health burden of wheezing, asthma and eczema, and Papers 3 and 4 deployed the advanced time-to-event approach to perform the survival analysis and assess the health burden of any medical condition or disability that lasted six months or more. All three of these studies used data from eight waves of the LSAC to enable the examination of the long-term health burden of children in Australia.

Papers 5 and 6 undertook a cross-sectional exploration to identify the latent class clustering of adolescents. In addition to the structural modelling of latent class clustering, these two studies also deployed logistic and OLS regressions to determine the risk factors associated with the defined clusters of adolescents. Finally, Papers 7 and 8 deployed the longitudinal study design and examined both cross-sectional and longitudinal techniques to assess the additional healthcare costs for the diseases of asthma and any medical condition or disability. In terms of statistical modelling, these studies used generalised linear modelling (GLM) with the combination of log link and Gamma distribution.

Table 1 demonstrates the research focus, research question, study design, data source, analytic sample and method of each study at a glance. Subsequently, Figure 3 lists the studies included under each of the research themes and the publication or journal submission details of each paper.

Table 1: Objectives, research questions and study designs of eight papers in brief

Research themes	Study No.	Study objective/s	Research questions (RQ)	Data source and study sample	Main variables	Study design and statistical measures
Extend the understanding of foetal and developmental origins factors of infant and adolescents' disease	Paper 1	- To determine the foetal and developmental origins factors associated with infant and adolescent health	- RQ1: What maternal health factors during pregnancy or in the year after childbirth are associated with infant and adolescent health outcomes? - RQ2: To what extent do these associations exist in infancy and adolescence?	- B-cohort data from the LSAC - 5,019 infants born in 2004 (Wave 1) - 3,327 adolescent children in 2016 (Wave 7)	Outcome variables: general health, presence of a medical condition or disability and physical health outcome index of children Explanatory variables: general maternal health, presence of a medical condition or disability and mental health during pregnancy	- Cross-sectional study from longitudinal data from two points in time - Multivariate logistic regression model - Ordinary least square regression model
	Paper 2	- To determine the prevalence and in-utero and environmental effect of childhood wheezing, asthma and eczema	- RQ3: What are the sex-specific longitudinal prevalence rates for respiratory and allergic diseases – wheezing, asthma and eczema? - RQ4: What maternal health factors during pregnancy are associated with children's wheezing, asthma and eczema? - RQ5: What are the age and sex-segregated differences of the associations?	- B-cohort data from the LSAC - 31,367 person-year observations from 4,977 children across eight waves (Waves 1–8)	Outcome variables: wheezing, asthma and eczema Explanatory variables: gestational age at birth; pre-pregnancy obesity; maternal asthma, smoking habits and medications during pregnancy	- Longitudinal prospective study - Multivariate logistic regression model
Survival analysis of the hazard of any childhood medical condition or disability	paper 3	- To determine the developmental origin factors (with a maternal health focus) associated with the risk of developing long-term medical conditions or disabilities in childhood	- RQ6: What is the hazard rate of any medical condition or disability acquisition in Australian children? - RQ7: Are maternal health-related characteristics (during pregnancy and over 15 years after childbirth) associated with developing any medical condition or acquiring a disability?	- B-cohort data from the LSAC (Waves 1–8) - 51,009 person-year survival data from 5,107 children	Outcome variable: any medical condition or disability Explanatory variables: obesity, general health, any medical condition, mental illness, mental stress during pregnancy	- Longitudinal prospective study - Survival Analysis approach - Parametric panel regression modelling of survival data

Research themes	Study No.	Study objective/s	Research questions (RQ)	Data source and study sample	Main variables	Study design and statistical measures
	Paper 4	To determine the developmental origin factors (with an infant and childhood health focus) associated with the risk of developing long-term medical conditions or disabilities in childhood	- RQ8: Are infant and child health characteristics (birth weight, gestational age, after-birth emergency service use and obesity status) associated with developing any medical condition or acquiring a disability among Australian children?	- B-cohort data from the LSAC (Waves 1–8) - 51,009 person-year survival data from 5,107 children	Outcome variables: any medical condition or disability Explanatory variables: birth weight, gestational age, obesity, after-birth emergency services use	- Longitudinal prospective study - Survival analysis approach - Parametric panel regression modelling of survival data
Understanding classifications of health morbidity or health-related characteristics and identifying vulnerable clusters of adolescents	Paper 5	- To identify the distinct latent class clusters of adolescents based on the characteristics of asthma and related comorbidities - To assess the association between maternal health during pregnancy and the identified clusters	- RQ9: Do there exist distinct clusters of asthma and related comorbidities (wheezing, eczema and others) among Australian children? - RQ10: Do the health outcomes differ by the distinct clusters? - RQ11: Are the distinct clusters of adolescents associated with maternal health status during pregnancy?	- Health CheckPoint survey and B-cohort data from the LSAC - 1,777 Australian children aged 12–13 years who participated in both Health CheckPoint and Wave 7 surveys	Outcome (latent) variable: asthma clusters Explanatory variables: ever diagnosed with asthma, currently treating asthma, wheezing, eczema, sleep problem, general health, any health condition, food allergy Comparison variables: lung function, general well-being	- Cross-sectional study of longitudinal prospective data of two waves - Latent Class Cluster Analysis - Multivariate logistic regression model
	Paper 6	- To identify the distinct latent class clusters of adolescents based on adolescent lifestyle characteristics and health-related behaviours - To estimate the association between obesity-related health outcomes and the identified clusters	- RQ12: Do there exist distinct clusters of Australian children based on lifestyle characteristics and health behaviours (for example, physical activity, diet, sedentary behaviour, smoking, alcohol consumption, sleep problems, eating disorders and weight consciousness)? - RQ13: Do health outcomes differ between the distinct clusters? - RQ14: Are the distinct clusters of adolescents associated with obesity, general health status and paediatric quality of life (PedsQL)?	- B-cohort data from LSAC - 3,127 Australian children aged 14–15 years (Wave 8)	Outcome variable: lifestyle and health behaviour clusters Explanatory variables: physical activity, sedentary behaviour, alcohol consumption, smoking, diet, eating disorder, sleep, weight-control behaviours Comparison variables: obesity, general health, health-related quality of life	- Unsupervised machine learning approach for clustering - Cross-sectional study of longitudinal prospective data - Latent Class Cluster Analysis - Multivariate logistic regression model - Ordinary least square regression model

Research themes	Study No.	Study objective/s	Research questions (RQ)	Data source and study sample	Main variables	Study design and statistical measures
Investing the cost of illness from the perspective of healthcare costs	Paper 7	- To evaluate the direct healthcare costs and their differences by asthma morbidity status in children - To estimate the excess healthcare cost of asthma illness in the Australian population by examining the longitudinal cost data	- RQ15: What are the total excess healthcare costs for children who are experiencing asthma currently across the waves? - RQ16: What are the total excess healthcare costs for children who are experiencing asthma in multiple waves or persistently in all waves? - RQ17: What are the excess healthcare costs for asthma illness for the Australian children at population level?	- B- and K-cohort data from the LSAC (Waves 1–8) - 51,839 observations from 8,657 children - Linked MBS and PBS cost data	Outcome variable: total healthcare costs (MBS + PBS costs) Explanatory variable: currently treating asthma	- Longitudinal study design of disease prevalence and healthcare costs - Generalised linear modelling (GLM) with log-link data and Gamma distribution - Marginal estimate of cost differences
	Paper 8	- To evaluate direct healthcare costs and their differences by medical condition or disability status in children - To estimate the excess healthcare cost of having any medical condition or disability in the Australian population by examining the longitudinal cost data	- RQ18: What are the total excess healthcare costs for children who are experiencing any medical condition or disability currently across the waves? - RQ19: What are the total excess healthcare costs for children who are experiencing any medical condition or disability in multiple waves? - RQ20: What are the excess healthcare costs associated with having any medical condition or disability for the Australian children at population level?	- B- and K-cohort data from the LSAC (Waves 1–8) - 51,839 observations from 8,657 children - Linked MBS and PBS cost data	Outcome variable: total healthcare costs (MBS + PBS costs) Explanatory variable: any medical condition or disability	- Longitudinal study design of disease prevalence and healthcare costs - Generalised linear modelling (GLM) with log-link data and Gamma distribution - Marginal estimate of cost differences

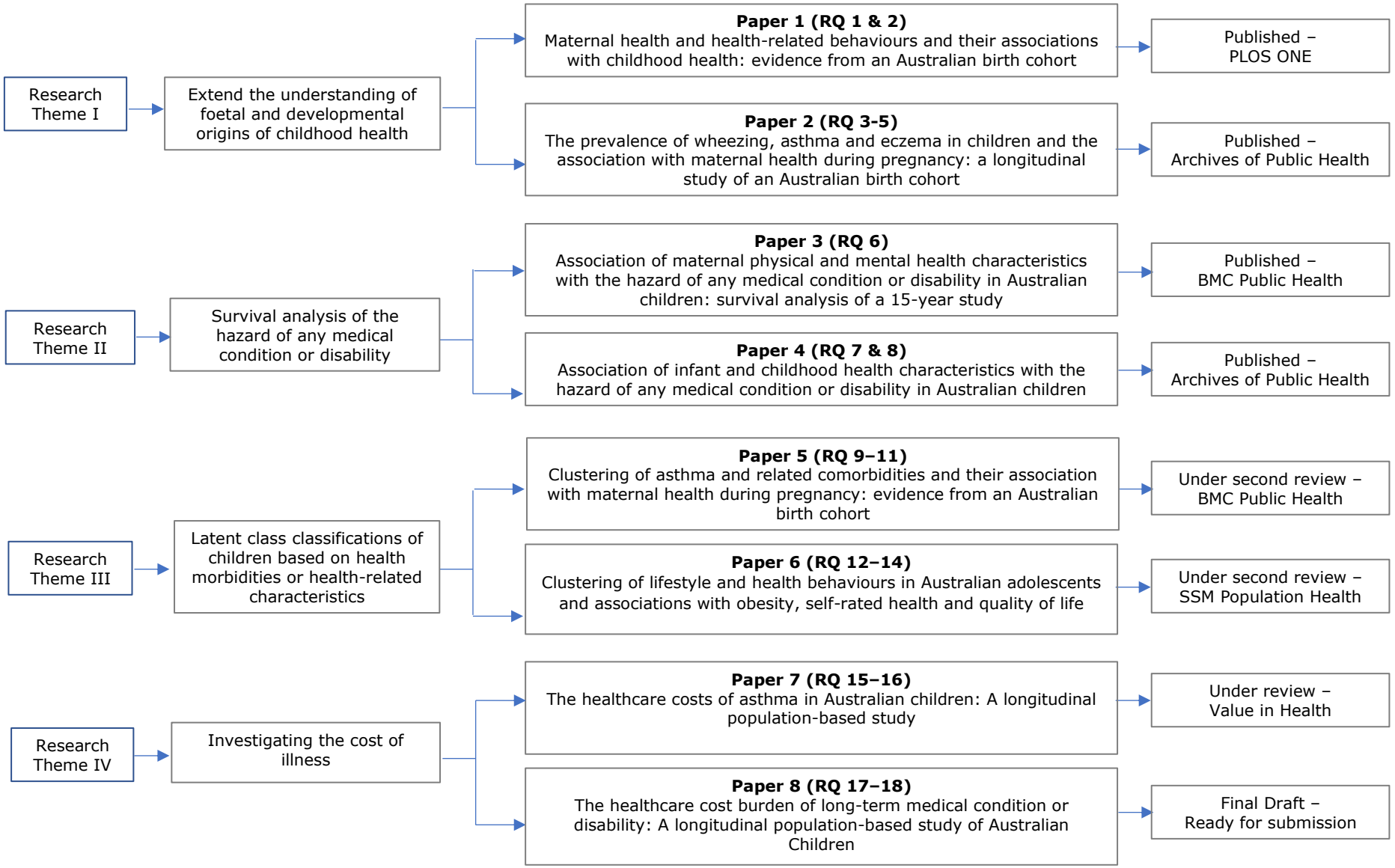

Figure 3: Research theme and study papers included in the thesis

1.7 Theoretical framework

1.7.1 Foetal Origins of Adult Disease

Prominent physician and epidemiologist David J. Barker first established that foetal conditions are responsible for emerging diseases in later life. He posited that a lack of nutrition in utero during pregnancy that causes low birth weight in the prenatal stage is responsible for 'programming' the foetus to develop metabolic syndromes such as obesity, diabetes, insulin insensitivity and hypertension, and as a result, that person is more likely to suffer from coronary heart disease or diabetes in adulthood (Barker, 1992). The study indicates that the effects of foetal conditions are persistent and can remain latent for many years; for example, heart disease does not arise as a problem until middle age. Following Barker's study, epidemiologists conducted further studies on the effects of foetal conditions, and the hypothesis became known as the foetal origins of adult disease (FOAD) or 'Barker Hypothesis'.

The Baker hypothesis outlines two different scenarios for a mother and baby, which were described by Edward M. (2017) (Edwards, 2017). His study suggested that irrespective of genotype in both situations, normal maternal nutrition would result in a normal-sized baby who would become a healthy adult, while maternal malnutrition during pregnancy would result in the growth restriction of the child, who would then develop metabolic syndrome in later life (Edwards, 2017). It also emerged from the study that periods of rapid postnatal growth accompanied by a high energy intake seem to be risk factors for health complications like coronary heart disease and stroke.

Most study findings until the early 1980s examined this hypothesis under the assumption that foetal shocks are correlational, and they did not effectively consider the potential confounding factors (Almond and

Currie, 2011). The 'birth weight effect' in the papers of Barker and his associates refers to associations between birth weight values primarily within the normal range (i.e. 2,500–4,000 g) and outcomes in later life (Barker, 1997, Barker and Clark, 1997, Barker and Osmond, 1986). However, over the last several decades, many studies have begun to consider the confounding factors, taking a broader view of the impact of the health behaviours of adults (e.g. smoking, exercise and diet) on the well-being of the foetus (Almond and Currie, 2011).

In this thesis, several research questions were devised to test the hypothesis of foetal origins. The investigations focused on the following risk factors: status of birth weights; gestational age; the mother's general health, mental health and physical health (primarily asthma and obesity); and maternal health risk behaviours (including smoking and alcohol consumption during pregnancy). It was then determined to what extent these risk factors generated a risk of chronic diseases like asthma, eczema, obesity and any health condition or disability for adolescents.

1.7.2 Developmental Origin of Health and Disease

From the follow-up studies of the 'foetal origins' hypothesis, other hypothesised effects were established. These later became known as the DOHaD, and they reflect a specific biological mechanism termed foetal 'programming' (Almond and Currie, 2011). This hypothesis tests the effects of the environment on the foetus while it is in utero. The effects of the environment on the epigenome can cause or inhibit many parts of the genome from being expressed, and the period of the foetus in utero is particularly important for setting these switches (Petronis, 2010). This hypothesis, which reflects the notions of biological mechanism, also expanded the conventional focus on the health behaviours of adults, especially mothers, such as smoking, exercise and diet, to include earlier environmental factors that might affect the well-being of the foetus

(Almond and Currie, 2011). However, researchers are just beginning to widely understand these hypothesised effects.

Stiemsma and Michels (2018) have explained the DOHaD hypothesis, focusing on the role of the microbiome. The infant microbiome is most vulnerable to environmental influences in early life. Maternal to foetal microbial transfer, mode of birth, antibiotics and diet can alter the colonisation and maturation of the early-life microbiome. These lifestyle-induced variations in microbiome composition and function, such as mode of birth, breastfeeding and maternal diet and antibiotic usage, can have prolonged influences on human health and may lead to the development of diseases later in life, such as asthma, obesity and neurodevelopmental disorders (Stiemsma and Michels, 2018).

In this thesis, the effects of health risk behaviours like smoking and alcohol consumption and diet practices of pregnant mothers and sociodemographic and environmental factors like the gender of the child, their age, their housing conditions, the remoteness of the residence, neighbourhood status and disease conditions during childhood (for example, obesity) were investigated by applying the DOHaD hypothesis. Furthermore, the effect of the early childhood environment (for example, mother's mental health and stressful life events experiences) on child and adolescent health was also examined to test this hypothesis. Specifically, Papers 3 and 4 in the context of survival analysis were undertaken to account for the theme of the DOHaD hypothesis.

1.7.3 The bio-ecological framework of child development

Researchers have long sought to identify a range of influences on children's developmental outcomes that span individual and family characteristics and the broader social, economic and physical environments in which children are raised (Kawachi and Berkman, 2000,

Li et al., 2009). The 'ecological' model of child development, described by Zubrick et al. (2000), is helpful in understanding the complex aetiology of childhood health and disease outcomes (Zubrick et al., 2000). The theoretical framework, which originated from Urle Bronfenbrenner (1979), shows that child development is a process in which biological and other characteristics of a child interact reciprocally with the environment over the course of life, so children affect their environments and are influenced by them (Bronfenbrenner, 1979). This approach emphasises the importance of parents and family as significant influencers of child development while at the same time considering the added influences of peers and the school environment. Additionally, the larger social, structural, economic, political and cultural context impacts the setting and the resources available to the children and families encompassed in this framework. This framework was considered in devising the LSAC (Australian Institute of Family Studies, 2002). Our thesis study have used the LSAC datasets along with the linkage datasets of Health CheckPoint Survey and Medicare databases.

Therefore, by following this theoretical framework, this thesis investigates the factors that influence childhood health problems. Of particular interest to this thesis work is the manner in which these contexts define, enhance and/or limit opportunities for healthy development and a higher quality of life. Study findings based on this model would enable the implementation of a flexible program that can mitigate risk factors and promote protective factors from each of the different interactive domains of the model.

1.8 Conceptual framework of the thesis

This thesis is grounded in all of the previously discussed theoretical frameworks: the FOAD, the DOHaD and the 'ecological' model of child development. The conceptual outline of the interactions of the theoretical frameworks along with their targeted study subjects and environments is shown in Figure 4. This study will utilise the ecological model of child development to study the relationship between behaviours in households and the perceived hypotheses of the FOAD and/or the DOHaD. For example, indulging in smoking or alcohol consumption can impact foetal conditions, an idea that relates to Papers 1 and 2 of this thesis, which aimed to re-examine the foetal origins hypothesis. Likewise, junk food intake, influenced by the family or adverse childhood health conditions, might pose health threats or impact the quality of life of the children in households. This idea relates to Papers 6 of this thesis, which re-examine the DOHaD hypothesis while identifying the vulnerable clusters of adolescents. Lastly, personal behaviours or dietary practices might influence (i.e. aggravate or reduce) the impact of the FOAD or the DOHaD on the health outcomes of adolescents, an idea that was also hypothesised and tested in Paper 6 of this thesis. Thus, all the objectives and sub-studies are aligned with the theoretical frameworks presented in this thesis.

This linkage of the studies has been presented in Figure 4, along with their relation to the in-utero and developmental origins determinants and biological or social determinants of childhood health outcomes that were studied over the course of this thesis.

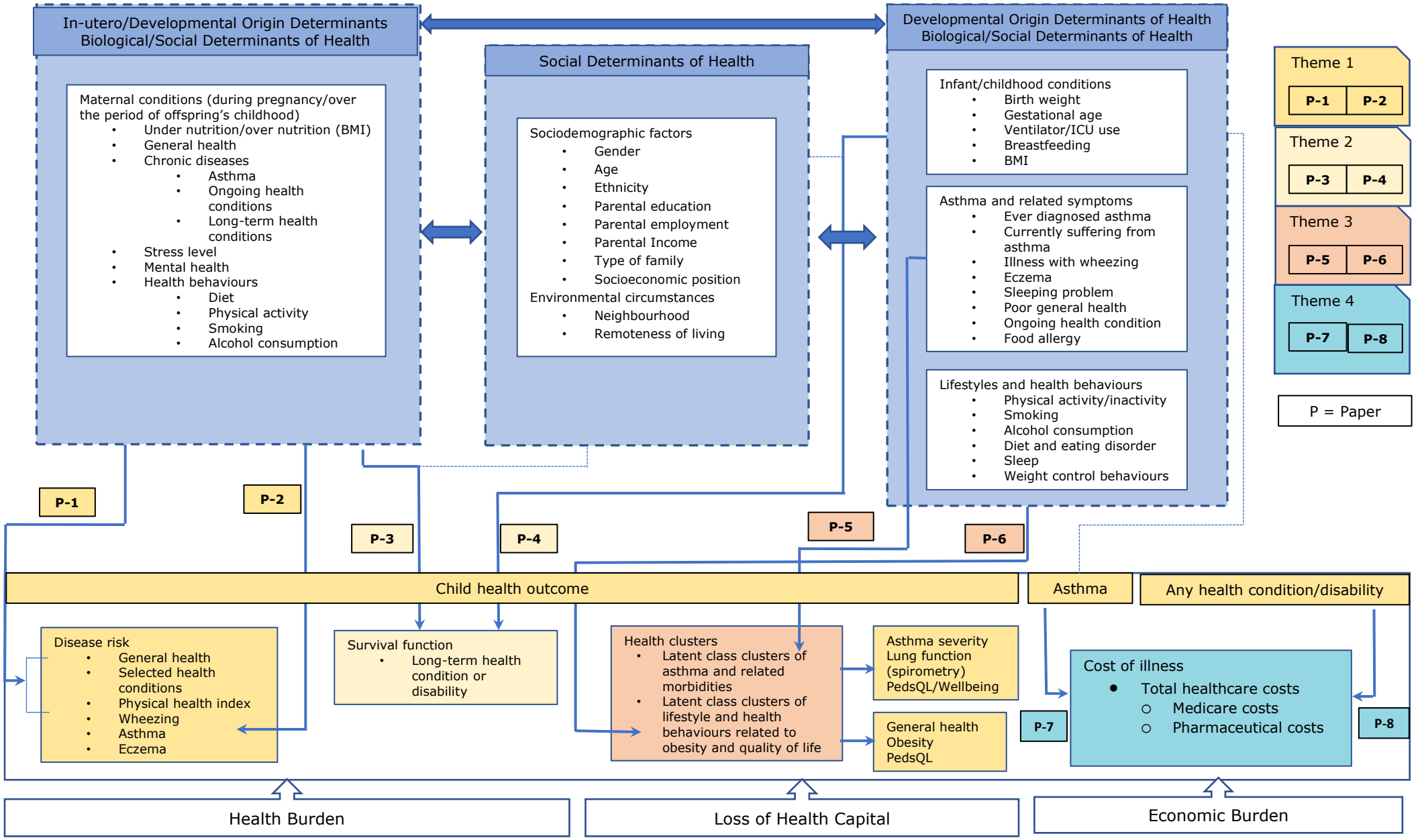

Figure 4: Conceptual framework of the study

1.9 Thesis structure

This PhD thesis is a 'thesis by publication'. There are eight chapters in the thesis. Chapter 1 provides background to the study, including problem statements, research objectives and questions and the theoretical and conceptual frameworks of the study. Chapter 2 describes the literature review and the identification of research gaps in the targeted field of research of this thesis. Chapters 3 through 10 present the thesis' empirical studies. In Chapter 3, Paper 1 addresses the empirical findings on the association between maternal health and childhood health outcomes, considering common non-communicable diseases that are prevalent among children and pregnant mothers. Paper 2 covers key findings on respiratory and allergic diseases, including wheezing, asthma and eczema, presented in Chapter 4. Chapters 5 and 6 presents the findings of a survival analysis for any medical condition or disability. Paper 3 conducted the survival analysis focusing maternal health characteristics and Paper 4 was focused on infant and child health characteristics. Chapters 7 and 8 identify the vulnerable clusters of adolescents in two consecutive studies using the LCA approach; Paper 5 identifies distinct clusters of asthma and related comorbidities (wheezing, eczema and others), and Paper 6 identifies distinct lifestyle and health behaviours groups that are related to obesity and quality of life. Chapters 9 and 10 include two studies, Papers 7 and 8 respectively, which address key findings from the costs of illness analyses associated with asthma and children's long-term health condition or disability. Chapter 11 concludes by summarising all of the empirical studies conducted for this thesis and discussing the limitations and strengths of the study. Implications for policy and future research considerations are also discussed.

CHAPTER 2: LITERATURE REVIEW

2.1 Literature review

The literature on childhood health and well-being outcomes is currently growing worldwide compared to in earlier decades. Child health studies primarily focus on paediatrics or maternal obstetrics issues related to childhood health. A significant portion of the research covers medical expenses, health insurance and the status of healthcare services. Studies of the aetiology of the diseases of children and childhood health outcome studies have become increasingly common; however, these are mainly from the perspective of the US and European countries and are limited from the longitudinal perspectives. This chapter outlines the available evidence on the risk factors of childhood asthma, obesity and any health condition or disability. A brief overview of the literature on six distinct topics will highlight existing knowledge that can help readers understand why the current set of studies for this thesis has been undertaken.

2.2 Study topic wise literature review

2.2.1 Maternal health and childhood health outcome

Barker and colleagues in the UK first revealed that poor foetal health is responsible for the increasing rate of non-communicable diseases such as cardiovascular disease and diabetes among individuals in their adult years. This phenomenon is now known as the foetal origins of adult disease (FOAD) (Barker, 1997, Rich-Edwards et al., 1999). Subsequent studies inspired by the foetal origin hypothesis have corroborated that poor maternal prenatal and postnatal physical and mental health conditions contribute to poor general health and chronic illness among offspring in later life (Hoy et al., 1998, West et al., 2015,

Kennedy, 1999, Bussing et al., 1995, Tegethoff et al., 2011, Roura and Arulkumaran, 2015a). Studies have also shown evidence that children's risk of experiencing chronic disease (asthma, eczema, obesity, affective disorders or behavioural problems) is associated with particular maternal health conditions, including asthma, malnutrition, obesity, gestational diabetes and mental distress (Ingstrup et al., 2012, Barker, 1997, Bussing et al., 1995, Kennedy, 1999, Tegethoff et al., 2011, Harvey et al., 2020). Further, maternal exposure to antibiotic or antidepressant medications during pregnancy poses significant risks that their children will develop asthma or other respiratory and allergic chronic conditions (Harvey et al., 2020, Mulder et al., 2016, Liu et al., 2015).

Further studies have expanded on the foetal origins hypothesis to show that children's risk of experiencing chronic illness as adults is also associated with the mothers' lifestyle and health risk behaviours during pregnancy and after childbirth. These include unhealthy dietary practices, lack of physical activity, tobacco smoking, and harmful consumption of alcohol during pregnancy (Chavatte-Palmer et al., 2016, Obel et al., 2009, Sutin et al., 2018, Alati et al., 2007, Burns et al., 2013). These findings indicate a growing need to better understand the prevalence of these common health conditions among mothers and how they impact their offspring's long-term health.

2.2.2 Childhood respiratory and allergic morbidities

To date, several studies have shown that pre-pregnancy obesity, gestational weight gain and maternal asthma during pregnancy are associated with an increased risk of asthma or wheezing in the offspring (Harvey et al., 2020, Da Silva Sena et al., 2020, Polinski et al., 2017, Gaillard et al., 2014). However, most of these existing studies followed children from the first year of life to preschool or early school age (Harvey et al., 2020, Giallo et al., 2015). A growing body of literature has revealed that maternal risk behaviours, such as smoking during pregnancy (Jaakkola and Gissler, 2004) and the use of some medications (Stokholm

et al., 2014, Zetstra-van der Woude et al., 2014), are associated with an increased risk of wheezing or asthma in the offspring. Some studies have shown that the use of medications, including paracetamol (Lowe et al., 2010) or high doses of folic acid (Zetstra-van der Woude et al., 2014) during pregnancy, influences health outcomes in children, such as an increased risk of childhood asthma (Chen et al., 2020a, Zhang et al., 2018). In Canada, the Manitoba province population-based study from 1996 to 2012 revealed that prenatal antibiotic exposure was associated with an increased risk of asthma (Loewen et al., 2018).

2.2.3 Clustering of asthma and related comorbidities

Asthma is more prevalent as a chronic disease among children and young adults than it is in adults, particularly because of its early onset (To et al., 2012) and diverse symptoms, which are accompanied by other comorbidities. These include wheezing, atopic allergy, food allergy or poor health (Newby et al., 2014). Current descriptions of asthma phenotypes and their classifications have been identified, but researchers have not considered several other domains of comorbidities, such as eczema, snoring/breathing problem or food allergy, that may be related to asthma (Kurukulaaratchy et al., 2015, Wenzel, 2012). The inclusion of these related diseases with asthma and the use of a classification system may provide a framework for identifying distinct asthma phenotypes and foster a better understanding of its aetiology.

Currently, the literature describes diverse classifications of the cluster analysis of asthma phenotypes. A UK study identified the clusters according to varying combinations of wheezing disorders, atopic allergies and impaired lung function with high or low severity of asthma (Kurukulaaratchy et al., 2015). In the US, Moore et al. (2010) identified clusters within the Severe Asthma Research Program cohort based on distinct clinical phenotypes using unsupervised hierarchical cluster analysis. However, they also acknowledged the need for improved

classification of asthma morbidities (Moore et al., 2010). Similarly, in a European study, Siroux et al. (2011) proposed latent class analysis (LCA) to improve the classification of asthma morbidities by utilising multiple aspects of the disease in adults who participated in an epidemiological study (Siroux et al., 2011). The findings revealed different homogeneous groups with severe and mild asthma whose different phenotypes allowed the researchers to differentiate the quality of life and associated risk factors for each group (Siroux et al., 2011). A New Zealand study (Wellington Respiratory Survey) assessed clinical airway diseases and found varying aspects of asthma and related comorbidities in five distinct clusters of the population (Weatherall et al., 2009).

2.2.4 Clustering of lifestyle and health behaviours related to obesity and quality of life

In some countries, the identification of specific clusters of the national population across age and gender have helped to identify homogeneous groups that can be targeted for specific public health intervention or prevention strategies (Conry et al., 2011, Schuit et al., 2002, Berrigan et al., 2003, Poortinga, 2007). A Netherlands study (n=4,395) investigated the clustering of health-compromising and delinquent behaviours in adults and adolescents. The results showed that there were two relevant clusters (alcohol and delinquency) for young adolescents but three clusters (alcohol, delinquency and health) for older adolescents (van Nieuwenhuijzen et al., 2009). A Finnish study of adolescents (n=6,792) that assessed lifestyle (physical activity, sedentary behaviour, smoking, sleeping problems and excess weight/obesity) and psychosocial problems identified various subgroups of 16-year-old adolescents. Differences were observed among boys and girls, and it was found that lifestyle and psychosocial factors divided the adolescents into distinct subgroups that persisted in the follow-up study at the age of 18 years (Heikkala et al., 2014). Gender differences were also observed in two studies among adolescents and preschool children in the US and

France, respectively (Pate et al., 1996, Saldanha-Gomes et al., 2020). Children of different cluster groups differed by gender, age, lifestyle and socioeconomic positions; however, their relationships with obesity, their self-rated health and their quality of life are still unclear (Leech et al., 2015). There have been few similar studies in the Australian setting (Saldanha-Gomes et al., 2020).

2.2.5 Any childhood medical condition or disability

The available literature shows that the state of a child's health, such as having any medical condition or disability in childhood, depends on the health characteristics of the mother during pregnancy and childbirth (Chen et al., 2020b, Maïano et al., 2016, Schendel and Bhasin, 2008, Schieve et al., 2016, Zhong et al., 2017). Low birth weight and a shorter gestation period/preterm birth are significantly associated with an increased risk of medical conditions among children (Schendel and Bhasin, 2008, Schieve et al., 2016, Chen et al., 2020b). Past studies in the US and China have revealed that gender, a biological factor, substantially impacts disability (Schendel and Bhasin, 2008, Zhong et al., 2017). In addition, a systematic review has confirmed that the likelihood of being overweight and obese increases the risk of acquiring disabilities in children by 1.54 and 1.80 times, respectively (Maïano et al., 2016). Two earlier studies had found that perinatal factors, such as low birth weight and premature birth, are associated with a higher likelihood of disability acquisition (Langridge et al., 2013, Williams et al., 2008).

2.2.6 Additional burden in the Medicare costs associated with childhood morbidities

Few existing studies on children have evaluated healthcare costs using Medicare data on the subject of childhood health conditions other than asthma, or long-term medical conditions or disabilities, for example, obesity, ADHD, mental health and sleep problems (Clifford et al., 2015,

Au, 2012, Lucas et al., 2013, Quanch et al., 2013, Sciberras et al., 2013). A study in the US setting on the costs of childhood asthma hospitalisations revealed that between 2000 and 2009, the rate of hospitalisation decreased by 13%; however, nationwide hospital charges increased from $1.27 billion to $1.59 billion (Hasegawa et al., 2013). Two studies estimated the cost of illness for asthma in Portuguese adults and children (Barbosa et al., 2017, Ferreira de Magalhaes et al., 2017). The study on children revealed that the mean annualised cost per child was €929.35 in direct costs and €230.70 in indirect costs, while on average, each adult cost €708.16 a year, with indirect costs representing 7%. In the context of Australia, it is challenging to obtain hospital-based administrative data.

2.3 Research gaps

Health professionals and policymakers consider it fundamentally important to research childhood health outcomes, well-being and the risk factors for disease. Existing literature inspired by the foetal origins hypothesis provides evidence that poor maternal health (physical and mental) during the prenatal and postnatal period contributes to poor general health and chronic illness among offspring in later life. Further, it has been observed from subsequent research studies that were inspired by the developmental origin hypothesis that environmental effects during infancy and early childhood also play an important role in shaping development from childhood to adolescence. However, there is insufficient evidence in the literature from contemporary birth cohort studies to determine the factors related to the childhood health burden of respiratory and allergic diseases (wheezing, asthma and eczema), obesity, health-related quality of life and any health condition or disability using nationally representative longitudinal data in Australia. A number of studies on the FOAD or the DOHaD conducted in Australian settings have either covered a particular state or focused only on a specific acute disease during pregnancy and thus retained the gap in the literature.

Sex dimorphism has long been recognised in relation to childhood morbidities, but few studies have investigated the sex-specific differences in children's respiratory and allergic diseases (Anthracopoulos et al., 2011, Zein and Erzurum, 2015). For example, a 2003–2008 study in Greece demonstrated that the male to female ratio for current and lifetime wheezing and asthma increased during this period; although, irrespective of sex, asthma diagnoses declined among school-age children, though not among preschool wheezers (Anthracopoulos et al., 2011). Few studies have used a single population-based prospective study to examine both respiratory and allergic diseases (Osman et al., 2007, Motika et al., 2011) or adjusted for the confounding factors of maternal health during pregnancy to determine the age- and sex-specific effects on children's respiratory and allergic diseases (Giallo et al., 2015, Chen et al., 2020a).

While Barker (1992, 1997) claimed that foetal conditions are responsible for emerging non-communicable diseases in a person's later life, the research was conducted only based on the risk factor of low birth weight. Later, several studies ignited based only on the 'low birth weight' risk factor, or in some cases the 'gestational age' risk factor was added (Schendel and Bhasin, 2008, Polinski et al., 2017). However, using only this single risk factor with cross-sectional data, without considering a range of factors from maternal health confounders, causing bias due to unobserved heterogeneity. This is because the unobserved factors cause both poor birth and child health outcomes. Behrman and Rosenzweig (2004) and Lin and Liu (2009) revealed in their studies that the OLS coefficients for birth weight without controlling for genes and family backgrounds are underestimated by 50%. Hence, contemporary study considering a reasonable range of confounding factors is necessary to create a better understanding of the foetal origin hypothesis. As this thesis focuses on general health, long-term medical conditions,

respiratory and allergic diseases (wheezing, asthma and eczema) of children as the target child health outcome variables for the studies, rather than only focusing on birth weight and gestational age, maternal health indicators will be considered as the main risk factors and relevant socio-demographic variables will be considered as control variables.

Barker (1992, 1997) performed the cross tabulation with odds ratio calculation across different birthweights of cross-sectional data to analyse the foetal origins. Over time, till to date, the foetal origins studies adopted different regression analysis methods, for example OLS or logistic regressions, to determine the risk factors predicting the disease outcomes (Schendel and Bhasin, 2008, Polinski et al., 2017, Behrman and Rosenzweig, 2004). However, deploying longitudinal survival analysis to identify the risk factors associated with foetal origins or developmental origins of diseases is very scarce. Whereas, this modelling provides a better understanding of the risk factors, as they offer more precise information through time-to-event analysis and greater statistical power than methods for a binary or multinomial logistic regression. Because logistic regression simply answers the question of whether a child has faced the disease (of study) or not (George et al., 2014). On the contrary, the survival analysis answers to the following question: how long did it take until a child develop the disease? As this research gap prevails in the extant literature of foetal origins studies in Australia, this thesis intends to fill the gap in addition to the usual OLS and logistic regression analysis.

Epidemiological studies suggest that certain health conditions of mothers, such as having asthma or being overweight during pregnancy, are associated with childhood asthma (Scholtens et al., 2010, Cookson et al., 2009, Neuman et al., 2012, Turner et al., 2010, Martel et al., 2009). However, many LCAs or cluster analyses on asthma comorbidities in adolescents lack an investigation of the foetal origins of the children's cluster memberships (Moore et al., 2010, Kurukulaaratchy et al., 2015). However, adolescence is a crucial phase in the life cycle (Shlafer et al.,

2014) and a critical entry point for young people approaching adulthood (Schulenberg et al., 2004).

The World Health Organization (WHO) recommends a holistic approach to assessing the health risks of an individual. Thus, it is necessary to consider how patterns of risk behaviours might affect an individual's health rather than considering health behaviours in isolation. Some discernible patterns have been identified in adults; further investigation is needed within population studies to determine other possible synergistic relationships among children with obesity.

One of the main limitations of the existing literature is that most of the previous studies have focused on identifying the risk factors of disability among adults and older people (Claessen et al., 2009, Corona et al., 2017); however, a small number of the available childhood health-focused studies are either cross-sectional or do not involve contemporary birth cohorts (Chen et al., 2020b, Schendel and Bhasin, 2008, Schieve et al., 2016).

Very few studies focus on the economic burden of maternal health conditions on the lives of their offspring. From the extant literature search, it was evident that there are no costs of illness studies associated with asthma and long-term health condition or disability for Australian children in the perspective of direct healthcare costs. The existing studies using LSAC and Medicare data cover only the following morbidities - obesity, ADHD, mental health and sleep problems (Clifford et al., 2015, Au, 2012, Lucas et al., 2013, Quanch et al., 2013, Sciberras et al., 2013), some of which have used only three to four waves, from the currently available eight waves, as only those waves were available at the time of those studies.

This study project intends to fill these gaps and perform the assessments of childhood health problems using the population based LSAC study data, designed and maintained by the Australian Institute of Family Studies (AIFS). The study population were followed over the decades through several longitudinal surveys that ran from 2004 to 2018 in eight waves, a study design that has been highly effective in revealing the contemporary health and well-being outcomes of Australian children. Further, since adolescence is a critical phase of life and a crucial entry point for progressing towards adulthood, it is important to better understand the risk factors of adolescent health in the context of the FOAD and the DOHaD hypotheses, as well as how households are tackling these health issues.

CHAPTER 3: PAPER 1 - MATERNAL HEALTH AND HEALTH-RELATED BEHAVIOURS AND THEIR ASSOCIATIONS WITH CHILD HEALTH: EVIDENCE FROM AN AUSTRALIAN BIRTH COHORT

3.1 Introduction

This chapter of the thesis includes the first study that examines the foetal origins hypothesis on a contemporary birth cohort of Australian children. This paper first examines what maternal health factors during pregnancy or up to 15 months from childbirth are associated with the three dimensions of infant and adolescent health: general health, presence of a chronic illness, and physical health outcome index. Then, it also evaluates to what extent these associations exist among infants and adolescents. The following maternal health factors – general health, any medical condition and mental health and health-related behaviours – food consumption habits, physical activity, alcohol consumption and smoking were assessed to find their association with children's health outcomes in all three dimension among the cross-sectional samples of infants and adolescents, using logistic and linear regression models. This study revealed compelling findings which has set forth in the paper elaborately. This study deployed multivariate logistic and ordinary least square regression models to determine the associations of the study variables.

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Maternal health and health-related behaviours and their associations with child health: Evidence from an Australian birth cohort

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Abstract

Objective

This study investigates the associations between maternal health and health-related behaviours (nutrition, physical activity, alcohol consumption and smoking) both during pregnancy and up to 15 months from childbirth and children's health outcomes during infancy and adolescence (general health, presence of a chronic illness, and physical health outcome index).

Methods

This study used Wave 1 (2004) and Wave 7 (2016) data from the Longitudinal Survey of Australian Children (LSAC). We measured mothers' general health, presence of a medical condition during pregnancy and mental health during pregnancy or in the year after childbirth. We subsequently measured the children's general health, presence of a medical condition, and physical health outcome index at ages 0–1 (infancy) and 12–13 (adolescence). Binary logistic and linear regression analyses were performed to examine the association between the mothers' health-related variables and their children's health.

Results

Our results showed that poor general health of the mother in the year after childbirth was associated with higher odds of poor health in infants and adolescents in all three dimensions: poor general health (OR: 3.13, 95% CI: 2.16–4.52 for infants; OR: 1.39, 95% CI: 0.95–2.04 for adolescents), presence of a chronic condition (OR: 1.47, 95% CI: 1.19–1.81 for adolescents) and lower physical health score (b = −0.94, p-value <0.05 for adolescents). Our study also revealed that the presence of a chronic condition in mothers during pregnancy significantly increased the likelihood of the presence of a chronic condition in their offspring during infancy (OR: 1.31, 95% CI: 1.12–1.54) and during adolescence (OR: 1.45,

Government Department of Social Services. One can also email to ada@anu.edu.au requesting data access. The lead author was granted permission to the data through online application from the following web link: https://growingupinaustralia.gov.au/data-and-documentation/accessing-lsac-data.

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95% CI: 1.20–1.75). The study found that stressful life events faced by mothers increase the odds of poor general health or any chronic illness during adolescence, while stress, anxiety or depression during pregnancy and psychological distress in the year after childbirth increase the odds of any chronic illness during infancy.

Conclusions

The present study found evidence that poor maternal physical and mental health during pregnancy or up to 15 months from childbirth has adverse health consequences for their offspring as measured by general health, presence of chronic health conditions, and physical health index scores. This suggests that initiatives to improve maternal physical and mental health would not only improve child health but would also reduce the national health burden.

1. Introduction

Maternal chronic illness and poor general health, particularly during pregnancy and in the year after childbirth, are increasing public health concerns as they contribute to poor health outcomes for both mother and infant [1–5]. The incidence of maternal morbidity in Australia and other developed countries has been steadily rising during the past two decades [4, 6, 7]. In a Melbourne-based study, 39% of pregnant women reported having a chronic condition with long-term health implications [8]. A Brisbane based study revealed that 34% of the antenatal care receivers were overweight or obese with the implications of increased risk of hypertensive disorders, gestational diabetes and infections during pregnancy [4]. These pregnancy complications have adverse effects on child health outcomes which require further research [1–5].

Numerous studies have investigated the association between mothers' health conditions and children's health outcomes. Barker and colleagues in the UK first revealed that poor foetal health is responsible for the increasing rate of non-communicable diseases, such as cardiovascular disease and diabetes among individuals in their adult years. This phenomenon is now known as foetal origins of adult disease [9, 10]. Subsequent studies inspired by the foetal origin hypothesis have corroborated that poor maternal prenatal and postnatal physical and mental health conditions contribute to poor general health and chronic illness among offspring in later life [11–16]. Studies have also shown evidence that children's risk of experiencing chronic disease (asthma, eczema, obesity, affective disorders or behavioural problems) is associated with particular maternal health conditions, including asthma, malnutrition, obesity, gestational diabetes, and mental distress [3, 9, 13, 14, 16, 17]. Further, maternal exposure to antibiotic and anti-depressant medications during pregnancy poses significant risks of having asthma and other respiratory and allergic chronic conditions among their children [17–19].

Further studies have expanded on the foetal origins hypothesis to show that children's risk of experiencing chronic illness as adults is also associated with mothers' lifestyle and health risk behaviours during pregnancy and after childbirth. These include unhealthy dietary practices [20], lack of physical activity [20], maternal tobacco smoking [21, 22], and harmful consumption of alcohol by pregnant mothers [5, 23]. These findings indicate a growing need to better understand the prevalence of these common health conditions among mothers and how they impact their offspring's long-term health.

While many studies have linked sub-optimal foetal environments with adult disease, few have focused on children in infancy [24] or during adolescence [1, 21], and even fewer studies have addressed the health outcomes at these time points via a longitudinal survey. Adolescence

is a critical phase of life [25] and a crucial entry point for progressing toward adulthood [26]. The importance of understanding the risk factors associated with adolescent health in the context of foetal origins cannot be understated; these risk factors can offer an early warning about the health issues children and adolescents may encounter before adulthood. This study contributes to the literature by investigating the associations of maternal health (general health, chronic health conditions and mental health) and health-related behaviours (smoking, alcohol consumption, food habits and physical activity) during pregnancy or in the year after childbirth on infant and adolescent health. This study's primary aim is to identify associations between mothers' specific health conditions and health-related behaviours during pregnancy or up to 15 months from childbirth and their offspring's general health status, presence of chronic health conditions, and physical health outcome indices when they were aged 0–1 in 2004 and aged 12–13 in 2016.

2. Methods

2.1 Data

This study utilised data from the Longitudinal Study of Australian Children (LSAC). The LSAC is a nationally representative household survey that collected comprehensive data on the health, socioeconomic status, and demographic factors of birth (aged 0–1) and kindergarten (aged 4–5) cohorts and their parents or caregivers. The LSAC study followed a two-stage, stratified, clustered design using the Health Insurance Commission (HIC) Medicare database as the sampling frame. The details of the sampling design and the survey methodology have been described elsewhere [27].

This study used data of mothers and their offspring from the birth cohort of the LSAC dataset recruited in 2004. Data on mothers' health and health-related behaviours during pregnancy or in the year after childbirth and infants' health outcomes were extracted from Wave 1. This birth cohort's health outcome data were taken again from Wave 7, when they were adolescents, thus allowing a comparison of the children's health outcomes during infancy and adolescence against their biological mothers' health conditions. Although children of the kindergarten cohort (aged 4–5) in Wave 1 became adolescents (aged 12–13) in Wave 5, infant data for this cohort is not available. Moreover, although mothers of the kindergarten cohort provided information on maternal health, those would be retrospective, as they were four years earlier and might have more recall bias. Hence, this study did not use the data of the kindergarten cohort from the LSAC survey. The birth cohort surveyed in Wave 1 in 2004 included 5107 infants, 3381 (66.2%) of whom were retained as adolescents for Wave 7 in 2016. Of these children, this study included 5019 infants and 3327 adolescents after excluding primary caregivers who were not biological mothers of the children. Details of the exclusion and attrition of families and total sample are shown in Fig 1.

2.2 Ethics approval and consent

The LSAC study was approved by the Australian Institute of Family Studies Ethics Committee.

The researchers received access to the database by contacting the Longitudinal Study of Australian Children Dataverse of the National Centre for Longitudinal Data. In keeping with the national regulations, researchers may use this dataset after following certain regulations, if there is no identifiable information of individuals in the data. As there was no identifiable information of individuals in the secondary data used in this study, consent for publication is not applicable for this study.

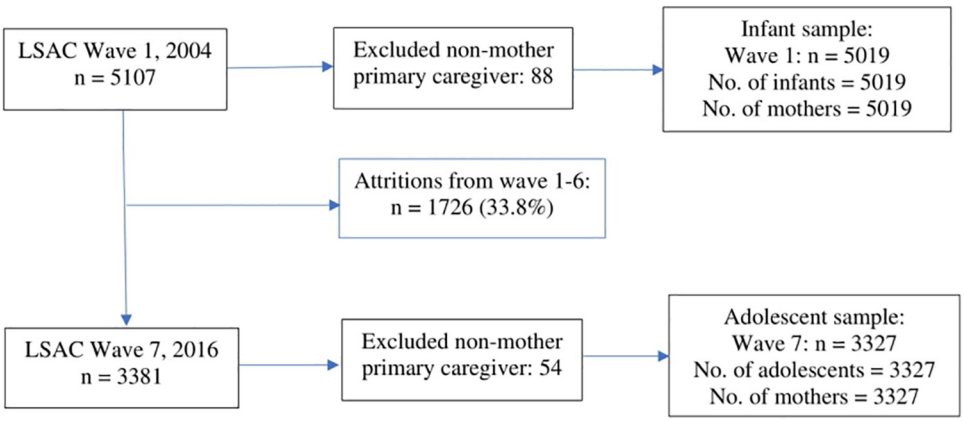

Fig 1. Longitudinal participant numbers of the study after exclusions and attritions.

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2.3 Variables

2.3.1 Dependent variables. This study considered the following three health outcome variables:

1. General health status. The general health status of each child was measured via a five-point Likert scale (1 –excellent; 2 –very good; 3 –good; 4 –fair; 5 –poor) reported by the biological mother of the child. The ordinal Likert scale values were converted into dichotomous groups: children of relatively good health (excellent/very good = 0) and children of relatively poor health (good/fair/poor = 1), in keeping with previous literature [28, 29]. These two health status categories were termed 'good health' and 'poor health', respectively.

2. Medical conditions. A health condition or disability encountered by a child that lasted or was likely to last for six months (or more) following its initial occurrence was considered a medical condition for this study. The health problems considered were wheezing, bronchiolitis, asthma, eczema, food or digestive allergies, ear infections, hearing problems, vision problems, attention deficit disorder, other illness, and other infections. The variable was assigned a value of 1 if any medical condition was present and 0 otherwise.

3. Physical health outcome index. This index is a composite score calculated using the global overall health rating and scores from six-item special health care needs screening. The special health care needs screening questions were: (i) Does the child currently need or use medicine prescribed by a doctor, other than vitamins? (ii) Is this because of any medical, behavioural, or other health condition? (iii) Is this a condition that has lasted or is expected to last for at least 12 months? (iv) Does the child need or use more medical care than is usual for most children of the same age? (v) Is this because of any specific medical, behavioural, or other health condition (not just the common cold)? and (vi) Is this a condition that has lasted or is expected to last for at least 12 months? This screening was designed to assess the physical health of a child at a particular point in time, in this case, during infancy (0–1 year of age) and adolescence (12–13 years of age).

The calculation of the physical health outcome index for infants and adolescents was performed following a set of guiding principles that were developed by the members of the Outcome Index Working Group of LSAC [30] and have been used in several studies [24]. The steps are as follows: (1) calculate the average of the six-item special health care needs screening responses; (2) standardise the overall health rating variable and the average health care need screening scores so that they are weighted equally in the index; (3) multiply the standardised

overall health rating variable by −1 so that a higher value indicates a more positive outcome; (4) take the average value of the two standardised variables; (5) for adolescent samples, standardise the BMI scores and take the average of all three variables; (6) standardise the grand sum of the values of the variables and then further standardise them to a normally distributed variable with mean 100 and standard deviation (SD) 10. This final standardised variable is the physical health outcome index utilised in this study.

2.3.2 Independent variables. Our independent variables of interest were selected based on the existing literature on maternal health conditions and health-related behaviours as well as the variables available in the LSAC data [24, 28, 31, 32]. Details of these variables are as follows:

Maternal health. This study utilised the following indicators to measure maternal health: (i) general health status, (ii) presence of a medical/chronic condition, and (iii) mental health status. The health-related variables of the mother were selected from Wave 1 when their child was 0–1 year old.

In the LSAC, the mother's self-reported general health status was originally reported using a 5-point Likert scale. This measure was taken from the mothers when their children were mostly (99.3%) between 3 to 15 months old. For this study, the score was recoded into dichotomous groups: good health (0) and poor health (1), following previous literature [28, 29] and the same process was utilised in constructing the children's general health status variable.

A key explanatory variable of the prenatal period examined in this study was whether the mothers had any medical conditions during pregnancy. The conditions considered were asthma, gestational diabetes, nausea, hypertensive disorder, medical conditions for which pregnant mothers used anti-depressant, anti-allergy, or antibiotic medications, and other physical problems during pregnancy.

This study also considered three maternal mental health-related variables available in the LSAC data. These variables are: (i) had stress, anxiety, or depression during the pregnancy (Yes = 1, No = 0); (ii) the number of stressful life events in the last 12 months from the time of their interviews (no events = 0, one or more events = 1); and (iii) psychological distress experienced in the past four weeks. To measure psychological distress, mothers were asked the following questions to answer through recalling the past four weeks from interviews while their children were 3 to 15 months old. The questions were: how often they felt (a) nervous, (b) hopeless, (c) restless or fidgety, (d) that everything was an effort, (e) so bad that nothing could cheer you up, and (f) worthless. Responses were recorded on a Likert-type scale ranging from 1 ('all of the time') to 5 ('none of the time'). These scores were summed and reverse coded. Finally, the mean score of the sum of these six questions constructed the measurement scale, where a higher score represented worse mental health than a lower score. The items on this questionnaire were taken from the Kessler K6 screening scale [33].

Mothers' health-related behaviours and risk factors. The health-related behaviours included were the number of usual daily servings of vegetables and fruits, the number of days per week that the mother engaged in at least 30 minutes of moderate/vigorous exercise when their children were 3 to 15 months old, and food exclusion behaviour during pregnancy. Health-related risk factors included smoking frequency in a day during the first trimester of pregnancy and the number of days per week alcohol was consumed during the first trimester of pregnancy.

It is worth mentioning that this study used the independent variables of maternal physical and mental health and health-related behaviours either during pregnancy or when their children were 3 to 15 months old, as LSAC measures these variables from these timepoints. Hence, the associations derived from these variables refer the odds of child health outcomes against the respective time points' maternal health or health-related behaviours.

Other health variables. Further, this study utilised the variables: birth weight status (<2500 gm = 1, >2500 gm = 0) and gestational age (<37 weeks = 1, > = 37 weeks = 0) as explanatory variables to analyse the health outcomes of the children. This is because these variables play important role in maternal and child health.

2.3.3 Control variables. Based on existing literature [24, 28, 29, 31], this study included several relevant socio-demographic and health-related variables of mothers, children and their families as control variables. The control variables considered in analysing the associations for both infant and adolescent regression models were as follows: gender of the child, birth type (normal/caesarean/others), immunization status of the children (completed/not completed), age of mothers (< = 18 years, 19–34 years, > = 35 years), home language (English, non-English), indigenous status of the child, marital status and education of the mother, income quantile of the family and remoteness of the living area (highly accessible, accessible, moderately accessible, or remote/very remote). It is expected that adolescent health outcomes could be confounded by their own health-related behaviours. Hence, for the adolescent models, the following additional control variables were considered: physical activity, smoking, alcohol consumption, and how often they ate fruits or vegetables in the previous day from the interview date. The distributions of all control variables are shown in Table 1.

2.4 Statistical analysis

This study applied binary logistic and linear regression models to assess the relationship between the predictor variables (mothers' health) and the three health outcome variables (children's health). The first and second binary logistic regression models assessed the children's general health status and chronic health conditions. The third model, a linear regression model, assessed the children's physical health outcome index. The study also conducted several collinearity diagnostic measures, including variance inflation factors, tolerance and eigenvalues for the independent variables specified in each regression model; no evidence of multi-collinearity was found. There was no evidence of heteroscedasticity, and the distributions were moderately normal. The socio-demographic factors were controlled for all models, and estimates were produced using population weights for all analyses. This study has sufficient statistical power regarding the sample size required to derive the statistics that represent the parameters or to avoid type 1 error of inference. Our study utilised logistic regression models for Tables 2 and 3 with 14 independent variables from the observational surveys, which require a minimum sample size of 800 in line with the recommended rules of thumb explained by Bujang et al. (2018), while our study had over 5000 observations for infants and over 3000 observations for adolescents [34]. Table 4 used the linear regression model, and its sample size was also sufficient to retain the expected level of statistical power in the analyses.

3. Results

Table 1 shows descriptive statistics for the mothers and children included in the samples of infants and adolescents. Among the mothers, 32.4% had poor general health, 40.2% had at least one medical condition, 15.4% had stress, anxiety, or depression during pregnancy, and 54.4% experienced one or more stressful life events in the twelve months prior to the interview at Wave 1. Among the children, 13.2% of the infants and 15.2% of the adolescents were in poor health. Further, 39.4% of the infants and 54.5% of the adolescents suffered from at least one of the selected chronic health conditions. It was found that 14.5% of the mothers smoked during pregnancy, and 20.3% had consumed alcohol in the first trimester.

Table 2 presents the associations between the mothers' general health status, chronic health conditions, mental health and health-related behaviours and their children's general health

Table 1. Characteristics of the sampled subjects during infancy and adolescence time of the study children*.

Variables	Infancy (aged 0/1, n = 5019)		Adolescence (Follow-up of the birth cohort at age 12/13, n = 3327)*	
	n	% /Mean (SD)	n	% /Mean (SD)
Dependent Variables				
General health status of children				
Excellent/very good	4,356	86.8	2,820	84.8
good/fair/poor	663	13.2	507	15.2
Children having any chronic conditions				
No	3,041	60.6	1,515	45.5
Yes	1,978	39.4	1,812	54.5
Physical Health Outcome Index–mean (SD)**	5018	99.9 (10.0)	3318	99.7 (10.3)
Independent Variables				
General health status of the mother				
Excellent/very good	3,393	67.6	2,262	63.3
Good/fair/poor	1,626	32.4	1,065	32.0
Mothers having any medical conditions				
No	3,001	59.8	1,961	59
Yes	2,018	40.2	1366	41
Mother's Mental health-related variables				
Mothers had stress, anxiety, or depression during pregnancy				
No	4246	84.6	2831	85.1
Yes	773	15.4	496	14.9
Number of stressful life events mothers faced in the previous 12 months prior to the interview				
No events faced	2,286	45.6	1,811	45.6
One or more events	2733	54.4	1516	54.4
Psychological distress–mean (SD) (K-6 depression scale)	4,194	1.6 (0.6)	2,976	1.6 (0.6)
Mother's Health behaviour related variables				
Smoking frequency in 1st trimester of pregnancy				
None	4,290	85.5	2,873	86.3
Less than 10 daily	509	10.1	321	9.7
11+ daily	220	4.4	133	4.01
Number of days per week alcohol was consumed in 1st trimester				
Zero days in a week	3,998	79.7	2,602	78.2
Once a week	743	14.8	538	16.2
More than once a week	278	5.5	187	5.6
Usual daily serves of vegetable intake by mother mothers (mean)	5,019	2.18 (1.3)	3,327	2.25 (1.3)
Usual daily serves of fruit intake by mother (mean)	5,019	1.5 (1.2)	3,327	1.5 (1.1)
Number of days in a week mothers engage in at least 30 minutes of moderate/vigorous exercise (mean)	5,019	2.51 (1.9)	3,327	2.46 (1.9)
Food exclusion behaviour during pregnancy				
All food included	2,730	54.8	1,786	53.7
One item excluded	1,673	33.6	1,129	33.9
Two items excluded	386	7.7	256	7.7
Three or more items excluded	228	4.5	156	4.6
Control Variables				
Sex of the children				
Male	2,563	48.9	1697	49.0
Female	2,456	51.1	1630	51.1
Child being breastfed less than 6 months				

(*Continued*)

Table 1. (Continued)

Variables	Infancy (aged 0/1, n = 5019)		Adolescence (Follow-up of the birth cohort at age 12/13, n = 3327)*	
	n	% /Mean (SD)	n	% /Mean (SD)
No	2,880	57.4	2,013	60.5
Yes	2,139	42.6	1,314	39.5
Age of mothers				
< = 18	72	1.4	39	1.2
19–34	3,625	72.2	2,402	72.2
> = 35	1,322	26.3	886	26.6
Is English spoken at home as the main language?				
No	634	12.6	435	13.1
Yes	4,385	87.4	2,892	86.9
Is the child from an indigenous household				
No	4,773	95.1	3,212	96.6
Yes	246	4.9	115	3.5
Marital Status when the child was born				
With married partner	3,540	70.5	2,452	73.7
With defacto partner	945	18.8	543	16.3
Single	534	10.6	332	10.0
Education of Mother				
Year 12 or less	1,703	33.9	1,049	31.5
Professional qualification	1,383	27.6	906	27.2
Graduate/ diploma	1,617	32.2	1,149	34.5
Post-graduate	316	6.3	223	6.7
Income Quantile of Weekly Family Income				
1st quantile	932	18.6	569	17.1
2nd quantile	948	18.9	624	18.8
3rd quantile	923	18.4	634	19.1
4th quantile	932	18.6	652	19.6
5th quantile	920	18.3	616	18.5
No response	364	7.3	232	7.0
Remoteness of area				
Highly accessible	2,939	58.6	1,718	51.6
Accessible	1,101	21.9	912	27.4
Moderately accessible	754	15.0	546	16.4
Remote/very remote	225	4.5	151	4.5
Adolescent's health behaviour related control variables				
Number of days in a week children engage in at least 30 minutes of moderate/vigorous exercise (mean)	-	-	3,327	4.0 (2.2)
Smoked in last 12 months				
No	-	-	3,284	98.7
Yes	-	-	43	1.3
Alcohol consumption—in the last 12 months				
No	-	-	3,278	98.5
Yes	-	-	49	1.5
How often children had fresh fruit yesterday?				
Not at all	-	-	614	18.4
Once	-	-	972	29.2

(*Continued*)

Table 1. (Continued)

Variables	Infancy (aged 0/1, n = 5019)		Adolescence (Follow-up of the birth cohort at age 12/13, n = 3327)*	
	n	% /Mean (SD)	n	% /Mean (SD)
Twice or more	-	-	1741	52.3
How often children had fresh fruit juice yesterday?				
Not at all	-	-	1860	55.9
Once	-	-	1004	30.2
Twice or more	-	-	463	13.9
How often had children cooked vegetables yesterday?				
Not at all	-	-	964	29.0
Once	-	-	1441	43.3
Twice or more	-	-	921	27.7
How often children had raw vegetables yesterday?				
Not at all	-	-	1490	44.8
Once	-	-	1194	35.9
Twice or more	-	-	643	19.3

*Univariate percentages presented.

**Missing data excluded from analyses; Abbreviation: SD Standard Deviation.

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status. We found that poor general health of mothers in the year after childbirth increased the likelihood of poor general health of their children during infancy (OR: 3.13, 95% CI: 2.16–4.52) and adolescence (OR: 1.39, 95% CI: 0.95–2.04). This study also finds that stress, anxiety, or depression during pregnancy and one or more stressful life events among mothers in the year after childbirth were associated with the poor general health of the children, but only during adolescence. The associations revealed in Table 2 were medium to large in effect size, while the magnitudes were higher in the associations of poor maternal general health and poor general health of children for infants, compared to adolescents.

Table 3 reports the associations between the mothers' health and health-related behaviours and their children's chronic health condition. The presence of a chronic condition during pregnancy significantly increased the likelihood of a chronic condition in the offspring during infancy (OR: 1.31, 95% CI: 1.12–1.54) and during adolescence (OR: 1.45, 95% CI: 1.20–1.75). The children of mothers who experienced poor general health (OR: 1.41, 95% CI: 1.16–1.72) or at least one stressful life event (OR: 1.41, 95% CI: 1.16–1.72) in the year after childbirth were more likely to suffer from a chronic illness during their adolescence than children of mothers who did not experience that illness. Mothers having stress, anxiety, or depression during pregnancy (OR: 1.21 95% CI: 0.97–1.50) and psychological distress in the past 4 weeks from the interview in the year after childbirth (OR: 1.22, 95% CI: 1.05–1.42) were also associated with the presence of a chronic health condition in the infants. However, these risk factors did not have any significant associations for the adolescents. The associations revealed in Table 3 were small to medium in effect size, while the magnitude was higher for adolescents.

Table 4 presents the associations between maternal health and health-related behaviours during pregnancy and their children's physical health outcome index scores. Stress, anxiety or depression during pregnancy was associated with lower physical health outcomes among the offspring during infancy (b = -0.93, 95% CI: -1.77 to –0.09). Children with gestational age less than 37 weeks were more likely to have lower physical health outcome score (b = -1.51, 95%

Table 2. Maternal health and health-related behaviours and their associations with children's general health status during infancy (0–1 year of age) and adolescence (12–13 years of age).

Explanatory Variables	Risk of having poor general health status at:	
	Infancy (N = 5019)	Adolescence (N = 3327)
	OR (95% CI)	OR (95% CI)
Mother's Health		
Poor general health status of mothers	**3.13*** (2.16–4.52)**	**1.39* (0.95–2.04)**
Mothers having at least one of the selected medical conditions during pregnancy	1.22 (0.86–1.74)	1.18 (0.83–1.67)
Mothers having stress, anxiety or depression during pregnancy	0.71 (0.44–1.13)	**1.57** (1.02–2.42)**
Any stressful life events mothers faced in 12 months prior interview		
No events faced (ref.)		
Yes, one or more events faced	1.08 (0.74–1.58)	**1.94*** (1.32–2.85)**
Psychological distress—(mean) (K6 depression scale)	1.12 (0.86–1.47)	0.74* (0.53–1.04)
Mother's Health Behaviours		
Smoking frequency in 1st trimester of pregnancy		
None (ref.)		
Less than 10 daily	**1.79** (1.04–3.09)**	1.22 (0.72–2.09)
11+ daily	1.75 (0.88–3.47)	0.62 (0.19–1.98)
Number of days per week alcohol was consumed in 1st trimester		
Zero days in a week (ref.)		
Once a week	1.39 (0.89–2.16)	0.76 (0.49–1.18)
More than once a week	**1.68* (0.93–3.04)**	1.17 (0.54–2.52)
Usual daily serves of vegetables that mothers have	**0.87* (0.75–1.02)**	0.97 (0.84–1.13)
Usual daily serves of fruit that mothers have	1.06 (0.90–1.25)	**0.84** (0.71–0.99)**
Number of days/week mothers engage in at least 30 minutes of exercise	1.05 (0.96–1.15)	0.95 (0.85–1.05)
Food exclusion during pregnancy		
All food included (ref.)		
One item excluded	0.96 (0.66–1.40)	1.23 (0.56–1.87)
Two items excluded	0.82 (0.40–1.67)	1.02 (0.56–1.87)
Three or more items excluded	1.64 (0.73–3.70)	1.06 (0.41–2.74)
Other Health Variables		
Birth weight < 2500 gm	0.98 (0.38–2.53)	1.56 (0.75–3.25)
Gestational age <37 week	0.71 (0.32–1.55)	0.54 (0.25–1.19)

Notes: (i) The infancy model is are adjusted for type of birth delivery, immunisation status and breastfeeding of children and socio-demographic characteristics—age, gender of the child, education and marital status of mother, family income, language spoken at home, remoteness of the residence and for the dependent variables of other health outcome models; (ii) The adolescence model is adjusted for all the variables of infancy model and additionally adolescent health behaviour related variables mentioned in the section "Adolescent's health behaviour related control variables" of Table 1. Abbreviations: OR Odds Ratio; CI Confidence Interval; ref. Reference Category.

*** OR and 95% CI at 1% level of significance

** OR and 95% CI at 5% level of significance

* OR and 95% CI at 10% level of significance.

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CI: -2.95 to -0.08) during infancy. However, these negative relationships were no longer significant during adolescence. The children of mothers who experienced poor general health in the year after childbirth were more likely to suffer from poor general health (b = -0.94, 95% CI:

Table 3. Maternal health and health-related behaviours and their associations with children's having any of the selected medical conditions during infancy (0–1 year of age) and adolescence (12–13 years of age).

Explanatory Variables	Risk of having any of the selected medical conditions at:	
	Infancy (N = 5019)	Adolescence (N = 3327)
	OR (95% CI)	OR (95% CI)
Mother's health		
Poor general health status of mothers	1.10 (0.92–1.31)	**1.47*** (1.19–1.81)**
Mothers having at least one of the selected medical conditions during pregnancy	**1.31*** (1.12–1.54)**	**1.45*** (1.20–1.75)**
Mothers having stress, anxiety or depression during pregnancy	**1.21* (0.97–1.50)**	1.11 (0.84–1.48)
Any stressful life events mothers faced in 12 months prior interview		
No events faced (ref.)		
Yes, one or more events faced	0.91 (0.77–1.07)	1.30** (1.07–1.57)
Psychological distress—(mean) (K6 depression scale)	**1.22** (1.05–1.42)**	1.19 (0.97–1.46)
Mother's health behaviours		
Smoking frequency in 1st trimester of pregnancy		
None (ref.)		
Less than 10 daily	0.85 (0.64–1.11)	1.38* (0.98–1.95)
11+ daily	0.65** (0.43–0.97)	1.05 (0.62–1.79)
Number of days per week alcohol was consumed in 1st trimester		
Zero days in a week (ref.)		
Once a week	**1.35*** (1.11–1.64)**	1.07 (0.85–1.34)
More than once a week	1.14 (0.82–1.58)	0.91 (0.64–1.28)
Usual daily serves of vegetables that mothers have	1.02 (0.95–1.09)	1.07 (0.98–1.16)
Usual daily serves of fruit that mothers have	1.02 (0.95–1.10)	**0.91** (0.83–1.00)**
Number of days/week mothers engage in at least 30 minutes of exercise	0.99 (0.95–1.04)	1.02 (0.97–1.08)
Food exclusion during pregnancy		
All food included (ref.)		
One item excluded	0.91 (0.77–1.08)	1.01 (0.82–1.23)
Two items excluded	1.07 (0.80–1.44)	1.31 (0,92–1.88)
Three or more items excluded	1.36 (0.91–2.06)	1.20 (0.75–1.90)
Other health variables		
Birth weight < 2500 gm	1.06 (0.70–1.61)	1.18 (0.72–1.93)
Gestational age <37 week	1.03 (0.71–1.49)	0.74 (0.47–1.16)

Notes: As above mentioned in Table 2. Abbreviations: OR Odds Ration; CI Confidence Interval; ref. Reference Category.

*** OR and 95% CI at 1% level of significance

** OR and 95% CI at 5% level of significance

* OR and 95% CI at 10% level of significance.

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-1.89 to –0.01) during their adolescence than children of mothers who did not experience poor general health.

Among the maternal health-related behaviours, smoking habits during pregnancy had a significant negative impact on the infants' general health (OR: 1.79, 95% CI: 1.04–3.09) and the adolescents' chronic health conditions (OR: 1.38, 95% CI: 0.98–1.95). Infants whose mothers consumed alcohol more than once a week during the first trimester were 1.68 (95% CI:

Table 4. Maternal health and health-related behaviours and their associations with children's physical health outcome index score during infancy (0–1 year of age) and adolescence (12–13 years of age).

Explanatory Variables	Physical health outcome index score at:	
	Infancy (N = 5019)	Adolescence (N = 3327)
	b (95% CI)	b (95% CI)
Mother's health		
Poor General Health Status of Mothers	-0.40 (-1.00 to 0.21)	**-0.94**** **(-1.89 to -0.01)**
Mothers having at least one of the selected medical conditions during pregnancy	0.04 (-0.49 to 0.56)	0.57 (-0.24 to 1.39)
Mothers having stress, anxiety or depression during pregnancy	**-0.93**** **(-1.77 to -0.10)**	0.86 (-0.37 to 2.08)
Any stressful life events mothers faced in 12 months prior interview		
No events faced (ref.)		
Yes, one or more events faced	-0.01 (-0.55 to 0.53)	0.05 (-0.78 to 0.88)
Psychological distress—(mean) (K-6 depression scale)	0.01 (-0.51 to 0.53)	-0.44 (-1.31 to 0.42)
Mother's health behaviours		
Smoking frequency in 1st trimester of pregnancy		
None (ref.)		
Less than 10 daily	0.50 (-0.39 to 1.39)	0.70 (-0.78 to 2.18)
11+ daily	0.68 (-0.53 to 1.89)	-2.24 (-5.08 to 0.60)
Number of days per week alcohol was consumed in 1st trimester		
Zero days in a week (ref.)		
Once in a week	-0.02 (-0.66 to 0.62)	-0.66 (-1.65 to 0.33)
More than once in a week	-0.21 (-1.21 to 0.78)	1.10 (-0.43 to 2.62)
Usual daily serves of vegetables that mothers have	-0.04 (-0.26 to 0.17)	-0.26 (-0.60 to 0.08)
Usual daily serves of fruit that mothers have	0.07 (-0.17 to 0.30)	-0.19 (-0.58 to 0.21)
Number of days/week mothers engage in at least 30 minutes of exercise	**0.15**** **(0.01 to 0.30)**	0.01 (-0.24 to 0.25)
Food exclusion during pregnancy		
All food included (ref.)		
One item excluded	**-0.52*** **(-1.09 to 0.04)**	0.96 (0.11 to 1.80)
Two items excluded	-0.61 (-1.57 to 0.35)	1.13 (-0.30 to 2.56)
Three or more items excluded	0.01 (-1.36 to 1.39)	-0.72 (-3.34 to 1.90)
Other health variables		
Birth weight < 2500 gm	-0.88 (-2.42 to 0.66)	1.00 (-0.99 to 2.99)
Gestational age <37 week	**-1.51**** **(-2.95 to -0.08)**	-0.85 (-2.87 to 1.18)

Notes: As above mentioned in Table 2. Abbreviations: b beta coefficient; CI Confidence Interval; ref. Reference Category.

*** OR and 95% CI at 1% level of significance

** OR and 95% CI at 5% level of significance

* OR and 95% CI at 10% level of significance.

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0.93–3.04) times more likely to suffer from poor general health. However, if mothers consumed alcohol even once a week, then infants of those mothers were 1.35 (95% CI: 0.93–3.04) times more likely to suffer from at least one health condition. Furthermore, if mothers avoided eggs, milk or fish during pregnancy or breastfed for less than six months, their infants were more likely to experience lower physical health outcomes during infancy. On the other hand,

more days spent with moderate to rigorous exercise by mothers increased the physical health outcome scores of the infants (Table 4).

4. Discussion

This study comprehensively evaluated the foetal origins of a wide range of child health outcomes from a contemporary nationally representative Australian children's birth cohort. This study found that poor maternal health status during pregnancy or in the year after childbirth was significantly associated with an increased risk of poor general health, chronic health conditions, and poor physical health outcomes in their children. These findings corroborate previous literature [1, 21, 24], showing that poor maternal health and health-related behaviours increase the odds of poor health in infants or adolescents.

Our results indicate that maternal chronic conditions during pregnancy are significantly associated with a higher likelihood of poor general health, chronic conditions or lower physical health in their offspring during infancy or adolescence. Previous studies provide evidence that chronic conditions such as obesity during pregnancy are associated with poor general health, obesity [1, 3] or heart disease [35] in their children. While the study by Callaway et al. (2006) confirms the association of maternal overweight or obesity and chronic conditions (birth defects, hypoglycaemia or jaundice) of children at their infancy, our study asserts the likelihood of having a chronic condition among the children up to their adolescence.

This study reveals that mother's poor general health in the year after childbirth was significantly associated with infants' and adolescents' poor general health. A study in the US setting corroborates our findings that mothers' rating of their general health plays a role in the maternal perception of their infant's general health status [32]. Another study conducted by Waters et al. (2000) on children aged 5 to 18 confirms our findings that mother's poor general health is associated with children's poor general health up to their adolescence [36]. However, in general, our study reveals that the odds of having poor general health during infancy is greater while the odds of this health outcome is small for adolescents. Moreover, the current study reveals the associations between mothers' poor general health and children's chronic illness and lower physical health index score, but these are significant only during the adolescent period.

The present study did not find any significant associations of low birth weight or gestational age less than 37 weeks with poor general health status or any chronic health conditions for infants and adolescents, except for a lower physical health outcome index score among infants. This may relate to the explanation by Dauglas and Gear (1976) in another study that a national survey can contribute little to the understanding of low birthweight children due to the small number of low birthweight children who suffer from problems of morbidities [37]. Our population-based study might be interpreted to indicate that low birthweight children are relatively low in numbers in relation to all births and contribute little to the total burden of children with morbidities in Australia. However, hospital-based studies with special interest groups or a subgroup of the population may have been reported with higher odds of child health outcomes for low birth weights and gestational age at birth. These two risk factors may have mediating effects on child health outcomes that need further research.

This study results reveal that stressful life events experienced by mothers in the 12 months prior to interview in the year after childbirth or the stress, anxiety or depression during pregnancy increase the odds that of poor general health among children in the long run, particularly for adolescents. On the contrary, anxiety or depression during pregnancy or psychological distress in the year after childbirth increases the odds of poor health among infants (for chronic illness or poor physical health index score), but it diminishes in the long-

term. This might relate to chronic illness during infancy which may imprint a long-term consequence of poor general health perception among parents and children, although by adolescence those children were able to self- manage the chronic illness. Our study results are in line with earlier evidence: poor perinatal maternal mental health is linked to poor infant physical health [38]; maternal psychological distress during pregnancy is associated with paediatric diseases in their offspring such as eye, ear, respiratory, digestive, and skin diseases [16] and childhood overweight [3]. Additionally, depression is associated with an unhealthy lifestyle, for example smoking and poor diet, which may also adversely affect children born to depressed mothers [39]. While these studies evaluated the association of any specific maternal mental health condition with a child health outcome, our study considers three different measures of maternal mental health either during pregnancy or when children were 3 to 15 months old, as LSAC measures these variables from these timepoints. As a result, this study has been able to evaluate the associations with confounding influence of all three types of maternal mental health. However, all these three different measurements may create a difficulty in focusing on the associations of health outcomes by specific timepoints.

The present study results showed that smoking during pregnancy was associated with children's poor health status during infancy. Similarly, a study of three birth cohorts in Finland and Denmark found that the children in each of the cohorts whose mothers smoked during pregnancy had higher hyperactivity–inattention scores compared with the children of non-smokers [21]. The findings of the present study have implications for child health outcomes in contemporary demographics of Australia, as, in 2015, almost 1 in 4 (23%) of the mothers who gave birth reported smoking during the first 20 weeks of pregnancy [7]. Our results also revealed that alcohol consumption more than once a week during the first trimester was associated with children with chronic conditions during infancy; the Western Australia study also found that Prenatal Alcohol Exposure (PAE) increases the odds of child behavioural problems [40]. These results indicate that substance use during pregnancy potentially causes impairment of the foetus.

Given that this study discussed the poor child health outcomes for women with prenatal and postnatal health conditions from a birth cohort of 2004, it might be worsened with the current Australian population. Women in Australia are continuing to give birth at an increasing age: the average age rose from 29.7 in 2005 to 30.3 in 2015 [7], with a proportion giving birth after 40 years age [41]. It was observed from a longitudinal study on women's health that the chronic conditions–hypertension, heart disease and diabetes–along with the risk factors (increasing weight and lower physical activity) were more prevalent among mid-aged (45–50 years) women [42]. Thus, adverse child physical health outcomes are more likely to increase at the population level in Australia due to the increasing maternal age of the pregnancy and increased risk of pregnancy with chronic conditions [7].

This study's main strength lies in the use of large, nationally representative and population-based contemporary birth cohort generalisable to all Australian children born in 2004. Hence the study could re-examine the foetal origins for the almost current youth population of Australia. Using the longitudinal data, this study could compare the child health outcomes for infants and adolescents against a range of maternal health indicators, including physical and mental health and health-related behaviours of mothers during pregnancy or in the year after childbirth. Another strength of the study is the adjustment of important confounders of maternal and child health. Further, for adolescent health models, this study adjusted for adolescent health behaviours related variables, which are available in LSAC, to make the estimates more reliable.

This study has several limitations that need to be discussed. As this study is not designed to assess the causal effects, we cannot ascertain the causality and its directions. Further study with

advanced techniques is required to determine the underlying mechanism to explain the associations revealed in this study. In addition, more research is necessary before any generalisations of the present study's findings to other countries can be made. Another limitation is that the general health status data for the mothers and children were self-reported and might have recall bias. However, there was no subjective bias in reporting chronic conditions or calculating the physical health outcome index. Multiple testing is another concern for this study. It tested the study sample three times to test the three hypotheses regarding the child health outcomes for each infant and adolescent sample. To address this concern, we reported the significance level of p-values and discussed the effect size where it was possible to understand the statistical power of the analysis and also discussed the scientific plausibility and supporting data from other studies to validate our study results. Further, there were different sample sizes from infants to adolescents due to dropouts. Hence, the statistical power of the analyses differs, though we got the benefit of longitudinal surveys and observing the same children. Therefore, this study results require caution to interpret the findings.

5. Conclusion

The present study re-examines the foetal origins hypothesis using a contemporary birth cohort dataset from Australia. The study found evidence that poor maternal physical health status and health-related behaviours during pregnancy or up to 15 months from childbirth has adverse health consequences for their children during infancy and adolescence in all three dimensions examined: poor general health, presence of chronic health conditions, and lower physical health scores. Maternal psychological distress during pregnancy also increased the odds of chronic health conditions and lower physical health scores in their offspring. These study findings emphasise the importance of improving maternal physical and mental health and promoting a healthy lifestyle during pregnancy or in the year after childbirth to improve child health. These results have policy implications for undertaking preventive measures to improve maternal health and create awareness of the importance of a healthy lifestyle during pregnancy to reduce poor health outcomes in their offspring.

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References

1. O'Reilly JR, Reynolds RM. The risk of maternal obesity to the long-term health of the offspring. Clinical Endocrinology. 2013; 78(1):9–16. Epub 2012/09/27. https://doi.org/10.1111/cen.12055 PMID: 23009645.
2. Robinson M, Zubrick SR, Pennell CE, Van Lieshout RJ, Jacoby P, Beilin LJ, et al. Pre-pregnancy maternal overweight and obesity increase the risk for affective disorders in offspring. Journal of Developmental Origins of Health and Disease. 2013; 4(1):42–8. Epub 2013/02/01. https://doi.org/10.1017/S2040174412000578 PMID: 25080181.
3. Ingstrup KG, Andersen CS, Ajslev TA, Pedersen P, Sorensen TI, Nohr EA. Maternal Distress during Pregnancy and Offspring Childhood Overweight. Journal of Obesity. 2012; 2012:7. Epub 2012/06/12. https://doi.org/10.1155/2012/462845 PMID: 22685634; PubMed Central PMCID: PMC3364588.
4. Callaway L, Prins J, Chang A, McIntyre H. The prevalence and impact of overweight and obesity in an Australian obstetric population. Medical Journal of Australia. 2006; 184(2):4.
5. Alati R, Lawlor DA, Mamun AA, Williams GM, Najman JM, O'Callaghan M, et al. Is there a fetal origin of depression? Evidence from the Mater University Study of Pregnancy and its outcomes. American Journal of Epidemiology. 2007; 165(5):575–82. Epub 2006/12/07. https://doi.org/10.1093/aje/kwk036 PMID: 17148497.
6. Lutomski JE, Morrison JJ, Greene RA, Lydon-Rochelle MT. Maternal morbidity during hospitalization for delivery. Obstetrics & Gynecology. 2011; 117(3):596–602. Epub 2011/02/24. https://doi.org/10.1097/AOG.0b013e31820ac074 PMID: 21343763.
7. Australian Institute of Health and Welfare. Australia's Health 2018. Canbera: AIHW.
8. Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. Australian and New Zealand Journal of Obstetrics and Gynaecology 2011; 51(4):333–8. Epub 2011/08/03. https://doi.org/10.1111/j.1479-828X.2011.01312.x PMID: 21806573.
9. Barker DJP. Maternal Nutrition, Fetal Nutrition, and Disease in Later Life. Nutrition. 1997; 13(9):7.
10. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Annals of Internal Medicine. 1999; 130(4 Pt 1):7. Epub 1999/03/06. https://doi.org/10.7326/0003-4819-130-4_part_1-199902160-00005 PMID: 10068385.
11. Hoy WE, Mathews JD, McCredie DA, Pugsley DJ, Hayhurst BG, Rees M, et al. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. Kidney International. 1998; 54(4):1296–304. Epub 1998/10/10. https://doi.org/10.1046/j.1523-1755.1998.00099.x PMID: 9767547.
12. West CE, Jenmalm MC, Prescott SL. The gut microbiota and its role in the development of allergic disease: a wider perspective. Clinical & Experimental Allergy. 2015; 45:43–53. Epub 2014/04/30. https://doi.org/10.1111/cea.12332 PMID: 24773202.
13. Kennedy JD. Lung function outcome in children of premature birth. Journal of Paediatrics and Child Health. 1999; 35:516–21. https://doi.org/10.1046/j.1440-1754.1999.00422.x PMID: 10634975
14. Bussing R, Halfon N, Benjamin B, Wells KB. Prevalence of behavior problems in US children with asthma. Pediatrics & Adolescent Medicine. 1995; 149:565–72. https://doi.org/10.1001/archpedi.1995.02170180095018 PMID: 7735414
15. Roura LC, Arulkumaran SS. Facing the noncommunicable disease (NCD) global epidemic—the battle of prevention starts in utero—the FIGO challenge. Best Practice & Research Clinical Obstetrics and Gynaecology. 2015; 29(1):5–14. Epub 2014/09/25. https://doi.org/10.1016/j.bpobgyn.2014.04.018 PMID: 25248554.
16. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Stress during pregnancy and offspring pediatric disease: A National Cohort Study. Environmental Health Perspectives. 2011; 119(11):1647–52. Epub 2011/07/22. https://doi.org/10.1289/ehp.1003253 PMID: 21775267; PubMed Central PMCID: PMC3226491.
17. Harvey SM, Murphy VE, Gibson PG, Collison A, Robinson P, Sly PD, et al. Maternal asthma, breastfeeding, and respiratory outcomes in the first year of life. Pediatr Pulmonol. 2020; 55(7):1690–6. Epub 2020/04/07. https://doi.org/10.1002/ppul.24756 PMID: 32250063.
18. Mulder B, Pouwels KB, Schuiling-Veninga CC, Bos HJ, de Vries TW, Jick SS, et al. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. Clin Exp Allergy. 2016; 46(9):1214–26. Epub 2016/05/10. https://doi.org/10.1111/cea.12756 PMID: 27159872.
19. Liu X, Olsen J, Pedersen LH, Agerbo E, Yuan W, Li J. Antidepressant use during pregnancy and asthma in the offspring. Pediatrics. 2015; 135(4):e911–7. Epub 2015/03/11. https://doi.org/10.1542/peds.2014-4073 PMID: 25755245.

20. Chavatte-Palmer P, Tarrade A, Rousseau-Ralliard D. Diet before and during Pregnancy and Offspring Health: The Importance of Animal Models and What Can Be Learned from Them. International Journal of Environtal Research and Public Health. 2016; 13(6). Epub 2016/06/18. https://doi.org/10.3390/ijerph13060586 PMID: 27314367; PubMed Central PMCID: PMC4924043.

21. Obel C, Linnet KM, Henriksen TB, Rodriguez A, Jarvelin MR, Kotimaa A, et al. Smoking during pregnancy and hyperactivity-inattention in the offspring—comparing results from three Nordic cohorts. International Journal of Epidemiology. 2009; 38(3):698–705. Epub 2008/02/06. https://doi.org/10.1093/ije/dym290 PMID: 18250076.

22. Sutin AR, Flynn HA, Terracciano A. Maternal smoking during pregnancy and offspring personality in childhood and adulthood. Journal of Personality. 2018; 86(4):652–64. Epub 2017/08/24. https://doi.org/10.1111/jopy.12342 PMID: 28833118; PubMed Central PMCID: PMC5817044.

23. Burns L, Breen C, Bower C, C OL, Elliott EJ. Counting fetal alcohol spectrum disorder in Australia: the evidence and the challenges. Drug and Alcohol Review. 2013; 32(5):461–7. Epub 2013/04/27. https://doi.org/10.1111/dar.12047 PMID: 23617437.

24. Ou L, Chen J, Hillman K, Eastwood J. The comparison of health status and health services utilisation between Indigenous and non-Indigenous infants in Australia. Australian and New Zealand Journal of Public Health. 2010; 34(1):50–6. Epub 2010/10/06. https://doi.org/10.1111/j.1753-6405.2010.00473.x PMID: 20920105.

25. Shlafer R, Hergenroeder AC, Jean Emans S, Rickert VI, Adger H Jr., Spear B, et al. Adolescence as a critical stage in the MCH Life Course Model: commentary for the Leadership Education in Adolescent Health (LEAH) interdisciplinary training program projects. Maternal and Child Health Journal. 2014; 18(2):462–6. Epub 2013/02/26. https://doi.org/10.1007/s10995-013-1243-8 PMID: 23435919; PubMed Central PMCID: PMC5535310.

26. Schulenmerg JE, Bryant AL, O'Malley PM. Taking hold of some kind of life: How developmental tasks relate to trajectories of well-being during the transition to adulthood. Development and Psychopathology 2004; 16(2004):1119–40.

27. Soloff C, Lawrence D, Johnstone R. Technical Paper no. 1: Sample design. Australian Institute of Family Studies, 2005 ISSN 1832-9918.

28. Khanam R, Nghiem HS, Connelly LB. Child health and the income gradient: evidence from Australia. Journal of Health Economics. 2009; 28(4):805–17. Epub 2009/06/16. https://doi.org/10.1016/j.jhealeco.2009.05.001 PMID: 19525024.

29. Khanam R, Nghiem HS, Connelly LB. What roles do contemporaneous and cumulative incomes play in the income-child health gradient for young children? Evidence from an Australian panel. Health Economics. 2014; 23(8):879–93. Epub 2013/06/20. https://doi.org/10.1002/hec.2961 PMID: 23780648.

30. Sanson A, Misson S, Wake M, Zubrick SR, Silburn SR, Rothman S, et al. Summarising children's well-being: the LSAC Outcome Index. Australian Institute of Family Studies, 2005.

31. Qu L, Soriano G, Weston R. Starting early,starting late: The health and wellbeing of mother and child. Family Matters. 2006; 2006(74):4–11.

32. McCormack C, Brooks-Gunn J, Shorter T, Holmes JH, Heagarty MC. Factors Associated with Maternal Rating of Infant Health in Central Harlem. Developmental and Behavioural Pediatrics. 1989; 10(3):139–44.

33. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychological Medicine. 2002; 32(6):959–76. Epub 2002/09/07. https://doi.org/10.1017/s0033291702006074 PMID: 12214795.

34. Bujang MA, Sa'at N, Sidik T, Joo LC. Sample Size Guidelines for Logistic Regression from Observational Studies with Large Population: Emphasis on the Accuracy Between Statistics and Parameters Based on Real Life Clinical Data. Malays J Med Sci. 2018; 25(4):122–30. Epub 2019/03/28. https://doi.org/10.21315/mjms2018.25.4.12 PMID: 30914854; PubMed Central PMCID: PMC6422534.

35. Watkins ML, Botto LD. Maternal Prepregnancy Weight and Congenital Heart Defects in the Offspring. Epidemiology. 2001; 12(4):439–46. PMID: 11428386

36. Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L. Influence of parental gender and self-reported health and illness on parent-reported child health. Pediatrics. 2000; 106(6):1422–8. Epub 2000/01/11. https://doi.org/10.1542/peds.106.6.1422 PMID: 11099598.

37. Douglas JW, Gear R. Children of low birthweight in the 1946 national cohort. Behaviour and educational achievement in adolescence. Arch Dis Child. 1976; 51(11):820–7. Epub 1976/11/01. https://doi.org/10.1136/adc.51.11.820 PMID: 137695; PubMed Central PMCID: PMC1546058.

38. Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M, et al. Effects of perinatal mental disorders on the fetus and child. The Lancet. 2014; 384(9956):1800–19. https://doi.org/10.1016/S0140-6736(14)61277-0 PMID: 25455250

39. Milberger S J. B, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children?. The American Journal of Psychiatry. 1996; 153 (9):1138–42. https://doi.org/10.1176/ajp.153.9.1138 PMID: 8780415

40. O'Leary CM, Nassar N, Zubrick SR, Kurinczuk JJ, Stanley F, Bower C. Evidence of a complex association between dose, pattern and timing of prenatal alcohol exposure and child behaviour problems. Addiction. 2009; 105(1):74–86. Epub 2009/11/20. https://doi.org/10.1111/j.1360-0443.2009.02756.x PMID: 19922516.

41. Carolan MC, Davey M-A, Biro M, Kealy M. Very advanced maternal age and morbidity in Victoria, Australia: a population based study. BMC Pregnancy and Childbirth. 2013; 13(80). https://doi.org/10.1186/1471-2393-13-80 PMID: 23537152

42. Lucke J, Waters B, Hockey R, Spallek M, Gibson R, Byles J, et al. Trends in women's risk factors and chronic conditions: findings from the Australian Longitudinal Study on Women's Health. Women's Health. 2007; 3(4):423–32. https://doi.org/10.2217/17455057.3.4.423 PMID: 19804018

3.2 Links and implications

This paper reiterates the foetal origins hypothesis in the broad aspects of maternal and child health, in the context of contemporary birth cohort of Australian children. This study signifies that poor general health of the mother in the year after childbirth are associated with higher odds of poor health in infants and adolescents in several aspects including general health and chronic illness. Another key finding of the study is that presence of a chronic condition and stress, anxiety or depression during pregnancy among mothers significantly increase the likelihood of contracting chronic diseases in their infants. Thus, this study concludes that initiatives to improve maternal physical and mental health would not only reduce the national health burden of children, it will also improve maternal health capital and will build a healthy next generation in Australia.

As this is a cross-sectional study revealing association of maternal health conditions during pregnancy and contraction of chronic diseases in their offspring, it creates a ground to investigate them longitudinally. Further, Australian health survey (2018) reveals that asthma is the leading health burden among the children aged 5-14 years in Australia. Hence, in the next study this thesis investigated the prevalence of wheezing, asthma, and eczema among Australian children using longitudinal data from birth to 15 years of age; it also examined the association between maternal health status during pregnancy and their offspring's respiratory and allergic morbidities using sex-segregated data.

CHAPTER 4: PAPER 2 - ARE WHEEZING, ASTHMA AND ECZEMA IN CHILDREN ASSOCIATED WITH MOTHER'S HEALTH DURING PREGNANCY? EVIDENCE FROM AN AUSTRALIAN BIRTH COHORT

4.1 Introduction

This chapter presents the second study of the thesis investigating the prevalence of wheezing, asthma and eczema among Australian children from birth to 15 years of age and also examining the association between maternal health during pregnancy and respiratory and allergic diseases of their children. Thus, this paper is the second study that examines the foetal origins hypothesis on a contemporary birth cohort of 4977 children across eight waves comprising 31,367 person-years. This study deployed the longitudinal prospective study method and implemented multivariate logistic regression models to respond to the research questions.

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Are wheezing, asthma and eczema in children associated with mother's health during pregnancy? Evidence from an Australian birth cohort

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Abstract

Background: This study investigated the prevalence of wheezing, asthma, and eczema among Australian children using longitudinal data from birth to 15 years of age. This study also examined the association between maternal health status during pregnancy and their offspring's respiratory and allergic morbidities using sex-segregated data.

Methods: This study used data from the Longitudinal Study of Australian Children (LSAC) where approximately 5000 children of a birth cohort across Australia were surveyed in 2004. These children were followed biennially in eight waves up to their age of 15 years until 2018. The status of the children's wheezing, asthma, and eczema were reported by the mothers upon doctors' diagnosis (for asthma) or self-assessment (for wheezing or eczema). Binomial logistic regression models were used to analyse associations between maternal health during pregnancy and their children's health outcomes.

Results: Asthma prevalence among 0–1-year aged children was 11.7%, increased to 15.4% when the children were 10–11 years old, and then decreased to 13.6% when they were 14–15 years old. Wheezing and eczema were most prevalent when the children were 2–3 years old (26.0 and 17.8% respectively) and were least prevalent when the children were 14–15 years old (7.3 and 9.5% respectively). Maternal asthma, smoking during pregnancy, and pre-pregnancy obesity were significantly associated with an increased risk of wheezing and asthma in Australian children. Childhood eczema was associated only with maternal asthma. These associations were stronger among male children up to age 10–11 and during adolescence (12–15 years of age), female children were more prone to wheezing, asthma, and eczema.

Conclusion: This is a comprehensive longitudinal study of Australian children (0–15 years of age) to assess the prevalence (with sex-specific differences) of wheezing, asthma and eczema as well as the association between these respiratory and allergic morbidities and maternal health during pregnancy. The study findings suggest that careful medical and obstetric monitoring, improved specific age-sex wise risk factor prevention for children and health promotion for pregnant women would help protect child health.

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Keywords: Children's respiratory disease, Allergic disease, Wheezing, Asthma, Eczema, Maternal health in pregnancy, Maternal medications, Maternal body mass index, Maternal smoking

Background

Childhood respiratory and allergic diseases, wheezing, asthma, and eczema, are leading causes of global morbidity [1]. The 2000–2003 International Study of Asthma and Allergies in Childhood found that 14.1 and 7.3% of children aged 13–14 years were currently suffering from asthma or eczema, respectively [1]. The 2018 Australian health survey revealed that among children aged 5–14 years, 11% reported current asthma, making asthma the leading health burden in that age group [2]. A longitudinal study conducted in 2009 found that 16.9% of Australian children, born in 2004, experienced wheezing or asthma within the first 3 years of life [3]. Wheezing, asthma and eczema [4] pose significant long-term health burdens to children, such as poor lung function or development of persistent asthma in later life [5–8]. Furthermore, the incidences of wheezing, asthma or eczema are influenced by maternal health and environmental conditions [9–11] which include maternal exposures to asthma, obesity, antibiotic/antidepressant medication use or smoking during pregnancy [4, 8, 12–16]. Therefore, comprehensive research related to longitudinal prevalence of wheezing, asthma, and eczema among children, taking maternal health during pregnancy into account, is a public health priority.

As a definition, wheezing has been defined as a "continuous high-pitched sound with musical quality emitting from the chest during expiration" and results in "the narrowing of intrathoracic airways and expiratory flow limitation" [17]. Some studies have shown that approximately 25% of children with persistent asthma had wheezing symptoms in their early life [17–19]. The Global Initiative for Asthma (GINA) states that "asthma is a syndrome with a highly variable clinical spectrum, characterised by airway inflammation" [17].

Asthma also causes shortness of breath and chest tightness, and can cause cough [5]. The definition of eczema is based on the Hanifin and Rajka validated criteria [20], which include: itchy skin conditions in the past 12 months, history of skin creases, history of dry skin in the past 12 months and visible flexural dermatitis. Though there are several cross-sectional studies [21], the prevalence of each of these conditions (wheezing, asthma and eczema) are understudied in contemporary population-based longitudinal studies of children's health.

Pregnancy is a crucial period in determining the future health of the offspring [10] and hence, further understanding on mother's pregnancy health and children's respiratory and allergic diseases are necessary. To date several studies have shown that maternal asthma during pregnancy, pre-pregnancy obesity, and gestational weight gain are associated with an increased risk of asthma or wheezing in the offspring [12, 22–24]. However, most of these existing studies followed children from the first year of life to preschool or early school age [12, 25]. There is little longitudinal information about associations between maternal health during pregnancy and long-term respiratory or allergic health outcomes in children through following the participants up from birth to adolescence [8, 26].

A growing body of literature reveals that maternal risk behaviours, such as smoking during pregnancy [27] and maternal use of some medications [28, 29], are associated with increased risk of wheezing or asthma in the offspring. Although prenatal or postnatal smoking is a significant risk factor for wheezing and asthma among infants and preschool-age children [27, 30], it is not well known how the number of cigarettes smoked during pregnancy effects the association. Some studies have shown that maternal use of medications, which includes paracetamol use [31] or high doses of folic acid [29] during pregnancy had influenced health outcomes in children such as increased risk of childhood asthma [14, 32]. However, few studies have examined the effects of anti-depressant or antibiotic medication use during pregnancy on childhood wheezing, asthma or eczema [31, 33]. In Canada, the Manitoba province population-based study from 1996 to 2012, revealed that prenatal antibiotic exposure was associated with an increased risk of asthma [33]. No population based comprehensive study examined the effects of anti-depressant or antibiotic medication use during pregnancy on Australian children.

Sex dimorphism has long been recognised to childhood morbidities, but few studies investigated the sex-specific differences on children's respiratory and allergic diseases [34, 35]. For example, a 2003–2008 study in Greece showed that male:female ratio of current and lifetime wheezing and asthma increased; although, irrespective of sex, asthma diagnosis declined among school-age children, but not among preschool wheezers [34]. However, these studies only focused on prevalence and lacked investigation on the sex-specific associations of familial heredity or maternal health during pregnancy. Few studies have used a single population-based prospective study on both respiratory and allergic diseases [36, 37], or adjusted for confounding factors of maternal health during pregnancy to determine the age and sex-specific effects on children's respiratory and allergic diseases [14, 25]. Longitudinal

investigation of sex differences of wheezing, asthma and eczema in Australian children (birth to 15 years of age), associated with maternal health during pregnancy, is limited.

The present study, therefore, aims to determine the sex-specific longitudinal prevalence of respiratory and allergic diseases, wheezing, asthma, and eczema, among children from birth to the age of 15 years on a population based longitudinal data of Australian children. Further, it investigates the association between maternal health or health risk behaviours (asthma, gestational age, maternal pre-pregnancy BMI, maternal smoking or use of antibiotics or antidepressants) during pregnancy and the offspring's wheezing, asthma, and eczema throughout childhood (including sex-disaggregated differences) to the age of 15 years. Findings of this study would broaden the understanding of the age and sex specific long-term aetiology of childhood respiratory and allergic morbidities.

Methods

Data source and sample selection

The data was obtained from eight waves of the 2004–2018 Longitudinal Study of Australian Children (LSAC). LSAC is a representative household survey of Australian children that biennially collects information on the health (physical and socio-emotional), and learning development of Australian children based on the context of the bio-ecological framework of human development [38]. The LSAC data is collected from the parents or caregivers of the children of participating households and from the children themselves (from age 12 onward), through self-completed questionnaires or face-to-face interviews with trained interviewers. A multi-stage sampling technique was used to select the LSAC respondents. The household is the primary sampling unit. Further details regarding LSAC survey design and methodology can be found elsewhere [39].

The LSAC dataset contained information on children's wheezing, asthma, and eczema-related health and their mothers' self-reported health (asthma, pre-pregnancy obesity) and health-risk behaviours (medications, smoking habits) during pregnancy from the biological mother-child pair as well as eight waves of the child's ongoing health up to 15 years of age.

After excluding children from non-biological parents, the final sample was 4977 in Wave 1. There were drop-outs in the subsequent waves and at Wave 8 the attrition rate was 38.8% sustaining 2960 mothers and children in the sample. An additional appendix file shows the total LSAC participants, the attrition rates and the final study sample after exclusion of non-mother parents for each of the waves in Fig. A1 (see Additional file 1). This figure also shows the loss to follow-up sample for Wave 2 to Wave 8 calculated from eligible sample of the first wave (baseline wave) to the particular wave.

Outcome variables

The outcome variables of this study were whether the children: (i) had wheezing, (ii) were ever diagnosed with asthma, (iii) had current asthma for which they took medication, or (iv) had eczema. The LSAC survey respondents' (parents/caregivers) were asked the following questions: (i) Has your child had an illness with wheezing in the chest which lasted for a week or more in the last 12 months?; (ii) Has a doctor ever told you that your child has asthma?; (iii) Has your child taken any medication for asthma in last 12 months?; and (iv) Does your child have any ongoing conditions with eczema? A binary variable was used to capture each of these responses (Yes = 1 and No = 0).

Existing literature shows that although a good portion of preschool children have wheezing, not all of them diagnosed with asthma when they reach school age [17, 19]. In LSAC, wheezing condition was monitored in every wave, however, asthma was identified if the respondents reported doctor diagnosed asthma and it was started to trace first when the children reached 2–3 years age. Hence, this study followed up both wheezing and asthma separately, though many international multi-country or national studies determined asthma prevalence by assessing presence of wheezing as a symptom of asthma [5]. We took the opportunity to separately identify wheezing and asthma of LSAC to increase the specificity of these respiratory diseases among children over time.

Independent variables

The independent variables considered in this study were based on the existing literature on this topic [13, 23, 40, 41]. The following independent variables were used: (i) incidence of asthma during pregnancy, (ii) mother's pre-pregnancy BMI, (iii) gestational age at birth, (iv) maternal smoking during pregnancy, (v) the number of cigarettes smoked by mother during pregnancy, and (vi) the use of antibiotics or antidepressant medications taken by mother during pregnancy.

The data for the variable maternal asthma come from this question: 'During the pregnancy with child, did (you/child's mother) take any medicines or tablets on a doctor's prescription for asthma?'. If a mother used any medication for the treatment of asthma, then the response was categorised as Yes =1; if not, it was categorised as No = 0. Maternal BMI was calculated from their pre-pregnancy height and weight recorded in Wave 1. Mothers' BMI was categorised into four groups according to World Health Organization (WHO) guidelines: (i) 'underweight' (BMI < 18.50), (ii) 'healthy weight' (18.5 ≤ BMI < 25), (iii) 'overweight' (25 ≤ BMI < 30), and (iv) 'obese' (BMI ≥ 30). Approximately 20% of respondents did not provide height or weight; therefore, these

mothers were grouped into a 'not measured' category. The children's gestational age was recorded in weeks and categorised into three categories: (i) on time (37–41 weeks), (ii) early (36 weeks or less), (iii) or late (42 weeks or more). Information on maternal smoking during pregnancy was collected in Wave-1 of LSAC surveys. If mothers smoked during their pregnancy, the number of cigarettes smoked during the first trimester of pregnancy was recorded in the study. From this record, this study categorised data as follows: (i) none, (ii) < 10 daily, and (iii) 11+ daily. The information on medication use during pregnancy was also collected via mothers' responses to 'What prescribed medicines or tablets were taken during pregnancy?'. If mothers took any medications related with antibiotics or antidepressants, the responses were coded with dichotomous values where 'Yes' = 1 and 'No' = 0 for each of these two types of medications.

Control variables

Based on existing literature [3, 13, 14, 32], this study considered the following confounding variables. Socio-demographic covariates included were (i) age of the mother (<=18, 19–34, > = 35 years), (ii) gender of the child (male or female), (iii) whether English is spoken at home (yes or no), (iv) whether mother is married with a partner, with a de facto partner, or single, (vi) indigenous status (yes or no), (vii) education of the mother (year 12 or less, professional qualification, graduate diploma, or postgraduate), (viii) family income (five quantiles), and (ix) remoteness of the family residence (highly accessible, accessible/moderately accessible, or remote/very remote). Other health or health-behaviour related confounders considered were (i) the type of birth (normal, caesarean, or other), (ii) birthweight (<=2500 g or > 2500 g), (iii) the immunisation status of the child (completely up to date or not), and (iv) the mother's quality of sleep in the year prior to childbirth (very good/fairly good, fairly bad or very bad). The home condition related one relevant confounder was (i) home exterior condition (fair/well-kept exterior, bad/poor Exterior or not sighted).

Statistical analysis

Descriptive statistics of the characteristics of the eight LSAC waves of sampled children and mothers have been presented using weighted frequency (n) and percentages (%). Further, descriptive analysis of the characteristics of the loss to follow-up samples on the outcome and explanatory variables have been performed. We performed this analysis to assess whether there were any bias on the loss of the sampled subjects. Multivariate analyses of binomial logistic regressions were employed to investigate the associations between maternal asthma, maternal obesity, gestation age, smoking and medication use (antibiotics or antidepressants) with the offspring's risk of exposure to childhood wheezing, asthma and eczema. All of the maternal illness and health risk exposure variables were measured during the pregnancy, with the exception of obesity, for which the mothers reported their pre-pregnancy height and weight. This study also investigated these associations with sex-segregated data. For ease of interpretation, results of the multivariate analyses of the binomial logistic regressions are presented in the form of odds ratios (OR) with 95% confidence intervals (CI). A p-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using Stata (release 15) statistical software.

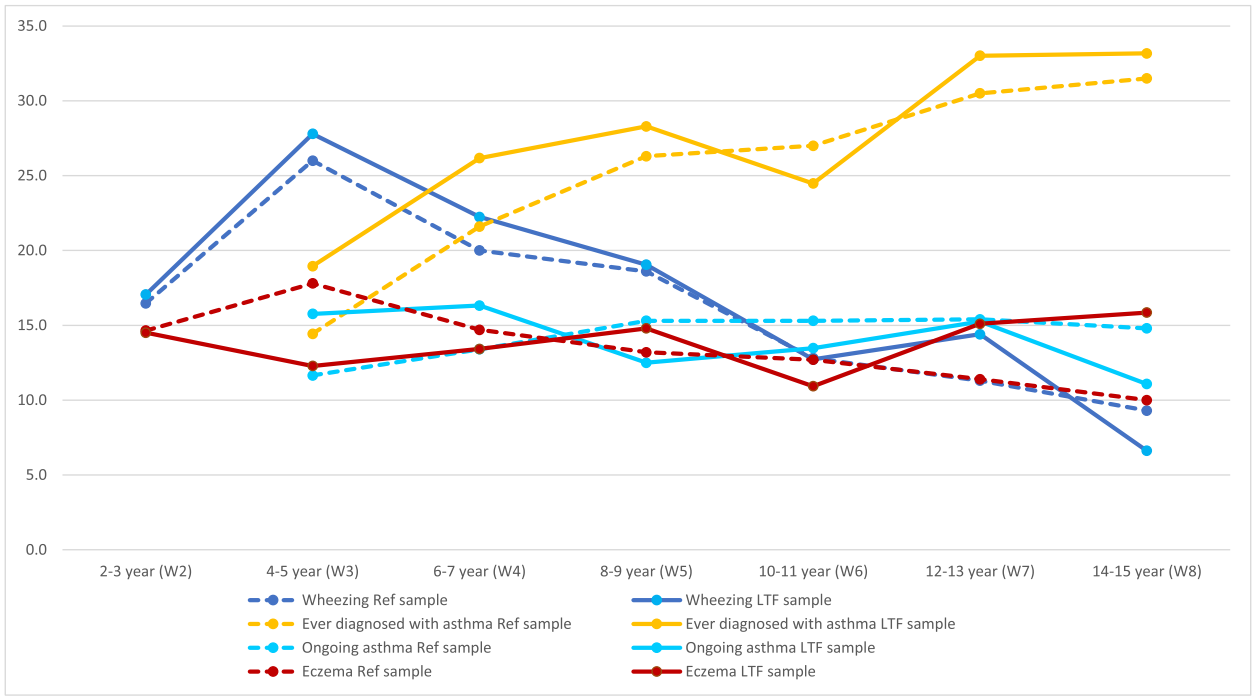
Loss to follow-up

Figure 1 showed the comparison of the prevalence of wheezing, asthma and eczema among the children who were lost in the follow-up wave compared to the whole sample of that wave. The results of the analysis showed minor differences in the prevalence of loss to follow-up sample of each wave compared to the whole sample of the that wave. Moreover, the trends of the prevalence for each of the diseases were almost similar in the loss to follow-up sample. In addition to Fig. 1, we have presented a detailed picture of this outcome variables' analysis in Table A1 of Additional file 1. Further, we have anlysed the frequency and percentages of the independent variables of this study on the loss to follow-up sample and it has been shown in Table A2 of the Additional file 1. The baseline characteristics of the loss to follow-up sample of each wave were similar to the characteristics of whole baseline sample regarding the explanatory variables. So, we may expect that there are no bias in the estimates of the statistical models as we observed no bias in the loss to follow-up samples over time.

Results

Prevalence of respiratory and allergic morbidities

The prevalence of wheezing among children in this study in their first year of life was 16.5% and increased to 26.0% when the children were aged 2–3 years (Fig. 2). However, in every subsequent follow-up, there was a gradual decrease, and the prevalence of wheezing dropped to 7.3% by the children's 14-15th year. The prevalence of asthma among children 2–3 years old was 11.7%. It increased to 15.3% between 6 and 10 years but then went down to 13.6% among adolescents aged 14–15 years. Prevalence of current asthma was slightly higher among male children up to the age of 12–13 years; however, increased prevalence was observed among female children aged 14–15 years. The prevalence of eczema was 14.7% among children aged 0–1, and it decreased to 9.5% by the time children reached adolescence. Eczema prevalence was higher among male children until age 4–5 years but increased among female children until it was 12.1% among females



Abbreviation: LTF, Loss to follow-up; Ref, Reference; W2, Wave 2; W3, Wave 3; W4, Wave 4; W5, Wave 5; W6, Wave 6; W7, Wave 7; W8, Wave 8

Fig. 1 The prevalence of wheezing, asthma and eczema among the children of loss to follow-up sample compared to the reference wave's whole sample

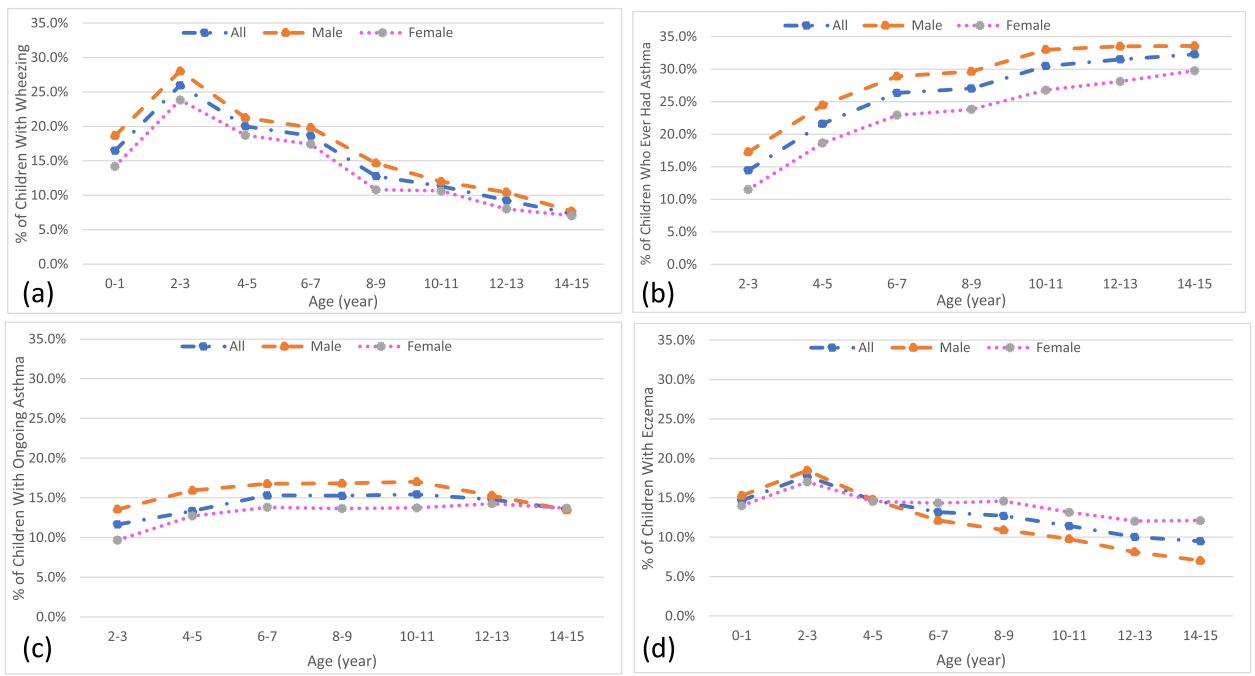


Fig. 2 The percentage of Australian children, by age and sex, who (a) experienced wheezing in the last 12 months, (b) ever had diagnosed with asthma, (c) experienced ongoing asthma, and (d) experienced eczema in the last 12 months. The values of data points are shown in an additional appendix (see Additional file 2)

aged 14–15 years, compared to 7.0% among males in the same age group (Fig. 2).

Maternal health

In Wave 1, among the mothers, 7.2% had asthma during their pregnancy, 14.4% were obese, and 15.1% smoked during the pregnancy. Furthermore, 4.4% of mothers smoked 11 cigarettes (or more) daily in their 1st trimester of pregnancy, 10.5% took antibiotic medication, and 2.1% took antidepressant medication during the pregnancy period (Table 1).

Association of maternal health during pregnancy with offspring's morbidities

Table 2 presents the associations between child wheezing and maternal health (asthma, BMI), risk factors (gestational age, smoking), and medication use (antibiotics, antidepressants) during pregnancy. Children of mothers who had asthma during pregnancy had an increased odds (OR: 1.5–2.5) of having wheezing until age 12–13. However, there was no significant association at the age of 14–15. Table 3 represents the associations between the above-mentioned maternal health and whether the children were ever diagnosed with asthma (cumulative effect). In all age groups at all the follow-ups, children's odds of having been diagnosed with asthma (by a doctor or physician) were 2.5 times greater if their mother had asthma during the pregnancy. In all follow-up groups, the odds of experiencing current asthma were significantly higher (OR: 2.5–3.7) among children whose mothers had experienced asthma during their pregnancy compared to the children of mothers who did not have asthma (Table 4).

The odd of experiencing eczema was around 1.4 times higher among the children 0–1 and 4–5 years of age whose mother had experienced asthma in pregnancy compared to the offspring of non-asthmatic mothers (Table 5); this odds increased to 1.9 times when the children reached 6–7 years of age. However, from the age of 8–9 years until adolescence, the influence of maternal asthma during pregnancy on the odds of having eczema was insignificant (Table 5). Interestingly, maternal asthma during pregnancy had a greater effect on the odds of the offspring having asthma than on the odds of having eczema. This was the pattern across all age groups.

The smoking status of mothers during pregnancy influenced their offspring's health to varying extents across the respiratory and allergic morbidities. Children of mothers who smoked either less than 10 or 11 plus cigarettes during pregnancy showed 1.52 to 2.61 times greater odds to suffer from wheezing, although the odds ratio decreased after the age of seven years (Table 2). Children of mothers who smoked 11+ cigarettes a day during the first trimester showed higher odds to have ever been diagnosed with asthma (OR: 1.54–1.88) compared to the children of non-smoking mothers during pregnancy (Table 3). These children also showed higher odds to have been currently experiencing asthma until the age of 10–11 years (Table 4). However, maternal smoking during pregnancy, with any number of cigarettes, did not influence the odds of having eczema among the children at any of age groups (Table 5).

Maternal pre-pregnancy obesity had an influence on the offspring's risk of experiencing wheezing and current or past asthma but not eczema (Tables 2, 3, 4 and 5). The odds of encountering wheezing illness was higher in children aged 2–5 of overweight and obese mothers compared to mothers of healthy weight, with odds ratio ranging from 1.31 to 1.42 (Table 2). The odds ratio of ever having been diagnosed with asthma ranged from 1.27 to 1.37 for children of overweight mothers and from 1.39 to 1.45 for children of obese mothers compared to the children of healthy weight mothers until age 10–11 (Table 3). A similar trend was present in the risk of currently having asthma among the children of overweight and obese mothers (Table 4).

If the mothers had taken antibiotics or antidepressant medication during pregnancy, their children showed higher odds of being afflicted with wheezing between ages 2 and 5 years than the children of mothers who did not take these medications. However, maternal medication use showed no association with the risk of children having asthma or eczema. Gestational age had a weak association with wheezing among preschool-aged children (0–5 years), but there was no association with asthma or eczema among the children at any age.

Sex differences

This study also separately assessed the risks of and maternal associations with having respiratory or allergic morbidities among male and female children across all eight follow-ups. The statistical analyses were performed with sex-segregated data for all the outcome variables of this study with the same independent and control variables as shown in Table 2, 3 and 4. The detailed results of this sex-segregated analysis have been shown in Additional file 3. In Table 6, the compilation of odds of each of the disease outcomes (wheezing, ever diagnosed with asthma, ongoing asthma or eczema) of the children of mothers exposed to asthma during pregnancy, compared to the children of mothers who did not experience asthma during pregnancy, have been shown for all children and segregated by sex for the purpose of comparison. Up until the age of 10–11 years, male children had higher odds to encounter these morbidities than their female counterparts. However, as adolescents (12–15 years old), female children showed higher odds of having these morbidities (wheezing, ever had asthma, ongoing asthma

Table 1 Sample characteristics across the LSAC Waves

VARIABLES	Age 0–1 n (%)	Age 2–3 n (%)	Age 4–5 n (%)	Age 6–7 n (%)	Age 8–9 n (%)	Age 10–11 n (%)	Age 12–13 n (%)	Age 14–15 n (%)
N	4977	4485	4264	4088	3922	3574	3097	2960
EXPOSURE VARIABLES								
Mother had asthma during pregnancy								
No	4619 (92.81)	4166 (92.89)	3960 (92.87)	3799 (92.93)	3633 (92.63)	3310 (92.61)	2862 (92.41)	2735 (92.40)
Yes	358 (7.19)	319 (7.11)	304 (7.13)	289 (7.07)	289 (7.37)	264 (7.39)	235 (7.59)	225 (7.60)
Pre-pregnancy Obesity of Mother								
Underweight	469 (9.42)	429 (9.57)	403 (9.45)	385 (9.42)	367 (9.36)	339 (9.49)	283 (9.14)	271 (9.16)
Healthy weight	1786 (35.89)	1675 (37.35)	1617 (37.92)	1567 (38.33)	1516 (38.65)	1395 (39.03)	1249 (40.33)	1191 (40.24)
Overweight	1007 (20.23)	944 (21.05)	917 (21.51)	877 (21.45)	837 (21.34)	782 (21.88)	682 (22.02)	648 (21.89)
Obesity	714 (14.35)	674 (15.03)	642 (15.06)	619 (15.14)	602 (15.35)	550 (15.39)	483 (15.6)	459 (15.51)
Not measured	1001 (20.11)	763 (17.01)	685 (16.06)	640 (15.66)	600 (15.3)	508 (14.21)	400 (12.92)	391 (13.21)
Gestational age at birth								
On time (37–41 weeks)	4407 (88.55)	3977 (88.67)	3786 (88.80)	3620 (88.54)	3492 (89.03)	3197 (89.46)	2782 (89.82)	2641 (89.22)
Early (36 weeks or less)	338 (6.80)	302 (6.73)	290 (6.80)	279 (6.83)	250 (6.37)	220 (6.15)	190 (6.13)	179 (6.04)
Late (42 weeks or more)	232 (4.65)	206 (4.60)	188 (4.40)	189 (4.63)	180 (4.60)	157 (4.39)	125 (4.04)	140 (4.74)
Mother ever smoked during pregnancy								
No	4224 (84.88)	3797 (84.67)	3616 (84.81)	3451 (84.43)	3368 (85.87)	3063 (85.72)	2655 (85.72)	2549 (86.11)
Yes	753 (15.12)	688 (15.33)	648 (15.19)	637 (15.57)	554 (14.13)	511 (14.28)	442 (14.28)	411 (13.89)
Mother's smoking during 1st trimester								
None	4347 (87.35)	3906 (87.08)	3724 (87.33)	3560 (87.09)	3463 (88.3)	3149 (88.11)	2721 (87.84)	2609 (88.13)
< =10 cigarettes daily	410 (8.23)	372 (8.29)	346 (8.11)	338 (8.26)	301 (7.68)	287 (8.03)	250 (8.09)	233 (7.86)
11+ cigarettes daily	220 (4.42)	207 (4.62)	194 (4.56)	190 (4.65)	157 (4.01)	138 (3.86)	126 (4.07)	119 (4.01)
Antidepressant medication during pregnancy								
No	4870 (97.86)	4385 (97.78)	4170 (97.79)	3989 (97.59)	3840 (97.92)	3501 (97.97)	3033 (97.93)	2919 (98.63)
Yes	107 (2.14)	100 (2.22)	94 (2.21)	99 (2.41)	82 (2.08)	73 (2.03)	64 (2.07)	41 (1.37)
Antibiotic medication during pregnancy								
No	4452 (89.46)	4009 (89.38)	3816 (89.5)	3658 (89.49)	3502 (89.28)	3202 (89.59)	2773 (89.53)	2642 (89.27)
Yes	525 (10.54)	476 (10.62)	448 (10.5)	430 (10.51)	420 (10.72)	372 (10.41)	324 (10.47)	318 (10.73)
CONTROL VARIABLES								
Child Health Issues								
Birth weight								
Normal (2500–3999)	4071 (81.79)	3677 (81.99)	3490 (81.84)	3343 (81.78)	3198 (81.53)	2896 (81.02)	2510 (81.04)	2400 (81.08)
Low (< 2500)	279 (5.61)	237 (5.29)	245 (5.75)	237 (5.79)	202 (5.15)	192 (5.38)	168 (5.42)	156 (5.27)
High (> = 4000)	627 (12.59)	571 (12.73)	529 (12.41)	508 (12.43)	522 (13.32)	486 (13.61)	419 (13.54)	404 (13.65)
Immunisation status of children								
Up to date	4516 (90.74)	4091 (91.21)	3885 (91.1)	3694 (90.36)	3557 (90.7)	3258 (91.16)	2841 (91.72)	2700 (91.21)
Not up to date	461 (9.26)	394 (8.79)	379 (8.9)	394 (9.64)	365 (9.3)	316 (8.84)	256 (8.28)	260 (8.79)
Breastfed children up to 6 months								
Yes	2328 (46.78)	2092 (46.65)	2008 (47.1)	1934 (47.31)	1891 (48.22)	1745 (48.83)	1551 (50.07)	1491 (50.39)
No	2649 (53.22)	2393 (53.35)	2256 (52.9)	2154 (52.69)	2031 (51.78)	1829 (51.17)	1546 (49.93)	1469 (49.61)
Mother's sleep quality in the year of childbirth								
Very good/Fairly good	3478 (69.89)	3127 (69.72)	2966 (69.56)	2844 (69.57)	2736 (69.77)	2484 (69.5)	2149 (69.39)	2047 (69.16)
Fairly bad	1118 (22.46)	1000 (22.3)	961 (22.53)	921 (22.53)	899 (22.91)	817 (22.85)	715 (23.08)	685 (23.13)
Very bad	381 (7.66)	358 (7.98)	337 (7.91)	323 (7.9)	287 (7.32)	273 (7.65)	233 (7.53)	228 (7.71)

Table 2 The risk of experiencing wheezing among children based on the incidence of maternal asthma, other morbidities, and maternal health behaviours during pregnancy

Maternal health, risk factors, and medications during pregnancy	Age 0–1 OR (95% CI) *N* = 4977	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Had asthma								
No (ref.)								
Yes	1.49 (1.13–1.97)*	1.83 (1.4–2.4)**	1.47 (1.08–1.99)†	1.8 (1.3–2.49)**	1.91 (1.34–2.71)**	2.47 (1.69–3.61)**	1.69 (1.02–2.78)†	1.27 (0.72–2.24)
Gestational age at birth								
On time (37–41 weeks, ref.)								
Early (36 weeks or less)	1.37 (0.98–1.92)	1.54 (1.09–2.18)†	1.35 (0.91–2.01)	1.48 (0.97–2.26)	1.09 (0.66–1.78)	0.78 (0.38–1.57)	0.5 (0.21–1.19)	1.08 (0.49–2.39)
Late (42 weeks or more)	0.63 (0.41–0.98)†	1.00 (0.69–1.45)	1.53 (1.02–2.30)†	1.04 (0.67–1.63)	1.03 (0.63–1.70)	1.19 (0.67–2.1)	1.25 (0.66–2.38)	1.03 (0.50–2.1)
Pre-pregnancy obesity								
Healthy weight (ref.)								
Underweight	0.68 (0.48–0.96)†	0.89 (0.66–1.18)	0.87 (0.62–1.22)	0.77 (0.54–1.09)	0.85 (0.56–1.29)	0.91 (0.56–1.49)	1.21 (0.7–2.09)	0.60 (0.29–1.24)
Overweight	1.19 (0.94–1.51)	1.42 (1.15–1.74)**	1.12 (0.89–1.42)	1.02 (0.79–1.31)	1.22 (0.92–1.64)	1.1 (0.77–1.56)	1.47 (0.97–2.25)	1.28 (0.82–2.00)
Obesity	1.19 (0.91–1.56)	1.39 (1.1–1.75)*	1.31 (1.01–1.70)†	1.22 (0.93–1.61)	1.27 (0.92–1.75)	1.57 (1.1–2.23)†	1.41 (0.89–2.24)	1.27 (0.79–2.06)
Not known	1.50 (1.20–1.89)**	1.54 (1.23–1.93)**	1.36 (1.05–1.76)†	1.39 (1.06–1.82)†	1.21 (0.89–1.65)	1.39 (0.96–2)	1.82 (1.18–2.83)*	1.87 (1.17–2.99)*
Smoking during 1st trimester								
None (ref.)								
< =10 cigarettes daily	1.57 (1.17–2.1)*	1.52 (1.15–2.00)*	1.36 (0.99–1.86)	1.61 (1.16–2.25)*	1.36 (0.91–2.03)	1.03 (0.63–1.68)	1.3 (0.74–2.29)	1.18 (0.62–2.24)
11+ cigarettes daily	1.38 (0.95–2.00)	1.75 (1.21–2.52)*	1.8 (1.20–2.71)*	1.97 (1.28–3.01)*	1.54 (0.94–2.53)	1.56 (0.89–2.76)	1.11 (0.53–2.32)	2.61 (1.26–5.4)*
Antibiotic medication								
No (ref.)								
Yes	1.27 (0.99–1.62)	1.39 (1.1–1.77)*	1.48 (1.13–1.94)*	1.16 (0.87–1.55)	1.06 (0.76–1.47)	1.29 (0.88–1.88)	1.01 (0.61–1.67)	0.96 (0.54–1.71)
Anti-depressant medication								
No (ref.)								
Yes	1.29 (0.76–2.17)	1.92 (1.18–3.11)*	1.07 (0.60–1.93)	1.18 (0.65–2.11)	0.69 (0.31–1.53)	1.56 (0.76–3.2)	1.58 (0.62–4.01)	0.91 (0.27–3.03)

Notes: † $p < 0.05$ & > 0.01, * $p < 0.01$ & > 0.001, ** $p < 0.001$, the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section

Table 3 The risk of having ever been diagnosed with asthma among children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy (cumulative effect over age)

Maternal health, Risk factors, and medications during pregnancy	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Had Asthma							
No (ref.)							
Yes	2.22 (1.65–3.00)**	2.34 (1.77–3.10)**	2.58 (1.94–3.44)**	2.42 (1.83–3.2)**	2.64 (1.96–3.56)**	2.9 (2.09–4.02)**	2.5 (1.78–3.52)**
Gestational age at birth							
On time (37–41 weeks, ref.)							
Early (36 weeks or less)	1.39 (0.88–2.18)	1.3 (0.88–1.91)	1.05 (0.71–1.55)	1.29 (0.88–1.89)	1.08 (0.71–1.64)	0.82 (0.50–1.35)	0.87 (0.54–1.41)
Late (42 weeks or more)	0.79 (0.49–1.28)	1 (0.66–1.52)	0.88 (0.59–1.32)	0.83 (0.56–1.24)	0.84 (0.55–1.28)	1.05 (0.66–1.67)	0.97 (0.62–1.52)
Pre-pregnancy obesity							
Healthy weight (ref.)							
Underweight	0.98 (0.68–1.4)	0.85 (0.61–1.17)	0.85 (0.63–1.16)	0.86 (0.64–1.16)	0.82 (0.60–1.12)	0.87 (0.62–1.21)	0.91 (0.65–1.28)
Overweight	1.37 (1.06–1.78)†	1.29 (1.03–1.62)†	1.27 (1.03–1.58)†	1.29 (1.04–1.59)†	1.27 (1.02–1.59)†	1.22 (0.96–1.56)	1.24 (0.97–1.58)
Obesity	1.54 (1.16–2.05)*	1.48 (1.15–1.89)*	1.39 (1.09–1.78)*	1.42 (1.12–1.80)*	1.41 (1.09–1.81)*	1.21 (0.92–1.59)	1.27 (0.97–1.67)
Not known	1.42 (1.08–1.88)†	1.33 (1.04–1.7)†	1.34 (1.05–1.71)†	1.36 (1.07–1.72)†	1.62 (1.26–2.09)**	1.65 (1.25–2.19)**	1.69 (1.26–2.25)**
Smoking during 1st trimester							
None (ref.)							
< =10 cigarettes daily	1.10 (0.78–1.54)	0.95 (0.69–1.30)	1.05 (0.77–1.43)	0.98 (0.72–1.35)	1.08 (0.77–1.51)	1.03 (0.71–1.5)	0.88 (0.59–1.32)
11+ cigarettes daily	1.67 (1.1–2.54)†	1.84 (1.24–2.72)*	1.66 (1.12–2.47)†	1.54 (1.01–2.34)†	1.6 (1.02–2.52)†	1.58 (0.97–2.57)	1.88 (1.14–3.09)†
Antibiotic medication							
No (ref.)							
Yes	1.20 (0.89–1.60)	1.09 (0.84–1.41)	1.19 (0.91–1.55)	1.15 (0.89–1.49)	1.18 (0.90–1.54)	1.01 (0.75–1.36)	1.02 (0.75–1.38)
Anti-depressant medication							
No (ref.)							
Yes	0.95 (0.49–1.85)	1.30 (0.74–2.29)	1.83 (1.07–3.12)†	1.27 (0.71–2.26)	1.49 (0.82–2.71)	1.3 (0.65–2.60)	0.50 (0.21–1.20)

Notes: † $p < 0.05$ & > 0.01, * $p < 0.01$ & > 0.001, ** $p < 0.001$; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section. Abbreviation: *OR* Odds Ratio; ref., reference category

Table 4 The risk of having ongoing asthma among children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Had asthma							
No (ref.)							
Yes	2.53 (1.85–3.46)**	3.29 (2.47–4.40)**	3.32 (2.45–4.50)**	2.75 (2.03–3.73)**	3.74 (2.72–5.15)**	3.18 (2.22–4.56)**	2.63 (1.79–3.87)**
Gestational age at birth							
On time (37–41 weeks, ref.)							
Early (36 weeks or less)	1.26 (0.74–2.14)	1.23 (0.77–1.95)	1.00 (0.63–1.58)	0.81 (0.48–1.37)	0.63 (0.34–1.17)	0.65 (0.32–1.34)	0.72 (0.34–1.53)
Late (42 weeks or more)	0.83 (0.49–1.42)	1.03 (0.63–1.69)	1.21 (0.75–1.96)	0.99 (0.60–1.63)	1.30 (0.77–2.21)	1.11 (0.63–1.95)	1.30 (0.73–2.30)
Pre-pregnancy obesity							
Healthy weight							
Underweight	0.81 (0.53–1.23)	0.73 (0.48–1.1)	0.91 (0.62–1.32)	0.99 (0.69–1.44)	0.94 (0.62–1.42)	1.02 (0.66–1.58)	0.98 (0.61–1.55)
Overweight	1.37 (1.03–1.82)†	1.20 (0.92–1.56)	1.25 (0.96–1.63)	1.34 (1.03–1.74)†	1.3 (0.98–1.73)	1.37 (1.00–1.89)	1.18 (0.84–1.68)
Obesity	1.50 (1.10–2.06)†	1.39 (1.04–1.86)†	1.55 (1.15–2.09)*	1.40 (1.04–1.87)†	1.29 (0.94–1.78)	1.31 (0.92–1.86)	1.37 (0.96–1.96)
Not known	1.40 (1.04–1.89)†	1.23 (0.93–1.64)	1.46 (1.09–1.96)†	1.57 (1.18–2.09)*	1.78 (1.30–2.44)**	1.47 (1.03–2.11)†	1.41 (0.97–2.04)
Smoking during 1st trimester							
None (ref.)							
< =10 cigarettes daily	0.98 (0.66–1.44)	0.94 (0.64–1.38)	1.01 (0.68–1.52)	1.14 (0.77–1.7)	1.22 (0.77–1.91)	1.23 (0.76–1.99)	0.77 (0.44–1.36)
11+ cigarettes daily	1.53 (0.96–2.43)	1.91 (1.23–2.96)*	1.71 (1.08–2.71)†	1.40 (0.83–2.36)	1.78 (1.06–2.99)†	1.49 (0.84–2.65)	1.70 (0.89–3.25)
Antibiotic medication							
No (ref.)							
Yes	1.22 (0.89–1.68)	1.14 (0.85–1.54)	1.27 (0.95–1.72)	1.19 (0.88–1.61)	1.19 (0.86–1.64)	0.89 (0.61–1.31)	0.93 (0.62–1.39)
Anti-depressant medication							
No (ref.)							
Yes	0.95 (0.47–1.95)	1.33 (0.7–2.53)	1.53 (0.84–2.8)	0.86 (0.41–1.83)	1.48 (0.70–3.12)	1.43 (0.61–3.38)	0.90 (0.32–2.55)

Notes: † $p < 0.05$ & > 0.01, * $p < 0.01$ & > 0.001, ** $p < 0.001$, the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section. Abbreviation: *OR* Odds Ratio, ref., reference category

Table 5 The risk of experiencing eczema among children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	Age 0–1 OR (95% CI) *N* = 4977	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Had asthma								
No (ref.)								
Yes	1.43 (1.06–1.94)†	1.2 (0.88–1.63)	1.45 (1.04–2.04)†	1.97 (1.40–2.77)**	1.38 (0.95–1.99)	1.56 (1.04–2.35)†	1.71 (1.09–2.67)†	1.48 (0.92–2.36)
Gestational age at birth								
On time (37–41 weeks, ref.)								
Early (36 weeks or less)	0.68 (0.44–1.05)	0.88 (0.57–1.34)	0.90 (0.56–1.46)	1.18 (0.71–1.95)	0.85 (0.45–1.62)	0.66 (0.31–1.44)	0.53 (0.22–1.26)	0.67 (0.28–1.62)
Late (42 weeks or more)	0.73 (0.47–1.14)	0.63 (0.4–1.01)	0.49 (0.27–0.89)†	1.03 (0.62–1.69)	0.97 (0.58–1.62)	0.63 (0.35–1.14)	0.53 (0.23–1.18)	1.00 (0.49–2.01)
Pre-pregnancy obesity								
Healthy weight (ref.)								
Underweight	0.98 (0.73–1.33)	0.67 (0.49–0.93)†	0.68 (0.48–0.97)†	0.76 (0.51–1.13)	0.73 (0.47–1.12)	1.14 (0.74–1.76)	0.92 (0.55–1.54)	0.82 (0.48–1.38)
Overweight	1.08 (0.86–1.36)	1.00 (0.80–1.25)	1.04 (0.81–1.34)	0.99 (0.75–1.3)	1.16 (0.88–1.53)	1.33 (0.98–1.82)	1.24 (0.86–1.77)	0.91 (0.62–1.33)
Obesity	1.06 (0.81–1.39)	1.14 (0.89–1.46)	1.17 (0.89–1.56)	1.32 (0.98–1.78)	1.27 (0.94–1.72)	1.24 (0.87–1.76)	1.23 (0.82–1.85)	1.77 (1.20–2.61)*
Not known	1.07 (0.84–1.36)	0.94 (0.73–1.2)	1.2 (0.91–1.59)	1.06 (0.77–1.46)	1.00 (0.72–1.4)	1.12 (0.77–1.65)	1.45 (0.95–2.20)	1.02 (0.65–1.61)
Smoking during 1st trimester								
None (ref.)								
Occasional/< 10 daily	0.95 (0.67–1.35)	1.18 (0.85–1.62)	1.16 (0.80–1.67)	0.83 (0.53–1.30)	0.84 (0.54–1.32)	0.81 (0.48–1.37)	0.63 (0.33–1.2)	0.56 (0.27–1.16)
11+ daily	0.71 (0.42–1.19)	0.92 (0.58–1.49)	0.76 (0.43–1.34)	1.42 (0.82–2.44)	0.84 (0.44–1.58)	0.70 (0.32–1.55)	1.09 (0.44–2.71)	1.12 (0.52–2.42)
Antibiotic medication								
No (ref.)								
Yes	0.95 (0.73–1.26)	1.03 (0.79–1.35)	1.03 (0.77–1.39)	1.30 (0.95–1.77)	1.29 (0.94–1.78)	1.19 (0.83–1.71)	1.14 (0.72–1.81)	1.35 (0.87–2.09)
Anti-depressant medication								
No (ref.)								
Yes	0.85 (0.47–1.54)	1.71 (0.97–2.99)	1.34 (0.72–2.48)	1.11 (0.56–2.21)	1.00 (0.49–2.05)	1.03 (0.47–2.28)	1.04 (0.37–2.91)	0.48 (0.13–1.75)

Notes: † $p < 0.05$ & > 0.01, * $p < 0.01$ & > 0.001, ** $p < 0.001$, the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section. Abbreviation: *OR* Odds Ratio; ref., reference category

Table 6 Compilation of the odds of experiencing wheezing, having ever been diagnosed with asthma, having ongoing asthma, or having eczema among the children whose mothers experienced asthma during pregnancy, compared to the offspring of non-asthmatic mothers, for all children, male only and female only regression models of different ages

Respiratory or allergic morbidities	Age 0–1 OR (95% CI) *N* = 4977	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Wheezing								
All children								
Wheezing = Yes	1.49 (1.13–1.97)*	1.83 (1.4–2.4)**	1.47 (1.08–1.99)†	1.8 (1.3–2.49)**	1.91 (1.34–2.71)**	2.47 (1.69–3.61)**	1.69 (1.02–2.78)†	1.27 (0.72–2.24)
Wheezing = No (ref.)								
Male only								
Wheezing = Yes	*1.5(1.03–2.18)*†	1.93(1.34–2.76)**	1.77(1.20–2.63)*	2.07(1.35–3.18)**	1.97(1.22–3.17)*	3.28(2.01–5.34)**	1.56(0.78–3.11)	1.13(0.49–2.61)
Wheezing = No (ref.)								
Female only								
Wheezing = Yes	*1.46(0.94–2.24)*	1.73(1.14–2.65)*	1.15(0.70–1.91)	1.59(0.96–2.66)	1.8(1.03–3.15)†	1.72(0.92–3.21)	1.67 (0.81–3.46)	1.47 (0.69–3.15)
Wheezing = No (ref.)								
Ever diagnosed asthma								
All children								
Ever had asthma = Yes		2.22 (1.65–3)**	2.34 (1.77–3.10)**	2.58 (1.94–3.44)**	2.42 (1.83–3.20)**	2.64 (1.96–3.56)**	2.9 (2.09–4.02)**	2.5 (1.78–3.52)**
Ever had asthma = No (ref.)								
Male only								
Ever had asthma = Yes		2.76(1.86–4.11)**	2.75(1.86–4.07)**	2.69(1.81–3.98)**	2.87(1.93–4.28)**	3.04(1.98–4.67)**	2.66(1.69–4.18)**	2.35(1.46–3.79)**
Ever had asthma = No (ref.)								
Female only								
Ever had asthma = Yes		1.77(1.10–2.86)†	2.01(1.30–3.10)*	2.44(1.57–3.81)**	1.98(1.30–3.01)**	2.29(1.46–3.59)**	3.42(2.06–5.69)**	2.83(1.73–4.62)**
Ever had asthma = No (ref.)								
Ongoing asthma								
All children								
Ongoing asthma = Yes		2.53 (1.85–3.46)**	3.29 (2.47–4.40)**	3.32 (2.45–4.50)**	2.75 (2.03–3.73)**	3.74 (2.72–5.15)**	3.18 (2.22–4.56)**	2.63 (1.79–3.87)**
Ongoing asthma = No (ref.)								
Male only								
Ongoing asthma = Yes		3.17(2.10–4.77)**	4.09(2,76–6.08)**	3.30(2.17–5.00)**	2.74(1.79–4.20)**	3.66(2.36–5.68)**	3.17(1.93–5.21)	2.00(1.14–3.48)*
Ongoing asthma = No (ref.)								
Female only								
Ongoing asthma = Yes		2.08(1.27–3.41)*	2.68(1.69–4.24)**	3.40(2.14–5.39)**	2.83(1.81–4.43)**	4.09(2.55–6.56)**	3.38(1.94–5.86)**	3.30(1.88–5.82)**

Table 6 Compilation of the odds of experiencing wheezing, having ever been diagnosed with asthma, having ongoing asthma, or having eczema among the children whose mothers experienced asthma during pregnancy, compared to the offspring of non-asthmatic mothers, for all children, male only and female only regression models of different ages *(Continued)*

Respiratory or allergic morbidities	Age 0–1 OR (95% CI) *N* = 4977	Age 2–3 OR (95% CI) *N* = 4485	Age 4–5 OR (95% CI) *N* = 4264	Age 6–7 OR (95% CI) *N* = 4088	Age 8–9 OR (95% CI) *N* = 3922	Age 10–11 OR (95% CI) *N* = 3574	Age 12–13 OR (95% CI) *N* = 3097	Age 14–15 OR (95% CI) *N* = 2960
Ongoing asthma = No (ref.)								
Eczema								
All children								
Eczema = Yes	1.43 (1.06–1.94)†	1.2 (0.88–1.63)	1.45 (1.04–2.04)†	1.97 (1.4–2.77)**	1.38 (0.95–1.99)	1.56 (1.04–2.35)†	1.71 (1.09–2.67)†	1.09 (2.67–0.018)
Eczema = No (ref.)								
Male only								
Eczema = Yes	1.46(0.96–2.21)†	1.13(0.73–1.75)	1.33(0.83–2.12)	2.08(1.29–3.36)*	1.76(1.05–2.96)†	2.18(1.24–3.84)*	1.16(0.58–2.34)	0.93(0.41–2.09)
Eczema = No (ref.)								
Female only								
Eczema = Yes	1.39(0.90–2.15)	1.28(0.82–2.01)	1.62(0.99–2.66)	1.88(1.15–3.07)	1.11(0.67–1.85)	1.03(0.58–1.83)	2.15(1.21–3.83)	1.95(1.08–3.51)
Eczema = No (ref.)								

Notes: † $p < 0.05$ & > 0.01, * $p < 0.01$ & > 0.001, ** $p < 0.001$, the regression models were adjusted for covariates outlined in 'Control variables' sub-section of 'Methods' section. Abbreviation: *OR* Odds Ratio; ref., reference category

or eczema) if their mother had asthma during pregnancy.

Discussion

This study comprehensively investigated the prevalence of respiratory and allergic morbidities (wheezing, asthma, and eczema) among children (birth to adolescence) and their association with maternal health factors and exposures during pregnancy (asthma, smoking, medication use, and pre-pregnancy obesity) using the LSAC data. The longitudinal prevalence of asthma in children aged 0–15 years of age measured in the eight biennial LSAC surveys (2004–2018) was 2–4 percentage points higher than the prevalence (11%) measured by the national health survey of Australian children aged 5–14 in 2018 [2].

Consistent with earlier studies [12, 14, 23, 27, 40, 42], this study also found that maternal asthma during pregnancy, smoking during pregnancy, and pre-pregnancy obesity were significantly associated with increased risks of wheezing and asthma among Australian children. Childhood eczema was associated only with maternal asthma during pregnancy and not with pre-pregnancy obesity, smoking during pregnancy, or antibiotic/antidepressant medication use during pregnancy. These findings are consistent with a Swedish study that concluded that maternal BMI was associated with an increased risk of asthma, but not with eczema or sensitisation in offspring [13].

This study found that children's risk of having ever been diagnosed with asthma was positively associated with maternal asthma during pregnancy. This association was consistent and increased up to the age of 12–13 years. Among the children whose mothers had been experiencing asthma during pregnancy, the odds of having been diagnosed with asthma and the odds of having ongoing asthma were higher than the odds of having wheezing or eczema and consistently increased until the age of 10–11 years. A Danish study from a cohort of 675,379 singleton births (1996–2006) showed that children of mothers who had severe asthma during pregnancy had a higher prevalence of asthma (OR: 1.37; 95% CI: 1.17–1.61) compared with children of mothers with mild or no asthma during pregnancy [40]. Thus, this study reiterates previous findings of an association of maternal asthma during pregnancy with the risk of the offspring having asthma, but it also contributes further insight into the trend of asthma morbidity risks across age groups (birth to 15 years of age) among Australian children.

Children of mothers who were overweight or obese just before their pregnancy were highly likely to have at some point, been diagnosed with asthma. However, this likelihood diminished when they reached age 12 years. These findings corroborate earlier studies, one of which showed that United States children of obese mothers were 1.63 times more likely to have asthma than those of mothers with a healthy weight [23]. Though studies have revealed that gestational age and birth weight influence the risk of having asthma in early childhood [26], our study did not show any association with these confounding variables. These findings may imply a relationship between childhood obesity and asthma exposure among children but further research is needed [26, 43].

The adverse effects of smoking during pregnancy on childhood asthma are already evident in the existing literature [44]. Children may suffer from asthma morbidities due to exposure to environmental tobacco smoke or parental prenatal/postnatal smoking [42]. Although the rate of maternal cigarette smoking during pregnancy has decreased in the last decade in Australia [4], the evidence of the influence of smoking during pregnancy on childhood asthma persists [45]. However, few studies have investigated the number of cigarettes smoked during pregnancy and its effects on respiratory and allergic morbidities in their children [27]. This study investigated the influence of maternal smoking during pregnancy according to the category of number of cigarettes smoked. The prevalence of wheezing was higher among the children of mothers who smoked 11 or more cigarettes daily and was lower among the children of mothers who smoked fewer than ten cigarettes daily than the children of mothers who did not smoke during their pregnancy. The risk of asthma was only higher among the children of mothers who had 11 or more cigarettes daily during the first trimester of the pregnancy. Similarly, a Finish study (children born in 1987) found that mothers' smoking, < 10 cigarettes per day or 11+ cigarettes per day during pregnancy, increased the probability of their offspring's asthma [27].

Research on the association between maternal antibiotic or antidepressant use during pregnancy and respiratory and allergic morbidities in offspring is rare. Two studies found that maternal use of antibiotics in the third trimester of pregnancy, slightly increased the risk of their preschool-aged children having asthma [15, 33]. A Danish study of a birth cohort by Stockhome et al. [28] also found a causal effect but did not identify any trimester-specific effects of antibiotic use. In our study, except for wheezing among children of 2–5 years of age, no significant associations were observed between maternal medication use (antibiotics or antidepressants) during pregnancy and increased the risk of their offspring's respiratory or allergic morbidities. Further, our findings corroborate with previous research on the use of modern antidepressants during pregnancy [16] which concluded that antidepressant use during pregnancy generally does not increase asthma risk. However, a

study by Liu et al. of the Danish children, revealed that the use of an earlier variant of antidepressants during pregnancy [16] was associated with an increased risk of asthma among their offspring.

Our results indicate that maternal asthma during pregnancy increases the risk of children experiencing eczema, although in our sample, the prevalence of eczema was intermittent across the years until their adolescence. Significant risk of exposure was evident when the children were infants, aged 4–7 years, and again during adolescence at 10–13 years of age. However, these associations were not as strong as the children's risk of encountering wheezing or asthma. A key finding of this study is that among the maternal health conditions during pregnancy, except for maternal asthma, none were associated with the risk of their children having eczema.

The age at onset of wheezing, asthma or eczema shows a pattern in our study with increasing prevalence in early childhood and decreasing prevalence during adolescents. Along with the maternal health risk factors revealed by our study, several other environmental risk factors showing association with these diseases revealed by other studies might be useful to explain the prevalence pattern [46, 47]. For example, a study demonstrates that early life sensitization to indoor allergens or mould is a predictor of asthma development [46]. Further, another study shows evidence that the indoor school environment is a significant reservoir of allergens, moulds, pollutants, and endotoxin and that there is an association between school exposure and pediatric asthma morbidity [47]. Previous studies also show that early childhood asthma is more common in children who are exposed to soot, exhaust, household tobacco smoking by household members, or oil smoke [48, 49]. Other studies have concluded that nylon clothing, unfamiliar pets, dust, and sweat are responsible for childhood eczema [50, 51]. All of these studies revealing the risk factors of influencing asthma or eczema are among the children in their early childhood, which are in line with the results of our study. Further, genetic influence on the age at onset of asthma may also explain the prevalence pattern or the association of risk factors of asthma. A study on Danish twins by Thomsen et al. in 2010 reveals that the risk of asthma in the co-twin decreases with increasing age at onset of asthma in the index twin [52]. Another biometric analysis study by Skadhauge et al. emphasized a major influence of genetic factors in the aetiology of asthma. However, a substantial part of the variation in liability to asthma is due to the impact of environmental factors specific to the individual. The study found no evidence for a substantial impact of genetic dominance or the shared environment [53].

Our study findings support gender dimorphism for both prevalence and risk factor associations of the respiratory and allergic diseases. As evidence of the gender differences, this study found that for both asthma and eczema boys had increased prevalence compared to girls in their early childhood, while it was reversed during their adolescence. Further, regarding the odds of having these diseases our study found that children whose mothers had asthma during pregnancy, boys had higher odds of having wheezing or asthma than girls until age 10–11 years. However, in the adolescent age group (12–15 years), the girls had higher odds of being ill with ongoing asthma compared to the boys. These study finding are supported by previous two studies conducted on asthma and puberty [54]. Findings of other studies also support a gender dimorphism in the obesity–asthma phenotype; they have found that the odds of asthma impairment related to obesity is highest among women aged 12 to 44 years of age [55, 56]. The gender differences may have been potentially linked to fluctuations of hormones during puberty and menstruation [54], physical activity levels, and eating habits [35]. These variations may also occur due to the differences in gender-specific responses to immunological, environmental, or occupational exposures [57–60].

A main strength of our study is its use of a large, nationally representative, ethnically inclusive, population-based birth cohort generalisable to all Australian children born in 2004. A range of maternal health indicators, including maternal asthma, pre-pregnancy obesity, gestational age, antibiotic use, and antidepressant use, were considered key explanatory variables. Adjustments were made for important confounders such as the children's birth weight, breastfeeding status, housing environment and other socioeconomic covariates.

There are some limitations. First, the pre-pregnancy BMI was calculated using self-reported data on height and weight. Second, we did not have information about the severity of maternal asthma, genetic factors, or environmental exposures such as maternal mental health during pregnancy, infections during pregnancy, and maternal or child exposure to air pollutants. Thus, though we accounted for as many potential confounders as possible, our analyses were limited by the measurements available in the LSAC data. Future research could include other such factors that may exacerbate or mitigate the effects of maternal asthma, smoking, and other health status during pregnancy on their children's respiratory or allergic outcomes.

Conclusion

This longitudinal study revealed the prevalence trends of childhood wheezing, asthma, and eczema at 0–15 year of age and found increasing trend in early childhood and decreasing trend from 6 to 7 years to until their age of 14–15 years. Wheezing decreased to a greater extent

than asthma and eczema. There were gender differences in the prevalence of these respiratory and allergic morbidities over time. This study also found that maternal asthma, obesity, and smoking during pregnancy were significantly associated with an increased risk of offspring's wheezing or asthma. Only maternal asthma during pregnancy was significantly associated with the risk of eczema of their offspring. There were age and sex specific differences in the associations of maternal health or health risk factors with disease outcomes: a shift in the extent of the associations started at 6–7 years of age; where, at this age point, higher odds of both asthma and eczema were observed in female children. These findings have important public health implications for Australia. Our findings suggest that careful medical and obstetric monitoring, improved specific age-sex wise risk factor prevention where wheezing, asthma and eczema effect children and health promotion for pregnant women and children by the policy makers are highly warranted and may help protect child health.

Abbreviations

CI: Confidence Interval; GINA: Global Initiative for Asthma; LSAC: Longitudinal Study of Australian Children; OR: Odds Ratio; WHO: World Health Organization

Additional fles

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Authors' contributions

KA is the principal investigator, designed the study, conducted the data analysis, and drafter the manuscript. GO critically reviewed the manuscript and assisted with the final editing and writing of the manuscript. RK and EK contributed to the study design and development, supervised the project, and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used for the study were collected from the Longitudinal Study of Australian Children Dataverse of National Centre for Longitudinal Data. Those interested in accessing this data should contact the Longitudinal Study of Australian Children Dataverseof National Centre for Longitudinal Data, Australia. There are some restrictions on the use of this data and the data application's approval is subject to a signed confidentiality deed.

Declarations

Ethics approval and consent to participate

The LSAC study was approved by the Australian Institute of Family Studies Ethics Committee. The de-identified unit record dataset was released to the current researchers at the University of Southern Queensland for the purposes of this doctoral research. To obtain this data, the authors completed and signed the Confidentiality Deed Poll and sent it to NCLD (ncldresearch@dss.gov.au) and ADA (ada@anu.edu.au). Therefore, datasets analysed and/or generated during the current study are subject to the signed confidentiality deed.

Consent for publication

Not applicable.

Competing interests

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

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References

1. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A, et al. The international study of asthma and allergies in childhood (ISAAC) phase three: a global synthesis. Allergol Immunopathol. 2013;41(2):73–85. https://doi.org/10.1016/j.aller.2012.03.001.
2. Australian Institute of Health and Welfare. Australia's health. Canbera: AIHW; 2018.
3. Australian Centre for Asthma Monitoring. Asthma in Australian children: findings from Growing Up in Australia, the Longitudinal Study of Australian Children. Canberra: AIHW; 2009.
4. Gray LEK, Ponsonby AL, Lin TX, O'Hely M, Collier F, Ranganathan S, et al. High incidence of respiratory disease in Australian infants despite low rate of maternal cigarette smoking. J Paediatr Child Health. 2019;55(12):1437–44. https://doi.org/10.1111/jpc.14436.
5. Asher I, Pearce N. Global burden of asthma among children. Int J Tuberc Lung Dis. 2014;18(11):1269–78. https://doi.org/10.5588/ijtld.14.0170.
6. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374(19):1842–52. https://doi.org/10.1056/NEJMoa1513737.
7. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet. 2007;370(9589):758–64. https://doi.org/10.1016/S0140-6736(07)61379-8.
8. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol. 2007;119(5):1105–10. https://doi.org/10.1016/j.jaci.2006.12.669.
9. Watson PE, McDonald BW. Water and nutrient intake in pregnant New Zealand women: association with wheeze in their infants at 18 months. Asia Pac J Clin Nutr. 2014;23(4):660–70. https://doi.org/10.6133/apjcn.2014.23.4.13.
10. Lebold KM, Jacoby DB, Drake MG. Inflammatory mechanisms linking maternal and childhood asthma. J Leukoc Biol. 2020;108(1):113–21. https://doi.org/10.1002/JLB.3MR1219-338R.
11. Andersen ZJ, Bonnelykke K, Hvidberg M, Jensen SS, Ketzel M, Loft S, et al. Long-term exposure to air pollution and asthma hospitalisations in older adults: a cohort study. Thorax. 2012;67(1):6–11. https://doi.org/10.1136/thoraxjnl-2011-200711.
12. Harvey SM, Murphy VE, Gibson PG, Collison A, Robinson P, Sly PD, et al. Maternal asthma, breastfeeding, and respiratory outcomes in the first year of life. Pediatr Pulmonol. 2020;55(7):1690–6. https://doi.org/10.1002/ppul.24756.
13. Ekstrom S, Magnusson J, Kull I, Lind T, Almqvist C, Melen E, et al. Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. Clin Exp Allergy. 2015;45(1):283–91. https://doi.org/10.1111/cea.12340.

14. Chen Y, Lyu J, Xia Y, Zhu J, Tong S, Ying Y, et al. Effect of maternal sleep, physical activity and screen time during pregnancy on the risk of childhood respiratory allergies: a sex-specific study. Respir Res. 2020;21(1):230. https://doi.org/10.1186/s12931-020-01497-8.
15. Mulder B, Pouwels KB, Schuiling-Veninga CC, Bos HJ, de Vries TW, Jick SS, et al. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. Clin Exp Allergy. 2016;46(9):1214–26. https://doi.org/10.1111/cea.12756.
16. Liu X, Olsen J, Pedersen LH, Agerbo E, Yuan W, Li J. Antidepressant use during pregnancy and asthma in the offspring. Pediatrics. 2015;135(4):e911–7. https://doi.org/10.1542/peds.2014-4073.
17. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008;32(4):1096–110. https://doi.org/10.1183/09031936.00002108.
18. Martinez FD, Wright AL, Taussing LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. New Eng J Med. 1995;332(3):133–8.
19. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol. 2007;42(8):723–8. https://doi.org/10.1002/ppul.20644.
20. Williams HC, Grindlay DJ. What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 1. Definitions, causes and consequences of eczema. Clin Exp Dermatol. 2010;35(1):12–5. https://doi.org/10.1111/j.1365-2230.2009.03733.x.
21. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. CMAJ. 2009;181(9):E181–90. https://doi.org/10.1503/cmaj.080612.
22. Da Silva Sena CR, Morten M, Meredith J, Kepreotes E, Murphy VE, Gibson P, et al. Rhinovirus bronchiolitis, maternal asthma, and the development of asthma and lung function impairments. Pediatr Pulmonol. 2020;56(2):362–70.
23. Polinski KJ, Liu J, Boghossian NS, McLain AC. Maternal obesity, gestational weight gain, and asthma in offspring. Prev Chronic Dis. 2017;14:E109. https://doi.org/10.5888/pcd14.170196.
24. Gaillard R, Felix JF, Duijts L, Jaddoe VW. Childhood consequences of maternal obesity and excessive weight gain during pregnancy. Acta Obstet Gynecol Scand. 2014;93(11):1085–9. https://doi.org/10.1111/aogs.12506.
25. Giallo R, Bahreinian S, Brown S, Cooklin A, Kingston D, Kozyrskyj A. Maternal depressive symptoms across early childhood and asthma in school children: findings from a longitudinal Australian population based study. PLoS ONE. 2015;10(3):e0121459. https://doi.org/10.1371/journal.pone.0121459.
26. Noal RB, Menezes AM, Macedo SE, Dumith SC, Perez-Padilla R, Araujo CL, et al. Is obesity a risk factor for wheezing among adolescents? A prospective study in southern Brazil. J Adolesc Health. 2012;51(6 Suppl):S38–45. https://doi.org/10.1016/j.jadohealth.2012.08.016.
27. Jaakkola J, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Heaith. 2004;94(1):136–40. https://doi.org/10.2105/AJPH.94.1.136.
28. Stokholm J, Sevelsted A, Bønnelykke K, Bisgaard H. Maternal propensity for infections and risk of childhood asthma: a registry-based cohort study. Lancet Respir Med. 2014;2(8):631–7. https://doi.org/10.1016/S2213-2600(14)70152-3.
29. Zetstra-van der Woude PA, De Walle HE, Hoek A, Bos HJ, Boezen HM, Koppelman GH, et al. Maternal high-dose folic acid during pregnancy and asthma medication in the offspring. Pharmacoepidemiol Drug Saf. 2014;23(10):1059–65. https://doi.org/10.1002/pds.3652.
30. Zacharasiewicz A. Maternal smoking in pregnancy and its influence on childhood asthma. ERJ Open Res. 2016;2(3):00042–2016.
31. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, et al. Paracetamol use in early life and asthma: prospective birth cohort study. BMJ. 2010;341(sep15 1):c4616. https://doi.org/10.1136/bmj.c4616.
32. Zhang M, Litonjua AA, Mueller NT. Maternal antibiotic use and child asthma: is the association causal? Eur Respir J. 2018;52(1):1801007.
33. Loewen K, Monchka B, Mahmud SM, Geer 't J, Azad MB. Prenatal antibiotic exposure and childhood asthma: a population-based study. Eur Respir J. 2018;52(1):1702070.
34. Anthracopoulos MB, Pandiora A, Fouzas S, Panagiotopoulou E, Liolios E, Priftis KN. Sex-specific trends in prevalence of childhood asthma over 30 years in Patras. Greece Acta Paediatr. 2011;100(7):1000–5. https://doi.org/10.1111/j.1651-2227.2011.02255.x.
35. Zein JG, Erzurum SC. Asthma is Different in Women. Curr Allergy Asthma Rep. 2015;15(6):28. https://doi.org/10.1007/s11882-015-0528-y.
36. Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, McNeill G, et al. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. Pediatr Pulmonol. 2007;42(1):60–5. https://doi.org/10.1002/ppul.20545.
37. Motika CA, Papachristou C, Abney M, Lester LA, Ober C. Rising prevalence of asthma is sex-specific in a US farming population. J Allergy Clin Immunol. 2011;128(4):774–9. https://doi.org/10.1016/j.jaci.2011.06.046.
38. Zubrick S, Williams A, Silburn S, Vimpani G. Indicators of social and family functioning. Canberra: Department of Family and Community Services. Commonwealth of Australia; 2000.
39. Soloff C, Lawrence D, Johnstone R. Sample design. Melbourne: Australian Institute of Family Studies; 2005.
40. Liu X, Agerbo E, Schlunssen V, Wright RJ, Li J, Munk-Olsen T. Maternal asthma severity and control during pregnancy and risk of offspring asthma. J Allergy Clin Immunol. 2018;141(3):886–92 e3. https://doi.org/10.1016/j.jaci.2017.05.016.
41. Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S, von Mutius E, et al. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: international study of asthma and allergies in childhood phase III. J Allergy Clin Immunol. 2009;124(5):982–9. https://doi.org/10.1016/j.jaci.2009.08.017.
42. Park B, Park B, Kim EJ, Kim YJ, Lee H, Ha EH, et al. Longitudinal association between environmental tobacco smoke exposure and behavioral problems in children from ages 5 to 9. Sci Total Environ. 2020;746:141327. https://doi.org/10.1016/j.scitotenv.2020.141327.
43. Lucas SR, Platts-Mills TA. Paediatric asthma and obesity. Paediatr Respir Rev. 2006;7(4):233–8. https://doi.org/10.1016/j.prrv.2006.08.001.
44. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. Eur Respir J. 2013;41(3):716–26. https://doi.org/10.1183/09031936.00073312.
45. Kurinczuk JJ, Parsons DE, Dawes V, Burton PR. The relationship between asthma and smoking during pregnancy. Women Health. 1999;29(3):31–47. https://doi.org/10.1300/J013v29n03_03.
46. Sheehan WJ, Phipatanakul W. Indoor allergen exposure and asthma outcomes. Curr Opin Pediatr. 2016;28(6):772–7. https://doi.org/10.1097/MOP.0000000000000421.
47. Esty B, Phipatanakul W. School exposure and asthma. Ann Allergy Asthma Immunol. 2018;120(5):482–7. https://doi.org/10.1016/j.anai.2018.01.028.
48. Balmes JR, Cisternas M, Quinlan PJ, Trupin L, Lurmann FW, Katz PP, et al. Annual average ambient particulate matter exposure estimates, measured home particulate matter, and hair nicotine are associated with respiratory outcomes in adults with asthma. Environ Res. 2014;129:1–10. https://doi.org/10.1016/j.envres.2013.12.007.
49. Hafkamp-de Groen E, Sonnenschein-van der Voort AM, Mackenbach JP, Duijts L, Jaddoe VW, Moll HA, et al. Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: the Generation R Study. PLoS ONE. 2013;8(11):e78266.
50. Langan SM, Silcocks P, Williams HC. What causes flares of eczema in children? Br J Dermatol. 2009;161(3):640–6. https://doi.org/10.1111/j.1365-2133.2009.09320.x.
51. Goudarzi H, Konno S, Kimura H, Araki A, Miyashita C, Itoh S, et al. Contrasting associations of maternal smoking and pre-pregnancy BMI with wheeze and eczema in children. Sci Total Environ. 2018;639:1601–9. https://doi.org/10.1016/j.scitotenv.2018.05.152.
52. Thomsen SF, Duffy DL, Kyvik KO, Backer V. Genetic influence on the age at onset of asthma: A twin study. J Allergy Clin Immunol. 2010;126(3):626–30. https://doi.org/10.1016/j.jaci.2010.06.017.
53. Skadhauge LR, Christensen K, Kyvik KO, Sigsgaard T. Genetic and environmental influence on asthma: a populationbased study of 11,688 Danish twin pairs. Eur Respir J. 1999;13(1):8–14. https://doi.org/10.1183/09031936.99.13100899.
54. Shah R, Newcomb DC. Sex Bias in asthma prevalence and pathogenesis. Front Immunol. 2018;9:2997. https://doi.org/10.3389/fimmu.2018.02997.
55. Lang JE, Hossain J, Dixon AE, Shade D, Wise RA, Peters SP, et al. Does age impact the obese asthma phenotype? Longitudinal asthma control, airway function, and airflow perception among mild persistent asthmatics. Chest. 2011;140(6):1524–33. https://doi.org/10.1378/chest.11-0675.
56. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, et al. Relationship between body composition, inflammation and lung function in overweight and obese asthma. Respir Res. 2012;13(1):10.
57. Vink NM, Postma DS, Schouten JP, Rosmalen JG, Boezen HM. Gender differences in asthma development and remission during transition through

puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. J Allergy Clin Immunol. 2010;126(3):498–504 e1–6.
58. Almqvist C, Worm M, Leynaert B. Working group of GALENWPG. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. Allergy. 2008;63(1):47–57. https://doi.org/10.1111/j.1398-9995.2007.01524.x.
59. Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? Asthma. 2007;7(2):143–50.
60. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. Thorax. 1999;54(12):1119–38.

Publisher's Note

4.2 Links and implications

The significance of this paper is that it re-examines the foetal origins hypothesis in the context of contemporary birth cohort of Australian children and revealed that wheezing, asthma and eczema in children are associated with mother's health during pregnancy using longitudinal data from birth to 15 years of age. The most significant risk factors associated with contracting wheezing and asthma in Australian children were maternal asthma, smoking during pregnancy and pre-pregnancy obesity. However, childhood eczema was associated only with maternal asthma. The study results also conclude that these associations were stronger among male children up to age 10–11 and during adolescence (12–15 years of age), female children were more prone to wheezing, asthma, and eczema. The policymakers may, therefore, adopt an age-sex specific medical and obstetric monitoring and improved prevention for children and health promotion for pregnant women, which could reduce the burden of wheezing, asthma and eczema in children.

While this paper utilised logistic regression models to test whether the maternal health risk factor affects the odds of disease, this thesis intended to use survival model in the next study to test whether a risk factor affects the age of onset of the disease. Survival analysis technique enables to capture the time to event feature of the morbidity in children with greater statistical power. Furthermore, the next study will determine the developmental origin factors (with a maternal health focus) associated with the risk of developing long-term medical conditions or disabilities in childhood.

CHAPTER 5: PAPER 3 - ASSOCIATION OF MATERNAL PHYSICAL AND MENTAL HEALTH CHARACTERISTICS WITH THE HAZARD OF HAVING ANY MEDICAL CONDITION OR DISABILITY: A 15-YEAR STUDY OF AUSTRALIAN CHILDREN

5.1 Introduction

This chapter presents the third paper of the thesis examining whether maternal physical and mental health characteristics might be the predictors of subsequent medical conditions or disabilities in children in the first 15 years of life, in the perspective of survival analysis. Thus, this paper is the first study aiming to determine what developmental origin factors, with a maternal health focus, are associated with the risk of developing long-term medical conditions or disabilities in childhood. This is a longitudinal prospective study of 5,107 children from B cohort of LSAC, covering 51,009 person-year survival data with the incidence of having any medical condition or disability, and utilised the parametric survival model for resolving the research question.

Association of maternal physical and mental health characteristics with the hazard of having any medical condition or disability: A 15-year study of Australian children

Abstract

Any long-term medical condition or disability among children is a significant health issue. This study measured the incidence rate of any medical condition or disability among children from a nationally representative birth cohort, then used the random effect parametric survival regression model to assess whether the hazard of any medical condition or disability in children is associated with maternal physical and mental health characteristics (obesity, general health status, having a medical condition, stressful life events or mental illness). The study followed up 5107 children from the Longitudinal Study of Australian Children, assessing their time-to-event data from birth (2004) to 14 or 15 years of age (2018). At 0 to 1 years old, 5.54% had a medical condition or disability and 51.07% were male. The hazard rate of any medical condition or disability was 26.13 per 1000 person-years for all the children and 29.49 for the males—a noticeable gender difference. It was highest (62.98) among the children when their mothers had a medical condition; it was 22.39 when the mothers had no medical conditions. The parametric panel regression results also suggested that the children of mothers with a medical condition during the 15-year study period were more likely to have a medical condition or disability (hazard ratio [HR]: 2.58, 95% confidence interval [CI]: 2.25–2.96) compared to the children of mothers with none. Similar trends were observed among children of mothers who experienced fair or poor health (HR: 1.42, 95% CI: 1.12–1.80), obesity (HR: 1.38, 95% CI: 1.18–1.62) or mental illness (HR: 1.40, 95% CI: 1.05-1.86) over time compared to those

whose mothers did not. These findings suggest that additional healthcare interventions targeting mothers with medical conditions, obesity, fair or poor health, or mental illness would help minimise the risk of medical conditions and disabilities among children.

Keywords: Longitudinal study, maternal health, child health, hazard rate, hazard ratio, long-term health condition, disability

Introduction

Medical conditions and disabilities are significant disease burdens for children. Based on the Centers for Disease Control and Prevention's definitions, the term 'medical condition or disability' refers to any disability or long-term medical condition of adults or children. Such conditions include sight, hearing and speech problems, blackouts, chronic pain, nervousness, head injury, difficulty breathing, gripping, or learning, limited use of arms, fingers, legs, or feet, and other long-term health conditions [1]. The Global Burden of Disease study estimates that of children aged 14 or younger worldwide, 5.1% (93 million) and 0.7% (13 million) live with moderate and severe disability respectively [2]. Likewise, within Australia, disability among children is a significant health issue. In 2018, almost 7.7% (357,500) of children under 15 years of age had a medical condition or disability. Further, of all the children, 4.5% (209,300) had profound or severe disability [3].

Universal health coverage is a core aim of the United Nations' Sustainable Development Goal 3: 'to ensure healthy lives and promote wellbeing for all, at all ages' [4]. To promote the wellbeing of children and adolescents, who are a significant proportion of the population, and monitor their ongoing health, there is a dire need to better identify problems and essential indicators in health areas to inform national programs and policies. Only a few epidemiological studies have investigated the relationship between maternal health characteristics and medical conditions or disabilities in children from national longitudinal cohorts [5–7]. Identifying children's health and disability issues in a national population can contribute to planning appropriate prevention and intervention strategies for target population groups.

The extant literature shows that children's health status, such as having medical conditions or disabilities in childhood, depends on their mothers' physical and mental health characteristics [8–12]. It is well established that

mothers' good physical health and healthy lifestyles can reduce chronic morbidity risks for children [6, 7, 13]. Several studies have linked suboptimal children's health and lifestyle environments to adult disease [5, 7, 14]. For example, obese mothers are more likely to have obese children who, in turn, are more likely to become obese adults [14]. Maternal obesity is associated with increased body mass index (BMI) of offspring across infancy [15], adolescence [16] and adulthood [17, 18]. Maternal stress or anxiety during pregnancy and mental illness during later life after childbirth are also associated with children's and adolescents' poor general health and long-term health condition [19]. A Canadian study of 2910 mother–youth pairs in a nationally representative prospective study found that adolescents (aged 16–17 years) exposed to maternal depressive symptoms during middle childhood were more likely to use alcohol, cigarettes or marijuana [20]. They were also more likely to engage in both violent and nonviolent delinquent behaviour. A recent review paper determined that maternal obesity during pregnancy negatively affected aspects of children's learning, memory and motivation and increased their likelihood of experiencing affective disorders, attention-deficit hyperactivity disorder or autism spectrum disorders [21].

To overcome the limitations of current literature and to contribute knowledge about the developmental origins of health and disease, the present study hypothesised that mothers' physical and mental health characteristics (namely obesity, general health, medical conditions, stressful life events, and mental illness) are associated with medical conditions and disabilities among their children. To test this hypothesis, it examined a nationally representative Australian birth cohort (a 15-year follow-up study) to determine their hazard rate of having any medical condition or disability, then assessed the association of this hazard rate with maternal physical and mental health.

Methods

Data source and sample selection

The Longitudinal Study of Australian Children (LSAC) Birth Cohort was used as the data source. LSAC is a representative household survey of Australian children that began in 2004. Every two years, it collects information about the children's development and physical and socio-emotional health using a model based on the bio-ecological framework of human development [22]. The present study used LSAC Wave 1 (2004) as its baseline (n = 5107) and followed the children up to Wave 8 (n = 3127). All the children in the baseline survey were included, whether or not they had a medical condition or disability. This study considered all the relevant maternal demographic characteristics and health indicators that the LSAC study measured across the waves. It used the LSAC study's data dictionary to identify the children's medical conditions and disabilities.

Outcome variables

The children's caregivers provided information about the children's medical conditions and disabilities. The term 'any medical condition or disability' included long-term medical conditions and disabilities and other disabilities that limited everyday activities. Long-term medical conditions and disabilities were defined as any of the following: sight problems, hearing problems, speech problems, blackouts, difficulty learning, limited use of arms or fingers, difficulty gripping, limited use of legs and feet, other physical conditions or disfigurements, shortness of breath or breathing difficulties, chronic or recurring pain or discomfort causing restriction, nervous conditions causing restriction, head injuries and long-term effects as a result of head injuries or brain damage or brain stroke, other long-term conditions causing restriction, or other long-term treated conditions such as arthritis, asthma, heart disease, Alzheimer's disease, or dementia that had lasted or were likely to last for six months or more. A dichotomous variable

was generated and coded with the value 1 for having any of these conditions and 0 for not having any of them up to Wave 8. Later, to estimate the hazard rate of any health condition or disability, time-to-event data were generated from the longitudinal data of all waves using the survival function of the statistical software package Stata 16.

Independent variables

Based on the existing literature, this study included the variables explained in this section as independent variables. Maternal obesity was measured based on BMI scores and categorised as follows: underweight (BMI < 18.00), healthy weight (BMI 18.00–24.99), overweight (BMI > 25.00) and obese (BMI > 30.00). The general health was measured from the self-rated health status reported by the mothers and categorised as per the following ordinal scale: excellent, very good, good, fair/poor. Mothers having a medical condition (yes or no) were measured based on whether the mothers had any medical condition or disability listed in the outcome variable section that had lasted or were likely to last for six months or more. Any stressful life events (yes or no) variable accounts for capturing whether mothers faced any of the more than twenty listed events in the last year from the date of interviews, for example, marriage separation or demise of friend or relatives, losing job or thought of losing job, valuable lost or stolen, legal problems, moving to a new house, affected by natural disaster, etc. Mental illness of mothers were measured from the Kessler-6 depression scale scores. These variables were measures in all the waves and reflect the physical and mental health status of mothers over the 15-year follow-up period of this study. Besides, this study also considered maternal mental stress or anxiety during pregnancy (yes or no) as a time-invariant independent variable, measured only at Wave 1, to analyse whether it predicted longitudinal medical conditions or disabilities in the children.

Control variables

This study considered the following socio-demographic covariates as confounding variables: the child's age, their sex (male or female), whether English was spoken at home (yes or no), whether the child was living with both parents or with a single parent, the Indigenous status of the child (yes or no), the age of the mother at childbirth, the employment statuses of the parents (employed, unemployed, or not in the labour force), the mother's level of education (Year 12 or less, certificate, graduate degree or diploma, or postgraduate) and the remoteness of the family residence (highly accessible, accessible to moderately accessible, or remote to very remote).

Statistical analyses

The key statistical analysis performed in this study was a survival analysis to determine the incidence (hazard) of any medical condition or disability from the 15 years of longitudinal data. To estimate the cumulative hazard rate and the hazard ratio of developing any medical condition or disability, the panel data parametric hazard model was used. The assumptions for building the model were checked, and the multivariate model was fitted to adjust for confounders related to infant and maternal health. If the p-value of a particular exposure was less than or equal to 0.05 in the multivariate regression analyses, only then was the predictor considered statistically significant. Descriptive statistics were used to summarise the characteristics of the children and mothers. Analyses were performed using Stata 16 (Stata Inc.).

Results

Study participants

Table 1 shows the mothers and children's characteristics both at the baseline (Wave 1) and in the follow-ups (Waves 2 to 8). Among the 5107 participating children at baseline, 5.54% had a medical condition or disability and 51.07%

Table 1. Characteristics of the participants during baseline (Wave 1) and subsequent follow-ups, LSAC study, 2004–2018

Characteristics of the study participants	Baseline	Subsequent follow-ups							Baseline characteristics of dropouts & losses in follow-ups (Waves 2–8, n = 1980)
	Total sample in Wave 1, 2004 (n = 5017)	Wave 2, 2006 (n = 4606)	Wave 3, 2008 (n = 4386)	Wave 4, 2010 (n = 4242)	Wave 5, 2012 (n = 4085)	Wave 6, 2014 (n = 3764)	Wave 7, 2016 (n = 3381)	Wave 8, 2018 (n = 3127)	
	%	%	%	%	%	%	%	%	%
CHILDREN'S CHARACTERISTICS									
Have any medical condition or disability									
Yes	5.54	7.97	9.44	8.44	4.04	4.94	4.82	5.85	6.46
Gender									
Female	48.93	49.00	48.68	48.44	48.69	48.75	48.71	48.64	49.39
Male	51.07	51.00	51.32	51.56	51.31	51.25	51.29	51.36	50.61
MATERNAL HEALTH CHARACTERISTICS, 2004-2018									
Obesity									
Underweight	9.40	7.92	7.59	8.20	7.32	6.62	5.83	5.31	9.90
Healthy weight	35.68	34.72	37.71	39.84	39.78	38.20	35.31	33.32	28.84
Overweight	20.15	16.87	21.43	24.42	25.53	25.35	26.18	27.34	17.63
Obese	14.27	11.35	15.21	20.01	22.89	23.78	26.00	28.05	12.47
Missing	20.50	29.14	18.06	7.52	4.48	6.06	6.68	5.98	31.16
General health									
Excellent	15.65	15.46	18.54	20.49	17.26	18.54	15.50	15.70	12.17
Very good	36.73	35.97	38.81	43.99	43.43	41.95	41.26	40.07	30.96
Good	25.08	19.84	22.23	26.43	27.71	27.66	28.16	30.28	24.09
Fair or poor	6.74	4.75	7.14	6.93	8.13	7.20	10.29	10.27	7.68
Missing	15.80	23.97	13.29	2.17	3.48	4.65	4.79	3.68	25.10
Have a medical condition									
Yes	24.50	10.29	7.91	7.36	9.82	11.32	11.65	13.21	24.39
Facing any stressful life events									
Yes	54.55	51.32	48.06	83.36	79.73	78.48	78.76	78.32	51.11
Mental illness of mothers based on Kessler-6 depression scale score									
Yes, have probable serious mental illness	2.23	1.87	1.14	2.43	1.88	2.36	2.60	2.94	2.53

Characteristics of the study participants	Baseline	Subsequent follow-ups							Baseline characteristics of dropouts & losses in follow-ups (Waves 2–8, n = 1980)
	Total sample in Wave 1, 2004 (n = 5017)	Wave 2, 2006 (n = 4606)	Wave 3, 2008 (n = 4386)	Wave 4, 2010 (n = 4242)	Wave 5, 2012 (n = 4085)	Wave 6, 2014 (n = 3764)	Wave 7, 2016 (n = 3381)	Wave 8, 2018 (n = 3127)	
	%	%	%	%	%	%	%	%	%
MENTAL HEALTH CHARACTERISTICS DURING PREGNANCY									
Mental stress or anxiety during pregnancy [a]									
Yes	15.33	-	-	-	-	-	-	-	-
SOCIO-DEMOGRAPHIC CHARACTERISTICS OF MOTHERS									
Age at childbirth									
≤ 18	1.17	0.89	0.87	0.73	0.66	0.50	0.41	0.35	2.47
19–34	72.41	71.69	71.34	71.52	71.14	70.75	70.10	69.84	76.46
≥ 35	26.41	27.42	27.79	27.75	28.20	28.75	29.49	29.80	21.06
Has a partner									
Yes	90.54	89.58	88.42	87.08	85.78	84.56	82.17	81.74	84.09
Employment status									
Employed	49.66	58.45	64.77	68.74	73.41	77.55	79.15	83.63	40.45
Unemployed	3.21	2.76	1.80	2.57	2.69	2.76	2.66	1.98	3.74
Not in the labour force	47.13	38.79	33.43	28.69	23.89	19.68	18.19	14.39	55.80
Education									
< 12 years of education	31.72	30.37	29.72	29.64	29.14	27.82	26.74	26.12	40.60
12 years of education	25.60	25.39	25.11	24.64	24.48	24.39	23.84	23.82	28.43
Graduate or diploma	35.59	36.72	37.59	38.12	38.59	39.73	40.85	41.20	26.71
University Masters	7.08	7.52	7.58	7.60	7.79	8.06	8.56	8.87	4.26

[a] This variable, maternal stress or anxiety during pregnancy, was measured only once, in Wave 1; in the subsequent waves of the retained samples, the recollected percentages of 'yes' were close to 15%.

were male. Among the mothers, 35.59% had a graduate degree or diploma and 49.66% were employed, 20.15% and 14.27% were overweight and obese respectively, 24.50% had a medical condition, 54.55% were facing stressful life events and 15.33% had mental stress or anxiety during pregnancy. Repeated measures of maternal health characteristics of obesity, general health status, having any medical condition, stressful life events and mental illness based on Kesssler-6 scores have been presented in Table 1. During the 15-year follow-up period, 1980 participants (mother–child pairs) dropped out or were lost to follow-up. In Wave 8, 3127 mother–child pairs participated; among the mothers, 5.85% had a medical condition or disability, 26% were obese, 78.32% had stressful life events and 2.94% were experiencing mental illness.

Hazard rate of any medical condition or disability

For all participants, the hazard rate of having at least one medical condition or disability between ages 0 and 15 (2004 to 2018) was 26.13 per 1000 person-years. As Table 2 shows, this rate was highest among the children of mothers with a medical condition (62.98), much higher than those of mothers without medical conditions (22.39). Similar trends were observed among the children of mothers experiencing mental illness (54.00), fair or poor health (44.55), obesity (31.61) and stressful life events (26.17), compared to the children of healthier mothers.

Table 2. Hazard rate of any medical condition or disability[a] per 1000 person-years according to maternal health conditions for Australian children followed from age 0 to 15 (2004–2018)

Characteristics	All children	Female	Male
	Hazard rate (95% CI[b])	Hazard rate (95% CI)	Hazard rate (95% CI)
All participants	26.13 (24.77–27.57)	22.77 (21.00–24.70)	29.49 (27.46–31.67)
MATERNAL HEALTH 2004-2018			
Obesity			
Underweight	24.20 (19.77–29.62)	19.45 (13.90–27.22)	28.08 (21.80–36.16)
Healthy weight	21.25 (19.29–23.40)	19.31 (16.73–22.27)	23.21 (20.36–26.46)
Overweight	25.30 (22.57–28.35)	22.64 (19.13–26.80)	28.08 (24.05–32.78)
Obese	31.61 (28.18–35.47)	27.64 (23.21–32.91)	35.54 (30.49–41.41)
General health status			
Excellent	18.80 (16.19–21.83)	18.04 (14.51–22.43)	19.52 (15.90–23.98)
Very good	22.55 (20.60–24.69)	18.81 (16.34–21.64)	26.29 (23.35–29.60)
Good	29.86 (26.99–33.03)	27.12 (23.33–31.51)	32.57 (28.41–37.34)
Fair or poor	44.55 (38.02–52.20)	40.26 (31.91–50.81)	49.07 (39.52–60.92)
Had a medical condition			
No	22.39 (21.04–23.82)	19.63 (17.88–21.56)	25.14 (23.15–27.30)
Yes	62.98 (56.40–70.32)	54.91 (46.44–64.92)	70.96 (61.29–82.16)
Faced stressful life events			
No	22.59 (20.06–25.45)	18.30 (15.18–22.06)	26.90 (23.05–31.40)
Yes	26.17 (24.52–27.94)	23.85 (21.65–26.28)	28.47 (26.06–31.10)
Mental illness based on Kessler-6 scores			
No mental illness	24.41 (23.01–25.91)	21.36 (19.52–23.37)	27.45 (25.37–29.71)
Have mental illness	54.00 (41.36–70.51)	58.08 (40.10–84.12)	50.21 (34.19–73.74)
Mental stress or anxiety during pregnancy in 2004			
No	24.34 (22.92–25.85)	21.10 (19.25–23.13)	27.53 (25.42–29.82)
Yes	36.68 (32.57–41.30)	32.16 (26.97–38.35)	41.57 (35.38–48.83)

[a] 'Any medical condition or disability' meant long-term medical conditions or disabilities and other disabilities that limited everyday activities. Long-term medical conditions or disabilities meant sight problems, hearing problems, speech problems, blackouts, difficulty learning, limited use of arms or fingers, difficulty gripping, limited use of legs and feet, and other physical conditions or disfigurements that lasted or were expected to last six months or more. Disabilities that limited everyday activities meant difficulty breathing, chronic pain, nervous conditions, head injuries, other long-term conditions, or other treated conditions.
[b] Confidence interval

Figure 1 displays the random-effects proportional Weibull hazard regression curves relating the hazard ratio of children's incurring any medical condition or disability over time to mothers' obesity, medical-condition and mental-illness characteristics. The graph clearly shows that the hazard ratios for all risk factors increased over time. The increase was greatest for the children of mothers who had medical conditions. Figure 2 displays the corresponding survival function, showing diminishing trends in the children's survival of morbidity related to potential medical conditions or disabilities. Lower survival ratios were observed for the children of mothers who were overweight, had a medical condition or were experiencing mental illness compared to the respective reference categories. The downward trend is steepest for the children of mothers who were suffering from a medical condition.

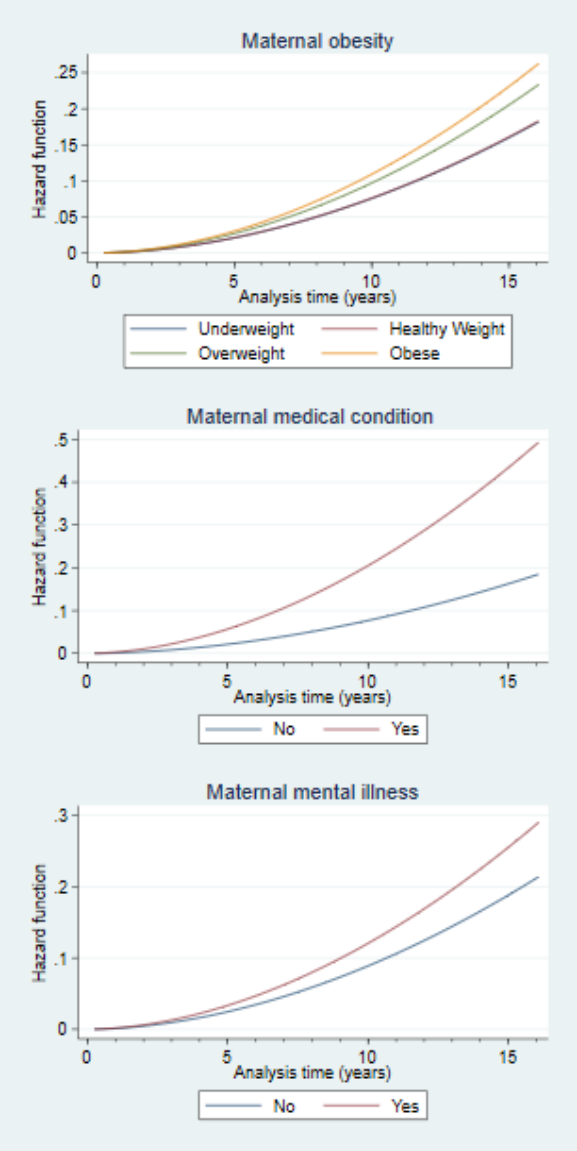

Figure 1. Hazard function curves. Random-effects panel hazard regression curve over time (in years) on the hazard function relating children's having any medical condition or disability to their mother's health-related characteristics.

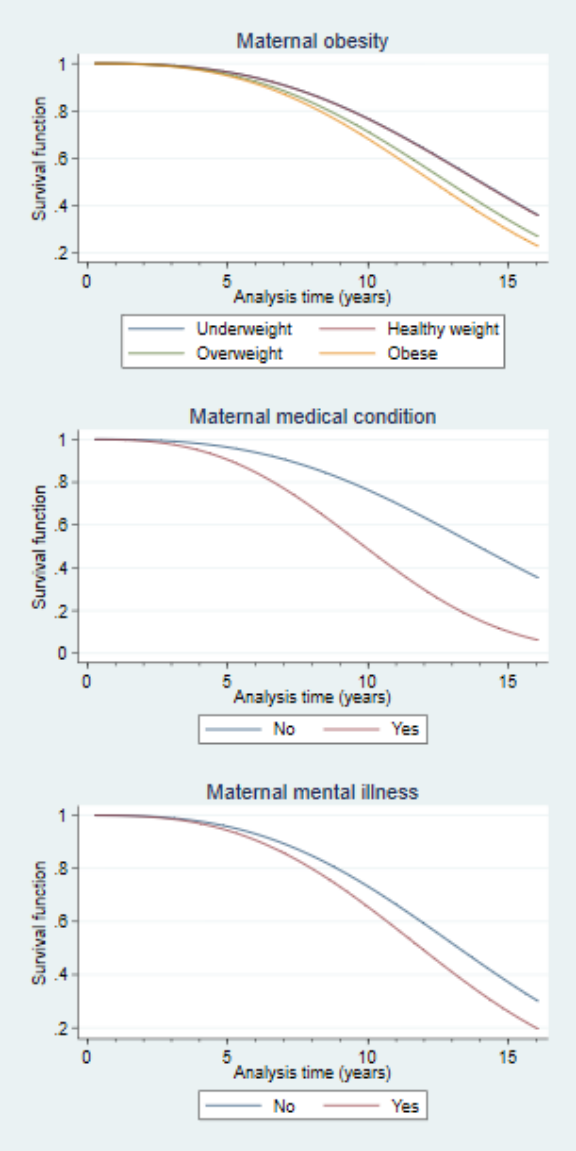

Figure 2. Survival function curves. Random-effects panel hazard regression curve over time (in years) on the survival function relating children's surviving a potential medical condition or disability to their mother's health-related characteristics.

Regression results

Table 3 presents the results of panel data parametric survival modelling of having any medical condition or disability. The parametric panel regression results suggested that children of mothers who had medical conditions during the follow-up period were more likely to have a medical condition or disability (HR: 2.58, 95% CI: 2.25–2.96) than the children of mothers who did not. Similar trends were observed among children of mothers who experienced obesity (HR: 1.38, 95% CI: 1.18–1.62), fair or poor health (HR: 1.42, 95% CI: 1.12–1.80) and stressful life events (HR: 1.26, 95% CI: 1.09–1.44) compared to the children of mothers who did not experience the respective problems.

Gender differences were observed in the hazard ratio of having any medical condition or disability. Although girls whose mothers experienced mental stress or anxiety during pregnancy had a higher risk of having a medical condition or disability (HR: 1.26, 95% CI: 1.03–1.54) compared to the female children of mothers who did not, the same association was not significant among boys. Moreover, mothers' mental illness and stressful life events during the 15-year follow-up period had a statistically significant influence on girls' medical conditions (HR: 1.61, 95% CI: 1.08–2.41 and HR: 1.38, 95% CI: 1.11–1.72 respectively) but not on those of boys.

Table 3. Panel data parametric survival model for any medical condition/disability health hazard among Australian children, 2004–2018

Risk factors	Random-effects hazard regression model		
	All children	**Female children**	**Male children**
	HR[a] (95% CI[b]), p-value	**HR (95% CI), p-value**	**HR (95% CI), p-value**
MATERNAL HEALTH CHARACTERISTICS DURING THE FOLLOW-UP PERIOD			
Obesity			
Healthy weight (ref.)[c]			
Underweight	1.09 (0.86–1.36), 0.465	0.98 (0.67–1.42), 0.920	1.16 (0.87–1.55), 0.303
Overweight	**1.18 (1.01–1.37), 0.034**	1.17 (0.93 –1.47), 0.168	1.19 (0.97–1.46), < 0.095
Obese	**1.38 (1.18–1.62), < 0.001**	**1.30 (1.02–1.65), 0.032**	**1.46 (1.19–2.07), < 0.001**
General health status			
Excellent (ref.)			
Very good	1.15 (0.97 –1.37), 0.115	1.02 (0.79 –1.33), 0.844	**1.27 (0.99 –1.61), 0.050**
Good	**1.32 (1.10 –1.60), 0.003**	1.28 (0.97 –1.69), 0.076	**1.38 (1.07 –1.78), 0.014**
Fair or poor	**1.42 (1.12 –1.80), 0.004**	1.28 (0.91 –1.83), 0.153	**1.55 (1.12 –2.14), 0.008**
Had a medical condition			
No (ref.)			
Yes	**2.58 (2.25–2.96), 0.000**	**2.64 (2.15–3.27), < 0.001**	**2.56 (2.13–3.08), < 0.001**
Faced stressful life events			
No (ref.)			
Yes	**1.26 (1.09–1.44), 0.001**	**1.38 (1.11–1.72), 0.003**	1.17 (0.98–1.41), 0.084
Mental illness based on Kessler-6 scores			
No (ref.)			
Yes	**1.40 (1.05–1.86), 0.021**	**1.61 (1.08–2.41), 0.020**	1.23 (0.82–1.85), 0.984
Mental stress or anxiety during pregnancy			
No (ref.)			
Yes	**1.21 (1.05–1.39), 0.006**	**1.26 (1.03–1.54), 0.027**	1.18 (0.97–1.41), 0.091

[a] Hazard ratio; [b] Confidence interval; [c] Reference category
Note: Statistically significant HR are bold in font

Discussion

This study measured the incidence rate of any medical condition or disability among children from LSAC, a nationally representative birth cohort, then assessed to what extent the hazard rate of this incidence was associated with maternal health characteristics such as obesity. The key point revealed by the study is that the children of mothers who had medical conditions during 15-year study period had a higher hazard ratio depicting the increased risk of incurring a medical condition or disability than those

whose mothers did not. This reinforces the findings of earlier studies that provided evidence that mothers' having chronic medical conditions, such as hypoglycaemia or jaundice, increases their children's likelihood of acquiring a chronic condition up to adolescence [7, 23–25]. The results also agree with those of other studies that have shown associations between maternal obesity and increased BMI of their offspring in adulthood [17, 18]. However, the present study reveals that the hazard of having a medical condition or disability is greater among children of mothers with medical conditions than among those of mothers with other morbidities such as poor general health or mental stress. It also reveals that in the context of survival analysis, children's medical condition or disability significantly depends on their mothers' health status.

This study indicates that the hazard of facing a medical condition or disability is higher for children of obese or overweight mothers compared to those of mothers whose weight is healthy. The result agrees with those of other studies that have shown associations between maternal obesity and increased BMI from infancy to adulthood [17, 18]. Similarly, a review of UK clinical studies reports that maternal obesity has been associated with several long-term adverse health outcomes in the offspring. These include lifelong risk of obesity and metabolic dysregulation with increased insulin resistance, hypertension and dyslipidaemia, as well as behavioural problems [7]. Another study revealed that maternal pre-pregnancy obesity and excessive weight gain during pregnancy are common and important risk factors for adverse childhood adiposity, cardiovascular, and respiratory outcomes [26]. The present study contributes the further insight that in the context of time-to-event survival up to 15 years from birth, the likelihood of medical conditions or disabilities is higher among children of overweight and obese mothers than among those of mothers whose weight is healthy.

The present study observed that children whose mothers faced stressful life events had a greater risk of living with disabilities or medical conditions in childhood. Likewise, a study of the existing literature reported a significant association between maternal stressful life events and poor general health status [19]. The causes of this association are likely to be mothers' mental or behavioural difficulties resulting in reduced access to health care services for their children, which may worsen the children's health. Interestingly, our study revealed that mental stress or anxiety during pregnancy and maternal mental illness occurring longitudinally over time increase the risk of experiencing a medical condition or disability only for the mothers' female children. Further research is needed to explain this gender difference.

This study also suggests that the children of mothers with poor general health are more likely to develop a medical condition or disability than the children of mothers with excellent general health. Two studies in Australian and US settings corroborate this finding; however, the later study reveals the associations between mothers' poor general health and children's chronic illness and lower physical health index scores only during adolescence, not in infancy [19, 27]. Using a different context to the present study, one conducted with children aged 5 to 18 confirmed that mothers' poor general health is associated with children's poor general health up to adolescence [28]. One possible reason could be that these children's poor self-ratings of general health were generated from experiences of health complications, including disability.

The present study contributes to the current literature in several ways. It is the first study to investigate the association between maternal health characteristics and Australian children's medical conditions and disabilities from the perspective of survival analysis. Moreover, it considered 15 years of follow-up data from a large, nationally representative children's birth cohort,

and by considering a wide range of diseases under the term ‘any medical condition or disability’, it encompassed the many diseases that frequently occur during childhood [29]. Further, it included a wide range of maternal health characteristics while controlling for confounding variables related to maternal and child health problems.

The current study findings and discovery of existing literature on environment impact [30–32] portrays the extended thought that intergenerational disease association is usually a mix of genetics and environment. Hence, the policy implication needs to address the risk of occurrence only when these can be changed. If not, then interventions should be designed with the aim to support families (both mothers and children) with the conditions to maximise their wellbeing. Further research is warranted to elaborate this thought and design the appropriate interventions.

The study has several limitations. First, the study methods were deployed to find the associations only and did not examine the causal relationships. Future studies could attempt to identify underlying causal associations. Second, self-reported weights and heights were used to calculate BMI and information of chronic conditions were obtained from self-reports which may have resulted in a reporting bias. Third, the inequality of the sample size across the waves may have influenced the statistical power. Further, analysis of this study’s intergenerational association is impacted with unknown extent of limitations on the gender differences. This is because, firstly, the study has engaged with analysing data only on the mothers (without including fathers), while genetic inheritance is from both parents. Secondly, family environments are shared by all living in the same household, but the analyses here (and in the existing literature) appear to be only of the association between mother and child.

Conclusion

Children of mothers who had medical conditions during pregnancy had a higher hazard ratio of having a medical condition or disability than those of mothers who did not. The ratio was also higher among children of obese mothers than among healthy-weight mothers. Children of mothers experiencing mental illness, fair or poor general health, or mental stress and anxiety during pregnancy had a higher hazard ratio of having a medical condition or disability, compared to the children of mothers with better health conditions in the respective categories. Gender variations were observed; these need further research. Overall, the findings confirm that maternal health influences children's health from birth to 14 or 15 years of age in the perspective of time-to-event or survival analysis. This suggests that additional healthcare monitoring of mothers experiencing prenatal mental stress during pregnancy or living with obesity, fair or poor health, medical conditions or mental illness over the period of 15 years after childbirth would help enhance the health and wellbeing of children as well as mothers.

List of abbreviations

BMI: Body Mass Index

CI: Confidence Interval

HR: Hazard Ratio

LSAC: Longitudinal Study of Australian Children

Ref.: Reference category

Declarations

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Authors' contributions

KA was the principal investigator, designed the study, conducted the data analysis and drafted the manuscript. GO partially wrote the manuscript and assisted with the critical review and final editing of the manuscript. RK and EK contributed to the study design and the development and editing of the manuscript. The authors followed the STROBE guidelines for writing the manuscript. All authors read and approved the final manuscript.

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Conflict of interests

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.

Availability of data and material

The data used for the study were collected from the LSAC Dataverse of the NCLD. Those interested in accessing the data should contact the LSAC Dataverse of the NCLD, Australia. There are restrictions on the data's use, and approval is subject to a signed confidentiality deed.

References

1. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention: Disability and Health Overview. Atlanta, GA: Centers for Disease Control and Prevention; 2020. [Updated 2020 Sep 16; cited 2022 Jan 04]. https://www.cdc.gov/ncbddd/disabilityandhealth/disability.html
2. World Health Organization: The global burden of disease: 2004 update. Geneva: World Health Organization; 2008. https://apps.who.int/iris/handle/10665/43942
3. Australian Bureau of Statistics: Disability, Ageing and Carers, Australia: Summary of Findings. Canberra: Australian Bureau of Statistics; 2019, Oct 24. https://www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/2018
4. United Nations: Transforming our World: The 2030 Agenda for Sustainable Development. New York: United Nations; 2015. https://sdgs.un.org/2030agenda
5. Ou L, Chen J, Hillman K, Eastwood J: The comparison of health status and health services utilisation between Indigenous and non-Indigenous infants in Australia. *Australian and New Zealand Journal of Public Health* 2010, 34(1):50–56.
6. Obel C, Linnet KM, Henriksen TB, Rodriguez A, Jarvelin MR, Kotimaa A, Moilanen I, Ebeling H, Bilenberg N, Taanila A *et al.*: Smoking during pregnancy and hyperactivity-inattention in the offspring—comparing results from three Nordic cohorts. *International Journal of Epidemiology* 2009, 38(3):698–705.
7. O'Reilly JR, Reynolds RM: The risk of maternal obesity to the long-term health of the offspring. *Clinical Endocrinology* 2013, 78(1):9–16.

8. Chen YC, Fan HY, Yang C, Lee YL: Early pubertal maturation and risk of childhood asthma: A Mendelian randomization and longitudinal study. *Allergy* 2020, 75(4):892–900.
9. Maïano C, Hue O, Morin AJ, Moullec G: Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. *Obesity Reviews* 2016, 17(7):599–611.
10. Schendel D, Bhasin TK: Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. *Pediatrics* 2008, 121(6):1155–1164.
11. Schieve LA, Tian LH, Rankin K, Kogan MD, Yeargin-Allsopp M, Visser S, Rosenberg D: Population impact of preterm birth and low birth weight on developmental disabilities in US children. *Annals of Epidemiology* 2016, 26(4):267–274.
12. Zhong Y, Wang J, Nicholas S: Gender, childhood and adult socioeconomic inequalities in functional disability among Chinese older adults. *International Journal for Equity in Health* 2017, 16(1):1–11.
13. Anderson LN, Sandhu R, Keown-Stoneman CDG, De Rubeis V, Borkhoff CM, Carsley S, Maguire JL, Birken CS: Latent class analysis of obesity-related characteristics and associations with body mass index among young children. *Obesity Science and Practice* 2020, 6(4):390–400.
14. Park MH, Falconer C, Viner RM, Kinra S: The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. *Obesity Reviews* 2012, 13(11):985–1000.
15. Linabery AM, Nahhas RW, Johnson W, Choh AC, Towne B, Odegaard AO, Czerwinski SA, Demerath EW: Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatric Obesity* 2013, 8(3):159–169.

16. Naess M, Holmen TL, Langaas M, Bjorngaard JH, Kvaloy K: Intergenerational transmission of overweight and obesity from parents to their adolescent offspring—the HUNT study. *PLoS One* 2016, 11(11):e0166585.
17. Eriksson JG, Sandboge S, Salonen M, Kajantie E, Osmond C: Maternal weight in pregnancy and offspring body composition in late adulthood: findings from the Helsinki Birth Cohort Study (HBCS). *Annals of Medicine* 2015, 47(2):94–99.
18. Hochner H, Friedlander Y, Calderon-Margalit R, Meiner V, Sagy Y, Avgil-Tsadok M, Burger A, Savitsky B, Siscovick DS, Manor O: Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation* 2012, 125(11):1381–1389.
19. [Anonymous 2007] Details omitted for double-blind reviewing.
20. Wickham ME, Senthilselvan A, Wild TC, Hoglund WL, Colman I: Maternal depressive symptoms during childhood and risky adolescent health behaviors. *Pediatrics* 2015, 135(1):59–67.
21. Contu L, Hawkes CA: A review of the impact of maternal obesity on the cognitive function and mental health of the offspring. *International Journal of Molecular Sciences* 2017, 18(5).
22. Zubrick S, Williams A, Silburn S, Vimpani G: Indicators of Social and Family Functioning. Canberra: Department of Family and Community Services, Commonwealth of Australia; 2000. https://www.dss.gov.au/our-responsibilities/families-and-children/publications-articles/indicators-of-social-and-family-functioning

23. Callaway L, Prins J, Chang A, McIntyre H: The prevalence and impact of overweight and obesity in an Australian obstetric population. *Medical Journal of Australia* 2006, 184(2):4.
24. Ingstrup KG, Andersen CS, Ajslev TA, Pedersen P, Sorensen TI, Nohr EA: Maternal distress during pregnancy and offspring childhood overweight. *Journal of Obesity* 2012, 2012:7.
25. Watkins ML, Botto LD: Maternal prepregnancy weight and congenital heart defects in the offspring. *Epidemiology* 2001, 12(4):439–446.
26. Gaillard R, Felix JF, Duijts L, Jaddoe VW: Childhood consequences of maternal obesity and excessive weight gain during pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 2014, 93(11):1085–1089.
27. McCormack C, Brooks-Gunn J, Shorter T, Holmes JH, Heagarty MC: Factors associated with maternal rating of infant health in central Harlem. *Developmental and Behavioural Pediatrics* 1989, 10(3):139–144.
28. Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L: Influence of parental gender and self-reported health and illness on parent-reported child health. *Pediatrics* 2000, 106(6):1422–1428.
29. World Health Organization: World Report on Disability. Geneva: World Health Organization; 2011. https://www.who.int/publications/i/item/9789241564182
30. Behrman JR, Rosenzweig MR: Returns to Birthweight. *The Review of Economics and Statistics* 2004, 86(2):586-601.
31. Lin MJ, Liu JT: Do lower birth weight babies have lower grades? Twin fixed effect and instrumental variable method evidence from Taiwan. *Social Science & Medicine* 2009, 68(10):1780-1787.
32. Nakamuro M, Uzuki Y, Inui T: The effects of birth weight: Does fetal origin really matter for long-run outcomes? *Economics Letters* 2013, 121(1):53-58.

5.2 Links and implications

The significance of this paper is that it found that the hazard of any medical condition or disability in children is associated with maternal physical and mental health characteristics (obesity, general health status, having a medical condition, stressful life events or mental illness). Children of mothers who had medical conditions during pregnancy had a higher hazard ratio of having a medical condition or disability than those of mothers who did not. The ratio was also higher among children of obese mothers than among healthy-weight mothers. Children of mothers experiencing mental illness, fair or poor general health, or mental stress and anxiety during pregnancy had a higher hazard ratio of having a medical condition or disability, compared to the children of mothers with better health conditions in the respective categories. Gender variations were observed, which have additional implication. The study findings suggest that the policymakers may, therefore, seek for additional healthcare interventions targeting mothers with medical conditions, obesity, fair or poor health, or mental illness would reduce the risk of medical conditions and disabilities among children.

This thesis intended to conduct the next study to determine the developmental origin factors (with infant and child health focus) associated with the risk of developing long-term medical conditions or disabilities in childhood. Furthermore, it utilised the survival analysis technique to capture the time to event feature of the morbidity in children. The survival model tests whether a risk factor affects the age of onset of the disease, with greater statistical power compared to the logistic regression models.

CHAPTER 6: PAPER 4 - ASSOCIATION OF INFANT AND CHILDHOOD HEALTH CHARACTERISTICS WITH THE HAZARD OF ANY MEDICAL CONDITION OR DISABILITY IN AUSTRALIAN CHILDREN

6.1 Introduction

This chapter presents the fourth paper of the thesis evaluating what infant and child health related characteristics are associated with developing any medical condition or disability in Australian children in their first 15 years of life. Thus, this paper is the second survival analysis study aiming to determine what developmental origin factors of infancy and childhood are associated with the risk of developing long-term medical conditions or disabilities in children. This is a longitudinal prospective study of 5,107 children, covering 51,009 person year survival data from eight waves of LSAC birth cohort surveys with the incidence of having any medical condition or disability, and utilised the parametric survival model for resolving the research question.

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Association of infant and child health characteristics with the hazard of any medical condition or disability in Australian children

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Abstract

Background: The incidence of any medical condition (e.g., sight, hearing, and speech problems, blackouts, chronic pain etc.) or disability (e.g., limited use of arms or fingers, legs, and feet, or other physical long-term health condition limiting everyday activities etc.) have been increasing among Australian children in recent decades.

Objectives: This study assessed whether infant or child health characteristics might be predictors of subsequent medical conditions or disabilities in children in the first 15 years of life.

Methods: Using time to event data of 5107 children, obtained from the Birth cohort of the Longitudinal Study of Australian Children, the study estimated the incidence of any medical condition or disability using the survival analysis technique. This study followed up the children from birth to 14 or 15 years of age (2004–2018) and assessed the association of infant and child health characteristics (birthweight, gestational age, use of intensive care unit or ventilator during their neonatal age and obesity) with hazard of any medical condition or disability using the random effect parametric survival regression model. The infant characteristics were measured in the Wave 1 while the children were aged 0/1 year and obesity characteristics were measured longitudinally over all the waves up to 14/15 years of age.

Results: The hazard rate of any medical condition or disability for all participants was 26.13 per 1000 person-years among children in Australia. This hazard incidence rate was higher among low birthweight (39.07) children compared to the children of normal birthweight (24.89) children. The hazard rate also higher among obese (34.37) children compared to the normal weight children (24.82) and among those who had received after-birth ventilation or intensive care unit emergency services (36.87) compared to those who have not received these services (24.20). The parametric panel regression model also suggests that children with low birthweight were 1.43 times (Hazard Ratio: 1.43, 95% Confidence Interval: 1.05–1.94) more likely to have any medical condition or disability than children with normal birthweight. The time to event analyses also revealed that being recipient of after-birth emergencies (HR: 1.47, 95% CI: 1.23–1.75), being male children (HR: 1.30, 95% CI: 1.14–1.48) or being obese (HR: 1.38, 95% CI: 1.07–1.79) significantly increased the likelihood of the incidence of a medical condition or disability among children. The regression model was adjusted for socio-demographic characteristics of children and mothers..

Conclusions: The study findings suggest that infants with low birth weight, hospital emergency service use and children with obesity would benefit from additional health care monitoring to minimize the risk of any medical condition or disability.

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Keywords: Medical condition, Disability, Hazard rate, Birthweight, Obesity, Intensive care unit

Background

Medical conditions or disabilities generate a disease burden for children worldwide. The term 'medical condition or disability' refers to any disabilities and related medical conditions of adults and children, for example, sight, hearing, and speech problems, blackouts, chronic pain, nervousness, head injuries, difficulty in breathing, learning difficulties, limited use of arms or fingers, legs, and feet, gripping problem, or other physical long-term health conditions [1]. The Global Burden of Disease study in 2004 estimated that a total of 5.1% (93 million) children aged 14 or under lived with moderate or severe disability, amongst 0.7% (13 million) survived with severe medical condition [2]. In addition, approximately 150 million children aged 18 years or under had medical condition or disability, most of whom live with the reality of exclusion in the world [3]. A similar picture has been observed in Australia. In 2018, nearly 7.7% (357,500) of children under 15 years had experienced any medical condition or disability, of which 4.5% and 1.6% had severe and moderate/mild conditions, respectively [4]. In addition, the proportion of children with disability has been increased from 6.9% (295,900) in 2012 [4].

The available literature shows that children's health state, such as having any medical condition or disability, in childhood depends on the health characteristics of the mother during pregnancy and of the infants [5–9]. Low birth weight and shorter gestation period/preterm birth are significantly associated with increased risk of any medical condition among children [7, 8, 10, 11]. Past studies in the US and China revealed that sex, a biological factor, substantially impacted disability [7, 9]. A systematic review confirmed that the likelihood of being overweight and obese increased the risk of acquiring disabilities in children by 1.54 and 1.80 times, respectively [6]. Two earlier studies had found that perinatal factors, such as low birth weight and premature birth, were associated with a higher likelihood of disability acquisition [12, 13].

Besides the biological risk factors, there are psychological and sociodemographic risk factors which are associated with hazard of any medical condition or disability [14, 15]. For example, prevalence of chronic pain was higher among people who are not in the employment or have lower income than those who are employed or have higher income [14]. Ethnicity and cultural background are other predictors of long-term medical conditions or disabilities [14]. This study intends to assess the longitudinal developmental origins of health and disease among children and hence provide importance to investigate the associations of biological risk factors from infancy and childhood characteristics with the acquisition of long-term medical conditions or disabilities in children over time.

However, one of the main limitations of the existing literature is that most of the previous studies that have provided evidence of different biological risk factors, including birthweight and obesity, for chronic conditions or disability acquisition are conducted among adults and older people [16, 17]. Though a small number of child health focused studies are available, these are either cross-sectional or not of contemporary birth cohorts [7, 8, 10]. Further, neither of earlier studies had the scope for, nor willing to investigate both birthweight and obesity factors in a single study. It is important to consider both variables because children with normal birth weight may sometimes be obese at any time point over the period of 14/15 years. Another limitation is that there is no longitudinal time to event studies or survival analyses in the Australian setting to identify the risk factors of medical condition or disability among children.

To overcome the limitations of current literature and to investigate the developmental origins of health and disease, the present study hypothesized that infant and child health-related characteristics (birthweight, obesity over childhood, gestational age and emergency service use after birth) are associated with any medical condition or disability acquisition in Australian children. This cohort study will reveal knowledge, as an early warning for the children before they enter into their adulthood, about the risk factors of the incidence of any medical condition or disability using 15-year of follow-up data from the nationally representative Australian birth cohort.

Methods

Data source and sample selection

The data came from the birth cohort of the Longitudinal Study of Australian Children (LSAC), a representative household survey of Australian children that began in 2004 and biennially collects information on the health (physical and socio-emotional) and development of Australian children based on the context of the bio-ecological framework of human development [18]. For the current analysis, we used Wave 1 as the baseline ($n=5107$) and followed the development of the children up to Wave 8 ($n=3127$) which resulted in 51,009 person-year data for the survival analysis. As this was a birth cohort, we considered all the children of the baseline survey as

being independent of any medical condition or disability. Demographic characteristics, any medical condition or disability and other health related status for children were all identified using the data dictionary of the LSAC study.

Outcome variable

The diagnostic of having long-term medical condition or disability was acquired by the LSAC study from the caregivers of the children at the survey of each wave, conducted between 2004 and 2018. Long-term medical condition or disability includes the incidence of long-term medical conditions or disabilities that have lasted or are likely to last for six months or more and restricts physical activity or physical work, as reported by the caregivers of the study children or by the study children themselves if they are aged 14 years or over. These long-term medical conditions or disabilities include any of the following 16 conditions: sight problems, hearing problems, speech problems, blackouts, difficulty learning, limited use of arms or fingers, difficulty gripping, limited use of legs and feet, other physical condition, disfigurement or deformity, shortness of breath or breathing difficulties, chronic or recurring pain or discomfort causing restriction, nervous condition causing restriction, head injuries and long-term effects as a result of head injury, stroke or other brain damage causing restriction, other long-term conditions causing restriction, or other long-term treated conditions such as arthritis, asthma, heart disease, Alzheimer's disease, dementia etc. Based on the knowledge of healthcare systems in Australia, this study assumes that the medical conditions or disabilities reported by the respondents were identified or treated by a General Practitioner or specialist earlier. A dichotomous variable was generated and coded with the value 1 for having any of these medical conditions or disabilities and 0 for not having any of these diseases at each wave's survey. Afterwards, time to event data were generated from the longitudinal data of all waves using the survival function to estimate the incidence rate of any health condition or disability.

Independent variables

Based on the existing literature, as mentioned in the background section [6–9, 11–13, 16, 17], the following variables were considered as the independent variables in this study: birthweight (low: < 2500 grams, normal: 2500 – 4000 grams, high: > 4000 grams), gestational age (early: < 37 weeks, on-time: 37–41 weeks, late: > 41 weeks), obesity status (underweight: < = 5th percentile, normal: 6th to 84th percentile, overweight: 85th to 94th percentile, obese: > = 95th percentile) of the children and after birth emergency service use (yes: ventilation or intensive care unit service use, no: none of these services use). The options of the responses of the selected variables were available in the LSAC data as mentioned in the brackets of the variables. Birthweight, gestational age and emergency service use were measured in the Wave 1 while the children were aged 0/1 year. Obesity status of the children were measured longitudinally over all the waves from the children's birth to 14/15 years of age.

Control variables

This study considered the following socio-demographic covariates as confounding variables: (i) age of the children, (ii) sex of the children (male or female), (iii) whether English is spoken at home (yes or no), (iv) whether children have both parents (both parents, single parent), (v) indigenous status (yes or no), (vi) education of mother (year 12 or less, certificate, graduate degree/diploma, postgraduate), (vii) remoteness of the family residence based on the accessibility of metropolitan and regional services (highly accessible, accessible/moderately accessible, or remote/very remote).

The health indicators of this longitudinal study of birth cohort were observed and measured bi-annually with varying age of children by 1 year. For example, at Wave 1 children were aged 0 to 1, and subsequently at Wave 2 to Wave 8, children were aged 2–3 to 14–15 years old. Hence, the measurement of survival time from the measured target diseases of this study have been affected by age due to inclusion of both younger and older child in each Waves. Hence, we controlled for age for eliminating the additional burden on survival rate due to older aged children.

Statistical analyses

Descriptive statistics were used to summarize characteristics of children and mothers. The occurrence of any health condition or disability was estimated from 51,009 person-year survival data which was derived from 5107 children followed up until 15 years age. The panel data parametric hazard model was used to estimate the hazard ratio of developing any medical condition or disability and the accumulation of incidence rate of the hazard among the participants. The random effects panel data method of survival analysis was employed to assess the impact of both time-varying and non-time variant independent variables on the occurrence of any health condition or disability. We defined the onset of having any health condition or disability as the point of time from which a child was identified having a health condition or disability by the caregiver in the follow-up surveys; and calculated the onset of time by calculating the age of the children during the reporting time. A person was

denoted as being censored if they were dropped out from any point of the follow-up survey. Panel regression hazard model assumptions were checked, and the multivariate model was fit adjusting for the following confounders: age of the child during survey of each wave, sex of the child, mother's age at childbirth, mother's education, remoteness of residence, language spoken at home, indigenous status of children and whether the study children have both parents at home. All the confounders were checked for multi-collinearity along with the variance inflation factor (VIF) test, and no multi-collinearity was found. A predictor was considered statistically significant if the respective p-value of a particular exposure was less than or equal to 0.05 in the multivariate regression analyses. Analyses were performed using Stata version 16 (Stata Inc.).

Results

Study participants

Table 1 shows the participants' baseline characteristics in Wave 1, and the representation of the baseline characteristics in the subsequent follow-ups up to Wave 8. Among the 5107 participants at baseline, 12.81% children had birthweight over 4000 grams, 5.68% of children's weight was over 95 percentiles, 6.57% children had premature birth and 16.86% children needed ventilation/intensive care unit support after their birth. During the 15-year follow-up period, 1980 participants dropped out or were lost to follow-up. Among these dropouts, there were no significant differences in terms of characteristics of gender, birthweight, gestational age and afterbirth emergency. In Wave 8, a total of 3127 children participated; among them 51.36% were male participants, 9.35% children were overweight, 6.36% children were obese, 5.86% children had a premature birth and 16.37% children required ventilation/intensive care unit intervention after birth. The prevalence of any medical condition or disability varied longitudinally among the children, ranged in between 4.04% to 9.44% and reached to its peak during Wave 3 (9.44%) and Wave 4 (8.44%), while the children were four to seven years old (see Fig. 1).

Hazard rate of any medical condition or disability

The hazard rate of any medical condition or disability (at least one) for all participants was 26.13 (95% CI: 24.77–27.57) per 1000 person-years in children followed-up from age 0 to 15 years in Australia, in the period between 2004 and 2018. The hazard rate was higher for those who had low birth weight (< 2500 grams) in 2004 compared with normal birthweight children (HR: 39.07, 95% CI: 32.15–47.95; and HR: 24.89, 95% CI: 23.43–26.45 per 1000 person-years, respectively). This pattern was also observed among the underweight and obese children; among them hazard rate was around 1.5 times higher compared with normal weight children (Table 2). Table 2 also presents the incidence rate (of hazards) by gestational age and after-birth emergency service categories. Children who were born early and received after-birth ventilation or intensive care unit (ICU) services had higher hazard rate (around 1.5 times) relative to those who born on time and did not receive any emergency services, respectively.

Figure 2 displays random effects Weibull proportional hazard regression curve on hazard ratio over time by birthweight, obesity status, gestational age and after birth emergency of the children. It is evident from the graph that hazard ratio for all risk factors increases over time. The increasing trend was higher for children with low birthweight, obese children and those who received ventilation or ICU services compared to other reference categories shown in Fig. 2. Figure 3 shows the cumulative hazard ratio and Fig. 4 shows the survival rate over time for the same risk factors shown in Fig. 2. Cumulative hazard ratio curves of Fig. 3 have the similar trends of hazard ratio curves shown in Fig. 2, revealing with a steeper increase while follow-up time advances. In Fig. 4, diminishing trends of survival are evident with lower survival rates for low birthweight, obese and emergency service recipient children compared to the children of reference categories.

Regression model results

Table 3 presents the results of the panel regression model for the hazards of any medical condition or disability among the children based on survival analysis. In the adjusted regression model, low birthweight and obesity were predictive of medical condition or disability, presenting a risk of 1.43 times (Hazard Ratio: 1.43, 95% Confidence Interval: 1.05–1.94) than those with normal birthweight. The time to event analysis also found that obese children were and 1.38 times (HR: 1.38, 95% CI: 1.07–1.79) more likely to have the hazard of a medical condition or disability compared to the normal weight children. However overweight was not significant to predict the medical condition or disability of the children. Among the other independent factors, male children and children who received after-birth emergency services were strongly associated with higher risk of any medical condition or disability with hazard ratio of 1.47 (95% CI: 1.23–1.75) and 1.30 (95% CI:1.14–1.48) respectively (p-value < 0.001).

Discussion

The present study focused on Australia and determined the incidence of any medical condition or disability among children based on time to event analysis and

Table 1 Baseline characteristics of the first wave and the subsequent follow-ups, LSAC study, 2004–2018

	Baseline	Subsequent follow-ups							Baseline characteristics of dropped-out subjects
	Wave 1, 2004 (*n* = 5107)	Wave 2, 2006 (*n* = 4606)	Wave 3, 2008 (*n* = 4386)	Wave 4, 2010 (*n* = 4242)	Wave 5, 2012 (*n* = 4085)	Wave 6, 2014 (*n* = 3764)	Wave 7, 2016 (*n* = 3381)	Wave 8, 2018 (*n* = 3127)	Dropouts/Loss to follow-up (W2-W8, *n* = 1980)
Baseline characteristics	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**
Sex									
Female	48.93	49.00	48.68	48.44	48.69	48.75	48.71	48.64	49.39
Male	51.07	51.00	51.32	51.56	51.31	51.25	51.29	51.36	50.61
Birthweight									
Low (< 2500 grams)	5.76	5.25	5.40	5.45	5.26	5.34	5.41	5.15	6.72
Normal (2500-4000 grams)	81.44	81.44	81.3	81.19	80.95	80.9	80.83	80.84	82.37
High (>4000 grams)	12.81	13.31	13.29	13.37	13.78	13.76	13.75	14.01	10.91
Weight percentile status									
Under-weight, < 15%	6.17	5.19	6.16	4.95	4.68	6.22	6.15	5.24	6.77
Normal weight, 15%-85%	79.05	70.67	69.97	74.3	71.06	65.75	64.21	62.49	80.51
Overweight, 85%-95%	8.44	17.85	17.01	13.79	16.03	17.48	18.07	19.06	7.07
Obese, > 95%	5.64	4.47	5.45	5.52	6.10	5.47	5.29	6.81	4.55
Missing	0.70	1.82	1.41	1.44	2.13	5.07	6.27	6.40	1.11
Gestational age									
Premature birth, < 37 weeks	6.57	6.39	6.44	6.35	6.28	6.28	6.07	5.86	7.70
On time birth, 37–42 weeks	88.86	89.1	89.16	89.07	89.19	89.2	89.63	89.31	88.15
Late birth, 42 + weeks	4.57	4.50	4.41	4.58	4.54	4.52	4.30	4.84	4.15
After birth emergency									
No emergency	83.14	83.41	83.68	83.57	83.94	83.53	83.82	83.63	82.37
Ventilation/ Intensive Care Unit required	16.86	16.59	16.32	16.43	16.06	16.47	16.18	16.37	17.63
Age of mothers at birth									
< = 18 years	1.17	0.89	0.87	0.73	0.66	0.50	0.41	0.35	2.47
19–34 years	72.41	71.69	71.34	71.52	71.14	70.75	70.10	69.84	76.46
> = 35 years	26.41	27.42	27.79	27.75	28.2	28.75	29.49	29.80	21.06
Have both parents									
Yes	90.54	89.58	88.42	87.08	85.78	84.56	82.17	81.74	84.09
Maternal education									
< 12 years of education	31.72	30.37	29.72	29.64	29.14	27.82	26.74	26.12	40.60
12 years of education	25.60	25.39	25.11	24.64	24.48	24.39	23.84	23.82	28.43
Graduate/ Diploma	35.59	36.72	37.59	38.12	38.59	39.73	40.85	41.20	26.71
University Masters	7.08	7.52	7.58	7.60	7.79	8.06	8.56	4.87	4.26

Table 1 (continued)

	Baseline	Subsequent follow-ups							Baseline characteristics of dropped-out subjects
	Wave 1, 2004 (*n* = 5107)	Wave 2, 2006 (*n* = 4606)	Wave 3, 2008 (*n* = 4386)	Wave 4, 2010 (*n* = 4242)	Wave 5, 2012 (*n* = 4085)	Wave 6, 2014 (*n* = 3764)	Wave 7, 2016 (*n* = 3381)	Wave 8, 2018 (*n* = 3127)	Dropouts/Loss to follow-up (W2-W8, *n* = 1980)
Baseline characteristics	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**	**Percent**
Remoteness of residence									
Highly accessible	55.46	55.63	55.29	55.15	54.64	55.03	54.67	55.19	55.89
Accessible	23.53	23.57	23.82	23.69	24.36	23.87	24.16	23.88	22.98
Moderately accessible	16.64	16.49	16.63	16.97	16.79	16.97	17.02	16.58	16.73
Remote/very remote	4.38	4.30	4.26	4.19	4.21	4.13	4.16	4.36	4.40

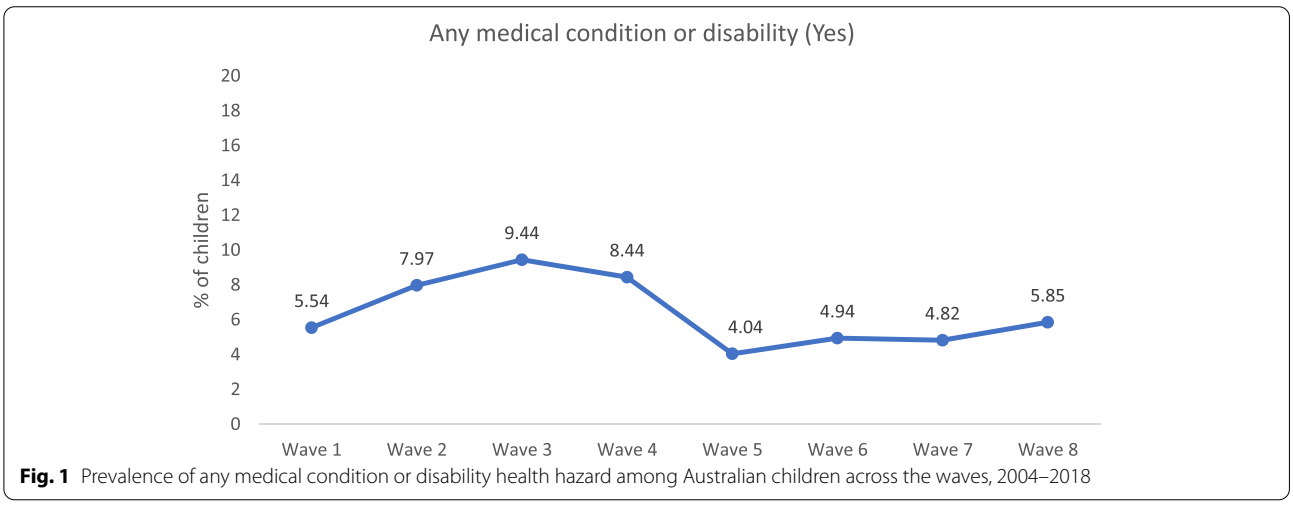

Fig. 1 Prevalence of any medical condition or disability health hazard among Australian children across the waves, 2004–2018

investigated its association with child health-related characteristics. The estimated incidence of any medical condition or disability was 26.13 per 1000 person-year among Australian children. The study also found that the hazard rate was higher for children born with low weight or receiving after-birth emergency services.

The main point revealed from the study is that children with low birthweight have higher hazards of developing any medical condition or disability compared to the children who have healthy birthweight. A follow-up study conducted in the USA aligns with our study findings that low birthweight increases children's risk of any medical condition [19]. In addition, similar results have been observed in some previous studies [7, 8, 10]. However, the results contradict an earlier study that revealed no significant association between low birthweight and subsequent disorder in children [20]. One possible reason could be that low birthweight generates complications for children's health because it is hard to gain weight and fight infectious diseases [21]. Immaturities in different organs, lower immunity, weakness, and low body fat are other plausible reasons for disease burden due to low birthweight [21].

The hazard of experiencing any medical condition or disability is higher for obese children compared to children who have normal weight. Our findings have added further insight into the existing literature which is consistent with this result [6, 22–24]. A previous Australian study also identified obesity as a risk factor

Table 2 Hazard rate of any medical condition or disability in the living per 1000 person-years in children followed-up from age 0 to 15 years in Australia, according to birthweight, gestational age and obesity, 2004–2018

	Total	
	Hazard Rate	**95% CI**
All participants	26.13	24.77–27.57
Birth weight		
Low (< 2500 grams)	39.07	32.15–47.49
Normal (2500–4000 grams)	24.89	23.43–26.45
High (> 4000 grams)	28.89	25.08–33.28
Gestational age		
Early (< 37 weeks)	35.16	29.92–44.38
On-time (37–41 weeks)	25.58	26.13–29.33
Late (> 41 weeks)	25.24	21.49–35.65
Obesity		
Underweight (< = 5th Percentile)	36.42	29.99–44.23
Normal (6th to 84th Percentile)	24.82	23.24–26.50
Overweight (85th to 94th Percentile)	26.23	22.94–29.99
Obese (> = 95th Percentile)	34.36	28.05–42.11
After birth emergency		
No	24.20	22.78–25.71
Yes (Ventilation/ICU)	36.87	32.85–41.40

Any medical condition/disability includes the incidence of long-term medical condition/disability and disability limiting everyday activities; Long-term medical condition/disability includes sight problems, hearing problems, speech problems, blackouts, difficulty learning, limited use of arms or fingers, difficulty gripping, limited use of legs and feet, other physical condition, or other disfigurement which lasted for six months or more; Disability limiting every day activities includes difficulty breathing, chronic pain, nervous condition, head injury, other long-term condition, or other treated condition

of acquiring a disability [25]. The possible reason could be defined by low physical activity and metabolism deformity among the children who face health problems due to obesity [24, 26].

The children who use emergency services after birth, such as the services of ventilation in the intensive care unit, have a greater risk of living with disabilities in childhood. This agreement equates to an extant study that reported a significant association between ventilation utilisation and health complications [27]. The probable causes might be for difficulties and inconsistencies in perinatal events as this situation increases various health hazards including respiratory and brain injury related health issues [28]. Further, existing research shows that majority of the children in ICU are premature and low birthweight [29–31]. Emergency care provides instant remedies; however, listed reasons create further medical issues among children, which are hard to deal with and have long term consequences [32, 33].

Our study did not find evidence that gestational age has a statistically significant influence on children's medical condition. However, some retrospective cohort studies have identified it as a contributing factor of disability [7, 34]. Therefore, a further large-scale investigation is required to examine the disparities across the studies through a systematic review.

Our study reveals risk factors of children's medical condition or disability that might contribute to inventing conservative approaches for public and private organisations to control the children's medical conditions or disabilities in Australia. First, screening programs based on nutritional and physical activity measurement for children could be planned to tackle the obesity epidemic. For example, each child could receive a diet chart and physical activity schedule considering their body mass index (BMI) through science-based intervention. According to the Australian Health and Wellbeing Strategic Framework 2017 to 2026, these proposed strategies create awareness about disease burden and provide knowledge about the necessity of maintaining a healthy lifestyle [35]. Second, accessible medical interventions are needed for pregnant women that promote understanding of pregnancy-related hazards and health checkup advantages. It might help women to have increased awareness of their health status during the gestation period, increasing the possibility of delivering healthy infants. Third, different health strategies for male children might be designed to provide special attention since birth to lessen disease severity.

This study adds further insights in the current literature. This is the first study identifying the association between infant and child health characteristics with any medical condition or disability among Australian children. Additionally, the study considers 15 years of follow-up data from a large, nationally representative children's birth cohort in Australia. To escape bias, 'any medical condition or disability' is constructed to mean all possible diseases that occurred in childhood because the variability nature of measurement is observed across the studies [36]. Further, a wide range of infant and child health characteristics is included in this cohort study after considering the effect of child health related problems.

This study also has limitations that should be acknowledged. First, examining the causal relationship is not possible due to the unbalanced longitudinal data. Therefore, future study is needed to identify the underlying association by considering the cause and generalizing the association for external settings in Australia. Second, the responses on long term medical conditions or disabilities, the outcome variable of this study, were provided by the respondents, who were either caregivers of the study children or the children themselves, if their age

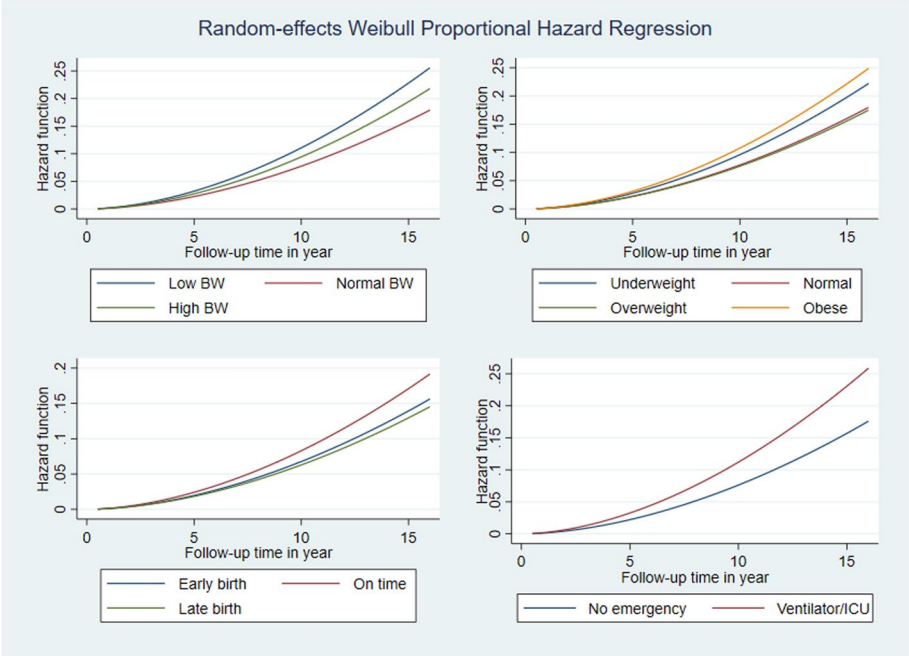

Fig. 2 Smooth curves of proportional hazard regression on hazard functions of children across the years by birthweight, obesity status, gestational age and after birth emergency of the children

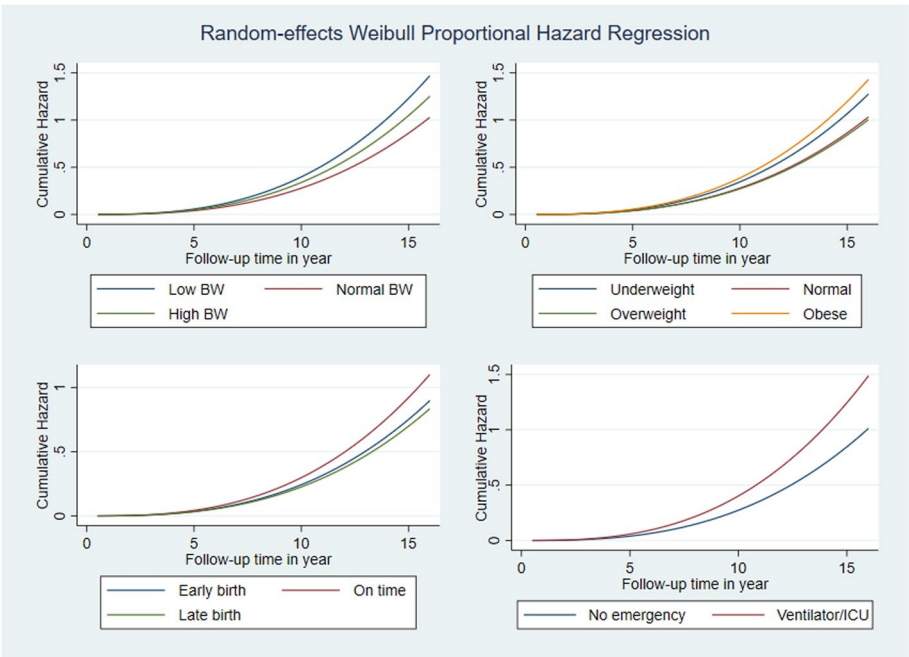

Fig. 3 Smooth curves of proportional hazard regression on cumulative hazard functions of children across the years by birthweight, obesity status, gestational age and after birth emergency of the children

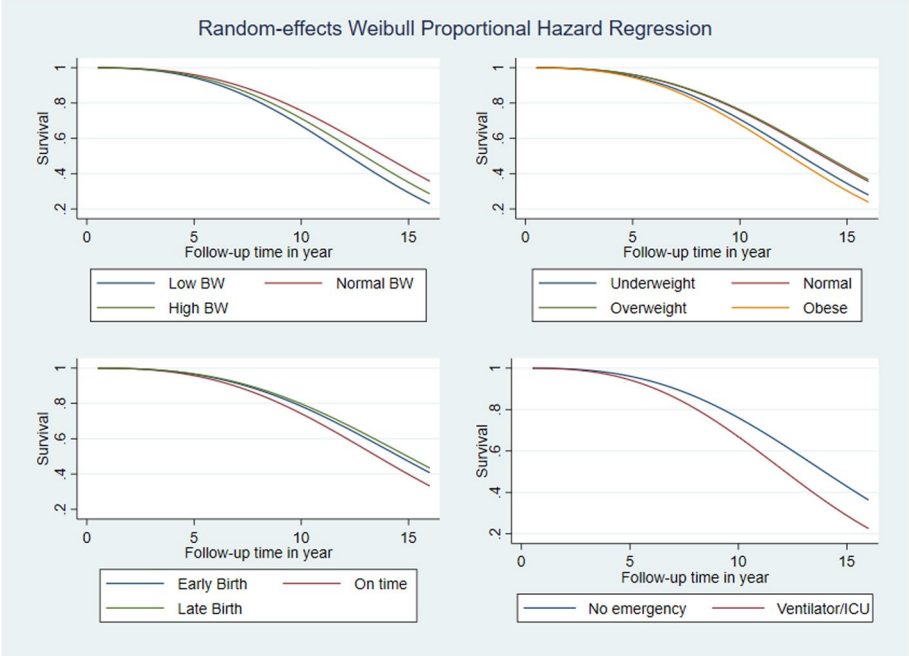

Fig. 4 Smooth curves of proportional hazard regression on survival functions of children across the years by birthweight, obesity status, gestational age and after birth emergency of the children

Table 3 Panel data parametric survival model for any medical condition/disability health hazard among Australian children, 2004–2018

	Regression Model		
	Hazard ratio	***p-value***	**95% CI**
Birthweight			
2500—4000 grams (ref.)			
< 2500 grams	**1.43**	**0.023**	**1.05–1.94**
4000 + grams	1.22	0.036	1.01–1.46
Obesity of children			
Normal weight (ref.)			
Underweight	1.23	0.117	0.95–1.61
Overweight	0.97	0.766	0.81–1.17
Obese	**1.38**	**0.013**	**1.07–1.79**
Gestational Age			
Matured birth, 37–42 weeks (ref.)			
Early birth, < 37 weeks	0.83	0. 190	0.60–1.11
Late birth, 42 + weeks	0.76	0.132	0.53–1.09
After birth emergency			
No emergency (ref.)			
Ventilation/Intensive Care Unit required	**1.47**	**0.000**	**1.23–1.75**
Gender of the child			
Female (ref.)			
Male	**1.30**	**0.000**	**1.14–1.48**

The regression model was adjusted for age of the children at each wave, sex of the children, language spoken at home, indigenous status, whether the study child has both parents, mothers age at birth, education of mothers, and region of residence

were 14 years or over. The study assumes that the medical conditions or disabilities reported by the respondents were identified or treated by a General Practitioner or specialist earlier, in the context of Australian health-care system. However, the self-reported nature of the outcome variable might lead to reporting bias in the study. Third, disparities among the statistics might have been found as the non-participants made the sample sizes unequal in the waves.

Conclusion

The current study assessed from a contemporary birth cohort of Australian children that low birthweight, receiving emergency hospital services just after birth, being male and being obese during childhood up to the age of 15 years are associated with increased hazard of having any medical condition or disability. These findings suggest that infants with low birth weight, children who have accessed hospital emergency services and children with obesity need further healthcare monitoring support from both private and public providers to improve the health and wellbeing of Australian children.

Abbreviations

HR: Hazard Ratio; LSAC: Longitudinal Study of Australian Children; ICU: Intensive Care Unit; BMI: Body Mass Index.

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Authors' contributions
KA was the principal investigator, designed the study, conducted the data analysis, and drafted the manuscript. SAK and NJS critically reviewed the manuscript and assisted with the final editing and writing of the manuscript. RK and EK contributed to the study design and development and edited the manuscript. The authors followed the STROBE guidelines for writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data used for the study were collected from the Longitudinal Study of Australian Children Dataverse of National Centre for Longitudinal Data. Those interested in accessing this data should contact the Longitudinal Study of Australian Children Dataverse of National Centre for Longitudinal Data, Australia. There are some restrictions on the use of this data and the data application's approval is subject to a signed confidentiality deed.

Declarations

Ethics approval and consent to participate
The LSAC study was approved by the Australian Institute of Family Studies Ethics Committee. The de-identified unit record dataset was released to the current researchers at the University of Southern Queensland for the purposes of this doctoral research. To obtain this data, the authors completed and signed the Confidentiality Deed Poll and sent it to NCLD (ncldresearch@dss.gov.au) and ADA (ada@anu.edu.au). Therefore, datasets analysed and/or generated during the current study are subject to the signed confidentiality deed.

Consent for publication
Not applicable.

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

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References

1. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention: Disability and Health Overview. Atlanta: Centers for Disease Control and Prevention; 2020. [Updated 2020 Sep 16]. Retrieved 2022 Jan 04 from https://www.cdc.gov/ncbddd/disabilityandhealth/disability.html.
2. World Health Organization: The global burden of disease: 2004 update. Geneva: World Health Organization; 2008. Retrieved 2022 Jan 04 from https://apps.who.int/iris/handle/10665/43942.
3. UNICEF: The state of the world's children 2006: excluded and invisible. New York: UNICEF; 2005.
4. Australian Bureau of Statistics: Disability, Ageing and Carers, Australia: Summary of Findings. Canberra: Australian Bureau of Statistics; 2019, Oct 24. Retrieved 2022 Jan 04 from https://www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release#data-download.
5. Ahmad K, Kabir E, Keramat SA, Khanam R. Maternal health and health-related behaviours and their associations with child health: evidence from an Australian birth cohort. PLoS ONE. 2021;16(9): e0257188.
6. Maïano C, Hue O, Morin AJ, Moullec G. Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. Obes Rev. 2016;17(7):599–611.
7. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics. 2008;121(6):1155–64.
8. Schieve LA, Tian LH, Rankin K, Kogan MD, Yeargin-Allsopp M, Visser S, Rosenberg D. Population impact of preterm birth and low birth weight on developmental disabilities in US children. Ann Epidemiol. 2016;26(4):267–74.
9. Zhong Y, Wang J, Nicholas S. Gender, childhood and adult socioeconomic inequalities in functional disability among Chinese older adults. International journal for equity in health. 2017;16(1):1–11.
10. Chen YC, Fan HY, Yang C, Lee YL. Early pubertal maturation and risk of childhood asthma: A Mendelian randomization and longitudinal study. Allergy. 2020;75(4):892–900.
11. Ahmad K, Kabir E, Ormsby GM, Khanam R. Are wheezing, asthma and eczema in children associated with mother's health during pregnancy? evidence from an Australian birth cohort. Arch Public Health. 2021;79(1):193.
12. Langridge AT, Glasson EJ, Nassar N, Jacoby P, Pennell C, Hagan R, Bourke J, Leonard H, Stanley FJ. Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability. PLoS ONE. 2013;8(1): e50963.
13. Williams K, Helmer M, Duncan G, Peat J, Mellis C. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales Australia. Child Care Health Dev. 2008;34(2):249–56.
14. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123(2):e273–83.
15. Lynch AM, Kashikar-Zuck S, Goldschneider KR, Jones BA. Psychosocial risks for disability in children with chronic back pain. J Pain. 2006;7(4):244–51.
16. Claessen H, Arndt V, Drath C, Brenner H. Overweight, obesity and risk of work disability: a cohort study of construction workers in Germany. Occup Environ Med. 2009;66(6):402–9.
17. Corona LP, Alexandre TD, Duarte YA, Lebrao ML. Abdominal obesity as a risk factor for disability in Brazilian older adults. Public Health Nutr. 2017;20(6):1046–53.
18. Zubrick S, Williams A, Silburn S, Vimpani G. Indicators of Social and Family Functioning. Canberra: Department of Family and Community Services; 2000.
19. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Andreias L, Wilson-Costello D, Klein N. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. JAMA. 2005;294(3):318–25.
20. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. J Autism Dev Disord. 2001;31(3):279–85.
21. Cutland CL, Lackritz EM, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, Nisar MI, Tapia MD, Pathirana J, Kochhar S. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48Part A):6492.
22. Ells LJ, Lang R, Shield JP, Wilkinson J, Lidstone J, Coulton S, Summerbell C. Obesity and disability–a short review. Obes Rev. 2006;7(4):341–5.
23. Krause S, Ware R, McPherson L, Lennox N, O'Callaghan M. Obesity in adolescents with intellectual disability: Prevalence and associated characteristics. Obes Res Clin Pract. 2016;10(5):520–30.
24. Lin JD, Yen CF, Li CW, Wu JL. Patterns of obesity among children and adolescents with intellectual disabilities in Taiwan. J Appl Res Intellect Disabil. 2005;18(2):123–9.

25. Keramat SA, Alam K, Sathi NJ, Gow J, Biddle SJH, Al-Hanawi MK. Self-reported disability and its association with obesity and physical activity in Australian adults: Results from a longitudinal study. SSM Popul Health. 2021;14: 100765.
26. Donini LM, Merola G, Poggiogalle E, Lubrano C, Gnessi L, Mariani S, Migliaccio S, Lenzi A. Disability, physical inactivity, and impaired health-related quality of life are not different in metabolically healthy vs. unhealthy obese subjects. Nutrients. 2016;8(12):759.
27. Clini E, Ambrosino N. Early physiotherapy in the respiratory intensive care unit. Respir Med. 2005;99(9):1096–104.
28. Barton SK, Tolcos M, Miller SL, Roehr CC, Schmolzer GM, Davis PG, Moss TJ, LaRosa DA, Hooper SB, Polglase GR. Unraveling the links between the initiation of ventilation and brain injury in preterm infants. Front Pediatr. 2015;3:97.
29. Balakrishnan A, Stephens BE, Burke RT, Yatchmink Y, Alksninis BL, Tucker R, Cavanaugh E, Collins AM, Vohr BR. Impact of very low birth weight infants on the family at 3 months corrected age. Early Hum Dev. 2011;87(1):31–5.
30. Claas MJ, de Vries LS, Koopman C, Uniken Venema MM, Eijsermans MJ, Bruinse HW, Verrijn Stuart AA. Postnatal growth of preterm born children </= 750g at birth. Early Hum Dev. 2011;87(7):495–507.
31. Heidari H, Hasanpour M, Fooladi M. The experiences of parents with infants in Neonatal Intensive Care Unit. Iran J Nurs Midwifery Res. 2013;18(3):208.
32. Bas AY, Okumus N, Demirel N, Zenciroglu A. Persistent pulmonary interstitial emphysema in a preterm infant. Indian Pediatr. 2008;45(9):775.
33. Mourani PM, Kinsella JP, Clermont G, Kong L, Perkins AM, Weissfeld L, Cutter G, Linde-Zwirble WT, Abman SH, Angus DC, et al. Intensive care unit readmission during childhood after preterm birth with respiratory failure. J Pediatr. 2014;164(4):749-755 e743.
34. Heuvelman H, Abel K, Wicks S, Gardner R, Johnstone E, Lee B, Magnusson C, Dalman C, Rai D. Gestational age at birth and risk of intellectual disability without a common genetic cause. Eur J Epidemiol. 2018;33(7):667–78.
35. Australian Health Ministers' Advisory Council. National Strategic Framework for Chronic Conditions. Canberra: Australian Government; 2017.
36. World Health Organization: World Report on Disability. Geneva: World Health Organization; 2011. Retrieved 2022 Jan 04 from https://www.who.int/publications/i/item/9789241564182.

Publisher's Note

6.2 Links and implications

This thesis paper found that the hazards of any medical condition or disability in children are significantly associated with the following infant or child health characteristics: birthweight, use of intensive care unit or ventilator during their neonatal age and obesity. The parametric panel regression model also suggests that children with low birthweight were 1.43 times more likely to have any medical condition or disability than children with normal birthweight. The time to event analyses also revealed that being recipient of after-birth emergencies significantly increased the likelihood of the incidence of a medical condition or disability among children. The study findings, therefore, suggest that infants with low birth weight, hospital emergency service use and children with obesity would benefit from additional health care monitoring to minimize the risk of any medical condition or disability of Australian children.

The first four papers of this thesis analyses the prevalence and risk factors of children's health, both in general and based on leading chronic diseases – wheezing, asthma and eczema; and survival analyses and risk factor assessments for long-term medical condition or disability. In the next two papers, this thesis performed investigation on the identification of clusters of vulnerable adolescents in relation to health morbidity or health-related behaviour or lifestyle characteristics. In Paper 5, this thesis implemented an unsupervised machine learning method known as latent class clustering to identify the vulnerable clusters of children aged 12-13 years who experience wheezing, asthma or eczema. Thus, through this study this thesis intended to get a better understanding on the characteristics of adolescents with respiratory or allergic morbidities.

CHAPTER 7: PAPER 5 - CLUSTERING OF ASTHMA AND RELATED COMORBIDITIES AND THEIR ASSOCIATION WITH MATERNAL HEALTH DURING PREGNANCY: EVIDENCE FROM AN AUSTRALIAN BIRTH COHORT

7.1 Introduction

This chapter presents the fifth paper of the thesis revealing the distinct clusters of children aged 12–13 years based on asthma and related comorbidities; determining health outcome differences among clusters; and investigating the associations between maternal health status during pregnancy and the distinct clusters of adolescents. This paper is the first study of this thesis conducted for understanding classifications of health morbidity or health-related characteristics and identifying vulnerable clusters in Australian adolescents. This cross-sectional study carried out the latent class analysis, an unsupervised machine learning technique, on 1,777 children aged 12-13 years who participated in both Health CheckPoint survey and Wave 7 of LSAC.

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RESEARCH Open Access

Clustering of asthma and related comorbidities and their association with maternal health during pregnancy: evidence from an Australian birth cohort

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Abstract

Background: The population-based classification of asthma severity is varied and needs further classification. This study identified clusters of asthma and related comorbidities of Australian children aged 12–13 years; determined health outcome differences among clusters; and investigated the associations between maternal asthma and other health conditions during pregnancy and the children's clustered groups.

Methods: Participants were 1777 children in the birth cohort of the Longitudinal Study of Australian Children (LSAC) who participated in the Health CheckPoint survey and the LSAC 7th Wave. A latent class analysis (LCA) was conducted to identify clusters of children afflicted with eight diseases, such as asthma (ever diagnosed or current), wheezing, eczema, sleep problem/snoring/breathing problem, general health status, having any health condition and food allergy. Multinomial logistic regression was used to investigate the association between maternal asthma or other health conditions and LCA clusters.

Results: The study identified four clusters: (i) had asthma – currently healthy (11.0%), (ii) never asthmatic & healthy (64.9%), (iii) early-onset asthmatic or allergic (10.7%), and (iv) asthmatic unhealthy (13.4%). The asthmatic unhealthy cluster was in poor health in terms of health-related quality of life, general wellbeing and lung functions compared to other clusters. Children whose mothers had asthma during pregnancy were 3.31 times (OR 3.31, 95% CI: 2.06–5.30) more likely to be in the *asthmatic unhealthy* cluster than children whose mothers were non-asthmatic during pregnancy.

Conclusion: Using LCA analysis, this study improved a classification strategy for children with asthma and related morbidities to identify the most vulnerable groups within a population-based sample.

Keywords: Latent class analysis, Cluster analysis, Asthma, Asthma related comorbidities, Paediatric quality of life, General well-being, Spirometry

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Background

Asthma, a chronic respiratory disease, poses a significant global health burden, particularly in developed countries [1]. This heterogeneous respiratory disorder is comprised of differing characteristics and phenotypes [1]. Globally, there were more than 262 million people affected by asthma in 2019 and caused 461,000 deaths [2]. The 2020 Australian health study revealed that around 11% of the Australian population (2.7 million) had asthma in 2017–18; during that time there were 38,792 hospitalizations for asthma, 80% of which were preventable [3]. The 2018 Australian health report mentioned that, as per Australian Burden of Disease Study, asthma is the leading cause of burden among children aged 5–14 years [4]. A longitudinal study from the birth cohort of 2004, conducted in 2015, found that 16.9% of Australian children experienced wheezing or asthma within the first 3 years of life [5]. Asthma is more prevalent chronic disease among children and young adults than adults, particularly because of its early onset [6] and diverse symptoms accompanied by other comorbidities - wheezing, atopic allergy, food allergy or poor health [7].

Current descriptions of asthma phenotypes and its classifications have been identified but have not considered several other domains of comorbidities, such as eczema, snoring/breathing problems or food allergies, related with asthma [8, 9] Inclusion of these related diseases with asthma and the use of a classification system may provide a framework to identify distinct asthma phenotypes and a better understanding of its aetiology.

Currently, the literature describes diverse classifications of the cluster analysis of asthma phenotypes. An UK study identified the clusters according to varying combinations of wheezing disorders, atopic allergies, and impaired lung functions with high or low severity of asthma [8]. In the USA, Moore et al. (2010) identified clusters within the Severe Asthma Research Program cohort based on distinct clinical phenotypes using unsupervised hierarchical cluster analysis. However, they also acknowledged the need for an improved classification of asthma morbidities [10]. Similarly, in an European study, Siroux et al. (2011) proposed latent class analysis (LCA) to improve asthma morbidities classification utilizing multiple aspects of the disease in adults who participated in an epidemiological study [11]. The findings revealed different homogeneous groups with severe and mild asthma whose different phenotypes, allowed them to differentiate the quality of life and associated risk factors [11]. A New Zealand study (Wellington Respiratory Survey) assessed clinical airway diseases and found varying aspects of asthma and related comorbidities in five distinct clusters of the population [12]. Many of these asthma clustering studies were conducted outside of Australia, and few studies have used a model-based cluster analysis of asthma and related comorbidities using a nationally representative sample.

Epidemiological studies suggest that certain health conditions such as having asthma or being overweight during pregnancy, are associated with childhood asthma [13–17]. However, many LCAs or cluster analyses on asthma comorbidities in children lack an investigation of the foetal origins of the children's cluster memberships [8, 10]. Furthermore, adolescence is a crucial phase in the life cycle [18] and a critical entry point for young people approaching adulthood [19].

Thus, the primary purpose of this study was to identify clusters of asthma and related comorbidities (wheezing, eczema and others) among Australian adolescent children (12/13 years of age in 2016) from the birth cohort of LSAC study recruited in 2004–2005. Secondly, the objective was to identify each cluster's characteristics and determine their differences as measured by spirometry tests, paediatric quality of life (PedsQL), and general wellbeing, in order to identify the most vulnerable cluster. Lastly, the study aimed to investigate potential associations between maternal health status during pregnancy and the health outcomes among the clusters of adolescents.

Methods

Setting and data

The study participants were 1777 Australian children aged 12–13 years, who participated in both the Health CheckPoint (HCP) survey and the 7th Wave of LSAC, conducted between 2015 and 2016. The LSAC is a prospective, nationally representative longitudinal household survey gathering data on a wide range of factors that influence child development. The LSAC commenced in 2004 and collects data every 2 years. The HCP survey was a special health assessment offered to the children in LSAC between Waves 6 and 7, in 2015. It assessed several health measurements and bio-specimens, including respiratory measurements. Details of the study designs and recruitment processes for the LSAC and HCP surveys are provided elsewhere [20–22]. This study performed the Latent Class Analysis (LCA) on the selected 1777 children to identify clusters of children afflicted with asthma and related comorbidities. The PedsQL and wellbeing scores were available for 1726–1757 children. The four lung function measures were available for 1319–1321 children, excluding the respective measures' missing values (Fig. 1). Comparison of the clusters' health outcomes were performed based on the available children's data of the respective measures.

Latent class analysis variables

The LCA was conducted using asthma and other diseases or symptoms linked with asthma taken from the 7th Wave of LSAC survey. The morbidity variables were

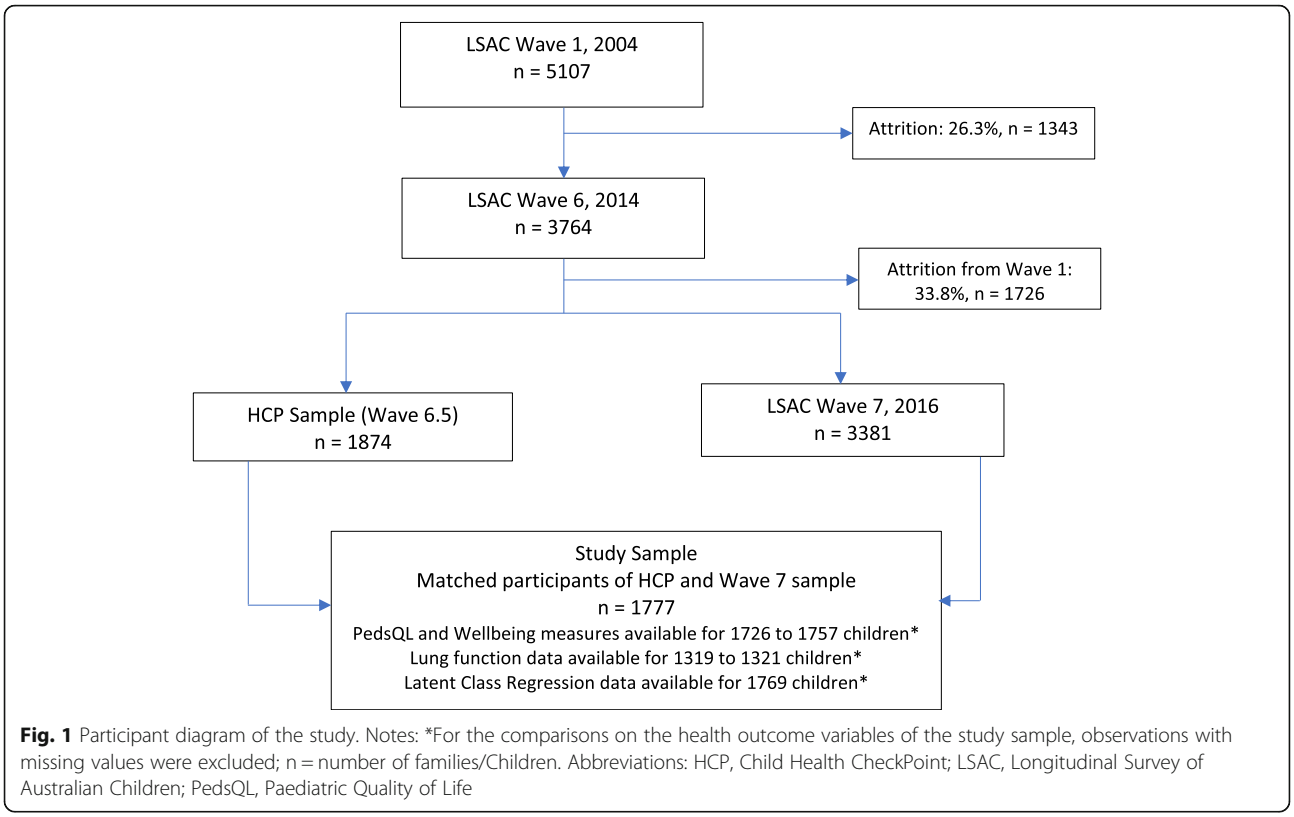

Fig. 1 Participant diagram of the study. Notes: *For the comparisons on the health outcome variables of the study sample, observations with missing values were excluded; n = number of families/Children. Abbreviations: HCP, Child Health CheckPoint; LSAC, Longitudinal Survey of Australian Children; PedsQL, Paediatric Quality of Life

asthma (ever diagnosed or current), wheezing, eczema, sleep problem/snoring/breathing problem, general health status, having any health condition and food allergy.

Health outcome variables

Three groups of health outcome indicators related to asthma and its comorbidities were used in this study: health-related quality of life, general wellbeing, and lung function.

Health-Related Quality of Life

PedsQL 4.0 Generic Core Scales, an integral part of LSAC and HCP surveys, are reliable and responsive measures of the health outcomes of both healthy children and children suffering from asthma-related comorbidities [23]. Each child in the study completed a health-related, 23-item questionnaire comprising the following subscales: (i) general health subscale, (ii) general wellbeing subscale, (iii) physical functioning subscale, (iv) emotional functioning subscale, (v) school functioning subscale, and (vi) social functioning subscale [23]. The summary scores of the physical and psychosocial health scales and the total score were calculated from these subscales; a higher value indicates better health. To calculate the scale scores, the mean was computed as the sum of the items over the number of items answered. Details of the procedure are described elsewhere [22, 23].

General wellbeing

These wellbeing variables were generated by taking the participants' responses to a six-item questionnaire, taken from two psychometric subscales used in the International Survey of Children's Well-being (ISCW). These questions were designed to measure children's satisfaction with their life as a whole and their satisfaction relating to their family life, friends, school experience, where they live, and their own body, measured on a scale from 0 (not satisfied at all) to 10 (fully satisfied). Then, the five-item Brief Multi-Dimensional Students' Life Satisfaction Scale (BMSLSS) and single-item Overall Life Satisfaction scale (OLS) were created after converting the total scores into a 100 scale. Details of the process are described in Seligson et al. and health checkpoint data user guide [24, 25].

Lung function measures

Spirometry tests to measure the lung function of the children were conducted during the HCP survey. Details of the procedures and steps of these measurements are described by Welsh et al. [26]. The pre-bronchodilator spirometry data were converted to z-scores using the Global Lung Initiative's 2012 reference eq. [25]. This study included the following lung function measures of the children aged 11–12 years from the HCP survey: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and mid-expiratory flow (MEF) -

which is forced expiratory flow between 25 and 75% of FVC (FEF 25–75%), and their z-scores. These variables were used to compare lung function variations among the clusters, as previous studies have shown that lung function varies with asthma-related morbidities [27].

Variables of regression analysis

In the regression analysis, this study used maternal health conditions during pregnancy: (i) asthma, (ii) smoking, (iii) obesity status, (iv) having any medical conditions, and two birth related variables: (i) gestational age, and (ii) birth weight of children as the independent variables. The children's cluster is the dependent variable that has four categories, namely, had asthma- currently healthy, never asthmatic & healthy, early-onset- asthma/allergic, and asthmatic unhealthy. These four categories were developed based on asthma and related comorbidities of children using latent class clustering procedure. The mothers' socio-economic status and child-related other variables are used as control variables to adjust the regression model.

Statistical analysis

An LCA was performed to classify 1777 children according to the incidence of asthma and other comorbidities. The analysis aimed to identify groups (classes) of 'similar' children using a model-based approach considering the distribution of these comorbidities. The LCA classified the children according to the probabilities of the observed values of all the variables listed in Table 1 for each of the children. We used STATA (version 15.0) to run intercept-only models and to fit the logistic regression models for all the selected cluster variables.

The goal of LCA was to select a final LCA model that maximized the log-likelihood and minimized the Bayesian Information Criterion (BIC), Akaike's Information Criterion (AIC) and the likelihood ratio function L^2 (deviance statistics). During the analyses, we estimated the model for one to seven latent clusters to obtain the best classification. For each number of clusters, the model was repeated 100 times so that the parameter estimates corresponding to the model could produce the greatest log-likelihood. Sensitivity of clusters/groups was also tested by observing changes of pattern of clusters due to inclusion/exclusion of related variables from the analysis. The optimal number of clusters was determined based on a combination of the log-likelihood, BIC, AIC and the likelihood function (L^2, the likelihood-ratio/deviance statistics) for achieving the optimal model.

The information criteria values, shown in Table 1, suggested a four-cluster solution based on Akaike's Information Criterion (AIC) and a two-cluster model based on Bayes' Information Criterion (BIC). However, 83.9% reduction in L^2 from one class (H_0) to four class suggests that four-cluster model is beneficial. In the five or six cluster models, L^2 reduced by only a further 1.3% or less, hence not so beneficial. On the basis of these results, and the characteristics and size of the clusters, the four-cluster solution was selected as optimal.

Frequency analysis was used to describe the characteristics of children included and excluded from the study. Furthermore, after defining the clusters, cluster-based mean comparison analyses and significance tests of the PedsQL scores, wellbeing scores and spirometry measures were performed. All these statistical measures were weighted to represent the population of Australian children. Subsequently, multinomial logistic regression analysis was conducted to investigate the associations between maternal health-related risk factors and the cluster groups. The regression model was adjusted with control variables and the *never asthmatic & healthy* cluster was considered the reference cluster.

Results

Sample characteristics

The percentage distributions of the basic characteristics of the included and excluded LSAC participants of this study in the baseline wave are shown in Table 2. The excluded children were those who could not participate in the 7th wave and in the HCP survey. Among the included children, 50.9% were male, 5.8% weighed less than 2500 g at birth, 62.1% had a normal birth, 8.1% were not immunized completely and 43.9% were not

Table 1 Goodness of fit statistics for cluster models

Model	LL	BIC	AIC	Npar	L^2	% reduction in L^2	residual df	*p*-value
One class (H_0)	− 4698.805	9464.953	9415.609	9	1330.987		502	0.000
Two class	− 4175.756	8493.682	8389.511	19	284.889	78.6	492	1.000
Three class	− 4154.712	8511.456	8363.423	27	242.802	81.8	484	1.000
Four class	− 4140.697	8550.771	8353.394	36	214.772	83.9	475	1.000
Five class	−4140.679	8625.561	8373.358	46	214.736	83.9	465	1.000
Six class	− 4131.795	8637.725	8363.591	50	196.969	85.2	461	1.000
Seven class	− 4135.595	8660.289	8375.189	52	204.568	84.6	459	1.000

Abbreviations: *AIC* Akaike's Information Criterion, *BIC* Bayesian Information Criterion, *df* degrees of freedom, *Npar* Number of parameters, *LL* log-likelihood, L^2 likelihood-ratio

Table 2 Baseline characteristics of the excluded and included children

Characteristics		Children excluded *n* = 3330 n (%)	Children included *n* = 1777 n (%)
Sex of the study child (1 = male)		1706 (51.2)	904 (50.9)
Birth Weight < 2500 g (yes = 1)		185 (5.6)	103 (5.8)
Gestational age < 37 weeks (yes = 1)		231 (6.9)	119 (6.7)
Breastfed less than 6 months (yes = 1)		1394 (41.9)	779 (43.9)
Type of birth – Normal (Yes = 1)		2132 (64.0)	1103 (62.1)
Type of birth – Caesarean (Yes = 1)		977 (29.3)	542 (30.5)
Immunization not completed (yes = 1)		330 (9.9)	144 (8.1)
Is English spoken at home? (yes = 1)		2845 (85.5)	1612 (90.8)
Is the child Indigenous? (yes = 1)		209 (6.3)	38 (2.1)
Educational Qualification of Mother:			
Year 12 or equivalent (Yes = 1)		1667 (50.1)	1248 (70.2)
University education	Graduate/diploma	904 (27.2)	748 (42.1)
	Post-graduate	161 (4.8)	167 (9.4)
Remoteness of Area	Metropolitan cities	2244 (67.4)	1298 (73.1)
	Inner cities	620 (18.6)	290 (16.3)
	Outer region/ Remote areas	466 (14.0)	189 (10.6)

breastfed until 6 months of age. Over one-fourth of the children (28.7%) had been diagnosed with asthma during their lives, and 13.4% were currently suffering from asthma and taking medication. Around one in every ten children had ongoing eczema or wheezing. Only 5.4% mentioned sleeping problems due to snoring or breathing problems.

Latent class identification

In the latent class cluster analyses, we found that the optimal solution was four clusters (AIC value: 8353.394, BIC value: 8550.771, log-likelihood ratio: 214.772). These clusters were identified as follows: (i) had asthma – currently healthy, (ii) never asthmatic & healthy, (iii) early-onset asthmatic or allergic, and (iv) asthmatic unhealthy. Table 3 shows the prevalence of comorbidities for all the study children and by cluster. Table 4 shows the mean comparisons of the quality of life, wellbeing, and the lung functions among children by cluster.

Cluster 1: had asthma – currently healthy

This group consisted of children who suffered from early childhood asthma but currently had no asthma and accounted for 11.0% of the participants. Within the

Table 3 Prevalence of asthma and related morbidities by clusters (*n* = 1777)

Asthma and related morbidity criteria of the study child		All Sample (*n* = 1777) n (%)	Cluster 1 (*n* = 195, 11.0%) Had asthma-currently healthy n (%)	Cluster 2 (*n* = 1154, 64.9%) Never asthmatic & healthy n (%)	Cluster 3 (*n* = 190, 10.7%) Early-onset-asthma/allergic n (%)	Cluster 4 (*n* = 238, 13.4%) Asthmatic unhealthy n (%)
Ever diagnosed with asthma	Yes	510 (28.7)	195 (100)	0 (100)	77 (40.5)	238 (100)
Currently suffering from Asthma	Yes	238 (13.4)	0 (100)	0 (100)	0 (100)	238 (100)
Has illness with wheezing	Yes	155 (8.7)	0 (100)	33 (2.9)	30 (15.8)	92 (38.7)
Has ongoing eczema	Yes	169 (9.5)	16 (8.2)	56 (4.9)	42 (22.1)	55 (23.1)
Diagnosed with sleep problem related with snoring/breathing problem	Yes	96 (5.4)	0 (100)	30 (2.6)	40 (21.1)	26 (10.9)
Reported as not having excellent/very good Health	Yes	198 (11.1)	0 (100)	82 (7.1)	66 (34.7)	50 (21.0)
Has reported at least one health condition	Yes	68 (3.8)	0 (100)	23 (2.0)	25 (13.2)	20 (8.4)
Has food allergy	Yes	155 (8.7)	0 (100)	0 (100)	114 (60.0)	41 (17.2)

Table 4 Average scores of PedsQL, well-being and lung function measures by the cluster group of the children

PedsQL, Well-being and Lung Function Measures	Total Sample		Cluster 1		Cluster 2		Cluster 3	Cluster 4			*p*-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
A. Paediatric Quality of Life Inventory											
Inventory physical health summary	1750	83.1 (13.6)	192	84.5 (12.3)	1141	84.0 (13.0)	181	81.5 (13.6)	236	79.4 (16.4)	**< 0.001**
Inventory psychosocial health summary	1750	75.8 (14.6)	191	77.4 (14.7)	1141	76.7 (14.0)	182	72.1 (15.2)	236	73.1 (15.9)	**< 0.001**
Inventory total score	1751	78.4 (13.0)	192	79.9 (13.1)	1141	79.3 (12.6)	182	75.4 (13.3)	236	75.3 (14.2)	**< 0.001**
B. International Survey of Children's Well-being											
Brief Multi-dimensional Students' Life Satisfaction Scale	1750	82.8 (13.8)	190	85.0 (13.4)	1143	83.0 (13.7)	182	81.0 (14.2)	235	81.5 (14.5)	**0.014**
Overall Life Satisfaction	1745	80.6 (18.5)	190	84.3 (17.7)	1137	81.0 (18.1)	183	78.7 (17.7)	235	77.5 (21.2)	**< 0.001**
C. Lung Function Measures											
Raw											
FEV_1 (L)	1321	2.54 (0.42)	147	2.54 (0.40)	858	2.57 (0.41)	134	2.51 (0.42)	182	2.46 (0.42)	**0.016**
FVC (L)	1321	2.99 (0.51)	147	3.03 (0.51)	858	2.99 (0.51)	134	2.95 (0.51)	182	2.96 (0.50)	0.493
FEV_1/FVC ratio	1319	0.88 (0.02)	147	0.87 (0.01)	857	0.88 (0.02)	133	0.88 (0.02)	182	0.88 (0.02)	**0.032**
MEF (FEF 25–75%)	1319	2.90 (0.29)	147	2.90 (0.30)	857	2.92 (0.29)	133	2.88 (0.29)	182	2.86 (0.30)	0.132
Z-Scores											
FEV_1 (L)	1319	0.53 (0.99)	147	0.45 (0.97)	857	0.60 (0.97)	133	0.52 (1.00)	182	0.31 (1.08)	**0.002**
FVC (L)	1319	0.83 (1.10)	147	0.84 (1.13)	857	0.83 (1.10)	133	0.82 (1.05)	182	0.81 (1.17)	0.991
FEV_1/FVC ratio	1319	−0.39 (1.10)	147	−0.57 (1.00)	857	−0.29 (1.10)	133	−0.41 (1.08)	182	−0.71 (1.15)	**< 0.001**
MEF (FEF 25–75%)	1319	−0.06 (1.06)	147	−0.28 (0.94)	857	0.05 (1.03)	133	−0.13 (1.13)	182	−0.37 (1.15)	**< 0.001**

Note: One way ANOVA mean comparison tests were performed to define the significance of the mean differences across the clusters; *Abbreviations*: *FEF* forced expiratory flow, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *MEF* mid expiratory flow (FEF25–75%)

cluster, only 8.2% of the children had ongoing eczema. No children in this group reported suffering from any other comorbidities. The mean PedsQL scores of children in this cluster on the physical, psychosocial summary and total inventory were 84.5, 77.4 and 79.9, respectively. All these scores were very close to the scores of the *never asthmatic & healthy* cluster (Table 4). The average values of the lung function measures (FEV, FVC, FEV1/FVC ratio, MEF and their z-scores) among the children of this cluster were slightly higher than the *asthmatic unhealthy* cluster (Table 4).

Cluster 2: never asthmatic & healthy

The *never asthmatic & healthy* cluster, the largest group of the children (64.9%), reported no incidence of asthma in their childhood or at present. Less than 5% of children within this cluster experienced wheezing, eczema, sleeping problems or reported at least one health condition; none suffered from a food allergy. Furthermore, only 7.1% of this group reported poor health. The average physical (84.0), psychosocial (76.7), and summary (79.3) PedsQL scores were higher than the early-onset asthmatic or allergic and asthmatic unhealthy clusters. The average scores of the lung functions measure (2.57, 2.99, 0.88 and 2.92 for FEV, FVC, FEV1/FVC ratio and MEF respectively) were also higher in this cluster compared to the early-onset asthmatic or allergic and asthmatic unhealthy clusters. Given that none of the children of this group ever had asthma or any ongoing condition associated with asthma, this was the healthiest cluster with respect to asthma, its related comorbidities, and the health outcome measures.

Cluster 3: early-onset asthmatic or allergic

The *early-onset-asthmatic/allergic* cluster, comprising 10.7% of children, were suffering from multiple morbidities. Approximately 40% of this cluster were diagnosed with asthma in their early childhood, 15.8% were currently suffering from wheezing and 22.1% reported ongoing eczema. This group performed worse than the never asthmatic & healthy cluster with respect to PedsQL measures related to physical health. For inventory physical health summary, inventory psychosocial health summary and inventory total score, this cluster's average scores were 81.5, 72.1 and 75.4, respectively, while the never asthmatic & healthy cluster's scores were 84.0, 76.7 and 79.3 respectively (Table 4). The brief multi-dimensional student's life satisfaction scale and overall life satisfaction of never asthmatic & healthy cluster were 83.0 and 81.0 which is better than early-

onset-asthmatic/allergic cluster. The lung function average scores (FEV_1, FVC, FEV_1/FVC ratio, MEF and their z-scores) of this cluster were lower than those of the never asthmatic & healthy cluster (Table 4).

Cluster 4: asthmatic unhealthy

Among the sample, 13.4% of children were classified as being in the asthmatic unhealthy cluster. Every child in this cluster was currently taking medication for asthma and all were diagnosed with asthma in their early childhood. Moreover, 38.7% had an illness with wheezing, just over one in five had either atopic eczema or reported not having excellent or very good health, and more than one in ten of them reported a sleeping disorder due to breathing or snoring problems. The average physical (79.4) and psychosocial (73.1) summary scores and the inventory total score (75.3) of this group were lower than the had asthma – currently healthy and never asthmatic & healthy groups. However, these scores were very close to the average scores of the children of the early-onset asthmatic or allergic cluster (Table 4). The average lung function values (2.46, 2.96, 0.88 and 2.86 for FEV_1, FVC, FEV_1/FVC ratio and MEF, respectively) of this cluster were lower than those of all other clusters (Table 4).

Lung functions

The distributions of the four different lung function measures (z-score of FEV, FVC, FEV1/FVC ratio and MEF) for the children of the full sample and each of the clusters are shown in Fig. 2. The asthmatic unhealthy cluster, followed by the early-onset asthmatic or allergic cluster, shows lower peaks compared to the never asthmatic & healthy cluster; all are fairly normally distributed. Figure 3 shows the LOWESS curve of all lung function measures segregated by sex against the children's height for each of the clusters. These visual graphs clearly show that children in the asthmatic unhealthy cluster had lower spirometry results compared to all other clusters. In all clusters, shorter children had poorer lung function. In addition, the section C of Table 4 shows the mean, standard deviation (SD) and z-scores of FEV_1, FVC, FEV_1/FVC ratio and MEF measures among children by cluster.

Table 5 shows the prevalence of lung function impairments. The prevalence of decreased ventilator capacity (FEV_1 less than the lower limit of normal (LLN)) was found among 8.86 and 5.25% of children in the asthmatic unhealthy (cluster 4) and had asthma – currently healthy (cluster 1) clusters, respectively. These values were 6.14 and 2.53 percentage points higher than those

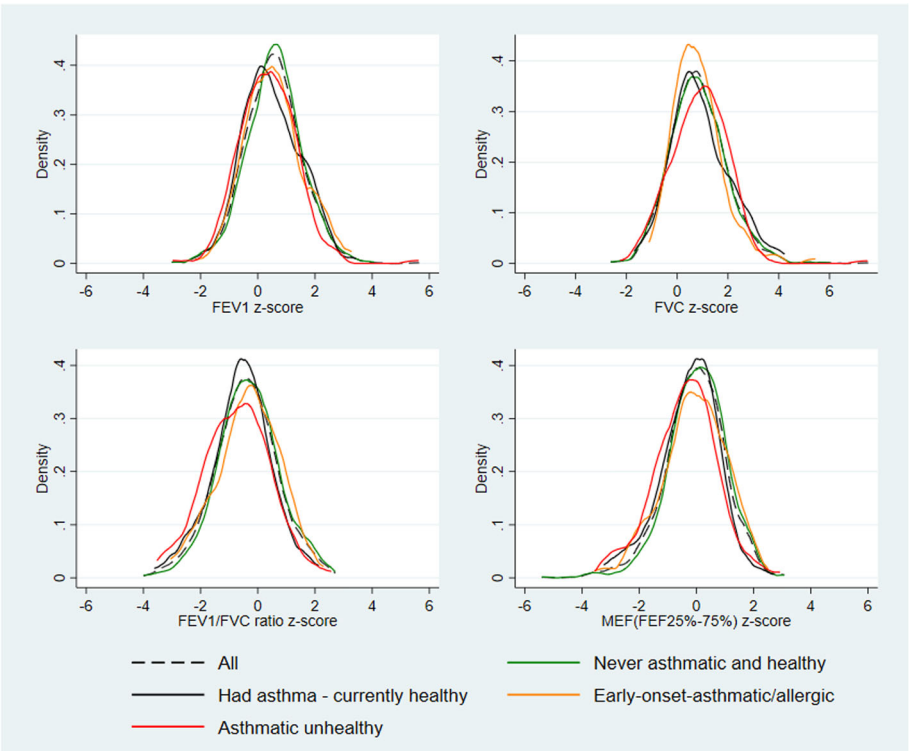

Fig. 2 Lung function distribution and density plots for children by clusters. Abbreviations: FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow (FEF25–75%)

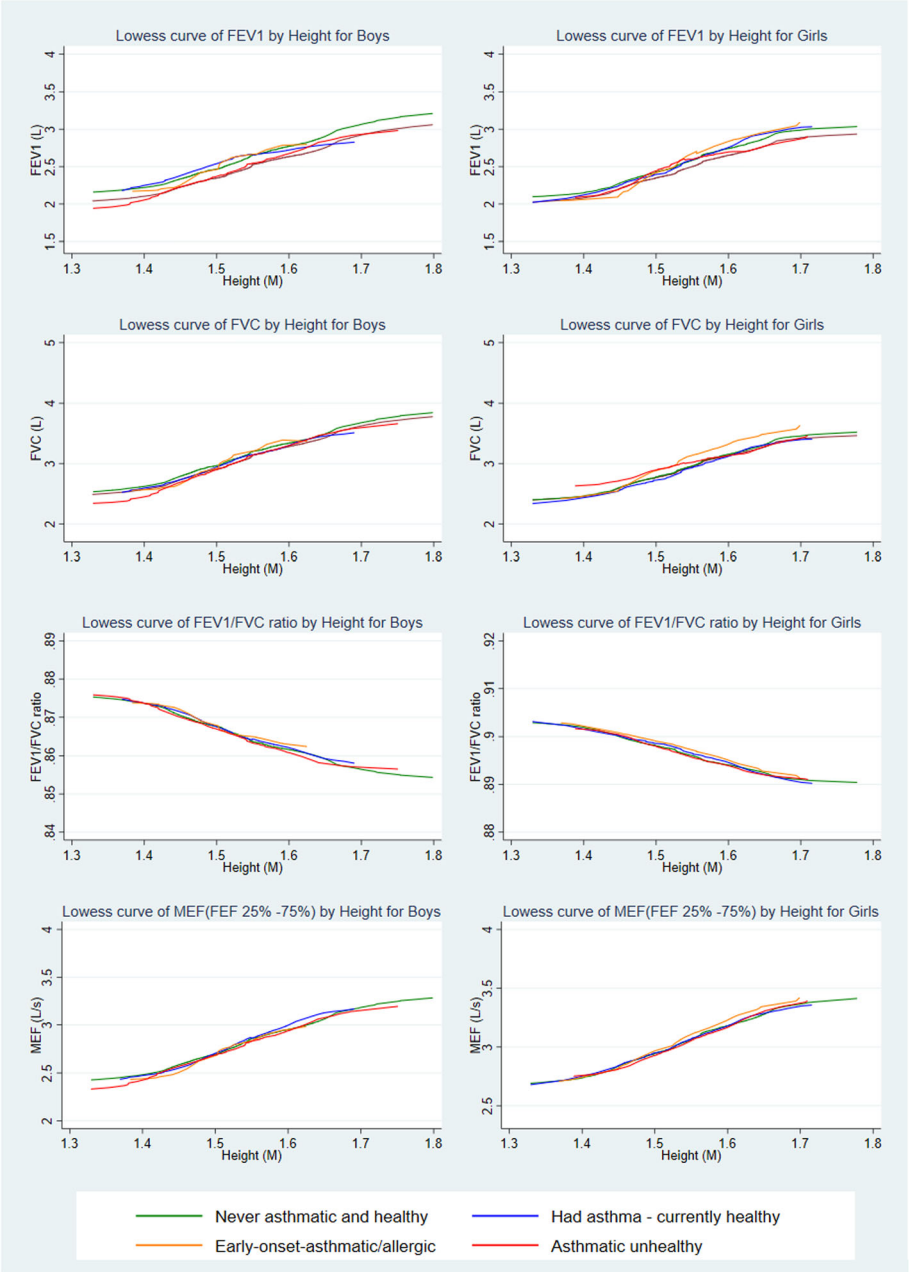

Fig. 3 Lowess curve against height for the lung function of boys and girls by clusters. Abbreviations: FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow (FEF 25–75%)

of the never asthmatic & healthy cluster (cluster 2). Similarly, more children in the asthmatic unhealthy cluster were in the critical zones (LLN < -2 z-value or LLN < 1.645 z-value) of FEV_1 compared to other clusters (Table 5).

The prevalence of possible restrictive patterns (FVC < LLN) was negligible among the children across all the clusters. Airway obstruction was not present among the children of all clusters when we considered 80% of the predicted value for the FEV_1/FVC ratio to be the lower limit of normal. However, obstruction was present among the children across the clusters if we considered the z-score of − 2 for the FEV_1/FVC ratio to be the lower limit of normal. Then, the highest prevalence (21.65%) was observed among the children of the asthmatic unhealthy cluster and the lowest (10.19%) was in the never asthmatic & healthy cluster (Table 5).

The lack of flow rate results between 25 and 75% vital capacity (MEF < LLN L/s) indicated small airway impairment among the children in all the clusters. The lowest

Table 5 Prevalence of decreased ventilator capacity, possible restrictive pattern, and obstruction as per the raw measures and Z-score (for both 2.5th and 5th percentile limit) of Health CheckPoint Survey, stratified by cluster and sex (in percent within the cluster)

	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
	All (%)	Male (%)	Female(%)	All (%)	Male (%)	Female(%)	All (%)	Male (%)	Female(%)	All (%)	Male (%)	Female(%)
Raw												
Decreased ventilator capacity FEV_1 (L) < LLN (L)	5.25	8.30	0.83	2.72	2.25	3.17	3.51	3.96	3.03	8.86	12.36	4.65
Possible restrictive pattern FVC (L) < LLN(L)	1.24	1.33	1.11	1.22	1.19	1.25	1.90	0	3.93	1.21	1.84	0.46
Obstruction FEV_1/FVC ratio < LLN (80%)	0	0	0	0	0	0	0	0	0	0	0	0
Small Airway Impairment MEF (FEF 25–75%) < LLN (L/s)	18.65	21.14	15.04	11.46	11.32	11.60	14.84	10.94	19.03	26.10	32.16	18.80
Z-score												
LLN for 2.5th percentile												
FEV_1 < -2 z score	4.93	7.75	0.83	0.67	0.64	0.70	1.28	2.48	0	5.08	8.79	0.61
FVC < −2 z score	0.45	0	1.11	0.35	0.28	0.43	1.07	0	2.21	1.01	1.84	0
FEV_1/FVC ratio < −2 z score	16.95	19.79	12.83	10.19	10.18	10.20	10.57	11.72	9.33	21.65	27.32	14.81
MEF (FEF 25–75%) < − 2 z score	12.00	14.68	8.12	6.32	6.03	6.59	10.32	9.30	11.41	18.62	24.05	12.08
LLN for 5th percentile												
FEV_1 < -1.645 z score	5.25	8.30	0.83	2.72	2.25	3.17	3.51	3.96	3.03	8.86	12.36	4.65
FVC < −1.645 z score	1.24	1.33	1.11	1.22	1.19	1.25	1.90	0	3.93	1.21	1.84	0.46
FEV_1/FVC ratio < −1.645 z score	22.34	24.27	19.55	17.63	17.38	17.87	18.24	16.63	19.96	33.57	38.35	27.81
MEF (FEF 25–75%) < − 1.645 z score	18.65	21.14	15.04	11.46	11.32	11.60	14.84	10.94	19.03	26.10	32.16	18.80

Abbreviations: *FEF* forced expiratory flow, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *MEF* mid expiratory flow (FEF25–75%), *LLN* lower limit to normal

prevalence (11.46%) was among the children of the never asthmatic & healthy cluster and the highest (26.10%) was among the children of the asthmatic unhealthy cluster. However, a lower prevalence was observed if an MEF z-score of − 2 (2.5th percentile) was considered to be the lower limit of normal. Then, the impairment ranged from 6.32 to 18.62% among the clusters.

Regression results

Results from a multinomial regression analysis revealed that children from mothers who experienced asthma during their pregnancy were 3.31 times (OR 3.31, 95% CI: 2.07–5.30) more likely to fall into the asthmatic unhealthy cluster, compared to the children of the never asthmatic & healthy cluster (Table 6). The study also found that if the mothers had any of the medical conditions diagnosed during the year of childbirth, their children were 1.72 times (OR: 1.72, 95% CI: 1.23–2.42) more likely to belong to the asthmatic unhealthy group. The findings also confirmed that the children from mothers who had asthma during pregnancy were 2.5 times (OR: 2.50, 95% CI: 1.42–4.39) more likely to experience early childhood asthma, though they might have been cured before the age of 12–13 years, compared to the children from mothers who did not have asthma during pregnancy.

Discussion

This study investigated a birth cohort of Australian children ($n = 1777$) aged 12–13 years and applied LCA to identify four statistically distinct clusters based on the prevalence of asthma and related comorbidities. The four clusters were defined as (i) had asthma – currently healthy, (ii) never asthmatic & healthy, (iii) early-onset asthmatic or allergic, and (iv) asthmatic unhealthy. The clusters' characteristics were described and compared based on the specific health outcomes as measured by spirometry, PedsQL and general wellbeing. Findings of the regression modelling revealed that children whose mothers had asthma during pregnancy were more likely to be in the asthmatic unhealthy cluster than children of non-asthmatic mothers.

This study found that the mean scores of the FEV1, FVC, and MEF measures of the children of the never

Table 6 Multinomial logistic regression of class memberships on covariates of health risk exposures of mothers during pregnancy or in the year of childbirth[a]

health risk exposures of mothers	Had asthma – currently healthy		Early-onset-asthmatic/allergic		Asthmatic unhealthy	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Mother had asthma during pregnancy						
No (ref.)						
Yes	**2.50 (1.42–4.39)**	**0.002**	1.7 (0.91–3.18)	0.093	**3.31 (2.07–5.30)**	**< 0.001**
Had any medical condition in the year of childbirth						
No (ref.)						
Yes	1.03 (0.69–1.54)	0.872	1.23 (0.84–1.8)	0.297	**1.72 (1.23–2.42)**	**0.002**
General health status of mother						
Excellent/Very good health (ref.)						
Good health	0.93 (0.63–1.38)	0.73	1.45 (1–2.09)	0.051	1.26 (0.88–1.8)	0.208
Fair/Poor health	1.53 (0.81–2.89)	0.190	1.22 (0.63–2.36)	0.561	1.7 (0.96–3.01)	0.069
Obesity status of mothers before pregnancy						
Healthy weight (ref.)						
Underweight	0.91 (0.5–1.65)	0.750	1.21 (0.69–2.12)	0.495	0.96 (0.55–1.69)	0.885
Overweight	1.41 (0.94–2.1)	0.094	1.09 (0.72–1.66)	0.688	1.23 (0.83–1.81)	0.301
Obese	1.1 (0.66–1.82)	0.724	1.07 (0.65–1.75)	0.803	1.19 (0.75–1.89)	0.462
Birth Weight of children						
Healthy weight (ref.)						
Low birth weight (< 2500 g)	1.42 (0.61–3.3)	0.410	0.86 (0.34–2.19)	0.754	1.91 (0.87–4.18)	0.106
High birth weight (> = 4000 g)	1.41 (0.92–2.16)	0.110	1.23 (0.79–1.94)	0.361	0.87 (0.55–1.38)	0.553
Gestational Age of birth						
On time birth (ref.)						
Pre-term birth (< 37 weeks)	1.22 (0.56–2.65)	0.613	1.29 (0.58–2.87)	0.534	0.87 (0.4–1.88)	0.715
Late birth (> = 42 weeks)	0.73 (0.3–1.77)	0.493	1.07 (0.5–2.27)	0.859	1.34 (0.69–2.59)	0.385
Frequency of smoking in 1st Trimester						
No smoking (ref.)						
Occasional / < 10 cigarettes per day	0.35 (0.14–0.93)	0.035	0.87 (0.44–1.72)	0.699	1.28 (0.72–2.27)	0.403
10+ cigarettes per day	1.04 (0.43–2.57)	0.924	1.33 (0.58–3.04)	0.496	1.34 (0.63–2.86)	0.449

[a]*Note*: The Multinomial logistic regression model has been constructed using *never asthmatic & healthy cluster* as reference category. Further, for each of the independent variables, the reference category (ref.) has been mentioned at the beginning of the categorical values. The regression model has been controlled with mothers' other health related and socio-economic variables listed as follows: breastfeeding, type of birth delivery, immunisation status of children, gender of the child, education and marital status of mother, family income, language spoken at home and remoteness of the residence

asthmatic & healthy cluster were higher than the values of the healthy reference population of Hibbert et al. [28]. This study also found that most of these values for the asthmatic unhealthy cluster children were lower than the values of the healthy reference population of Hibbert et al. [28]. These study findings support the earlier literature's assessment that clinical asthma is correlated with lower airway function, with variations depending upon the severity of the asthma [27].

One-fifth of the asthmatic cluster children showed signs of airway obstruction when an FEV1/FVC z-score < – 2 was considered. This measure indicates airway size relative to lung volume, which was lower among asthmatic unhealthy children [26]. This measure may indicate the risk of several health issues among the children of this group, including dysanaptic lung growth and airway obstruction [26, 29, 30]. However, this ratio may be lower in a portion of the children due to differences in measurement technique and equipment or the influence of gender-specific pubertal status [26].

The lack of performance in the measures of mid-expiratory flow (MEF, FEF 25–75% < LLN L/s) revealed a common prevalence of small airway impairment among the children of all four clusters to varying extents. The highest prevalence of this small airway impairment was observed in the asthmatic unhealthy cluster, where 1 in 4 children were affected. A study undertaken by Marseglia et al. revealed that small airway

impairment or disease was present among subjects who were affected with early allergic or inflammatory symptoms with allergic disease and no asthma [31]. A portion of children from all the clusters of this study population were affected by small airway disease, perhaps due to atopic allergy or food allergy across all the clusters. A Western Australian study by Palmer et al. [32] also found that the presence of asthma lowered spirometry performance. Xu et al. revealed significant impairment of lung function in the families of both children with asthma and healthy non-asthmatic children [33]. The predominance of obstruction, decreased ventilator capacity and possible restrictive pattern in the *asthmatic unhealthy* cluster revealed by the four measures of pulmonary functions support the findings of Palmer et al., Xu et al. and Weatherall et al. [12, 32, 33].

Our regression analyses showed that 'membership' in the *asthmatic unhealthy* group was significantly associated with the incidence of maternal asthma during pregnancy. These findings are consistent with previous research that found that maternal asthma was significantly associated with the increased prevalence of asthma in children [32]. The incidence of maternal medical conditions during the year of pregnancy also significantly increased the likelihood of a child's classification in the asthmatic unhealthy group. The severity of children's health conditions in the asthmatic unhealthy group was aggravated to a great extent by the comorbidities of wheezing, eczema, snoring or breathing problems, or food allergies. Analogous to the findings of this study, Martel et al. found that the severity of mothers' asthma, lack of asthma control and comorbidity with any medical conditions were all associated with increased incidences of recurring asthma in their children, along with the possible comorbidities of wheezing, eczema, snoring or breathing problems and food allergies [17].

In contrast with other studies [34, 35], our study found no evidence that maternal smoking during pregnancy increased the probability of a child being included in the asthmatic unhealthy cluster. One reason might be that this study investigated the association with the cluster memberships, rather than with the whole sample of children affected by asthma morbidity in early childhood or at present. Our findings warrant further research, as previous studies have shown evidence of an association between maternal smoking and childhood asthma [15, 34–37]. Future studies may consider the significant decline in Australian smoking rates [38], which might contribute to the decrease in this adverse health outcome at the national population level.

The study's strengths included its utilisation of cluster analysis instead of characterisation of isolated individual morbidities and its examination of co-factors related to asthma to investigate the differences in health status between asthma morbidity clusters. This study utilized Australia's nationally representative sample which would help understand the cluster identifications for the adolescents at national level. A limitation included its dependence on self-reported data for general health, wellbeing and PedsQL measures. There were some missing data for the lung function measurements, which may modify the interpretation of the analyses.

Conclusion

This study supports the necessity to consider multiple morbidity factors related to asthma when classifying individuals and identifying high-risk asthma groups. Our analyses identified four main clusters of children, based on their experiences of asthma and related morbidities and their association with maternal health during pregnancy. The most vulnerable group was the asthmatic unhealthy cluster and children whose mothers had asthma during pregnancy were threefold more likely to be in this cluster. This study suggests that an improved classification strategy helps to identify the most vulnerable group among the children with asthma and related morbidities.

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Authors' contributions

KA: Conception, Design of the work, Data acquisition, Curation and analysis, Writing- Original draft, Writing- Reviewing and Editing. *EK:* Supervision, Writing- Reviewing and Editing. GO: Writing- Original draft, Writing- Reviewing and Editing. RK: Supervision, Writing- Reviewing and Editing. The author(s) read and approved the final manuscript.

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Availability of data and materials

There are some restrictions on the use of this data and the data application's approval is subject to a signed confidentiality deed. Those interested in accessing this data should contact the Longitudinal Study of Australian Children Dataverse of NCLD, Australian Government Department of Social Services over email or lodge an online application from the following web link: https://growingupinaustralia.gov.au/data-and-documentation/ accessing-lsac-data.

Declarations

Ethics approval and consent to participate

This study used the secondary data from the LSAC survey dataset, which was approved by the Australian Institute of Family Studies Ethics Committee. The researchers get access to the database by contacting the Longitudinal Study of Australian Children Dataverse of National Centre for Longitudinal Data (NCLD). To obtain this data, the authors completed and signed the Confidentiality Deed Poll and sent it to NCLD (ncldresearch@dss.gov.au) and ADA (ada@anu.edu.au). Therefore, datasets analysed and/or generated during the current study are subject to the signed confidentiality deed.

Consent for publication
The manuscript used secondary data and did not contain any identifiable individual person's data in any form. Hence, consent for publication is not applicable.

Competing interests
The authors declare no conflicts of interests.

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References
1. Loza MJ, Djukanovic R, Chung KF, Horowitz D, Ma K, Branigan P, et al. Validated and longitudinally stable asthma phenotypes based on cluster analysis of the ADEPT study. Respir Res. 2016;17(1):165. https://doi.org/10.1186/s12931-016-0482-9.
2. Asthma. https://www.who.int/news-room/fact-sheets/detail/asthma. Accessed 7 Nov 2020.
3. Asthma Basic Facts. https://asthma.org.au/wp-content/uploads/2020/05/AABF2020-Asthma-Basic-Facts-DL_v6_digital.pdf. Accessed 7 Nov 2020.
4. Australian Institute of Health and Welfare. Australia's health. In: Australia's health series no 16. vol. AUS 221. Canbera: AIHW; 2018.
5. Australian Centre for Asthma Monitoring. Asthma in Australian children: findings from Growing Up in Australia, the Longitudinal Study of Australian Children. Canberra: AIHW; 2009.
6. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12(1):204. https://doi.org/10.1186/1471-2458-12-204.
7. Newby C, Heaney LG, Menzies-Gow A, Niven RM, Mansur A, Bucknall C, et al. Statistical cluster analysis of the British Thoracic Society severe refractory asthma registry: clinical outcomes and phenotype stability. PLoS One. 2014;9(7):e102987. https://doi.org/10.1371/journal.pone.0102987.
8. Kurukulaaratchy RJ, Zhang H, Patil V, Raza A, Karmaus W, Ewart S, et al. Identifying the heterogeneity of young adult rhinitis through cluster analysis in the Isle of Wight birth cohort. J Allergy Clin Immunol. 2015;135(1):143–50. https://doi.org/10.1016/j.jaci.2014.06.017.
9. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. Clin Exp Allergy. 2012;42(5):650–8. https://doi.org/10.1111/j.1365-2222.2011.03929.x.
10. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir Crit Care Med. 2010;181(4):315–23. https://doi.org/10.1164/rccm.200906-0896OC.
11. Siroux V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. Eur Respir J. 2011;38(2):310–7. https://doi.org/10.1183/09031936.00120810.
12. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J. 2009;34(4):812–8. https://doi.org/10.1183/09031936.00174408.
13. Scholtens S, Wijga AH, Brunekreef B, Kerkhof M, Postma DS, Oldenwening M, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. Int J Obes. 2010;34(4):606–13. https://doi.org/10.1038/ijo.2009.194.
14. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. J Allergy Clin Immunol. 2009;123(4):847–53 e811. https://doi.org/10.1016/j.jaci.2009.01.042.
15. Neuman A, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. Am J Respir Crit Care Med. 2012;186(10):1037–43. https://doi.org/10.1164/rccm.201203-0501OC.
16. Turner SW, Campbell D, Smith N, Craig LC, McNeill G, Forbes SH, et al. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. Thorax. 2010;65(5):391–7. https://doi.org/10.1136/thx.2008.111385.
17. Martel MJ, Rey E, Beauchesne MF, Malo JL, Perreault S, Forget A, et al. Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. Eur Respir J. 2009;34(3):579–87. https://doi.org/10.1183/09031936.00074608.
18. Shlafer R, Hergenroeder AC, Jean Emans S, Rickert VI, Adger H Jr, Spear B, et al. Adolescence as a critical stage in the MCH life course model: commentary for the leadership education in adolescent health (LEAH) interdisciplinary training program projects. Matern Child Health J. 2014;18(2):462–6. https://doi.org/10.1007/s10995-013-1243-8.
19. Schulenmerg JE, Bryant AL, O'Malley PM. Taking hold of some kind of life: how developmental tasks relate to trajectories of well-being during the transition to adulthood. Dev Psychopathol. 2004;16(2004):1119–40. https://doi.org/10.1017/S0954579404040167.
20. Sanson A, Johnston R. 'Growing up in Australia' takes its first steps. Fam Matters. 2004;67:46–53.
21. Soloff C, Lawrence D, Johnstone R. LSAC Technical Paper No. 1: Sample design. In: Australian Institute of Family Studies; 2005.
22. Clifford S, Davies S, Gillespie A, Lange K, Wake M. Longitudinal study of Australian Children's child health CheckPoint data user guide – December 2018. Melbourne: Murdoch Children's Research Institute; 2018.
23. Varni JW, Burwinkle TM, Rapoff MA, Kamps JL, Olson N. The PedsQL™ in Pediatric Asthma: Reliability and Validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Asthma Module. J Behav Med. 2004;27(3):318. https://doi.org/10.1023/B:JOBM.0000028500.53608.2c.
24. Seligson JL, Huebner ES, Valois RF. Preliminary validation of the brief multidimensional Students' life satisfaction scale (BMSLSS). Soc Indic Res. 2003;61(2):121–45. https://doi.org/10.1023/A:1021326822957.
25. Clifford S, Davies S, Gillespie A, Lange K, Liu M, Wang Y, et al. Longitudinal study of Australian Children's child health CheckPoint data user guide – June 2020. Melbourne: Murdoch Children's Research Institute; 2020.
26. Welsh L, Kathriachchige G, Raheem T, Grobler AC, Wake M, Ranganathan S. Lung function: population epidemiology and concordance in Australian children aged 11-12 years and their parents. BMJ Open. 2019;9(Suppl 3):53–62. https://doi.org/10.1136/bmjopen-2018-023486.
27. Stahl E. Correlation between objective measures of airway calibre and clinical symptoms in asthma: a systematic review of clinical studies. Respir Med. 2000;94(8):735–41. https://doi.org/10.1053/rmed.2000.0814.
28. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. Pediatr Pulmonol. 7(2):101–9.
29. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43. https://doi.org/10.1183/09031936.00080312.
30. Hall GL, Thompson BR, Stanojevic S, Abramson MJ, Beasley R, Coates A, et al. The global lung initiative 2012 reference values reflect contemporary Australasian spirometry. Respirology. 2012;17(7):1150–1. https://doi.org/10.1111/j.1440-1843.2012.02232.x.
31. Marseglia GL, Cirillo I, Vizzaccaro A, Klersy C, Tosca MA, La Rosa M, et al. Role of forced expiratory flow at 25-75% as an early marker of small airways impairment in subjects with allergic rhinitis. Allergy Asthma Proc. 2007;28(1):74–8. https://doi.org/10.2500/aap.2007.28.2920.
32. Palmer L, Knuiman M, Divitini M, Burton P, James A, Bartholomew H, et al. Familial aggregation and heritability of adult lung function: results from the Busselton health study. Eur Respir J. 2001;17(4):696–702. https://doi.org/10.1183/09031936.01.17406960.
33. Xu X, Yang J, Chen C, Wang B, JIN Y. Familial aggregation of pulmonary function in a rural Chinese community. Am J Respir Crit Care Med. 1999;160(6):1928–33. https://doi.org/10.1164/ajrccm.160.6.9902013.
34. Jaakkola JJK, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health. 2004;94(1):136–40. https://doi.org/10.2105/AJPH.94.1.136.
35. Henderson AJ, Warner JO. Fetal origins of asthma. Semin Fetal Neonatal Med. 2012;17(2):82–91. https://doi.org/10.1016/j.siny.2012.01.006.
36. Simons E, To T, Moineddin R, Stieb D, Dell SD. Maternal second-hand smoke exposure in pregnancy is associated with childhood asthma development. J Allergy Clin Immunol Pract. 2014;2(2):201–7. https://doi.org/10.1016/j.jaip.2013.11.014.

37. Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. J Allergy Clin Immunol. 2002;110(1):65–7. https://doi.org/10.1067/mai.2002.125296.
38. Vuillermin P, Saffery R, Allen KJ, Carlin JB, Tang ML, Ranganathan S, et al. Cohort profile: the Barwon infant study. Int J Epidemiol. 2015;44(4):1148–60. https://doi.org/10.1093/ije/dyv026.

Publisher's Note

7.2 Links and implications

This thesis paper identified four clusters, among which adolescents from *early-onset asthmatic or allergic* and *asthmatic unhealthy* clusters, comprising one fourth of all children, were more vulnerable in terms of respiratory functions, health-related quality of life and general wellbeing. The study revealed that children whose mothers had asthma during pregnancy were over three times more likely to be in the asthmatic unhealthy cluster than children whose mothers were non-asthmatic during pregnancy. It also affirmed that children of mothers having a medical condition in the year of childbirth were more likely to be in the asthmatic unhealthy cluster than children whose mothers were in normal health. Thus, the study result signifies that the foetal origins theory is applicable to an extant among the latent class groups of children. However, there was a lack of associations between cluster membership and other maternal health factors – general health, obesity status before pregnancy, and frequency of smoking in 1st Trimester. This study also signified that Latent Class Analysis is an improved classification strategy to identify the most vulnerable adolescents and thus would help the policy makers to identify the targeted sub-groups of the population for appropriate interventions.

In the next, a second paper on cluster analysis has been commenced for the identification of clusters of vulnerable adolescents in relation to health-related behaviour or lifestyle characteristics. Thus, in Paper 6, this thesis implemented an unsupervised machine learning method known as latent class clustering to identify the vulnerable clusters of children aged 14-15 years based on the characteristics of physical activity, sedentary behaviour, alcohol consumption, smoking, diet, eating disorders, sleep problems and weight gain consciousness.

CHAPTER 8: PAPER 6 - CLUSTERING OF LIFESTYLE AND HEALTH BEHAVIOURS IN AUSTRALIAN ADOLESCENTS AND ASSOCIATIONS WITH OBESITY, SELF-RATED HEALTH AND QUALITY OF LIFE

8.1 Introduction

The sixth paper of this thesis, presented in this chapter, first identifying the distinct clusters of children aged 14–15 years based on the following health behaviour and lifestyle factors: physical activity, sedentary behaviour, alcohol consumption, smoking, diet, eating disorders, sleep problems and weight gain consciousness. Then, this study explored the association of these clusters with obesity, self-rated health and quality of life. Thus, this paper is the second study of this thesis conducted for understanding classifications of health-related characteristics and identifying vulnerable clusters in Australian adolescents. This cross-sectional study carried out the latent class analysis, an unsupervised machine learning technique, on 3,127 children aged 14-15 years from the Wave 8 of LSAC surveys.

Clustering of lifestyle and health behaviours in Australian adolescents and associations with obesity, self-rated health and quality of life

Abstract

Objective: The primary aim of this study was to identify clusters of lifestyle and health behaviours in a nationally representative sample of Australian adolescents and to explore the association of these clusters with obesity, self-rated health and quality of life.

Methods: The study participants were 3127 adolescents aged 14–15 years who participated in the eighth wave of the birth cohort of the Longitudinal Study of Australian Children (LSAC). A latent class analysis (LCA) was performed to identify clusters based on the following health behaviours: physical activity, sedentary behaviour, alcohol consumption, smoking, diet, eating disorders, sleep problems and weight gain consciousness. Multinomial logistic regression models were fitted to the following health outcome variables: obesity, self-rated general health and pediatric health-related quality of life, to investigate their associations with LCA clusters.

Results: Based on the lifestyle and health behaviour characteristics, LCA had better model fits for identifying distinct clusters among male and female adolescents. Five clusters were identified for male participants: healthy lifestyle (n=624, 38.9%), temperate (n=440, 27.4%), physically inactive (n=73, 4.6%), mixed lifestyle (n=347, 21.6%) and multiple risk factors (n=122, 7.6%). For female participants, four clusters were identified: healthy lifestyle (n=659, 43.3%), temperate (n=558, 36.7%), mixed lifestyle (n=63, 4.2%) and multiple risk factors (n=241, 15.8%). Adolescents in the healthy lifestyle and temperate clusters reported low and moderately active health risk behaviours, respectively. For both male and female participants, mixed lifestyle or multiple risk factors clusters

had a stronger negative association with health-related quality of life scores compared to healthy lifestyle clusters.

Conclusion: This current study identified specific gender-based lifestyle patterns and health behaviours in Australian adolescents. The study offers novel insights into latent class classification through the utilisation of different lifestyles and health-related behaviours of adolescents, to identify characteristics of vulnerable groups concerning obesity, general health status and quality of life. This classification strategy may help health policy makers to target vulnerable groups and develop appropriate interventions.

Background

Overweight and obesity affect 25% of Australian children and adolescents, causing excess weight-related health and wellbeing problems and higher health care costs [1]. A healthy lifestyle is strongly associated with reduced morbidities for all age groups, including adolescents [2-4]. While many studies have linked children's suboptimal health behaviours and lifestyle (physical activity, smoking, alcohol consumption, diet/nutrition etc.) to the development of chronic diseases, few have focused on patterns of health-related behaviours with respect to how risk behaviours cluster and impact health [5-7]. For example, children who eat more and are physically inactive are more likely to become obese adults [8]. Adolescence is the transition stage from childhood to adulthood, as well as a critical developmental period, during which many health practices emerge or are discarded, which in turn influence subsequent behavioural and health trajectories [9, 10]. For instance, a large proportion of adolescents do not engage in the recommended levels of physical activity, while they lead a sedentary lifestyle for longer than recommended [11], get insufficient sleep, and engage in cigarette smoking and alcohol consumption [12]. Hence, exploring distinct clusters of health-related behaviours is vital to assess how these might affect adolescents' long-term health [13].

Overweight and obesity in childhood are complex conditions [3, 14, 15]. To add to this complexity, existing health measures are not clear or standardised. For example, body mass index (BMI), as a stand-alone indicator, cannot adequately capture the nature of obesity and may not serve as a sufficient basis to develop appropriate interventions [14, 15]. In paediatrics, the Edmonton Obesity Staging System classifies the functional limitations of obesity by four domains: metabolic, mechanical and mental health and social milieu [16, 17]. Further, problem behaviour theory and health lifestyle theory suggest specific potential indicators (physical activity, sedentary behaviours, smoking, alcohol consumption, diet, eating disorders from stress, sleep and weight-control behaviours),

which can be gauged through social surveys, to predict health conditions [18-20]. Both theories predict that a range of negative and risky behaviours would cluster if these behaviours result from an underlying tendency towards deviant behaviour [18] or a set of choices that are available and socially acceptable for a status group [19]. If this is the case, many adolescents' lifestyles and psychosocial behaviours are interrelated rather than having separate effects [12]. Accordingly, interventions should target this range of potential behaviours rather than a particular behaviour in isolation [9] and consider the underlying structural, normative and personality factors to improve the effectiveness of the intervention. However, to our knowledge, limited studies have explored the co-occurrence of psychosocial and lifestyle factors.

In some countries, identifying specific clusters of the national population across age and gender groups has helped identify homogeneous groups that can be targeted for specific public health interventions or prevention strategies [4, 21-24]. A study conducted in the Netherlands (n=4395) investigated the clusters of health-compromising and delinquent behaviours in adolescents and adults. The results revealed two relevant clusters (alcohol and delinquency) for young adolescents and three clusters (alcohol, delinquency and health) for older adolescents [25]. A Finnish study of adolescents (n=6792) that assessed lifestyle (physical activity, sedentary behaviour, smoking, sleeping problems and overweight/obesity) and psychosocial problems identified various subgroups of 16-year-old adolescents. There were differences between male and female participants, and the adolescents were classified into distinct subgroups based on lifestyle and psychosocial factors, which persisted in the follow-up at 18 years [12]. Gender differences were also observed in two studies of adolescents and preschool children in the US and France, respectively [26, 27]. Children of different clusters were classified by gender, age, lifestyle and socioeconomic positions; however, the relationships of these clusters with obesity, self-rated health and quality of life remain unclear [28].

Moreover, limited studies have been conducted in the Australian context [27].

The World Health Organization recommends a comprehensive approach to assessing an individual's health risks. Thus, it is necessary to consider how all possible patterns of risk behaviours might affect an individual's health rather than their health behaviours in isolation, for example, patterns of eating, stress-related eating, trajectories of smoking or drinking and physical fitness risk behaviours [9, 29-31]. Latent Class Analysis (LCA) is an innovative statistical approach that utilises person-centred characteristics of categorical and cross-sectional indicators to identify distinct subpopulations. By examining varying response pattern assemblages, LCA yields unobserved (latent) classes of individuals to ascertain the most parsimonious and interpretable set of classes. The LCA-generated latent class variable represents groups of homogeneous individuals within the class to which they belong; however, they are heterogeneous across different classes [32]. Recent literature shows that LCA has been used increasingly to identify latent subgroups of related characteristics of various morbidities including asthma and obesity [24, 33]. The results revealed that LCA is a practical and valid approach to categorising individuals with similar characteristics. Existing studies have mostly been conducted in European and North American settings and among adults, and available studies among children to identify patterns of health behaviours related to obesity have primarily used a subset of health behaviours [4, 21-24].

Therefore, the primary aim of this study was to identify the clusters of health behaviours in a nationally representative sample of Australian adolescents and to explore the association of defined clusters of lifestyles and health behaviours with obesity, self-rated health and quality of life. Adolescents' lifestyle characteristics and health behaviours include physical activity, diet, sedentary behaviour, smoking, alcohol consumption, sleep problems, eating disorders and concerns regarding weight gain. Given the previous findings of gender-related differences in

the aforementioned variables [11, 12] and based on the findings that the model fit statistics are better suited for gender-based analyses, LCA models were analysed separately for male and female participants.

Methods

Setting and data

The data were obtained from the birth cohort of the eighth wave of the Longitudinal Study of Australian Children (LSAC). The LSAC is a representative household survey of Australian children and adolescents that biennially collects information on the health (physical and socio-emotional) and learning development of Australian children from their birth based on the context of the bio-ecological framework of human development [20]. The LSAC launched the first wave survey in 2004 and completed the eighth wave survey in 2018 when the children of the brith cohort were 15–16 years. The LSAC data were collected from parents or caregivers of the children of participating households or the children themselves (from age 12 onward) through self-completed questionnaires or face-to-face interviews with trained interviewers. Details of the LSAC survey are available elsewhere [20].

Study design and participants

This cross-sectional study utilised the eighth wave data of the LSAC. For cluster analysis, all 3127 adolescents aged 14–15 years in the eighth wave of the birth cohort of the LSAC were included in this study. This is because adolescents who participated in this wave provided data on a variety of dimensions concerning lifestyles and health-related behaviours: physical activity, sedentary behaviours, alcohol consumption and smoking, sleep, eating disorders, concerns on weight gain, obesity status, self-rated general health and quality of life. A multistage sampling technique was used to select the LSAC respondents at wave 1, followed

up at wave 8. Household was the primary sampling unit, and information was acquired from the children themselves.

LCA variables

The LCA was performed using variables related to lifestyle and health-related behaviours of the adolescents. Based on the bio-ecological framework followed in the LSAC study, only variables that are risk factors for obesity, self-rated health and quality of life [20] were selected. These variables were measured by the LSAC survey team using the LSAC questionnaire in the eighth wave survey. These variables are described ahead.

Physical Activity: The LSAC collects data on the number of days the adolescents performed at least one hour of moderate-to-vigorous physical activity per week. From these data, we summed the total number of exercise hours per week. Existing literature recommends at least two hours of physical activity per week [28, 34, 35]. Based on this cut-off point, we categorised participants into the following groups: 'less than two hours of physical activity per week', 'two to three hours of physical activity per week' and 'more than three hours of physical activity per week'.

Sedentary behaviour: Sedentary behaviour was measured based on two activities: the number of hours spent per week (including both weekdays and weekends) on electronic games (does not play, up to 3 hours, more than three hours) and the frequency of sharing or posting content on social media (frequently or daily, weekly/monthly, never). The categories were defined based on the extent of hours spent on screen games or the level of engagement in social media. More frequent engagement in games or social media activity indicated higher sedentary behaviours.

Alcohol consumption: Data on alcohol consumption data were self-reported by the participants. The participants were classified into two

categories based on their responses to alcohol consumption in the last four weeks: no (non-drinkers) and yes (drinkers).

Smoking: Participants were asked if they had smoked in the last four weeks; they were dichotomised as smokers or non-smokers based on whether they smoked cigarettes during the time period (yes = smoker; no = non-smoker).

Diet: Diet was assessed by the frequency of consumption of fruits and vegetables, skim/low/no-fat milk, high-fat food, full-cream milk products and high-sugar drinks. Following the observance of different dietary approaches, participants were categorised according to their dietary intake. Intake of fruits and vegetables and high-fat foods was categorised as 'none', '1–2 times a day', '3–4 times a day', '≥ 5 times a day'. Meanwhile, consumption of full-cream milk products, skim/low/no-fat milk and high-sugar drinks was categorised as 'none', 'once a day', 'twice a day', 'thrice or more a day'. These categories were taken from the preferred classification of the LSAC based on the frequency of consumption per day.

Eating disorders: Stress-related eating or eating disorders are linked to an increased risk of obesity [31]. Hence, this study sought to consider these variables in the analysis. In wave 8 of the LSAC, the birth cohort children completed the Branched Eating Disorders Test, which can identify partial syndrome eating disorders. The tool has high validity and reliability, and meeting at least two of the three diagnostic criteria for anorexia nervosa or bulimia nervosa included in the Diagnostic and Statistical Manual – III R [36, 37] indicates the presence of a partial syndrome eating disorder. Based on this assessment, the LSAC survey determined whether the child has partial syndrome anorexia and/or bulimia. Further, to assess binge eating, the following question was asked in the LSAC survey: 'How often did the child lose control of eating?' Possible responses included 'none', 'around once a week' and 'two or more days a week'.

Sleep: The LSAC measured sleep duration and sleep quality by asking the following questions: 'On average, how much sleep do you get per night?' and 'During the last month, how well do you feel you have slept in general?' Sleep quality was grouped as 'very well', 'well' and 'not well', and sleep duration was categorised as 'less than 8 hours', '8–9 hours' and 'greater than 9 hours'.

Weight-control behaviours: Adolescents' dieting behaviour and exercising to control weight were also measured in wave 8. The following questions were asked to the participants: how would you feel if you gained one or two kilos of weight ('no concern', 'a little concerned' and 'would worry/upset me'). Participants were also asked about the frequency of having gone all day without eating to control weight ('never', 'one day a week' and 'two or more days a week') and the frequency of exercise to control weight ('none', 'one to three days a week' and 'four or more days a week').

Health status-related outcome variables

Several health-related variables were measured in this study to compare the defined clusters of health status among adolescents. These variables are obesity, self-rated general health and paediatric health-related quality of life.

Obesity: Obesity was measured using the BMI score of the adolescents. The LSAC categorised participants' BMIs based on the cut-offs suggested by Cole et al. (2000, 2007) for adolescents by age and sex as follows: underweight, normal weight, overweight and obese. In this study, obesity was one of the key outcome variables.

Self-rated general health: Adolescents were asked to rate their general health on an ordinal scale as follows: 'excellent', 'very good', 'good', 'fair' and 'poor'. These categories were then regrouped into three categories for this study as follows: excellent, very good and good/fair/poor.

Health-related quality of life (HRQoL): In the LSAC, adolescents' physical, emotional, school and Social Functioning and peer relationships were measured using the Pediatric Quality of Life (PedsQL) inventory [38]. This study used HRQoL as the outcome variable as it is a reliable and responsive measure of health outcomes of adolescents. The following subscales of the PedsQL were used in this study: (i) Physical Functioning, (ii) Emotional Functioning, (iii) School Functioning, (iv) Social Functioning and (v) Psychosocial Health Summary [39].

The Physical Functioning subscale assesses participants' physical development. Parents were asked about how often their children experienced the following problems in the past month: a) difficulty walking more than one block, b) difficulty in running, c) difficulties in sport or exercise, d) difficulty lifting something heavy, e) difficulty taking a bath or showering by themselves, f) difficulty doing chores in the house, g) having aches or pains and h) having low energy levels. The Emotional Functioning subscale measures the frequency of negative emotional states such as sadness and anxiety displayed by the children. Parents were asked how often the study children experienced the following problems in the past month: a) feeling afraid or scared, b) feeling sad or blue, c) feeling angry, d) trouble sleeping and e) worrying about what will happen to them. The School Functioning subscale assesses school adjustment and performance of the children. Parents were asked how often the children experienced the following problems in the past month: a) difficulty paying attention in class, b) forgetting things, c) difficulty keeping up with school activities, d) missing school because of not feeling well, e) missing school to go to the doctor or hospital. The Social Functioning subscale measures children's relationships with their peers. Parents were asked to rate how frequently children experienced the following problems in the past month: a) difficulty getting along with other children, b) other kids not wanting to be their friends, c) getting teased by other children, d) not being able to do things that other children their age can do, e) difficulty keeping up when playing with other

children. The Psychosocial Health Summary subscale involved combining the scores on the Emotional Functioning and Social Functioning subscales.

To calculate the scale scores, children's primary caregivers (in most cases, their mothers) were asked to rate each item on a five-point scale: Never (1), Almost never (2), Sometimes (3), Often (4), and Almost always (5). Items were reverse-scored and transformed to a 0–100 scale (1 = 100, 2 = 75, 3 = 50, 4 = 25, 5 = 0), where higher scores indicated a higher level of functioning. Average scores were then calculated to obtain scores on the Physical, Emotional, School and Social Functioning subscales and Psychosocial Health Summary subscale. Details of the questionnaire and the validity and reliability of the PedsQL inventory are described elsewhere [38, 39].

Statistical analysis

Clusters of health-related behaviours were identified for 3127 adolescent male and female adolescents using LCA, a subcategory of structural equation modelling. This unsupervised machine learning algorithm is designed to handle large datasets and categorical variables, and it has features to determine the optimal number of clusters from a set of observed variables [40]. An advantage of using the LCA method in this study is that in contrast to the traditional approach of describing the variability of a single health behaviour, it provides a framework for describing heterogeneity among adolescents in terms of health behavioural indicators [32]. Thus, LCA was used to identify unobserved (latent) classes based on categorical indicators of lifestyles and health-related behaviours. This method designates each participant a 'best' class assignment based on their maximum likelihood of belonging to an identified distinct class. Participants within the same class are regarded as homogeneous based on the indicator variables [3, 40]. This distinction is a person-centred approach, as opposed to more traditional variable-centred approaches such as multiple logistic regression analysis [32].

Analyses were performed using the LCA procedure in STATA (version 16.0) software. Based on previous studies [24, 32], models with one to eight classes were tested to determine the optimal number of classes. No covariates were included in this procedure. To determine the optimal number of classes, Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC) and the likelihood functions L^2 (deviance statistics) values for each model were compared. The model with the lowest BIC value and lower likelihood-ratio and log-likelihood values was the best fit. LCAs found better model fits for identifying distinct clusters among male and female participants separately, rather than all adolescents. The study identified five significant clusters for male participants and four clusters for female participants, as shown in Table 1. The distributions of the item response probabilities were evaluated, and the identified classes were named based on characteristics that were more likely to reflect the members of the class. Participants were assigned to classes in which they had the highest probability of membership; that is, they exhibited the traits that are representative of that class.

Table 1: Model fit statistics of the LCA models

Model	**N**	**Log-likelihood**	**df**	**AIC**	**BIC**	**L^2**	**% reduction in L^2**
For male participants							
One class	1606	-24527.86	38	49131.72	49336.22	25426.43	-
Two class	1606	-24041.07	74	48230.14	48628.37	24452.85	3.8
Three class	1606	-23755.00	98	47706.00	48233.39	23880.71	6.1
Four class	1606	-23568.01	138	47412.02	48154.67	23503.99	7.6
Five class*	**1606**	**-23403.70**	**175**	**47157.40**	**48099.16**	**23178.11**	**8.8**
Six class	1606	-23336.56	210	47093.12	48223.24	23043.83	9.4
Seven class	1606	-23225.17	249	46948.34	48288.33	22821.05	10.2
Eight class	1606	-23151.64	278	46859.28	48355.33	22673.98	10.8
For female participants							
One class	1521	-23868.59	38	47813.18	48015.61	25574.27	-
Two class	1521	-23472.68	75	47095.36	47494.89	24782.45	3.1
Three class	1521	-22745.39	115	45720.78	46333.4	23327.87	8.8
Four class*	**1521**	**-22475.41**	**133**	**45216.82**	**45925.33**	**22787.91**	**10.9**
Five class	1521	-22311.89	190	45003.77	46015.93	22460.87	12.2

Model	N	Log-likelihood	df	AIC	BIC	L^2	% reduction in L^2
Six class	1521	-22214.14	207	44842.28	45944.99	22265.37	12.9
Seven class	1521	-22135.76	244	44759.52	46059.33	22108.61	13.6
Eight class	1521	-22042.32	277	44638.64	46114.26	21921.73	14.3

Further, descriptive analyses of the responses for each of the 17 latent class variables of health-related behaviours were performed and presented by sex and cluster groups. The associations between the identified latent classes and BMI categories or quality of life were evaluated using multinomial logistic regression adjusted for child age. The adjusted odds ratios (ORs) and 95% confidence intervals were reported. All analyses were performed stratified by sex. Data were analysed in STATA (version 16.0).

Results

Sample characteristics

Of the 3127 participants, 49% were female. Regarding health risk behaviours, approximately 2.37% of adolescents smoked cigarettes, whereas alcohol consumption was prevalent among 6.75% of adolescents. Male participants spent more time on exercise (>3 hours/week: 41.53%) and playing electronic games on weekdays (up to 3 hours: 57.38%) and weekends (>3 hours/week: 58.78%). In contrast, female participants spent more time on social media on a daily (34.19%) or weekly/monthly basis (52.99%). However, consumption of fatty foods and high-sugar drinks was lower among girls. Meanwhile, girls were more likely to engage in weight control through exercises and skipping meals and to be more concerned about weight gain (see Table 2).

Cluster profiles

The cluster analysis revealed a five-class model for male participants and a four-class model for female participants based on lowest BIC and lower AIC, likelihood-ratio (L^2) and log-likelihood values compared to other models. The prevalence of 18 indicators across seven thematic areas, based on response probabilities of the defined clusters, is illustrated in Table 3. The clusters were named according to the indicators with high response probabilities as follows for male adolescents: i) temperate (27.4%), ii) physically inactive (4.6%), iii) mixed lifestyle (21.6%), iv) multiple risk factors (7.6%), and v) healthy lifestyle (38.9%); and for female adolescents: i) temperate (36.7%), ii) healthy lifestyle (43.3%, iii) multiple risk factors (15.8%) and iv) mixed lifestyle (4.2%). The healthy lifestyle cluster was the largest cluster for both boys and girls and was considered as the reference category, while multinomial regression models were developed. Figure 1 shows that among different clusters, the proportion of adolescents with normal BMI was the highest (over 70%) among the healthy lifestyle clusters of both male and female participants.

Meanwhile, a higher number of adolescents in the mixed lifestyle and multiple risk factors clusters were overweight (17-34%) or obese (9-14%) compared to other clusters. Figure 2 shows the sex-based distribution of self-rated general health status across clusters, which reveals that poor health status (poor/fair/good) was less prevalent among adolescents in the healthy lifestyle cluster (26% or less) compared to adolescents in other clusters (27%–46%). Figure 3 shows the average scores on the five dimensions of the PedsQL among the clusters of male and female participants. Adolescents in the healthy lifestyle cluster obtained higher scores on all five dimensions compared to adolescents in other clusters.

Table 2: Distribution of the attributes of the latent class variables by gender

Description	Value	Total (n=3127)		Male (n=1606)		Female (n=1521)	
		n	%	n	%	n	%
Consumed alcohol in the last four weeks	No	2916	93.25	1500	93.4	1416	93.1
	Yes	211	6.75	106	6.6	105	6.9
Smoked in the last four weeks	No	3053	97.63	1581	98.44	1472	96.78
	Yes	74	2.37	25	1.56	49	3.22
Partial syndrome anorexia and/or bulimia	No	97.09	97.09	1568	97.63	1468	96.52
	Yes	91	2.91	38	2.37	53	3.48
Exercise hours per week	<2 hours/week	808	25.84	401	24.97	407	26.76
	2 hours/week	1128	36.07	538	33.5	590	38.79
	>3 hours/week	1191	38.09	667	41.53	524	34.45
Weekday hours on e-games	Does not play on weekdays	1199	38.34	336	20.92	863	56.74
	Up to 3 hours	1529	48.9	928	57.78	601	39.51
	More than 3 hours	399	12.76	342	21.3	57	3.75
Weekend hours on e-games	Does not play on weekend days	883	28.24	127	7.91	756	49.7
	Up to 3 hours	1128	36.07	535	33.31	593	38.99
	More than 3 hours	1116	35.69	944	58.78	172	11.31
Frequency of sharing/posting on social media	Frequently or several times a day	1038	33.19	518	32.25	520	34.19
	On a weekly or monthly basis	1597	51.07	791	49.25	806	52.99
	Never	492	15.73	297	18.49	195	12.82
Sleep quality	Very well	868	27.76	478	29.76	390	25.64
	Well	1824	58.33	943	58.72	881	57.92
	Not well	435	13.91	185	11.52	250	16.44
Sleep duration	<8 hours	408	13.05	207	12.89	201	13.21
	8–9 hours	1223	39.11	627	39.04	596	39.18
	>9 hours	1496	47.84	772	48.07	724	47.6
Frequency of fruit and vegetable consumption	None	336	10.75	201	12.52	135	8.88
	1–2 times/day	849	27.15	474	29.51	375	24.65
	3–4 times/day	1033	33.03	516	32.13	517	33.99
	≥5 times/day	909	29.07	415	25.84	494	32.48
Frequency of high-fat food consumption	None	608	19.44	287	17.87	321	21.1
	1–2 times/day	1599	51.14	774	48.19	825	54.24
	3–4 times/day	674	21.55	385	23.97	289	19
	≥5 times/day	246	7.87	160	9.96	86	5.65

Description	Value	Total (n=3127)		Male (n=1606)		Female (n=1521)	
		n	%	n	%	n	%
SC had full-cream milk products	None	1082	34.6	491	30.57	591	38.86
	Once/day	1126	36.01	561	34.93	565	37.15
	Twice/day	618	19.76	344	21.42	274	18.01
	Thrice or more/day	301	9.63	210	13.08	91	5.98
SC had skim/low/no fat milk	None	1924	61.53	992	61.77	932	61.28
	Once/day	762	24.37	367	22.85	395	25.97
	Twice/day	301	9.63	157	9.78	144	9.47
	Thrice or more/day	140	4.48	90	5.6	50	3.29
Frequency of high-sugar drink consumption	None	1395	44.61	650	40.47	745	48.98
	Once/day	843	26.96	430	26.77	413	27.15
	Twice/day	498	15.93	284	17.68	214	14.07
	Thrice or more/day	391	12.5	242	15.07	149	9.8
Frequency of losing control of eating	None	2167	69.3	1264	78.7	903	59.37
	Around Once a week	598	19.12	264	16.44	334	21.96
	Two or more days a week	362	11.58	78	4.86	284	18.67
How would you feel if you gained one or two kilos of weight?	No concern	1542	49.31	1006	62.64	536	35.24
	A little concerned	806	25.78	391	24.35	415	27.28
	Would worry/upset me	779	24.91	209	13.01	570	37.48
Frequency of skipping meals throughout a day to control weight	None	2826	90.37	1503	93.59	1323	86.98
	One day a week	231	7.39	89	5.54	142	9.34
	Two or more days a week	70	2.24	14	0.87	56	3.68
Frequency of exercises to control weight	None	1678	53.66	949	59.09	729	47.93
	One to three days a week	922	29.49	399	24.84	523	34.39
	Four or more days a week	527	16.85	258	16.06	269	17.69

Table 3: The prevalence of the characteristics by lifestyle and health behaviours among the identified clusters for male and female participants

			Clusters for male participants (n=1606)					Clusters for female participants (n=1521)			
		Cluster #	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**
		Cluster Name	**Temperate**	**Physically inactive**	**Mixed lifestyle**	**Multiple risk factors**	**Healthy lifestyle**	**Temperate**	**Healthy lifestyle**	**Multiple risk factors**	**Mixed lifestyle**
		N (%)	**440 (27.4)**	**73 (4.6)**	**347 (21.6)**	**122(7.6)**	**624(38.9)**	**558 (36.7)**	**659 (43.3)**	**241 (15.8)**	**63 (4.2)**
Behaviour group	**Variable description**	**Categories**	%	%	%	%	%	%	%	%	%
Physical activity	Exercise hours per week	<2 hours	41.4	89.0	17.9	16.4	11.5	27.4	20.6	25.3	90.5
		2–3 hours	33.6	4.1	43.8	33.6	31.1	41.9	38.1	42.3	4.8
		>3 hours	25.0	6.9	38.3	50.0	57.4	30.7	41.3	32.4	4.8
Sedentary behaviour	Weekday hours on e-games	Does not play on weekdays	0.2	20.6	25.7	17.2	33.7	5.9	99.4	55.6	65.1
		Up to 3 hours	40.7	54.8	64.0	59.8	66.4	87.1	0.6	38.2	30.2
		More than 3 hours	59.1	24.7	10.4	23.0	0.0	7.0	0.0	6.2	4.8
	Weekend hours on e-games	Does not play on weekend days	0.0	11.0	8.9	9.0	12.3	3.1	89.8	48.1	49.2
		Up to 3 hours	3.9	35.6	36.0	27.9	53.4	75.1	10.2	34.9	36.5
		More than 3 hours	96.1	53.4	55.0	63.1	34.3	21.9	0.0	17.0	14.3
	Frequency of sharing/posting on social media	Frequently or several times a day	33.0	2.7	36.9	45.1	30.1	29.4	34.3	53.9	0.0
		Weekly or monthly basis	47.3	4.1	52.7	45.1	54.8	58.4	58.0	40.3	1.6
		Never	19.8	93.2	10.4	9.8	15.1	12.2	7.7	5.8	98.4
Health risk behaviour	Alcohol consumption in the last 4 weeks	No	93.4	100.0	89.9	84.4	96.3	97.1	96.2	73.4	100.0
		Yes	6.6	0.0	10.1	15.6	3.7	2.9	3.8	26.6	0.0
	Smoking in the last 4 weeks	No	98.4	100.0	97.1	93.4	100.0	98.9	99.9	82.6	100.0
		Yes	1.6	0.0	2.9	6.6	0.0	1.1	0.2	17.4	0.0
Sleep	Sleep quality	Very well	28.4	9.6	20.5	30.3	38.1	31.9	27.8	10.8	4.8

		Cluster #	Clusters for male participants (n=1606) Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Clusters for female participants (n=1521) Cluster 1	Cluster 2	Cluster 3	Cluster 4
		Cluster Name	**Temperate**	**Physically inactive**	**Mixed lifestyle**	**Multiple risk factors**	**Healthy lifestyle**	**Temperate**	**Healthy lifestyle**	**Multiple risk factors**	**Mixed lifestyle**
		N (%)	**440 (27.4)**	**73 (4.6)**	**347 (21.6)**	**122(7.6)**	**624(38.9)**	**558 (36.7)**	**659 (43.3)**	**241 (15.8)**	**63 (4.2)**
Behaviour group	**Variable description**	**Categories**	%	%	%	%	%	%	%	%	%
		Well	57.5	24.7	69.5	57.4	57.9	60.6	62.2	52.7	9.5
		Not well	14.1	65.8	10.1	12.3	4.0	7.5	10.0	36.5	85.7
	Sleep duration	<8 hours	19.8	9.6	16.1	25.4	4.2	9.0	9.6	33.2	12.7
		8-9 hours	42.1	43.8	43.5	32.0	35.3	39.1	40.5	37.3	33.3
		>9 hours	38.2	46.6	40.4	42.6	60.6	52.0	49.9	29.5	54.0
Diet	Frequency of fruit and vegetable consumption	None	16.8	100.0	3.8	10.7	4.5	4.1	2.7	12.9	100.0
		1-2 times/day	52.7	0.0	32.0	21.3	16.8	30.8	21.1	26.6	0.0
		3-4 times/day	24.3	0.0	43.2	19.7	37.7	35.0	35.5	36.5	0.0
		≥5 times/day	6.1	0.0	21.0	48.4	41.0	30.1	40.7	24.1	0.0
	Frequency of high-fat food consumption	None	12.7	98.6	13.8	0.8	17.6	10.9	21.7	22.4	100.0
		1-2 times/day	50.7	1.4	54.5	1.6	57.5	61.7	55.4	48.1	0.0
		3-4 times/day	30.2	0.0	28.2	16.4	21.5	20.4	19.3	19.9	0.0
		≥5 times/day	6.4	0.0	3.5	81.2	3.4	7.0	3.6	9.5	0.0
	SC had full-cream milk products	None	33.2	100.0	33.1	5.7	24.0	33.0	36.4	43.2	100.0
		Once/day	41.8	0.0	37.8	23.0	34.9	36.7	41.7	35.3	0.0
		Twice/day	13.6	0.0	23.9	30.3	24.2	23.3	16.8	13.7	0.0
		Thrice or more/day	8.4	0.0	5.2	41.0	16.8	7.0	5.0	7.9	0.0
	SC had skim/low/no fat milk	None	65.2	100.0	55.6	45.9	67.4	58.8	57.8	66.4	100.0
		Once/day	23.9	0.0	31.7	9.8	22.4	26.3	28.2	25.7	0.0
		Twice/day	6.4	0.0	12.7	20.5	9.6	11.3	11.2	2.9	0.0
		Thrice or more/day	4.6	0.0	0.0	23.8	6.6	3.6	2.7	5.0	0.0
		None	37.7	97.3	36.0	5.7	46.2	38.5	55.1	43.6	98.4

			Clusters for male participants (n=1606)					Clusters for female participants (n=1521)			
		Cluster #	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 1	Cluster 2	Cluster 3	Cluster 4
		Cluster Name	Temperate	Physically inactive	Mixed lifestyle	Multiple risk factors	Healthy lifestyle	Temperate	Healthy lifestyle	Multiple risk factors	Mixed lifestyle
		N (%)	440 (27.4)	73 (4.6)	347 (21.6)	122(7.6)	624(38.9)	558 (36.7)	659 (43.3)	241 (15.8)	63 (4.2)
Behaviour group	**Variable description**	**Categories**	%	%	%	%	%	%	%	%	%
	Frequency of high-sugar drink consumption	Once/day	26.4	1.4	35.2	0.0	29.5	34.1	25.6	22.4	0.0
		Twice/day	26.1	1.4	18.7	14.8	13.8	16.7	11.5	18.3	1.6
		Thrice or more/day	9.8	1.4	10.1	79.5	10.6	10.8	7.7	15.8	0.0
Eating Disorder	Frequency of losing control of eating	None	87.3	97.3	40.1	80.3	91.7	66.7	66.8	11.6	100.0
		Around Once a week	10.2	2.7	44.7	13.1	7.4	23.1	20.6	28.6	0.0
		Two or more days a week	2.5	0.0	15.3	6.6	1.0	10.2	12.6	59.8	0.0
	Partial syndrome anorexia and/or bulimia	No	99.6	100.0	92.8	95.9	100.0	100.0	98.2	83.0	100.0
		Yes	0.5	0.0	7.2	4.1	1.0	0.0	1.8	17.0	0.0
Weight-control behaviours	How would you feel if you gained one or two kilos of weight?	No concern	68.0	50.7	17.3	80.3	82.1	43.9	38.1	5.0	44.4
		A little concerned	22.1	27.4	49.9	9.0	14.4	34.2	27.6	10.4	27.0
		Would worry/upset me	10.0	21.9	32.9	10.7	3.5	21.9	34.3	84.7	28.6
	Frequency of skipping meals throughout a day to control weight	None	94.8	98.6	85.6	90.2	97.3	94.3	95.3	44.4	98.4
		One day a week	5.0	1.4	11.8	6.6	2.7	5.7	3.8	35.3	0.0
		Two or more days a week	0.2	0.0	2.6	3.3	0.0	0.0	0.9	20.3	1.6
	Frequency of exercises to control weight	None	75.9	97.3	8.1	51.6	72.6	53.4	48.6	19.9	100.0
		One to three days a week	18.9	2.7	55.0	36.9	12.5	35.3	33.2	44.4	0.0
		Four or more days a week	5.2	0.0	36.9	11.5	14.9	11.3	18.2	35.7	0.0

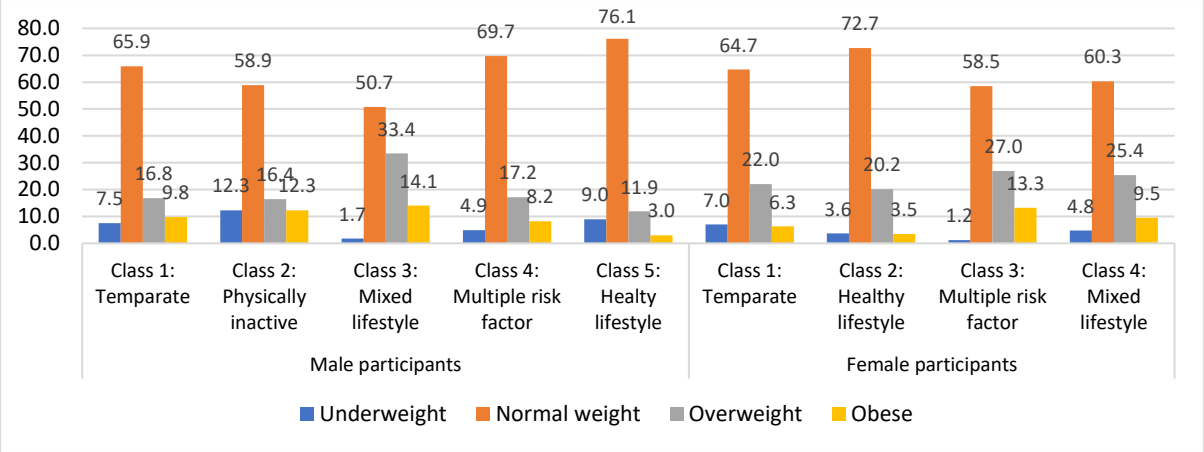

Figure 1: Percentage of BMI categories by clusters among male and female participants

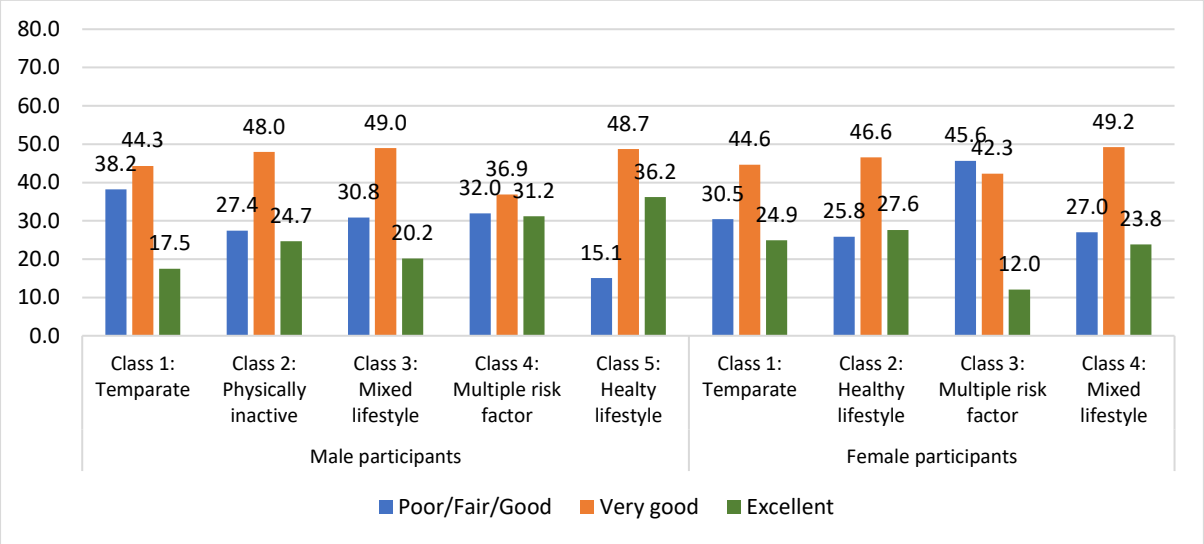

Figure 2: Percentage of general health categories by clusters among male and female participants

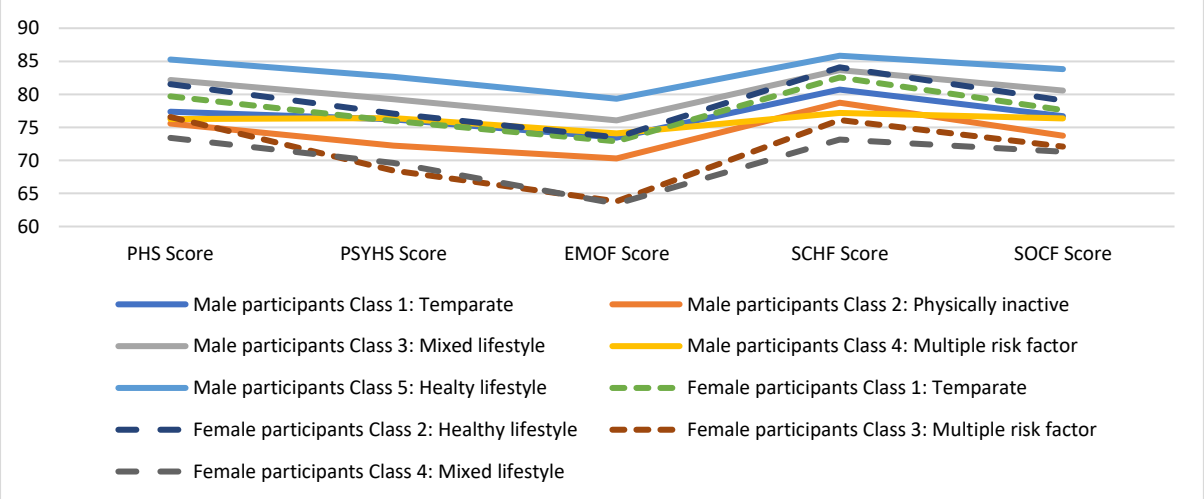

Figure 3: Pediatric quality of life average scores by clusters among male and female participants

Note: Abbreviations: PHS score, Physical Health Summary score; PSYHS Score, Psychosocial Health Summary score; EMOF Score, Emotional Functioning score; SCHF Score, School Functioning score; SOCF Score, Social Functioning score.

Table 4 presents the associations between cluster membership and obesity or general health status. Table 5 presents the association between cluster membership and pediatric quality of life (PedsQL) outcome scores. Based on the descriptive statistics and the results shown in Tables 4 and 5, specific findings are presented ahead.

For male participants, healthy lifestyle, temperate, physically inactive, mixed lifestyle and multiple risk factors clusters were identified.

i) Male participants in the **healthy lifestyle cluster** (n=624, 38.9%) reported the lowest levels of health risk behaviours (no smoking and almost no alcohol consumption), higher physical activity (>3 hours/week: 57.4%), low sedentary behaviour (33.7% adolescents did not play e-games and 66.4% played e-games less than 3 hours in a week), high sleep duration (> 9 hours: 60.6%), healthy diet practices (78.7% adolescents ate fruits and vegetables more than three times a day), almost no eating disorders (see Table 3).

ii) Male participants in the **temperate cluster** (n=440, 27.4%) reported moderate levels of health risk behaviours (6.6% consumed alcohol and 1.6% smoked cigarettes), physical activity (<2 hours exercise/week: 41.4% adolescents), sleep (<8 hours sleep: 19.8% adolescents), diet (only 30.4% adolescents consumed vegetables/fruits three or more times per day), eating disorder (12.7% adolescents reported losing control of eating one or more days per week) and being conscious of weight gain (32.1% of adolescents reported being concerned about weight gain); however, adolescents in this cluster reported higher levels of sedentary behaviour during weekends (96.1% adolescents spend more than three hours on e-games). Compared to the healthy lifestyle cluster, male participants in this cluster were two times (OR=2.37, 95% CI: 1.32 – 4.23) more likely to be obese. Further, male participants in this cluster were three times (OR=2.99, 95% CI: 2.21 – 4.05) more likely to be in poor

general health, compared to those of healthy lifestyle cluster (see Table 4). In the case of the paediatric quality of life, male participants in this cluster were more likely to obtain lower scores (b= - 6.93 for the Physical Health Summary score, b = -5.80 for the Psychosocial Health Summary score and b = -6.05 for Total PedsQL score) compared to the healthy lifestyle cluster (see Table 5).

iii) Male participants in the **physically inactive cluster** (n=73, 4.6%) had the lowest level of physical activity (89% of adolescents engaging in <2 hours of exercise/week) and inadequate sleep quality (65.8% adolescents reported not getting good sleep). Adolescents in this cluster also engaged in less healthy dietary practices (almost none of the participants consumed fruits or vegetables any day) and were less conscious of weight gain (almost none of the participants engaged in restrained eating or exercises to control weight). Compared to the healthy lifestyle cluster, adolescents in this cluster were four times (OR=3.87, 95% CI: 1.12 – 13.33) more likely to be obese. Moreover, adolescents in this cluster were three times (OR=2.97, 95% CI: 1.29 - 6.83) more likely to be in poor general health (see Table 4). In the case of the paediatric quality of life, male participants in this cluster were more likely to have lower scores (b = -9.00 for Physical Health Summary score, b = -9.81 for Psychosocial Health Summary score and b = -9.42 for Total PedsQL score) compared to those of healthy lifestyle cluster (see Table 5).

iv) Male participants in the **mixed lifestyle** (n=347, 21.6%) cluster reported a miscellaneous routine regarding physical activity, health risk behaviour, sedentary behaviour, high-quality sleep, healthy diet and weight-gain consciousness. For example, though a majority of adolescents in this cluster engaged in 2 hours (43.8%) or more (38.3%) of physical exercise per week, 10.1%

of adolescents consumed alcohol and 2.9% smoked cigarettes, accounting for the second-highest prevalence among all the clusters. Furthermore, though around half of the adolescents slept 8–9 hours and consumed fruits or vegetables 3-4 times per day, over 80% of adolescents consumed high-fat food at least once per day (up to 4 times/day). On the contrary, over 80% of adolescents were concerned about weight gain, and over half of the adolescents engaged in exercise one to three days per week to control weight. However, around 60% of adolescents lost control of eating at least once a week, and a few adolescents (7.2%) had partial syndrome anorexia and/or bulimia. Male participants in this cluster were more likely to be either overweight (OR=3.88, 95% CI: 2.75 – 5.49) or obese (OR=5.57, 95% CI: 3.15 – 9.84) and were more likely to have poor general health (OR = 1.85, 95% CI: 1.32 – 2.60) compared to those in the healthy lifestyle cluster (see Table 4). Further, members of this cluster more likely to obtain lower HRQoL scores (b = -2.71 for Total PedsQL score) compared to those in the healthy lifestyle cluster (see Table 5).

v) Male participants in the **multiple risk factors** (n=122, 7.6%) cluster had the highest percentage of smokers (6.6%) and alcohol drinkers (15.6%) compared to those in other clusters. Male participants in this cluster had high levels of sedentary behaviour: over 80% played e-games 3 hours or more on weekdays, and over 90% played e-games 3 hours or more on weekends (see Table 3). They also engaged in social media more frequently and were indifferent about weight gain. Members of this cluster were more likely to have poor general health (OR = 2.19, 95% CI: 1.38 – 3.47) and more likely to obtain lower HRQoL scores (b = -6.22 for Total PedsQL score) compared to those in the healthy lifestyle cluster (see Table 4 and 5).

For female participants, healthy lifestyle, temperate, mixed lifestyle and multiple risk factors clusters were identified.

i) Female participants in the **healthy lifestyle** cluster (n=659, 43.3 %) reported the lowest levels of health risk behaviours (no smoking and almost no alcohol consumption), higher physical activity (around 80% of adolescents exercising 2 hours or more per week), low levels of sedentary behaviour (almost no adolescents playing e-games in the weekdays, and 89.8% did not play e-games on weekends), long sleep duration (90% adolescents slept 8 hours or more per night) with good quality sleep, healthy diet practices (over 97% adolescents ate fruits and vegetables regularly) and almost no eating disorders (see Table 3).

ii) Female participants in the **temperate cluster** (n=558, 36.7 %) had moderately active health behaviours, physical activity (around 67% of adolescents engaged in 2 hours or more exercise per week), moderate hours of sleep (39% of adolescents sleep 8–9 hours and 52% of adolescents slept more than 9 hours), healthy diet (65% adolescents ate fruit and vegetables 3 times or more per day), less eating disorders, moderate consciousness of weight gain and low levels of sedentary behaviour on weekends. Female participants were more likely to be obese (OR=1.79, 95% CI: 1.03 – 3.12) in this cluster compared to those in the healthy lifestyle cluster (see Table 4).

iii) Female participants in the **mixed lifestyle (**n= 63, 4.2 %) reported no smoking or alcohol consumption but engaged in less physical activity (90.5% of adolescents with less than 2 hours of physical activity/week). The majority of adolescents in this cluster never used social media, and although their sleep duration was good, their sleep quality was not good. Further, they had a lower intake of inappropriate diet and low eating

disorders and weight-gain consciousness. There were no significant associations between membership of the participants to this cluster and obesity or poor general health (see Table 4). Regarding the paediatric quality of life, female participants in the mixed lifestyle cluster were more likely to obtain lower HRQoL scores (b = -6.12 for the Physical Health Summary score, b = -6.46 for Psychosocial Health Summary score and b = -6.32 for Total PedsQL score) compared to those in the healthy lifestyle cluster (see Table 5).

iv) Female participants in the **multiple risk factors** (n=241, 15.8 %) cluster reported multiple risks in various indicators, including physical activity or exercise (42.3% engaged in more than 2 hours of physical activity but less than 3 hours/week). Adolescents in this cluster had high sedentary behaviour, engaged in social media several times a day and had the lowest sleep quality and reported more eating disorders. Adolescents in this cluster were around four times more likely to be obese (OR=3.61, 95% CI: 2.00 – 6.51) compared to those in the healthy lifestyle cluster. Further, they were two times (OR=2.16, 95% CI: 1.57 - 2.98) more likely to have poor general health (see Table 4). Regarding the paediatric quality of life, female participants in this cluster were more likely to obtain lower HRQoL scores (b = -4.15 for the Physical Health Summary score, b = -8.09 for Psychosocial Health Summary score and b = -6.35 for Total PedsQL score) compared to those in the healthy lifestyle cluster (see Table 5).

Table 4: Associations between cluster membership and obesity or general health status

Cluster name	Obesity Status								
	Overweight			Obese			Poor health		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Models for male participants' clusters									
Class 1 Temperate	1.34	0.93 - 1.93	0.121	**2.37**	**1.32 - 4.23**	**0.004**	**2.99**	**2.21 – 4.05**	**<0.001**
Class 2 Physically inactive	1.66	0.60 – 4.62	0.328	**3.87**	**1.12 – 13.33**	**0.032**	**2.97**	**1.29 – 6.83**	**0.010**
Class 3 Mixed lifestyle	**3.88**	**2.75 – 5.49**	**<0.001**	**5.57**	**3.15 – 9.84**	**<0.001**	**1.85**	**1.32 – 2.60**	**0.025**
Class 4 Multiple risk factors	1.37	0.79 - 2.39	0.257	1.93	0.84 – 4.42	0.118	**2.19**	**1.38 – 3.47**	**0.001**
Class 5 Healthy lifestyle (ref.)									
Models for female participants' clusters									
Class 1 Temperate	1.18	0.89 - 1.58	0.234	**1.79**	**1.03 - 3.12**	**0.040**	1.17	0.90 – 1.52	0.229
Class 2 Healthy lifestyle (ref.)									
Class 3 Multiple risk factors	**1.48**	**1.03- 2.12**	**0.032**	**3.61**	**2.00 – 6.51**	**<0.001**	**2.16**	**1.57 – 2.98**	**<0.001**
Class 4 Mixed lifestyle	1.21	0.36- 4.14	0.750	1.68	0.27 – 10.59	0.578	2.18	0.63 – 7.56	0.219

Table 5: Associations between cluster membership and the pediatric quality of life (PedsQL) outcome scores

Clusters	PHS Score		PSYHS Score		EMOF Score		SCHF Score		Total PedsQL Score	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Models for male participants' clusters										
Class 1 Temperate	**-6.68**	**-9.23 to -4.13**	**-5.55**	**-7.41 to -3.69**	**-5.27**	**-7.31 to -3.23**	**-4.10**	**-6.35 to -1.85**	**-6.05**	**-7.95 to -4.15**
Class 2 Physically inactive	**-9.00**	**-14.16 to -3.82**	**-9.81**	**-13.59 to -6.04**	**-8.61**	**-12.75 to -4.48**	**-6.22**	**-10.78 to -1.66**	**-9.42**	**-13.28 to -5.56**
Class 3 Mixed lifestyle	-2.41	-5.11 to 0.29	**-2.95**	**-4.92 to -0.98**	**-2.97**	**-5.13 to -0.81**	-1.70	-4.08 to 0.68	**-2.71**	**-4.72 to -0.70**
Class 4 Multiple risk factors	**-7.47**	**-11.49 to -3.44**	**-5.23**	**-8.17 to -2.29**	**-4.50**	**-7.72 to -1.28**	**-7.20**	**-10.76 to -3.64**	**-6.22**	**-9.22 to -3.21**
Class 5 Healthy lifestyle (ref.)										
Models for female participants' clusters										
Class 1 Temperate	-1.22	-3.51 to 1.07	-0.63	-2.43 to 1.17	-0.26	-2.29 to 1.76	-0.93	-3.04 to 1.18	-090	-2.65 to 0.84
Class 2 Healthy lifestyle (ref.)										
Class 3 Multiple risk factors	**-4.15**	**-7.16 to -1.15**	**-8.09**	**-10.46 to -5.73**	**-9.29**	**-11.94 to -6.63**	**-7.22**	**-9.99 to -4.46**	**-6.35**	**-8.65 to -4.06**
Class 4 Mixed lifestyle	**-6.12**	**-11.41 to -0.82**	**-6.46**	**-10.45 to -2.30**	**-9.34**	**-14.02 to -4.67**	**-9.37**	**-14.23 to -4.50**	**-6.32**	**-10.36 to -2.64**

Abbreviations: PHS Score, Physical Health Summary score; PSYHS Score, Psychosocial health summary score; EMOF Score, Emotional functioning score, SCHF Score, School functioning score; Total PedsQL Score , Total pediatric quality of life score.

Discussion

This study revealed a distinct pattern in health behaviours among Australian adolescents. The present research identified five clusters for male participants: healthy lifestyle (38.9%), temperate (27.4%), physically inactive (4.6%), mixed lifestyle (21.6%) and multiple risk factors (7.6%). For female participants, four clusters were identified: healthy lifestyle (43.3%), temperate (36.7%), mixed lifestyle (4.2%) and multiple risk factors (15.8%). Furthermore, the latent clusters were significantly associated with obesity, general health status and HRQoL. Both male and female participants in the healthy lifestyle and clusters reported lower health risk behaviours and hence were less likely to be obese, have poor general health or obtain lower HRQoL scores.

The healthy lifestyle cluster reported no smoking, little alcohol consumption, high physical activity, low sedentary behaviour, appropriate sleep hours, a healthy diet and no eating disorders. The temperate cluster reported moderate levels of physical activity, sleep time, diet, eating disorder and weight-gain consciousness. However, adolescents in the unhealthy clusters (physically inactive, mixed lifestyle and multiple risk factors) reported the lowest levels of physical activity, high sedentary behaviour on weekdays, poor sleep quality, less healthy diet, low levels of consciousness regarding weight management and higher smoking and alcohol consumption rates. Clustering the distinct patterns of health-related behaviours is crucial since these behaviours affect both health and life expectancy [41].

This study identified specific clusters concerning obesity, self-perceived general health status and pediatric HRQoL. The results showed that male participants from the temperate, physically inactive and mixed lifestyle clusters and female participants from the mixed lifestyle and multiple risk factors clusters were more likely to be obese than their counterparts in the healthy lifestyle clusters. Previous studies have also shown that unhealthy health behaviours are associated with higher BMI

[28, 29, 42-44]. However, these results do not align with some cross-sectional findings indicating an unexplained inverse relationship [45, 46] or no association [47] of higher BMI with unhealthy clusters. The possible reasons for this inconsistency may be the nature and quality of data, as well as any geographical, behavioural or methodological differences.
The present study also found that male participants in the temperate, physically inactive and mixed lifestyle clusters and female participants in the mixed lifestyle and multiple risk factors clusters were less likely to report very good or excellent general health than their counterparts with a healthy lifestyle. However, there are limited studies to corroborate this finding. A study conducted in Ireland found higher odds of negative perceptions about health in the unhealthy behaviour cluster than in the healthy cluster [4]. Furthermore, earlier studies have shown that a healthy lifestyle ensures very good or excellent general health [48-50]. Adolescents with adverse health practices may have unhealthy cardiovascular profiles and low peak bone masses, consequently deteriorating their general health [34].

The present study further revealed that male participants in the temperate and physically inactive clusters and female participants in the mixed and multiple risk factors clusters reported lower quality of life than did their healthy lifestyle counterparts. Unhealthy clusters, including those who engaged in minimal physical activity, sedentary habits, restrained diet and had lower dietary awareness, reported a reduced quality of life (HRQoL). Similar to previous study findings, individuals with undesirable lifestyles had a higher likelihood of poor HRQoL [4, 51, 52]. Possible reasons for this include body pain, inadequate energy supply to the body and psychosocial or emotional breakdown [50, 52]. In addition, clusters of unhealthy habits are associated with depression, anxiety, violent behaviours, insufficient social support and unpleasant perceptions of society, all of which can lead to poor HRQoL [51].

The present study also demonstrated that moderately healthy behaviour had a significant impact on male participants but not on female

participants. The temperate cluster—denoted by moderate health practices—also showed increased body fat, poor health and lower HRQoL among male participants; these findings are supported by a previous study [4]. Male participants were more vulnerable than female participants. However, there are limited studies to explain the causal relationships in these sex differences, suggesting the need for further large-scale investigations to consider unhealthy-to-moderate stability of lifestyles patterns through sex-stratified analyses.

This study further revealed specific clusters of unhealthy behaviours. The current findings showed that adolescents with unhealthy lifestyles were more likely to be obese and have poor HRQoL and less likely to report good or excellent general health compared to those in the healthy lifestyle cluster. These findings have substantial public health implications. Health policy makers should focus on developing and implementing interventions to promote a healthy lifestyle among adolescents since healthier behaviour is strongly associated with positive health outcomes. For example, policy makers may take up a multifaceted intervention approach to target multiple unhealthy behaviours, assuming this would be more effective than targeting a single risk factor at a time. Future studies should explore the effects of different treatments on obesity-related clusters. In addition, future studies should investigate the impact of biological and family factors on health-related behaviour patterns over an extended period using further longitudinal data. The main strength of the present study lies in its relatively large sample size, focusing on a range of health risk behaviours. This is one of the first studies to cluster a variety of health behaviours among adolescents and assess their association with three different health outcomes. Another strength of the study is that it has utilised the eighth wave data of the LSAC to capture the health outcomes of adolescents with different healthy and unhealthy behaviours. Further advantages of this study include the use of validated and well-accepted measures to assess the outcome variables. For example, weight and height data to calculate participants'

BMIs were collected by trained professionals. Moreover, the LCA is an advanced statistical approach that ensures diverse benefits for more precise estimations [3].

The present study has some limitations. First, this study provides an overview of adolescents' health behaviours and their association with obesity, self-rated health and HRQoL using unbalanced longitudinal data. This precludes causal inferences between the identified clusters and health outcomes. Second, while we analyse data based on the classes, the results are dependent on the choice of classes (made subjectively based on BIC, AIC and log-likelihood values). If a different choice would be made, that would lead to slightly different results. Third, data on some variables (e.g., general health) were self-reported. Therefore, response biases might be an issue. Fourth, the records of adolescents' health behaviour patterns were based on their memory. It might be possible that they failed to recall past events, leading to bias or over and underreporting of the results [3, 28].

Conclusions

The current study identified sex-based clusters of obesity-related health risk behaviours among Australian adolescents. All unhealthy clusters were associated with increased obesity and lower levels of self-rated general health; however, the magnitude of the risk of poor health outcomes varied by the risk characteristics of the clusters. Understanding various lifestyle clusters and health-related risk behaviours may be important for policy makers when developing obesity prevention interventions. Future studies should investigate the effects of various interventions on reducing these obesity-related clusters. Identifying the associations of these clusters with morbidity and lower quality of life scores is important to determine health behaviour patterns in national and international settings, which may help with obesity prevention and improving the quality of life.

Declarations

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Authors' contributions

KA is the principal investigator, designed the study, conducted the data analysis and drafted the manuscript. SAK and GO critically reviewed the manuscript and assisted with the final editing and writing of the manuscript. RK and EK contributed to the study supervision and manuscript editing. All authors read and approved the final manuscript.

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Competing interests

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

Ethics approval and consent to participate

This study used the secondary data from the LSAC survey dataset, which was approved by the Australian Institute of Family Studies Ethics Committee. For the survey, the LSAC authority obtained a written informed consent from all adolescents and/or their legal guardian(s). The de-identified unit record dataset was provided to us at the University of Southern Queensland for the purpose of this doctoral research. To obtain these data, we completed and signed the Confidentiality Deed Poll and sent it to NCLD (ncldresearch@dss.gov.au) and ADA (ada@anu.edu.au).

In the study, all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

The manuscript used secondary data and did not contain any identifiable data of the participants. Hence, consent for publication was not needed.

Availability of data and material

The data analysed during this study were collected from the Longitudinal Study of Australian Children, managed by the National Centre for Longitudinal Data. The authors cannot share the data publicly, as there are some restrictions on the use of the data. Moreover, the data application's approval is subject to a signed confidentiality deed. However, the data that support findings of this study are available at the National Centre for Longitudinal Data (NCLD), Australia. Anyone interested in accessing this data should contact the NCLD authority through the following email: ncldresearch@dss.gov.au, or complete an online application available in the following URL: https://growingupinaustralia.gov.au/data-and-documentation/accessing-lsac-data. Please contact the corresponding author (email: kabir_ahmad2000@yahoo.com) for further information the study data need to be accessed.

References

1. Australian Institute of Health and Welfare 2020. **Overweight and obesity among Australian children and adolescents.** Cat. no. PHE 274. Canberra: AIHW.
2. Abdel-Qadir HM, Lee DS: **The contribution of familial and heritable risks in heart failure**. *Curr. Opin. Cardiol.* 2007, **22**(3):214-219.
3. Anderson LN, Sandhu R, Keown-Stoneman CDG, De Rubeis V, Borkhoff CM, Carsley S, Maguire JL, Birken CS: **Latent class analysis of obesity-related characteristics and associations with body mass index among young children**. *Obes Sci Pract* 2020, **6**(4):390-400.
4. Conry MC, Morgan K, Curry P, McGee H, Harrington J, Ward M, Shelley E: **The clustering of health behaviours in Ireland and their relationship with mental health, selfrated health and quality of life**. *BMC Public Health* 2011, **11**(692).
5. Obel C, Linnet KM, Henriksen TB, Rodriguez A, Jarvelin MR, Kotimaa A, Moilanen I, Ebeling H, Bilenberg N, Taanila A *et al*: **Smoking during pregnancy and hyperactivity-inattention in the offspring--comparing results from three Nordic cohorts**. *Int J Epidemiol* 2009, **38**(3):698-705.
6. O'Reilly JR, Reynolds RM: **The risk of maternal obesity to the long-term health of the offspring**. *Clin Endocrinol (Oxf)* 2013, **78**(1):9-16.
7. Ou L, Chen J, Hillman K, Eastwood J: **The comparison of health status and health services utilisation between Indigenous and non-Indigenous infants in Australia**. *Aust N Z J Public Health* 2010, **34**(1):50-56.
8. Park MH, Falconer C, Viner RM, Kinra S: **The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review**. *Obes Rev* 2012, **13**(11):985-1000.

9. Daw J, Margolis R, Wright L: **Emerging adulthood, emergent health lifestyles: Sociodemographic determinants of trajectories of smoking, binge drinking, obesity, and dedentary behavior**. *J Health Soc Behav* 2017, **58**(2):181-197.
10. Harris KM, Gordon-Larsen P, Chantala K, Udry JR: **Longitudinal trends in race/ethnic disparities in leading health indicators from adolescence to young adulthood**. *Arch. pediatr. adolesc. med.* 2006, **160**(1):74-81.
11. Tammelin T, Ekelund U, Remes J, Nayha S: **Physical activity and sedentary behaviors among Finnish youth**. *Med Sci Sports Exerc* 2007, **39**(7):1067-1074.
12. Heikkala E, J. R, Paananen M, Taimela S, Auvinen J, Karppinen J: **Accumulation of lifestyle and psychosocial problems and persistence of adverse lifestyle over two-year follow-up among Finnish adolescents**. *BMC Public Health* 2014.
13. Schulenberg JE, Bryant AL, O'MALLEY PM: **Taking hold of some kind of life: How developmental tasks relate to trajectories of well-being during the transition to adulthood**. *Development and psychopathology* 2004, **16**(4):1119-1140.
14. Freedman DS, Wang J, Maynard LM, Thornton JC, Mei Z, Pierson RN, Dietz WH, Horlick M: **Relation of BMI to fat and fat-free mass among children and adolescents**. *Int J Obes (Lond)* 2005, **29**(1):1-8.
15. Sharma AM, Kushner RF: **A proposed clinical staging system for obesity**. *Int J Obes (Lond)* 2009, **33**(3):289-295.
16. Hadjiyannakis S, Buchholz A, Chanoine J-P, Jetha MM, Gaboury L, Hamilton J, Birken C, Morrison KM, Legault L, Bridger T: **The Edmonton Obesity Staging System for Pediatrics: a proposed clinical staging system for paediatric obesity**. *PCH* 2016, **21**(1):21-26.
17. Hadjiyannakis S, Ibrahim Q, Li J, Ball GDC, Buchholz A, Hamilton JK, Zenlea I, Ho J, Legault L, Laberge A-M *et al*: **Obesity class**

versus the Edmonton Obesity Staging System for Pediatrics to define health risk in childhood obesity: results from the CANPWR cross-sectional study. *Lancet Child Adolesc. Health* 2019, **3**(6):398-407.

18. Jessor R: **Problem-behavior theory**. In: *Risikoverhaltensweisen Jugendlicher.* edn.: Springer; 2001: 61-78.
19. Cockerham WC: **Health lifestyle theory and the convergence of agency and structure**. *JHSB* 2005, **46**(1):51-67.
20. Soloff C, Lawrence D, Johnstone R: **Technical Paper no. 1: Sample design**. In: *Growing Up in Australia.* Australian Institute of Family Studies; 2005.
21. Schuit AJ, van Loon AJ, Tijhuis M, Ocke M: **Clustering of lifestyle risk factors in a general adult population**. *Prev Med* 2002, **35**(3):219-224.
22. Berrigan D, Dodd K, Troiano RP, Krebs-Smith SM, Barbash RB: **Patterns of health behavior in U.S. adults**. *Prev. Med.* 2003, **36**(5):615-623.
23. Poortinga W: **The prevalence and clustering of four major lifestyle risk factors in an English adult population**. *Prev Med* 2007, **44**(2):124-128.
24. Ahmad K, Kabir E, Ormsby GM, Khanam R: **Clustering of asthma and related comorbidities and their association with maternal health during pregnancy: evidence from an Australian birth cohort**. *BMC Public Health* 2021, **21**(1):1952.
25. van Nieuwenhuijzen M, Junger M, Velderman MK, Wiefferink KH, Paulussen TW, Hox J, Reijneveld SA: **Clustering of health-compromising behavior and delinquency in adolescents and adults in the Dutch population**. *Prev Med* 2009, **48**(6):572-578.
26. Pate RR, Heath GW, Dowda M, Trost SG: **Associations between physical activity and other health behaviors in a representative sample of US adolescents**. *Am. J. Public Health* 1996, **86**(11):1577-1581.

27. Saldanha-Gomes C, Marbac M, Sedki M, Cornet M, Plancoulaine S, Charles MA, Lioret S, Dargent-Molina P: **Clusters of diet, physical activity, television exposure and sleep habits and their association with adiposity in preschool children: the EDEN mother-child cohort**. *Int J Behav Nutr Phys Act* 2020, **17**(1):20.
28. Leech RM, McNaughton SA, Timperio A: **Clustering of diet, physical activity and sedentary behaviour among Australian children: cross-sectional and longitudinal associations with overweight and obesity**. *Int J Obes (Lond)* 2015, **39**(7):1079-1085.
29. Huh J, Riggs NR, Spruijt-Metz D, Chou CP, Huang Z, Pentz M: **Identifying patterns of eating and physical activity in children: a latent class analysis of obesity risk**. *Obesity (Silver Spring)* 2011, **19**(3):652-658.
30. Tabacchi G, Faigenbaum A, Jemni M, Thomas E, Capranica L, Palma A, Breda J, Bianco A: **Profiles of physical fitness risk behaviours in school adolescents from the ASSO project: A latent class analysis**. *Int J Environ Res Public Health* 2018, **15**(9).
31. Jääskeläinen A, Nevanperä N, Remes J, Rahkonen F, Järvelin M: **Stress-related eating, obesity and associated behavioural traits in adolescents: a prospective population-based cohort study**. *BMC Public Health* 2014.
32. Lanza ST: **Latent Class Analysis for Developmental Research**. *Child Dev Perspect* 2016, **10**(1):59-64.
33. Madigan CD, Daley AJ, Kabir E, Aveyard P, Brown W: **Cluster analysis of behavioural weight management strategies and associations with weight change in young women: a longitudinal analysis**. *Int J Obes (Lond)* 2015, **39**(11):1601-1606.
34. Boreham C, Riddoch C: **The physical activity, fitness and health of children**. *J Sports Sci* 2001, **19**(12):915-929.

35. Butcher K, Sallis JF, Mayer JA, Woodruff S: **Correlates of physical activity guideline compliance for adolescents in 100 U.S. Cities**. *J Adolesc Health* 2008, **42**(4):360-368.
36. O'Connor M, Warren D, Daraganova G: **Eating problems in mid-adolescence**. In: *Growing Up In Australia – The Longitudinal Study of Australian Children, Annual Statistical Report 2017.* edn. Edited by Warren D, Daraganova G. Melbourne: Australian Institute of Family Studies; 2018.
37. Selzer R, Hamill C, Bowes G, Patton G: **The branched eating disorders test: validity in a nonclinical population**. *Int J Eat Disord* 1996, **20**(1):57-64.
38. Varni JW, Burwinkle TM, Rapoff MA, Kamps JL, Olson N: **The PedsQL™ in Pediatric Asthma: Reliability and Validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Asthma Module**. *J. Behav. Med.* 2004, **27**(3).
39. Clifford S, Davies S, Gillespie A, Lange K, Wake M: **Longitudinal Study of Australian Children's Child Health CheckPoint Data User Guide – December 2018**. In. Melbourne: Murdoch Children's Research Institute; 2018.
40. Schreiber JB: **Latent Class Analysis: An example of reporting results**. *RSAP* 2016, **13**(2017):1196-1201.
41. Khaw K-T, Wareham N, Bingham S, Welch A, Luben R, Day N: **Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study**. *PLoS Med.* 2008, **5**(1):e12.
42. Liu J, Kim J, Colabianchi N, Ortaglia A, Pate RR: **Co-varying patterns of physical activity and sedentary behaviors and their long-term maintenance among adolescents**. *J Phys Act Health* 2010, **7**(4):465-474.
43. Magee CA, Caputi P, Iverson DC: **Patterns of health behaviours predict obesity in Australian children**. *J Paediatr Child Health* 2013, **49**(4):291-296.

44. Gubbels JS, Kremers SP, Goldbohm RA, Stafleu A, Thijs C: **Energy balance-related behavioural patterns in 5-year-old children and the longitudinal association with weight status development in early childhood**. *Public Health Nutr* 2012, **15**(8):1402-1410.
45. Sanchez A, Norman GJ, Sallis JF, Calfas KJ, Cella J, Patrick K: **Patterns and correlates of physical activity and nutrition behaviors in adolescents**. *Am J Prev Med* 2007, **32**(2):124-130.
46. van der Sluis ME, Lien N, Twisk JW, Steenhuis IH, Bere E, Klepp KI, Wind M: **Longitudinal associations of energy balance-related behaviours and cross-sectional associations of clusters and body mass index in Norwegian adolescents**. *Public Health Nutr* 2010, **13**(10A):1716-1721.
47. Cameron AJ, Crawford DA, Salmon J, Campbell K, McNaughton SA, Mishra GD, Ball K: **Clustering of obesity-related risk behaviors in children and their mothers**. *Ann Epidemiol* 2011, **21**(2):95-102.
48. Harrington J, Perry IJ, Lutomski J, Fitzgerald AP, Shiely F, McGee H, Barry MM, Van Lente E, Morgan K, Shelley E: **Living longer and feeling better: healthy lifestyle, self-rated health, obesity and depression in Ireland**. *Eur J Public Health* 2010, **20**(1):91-95.
49. Akpinar A: **Urban green spaces for children: A cross-sectional study of associations with distance, physical activity, screen time, general health, and overweight**. *Urban For Urban Green* 2017, **25**:66-73.
50. Sanders TAB: **Diet and general health: dietary counselling**. *Caries Research* 2004, **38(suppl 1)**(Suppl. 1):3-8.
51. Chen X, Sekine M, Hamanishi S, Wang H, Gaina A, Yamagami T, Kagamimori S: **Lifestyles and health-related quality of life in Japanese school children: a cross-sectional study**. *Prev Med* 2005, **40**(6):668-678.

52. Wu XY, Han LH, Zhang JH, Luo S, Hu JW, Sun K: **The influence of physical activity, sedentary behavior on health-related quality of life among the general population of children and adolescents: A systematic review**. *PLoS One* 2017, **12**(11):e0187668.

8.2 Links and implications

This paper revealed that among the identified distinct clusters, children of mixed lifestyle or multiple risk factors clusters had a stronger negative association with health-related quality of life scores compared to healthy lifestyle clusters. Moreover, children of these unhealthy clusters were associated with increased obesity and lower levels of self-rated general health. Thus, these study findings implicate that understanding various lifestyle clusters and health-related risk behaviours might be important for policymakers when developing obesity prevention or quality of life improvement interventions.

While earlier six papers performed the risk factor analyses and identification of vulnerable clusters to understand the health burden in children and adolescents, it is also important to shed light on the cost of illness, generated from these health burdens. As LSAC has linked data of the Medicare costs against the received health services, this thesis indented to perform direct healthcare cost analyses on few selected health morbidities. The next study of this thesis analysed the direct healthcare costs of Australian children associated with asthma morbidity.

CHAPTER 9: PAPER 7 - THE HEALTHCARE COST BURDEN OF ASTHMA IN AUSTRALIAN CHILDREN: A LONGITUDINAL POPULATION-BASED STUDY

9.1 Introduction

This chapter presents the seventh paper of this thesis, evaluating the cost of illness due to asthma based on the direct healthcare costs among children aged two-to-eighteen years in Australia. This paper is the first study of this thesis conducted for estimating the excess healthcare cost of asthma illness in the Australian population by examining the longitudinal Medicare cost data. This study carried out Generalised linear modelling (GLM) with log-link data and Gamma distribution and utilised the marginal estimates of cost differences to determine the excess health care costs. This study used both B and K cohort data of 8,657 children, comprising 51,839 pooled observations from Wave 1 to Wave 8 that were linked with the Medicare Benefits Schedule data and Pharmaceutical Benefits Scheme data from Medicare costs databases.

The healthcare cost burden of asthma in Australian children: A longitudinal population-based study

Abstract

Objective: To investigate to what extent childhood asthma increases publicly funded healthcare costs. We aimed to investigate the cross-sectional relationship between asthma and healthcare costs among children aged two to 18 years and, in longitudinal analyses, whether costs increase with an increase in the duration of asthma prevalence.

Methods: Study participants are 4,175 and 4,482 children of Birth (B) and Kindergarten (K) cohorts from the nationally representative Longitudinal Study of Australian Children for whom the linked Medicare costs data are available. The children were followed in consecutive seven and eight waves for the B and K cohorts, respectively, with the pooled number of observations being 51,839. The influence of asthma morbidities on healthcare costs was estimated using generalised linear models. Healthcare costs include all general practitioners, a large proportion of paediatrician visits and prescription medication costs to the federal government, plus out-of-pocket costs, if any, over 12 years for the B cohort and 14 years for the K cohort. Models are controlled for demographic, socio-economic and several selected child health conditions.

Results: From the participants of the B and K cohorts aged 2–18 years, the study found that 12% to 16% across different waves were currently treated for asthma. In both cohorts, the duration of asthma and treatment strongly influenced the excess healthcare costs. Total excess healthcare costs among the sampled 2–18-year-old children associated with asthma are A$4316 per child. At the population level, the estimated total excess Medicare costs associated with asthma (currently being treated for asthma)

among 2–18-year-old children are, on average, A$190.6 million per year. Compared to the non-asthmatic children, peers with persistent asthma morbidity and treatment requirements had excess costs up to A$20,727 for the B cohort children until 14 years of age, while excess costs for the K cohort children were A$19,571 until 18 years of age.

Conclusions: Early childhood asthma imposes a huge financial burden on the public health system. Higher excess healthcare costs of all asthmatic children compared to the costs of non-asthmatic children, provide further economic justification for promoting preventive efforts at early ages.

Keywords: children, healthcare cost, Medicare Benefits Scheme, Pharmaceutical Benefits Scheme, asthma

Introduction

Asthma is the leading cause of disease burden among children [1]. Globally, there were more than 262 million people affected by asthma in 2019. In 2017–2018, around 2.7 million of the Australian population (11 per cent) had asthma, of which there were 38,792 hospitalisations, 80 per cent of which could be prevented [2, 3]. Asthma is a more prevalent chronic disease among children and young adults than adults, particularly because of its early onset and diverse symptoms [4]. A longitudinal birth cohort study conducted in 2015 found that 16.9 per cent of Australian children experienced wheezing or asthma within the first three years of life [5]. It was found from another longitudinal study that asthma prevalence increases in early childhood and starts to decrease from six to seven years until adolescence [6]. However, it is unclear if there are corresponding differences in healthcare costs associated with asthma morbidities.

Studies on the direct and indirect cost of asthma morbidities are limited, especially in Australia, among children or adolescents. Few existing studies deal with evaluating healthcare costs from Medicare data on child health conditions other than asthma, for example, obesity, ADHD, mental health and sleep problems [7–11]. A study in the US on the costs of childhood asthma hospitalisations revealed that between 2000 and 2009, the hospitalisation rate decreased by 13 per cent; however, nationwide hospital charges increased from US$1.27 billion to US$1.59 billion [12]. Two studies estimated the cost of illness for asthma in Portuguese adults and children [13, 14]. The study on children revealed that the mean annualised cost per child was €929.35 for direct costs and €230.70 for indirect costs, while on average, each adult costs €708.16 a year, with indirect costs representing 7 per cent. In the Australian context, it is challenging to get hospital-based administrative data. However, the Longitudinal Study of Australian Children (LSAC) provides linked Medicare data that can be utilised to evaluate the healthcare costs of asthma among Australian children.

Hence, we aimed to report on the nationally representative LSAC which has prospective, repeated measurements of asthma and has linked data on healthcare costs from Medicare Australia. Further, this study spans the ages of two to 18, covering a period of 12 to 14 years of children's data. This length of study provides a whole childhood perspective that includes early childhood and adolescence and gives an in-depth insight into when and how associations develop between asthma morbidity and health care costs. Thus, we aimed to evaluate what amount of healthcare costs vary by asthma morbidity status over the childhood period by examining the longitudinal relationship between healthcare costs and asthma morbidity status. We would also estimate the population level total excess healthcare costs, which included costs of the federal government through Medicare (excluding the out-of-pocket costs of individuals, if any), for two to 18-year-old Australian children who are suffering from asthma.

Methods

Study design

The LSAC is the nationally representative longitudinal survey of Australian children. This study began in 2004 with two cohorts, where the Birth (B) cohort children were recruited at age 0–1 year, and the Kindergarten (K) cohort children were recruited at age 4–5 years. Since its initiation, data were collected through surveys biennially by a combination of face-to-face interviews and self-completed questionnaires by the children's primary parents at their homes. The sampling design for data collection was stratified cluster sampling, where postcodes were stratified by state/territory and by metropolitan and non-metropolitan areas. A set of postcodes from each strata were randomly selected, and then children (in the desired age cohort) were randomly selected from the Medicare enrolment database within each postcode. One child per family was included in the sample. The study design for LSAC data collection is described in detail by Soloff, Lawrence, and Johnstone (2005) [15]. This

study paper utilises data from seven waves of the B cohort and eight waves of the K cohort, collected between 2004 and 2018. The LSAC databases were linked to each child's Medicare records, from which the study collected the healthcare cost data. This study considered both the cohort and pooled data to analyse the longitudinal healthcare services costs associated with the illness of asthma.

Parent consent was obtained at wave one, with 97 per cent providing additional consent for data linkage with the child's Medicare records, the national government health scheme that subsidises virtually all Australians for visits to family doctors or specialists and prescription medications. The LSAC was approved by the Australian Institute of Family Studies Ethics Committee.

Sample

As LSAC captured asthma-related data from Wave-2 of the B cohort when the children were 2–3 years of age and Wave-1 of the K cohort when the children were 4–5 years of age, we could not use Wave-1 data of B cohort for this study. A total of 4,534 K cohort children in the first survey and 4,175 B cohort children in the second survey were linked to Medicare records and, therefore, eligible for inclusion in this study. After excluding children with missing values for any variables included in the model, the total sample size for the primary analysis was 4,175 B cohort children and 4,482 K cohort children. The total sample from these two cohorts was 8,657 children who were followed up in the subsequent waves. Hence, the eligible total pooled observations were 51,839 children from seven waves of B cohort and eight waves of K cohort surveys that were linked with Medicare data. The pooled number of children by age group is presented in the result section table. The number of children who were present for all the surveys until 2018 was 1,826 for the B cohort and 1,459 for the K cohort. The longitudinal asthma morbidity persistence analyses and asthma hospitalisation analyses were carried out with these samples.

Healthcare costs

Healthcare (Medicare) costs to the Australian Government through its universal healthcare system were obtained from the Medicare database, into which ≈ 98 per cent of children nationwide are enrolled by age one [7]. Costs included the subsidies for healthcare services/attendances (Medicare Benefit Schedule [MBS]) and prescription medications (Pharmaceutical Benefits Scheme [PBS]). The federal government subsidises almost all medical care costs (including all general practitioners, plus a large proportion of paediatrician visits) of virtually all Australians through the MBS, with only ≈ 15 per cent of scheduled fee are paid by the patient. The government pays around 83 per cent of the costs of approved pharmaceuticals for around 75 per cent of all prescriptions dispensed in Australia, with the remainder paid by the patient [7, 16]. The remainder of the medication costs can be termed as the gap between the scheduled fee and fee actually charged. These costs are the out-of-pocket cost borne by the patients and have not been considered in this study as these data are not collected in LSAC.

In the data depository, the Medicare costs of LSAC study children were accumulated continuously, but asthma morbidity was measured in the biennial surveys. Hence, for the age group excess healthcare costs analyses, costs data were collapsed into seven 24-month bands for the B cohort and eight 24-month bands for the K cohort, during which the child's asthma morbidity status was also measured. Costs were inflated to 2018 Australian dollars using the Australian Bureau of Statistics consumer price index. For asthma morbidity persistence and asthma hospitalisation analyses, cost implications of the duration of treating asthma were examined using the inflation-adjusted total costs available for those individuals who were present in all waves (B cohort: birth to 14th birthday; K cohort: 4th to 18th birthday). This study did not conduct any separate analysis for PBS costs. Instead, it considered the total Medicare

(MBS + PBS) costs in the models because MBS accounts for 97 per cent of total Medicare costs [7].

Asthma

To measure the children's asthma morbidity, in every LSAC survey, the caregivers (above 97 per cent of them are biological mothers) were asked whether a doctor had ever diagnosed the child with asthma. Then, in the follow-up question, it was asked if the child had taken any medication for asthma in the last 12 months. If the caregivers responded 'yes' to this question, then their children were considered 'currently being treated for asthma' in this study. If the caregivers responded 'no' to this question, then their children were considered 'currently not asthmatic'. Further, this study also measured whether the child was hospitalised for asthma treatment in each wave's survey.

Control variables

A range of demographic, socio-economic and child health characteristics were included in the base model to isolate the influence of asthma status on Medicare costs. These include indicators of gender, low birth weight, breastfeeding status, residential status, language spoken at home, both parents at home and socio-economic position. Among these characteristics, gender, low birth weight, breastfeeding status and language spoken at home were taken from the first survey and time-invariant. To account for the underlying determinants of child health, low birth weight (< 2,500 grams) and breastfeeding status (< 6 months) were included in the model as these characteristics increase the risk of multiple health morbidities, including asthma [17, 18]. The attributes of language spoken at home, whether single parent at home and the parents' socio-economic position score were included in the model to control for ethnic, cultural and access to health promotion information, which may impact on a child's health [19, 20]. Further, the attributes of whether the child

resides in inner-regional, rural or remote Australia were also included in the model to account for the accessibility of medical services.

As this study aimed to estimate the direct association between asthma morbidity and healthcare costs, other health conditions or general health measures were not included in the base model. This approach has the advantage of making no a priori decisions as to which additional health conditions may be caused by asthma. Still, it allows for the possibility that asthma may lead to high health costs in conjunction with other health conditions, for example, eczema. However, to further minimise the potential for confusion, several common child health conditions (which may increase health costs but are not likely attributable to asthma morbidities) were included in a supplementary model. This model included additional indicators for whether the child reportedly had hearing problems, vision problems, attention deficit hyperactivity disorder (ADHD) or obesity. Estimates for both the base model and supplementary model are presented, however, throughout the article estimates of the base model were interpreted or described.

Analytic strategy

Sample weights were employed in all analyses using STATA survey techniques to consider both the unequal likelihood of children being selected, recruited and retained in subsequent waves and adjustment for non-response. Cross-sectional associations between asthma status and total healthcare costs were examined using generalised linear modelling (GLM) with the combination of log link and gamma distribution, as Au (2013) reported that this is the best-fitted model in analysing healthcare cost data [8]. The regression models were then adjusted for covariates in two stages, which constitute the base model and substitute model. These covariates are described in the control variable section. However, throughout the study, we described the results from the base model. Using the GLM mean estimates per child from the base model and prevalence

rates from this study, we also modelled the costs to the population level to estimate the total Medicare costs accrued by all children from wave one to eight and also showed how much may have been avoided had all children been non-asthmatic. This study also devised the dynamic model to estimate the asthma morbidity persistency, first by the duration of current asthma treatment and then by the category of asthma hospitalisation at any point. The reference group was non-asthmatic children, with seven waves for the B cohort and eight waves for the K cohort.

The generalised linear models are derived from the equation of linear model which can be written as:

$$y = X\beta + \epsilon \quad (1)$$

where Є is a vector of n normal random errors. As a result, the residual sum of squares is given by:

$$(y - X\hat{\beta})'(y - X\hat{\beta}) = \sum_{i=1}^{n}(y_i - \hat{y}_i)^2 \quad (2)$$

Straightforward calculus gives $\hat{\beta}$ as the solution to

$$X'\left(y - X\hat{\beta}\right) = 0 \quad (3)$$

or alternatively,

$$\sum_{i=1}^{n}(y_i - \hat{y}_i)X_i = 0 \quad (4)$$

where x_i represents the ith row of the X matrix, thus describing the ith data point in model form. The equivalent expressions in (3) and (4) represent the score equation which characterizes generalized linear models. The set of regressor variables $x_1,\ x_2,\ \ldots,\ x_k$ enter through what is called the linear predictor $x'\beta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$. The complete model is constructed through a relationship that is assumed between the distribution mean and the linear predictor. This is not at all unlike ordinary normal theory linear modeling in which we have

$$E[y] = \mu = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

$$\mu = X'\beta \quad (5)$$

This equation (5) contains the GLM approach. In general, in the combination of log link and gamma distribution, the relationship between the population mean and the linear predictor is determined by the following log link function

$$ln(\mu) = X'\beta$$

which produces the model

$$\mu = e^{x'\beta} \quad (6)$$

For devising the GLM model and estimating the marginal means, we used the glm command of STATA 16 with options for gamma distribution and long link. Further details of the GLM model and Stata command are described elsewhere [21, 22].

Results

Among the 2–3 to 18–19-year-olds, 12–16 per cent were currently being treated for asthma across different age groups (see Figure 1). Table 1 shows that among the sampled children, total Medicare costs per child (A$980–A$1,237) for 14–19-year-olds in later childhood were approximately double those accrued during early childhood by 2–5-year-olds (A$530–A$660). The total pharmaceutical cost per child was five times higher (approximately A$250) during adolescence at age 14–19 than the cost of early childhood (approximately A$50). However, among the pooled data of all waves of the B and K cohort children, where the average age of children stands at around nine years, the prevalence of asthma is 14.9 per cent and the average total healthcare cost is A$878. The distribution of total healthcare costs accrued every two years by age group are shown in histograms with kernel density plot in Figure 2. Extreme costs (> 99 percentile) were excluded to draw the distribution graph to ensure smooth visibility.

Significant cost differences by asthma status were evident in all age groups of the children who were followed up in a subsequent two-year period (see Table 2). At all ages, costs rose as children grew older. In

particular, among the age group of 2–3-year-old children, the two-year costs accrued by the children currently being treated for asthma were A$305 higher compared with their non-asthmatic peers. These cost differences were A$766 among children aged 18–19 years who were currently being treated for asthma. Total excess healthcare costs among the sampled 2–18-year-old children associated with asthma are A$4,316 per child.

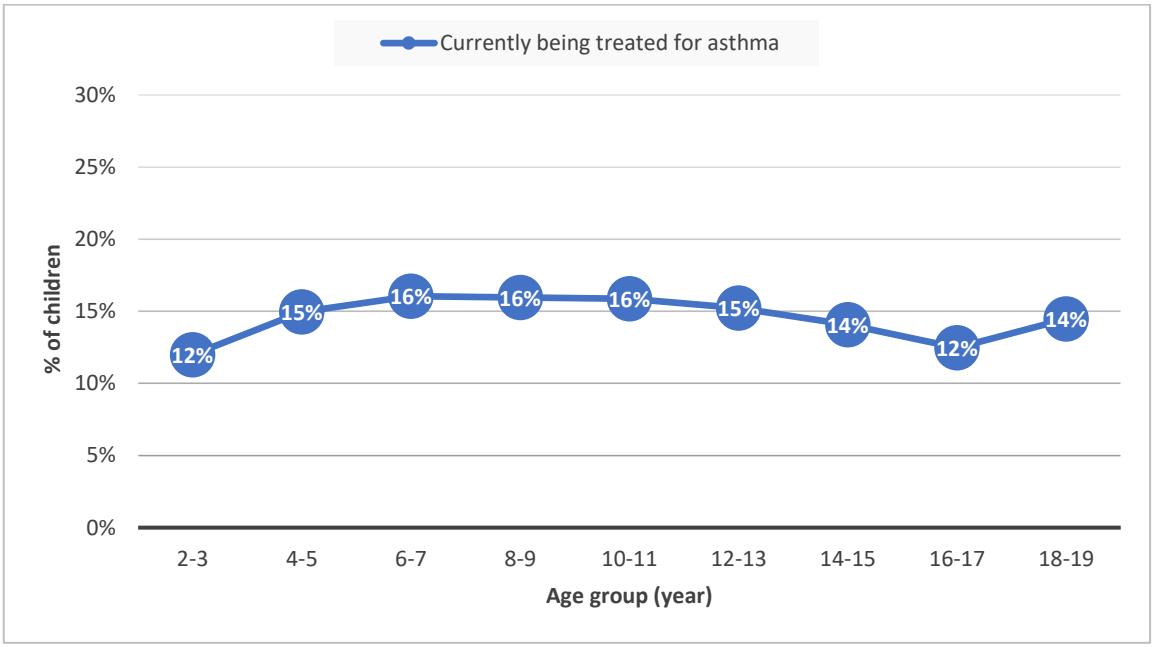

Figure 1: Prevalence of asthma morbidities among the study children by age group, 2004–2018

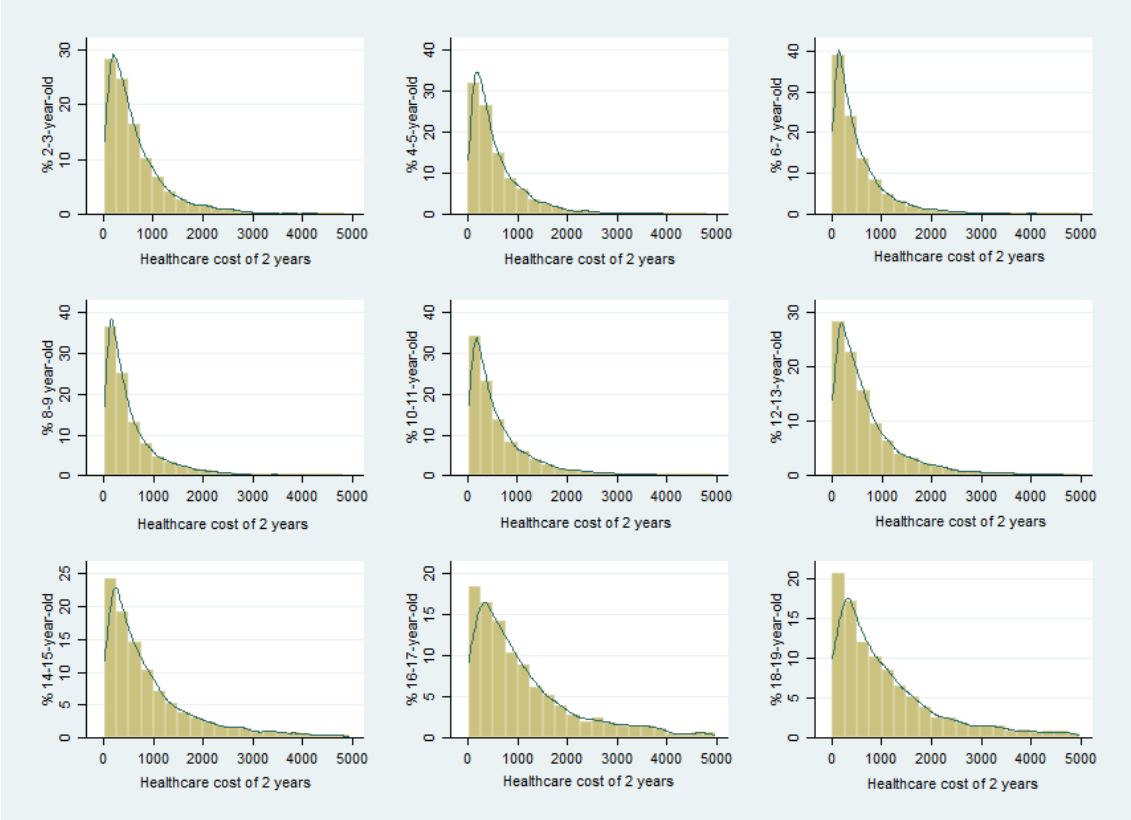

Figure 2: Distribution of total healthcare costs by age group, 2004–2018

Table 1: Characteristics of children in selected waves of B and K cohorts in the pooled data

Child Characteristics	Birth Cohort		Kindergarten Cohort		B & K Cohort
	Wave 2	Wave 8	Wave 1	Wave 8	Pooled
Unweighted sample size (n)	4,175	2,737	4,482	2,296	51,839
Age group (in years)	2–3	14–15	4–5	18–19	2–19
Average age, years: mean (SE)	2.3 (0.008)	14.3 (0.01)	4.2 (0.006)	18.4 (0.01)	9.15 (4.5)
Sex, male (%)	51.6	51.2	51.2	48.6	51.2
Asthma morbidity status (%)					
Currently not asthmatic	87.9	85.9	84.7	85.6	85.1
Currently being treated for asthma	11.9	14.0	15.3	14.5	14.9
Low birthweight, < 2,500 gm (%)	5.6	5.3	8.3	7.4	7.0
Breast fed < 6m (%)	46.3	49.4	54.4	58.8	52.2
Language spoken at home (%)					
Speaks English-*ref*	87.6	86.5	86.2	87.1	87.0
European language	3.5	3.9	4.1	3.6	3.8
Other language	8.7	9.5	9.9	9.3	9.2
Single parent	12.4	21.1	14.8	36.3	18.7
Remoteness of residence (%)					
Major Cities of Australia-*ref*	67.7	67.9	67.9	67.0	67.2
Inner Regional Australia	19.6	21.4	18.7	18.6	20.6
Outer Regional Australia	11.2	9.7	11.7	8.4	10.6
Remote Australia	1.41	0.9	1.6	6.0	1.6

Socio-economic position by quantile (%)					
Q1	25.4	27.4	23.2	25.9	25.0
Q2	21.2	21.3	21.3	21.3	20.9
Q3	18.9	19.3	19.9	20.1	19.0
Q4	17.6	16.5	18.6	17.2	17.4
Q5	16.9	15.4	17.0	15.5	17.7
Obesity (%)					
Normal-*ref*	71.5	64.9	74.0	48.7	65.6
Underweight	5.1	5.7	5.2	17.1	10.1
Overweight	18.5	20.5	15.4	20.7	17.5
Obese	4.7	8.9	5.4	13.5	6.7
Eczema (%)	17.7	9.9	12.4	8.3	11.5
Hospitalised for asthma (%)	1.6	0.3	0.8	0.2	0.6
ADHD (%)	0.97	4.4	1.3	3.4	2.8
Hearing problem (%)	1.1	0.5	2.1	0.3	0.9
Vision problem (%)	0.6	1.0	0.8	14.4	1.5
Speech problem (%)	3.1	0.7	0.7	0.5	2.4
Healthcare cost in A$: mean (SE)					
MBS	660.4 (11.6)	979.4 (27.9)	529.9 (9.23)	1,236.7 (38.8)	
PBS	51.6 (8.1)	249.2 (68.4)	47.2 (4.8)	246.4 (40.5)	
Total Medicare	712 (16.6)	1,228.7 (76.2)	577.0 (11.1)	1,483.1 (59.4)	877.7 (9.6)

Note: Units of the values are specified in parenthesis in the first column. Costs in 2018 A$. MBS, Medicare Benefit Scheme. PBS, pharmaceutical benefit scheme. Total healthcare costs = MBS + PBS.

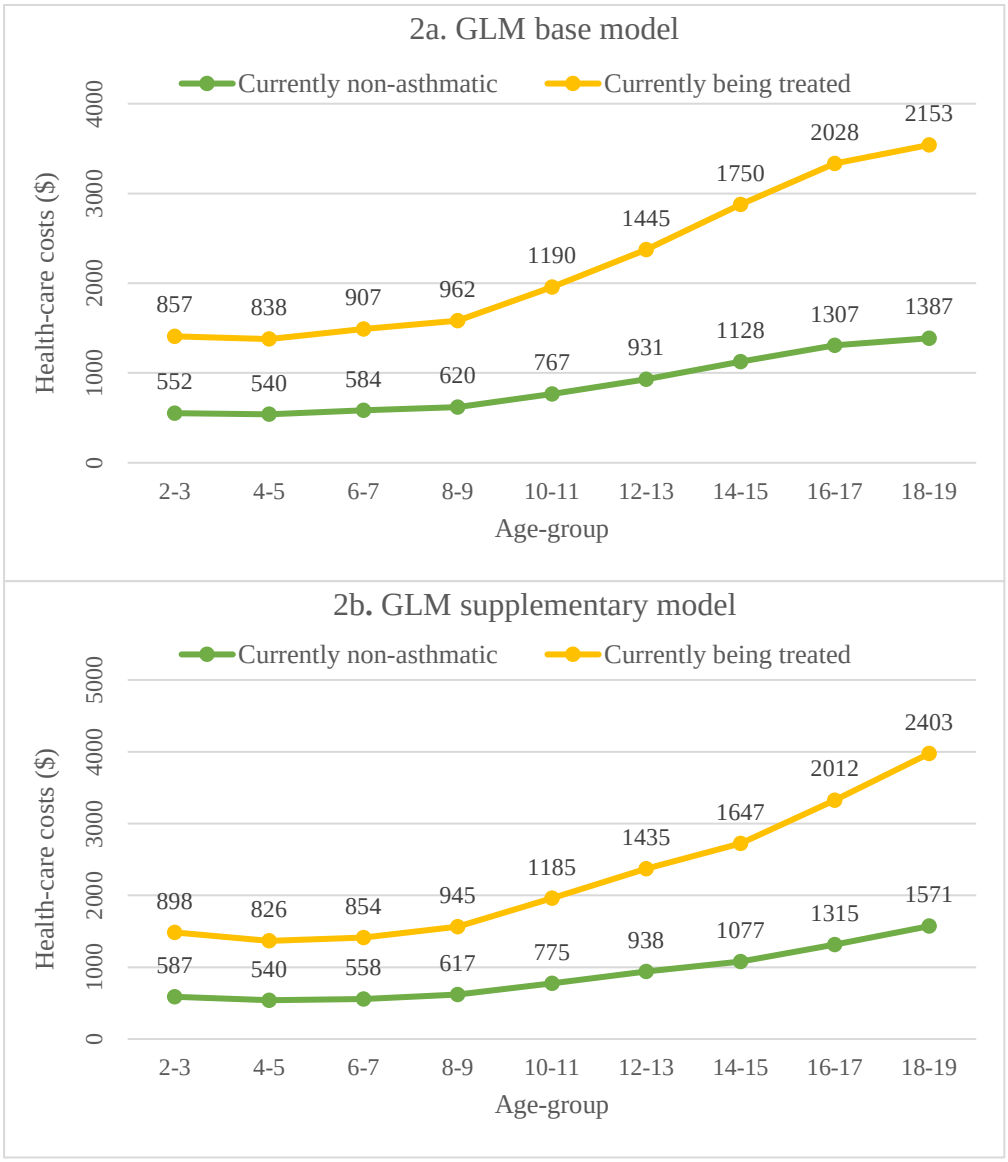

Figure 3: Two-year total Medicare costs (A$ mean) per child by asthma morbidity status and age (2a) GLM base model (2b) GLM supplementary model

Table 2: Two-year total Medicare costs ($ mean [SE]) per child by Asthma morbidity status and age

Age-group (year)	No. of children	Base Model[1] Children without asthma vs currently treating for asthma		Supplementary Model[2] Children without asthma vs currently treating for asthma	
		Diff (SE)	P-value[3]	Diff (SE)	P-value[3]
Pooled data					
2–3	4,175	305 (13)	< 0.001	311 (16)	< 0.001
4–5	8,509	298 (13)	< 0.001	286 (13)	< 0.001
6–7	7,608	323 (13)	< 0.001	296 (14)	< 0.001
8–9	7,380	342 (14)	< 0.001	327 (15)	< 0.001
10–11	6,956	423 (17)	< 0.001	410 (20)	< 0.001
12–13	6,716	514 (25)	< 0.001	497 (19)	< 0.001
14–15	5,684	623 (27)	< 0.001	570 (28)	< 0.001
16–17	2,515	722 (45)	< 0.001	697 (33)	< 0.001
18–19	2,296	766 (42)	< 0.001	832 (56)	< 0.001
Total excess costs[4]		A$4,316		A$4,126	

[1]Analyses are adjusted for socio-demographic (low birth weight, breastfeeding, residential status, language spoken at home, both parents at home, socio-economic position) variables in the base model. [2]Analyses are adjusted for child health conditions unrelated to asthma (obesity, ADHD, hearing problems, speech problems), in addition to socio-demographic variables for the supplementary model. [3]*P*-value for testing if children in the currently being treated category have unequal cost differences from children in the currently non-asthmatic category.[4]Total excess healthcare costs per child across 2-3-to-18–19-year age duration

Modelling individual-level data (mean healthcare cost and asthma prevalence) to the 2018 population of all Australian children aged 2–19 years, this study estimated the total excess Medicare costs associated with asthma to be approximately A$381.1 million every two years, or on average A$190.6 million per year (see Table 3). This study also investigated costs caused by the persistence of asthma morbidity compared with non-asthmatic children (see Table 4). Compared to the non-asthmatic children, peers with persistent asthma morbidity and treatment requirements had excess costs up to A$20,727 for the B cohort children until 14 years of age, while excess costs for the K cohort children were A$19,571 until 18 years of age. In both cohorts, the duration of persistence of asthma morbidity and treatment strongly influenced increasing the excess costs. This table also reported the healthcare cost differences of children ever treated asthma without hospitalization (A$2,628) and ever hospitalized for asthma (A$4,266), compared to healthcare costs of children in B cohort having no asthma treatment across

all the waves. For K cohort children these cost differences are a bit less compared to the B cohort children (see Table 4).

Table 5 shows the healthcare costs of Australian children associated with the following morbidities: ADHD, obesity, mental health, sleep problems and asthma, derived from existing studies and this study. To enable a comparison, we derived the excess healthcare costs per child with similar study duration and inflated to 2018 Australian dollar. It shows that ADHD incurs the highest healthcare costs, A$2,527, followed by asthma morbidity, A$963 for five years or $1268 for seven years for a child. All these costs indicate the total MBS and PBS costs. However, while interpreting, we should be cautious as these results come from a different duration of years or different age groups and the estimation methods are also different.

Table 3: Estimated total Medicare costs (A$) over two years for the Australian children aged 2–3 to 18–19 years

Age group (years)	Australian population†	Projected population (Currently treating asthma)	Costs in A$ millions for children without asthma Estimate (95% CI)	Excess costs in A$ millions for children currently treated for asthma‡ Estimate (95% CI)
(1) Base Model				
2–3	642,101	76,962	311.9 (299.7 to 324.1)	23.5 (22.4 to 24.5)
4–5	642,327	96,151	294.9 (287.5 to 302.2)	28.7 (27.1 to 30.2)
6–7	641,283	102,910	314.6 (306.7 to 322.4)	33.2 (31.8 to 34.6)
8–9	639,256	102,078	333.0 (323.9 to 342.1)	34.9 (33.2 to 36.7)
10–11	632,190	100,259	407.9 (397.1 to 418.8)	42.5 (40.7 to 44.2)
12–13	595,542	90,647	470.1 (434.8 to 505.4)	46.6 (43.6 to 49.6)
14–15	573,762	80,747	555.9 (517.7 to 594.1)	50.3 (47.6 to 52.9)
16–17	581,248	72,519	664.8 (593.2 to 736.3)	52.3 (47.1 to 57.6)
18–19	623,919	90,251	740.1 (665.1 to 815.1)	69.1 (63.3 to 74.9)
			Total excess costs:	A$381.1 million
(1) Supplementary Model (Includes adjustment for health conditions)				
2–3	642,101	76,962	331.8 (321.0 to 342.6)	23.9 (22.5 to 25.4)
4–5	642,327	96,151	295.0 (286.3 to 303.8)	27.5 (26.5 to 28.6)
6–7	641,283	102,910	300.4 (289.3 to 311.5)	30.4 (29.4 to 31.4)
8–9	639,256	102,078	331.7 (322.6 to 340.7)	33.4 (32.0 to 34.7)
10–11	632,190	100,259	412.1 (399.9 to 424.3)	41.1 (39.2 to 43.1)
12–13	595,542	90,647	473.5 (436.4 to 510.7)	45.0 (44.0 to 46.0)
14–15	573,762	80,747	530.9 (493.6 to 568.1)	46.1 (43.7 to 48.5)
16–17	581,248	72,519	669.0 (595.8 to 742.2)	50.5 (47.5 to 53.5)
18–19	623,919	90,251	838.4 (757.6 to 919.2)	75.1 (67.4 to 82.9)
			Total excess costs:	A$373 million

Analyses are adjusted for covariates. Values assume that the cohort at each age was representative of the population in June 2018. †Estimated Australian population by the age groups are as of June 2018. ‡Excess population cost accrued by the children currently treated for asthma above the amount accrued by their peers not treating for asthma.

Table 4: Total Medicare costs per child by the incidence of asthma, all waves

Asthma morbidity models		Total average costs (A$) accrued across all the waves					
		Base Model			Supplementary Model		
	n	Mean (SE)	Diff (95% CI)	*p*-value	Mean (SE)	Diff (95% CI)	*p*-value
B Cohort – 14 year total Medicare costs		*Costs (A$) are accumulated from age 2 to 14 years*					
Asthma morbidity persistence model							
No asthma across all waves	1,286	5462 (121)	reference	<0.001	5531 (127)	reference	< 0.001
Had asthma and treated for:							
1 wave only	111	7402 (713)	1941 (499 to 3382)		7378 (489)	1847 (861 to 2833)	
2 waves	94	7467 (575)	2006 (874 to 3137)		7272 (547)	1741 (679 to 2803)	
3 waves	76	7063 (822)	1601 (5 to 3197)		6534 (443)	1003 (126 to 1879)	
4 waves	61	7425 (783)	1963 (363 to 3563)		7169 (551)	1638 (475 to 2801)	
5 waves	63	7531 (595)	2069 (930 to 3209)		7733 (586)	2202 (1010 to 3393)	
6 waves	79	10705 (1066)	5243 (3153 to 7333)		10263 (1053)	4732 (2624 to 6841)	
7 waves	56	11366 (1033)	5904 (3907 to 7902)		11232 (849)	5701 (4011 to 7390)	
		Total excess costs:	**A$20,727**			**A$18,864**	
Asthma hospitalisation model							
No asthma across all waves	1,286	5465 (141)	reference	<0.001	5542 (128)	reference	<0.001
Ever treated, never hospitalised	483	8093 (275)	2628 (2002 to 3254)		7895 (223)	2354 (1785 to 2922)	
Ever hospitalised	58	9731 (1054)	4266 (2230 to 6302)		9190 (767)	3649 (2135 to 5163)	
K Cohort – 16 year total Medicare costs		*Costs (A$) are accumulated from age 4 to 18 years*					
Asthma morbidity persistence model							
No asthma across all waves	933	7616 (309)	*reference*	<0.001	7596 (295)	*reference*	< 0.001
Had asthma and treated for:							
1 wave only	157	8578 (612)	963 (-358 to 2283)		8606 (557)	1010 (-131 to 2151)	
2 waves	68	10516 (1888)	2900 (-874 to 6675)		10613 (1761)	3018 (-400 to 6436)	
3 waves	52	9319 (1007)	1704 (-164 to 3572)		9363 (1111)	1768 (-612 to 4147)	
4 waves	44	9614 (1242)	1998 (-487 to 4483)		9290 (1632)	1694 (-1468 to 4857)	
5 waves	47	9920 (1700)	2304 (-1165 to 5774)		10193 (1950)	2598 (-1251 to 6446)	
6 waves	49	10686 (1443)	3070 (153 to 5987)		10414 (1451)	2819 (7 to 5631)	
7 waves	48	10417 (1045)	2801 (548 to 5055)		11022 (1137)	3426 (1301 to 5551)	
8 waves	61	11447 (1017)	3831 (1772 to 5891)		11733 (1117)	4137 (1891 to 6383)	
		Total excess costs:	**A$19,571**			**A$20,470**	
Asthma hospitalisation model							
No asthma across all waves	933	7625 (325)	*reference*	<0.001	7640 (279)	*reference*	<0.001
Ever treated, never hospitalised	492	9843 (446)	2219 (1229 to 3208)		9843 (384)	2203 (1397 to 3009)	
Ever hospitalised	34	9019 (1086)	1395 (-863 to 3652)		8930 (974)	1290 (-687 to 3268)	

Table 5: Comparison of healthcare costs of children (associated with asthma and other health conditions) with the previous studies that used LSAC data

Study	Health condition	Age range and cohort	Study method	Excess cost per child (A$)			
				Costs per total study duration (price year)	Costs per total study duration in 2018 price (A$)	Costs at population level in reported price year (A$m)	Costs at population level inflated to 2018 price (A$m)
Sciberras et al. (2013)	ADHD	4/5 to 8/9 years–K cohort	GLM	2,245/5 years (2012)	2527	24.0	27.0
Sciberras et al. (2013)	ADHD symptoms	4/5 to 8/9 years–K cohort	GLM	753/5 years (2012)	827	30.0	33.8
Clifford et al. (2015)	Overweight	2/3 to 8/9 years–B/K cohort	OLS	214/7 years (2011)	244	13.7	15.6
Clifford et al. (2015)	Obese	2/3 to 8/9 years–B/K cohort	OLS	409/7 years (2011)	466	11.0	12.5
Au, Nicole (2012)	Overweight/Obese	4/5 to 8/9 years–K cohort	GLM	93/5 years (2008)	115	9.8	12.1
Lucas et al. (2013)	Mental health	4/5 to 8/9 years–K cohort	GLM	909/5 years (2009)	1106	4.7	5.7
Quanch et al. (2013)	Sleep problem	4/5 to 6/7 years–K cohort	OLS	226/4 years (2012)	254	11.0	12.4
This study (2022)	Asthma	2/3 to 8/9 years–B/K cohort	GLM	1,268/7 years (2018)	1268	120.3	120.3
This study (2022)	Asthma	4/5 to 8/9 years–B/K cohort	GLM	963/5 years (2018)	963	96.8	96.8

Discussion

This is the first Australian study that primarily examines the healthcare costs associated with asthma morbidity that accrue from age two to 19 years from nationally representative samples of Australian children. Over the 12 years for the B cohort children and 14 years for the K cohort children, children who were currently being treated for asthma or had been diagnosed with asthma at some point incurred significantly higher healthcare costs. Generally, non-asthmatic children accrued the lower costs and children currently being treated for asthma had the higher costs at each age group. These increased costs to the Australian healthcare system create an additional estimated burden of A$190.6 million per year in the population of 2-3-to–18-19-year-old Australian children. The more waves at which both B and K cohort children had asthma, the higher their excess costs tended to be. Total excess accumulated average cost per child was A$5,124 for the B cohort children and A$2,994 for the K cohort children who were asthmatic across all the waves.

In accordance with this study, there is existing literature on the healthcare costs of Australian children with the same cohorts of LSAC surveys. These studies evaluated the costs associated with ADHD, obesity, mental health and sleep problems and mostly used the first three waves of K cohort children aged 2/3-to-8/9 years [7–11]. Among these morbidities, ADHD incurs the highest total excess healthcare costs per child during the ages of 4/5-to-8/9 years (A$2,527), followed by asthma (A$1,268), mental health (A$1,106), ADHD symptoms (A$827) and obesity (A$244 for overweight and A$466 for obese children). While the individual excess costs per child were smaller for asthmatic children than children with ADHD, the estimated whole-population costs were collectively substantial and the highest (A$120.3 million) among all the reported NCDs for this comparable age group (ranging from A$5.7 million to A$33.8 million). This is due to the persistent and higher rate of prevalence of asthma in the population across childhood (12–16 per cent) as well as continuous requirement of healthcare costs. Further, these comparisons are reliable

given that all the comparisons are made on the contemporary Australian children and inflated to 2018 price.

This study adds value to the existing literature by highlighting that the increased healthcare costs associated with currently being treated for asthma emerge from as early as 2–3 years and steadily rise with the growth of children until 18–19 years. Higher Medicare costs appeared to be particularly driven by the higher MBS costs associated with specialist services at all ages (e.g., paediatricians), with differentials in general practitioner and allied health costs emerging with age [7, 16].

This study demonstrates that excess healthcare costs associated with asthma morbidity are significantly prevalent at all stages of childhood: in early childhood, primary school age and adolescence. However, among this excess healthcare cost burden, around half occurs during adolescence, while over one-third occurs at primary school age. This pattern of excess costs would inform health policy makers about the target groups and how to administer project interventions. Further, research evidence suggests that maternal health conditions and health-risk behaviours, for example, maternal asthma, smoking and anti-biotic or anti-depressant medication during pregnancy, increase the risk of childhood asthma [6, 23]. Environmental conditions and multi-morbidity of children also increase the risk of asthma [23, 24]. Hence, besides the pharmacological intervention strategies, non-pharmacological strategies of asthma management combined with education, environmental control and self-management with appropriate target groups would be most effective in reducing the extra healthcare costs of asthma [25].

One of the unique contributions of the study is to examine the relationship between healthcare costs and the persistence of childhood asthma. The persistent costs occur between the ages of two to 19 and increases with age. Similarly, healthcare costs also increased with the persistence of being treated for asthma over multiple waves. For example, excess healthcare costs (both MBS and PBS) for children treated for

asthma in two or more waves were over double or nearly triple that of children treated for asthma in only one wave. Further, this study also provides a comparative picture of excess healthcare costs of children who ever treated asthma but never hospitalised and who ever hospitalised for asthma treatment among Australian children. These study findings may support policymakers in the early detection and treatment of childhood asthma morbidities.

A strength of this study is that nationally representative longitudinal surveys with linked data on children were used to obtain information on healthcare costs over 12 to 14 years by the status of asthma morbidities. Further, analyses were adjusted for covariates of demographic and health conditions, providing relatively precise cost estimates and ensuring the generalisability of findings. Another strength of the study is that each child's lifelong healthcare costs were extracted directly from the linked data of Medicare, a complete record of primary medical care and pharmaceutical costs, excluding the out-of-pocket costs, that commonly informs the total healthcare cost of Australian government, excluding specialised private hospital or clinical costs. This study's findings enabled us to provide a public healthcare cost baseline to judge the additional costs of delivering treatments over a more extended period and an exploration of the dynamics of childhood asthma, consistent or periodic, concerning healthcare costs, which was not possible in previous cross-sectional studies [23, 24, 26].

A limitation of this study is that the analyses do not include private hospital cost data, which are difficult to access, particularly individual-level data. Our data include only the cost of healthcare services that Medicare reimburses which include public hospital's in-patient and outdoor costs and PBS costs. In contrast, total healthcare spending includes all hospital and non-doctor delivered community care costs, payments by the patients themselves and payments by the insurance companies on the patient's behalf. Our cost estimate also could not include broader costs regarding society's out-of-pocket expenditures of families, parent time and loss of

productivity and other indirect costs; and even the partial PBS cost borne by the patients as out of pocket cost. Hence, the total true healthcare expenditure associated with asthma morbidities would be substantially more than the Medicare costs reported in this study. Second, though this study adjusted for several health conditions, we may not infer that the excess costs revealed in this study are directly attributable to the children's asthma morbidity status. There are potentially residual confounding variables such as causes or comorbidities associated with persistent and non-persistent asthma or severe and non-severe asthma. Nevertheless, the increased costs associated with asthma morbidities demonstrate that they incur increased healthcare costs, even after accounting for differences in other health conditions (obesity, ADHD, hearing problems, vision problems and speech problems) between children with and without asthma. Additionally, the extrapolation of the excess costs accrued by the children with asthma morbidities to the population level should be interpreted with caution. As costs are based on the accuracy of the predicted average Medicare cost of asthmatic children, it assumes the weighted prevalence of asthma in LSAC corresponds to the actual population prevalence of asthma for children of different age groups: 2–3 years to 18–19 years.

Conclusion

In conclusion, using a nationally representative longitudinal data set of Australian children, this study found higher excess healthcare costs among asthmatic children compared to non-asthmatic children. The temporal trends of the excess healthcare costs indicate that, on a national level, childhood asthma at age 2–3 to 18–19 incur double the excess costs among children currently being treated for asthma compared to the excess cost of the children diagnosed with asthma but currently not being treated for it. The large population-level healthcare cost burden for asthma and continued excess cost over the time from age two to 19 represent an ongoing public health challenge. There is a need to prioritise solutions for childhood asthma to further improve childhood health and well-being. Future research should focus on the cost-effectiveness of prevention and

intervention programmes for childhood asthma problems, including persistent asthma. From an economic perspective, this study's findings suggest cost-effective strategies for both the prevention and early treatment of childhood asthma. In particular, reducing asthma incidences in childhood, averting persistent asthma, enhancing interventions of education and self-management could pay remarkable dividends to the government and society at large, both at present and in the future.

References

1. Australian Institute of Health and Welfare 2018: **Australia's health 2018**. In: *Australia's health series no 16.* vol. AUS 221. Canbera: AIHW.
2. World Health Organisation (2021) ***Asthma.*** Available at: https://www.who.int/news-room/fact-sheets/detail/asthma (Accessed: 29 August 2021)
3. Asthma Australia (2020) ***Asthma Basic Facts*****.** Available at: https://asthma.org.au/wp-content/uploads/2020/05/AABF2020-Asthma-Basic-Facts-DL_v6_digital.pdf (Accessed: 8 September 2020)
4. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP: **Global asthma prevalence in adults: findings from the cross-sectional world health survey**. *BMC Public Health* 2012, **12**:204.
5. Australian Centre for Asthma Monitoring: **Asthma in Australian children: findings from Growing Up in Australia, the Longitudinal Study of Australian Children**. In. Canberra: AIHW; 2009.
6. Ahmad K, Kabir E, Ormsby GM, Khanam R: **Are wheezing, asthma and eczema in children associated with mother's health during pregnancy? Evidence from an Australian birth cohort**. *Archive of Public Health* 2021, **79**(1):193.
7. Clifford SA, Gold L, Mensah FK, Jansen PW, Lucas N, Nicholson JM, Wake M: **Health-care costs of underweight, overweight and obesity: Australian population-based study**. *Journal of Paediatric and Child Health* 2015, **51**(12):1199–1206.
8. Au N: **The health care cost implications of overweight and obesity during childhood**. *Health Services Research* 2012, **47**(2):655–676.
9. Lucas N, Bayer JK, Gold L, Mensah F, Canterford L, Wake M, Westrupp EM, Nicholson JM: **The cost of healthcare for children with mental**

health difficulties. *Australian and New Zealand Journal of Psychiatry* 2013, **47**(9):849–858.

10. Quanch J, Gold L, Hiscock H, Mensah FK, Lucas N, Nicholson JM, Wake M: **Primary healthcare costs associated with sleep problems up to age 7 years: Australian population-based study**. *BMJ Open* 2013, 3(5).
11. Sciberras E, Lucas N, Efron D, Gold L, Hiscock H, Nicholson JM: **Health Care Costs Associated With Parent-Reported ADHD: A Longitudinal Australian Population-Based Study**. *Journal of Attention Disorders* 2013, **21**(13):1063–1072.
12. Hasegawa K, Tsugawa Y, Brown DF, Camargo CA, Jr.: **Childhood asthma hospitalizations in the United States, 2000**–2009. *Journal of Pediatrics* 2013, **163**(4):1127–1133 e1123.
13. Barbosa JP, Ferreira-Magalhaes M, Sa-Sousa A, Azevedo LF, Fonseca JA: **Cost of asthma in Portuguese adults: A population-based, cost-of-illness study**. *Revista Portuguesa de Pneumologia (English Edition)* 2017, **23**(6):323–330.
14. Ferreira de Magalhaes M, Amaral R, Pereira AM, Sa-Sousa A, Azevedo I, Azevedo LF, Fonseca JA: **Cost of asthma in children: A nationwide, population-based, cost-of-illness study**. *Pediatric Allergy and Immunology* 2017, **28**(7):683–691.
15. Soloff C, Lawrence D, Johnstone R: **Technical Paper no. 1: Sample design**. In: *Growing Up in Australia.* Australian Institute of Family Studies; 2005.
16. Krassnitzer L, Willis E. **The public health sector and Medicare**. In *Understanding the Australian Health Care System*, 4e. Fourth Edition ed. Elsevier Australia. 2020. p. 18-36.
17. Almond D, Chay KY, Lee DS: **The costs of low birth weight**. *The Quarterly Journal of Economics* 2005, **120**(3):1031–1083.
18. Cunningham AS, Jelliffe DB, Jelliffe EP: **Breast-feeding and health in the 1980s: a global epidemiologic review**. *The Journal of Pediatrics* 1991, **118**(5):659–666.

19. Flores G, Olson L, Tomany-Korman SC: **Racial and ethnic disparities in early childhood health and health care**. *Pediatrics* 2005, **115**(2):e183–e193.
20. Nickens H: **Race/ethnicity as a factor in health and health care**. *Health Services Research* 1995, **30**(1):151–162.
21. Myers RH, Montgomery DC. **A Tutorial on Generalized Linear Models**. *Journal of Quality Technology*. 2018;29(3):274-91. doi: 10.1080/00224065.1997.11979769.
22. stata.com. **glm — Generalized linear models.** Available at: https://www.stata.com/manuals/rglm.pdf (Accessed: 23 July 2022).
23. Lebold KM, Jacoby DB, Drake MG: **Inflammatory mechanisms linking maternal and childhood asthma**. *Journal of Leukocyte Biology* 2020, **108**(1):113–121.
24. Goudarzi H, Konno S, Kimura H, Araki A, Miyashita C, Itoh S, Ait Bamai Y, Kimura H, Shimizu K, Suzuki M *et al*: **Contrasting associations of maternal smoking and pre-pregnancy BMI with wheeze and eczema in children**. *Science of the Total Environment* 2018, **639**:1601–1609.
25. Yong YV, Shafie AA: **Economic evaluation of enhanced asthma management: a systematic review**. *Pharmacy Practice* 2014, **12**(4).
26. Motika CA, Papachristou C, Abney M, Lester LA, Ober C: **Rising prevalence of asthma is sex-specific in a US farming population**. *Journal of Allergy and Clinical Immunology* 2011, **128**(4):774–779.

9.2 Links and implications

This paper revealed that the increased costs to the Australian healthcare system due to currently being treated for asthma create an additional estimated burden of A$190.6 million per year in the population of 2–19-year-old Australian children. For the children who were asthmatic across all the waves, the total excess accumulated average cost per child was A$5,124 for the B cohort children and A$2,994 for the K cohort children. Furthermore, the excess healthcare costs for children treated for asthma in two or more waves were over double or nearly triple that of children treated for asthma in only one wave. Thus, these study findings implicate that early detection and treatment for asthma would be worthy for the nation to reduce health burden.

In the existing literature, there are cost of illness studies on Australian children's healthcare costs for several morbidities – obesity, mental health problem, sleeping problem and ADHD (Au, 2012, Clifford et al., 2015, Lucas et al., 2013, Quanch et al., 2013, Sciberras et al., 2013). However, our study on the healthcare costs associated with asthma is the first ever study accomplished so far, to the best of our knowledge. Hence, this study is a unique contribution to the extant literature. Furthermore, there exists no study on healthcare costs associated with long-term medical condition or disabilities. Hence, this thesis conducted this study as presented in the next chapter in Paper 8, the last study of the thesis.

CHAPTER 10: PAPER 8 - THE HEALTHCARE COST BURDEN OF LONG-TERM MEDICAL CONDITION OR DISABILITY: A LONGITUDINAL POPULATION-BASED STUDY OF AUSTRALIAN CHILDREN

10.1 Introduction

This chapter presents the eighth and last paper of this thesis, evaluating the cost of illness associated with having any medical condition or disability among children from birth to sixteen years in Australia. Thus, this paper is the second study of this thesis conducted for estimating the excess healthcare cost of illness in the Australian population by examining the longitudinal Medicare cost data. The Generalised Linear modelling (GLM) with log-link data and Gamma distribution was fitted and the marginal estimates were utilised to determine the excess health care costs. This study used both B and K cohort data of 9,224 children, comprising 54,258 pooled observations from Wave 1 to Wave 8 that were linked with the Medicare Benefits Schedule data and Pharmaceutical Benefits Scheme data to get the direct healthcare costs.

The healthcare cost burden of long-term medical condition or disability: A longitudinal population-based study of Australian children

Abstract

Objective: This study sought to evaluate the additional direct healthcare costs for children associated with any medical condition or disability that lasted six months or more. This study investigated the cross-sectional relationship between any medical condition or disability and healthcare costs among children aged 0 to 17 years and longitudinally assessed whether costs increase with an increase in the duration of the prevalence of medical conditions or disability.

Data sources and study setting: Study participants are 9224 children of Birth (B) and Kindergarten (K) cohorts from the nationally representative Longitudinal Study of Australian Children for whom the linked Medicare costs data are available. The children were followed in consecutive eight and seven waves for the B and the K cohort, respectively, and the pooled number of observations was 54285.

Study design: The influence of medical conditions or disabilities on healthcare costs over 14 years for the B cohort and 12 years for the K cohort were estimated using generalized linear models. All models are controlled for demographic, socioeconomic, and several selected child medical conditions.

Principal findings: From the participants of the B and K cohort, the prevalence of the medical condition or disability varies, ranging from 5 to 16%, across different age groups. However, this prevalence is 9.2% among the pooled observations of all the waves of this study for children aged 0-17 years. In both cohorts, the duration of medical conditions and treatment had a strong influence on increasing the excess healthcare

costs. Among the study children, the excess Medicare costs per child across the tenure of 0-1-to-16-17 years of age having any long-term medical condition or disability is $6247. At the population level, the estimated total excess Medicare costs associated with the medical condition or disability among 0-17 year-old children are, on average, $170 million/year.

Conclusions: Long-term medical conditions or disability incurs an additional financial burden on the public healthcare system. In Australia, at the population level, these high excess healthcare costs are evident for all ages of childhood. The estimated excess healthcare costs provide a further economic justification for promoting preventive efforts to reduce the incidence of any medical condition or disability at early ages.

Keywords: children, healthcare cost, Medicare Benefits Scheme, Pharmaceutical Benefits Scheme, medical condition, disability

Introduction

Long-term medical conditions or disabilities are the leading cause of disease burden among children. The 2004 study of the Global Burden of Disease estimated that a total of 5.1% (93 million) children aged 14 or under lived with moderate or severe disability, amongst 0.7% (13 million) survived with a severe medical condition (WHO 2008). In Australia in 2018, 7.7% (357,500) of children under 15 years had experienced a medical condition or disability with varying levels of severity conditions (ABS, 2022). The onset of medical conditions established earlier in life can influence both adult health and economic success and may impact the outcome on socioeconomic status in the long run (Palloni, Milesi, White, & Turner, 2009). However, the roles of the timing and duration of medical conditions or disabilities among children on their healthcare costs are unclear.

The impact of medical conditions or disabilities on society is immense, and it imposes huge financial pressure on the healthcare system. The cost of illness for children's medical condition or disability could be determined using the economic assessment approach, which includes two aspects: healthcare (direct cost) and societal (indirect cost). The direct cost comprises the assessment of the cost of patient care, whereas the indirect cost includes the cost of non-patient costs, such as loss of productivity (Van den Hout, 2010). The Australian healthcare system is ideal for analysing the direct healthcare costs since the system is very comprehensive and more than 99% of the population has full Medicare support. Furthermore, the Longitudinal Study of Australian Children (LSAC) captured information on childhood disability and has established the data linkage of the respondents with Medicare data. Thus, any medical condition or disability prevalence and associated healthcare costs, which included MBS and PBS costs, could be analysed.

However, to the best of the knowledge of the authors, studies on the direct and indirect costs of medical conditions or disabilities are very

limited, especially among children or adolescents in Australia. Vu et al. (2020) estimates the costs of disability in Australian adults by using the Standard of Living and a dynamic model approach. There are a few studies evaluating the healthcare costs from Medicare data on obesity, ADHD, mental health, and sleep problems in children in Australia (Au, 2012; Clifford et al., 2015; Lucas et al., 2013; Quanch et al., 2013; Sciberras et al., 2013). In US setting, hospitals costs had been made available for a research study, however those were for asthma hospitalizations, not for consolidated long-term health conditions or disabilities. These childhood asthma hospitalization data were between 2000 and 2009, which depicted that nationwide hospital expenses increased from US$1.27 billion to US$1.59 billion, though the rate of hospitalization decreased during this period by 13 percent (Hasegawa, Tsugawa, Brown, & Camargo, 2013). There are two cost of illness studies in Portuguese setting for asthma (Barbosa, Ferreira-Magalhaes, Sa-Sousa, Azevedo, & Fonseca, 2017; Ferreira de Magalhaes et al., 2017)). The study on children found that the mean annualized cost per child for asthma was €929.35 for direct costs and €230.70 for indirect costs, while for adult the costs were much less; per adult €708.16 a year, with indirect costs representing 7%. In the context of Australia, there are scarcity of hospital-based direct cost of illness data. However, the Medicare data on direct health care costs can be linked with LSAC data. As LSAC datasets contain information on medical conditions or disabilities of Australian children, a comparative analysis on healthcare costs can be performed on this type of morbidity.

This study spanned from age 0 to age 16, covering a longer period of children's data. This length of study provides a whole childhood perspective that includes early childhood and adolescence and gives an in-depth insight into when and how associations develop between disability and health care. Hence, the objective of this study is to evaluate

what amount of total healthcare costs vary by disability status over the childhood period by examining the longitudinal relationship between healthcare costs and disability status. We would also model costs to the population level to estimate the excess total healthcare costs, which included costs of the federal government through Medicare for all Australian 0- to 16 -year-old children with any medical condition or disability. This study would aid policymakers in building dynamic programs for children with any medical condition or disability to lessen their health burden, improve their performance, and reduce caregiver and society productivity losses.

METHODS

Data and setting

The LSAC is a national household survey of Australian children that biennially collects information on the health and learning development of Australian children. This study was launched in 2004 with two cohorts, where B cohort children were at age 0–1 year, and the K cohort children were at age 4–5 years. The LSAC data were collected from the parents or caregivers of the children of participating households and from the children themselves (from age 12 onward) through self-completed questionnaires or face-to-face interviews with trained interviewers. A multi-stage stratified sampling technique was used to select the LSAC respondents, where postcodes were stratified by state/territory and by metropolitan and nonmetropolitan area. A set of postcodes from each stratum were randomly selected, and then children (in the desired age cohort) were randomly selected from the Medicare enrolment database within each selected postcode. One child per household was included in the sample. Details of the LSAC survey are available elsewhere (Soloff, Lawrence, & Johnstone, 2005). Parent consent was obtained at wave 1, with 97% providing additional consent for data linkage with the child's Medicare records, the national government health scheme that subsidizes

virtually all Australians for visits to family doctors or specialists, and prescription medications. The Longitudinal Study of Australian Children was approved by the Australian Institute of Family Studies Ethics Committee. This study utilizes data from eight waves of the B cohort and seven waves of the K cohort until 2018. The LSAC databases were linked to each child's Medicare records, from which the study collected the healthcare cost data. This study considered pooled data of the waves of the B and K cohort for analysing the longitudinal healthcare services costs associated with any medical conditions or disability.

LSAC captured the medical conditions or disabilities that had lasted or were likely to last for six months or more from wave 1 of both B and K cohorts. A total of 4,742 children of the K cohort and 4482 children of the K cohort were linked to Medicare records and therefore eligible for inclusion in this study, constituting the total primary sample as 9224. Considering the subsequent followed up of eight waves from B and seven waves from the K cohort, the eligible total pooled sampled children was 54285. The number of children who were present for all the surveys until 2018 was 1818 for the B cohort and 1722 for the K cohort. The longitudinal any medical condition or disability persistence analyses were carried out with these samples.

Outcome variable: healthcare cost

The healthcare costs to the Australian government through its universal healthcare system were obtained from the Medicare database, into which ≈98% of children nationwide are enrolled by one year of age (Clifford et al., 2015). Costs were the subsidies for healthcare services/attendances (Medicare Benefits Schedule [MBS]) and prescription medications (Pharmaceutical Benefits Scheme [PBS]). The Federal Government subsidizes all sorts of medical care costs (including all general practitioners plus a large proportion of paediatrician visits) of virtually all Australians through the MBS, with only ≈15% of the costs paid by the patient. The government pays around 83% of the costs of

approved pharmaceuticals for around 75% of all prescriptions dispensed in Australia, with the remainder paid by the patient (Clifford et al., 2015; Willis, Reynolds, & Rudgea, 2019). The remainder of the medication costs, can be termed as the gap between scheduled fee and fee actually charged, are the out of pocket costs borne by the patient and have not considered in this study as these data are not collected in LSAC.

In the data depository, the costs of LSAC study children were accumulated continuously, but the medical condition or disability status was measured in the biennial surveys. Hence, for the age-group-wise excess healthcare costs analyses, costs data were collapsed into eight 24-month bands for the B cohort and seven 24-month bands for the K cohort, during which the child's medical condition or disability status was also measured. This study used the Australian Bureau of Statistics consumer price index to inflate the healthcare costs to 2018 Australian dollars. For any medical condition or disability persistence analyses, cost implications against the duration of medical condition or disability were examined using the inflation-adjusted total costs only for those individuals who were present in all the waves (B cohort: birth to 14th birthday; K cohort 4th to 16th birthday). This study conducted analyses on total Medicare (MBS + PBS) costs in the models instead of conducting separate analyses for MBS and PBS costs because MBS accounts for 97% of total Medicare costs (Clifford et al., 2015).

Independent variable: long-term medical condition or disability

The incidence of long-term medical condition/disability and disability limiting activities that had lasted, or were likely to last, for six months or more were included as any medical condition or disability. Sight problems, hearing problems, speech problems, blackouts, difficulty learning, limited use of arms or fingers, difficulty gripping, limited use of legs and feet, other physical conditions, or other disfigurements, shortness of breath or breathing difficulties, chronic or recurring pain or discomfort causing restriction, a nervous condition causing restriction, head injuries and

long-term effects as a result of head injury, stroke or other brain damage causing restriction, other long-term conditions causing restriction, or other long-term treated conditions such as arthritis, asthma, heart disease, Alzheimer's disease, dementia, etc. which have lasted or are likely to last for six months or more constitute the long-term medical conditions or disability status. A dichotomous variable was generated and coded with the value 1 for having any of this medical condition or disability and 0 for not having any of these conditions. For this study, wave 1 to 8 data were collected for the B cohort, and wave 1 to 7 data were collected for the K cohort children.

Further, the study children were also categorized as follows: (i) no disability, (ii) sensory disability only, (iii) physical disability only, (iv) psychological disability only, (v) other long-term conditions, and (vi) multiple disabilities, to perform the healthcare costs analysis by these categories of disabilities. Children with sight problems not corrected by glasses/lenses, speech problems, and hearing problems were grouped into sensory disabilities. In the physical disability category, we considered the following: any disfigurement or deformity, limited use of arms or fingers, limited use of feet or legs, difficulty gripping things, and any condition that restricts physical activity or physical work (for example, back problems, migraines), and shortness of breath or difficulty breathing. In the category of psychological disability, the following were included: any mental illness which requires help or supervision, a nervous or emotional condition that requires treatment, long-term effects as a result of a head injury, stroke, or other brain damage, and blackouts, fits or loss of consciousness. Difficulty learning or understanding things, a long-term condition or ailment which is still restrictive even though it is being treated, and any other long-term condition such as arthritis, asthma, heart disease, Alzheimer's disease, dementia, and chronic or recurring pain were considered in the category of other long-term conditions.

Control variables

A range of demographic, socioeconomic, and child health characteristics were included in the analytical model with an aim to isolate the influence of medical condition or disability status on Medicare costs. These include indicators of gender, low birth weight, breastfeeding, residential status, language spoken at home, both parents at home, and socioeconomic position. Among these characteristics, gender, low birth weight, breastfeeding, and language spoken at home were taken from the first survey and time-invariant. Low birth weight (<2500 g) and breastfeeding status (<6 months) were included in the model to account for the underlying determinants of child health, as these characteristics increase the risk of multiple health morbidities (Almond, Chay, & Lee, 2005; Cunningham, Jelliffe, & Jelliffe, 1991). The attributes of language spoken at home, whether single parent at home, and socioeconomic position score of the parents were included in the model to control for ethnicity, cultural differences, and access to health promotion information, which have all been shown to impact child's health (Flores, Olson, & Tomany-Korman, 2005; Nickens, 1995). Further, the attributes of whether the child resides in an inner-regional, rural, or remote Australia were also included in the model to account for the accessibility of medical services. For consistency, the same control variables were used throughout the analyses.

Analytical Strategy

The associations between any medical condition or disability status and total healthcare costs were examined using generalized linear modeling (GLM) with the combination of log link and gamma distribution. We opted for this modeling option as Au (2012) reported that this is the best-fitting model for analysing healthcare cost data. Details of the GLM regression modelling are presented in Chapter 9, and has not been described here as this study paper and the study of Chapter 9 used the same statistical model. The regression models were adjusted for

covariates that have been described in the control variables section. Using the GLM mean estimates per child and prevalence rates from this study, we also modelled the costs to the population level to estimate the total Medicare costs accrued by all children from wave 1 to 8 and showed how much may have been avoided had all children had no medical conditions or disability. This study also devised the dynamic model to estimate the persistency of long-term medical conditions by the duration of the morbidity. The reference group was children having no long-term medical condition at all eight waves for the B cohort and seven waves for the K cohort. Sample weights were employed in all the analyses using STATA survey techniques to take into account both the unequal likelihood of children being selected, recruited, and retained in subsequent waves and adjustment for non-response (refer to the data user guide of LSAC). All data were analysed using Stata 16.

RESULTS

The prevalence of having any medical condition or disability is 9.2% among the pooled observations of all the waves of this study children, aged 0-1 to 16-17 years (see Table 1). However, across different age groups, the prevalence of the medical condition or disability varies, ranging from 6 to 16% (see Figure 1). The higher prevalence was observed in the 4-to-7-year age group. Table 1 also shows that among the children having any medical conditions or disability, low birth weight (10.0%), breastfed less than six months (54.7%), mothers not in the labour force (42.4%), and single parents (21.5%) are more prevalent compared to the children having no long-term medical condition or disability. From the pooled data, the average healthcare costs (MBS + PBS) among all children regardless of any morbidities in a two-year period was $856, while it was $1,611 among the children who had at least a medical condition or disability.

Table 1. Descriptive Statistics of Explanatory Variables from pooled data (eight waves for B cohort and seven waves for K cohort)

Characteristics	All Children	Children having any medical condition or disability	
		Yes	No
Number of children in the first wave, B+K cohort (n)	9224	1193	8031
Pooled number of observations (n)	54258	4924	49361
Having any medical condition/disability (%)			
Yes	9.2	-	-
No	90.8	-	-
Age, years	8.7 (0.022)	8.0 (0.073)	8.7 (0.023)
Sex, male (%)	51.4	59.5	50.5
Low birthweight, <2500 gm (%)	6.9	10.0	6.6
Breastfed < 6m (%)	48.5	54.7	47.9
Language spoken at home (%)			
Speaks English - *ref*	87.0	92.0	86.5
European language	3.8	2.8	3.9
Other language	9.2	5.2	9.6
Remoteness of residence (%)			
Major Cities of Australia - *ref*	67.3	64.3	67.6
Inner Regional Australia	20.6	22.5	20.4
Outer Regional Australia	10.7	12.0	10.6
Remote Australia	1.4	1.2	1.4
Mother's characteristics			
Education (%)			
Has university degree - ref	29.1	22.5	29.7
Has diploma/certificate	42.5	44.1	42.3
High school graduate	9.9	10.1	9.9
Did not finish high school	18.5	23.3	17.8
Employment (%)			
Work full time	32.1	25.9	32.7
Part-time	36.7	31.7	37.2
Not in the labor force/others	31.2	42.4	30.1
Single Parents (%)	17.1	21.5	16.6
Carer Allowance (%)	4.8	17.1	3.6
Total mean healthcare cost in two-year span ($)			
MBS	747 (4.9)	1231 (26.9)	697 (4.5)
PBS	109 (6.9)	381 (57.9)	81 (4.7)
Total Medicare	856 (8.9)	1611 (66.5)	779 (6.9)

Values are mean (SE) unless otherwise specified. MBS, Medicare Benefits Scheme. PBS, pharmaceutical benefits scheme. Total Medicare costs = MBS + PBS. Costs are in 2018 $AUD.

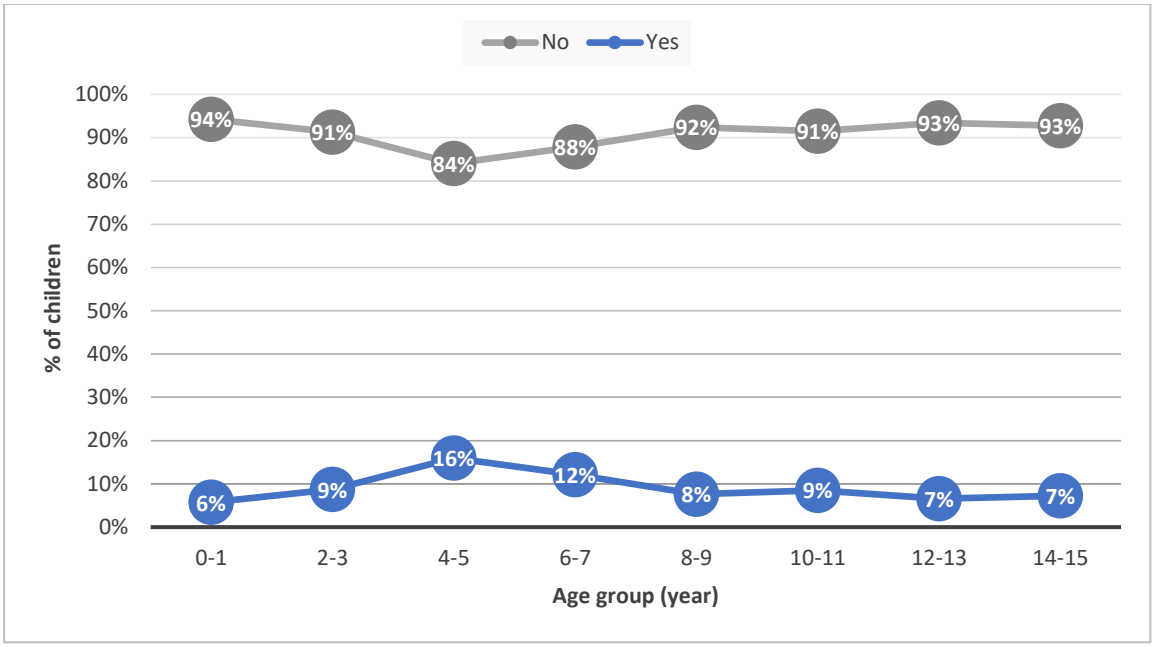

Figure 1: Longitudinal prevalence of having any medical condition or disability over age among the pooled children

The cost differences in healthcare services between children having any medical condition or disability and having none of them were significantly evident across all the age groups, as shown in Table 2. At all ages, the healthcare costs, as well as the cost differences, rose as children grew older. For example, among the age group of 0-1-year-old children, the 2-year costs accrued by the children who had any medical condition or disability were $520 higher compared with children having no medical conditions or disability. This cost difference was $876 for children aged 18-19 years who had long-term medical conditions or disability. Table 3 shows the average healthcare cost differences by age groups between children having a particular type of medical condition or disability and having none of them. It is observed that among different types of disabilities, children with psychological and multiple disabilities incur higher excess healthcare costs.

Table 2. Two-year total Medicare costs ($ mean (SE)) per child by age group and any medical condition or disability status

Age (years)	Children by age group	GLM model results for mean total Medicare expenditure (A$) over two years[1]			
		Having long -term medical condition or disability		Mean Difference (95% CI)	P-value
		No	Yes		
		$ Mean (SE)	$ Mean (SE)		
Pooled observation of B and K cohort					
0-1	4,742	572 (7)	1092 (52)	520 (419, 622)	<0.001
2-3	4,175	619 (5)	1182 (55)	563 (454, 673)	<0.001
4-5	8,509	660 (5)	1260 (58)	600 (484, 716)	<0.001
6-7	7,608	708 (6)	1353 (62)	644 (520, 769)	<0.001
8-9	7,380	758 (9)	1448 (68)	690 (556, 823)	<0.001
10-11	6,956	807 (12)	1542 (73)	734 (592, 877)	<0.001
12-13	6,716	862 (17)	1646 (80)	784 (631, 937)	<0.001
14-15	5,684	919 (21)	1754 (89)	836 (671, 1000)	<0.001
16-17	2,515	963 (25)	1839 (95)	876 (703, 1049)	<0.001
Total excess costs across 0-1-to-16–17-year age duration per child:				A$6247	

[1]Analyses are adjusted for socio-demographic (low birth weight, breastfeeding, residential status, language spoken at home, both parents at home, socio-economic position) variables.

Table 4 shows the population level excess costs incurred by the children having any medical condition or disability derived from the individual level data using the 2018 population of children in different age groups. This study projected the total excess Medicare costs associated with having any medical condition or disability to be approximately $340 million every two years or $170 million/year on average. These cost differences were higher among the age groups of 4-7 years old children. Table 6 shows the costs of the persistence of having any medical condition or disability compared with children having no medical condition or disability. Compared to the children having no medical condition or disability, peers having a medical condition or disability persistently for three or more waves had excess healthcare costs of $6,208 during the length of this study tenure (approximately 14-16 years), estimated from the 3540 children of B and K cohort who participated in all the waves in this study. Table 5 shows the estimated population level excess healthcare costs that might incur by type of disabilities. According to the

findings, it is revealed that children suffering from multiple disabilities spend most of the excess healthcare costs.

Table 3. Two-year total Medicare costs ($ mean (SE)) per child by age group and any health condition or disability status in the Pooled observation of the B and K cohort (N=54285)

Age (years)	Children by age group	GLM model results for mean total Medicare expenditure over two years											
		A$ Mean (SE) costs by the category of having long-term medical conditions or disability						Mean Difference (SE) across the different categories compared to the children with no disabilities (A$)					p-value
		No disability	Sensory only	Physical only	Psychological only	Long-term conditions only	Multiple (two or more types)	Sensory only	Physical only	Psychological only	Long-term conditions only	Multiple (two or more types)	
0-1	4,742	577 (5)	745 (29)	885 (42)	1272 (79)	1086 (37)	1506 (194)	168 (26)	309 (37)	695 (85)	509 (38)	929 (201)	<0.001
2-3	4,175	622 (4)	804 (30)	955 (44)	1372 (84)	1171 (41)	1625 (211)	182 (28)	333 (40)	750 (91)	549 (41)	1003 (218)	<0.001
4-5	8,509	661 (4)	854 (31)	1015 (47)	1458 (89)	1245 (44)	1727 (225)	193 (30)	354 (43)	797 (97)	584 (43)	1066 (231)	<0.001
6-7	7,608	708 (5)	915 (33)	1087 (50)	1562 (94)	1333 (49)	1849 (243)	207 (32)	379 (46)	853 (104)	625 (46)	1141 (249)	<0.001
8-9	7,380	756 (7)	977 (35)	1161 (53)	1667 (100)	1424 (54)	1975 (262)	221 (35)	405 (49)	911 (111)	667 (50)	1218 (267)	<0.001
10-11	6,956	803 (10)	1038 (37)	1233 (57)	1771 (106)	1512 (60)	2098 (281)	234 (37)	430 (52)	968 (118)	709 (53)	1294 (285)	<0.001
12-13	6,716	856 (13)	1106 (40)	1314 (61)	1887 (113)	1611 (67)	2235 (302)	250 (39)	458 (55)	1031 (126)	755 (57)	1379 (306)	<0.001
14-15	5,684	910 (17)	1175 (44)	1397 (66)	2006 (121)	1713 (76)	2376 (325)	266 (42)	487 (59)	1096 (134)	803 (61)	1466 (327)	<0.001
16-17	2,515	953 (20)	1231 (47)	1462 (71)	2100 (128)	1793 (83)	2488 (343)	278 (44)	510 (62)	1148 (141)	841 (65)	1535 (344)	<0.001
Total excess healthcare costs (mean differences) across 0-1-to-16–17-year age duration per child (A$):								1999	3665	8431	6042	11031	

Table 4. Estimated total Medicare costs ($) over two years for the Australian population aged 0-17 years

Age (years)	Australian Population	$AUD Costs in millions Estimate (95% CI)	Excess above cost of children having no medical condition or disability (95% CI) (A$m)
		No	Yes
0-1	642101	335.2 (327.8 to 342.7)	18.6 (15.4 to 21.7)
2-3	642327	363.0 (356.9 to 369.0)	31.4 (25.9 to 36.9)
4-5	641283	356.1 (350.8 to 361.5)	61.5 (50.8 to 72.1)
6-7	639256	399.3 (392.5 to 406.1)	50.0 (41.4 to 58.5)
8-9	632190	447.9 (437.5 to 458.3)	33.5 (27.9 to 39.1)
10-11	595542	466.9 (453.0 to 480.9)	39.5 (33.1 to 45.9)
12-13	573762	479.6 (461.6 to 497.6)	30.8 (25.9 to 35.7)
14-15	581248	488.8 (466.5 to 511.1)	34.8 (29.3 to 40.3)
16-17	623919	515.8 (489.7 to 542.0)	39.9 (33.6 to 46.1)
		Total excess cost* (A$m)	340.0

*Total excess costs across 0-1-to-16–17-year age group children in 2-year span

Table 5: Estimated excess Medicare costs ($) over two years for the Australian population aged 0-17 years by type of disability

Age (years)	Australian Population	Mean Difference (SE) across the different categories (A$m)				
		Sensory	Physical	Psychological	Long-term conditions	Multiple
0-1	642101	0.7 (0.6 to 0.9)	1.3 (1 to 1.6)	0.4 (0.3 to 0.5)	12.6 (11 to 14.2)	1.8 (1.1 to 2.5)
2-3	642327	3.5 (2.6 to 4.4)	2.1 (1.6 to 2.6)	2.4 (1.9 to 2.9)	8.3 (7.3 to 9.4)	12.0 (7.2 to 16.9)
4-5	641283	7.3 (5.4 to 9.3)	2.3 (1.8 to 2.9)	1.4 (1.1 to 1.6)	21.2 (18.4 to 24.1)	21.5 (12.8 to 30.1)
6-7	639256	4.1 (3.1 to 5.1)	3.2 (2.5 to 4)	2.9 (2.3 to 3.5)	14.8 (12.8 to 16.8)	25.2 (14.9 to 35.4)
8-9	632190	2.1 (1.6 to 2.5)	2.0 (1.5 to 2.4)	1.9 (1.5 to 2.3)	9.7 (8.4 to 11.1)	21.4 (12.7 to 30.2)
10-11	595542	1.8 (1.4 to 2.2)	3.4 (2.7 to 4.1)	3.5 (2.8 to 4.1)	12.2 (10.5 to 13.9)	22.0 (13.0 to 31.0)
12-13	573762	1.3 (1.0 to 1.5)	2.0 (1.6 to 2.4)	3.2 (2.6 to 3.8)	9.9 (8.5 to 11.3)	18.3 (10.8 to 25.8)
14-15	581248	1.2 (1.0 to 1.4)	1.3 (1.1 to 1.5)	8.3 (6.8 to 9.8)	10.1 (8.6 to 11.5)	20.8 (12.3 to 29.3)
16-17	623919	0.6 (0.5 to 0.7)	2.2 (1.8 to 2.6)	10.7 (8.7 to 12.7)	9.3 (8.0 to 10.7)	28.2 (16.6 to 39.7)
Total* (A$m)		22.6	19.9	34.5	108.0	171.2

*Total excess costs across 0-1-to-16–17-year age group children in 2-year span

Table 6: Total Medicare costs across all waves per child by persistence of any medical condition or disability

Any medical condition or disability persistence over all the waves (Both B and K cohort)	n	Total average healthcare costs accrued across all the waves (A$)		
		GLM model estimates		
		Mean (SE)	Diff (95% CI)	*p*-value
Morbidity persistence characteristics		*Costs accumulated from age 0-1 year to 16-17 years*		
No medical condition or disability across all waves	2275	5846 (99)	*reference*	<0.001
Had any medical condition or disability for:				
One wave only	722	7816 (379)	1969 (1184 to 2755)	
Two waves	304	9500 (371)	3654 (2893 to 4414)	
Three or more waves	239	12054 (537)	6208 (5130 to 7285)	

This study also investigated costs caused by the persistence of any medical condition or disability compared to children with no disability, shown in Table 6. Compared to the healthy children, peers with persistent medical condition or disability in three or more waves were A$12,054 for children over 16 years duration. The healthcare costs of Australian children associated with the different morbidities – ADHD, obesity, mental health, and sleep problem derived from existing studies, and the estimation results of this study are shown in Table 7. The total healthcare costs show that ADHD and long-term medical conditions or disability incur higher healthcare costs over the study duration of 5 years, $2,527 and $1,737, respectively, compared to other morbidities, which range from $115 to $1,106, if we consider excess costs across similar age groups (for example, here children of 2-3-to-8-9 years or 4-5-to-8-9 years age).

Table 7: Comparison of healthcare costs of children associated with medical conditions or disability and other diseases adopted from different studies

Study	Medical condition	Age range and cohort	Study method	Excess costs per child (A$)		Excess costs at population level (A$m)	
				Costs per total study duration (price year)	Costs per total study duration in 2018 price	Costs in reported price year	Costs inflated to 2018 price
Sciberras et al. (2013)	ADHD	4/5 to 8/9 years–K cohort	GLM	2,245/5 years (2012)	2527	24.0	27.0
Sciberras et al. (2013)	ADHD symptom	4/5 to 8/9 years–K cohort	GLM	753/5 years (2012)	827	30.0	33.8
Clifford et al. (2015)	Overweight	2/3 to 8/9 years–B/K cohort	OLS	214/7 years (2011)	244	13.7	15.6
Clifford et al. (2015)	Obese	2/3 to 8/9 years–B/K cohort	OLS	409/7 years (2011)	466	11.0	12.5
Au, Nicole (2012)	Overweight/Obese	4/5 to 8/9 years–K cohort	GLM	93/5 years (2008)	115	9.8	12.1
Lucas et al. (2013)	Mental health	4/5 to 8/9 years–K cohort	GLM	909/5 years (2009)	1106	4.7	5.7
Quanch et al. (2013)	Sleep problem	4/5 to 6/7 years–K cohort	OLS	226/4 years (2012)	254	11.0	12.4
This Study	Long-term medical condition/disability	4/5 to 8/9 years–B/K cohort	GLM	1737/5 years (2018)	1737	145.0	145.0
This Study	Long-term medical condition/disability	2/3 to 8/9 years–B/K cohort	GLM	2497/7 years (2018)	2497	176.4	176.4

DISCUSSION

This is the first study in Australia to assess the healthcare costs associated with childhood long-term health conditions or disability in a nationally representative longitudinal sample. Our study reveals that long-term medical conditions or disabilities in children incurred significantly higher Medicare costs from the start of life – from birth. We discovered that the additional Medicare expenditures associated with any medical condition or disability per child from birth to 16-17 years age is $6,247. The results also imply that the additional costs to the public health system brought on by the children's disabilities amount to an annual average of $170 million. Our findings support previous studies that childhood overweight is connected with increased medical expenses (Au, 2012; Hampl, Carroll, Simon, & Sharma, 2007). However, a US study found a decreased economic burden of asthma in children measured by the rate of hospitalization and in-hospital mortality (Hasegawa et al., 2013).

This study reveals that the mean cost differences of healthcare services for children with any medical condition or disability are significant from the very early ages – from birth – and increase over age, compared to the children having no medical condition or disability. In contrast, earlier studies conducted on the same cohorts of children aged 0-9 years revealed that the significant cost differences in BMI status and sleep problems were first evident at age 4-5 years (Clifford et al., 2015; Quanch et al., 2013). Healthcare cost studies on two other diseases, mental health, and ADHD, were not available from birth. These results reveal the severity of the cost burden for children with any medical condition or disability.

Compared to the additional costs for other childhood conditions such as mental health problems (A$1,106 per child over five years), ADHD symptom (A$827 per child over five years), Obese (A$466 per child over seven years), overweight (A$244 per child over seven years) and sleep problems (A$254 per child over four years), the individual excess

costs were higher (A$1737 per child over five years) for any medical condition or disability. However, this excess healthcare costs were highest for children with ADHD (A$2,527 per child over five years). While the magnitude of individual excess healthcare costs per child seems not so acute, the estimated whole-population costs were collectively substantial and the highest (A$145.0 million), compared to the reported population level excess costs of ADHD, ADHD symptoms, overweight, obesity, mental health and sleep problem (ranging from A$5.7 million to A$33.8 million), even after inflating the reported costs to 2018 price. This equates to children with any long-term medical condition or disability spending for their family doctors or specialists eight times or more high per year than children with obesity and sleep problems. Since treatment of both long-term medical conditions or disability and obesity typically involve multiple visits, and a recent study showed that it is uneven for primary and secondary care doctors to manage childhood obesity, these study findings warn health policymakers about the unusual healthcare load of long-term medical condition or disability in children and possible difficulty of manageability of this disease by the healthcare professionals.

One of the key contributions of the study is the population level projection of excess healthcare costs of the Australian children. Total population level excess healthcare costs for this disease is A$191.2 million per year for children 0-1-to-16-17-year age, which is higher than many other diseases (for example, obesity, mental health, and sleep problems) in children (Clifford et al., 2015; Lucas et al., 2013; Quanch et al., 2013; Sciberras et al., 2013). Though the prevalence of long-term medical conditions or disability is lower than obesity (overweight + Obesity), the total healthcare costs per child or population level for this disease is higher than obesity in children. This knowledge of total excess healthcare cost may help policymakers to perform the economic assessment or planning of any healthcare interventions. The comparative cost difference would also provide a clearer idea of disease-specific interventions and comparative target groups by age and their time of intervention. The

substantial excess healthcare costs among the children with chronicity of these diseases would provide valuable additional information for intervention program design by the policymakers. Further, responses to the childhood long-term medical condition or disability, along with other diseases, may need to embrace 'proportionate universalism' (Marmot et al., 2008), that is, health intervention and promotion activities universally available to all should be offered alongside a package of interventions increasing in reach and intensity proportionate to the prevalence and severity of long-term medical conditions, disability, and other diseases (Clifford et al., 2015).

The current study has several strengths. This study provides unique evidence that disability is associated with much greater public costs for Australian children. The present study, the first of its kind in Australia, collated information on direct total healthcare costs, which includes general health practitioners, allied health costs, and medications as well as specialist services associated with disabilities in children to the Australian government. This study used 15 waves of data from a nationally representative two cohorts of Australian children (seven waves of the B cohort and eight waves of the K cohort) and linked records from Medicare to reveal disability-related healthcare expenses. Utilizing longitudinal and linked data on children's disabilities and health care expenses over a 14-year period is the study's biggest strength, while available other healthcare cost studies from LSAC are of two to three waves only, spaning 4 to 7 years (Clifford et al., 2015; Lucas et al., 2013; Quanch et al., 2013; Sciberras et al., 2013). Utilizing longitudinal data with longer periods allowed for a more accurate estimation of health care expenses linked with disability than cross-sectional or shorter period longitudinal data.

A limitation of the current study is it does not distinguish between MBS and PBS costs associated with child impairments. Besides, private hospital costs were left out of this analysis since they are difficult to

obtain at the individual level. As public hospital costs were included and inpatient stays as private patient for this age range are uncommon, as such private hospital costs may not add much (Au, 2012). Another aspect of this study is that it doesn't focus on a single medical condition or disability in children. It also affect the comparison of excess healthcare costs with other single medical condition as costs of that single condition might be included in the excess healthcare cost of this study for 'any medical condition or disability'. Further, given the criteria of this study, future research may concentrate on the excess publicly financed expenses associated with specific categories of children's disabilities.

Given the growing number of disabled children and the extra costs that society has to pay, the results of this study have important policy implications. The findings imply that the government should immediately implement policies to prevent and treat impairments in children. In addition to its potential benefits for health, preventing disability in children may also have significant financial implications. The National Disability Insurance Scheme (NDIS) is Australia's first national disability program that provides financial support to people with disability, their families, and carers. The launch of the NDIS is a timely step in the right direction to reduce the societal and financial load. Government and other donor agencies should provide continuous support and additional fund to such programs fairly, equitably, and efficiently which would be helpful for the medical treatment of disabled children.

CONCLUSION

The current research provides an initial understanding of the substantial excess costs at the population level for the long-term health conditions and disabilities of Australian children. A fruitful promotion for restraining long-term medical conditions or disability through the early years of life could yield substantial savings in public health expenditure. These research findings also contribute a baseline against which to judge

the excess costs of providing treatments for children suffering from long-term medical conditions or disability.

REFERENCES

AUSTRALIAN BUREAU OF STATISTICS. 2018. Disability, Ageing and Carers, Australia: Summary of Findings [Online]. Available: https://www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release#data-download [Accessed 06 Nov 2021].

Almond, D., Chay, K. Y., & Lee, D. S. (2005). The costs of low birth weight. *The Quarterly Journal of Economics, 120*(3), 1031-1083.

Au, N. (2012). The health care cost implications of overweight and obesity during childhood. *Health Serv Res, 47*(2), 655-676. doi:10.1111/j.1475-6773.2011.01326.x

Barbosa, J. P., Ferreira-Magalhaes, M., Sa-Sousa, A., Azevedo, L. F., & Fonseca, J. A. (2017). Cost of asthma in Portuguese adults: A population-based, cost-of-illness study. *Revista Portuguesa de Pneumologia, 23*(6), 323-330. doi:10.1016/j.rppnen.2017.07.003

Clifford, S. A., Gold, L., Mensah, F. K., Jansen, P. W., Lucas, N., Nicholson, J. M., & Wake, M. (2015). Health-care costs of underweight, overweight and obesity: Australian population-based study. *Journal of Paediatrics and Child Health, 51*(12), 1199-1206. doi:10.1111/jpc.12932

Cunningham, A. S., Jelliffe, D. B., & Jelliffe, E. P. (1991). Breast-feeding and health in the 1980s: a global epidemiologic review. *The Journal of pediatrics, 118*(5), 659-666.

Ferreira de Magalhaes, M., Amaral, R., Pereira, A. M., Sa-Sousa, A., Azevedo, I., Azevedo, L. F., & Fonseca, J. A. (2017). Cost of asthma in children: A nationwide, population-based, cost-of-illness study. *Pediatric Allergy and Immunology, 28*(7), 683-691. doi:10.1111/pai.12772

Flores, G., Olson, L., & Tomany-Korman, S. C. (2005). Racial and ethnic disparities in early childhood health and health care. *Pediatrics, 115*(2), e183-e193.

Hampl, S. E., Carroll, C. A., Simon, S. D., & Sharma, V. (2007). Resource Utilization and Expenditures for Overweight and Obese Children. *Archives of Pediatrics & Adolescent Medicine, 161*(1), 11-14. doi:10.1001/archpedi.161.1.11

Hasegawa, K., Tsugawa, Y., Brown, D. F., & Camargo, C. A., Jr. (2013). Childhood asthma hospitalizations in the United States, 2000-2009. *Journal of Pediatrics, 163*(4), 1127-1133 e1123. doi:10.1016/j.jpeds.2013.05.002

Lucas, N., Bayer, J. K., Gold, L., Mensah, F., Canterford, L., Wake, M., . . . Nicholson, J. M. (2013). The cost of healthcare for children with mental health difficulties. *Australian and New Zealand Journal of Psychiatry, 47*(9), 849-858.

Marmot, M., Friel, S., Bell, R., Houweling, T. A., Taylor, S., & Health, C. o. S. D. o. (2008). Closing the gap in a generation: health equity through action on the social determinants of health. *The lancet, 372*(9650), 1661-1669.

Nickens, H. (1995). Race/ethnicity as a factor in health and health care. *Health Services Research, 30*(1), 151-162.

Palloni, A., Milesi, C., White, R. G., & Turner, A. (2009). Early childhood health, reproduction of economic inequalities and the persistence of health and mortality differentials. *Soc Sci Med, 68*(9), 1574-1582. doi:10.1016/j.socscimed.2009.02.009

Quanch, J., Gold, L., Hiscock, H., Mensah, F. K., Lucas, N., Nicholson, J. M., & Wake, M. (2013). Primary healthcare costs associated with sleep problems up to age 7 years: Australian population-based study. *BMJ Open*.

Sciberras, E., Lucas, N., Efron, D., Gold, L., Hiscock, H., & Nicholson, J. M. (2013). Health Care Costs Associated With Parent-Reported ADHD: A Longitudinal Australian Population-Based Study. *Journal of Attention Disorders, 21*(13), 1063-1072.

Soloff, C., Lawrence, D., & Johnstone, R. (2005). *Technical Paper no. 1: Sample design* (ISSN 1832-9918). Retrieved from

Van den Hout, W. (2010). The value of productivity: human-capital versus friction-cost method. *Annals of the rheumatic diseases, 69*(Suppl 1), i89-i91.

Willis, E., Reynolds, L., & Rudgea, T. (2019). Understanding the Australian health care system: how to use this book. *Understanding the Australian Health Care System*, 1.

10.2 Links and implications

This chapter evaluated that the additional Medicare expenditures for any medical condition or disability per child are A$805 per year. The study results of this last paper also implied that the additional costs to the public health system brought on by the children's disabilities amount to an annual average of $170 million in the population of 0–17-year-old Australian children. Thus, based on the results this study implicates that early detection and treatment for long-term medical condition or disability would reduce the national health burden. The key contribution of this paper work is the projection of excess healthcare costs at population level, which may help policymakers to perform the economic assessment or planning of any healthcare interventions.

This thesis put its efforts to accomplish eight studies in four thematic areas of child and adolescent health: a) prevalence and risk factor analyses, b) survival analyses and risk factor assessment, c) latent class analyses for identifying vulnerable clusters of children and d) costs of illness studies to assess the excess healthcare costs. In the next chapter, the concluding discussion and policy implications have been presented based on these study findings.

CHAPTER 11: CONCLUSIONS AND POLICY IMPLICATIONS

11.1 Overview

This PhD 'thesis by publication' has set out to encompass an empirical investigation of the following specific childhood health issues in Australia: respiratory and allergic diseases (wheezing, asthma and eczema) and obesity, and in general, the issue of long-term medical condition or disability. The thesis adopted the foetal origins and developmental origins frameworks and the bio-ecological model of child development to interpret the empirical findings in a contemporary population of Australian children. The main objectives of this thesis were to investigate the effect of maternal health conditions and health-related behaviours on childhood health outcomes (asthma and related comorbidities, obesity, long-term medical condition or disability), to identify vulnerable clusters of adolescents and to assess the direct healthcare costs associated with the selected morbidities (asthma and long-term medical condition or disability). In order to accomplish the research objectives, this study utilised a quantitative research approach based on a longitudinal and a health economic perspective. In total, eight studies were conducted under four broad research themes using the nationally representative data from the Longitudinal Study of Australian Children. Papers 1 and 2 were consolidated under Research Theme I, which addressed the prevalence and risk factor analyses of childhood health, both in general and based on leading chronic diseases (wheezing, asthma and eczema), as described in Chapters 3 and 4 of the thesis, respectively. Chapters 5 and 6 explained the findings of Papers 3 and 4 under Research Theme II, which involved longitudinal survival analyses and risk factor assessments of long-term health conditions or disabilities of children. Papers 5 and 6 were grouped under Research Theme III, in Chapter 7 and 8, respectively, which focused on identifying clusters of

vulnerable children in relation to respiratory and allergic diseases and obesity. Papers 7 and 8 assessed the excess healthcare cost associated with asthma and long-term health condition or disability among children, as presented in Chapter 9 and 10, respectively, under Research Theme IV. Finally, Chapter 11 of this thesis included the summary and research contribution of the thesis, along with the study limitations, future research directions and a conclusion outlining policy implications.

11.2 Summary of the key findings

11.2.1 Key findings against the research questions

The first paper of this thesis investigated the following research questions: RQ1) what maternal health factors during pregnancy or in the year after childbirth are associated with infant and adolescent health outcomes? RQ2) to what extent do these associations exist in infancy and adolescence? Utilizing multivariate logistic and ordinary least square regression models on the contemporary birth cohort of LSAC data, the study re-examined the foetal origin factors and revealed that there exist associations between maternal health (general health, any medical condition and mental health) and health-related behaviours (nutrition, physical activity, alcohol consumption and smoking) during pregnancy and up to 15 months from childbirth and children's health outcomes during infancy and adolescence (general health, presence of a chronic illness and physical health outcome index). In the quest of the above-mentioned research questions, the study specifically revealed that poor general health of the mother in the year after childbirth was associated with higher odds of poor health in infants and adolescents in all three dimensions: poor general health, presence of a chronic condition and a lower physical health score. This study further exposed that the presence of a chronic condition in mothers during pregnancy significantly increased the likelihood of the presence of a chronic condition in their offspring during infancy. Moreover, stressful life events faced by mothers increase

the odds of poor general health or any chronic illness during adolescence, while stress, anxiety or depression during pregnancy and psychological distress in the year after childbirth increase the odds of any chronic illness during infancy.

The second paper of this thesis investigated the following research questions: RQ3) what are the sex-specific longitudinal prevalence rates for respiratory and allergic diseases – wheezing, asthma and eczema? RQ4) what maternal health factors during pregnancy are associated with children's wheezing, asthma and eczema? and RQ5) what are the age and sex-segregated differences of the associations? Against the quest of RQ3, it was found that asthma prevalence among children in different age groups varied from 11.7% to 15.4%. Wheezing and eczema were highly prevalent among children ages 2–3 and were least prevalent when the children were 14–15 years old. The prevalence of current asthma was slightly higher among male children up to the age of 12–13 years; however, an increased prevalence was observed among female children aged 14–15 years. Eczema prevalence was higher among male children until age 4–5 years but increased among female children until it was 12.1% among females aged 14–15 years, compared to 7.0% among males in the same age group. In the quest of RQ4, the study found that maternal asthma, smoking during pregnancy and pre-pregnancy obesity were significantly associated with an increased risk of wheezing and asthma in Australian children. Childhood eczema was associated only with maternal asthma. To reveal the answer of whether there were any age and sex-segregated differences of the associations (RQ5), the study found that up until the age of 10–11 years, male children had higher odds to encounter the morbidities (wheezing, ever had asthma, ongoing asthma or eczema) than their female counterparts. However, as adolescents (12–15 years old), female children showed higher odds of having these morbidities if their mother had asthma during pregnancy.

Papers 3 and 4 of the thesis sought answer to the following research questions: RQ6) what is the hazard rate of any medical condition or disability acquisition in Australian children? RQ7) are maternal health-related characteristics (during pregnancy and over 15 years after childbirth) associated with developing any medical condition or acquiring a disability? RQ8) are infant and child health characteristics (birth weight, gestational age, after-birth emergency service use and obesity status) associated with developing any medical condition or acquiring a disability among Australian children? The study measured the hazard rate of any medical condition or disability among children in Australia in their first 15 years of life from the B cohort of the LSAC. It was found that the hazard rate for all participants was 26.13 per 1,000 person-years, while 29.49 was the hazard rate for the males—indicating a noticeable gender difference among children in Australia. The hazard rate was highest (62.98) among the children whose mothers had a medical condition. This hazard incidence rate was higher among children with a low birth weight (39.07), those who were obese (34.37) and those who received after-birth emergency services (36.87). In the quest of RQ7, the parametric panel regression results suggested that the children of mothers with a medical condition during the 15-year study period were more likely to have a medical condition or disability than those of mothers with none. Similar trends were observed among the children of mothers who experienced fair or poor health, obesity or mental illness over time compared to those whose mothers did not. In response to RQ9, the thesis study revealed that children with low birth weight, those who experienced after-birth emergencies, those who were male or those who were obese were significantly more likely to develop a medical condition or disability during childhood.

The fifth paper of the thesis quested for the following issues: RQ9) do there exist distinct clusters of asthma and related comorbidities (wheezing, eczema and others) among Australian children? RQ10) do the health outcomes differ by the distinct clusters? RQ11) are the distinct

clusters of adolescents associated with maternal health status during pregnancy? In response to the RQ9, the study identified clusters of asthma and related comorbidities of Australian children aged 12–13 years, determined health outcome differences among clusters and investigated the associations between maternal asthma and other health conditions during pregnancy and the children's clustered groups. The study identified the following four clusters: (i) had asthma – currently healthy (11.0%), (ii) never asthmatic – currently healthy (64.9%), (iii) early-onset asthmatic or allergic (10.7%), and (iv) asthmatic unhealthy (13.4%). In answering the RQ10, it was found that asthmatic unhealthy cluster was in poor health along with exhibiting poor lung function compared to other clusters. To provide answer to RQ11, the study found that children whose mothers had asthma during pregnancy were 3.31 times (OR 3.31, 95% CI: 2.06–5.30) more likely to be in the asthmatic unhealthy cluster, compared to the children whose mothers were non-asthmatic during pregnancy.

The sixth paper of the thesis aimed to investigate the following research questions: RQ12) do there exist distinct clusters of Australian children based on lifestyle characteristics and health behaviours (for example, physical activity, diet, sedentary behaviour, smoking, alcohol consumption, sleep problems, eating disorders and weight consciousness)? RQ13) do health outcomes differ between the distinct clusters? RQ14) are the distinct clusters of adolescents associated with obesity, general health status and paediatric quality of life (PedsQL)? In quest of these research questions, the study deployed Latent Class Analysis method, an unsupervised machine learning approach, using the variables related with lifestyles and health behaviours in a nationally representative sample of Australian adolescents and to identify distinct clusters and to explore the association of these clusters with obesity, self-rated health and quality of life. Five clusters were identified for male participants, and for female participants, four distinct clusters were

identified. Adolescents in the healthy lifestyle and temperate clusters reported low and moderately active health risk behaviours, respectively; a mixed lifestyle or multiple risk factors clusters for both male and female participants had a stronger negative association with health-related quality of life scores compared to healthy lifestyle clusters.

Paper 7 aimed to investigate the following research questions: RQ15) what are the excess healthcare costs for asthma illness for Australian children at the population level? RQ16) what are the total excess healthcare costs for the children who are experiencing asthma in multiple waves? RQ17) what are the excess healthcare costs associated with having any medical condition or disability for Australian children at the population level? RQ18) what are the total excess healthcare costs for children experiencing any medical condition or disability in multiple waves? In quest of the research questions of study 7, it was found that total excess healthcare costs among the sampled 2–18-year-old children associated with asthma are A$4,316 per child. This study also revealed that compared to the non-asthmatic children, peers with persistent asthma morbidity and treatment requirements had excess costs up to A$20,727 for the B cohort children until 14 years of age, while excess costs for the K cohort children were A$19,571 until 18 years of age. At the population level, the estimated total excess Medicare costs associated with current asthma treatment among children ages 2–18 are, on average, $A190.6 million/year.

Paper 8 sought to evaluate the following research questions: RQ18) what are the total excess healthcare costs for children who are experiencing any medical condition or disability currently across the waves? RQ19) what are the total excess healthcare costs for children who are experiencing any medical condition or disability in multiple waves? RQ20) what are the excess healthcare costs associated with having any medical condition or disability for Australian children at the population level? The study revealed that among the children, the excess Medicare costs per child per year for any medical condition or disability was $A390.

Further, compared to the healthy children, peers with persistent medical condition or disability in three or more waves were A$12,054 for children over 16 years duration. At the population level, the estimated total excess Medicare costs associated with the medical condition or disability among children ages 0–16 are, on average, $A170 million/year.

11.2.2 Maternal health and childhood health outcomes

The study findings revealed from the above studies affirmed the following common impact of maternal health on child health outcomes, regardless of the analytical approaches:

a) Poor general health and stressful life events of mothers in the year of childbirth were associated with poor general health in children.
b) Poor general health, stressful life events and psychological distress of mothers in the year of childbirth, and stress, anxiety or depression during pregnancy and the presence of a chronic condition in mothers during pregnancy were significantly associated with any chronic illness in their offspring.
c) Poor general health status and having stress, anxiety or depression during pregnancy significantly increased the likelihood of a lower physical health score in their offspring.
d) Maternal asthma, smoking during pregnancy and pre-pregnancy obesity were significantly associated with an increased risk of wheezing and asthma in Australian children. While a number of factors influence childhood asthma, childhood eczema was associated only with maternal asthma.
e) Up until the age of 10–11 years, male children had higher odds to encounter morbidities (wheezing, ever had asthma, ongoing asthma or eczema) than their female counterparts. However, as adolescents (12–15 years old), female children

showed higher odds of having these morbidities if their mother had asthma during pregnancy.

f) Children of mothers with a medical condition during the 15-year study period were more likely to have a medical condition or disability than those of mothers with none. Similar trends were observed among the children of mothers who experienced fair or poor health, obesity, stressful life events or mental illness over time compared to those whose mothers did not.

However, gender differences were observed both in the survival and logistic regression analyses when we deployed the gender segregated analyses. In the time-to-event analyses, it was found that although girls whose mothers experienced mental stress or anxiety during pregnancy had a higher risk of having a medical condition or disability compared to the female children of mothers who did not, the same association was not significant among boys. Moreover, mothers' mental illness and stressful life events during the 15-year follow-up period had a statistically significant influence on girls' medical conditions but not on those of boys. The thesis also found through logistic regression analyses that up until the age of 10–11 years, male children had higher odds of encountering the studied morbidities (wheezing, ever had asthma, ongoing asthma or eczema) than their female counterparts. However, as adolescents (12–15 years old), female children showed higher odds of having these morbidities if their mother had asthma during pregnancy. As different analytical approaches showed gender differences consistently, it indicates the strong gender-based differences of associations across the specified factors.

11.2.3 Childhood health conditions associated with child wellbeing and healthcare costs

The study findings revealed from the several other studies of this thesis work mentioned above also explain how the following childhood health conditions are associated with child wellbeing, identification of vulnerable group of children and healthcare costs (borne by the healthcare systems).

a) Children with low birth weight, those who experienced after-birth emergencies, those who were male or those who were obese were significantly more likely to develop a medical condition or disability during childhood.
b) Children who were currently taking medication for asthma, who were diagnosed with asthma in their early childhood, two in five had an illness with wheezing, just over one in five had atopic eczema or poor general health and more than one in ten of them reported a sleeping disorder due to breathing or snoring problem were grouped into the most vulnerable 'asthmatic unhealthy' cluster.
c) The asthmatic unhealthy cluster was in poor health along with exhibiting poor lung function compared to other clusters. Further, children whose mothers had asthma during pregnancy were three times more likely to be in the asthmatic unhealthy cluster than children whose mothers were non-asthmatic during pregnancy.
d) Children with lower levels of physical activity, high sedentary behaviour on weekdays, poor sleep quality, less healthy diet, low levels of consciousness regarding weight management and higher smoking and alcohol consumption rates belonged to the unhealthy clusters (physically inactive, mixed lifestyle and multiple risk factors). On the contrary, the healthy lifestyle cluster comprises children with no smoking, little alcohol

consumption, high physical activity, low sedentary behaviour, appropriate sleep hours, a healthy diet and no eating disorders.

e) Male participants from the temperate, physically inactive and mixed lifestyle clusters and female participants from the mixed lifestyle and multiple risk factors clusters were more likely to be obese than their counterparts in the healthy lifestyle clusters. Further, male participants in the temperate, physically inactive and mixed lifestyle clusters and female participants in the mixed lifestyle and multiple risk factors clusters were less likely to report very good or excellent general health. Moreover, male participants in the temperate and physically inactive clusters and female participants in the mixed and multiple risk factors clusters reported lower quality of life than their healthy lifestyle counterparts.

f) While among the sampled children over the age of 2 to 18 years, the pooled prevalence of asthma was 14.9%, the estimated total excess associated Medicare costs incurred by the asthmatic children at the population level were A$190.6 million/year. On the other hand, the pooled prevalence of any medical condition or disability among the sampled children over the age 0 to 16 years were 9.2% and the estimated total excess associated Medicare costs incurred by this group of children at the population level were A$170 million/year.

11.2.4 Overall explanation of the findings

While the thesis reflects on the findings of all the studies in an integrated way, the results signify and reaffirm the FOAD and the DOHaD hypotheses, blended with the 'ecological' model of child development, for several disease outcomes of children. Following is the summary of which theoretical framework was supported by what study results (of this thesis) and why:

- The evidence of the associations of foetal exposure to maternal poor general health, maternal long-term health conditions, stress during pregnancy, exclusion of food items during pregnancy, fruit and vegetable consumption, physical activity in the year of childbirth and alcohol consumption in the first trimester of pregnancy and child health outcome (general health, selected health conditions and physical health index score), from the study of Paper 1, reaffirms both FOAD and DOHaD hypotheses. While the associations of maternal health status factors with three dimension of child health outcome refurbish the FOAD hypothesis, associations of maternal health related behaviours and diet practices with child health outcomes indicate the refitting of developmental origins hypothesis encompassing the wider environmental factors.
- The evidence of the associations of foetal exposure to maternal asthma and smoking during pregnancy and pre-pregnancy obesity and childhood wheezing or asthma, from the study of Paper 2, renews the essence of the FOAD hypothesis. The findings that childhood eczema was associated only with maternal asthma during pregnancy, and not with pre-pregnancy obesity, smoking during pregnancy, or antibiotic/anti-depressant medication use during pregnancy, also extend the understanding of foetal origin factors.
- Time-to-event analyses of the effects of maternal health-related characteristics (obesity, general health, any medical condition and mental illness over 15 years after childbirth and mental stress during pregnancy) with developing any medical condition or acquiring a disability among Australian children were performed in Paper 3 with an aim to looking into the DOHaD factors with a different analytical approach. This longitudinal survival analytical approach is more robust than logistic or linear regression (whether cross-sectional or longitudinal) and yielded the same findings to reaffirm the DOHaD hypothesis. Similarly, survival analyses of the effects of child health characteristics (birth weight, gestational age, after-birth emergency

service use and obesity status) and child health outcome, focusing any medical condition or disability, also reaffirm the DOHaD hypothesis. However, the survival analyses of Paper 3 and 4 also reveal the ecological framework of child development in the perspective of health outcome, as these analyses sought to identify a range of influences on children's developmental outcomes that span through childhood including infancy and adolescence time encompassing individual and family characteristics and the broader social, economic and physical environments in which children are raised.

- Implementing the unsupervised machine learning method, namely the Latent Class Analysis, to identify the vulnerable group of children from the factors of asthma-related health morbidities gave this thesis study essential insights about the DOHaD hypothesis. It was evident from the findings of Paper 5 that children who were diagnosed with either asthma or wheezing in their early childhood or had either atopic eczema or reported not having excellent or very good health were reported to be in the most vulnerable group concerning asthma and related morbidities. The logistic regression on cluster membership also depicted the association of this most vulnerable group with maternal asthma during pregnancy and any chronic condition of mothers. The findings clearly depicted the development path of the health capital of children and expanded our understanding of the developmental origins of health and disease related to asthma.
- The Paper 6 of the thesis deployed again the latent class analysis (LCA) to identify clusters based on the following health behaviours: physical activity, sedentary behaviour, alcohol consumption, smoking, diet, eating disorders, sleep problems and weight gain consciousness. Based on the lifestyle and health behaviour characteristics the study found several vulnerable clusters which are more likely to be obese and have poor HRQoL and less likely to report good or excellent general health compared to those in the healthy lifestyle cluster. Thus, the findings of this paper indicated that personal behaviours or

dietary practices might influence (aggravate or reduce) the health outcomes of adolescents, reflecting the DOHaD hypothesis and further explaining the bio-ecological framework.

- Lastly, the cost of illness studies, carried out in Papers 7 and 8, reflected the bio-ecological framework in determining the societal cost in the wake of the loss of health capital for the morbidities of asthma and any medical condition or disability.

The thesis also intend to reflect, based on the findings of all the studies, on the extent of associations played by the control variables (such as age of the child, gender of the child, education and marital status of mother, family income, language spoken at home and remoteness of the residence) compared to the maternal health or other explanatory variables (health-related behaviours or early childhood indicators). Our findings suggest that though few of the control variables (for example, gender) had significant impact on the child health outcomes, none of them ever exceeded the impact of the factors of maternal health or health-related behaviours.

Moreover, while the thesis looked into the comparative effect of maternal health over health-related behaviours, it was clear from the study findings that maternal health confounders (for example, maternal asthma during pregnancy, obesity of mothers, having a medical condition in year of childbirth) had stronger and consistent effect sizes on the child health outcomes. But the health-related behaviours, for example, smoking and alcohol consumptions, were less in effect size and inconsistent over studies.

11.3 Contributions to the field of research

Built upon the foundation of previous research and underpinned by three theoretical frameworks, this thesis makes significant contributions to the existing literature in several ways. In general, this thesis (Papers

1–4) revealed the longitudinal pattern of prevalence and risk factors of childhood health morbidities on leading chronic diseases (wheezing, asthma and eczema) and long-term medical conditions or disabilities. The first four studies of the thesis re-examined the foetal origin and developmental origin hypotheses using a contemporary birth cohort (recruited in 2004 and followed until 2018) of Australian children and provided evidence of maternal and infant health-related determinants that influence childhood health outcomes. While most of the earlier studies in Australia were cross-sectional or state-based, this thesis provides longitudinal estimates that are nationally representative.

This thesis performed parametric longitudinal survival analysis to predict the long-term medical condition or disability of children, following both the foetal origins (Paper 3) and developmental origins (Papers 3 and 4) framework. The survival analyses estimated the hazard ratio of occurring a medical condition or disability in children by utilising the time-to-event outcome through a longitudinal research design. This modelling provided a better understanding of the risk factors, as they offer more information and greater statistical power than methods for a binary outcome that simply depicts whether or not an event occurred (George et al., 2014). To clarify, the survival analyses of the thesis provided an answer to the following question: How long did it take until a child developed a medical condition or disability? Logistic regression answers the question of whether a child has faced a medical condition or disability. Thus, this improved analytic technique added new knowledge in the domain of estimating burden of disease through depicting how many incidents of long-term medical condition or disability occur (26.13) per 1000 person-years, considering the continuous time of the longitudinal study period in the estimation process. This analysis also adding new knowledge in calculating the odds of child health outcomes for the confounding factors from a better time-to-event point of view.

An additional contribution of this thesis is that it has investigated the association of maternal health with child health outcomes in both regression and survival analysis techniques. It was found in both techniques that poor general health, obesity, having a medical condition, facing any stressful life events and mental illness of mothers and mental stress or anxiety during pregnancy are significantly associated with poor child health outcomes. Thus, these findings are robust as they hold across different techniques.

One major strength of the current research is the utilisation of latent class cluster analysis method, an unsupervised machine learning approach, instead of characterising isolated individual morbidities to identify the highly vulnerable children's cluster in relation to respiratory and allergic diseases and obesity-related lifestyles and health behaviours (Papers 5 and 6). Through this analytical technique, the thesis defined implicit statistically distinct groups of children based on the explicit characteristics available from the perspective of respiratory and allergic diseases and obesity-related lifestyles and health behaviours. After defining the groups, the most vulnerable group was identified through comparison of descriptive statistics based on the specific health outcomes measured by spirometry, PedsQL and general wellbeing. Further, through regression modelling which confounding factors of maternal health conditions or health-related behaviours were contributing significantly in predicting the most vulnerable clusters were identified. Thus, this thesis contributed tremendous valuable knowledge in the domain of health burden analysis and understanding the foetal origins and developmental origins of health and disease in a new analytical perspective.

This thesis pioneered in conducting the cost-of-illness studies (Papers 7 and 8), assessing the direct healthcare costs by linking Medicare cost data with the LSAC study children. Paper 7 assessed of national-level excess healthcare costs for Australian children associated with the burden of asthma morbidity. Study 8 evaluated the excess healthcare costs associated with long-term medical conditions or disabilities. In building these cost models, the studies utilised the log-

linked data with Gamma distribution through generalised linear models. While several recent and earlier studies used the OLS models for estimating Medicare costs and becoming outdated by not utilizing all the waves of LSAC surveys, our study methods are robust by employing better model fit parameters and using all the available waves of surveys, which provided more reliable knowledge resources for policymakers to facilitate better healthcare programming (Au, 2012).

11.4 Limitations of the study

Despite the compelling findings from the nationally representative sample and longitudinal studies, each study within this thesis had limitations. The limitations of each study have been mentioned in the chapters on the individual studies. One drawback of the present research is that information regarding general health, body mass index (BMI) and health-related quality of life were obtained from parent-reported data, which may have involved recall or social desirability bias (De Rubeis et al., 2019). However, experts in the field have confirmed that self-reporting is the most logical approach to data collection (Kessler and Walters, 1998). Another drawback of the present research is that BMI has been used to measure obesity. Numerous studies, including the studies of the present thesis, have used BMI as the measure of adiposity, yet it is only a marker of adiposity and has limitations, especially when measured through self-report (Gorber et al., 2007).

Since all the papers of this thesis were based on a secondary dataset, control over the selection of variables for analyses was limited and impacted the research interests of the papers. As it was not possible to design a survey tool that could reflect these research interests more accurately, the thesis could not extend its scope to explore other relevant factors of research. For example, dietary habits, exercise patterns, sedentary behaviours and health checkpoint data were not available in all

waves of the LSAC surveys, so we were unable to investigate them all longitudinally. Further, this thesis has the limitation of only having maternal data for consideration of the DOHaD and ecological models, which take a household environment/epigenetic perspective and therefore ideally require data on all household members/biological parents from pre-conception to childbirth and their upbringing in the whole period of childhood.

The thesis was also restricted to analysing the direct healthcare costs associated with asthma and long-term medical conditions or disabilities. There are indirect costs of childhood diseases; for example, costs arise from absenteeism, which may incur a loss of productivity for the carer of ill children or loss of educational and other attainments for the children who miss school days (Clifford et al., 2015). Further, there are indirect costs of disablement, for example, the costs triggered by the social welfare payments of the government agencies (for example. CenterLink payments for disabled children and/or their carers) (Kavanagh, 2020). These indirect costs of illness for asthma, obesity or disability were beyond the scope of this thesis due to time limitations.

11.5 Implications for policy and further research

11.5.1 Policy implications

All the eight papers of this thesis have discussed policy implications on the basis of their individual research findings. Overall, this thesis study provides systematic evidence on the current leading chronic disease status of children living in Australia and provides governments, health researchers and the community with important insights into the extent of the disease burden, its determinants and its associated direct healthcare costs.

First, the findings of first two studies revealing the contemporary extent of associations of maternal health and health behaviours with child

health outcomes emphasise the importance of improving maternal physical and mental health and promoting a healthy lifestyle during pregnancy or in the year after childbirth to improve childhood health. The study results also reveal the importance of undertaking preventive measures to improve maternal health and create awareness of the importance of a healthy lifestyle during pregnancy to reduce poor health outcomes in infants and children. Further, findings of the respiratory and atopic allergy study indicate that identifying specific age groups where wheezing, asthma and eczema affect children will enable clinical practitioners and policymakers to tailor appropriate treatment interventions for pregnant women and their children. This finding, therefore, has important implications for maternal-child public health strategies.

Second, the findings of this thesis study confirm that maternal health influences children's health from birth to 14 or 15 years of age from the perspective of time-to-event or survival analysis. This suggests that additional healthcare monitoring of mothers experiencing prenatal mental stress during pregnancy or living with obesity, fair or poor health, medical conditions or mental illness over the period of 15 years after childbirth would help enhance the health and well-being of children as well as mothers. The findings of another survival analysis of this thesis suggest that infants with low birth weight, children who have accessed hospital emergency services and children with obesity need further healthcare monitoring support from both private and public providers to improve the health and well-being of Australian children.

Third, the study of latent class clustering supports the necessity to consider multiple morbidity factors related to asthma when classifying individuals and identifying high-risk asthma groups. Our analyses identified four main clusters of children based on their experiences of asthma and related morbidities and their association with maternal health

during pregnancy. The most vulnerable group was the *asthmatic unhealthy* cluster, and children whose mothers had asthma during pregnancy were threefold more likely to be in this cluster. This finding suggests that an improved classification strategy helps to identify the most vulnerable group among the children with asthma and related morbidities. Another study found that all unhealthy clusters, classified based on lifestyles and health-related behaviours, were associated with increased obesity and lower levels of self-rated general health; however, the magnitude of the risk of poor health outcomes varied by the risk characteristics of the clusters. Understanding various lifestyle clusters and health-related risk behaviours may be important for policymakers when developing obesity prevention interventions. Future studies should investigate the effects of various interventions on reducing these obesity-related clusters. Identifying the associations of these clusters with morbidity and lower quality of life scores is important for determining health behaviour patterns in national and international settings, which may help with obesity prevention and improving the quality of life.

Fourth, given the alarming prevalence rate of asthma and disability in children and the extra cost that these diseases incur, the results of the studies have important policy implications. The findings imply that the government should immediately implement policies to prevent and treat asthma and impairments in children. In addition to the potential health benefits, preventing asthma and disability in children may also have significant financial implications. In the case of preventing asthma and reducing asthma prevalence, this study's findings suggest that cost-effective strategies for both the prevention and early treatment of childhood asthma, especially reducing asthma incidence in childhood, averting persistent asthma and enhancing educational and self-management interventions, could pay remarkable dividends to the government and society at large, both at present and in the future. The National Disability Insurance Scheme (NDIS) is Australia's first national

disability program that provides financial support to people with disabilities, their families and their carer. Government and other donor agencies should provide continuous support and additional fund to such programs fairly, equitably, and efficiently which would be helpful for the medical treatment of disabled children.

11.5.2 Further research

Since this PhD thesis has investigated the issues of children and adolescent health in relation to respiratory and allergic diseases, obesity and long-term medical condition or disability, it provides meaningful insights and directions for future research in this area. Findings from the current thesis on the associated risk factors of child and adolescent health outcomes will help researchers to formulate new hypotheses for conducting causal analysis. For example, based on our findings on the association of physically inactive clusters of children with obesity, future researchers may devise appropriate instrumental variables and conduct research to infer the causality of physical activity and reduction of BMI (Corona et al., 2017). Further, this thesis used cross-sectional data of adolescents to conduct the latent class clustering, which can be extended to longitudinal growth modelling. Growth modelling analysis on chronic morbidities like asthma and obesity, alternatively also known as trajectory analysis, would significantly widen the understanding of the pattern of chronic morbidities. In addition, another future research pathway might consider the multi-morbidities of a single subject and analyse their trajectories through a substantive understanding of the morbidities addressed in this thesis.

Several studies conducted under this thesis have the limitation of utilising BMI as the only measure of adiposity. In order to overcome this limitation, future research may use a composite score that combines waist circumference and BMI. A study involving a survival analysis of disability has used a composite indicator of BMI and waist circumference

in older populations and argues that this can more accurately predict body fat percentage (Corona et al., 2017). A similar approach can be utilised among children and adolescents in Australia for obesity-related studies.

This thesis assessed the associated direct healthcare costs for Australian children that result from the morbidities of asthma and other long-term medical conditions or disabilities. However, there are other direct costs, for example, the non-medical costs incurred by travels for obtaining care and related childcare costs, which have not been studied in the course of this research. This thesis research also excluded an examination of the indirect costs of childhood diseases: loss of productivity by the carer and loss of educational attainment from the absenteeism of the carer and children at workplaces and at schools, respectively. Future research can be conducted on these morbidities to evaluate the indirect healthcare costs. Further, researchers may engage in evaluating mortality costs, for example, the value of lost productivity due to premature death resulting from these illnesses. However, the researchers would require access to both hospital data and de-identified sociodemographic data to apply the social health perspective to health economics.

Further studies can be attempted on the causal analysis of longitudinal data on the research issues covered in this thesis. It is also recommended to perform experimental research that can directly test causal pathways - such as a randomised controlled trial of an intervention to increase physical activity to reduce BMI or abdominal adiposity and improve child wellbeing.

11.6 Conclusion

The majority of the health burden in children and adolescents originates from the leading chronic diseases – asthma, obesity and long-term medical conditions or disabilities. This PhD thesis has established an evidence-based understanding of maternal health and other determinants

related to the developmental origins that impact the health of children and adolescents in an Australian setting for the abovementioned leading chronic diseases. This thesis extracted data from the nationally representative birth (B) and kindergarten (K) cohorts of the LSAC surveys, with data linkages from the Health CheckPoint survey and Medicare expenditures between 2004 and 2018. The first three studies investigated the effects of maternal health and health-related behaviours on children's overall health, chronic illnesses (wheezing, asthma, and eczema) and other long-term medical conditions or disabilities. Another study examined the effects of infant or childhood health characteristics on the outcome of any medical condition or disability of children. A further two studies articulated the identification of a vulnerable health cluster of adolescents based on the characteristics of asthma and related comorbidities and lifestyle- and health-related behaviours. The final two studies evaluated the excess direct healthcare costs associated with asthma and long-term health conditions or disabilities. The findings of these studies have expanded previous research by offering significant policy implications. This thesis provides continuing and contemporary evidence to Australian policymakers regarding the strong association between maternal health and health-related behaviours and the following leading chronic diseases of children – asthma, obesity and other long-term medical conditions or disabilities. This thesis also details the extent of the health burden and excess Medicare costs associated with asthma and any medical condition or disability. It is hoped that the thesis findings will provide policymakers with the necessary knowledge to formulate appropriate strategies that reduce the health burden of children and adolescents.

REFERENCES

Note: Additional references included in Chapter 3 to Chapter 10 are included within those formatted chapters and do not appear on this list.

ALATI, R., LAWLOR, D. A., MAMUN, A. A., WILLIAMS, G. M., NAJMAN, J. M., O'CALLAGHAN, M. & BOR, W. 2007. Is there a fetal origin of depression? Evidence from the Mater University Study of Pregnancy and its outcomes. *American Journal of Epidemiology,* 165**,** 575-82.

ALMOND, D. & CURRIE, J. 2011. Killing me softly: The fetal origins hypothesis. *Journal of economic perspectives,* 25**,** 153-72.

ALMQVIST, C., WORM, M., LEYNAERT, B. & 'GENDER', W. G. O. G. L. W. 2008. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy,* 63**,** 47-57.

ANDERSEN, Z. J., BONNELYKKE, K., HVIDBERG, M., JENSEN, S. S., KETZEL, M., LOFT, S., SORENSEN, M., TJONNELAND, A., OVERVAD, K. & RAASCHOU-NIELSEN, O. 2012. Long-term exposure to air pollution and asthma hospitalisations in older adults: a cohort study. *Thorax,* 67**,** 6-11.

ANTHRACOPOULOS, M. B., PANDIORA, A., FOUZAS, S., PANAGIOTOPOULOU, E., LIOLIOS, E. & PRIFTIS, K. N. 2011. Sex-specific trends in prevalence of childhood asthma over 30 years in Patras, Greece. *Acta Paediatrica,* 100**,** 1000-5.

ASHER, I. & PEARCE, N. 2014. Global burden of asthma among children. *International Journal of Tuberculosis and Lung Disease,* 18**,** 1269-78.

AU, N. 2012. The health care cost implications of overweight and obesity during childhood. *Health Services Research,* 47**,** 655-76.

AUSTRALIAN BUREAU OF STATISTICS. 2018. *Disability, Ageing and Carers, Australia: Summary of Findings* [Online]. Available: https://www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release#data-download [Accessed 06 Nov 2021].

AUSTRALIAN CENTRE FOR ASTHMA MONITORING 2009. Asthma in Australian children: findings from Growing Up in Australia, the Longitudinal Study of Australian Children. Canberra: AIHW.

AUSTRALIAN INSTITUTE OF FAMILY STUDIES 2002. Introducing the Longitudinal Study of Australian Children.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE Australia's health 2018. *Australia's health series no. 16.* Canbera: AIHW.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE 2018. Australia's health 2018. *Australia's health series no. 16.* Canbera: AIHW.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE 2020. Australia's health 2020 data insights. *Australia's health series no. 17.* Canberra: AIHW.

BARBOSA, J. P., FERREIRA-MAGALHAES, M., SA-SOUSA, A., AZEVEDO, L. F. & FONSECA, J. A. 2017. Cost of asthma in Portuguese adults: A population-based, cost-of-illness study. *Revista Portuguesa de Pneumologia (English Edition),* 23**,** 323-330.

BARKER, D. J. 1992. Fetal growth and adult disease. *British journal of obstetrics and gynaecology,* 99**,** 275-276.

BARKER, D. J. P. 1997. Maternal Nutrition, Fetal Nutrition, and Disease in Later Life. *Nutrition,* 13**,** 7.

BARKER, D. J. P. & CLARK, P. M. 1997. Fetal undernutrition and disease in later life. *Journals of Reproduction and Fertility,* 2**,** 8.

BARKER, D. J. P. & OSMOND, C. 1986. Infant Mortality, Childhood Nutrition and Ischaemic Heart Disease in England and Wales. *The Lancet***,** 1077-81.

BELLI, P. C., BUSTREO, F. & PREKER, A. 2005. Investing in children's health: what are the economic benefits? *Bulletin of the World Health Organization,* 83**,** 777-784.

BERRIGAN, D., DODD, K., TROIANO, R. P., KREBS-SMITH, S. M. & BARBASH, R. B. 2003. Patterns of health behavior in U.S. adults. *Preventive Medicine,* 36**,** 615-623.

BRONFENBRENNER, U. 1979. *The ecology of human development: Experiments by nature and design*, Harvard university press.

BURNS, L., BREEN, C., BOWER, C., C, O. L. & ELLIOTT, E. J. 2013. Counting fetal alcohol spectrum disorder in Australia: the evidence and the challenges. *Drug and Alcohol Review,* 32**,** 461-7.

BUSSING, R., HALFON, N., BENJAMIN, B. & WELLS, K. B. 1995. Prevalence of behavior problems in US children with asthma. *Pediatrics & Adolescent Medicine,* 149**,** 565-572.

CDC. 2020. *Disability and Health Overview* [Online]. Available: https://www.cdc.gov/ncbddd/disabilityandhealth/disability.html [Accessed 07 Nov 2021].

CDC. 2021. *Benefits of Physical Activity* [Online]. Available: https://www.cdc.gov/physicalactivity/basics/pa-health/index.htm [Accessed 07 Nov 2021].

CHAVATTE-PALMER, P., TARRADE, A. & ROUSSEAU-RALLIARD, D. 2016. Diet before and during Pregnancy and Offspring Health: The Importance of Animal Models and What Can Be Learned from Them. *International Journal of Environtal Research and Public Health,* 13.

CHEN, Y., LYU, J., XIA, Y., ZHU, J., TONG, S., YING, Y., QU, J. & LI, S. 2020a. Effect of maternal sleep, physical activity and screen time during pregnancy on the risk of childhood respiratory allergies: a sex-specific study. *Respiratory Research,* 21**,** 230.

CHEN, Y. C., FAN, H. Y., YANG, C. & LEE, Y. L. 2020b. Early pubertal maturation and risk of childhood asthma: A Mendelian randomization and longitudinal study. *Allergy,* 75**,** 892-900.

CLAESSEN, H., ARNDT, V., DRATH, C. & BRENNER, H. 2009. Overweight, obesity and risk of work disability: a cohort study of construction workers in Germany. *Occupational and Environmental Medicine,* 66**,** 402-9.

CLIFFORD, S. A., GOLD, L., MENSAH, F. K., JANSEN, P. W., LUCAS, N., NICHOLSON, J. M. & WAKE, M. 2015. Health-care costs of underweight, overweight and obesity: Australian population-based study. *Journal of Paediatric and Child Health,* 51**,** 1199-206.

CONRY, M. C., MORGAN, K., CURRY, P., MCGEE, H., HARRINGTON, J., WARD, M. & SHELLEY, E. 2011. The clustering of health behaviours in Ireland and their relationship with mental health, selfrated health and quality of life. *BMC Public Health,* 11.

COOKSON, H., GRANELL, R., JOINSON, C., BEN-SHLOMO, Y. & HENDERSON, A. J. 2009. Mothers' anxiety during pregnancy is associated with asthma in their children. *Journal of Allergy and Clinical Immunology,* 123**,** 847-53 e11.

CORONA, L. P., ALEXANDRE, T. D., DUARTE, Y. A. & LEBRAO, M. L. 2017. Abdominal obesity as a risk factor for disability in Brazilian older adults. *Public Health Nutrition,* 20**,** 1046-1053.

DA SILVA SENA, C. R., MORTEN, M., MEREDITH, J., KEPREOTES, E., V, E. M., P, G. G., P, D. R., P, D. S., WHITEHEAD, B., KARMAUS, W., COLLISON, A. & MATTES, J. 2020. Rhinovirus bronchiolitis, maternal asthma, and the development of asthma and lung function impairments. *Pediatric Pulmonology*.

DE RUBEIS, V., BAYAT, S., GRIFFITH, L. E., SMITH, B. T. & ANDERSON, L. N. 2019. Validity of self-reported recall of anthropometric measures in early life: A systematic review and meta-analysis. *Obesity Reviews,* 20**,** 1426-1440.

EDWARDS, M. 2017. Famines, Pregnancy and Effect on the Adults. *Diet, Nutrition, and Fetal Programming.* Springer.

EKSTROM, S., MAGNUSSON, J., KULL, I., LIND, T., ALMQVIST, C., MELEN, E. & BERGSTROM, A. 2015. Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. *Clinical & Experimental Allergy,* 45**,** 283-91.

FERREIRA DE MAGALHAES, M., AMARAL, R., PEREIRA, A. M., SA-SOUSA, A., AZEVEDO, I., AZEVEDO, L. F. & FONSECA, J. A. 2017. Cost of asthma in children: A nationwide, population-based, cost-of-illness study. *Pediatric Allergy and Immunology,* 28**,** 683-691.

GAILLARD, R., FELIX, J. F., DUIJTS, L. & JADDOE, V. W. 2014. Childhood consequences of maternal obesity and excessive weight gain during pregnancy. *Acta Obstet Gynecol Scand,* 93**,** 1085-9.

GEORGE, B., SEALS, S. & ABAN, I. 2014. Survival analysis and regression models. *Journal of Nuclear Cardiology,* 21**,** 686-94.

GIALLO, R., BAHREINIAN, S., BROWN, S., COOKLIN, A., KINGSTON, D. & KOZYRSKYJ, A. 2015. Maternal depressive symptoms across early childhood and asthma in school children: findings from a Longitudinal Australian Population Based Study. *PLoS One,* 10**,** e0121459.

GLUCKMAN, P. D. & HANSON, M. A. 2004. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatric research,* 56**,** 311-317.

GORBER, S. C., TREMBLAY, M., MOHER, D. & GORBER, B. 2007. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obesity reviews,* 8**,** 307-326.

GRAY, L. E. K., PONSONBY, A. L., LIN, T. X., O'HELY, M., COLLIER, F., RANGANATHAN, S., SLY, P. D., PEZIC, A., TANG, M. L. K., BURGNER, D. & VUILLERMIN, P. 2019. High incidence of respiratory disease in Australian infants despite low rate of maternal cigarette smoking. *Journal of Paediatrics and Child Health,* 55**,** 1437-1444.

HARVEY, S. M., MURPHY, V. E., GIBSON, P. G., COLLISON, A., ROBINSON, P., SLY, P. D., MATTES, J. & JENSEN, M. E. 2020. Maternal asthma, breastfeeding, and respiratory outcomes in the first year of life. *Pediatric Pulmonology,* 55**,** 1690-1696.

HASEGAWA, K., TSUGAWA, Y., BROWN, D. F. & CAMARGO, C. A., JR. 2013. Childhood asthma hospitalizations in the United States, 2000-2009. *The Journal of Pediatrics,* 163**,** 1127-33 e3.

HEIKKALA, E., J., R., PAANANEN, M., TAIMELA, S., AUVINEN, J. & KARPPINEN, J. 2014. Accumulation of lifestyle and psychosocial problems and persistence of adverse lifestyle over two-year follow-up among Finnish adolescents. *BMC Public Health*.

HOY, W. E., MATHEWS, J. D., MCCREDIE, D. A., PUGSLEY, D. J., HAYHURST, B. G., REES, M., KILE, E., WALKER, K. A. & WANG, Z. 1998. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. *Kidney International,* 54**,** 1296-304.

INGSTRUP, K. G., ANDERSEN, C. S., AJSLEV, T. A., PEDERSEN, P., SORENSEN, T. I. & NOHR, E. A. 2012. Maternal Distress during Pregnancy and Offspring Childhood Overweight. *Journal of Obesity,* 2012**,** 7.

JAAKKOLA, J. & GISSLER, M. 2004. Maternal smoking in pregnancy, fetal development, and childhood asthma. *American Journai of Public Heaith*.

KAVANAGH, A. 2020. Disability and public health research in Australia. *Australia and New Zealand Journal of Public Health,* 44**,** 262-264.

KAWACHI, I. & BERKMAN, L. 2000. Social cohesion, social capital, and health. *Social Epidemiology,* 174**,** 290-319.

KENNEDY, J. D. 1999. Lung function outcome in children of premature birth. *Journal of Paediatrics and Child Health,* 35**,** 516–521.

KESSLER, R. C. & WALTERS, E. E. 1998. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the national comorbidity survey. *Depression and Anxiety,* 7**,** 3-14.

KURUKULAARATCHY, R. J., ZHANG, H., PATIL, V., RAZA, A., KARMAUS, W., EWART, S. & ARSHAD, S. H. 2015. Identifying the heterogeneity of young adult rhinitis through cluster analysis in the Isle of Wight birth cohort. *Journal of Allergy and Clinical Immunology,* 135**,** 143-50.

KUSEL, M. M., DE KLERK, N. H., KEBADZE, T., VOHMA, V., HOLT, P. G., JOHNSTON, S. L. & SLY, P. D. 2007. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *Journal of Allergy and Clinical Immunolgy,* 119**,** 1105-10.

LANGRIDGE, A. T., GLASSON, E. J., NASSAR, N., JACOBY, P., PENNELL, C., HAGAN, R., BOURKE, J., LEONARD, H. & STANLEY, F. J. 2013. Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability. *PloS one,* 8**,** e50963.

LEBOLD, K. M., JACOBY, D. B. & DRAKE, M. G. 2020. Inflammatory mechanisms linking maternal and childhood asthma. *Journal of Leukocyte Biology,* 108**,** 113-121.

LEECH, R. M., MCNAUGHTON, S. A. & TIMPERIO, A. 2015. Clustering of diet, physical activity and sedentary behaviour among Australian children: cross-sectional and longitudinal associations with overweight and obesity. *International Journal of Obesity (Lond),* 39**,** 1079-85.

LI, J., MATTES, E., STANLEY, F., MCMURRAY, A. & HERTZMAN, C. 2009. Social determinants of child health and well-being. Taylor & Francis.

LIU, X., OLSEN, J., PEDERSEN, L. H., AGERBO, E., YUAN, W. & LI, J. 2015. Antidepressant use during pregnancy and asthma in the offspring. *Pediatrics,* 135**,** e911-7.

LOEWEN, K., MONCHKA, B., MAHMUD, S. M., T JONG, G. & AZAD, M. B. 2018. Prenatal antibiotic exposure and childhood asthma: a population-based study. *European Respiratory Journal,* 52.

LOWE, A. J., CARLIN, J. B., BENNETT, C. M., HOSKING, C. S., ALLEN, K. J., ROBERTSON, C. F., AXELRAD, C., ABRAMSON, M. J., HILL, D. J. & DHARMAGE, S. C. 2010. Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ,* 341**,** c4616.

LUCAS, N., BAYER, J. K., GOLD, L., MENSAH, F., CANTERFORD, L., WAKE, M., WESTRUPP, E. M. & NICHOLSON, J. M. 2013. The cost of healthcare for children with mental health difficulties. *Australian and New Zealand Journal of Psychiatry,* 47**,** 849-858.

MAÏANO, C., HUE, O., MORIN, A. J. & MOULLEC, G. 2016. Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. *Obesity Review,* 17**,** 599-611.

MALLOL, J., CRANE, J., VON MUTIUS, E., ODHIAMBO, J., KEIL, U., STEWART, A. & GROUP, I. P. T. S. 2013. The International Study of Asthma and Allergies in Childhood (ISAAC) phase three: a global synthesis. *Allergologia et immunopathologia,* 41**,** 73-85.

MARTEL, M. J., REY, E., BEAUCHESNE, M. F., MALO, J. L., PERREAULT, S., FORGET, A. & BLAIS, L. 2009. Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. *European Respiratory Journal,* 34**,** 579-87.

MCGEACHIE, M. J., YATES, K. P., ZHOU, X., GUO, F., STERNBERG, A. L., VAN NATTA, M. L., WISE, R. A., SZEFLER, S. J., SHARMA, S., KHO, A. T., CHO, M. H., CROTEAU-CHONKA, D. C., CASTALDI, P. J., JAIN, G., SANYAL, A., ZHAN, Y., LAJOIE, B. R., DEKKER, J., STAMATOYANNOPOULOS, J., COVAR, R. A., ZEIGER, R. S., ADKINSON, N. F., WILLIAMS, P. V., KELLY, H. W., GRASEMANN, H., VONK, J. M., KOPPELMAN, G. H., POSTMA, D. S., RABY, B. A., HOUSTON, I., LU, Q., FUHLBRIGGE, A. L., TANTISIRA, K. G., SILVERMAN, E. K., TONASCIA, J., WEISS, S. T. & STRUNK, R. C. 2016. Patterns of growth and decline in lung function in persistent childhood asthma. *New England Journal of Medicine,* 374**,** 1842-1852.

MOORE, W. C., MEYERS, D. A., WENZEL, S. E., TEAGUE, W. G., LI, H., LI, X., D'AGOSTINO, R., JR., CASTRO, M., CURRAN-EVERETT, D., FITZPATRICK, A. M., GASTON, B., JARJOUR, N. N., SORKNESS, R., CALHOUN, W. J., CHUNG, K. F., COMHAIR, S. A., DWEIK, R. A., ISRAEL, E., PETERS, S. P., BUSSE, W. W., ERZURUM, S. C., BLEECKER, E. R. & FOR THE NATIONAL HEART LUNG BLOOD INSTITUTE'S SEVERE ASTHMA RESEARCH PROGRAM 2010. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *American Journal of Respiratory and Critical Care Medicine,* 181**,** 315-23.

MOTIKA, C. A., PAPACHRISTOU, C., ABNEY, M., LESTER, L. A. & OBER, C. 2011. Rising prevalence of asthma is sex-specific in a US farming population. *Journal of Allergy and Clinical Immunology,* 128**,** 774-9.

MULDER, B., POUWELS, K. B., SCHUILING-VENINGA, C. C., BOS, H. J., DE VRIES, T. W., JICK, S. S. & HAK, E. 2016. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. *Clinical & Experimental Allergy,* 46**,** 1214-26.

NEUMAN, A., HOHMANN, C., ORSINI, N., PERSHAGEN, G., ELLER, E., KJAER, H. F., GEHRING, U., GRANELL, R., HENDERSON, J., HEINRICH, J., LAU, S., NIEUWENHUIJSEN, M., SUNYER, J., TISCHER, C., TORRENT, M., WAHN, U., WIJGA, A. H., WICKMAN, M., KEIL, T., BERGSTROM, A. & CONSORTIUM, E. 2012. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *American Journal of Respiratory and Critical Care Medicine,* 186**,** 1037-43.

NEWBY, C., HEANEY, L. G., MENZIES-GOW, A., NIVEN, R. M., MANSUR, A., BUCKNALL, C., CHAUDHURI, R., THOMPSON, J., BURTON, P., BRIGHTLING, C. & BRITISH THORACIC SOCIETY SEVERE REFRACTORY ASTHMA, N. 2014. Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One,* 9**,** e102987.

OBEL, C., LINNET, K. M., HENRIKSEN, T. B., RODRIGUEZ, A., JARVELIN, M. R., KOTIMAA, A., MOILANEN, I., EBELING, H., BILENBERG, N., TAANILA, A., YE, G. & OLSEN, J. 2009. Smoking during pregnancy and hyperactivity-inattention in the offspring--comparing results from three Nordic cohorts. *International Journal of Epidemiology,* 38**,** 698-705.

OSMAN, M., TAGIYEVA, N., WASSALL, H. J., NINAN, T. K., DEVENNY, A. M., MCNEILL, G., HELMS, P. J. & RUSSELL, G. 2007. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. *Pediatric Pulmonology,* 42**,** 60-5.

PATE, R. R., HEATH, G. W., DOWDA, M. & TROST, S. G. 1996. Associations between physical activity and other health behaviors in a representative sample of US adolescents. *American Journal of Public Health,* 86**,** 1577-1581.

PETRONIS, A. 2010. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. *Nature,* 465**,** 721-727.

POLINSKI, K. J., LIU, J., BOGHOSSIAN, N. S. & MCLAIN, A. C. 2017. Maternal Obesity, Gestational Weight Gain, and Asthma in Offspring. *Preventing Chronic Disease,* 14**,** E109.

POORTINGA, W. 2007. The prevalence and clustering of four major lifestyle risk factors in an English adult population. *Preventive Medicine,* 44**,** 124-8.

QUANCH, J., GOLD, L., HISCOCK, H., MENSAH, F. K., LUCAS, N., NICHOLSON, J. M. & WAKE, M. 2013. Primary healthcare costs associated with sleep problems up to age 7 years: Australian population-based study. *BMJ Open*.

RICH-EDWARDS, J. W., COLDITZ, G. A., STAMPFER, M. J., WILLETT, W. C., GILLMAN, M. W., HENNEKENS, C. H., SPEIZER, F. E. & MANSON, J. E. 1999. Birthweight and the risk for type 2 diabetes mellitus in adult women. *Annals of Internal Medicine,* 130**,** 7.

ROURA, L. C. & ARULKUMARAN, S. S. 2015a. Facing the noncommunicable disease (NCD) global epidemic--the battle of prevention starts in utero--the FIGO challenge. *Best Practice & Research Clinical Obstetrics and Gynaecology,* 29**,** 5-14.

ROURA, L. C. & ARULKUMARAN, S. S. 2015b. Facing the noncommunicable disease (NCD) global epidemic--the battle of prevention starts in utero--the FIGO challenge. *Best Practice & Research Clinical Obstetrics and Gynaecology,* 29**,** 5-14.

SALDANHA-GOMES, C., MARBAC, M., SEDKI, M., CORNET, M., PLANCOULAINE, S., CHARLES, M. A., LIORET, S. & DARGENT-MOLINA, P. 2020. Clusters of diet, physical activity, television exposure and sleep habits and their association with adiposity in preschool children: the EDEN mother-child cohort. *International Journal of Behavioral Nutrition and Physical Activity,* 17**,** 20.

SCHENDEL, D. & BHASIN, T. K. 2008. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. *Pediatrics,* 121**,** 1155-1164.

SCHIEVE, L. A., TIAN, L. H., RANKIN, K., KOGAN, M. D., YEARGIN-ALLSOPP, M., VISSER, S. & ROSENBERG, D. 2016. Population impact of preterm birth and low birth weight on developmental disabilities in US children. *Annals of epidemiology,* 26**,** 267-274.

SCHOLTENS, S., WIJGA, A. H., BRUNEKREEF, B., KERKHOF, M., POSTMA, D. S., OLDENWENING, M., DE JONGSTE, J. C. & SMIT, H. A. 2010. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. *Internatioal Journal of Obesity,* 34**,** 606-13.

SCHUIT, A. J., VAN LOON, A. J., TIJHUIS, M. & OCKE, M. 2002. Clustering of lifestyle risk factors in a general adult population. *Preventive Medicine,* 35**,** 219-24.

SCHULENBERG, J. E., BRYANT, A. L. & O'MALLEY, P. M. 2004. Taking hold of some kind of life: How developmental tasks relate to trajectories of well-being during the transition to adulthood. *Development and Psychopathology* 16**,** 1119–1140.

SCIBERRAS, E., LUCAS, N., EFRON, D., GOLD, L., HISCOCK, H. & NICHOLSON, J. M. 2013. Health Care Costs Associated With Parent-Reported ADHD: A Longitudinal Australian Population-Based Study. *Journal of Attention Disorders,* 21**,** 1063-1072.

SHLAFER, R., HERGENROEDER, A. C., JEAN EMANS, S., RICKERT, V. I., ADGER, H., JR., SPEAR, B., IRWIN, C. E., JR., KREIPE, R. E., WALKER, L. R. & RESNICK, M. D. 2014. Adolescence as a critical stage in the MCH Life Course Model: commentary for the Leadership Education in Adolescent Health (LEAH) interdisciplinary training program projects. *Maternal and Child Health Journal,* 18**,** 462-6.

SIROUX, V., BASAGANA, X., BOUDIER, A., PIN, I., GARCIA-AYMERICH, J., VESIN, A., SLAMA, R., JARVIS, D., ANTO, J. M., KAUFFMANN, F. & SUNYER, J. 2011. Identifying adult asthma phenotypes using a clustering approach. *European Respiratory Journal,* 38**,** 310-7.

STERN, D. A., MORGAN, W. J., WRIGHT, A. L., GUERRA, S. & MARTINEZ, F. D. 2007. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *The Lancet,* 370**,** 758-764.

STIEMSMA, L. T. & MICHELS, K. B. 2018. The role of the microbiome in the developmental origins of health and disease. *Pediatrics,* 141.

STOKHOLM, J., SEVELSTED, A., BØNNELYKKE, K. & BISGAARD, H. 2014. Maternal propensity for infections and risk of childhood asthma: a registry-based cohort study. *The Lancet Respiratory Medicine,* 2**,** 631-637.

SUTIN, A. R., FLYNN, H. A. & TERRACCIANO, A. 2018. Maternal smoking during pregnancy and offspring personality in childhood and adulthood. *Journal of Personality,* 86**,** 652-664.

TEGETHOFF, M., GREENE, N., OLSEN, J., SCHAFFNER, E. & MEINLSCHMIDT, G. 2011. Stress during pregnancy and offspring pediatric disease: A National Cohort Study. *Environmental Health Perspectives,* 119**,** 1647-52.

TO, T., STANOJEVIC, S., MOORES, G., GERSHON, A. S., BATEMAN, E. D., CRUZ, A. A. & BOULET, L. P. 2012. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health,* 12**,** 204.

TURNER, S. W., CAMPBELL, D., SMITH, N., CRAIG, L. C., MCNEILL, G., FORBES, S. H., HARBOUR, P. J., SEATON, A., HELMS, P. J. & DEVEREUX, G. S. 2010. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. *Thorax,* 65**,** 391-7.

UNICEF 2006. THE STATE OF THE WORLD'S CHILDREN 2006: EXCLUDED AND INVISIBLE. New York.

VAN DEN HOUT, W. 2010. The value of productivity: human-capital versus friction-cost method. *Annals of the Rheumatic Diseases,* 69**,** i89-i91.

VAN NIEUWENHUIJZEN, M., JUNGER, M., VELDERMAN, M. K., WIEFFERINK, K. H., PAULUSSEN, T. W., HOX, J. & REIJNEVELD, S. A. 2009. Clustering of health-compromising behavior and delinquency in adolescents and adults in the Dutch population. *Preventive Medicine,* 48**,** 572-8.

WATSON, P. E. & MCDONALD, B. W. 2014. Water and nutrient intake in pregnant New Zealand women: association with wheeze in their infants at 18 months. *Asia Pacific journal of Clinical Nutrition,* 23**,** 660-70.

WEATHERALL, M., TRAVERS, J., SHIRTCLIFFE, P. M., MARSH, S. E., WILLIAMS, M. V., NOWITZ, M. R., ALDINGTON, S. & BEASLEY, R. 2009. Distinct clinical phenotypes of airways disease defined by cluster analysis. *European Respiratory Journal,* 34**,** 812-8.

WENZEL, S. 2012. Severe asthma: from characteristics to phenotypes to endotypes. *Clinical & Experimental Allergy,* 42**,** 650-8.

WEST, C. E., JENMALM, M. C. & PRESCOTT, S. L. 2015. The gut microbiota and its role in the development of allergic disease: a wider perspective. *Clinical & Experimental Allergy,* 45**,** 43-53.

WILLIAMS, K., HELMER, M., DUNCAN, G., PEAT, J. & MELLIS, C. 2008. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. *Child: care, health and development,* 34**,** 249-256.

WORLD HEALTH ORGANIZATION 2008. The global burden of disease: 2004 update. Geneva.

ZEIN, J. G. & ERZURUM, S. C. 2015. Asthma is Different in Women. *Current Allergy and Asthma Reports,* 15**,** 28.

ZETSTRA-VAN DER WOUDE, P. A., DE WALLE, H. E., HOEK, A., BOS, H. J., BOEZEN, H. M., KOPPELMAN, G. H., DE JONG-VAN DEN BERG, L. T. & SCHOLTENS, S. 2014. Maternal high-dose folic acid during pregnancy and asthma medication in the offspring. *Pharmacoepidemiology and Drug Safety,* 23**,** 1059-65.

ZHANG, M., LITONJUA, A. A. & MUELLER, N. T. 2018. Maternal antibiotic use and child asthma: is the association causal? *European Respiratory Journal,* 52.

ZHONG, Y., WANG, J. & NICHOLAS, S. 2017. Gender, childhood and adult socioeconomic inequalities in functional disability among Chinese older adults. *International journal for equity in health,* 16**,** 1-11.

ZUBRICK, S. R., WILLIAMS, A., SILBURN, S. & VIMPANI, G. 2000. Indicators of social and family functioning.

APPENDIX A

Details of the study participants (Paper 2)

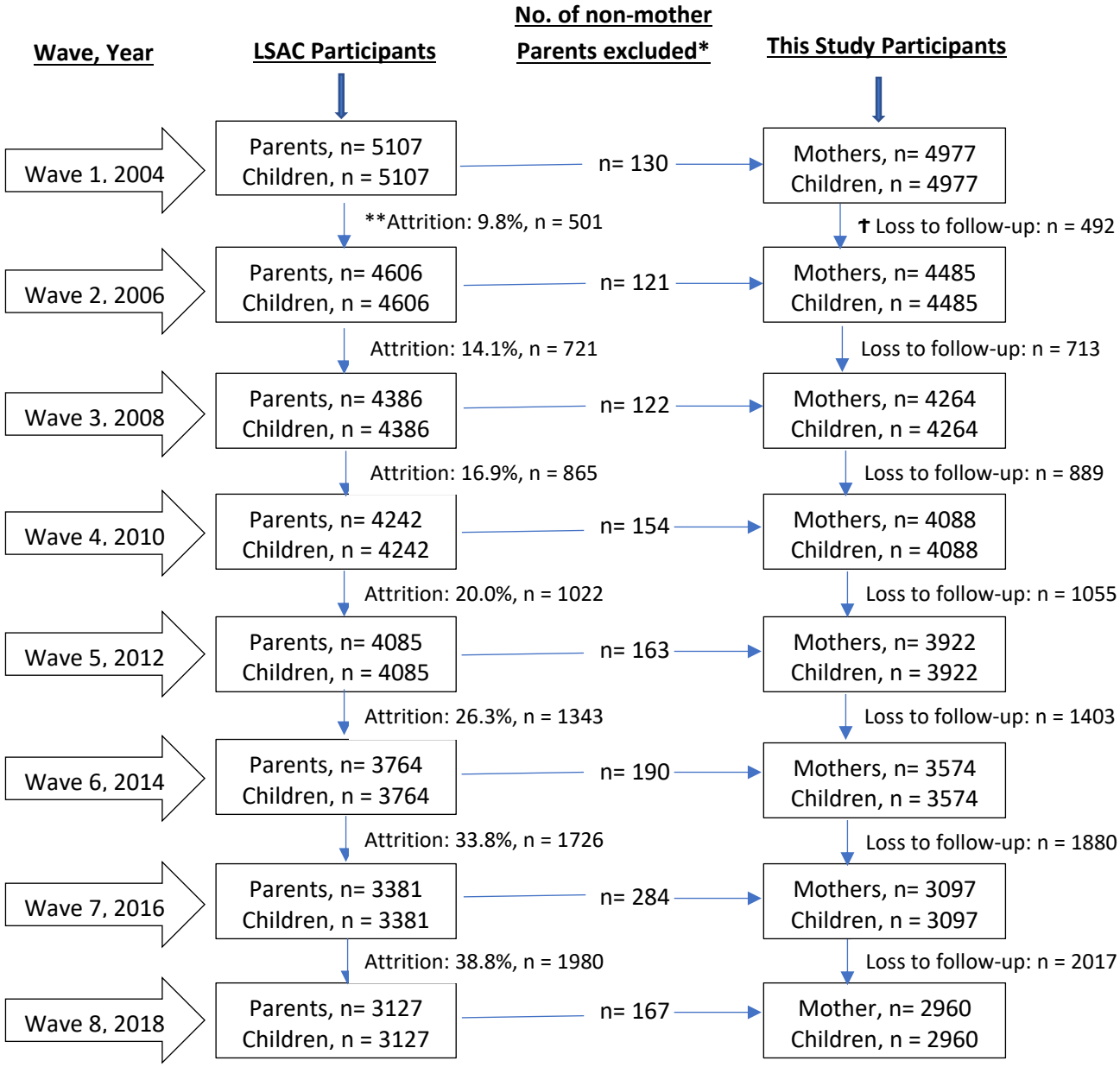

Figure A1: Participant diagram

Notes:
* Non-mother parents are those who responded as parent 1 in LSAC and had relationship to the study child as father, grandparent, adopted parent, step-parent, foster parent, aunt/uncle, sibling or unrelated adults in the respective waves.
** All attritions are calculated from the first wave to the particular wave.
† Loss to follow-up has been calculated from eligible sample of the first wave (baseline wave) to the particular wave.

Table A1: Loss of follow-up analysis of the prevalence of wheezing, ever diagnosed with asthma, ongoing asthma and eczema

Timeline	Wheezing	Ever had Asthma	Currently had asthma	Eczema
	n (%)	n (%)	n (%)	n (%)
Baseline at Age 0-1 year (Wave-1)	820 (16.47)			729 (14.65)
Baseline at Age 2-3 year (for asthma, Wave-2)		647 (14.43)	523 (11.65)	
Loss to follow-up at Age 2-3 year (Wave-2)				
With respect to baseline wave	84 (17.06)	-	-	71 (14.51)
Loss to follow-up at Age 4-5 year (Wave-3)				
With respect to baseline wave	140 (19.62)	65 (18.21)	54 (15.00)	96 (13.54)
With respect to Wave-2	98 (27.79)	67 (18.95)	55 (15.76)	43 (12.28)
Loss to follow-up at Age 6-7 year (Wave-4)				
With respect to baseline wave	189 (21.24)	109 (19.69)	87 (15.67)	117 (13.11)
With respect to Wave-3	65 (22.24)	76 (26.17)	47 (16.32)	39 (13.42)
Loss to follow-up at Age 8-9 year (Wave-5)				
With respect to baseline wave	209 (19.88)	114 (16.3)	94 (13.36)	147 (13.97)
With respect to Wave-4	58 (19.05)	86 (28.29)	38 (12.50)	45 (14.80)
Loss to follow-up at Age 10-11 year (Wave-6)				
With respect to baseline wave	271 (19.33)	171 (16.69)	145 (14.13)	183 (13.02)
With respect to Wave-5	56 (12.72)	107 (24.48)	59 (13.47)	48 (10.93)
Loss to follow-up at Age 12-13 year (Wave-7)				
With respect to baseline wave	357 (19.00)	224 (15.97)	185 (13.21)	253 (13.46)
With respect to Wave-6	84 (14.40)	193 (33.01)	89 (15.26)	89 (15.10)
Loss to follow-up at Age 14-15 year (Wave-8)				
With respect to baseline wave	374 (18.53)	256 (15.96)	215 (13.36)	272 (13.50)
With respect to Wave-7	23 (6.62)	114 (33.17)	38 (11.08)	55 (15.85)

Table A2: Loss of follow-up analysis of the baseline characteristics of the explanatory variables of the sampled children

VARIABLES	Baseline at Age 0-1 year n (%)	Loss to follow-up at Age 2-3 year n (%)	Loss to follow-up at Age 4-5 year n (%)	Loss to follow-up at Age 6-7 year n (%)	Loss to follow-up at Age 8-9 year n (%)	Loss to follow-up at Age 10-11 year n (%)	Loss to follow-up at Age 12-13 year n (%)	Loss to follow-up at Age 14-15 year n (%)
Number of children/mothers à	4977	492	713	889	1055	1403	1880	2017
Explanatory Variables								
Mother had asthma during pregnancy								
No	4619 (92.81)	452 (91.89)	662 (92.73)	822 (92.42)	990 (93.76)	1311 (93.41)	1759 (93.58)	1892 (93.78)
Yes	358 (7.19)	40 (8.11)	51 (7.29)	67 (7.58)	65 (6.24)	92 (6.59)	121 (6.42)	125 (6.22)
Pre-pregnancy Obesity of Mother								
Underweight	469 (9.42)	40 (8.02)	64 (8.98)	81 (9.16)	97 (9.19)	126 (8.96)	183 (9.71)	194 (9.61)
Healthy weight	1786 (35.89)	108 (22.02)	169 (23.76)	218 (24.52)	270 (25.54)	384 (27.38)	521 (27.71)	581 (28.78)
Overweight	1007 (20.23)	64 (12.96)	83 (11.59)	128 (14.41)	165 (15.58)	218 (15.54)	319 (16.96)	353 (17.52)
Obesity	714 (14.35)	43 (8.83)	80 (11.19)	99 (11.14)	118 (11.27)	174 (12.44)	242 (12.9)	264 (13.08)
Not measured	1001 (20.11)	237 (48.16)	317 (44.48)	362 (40.76)	406 (38.42)	501 (35.69)	615 (32.72)	625 (31.01)
Gestational age at birth							.	
On time (37–41 weeks)	4407 (88.55)	421 (85.48)	612 (85.86)	772 (86.88)	917 (86.89)	1212 (86.39)	1632 (86.82)	1765 (87.5)
Early (36 weeks or less)	338 (6.80)	45 (9.24)	58 (8.08)	71 (8.03)	88 (8.33)	117 (8.33)	146 (7.73)	159 (7.89)
Late (42 weeks or more)	232 (4.65)	26 (5.29)	43 (6.06)	45 (5.09)	50 (4.77)	74 (5.28)	102 (5.44)	93 (4.61)
Mother ever smoked during pregnancy								
No	4224 (84.88)	410 (83.33)	586 (82.14)	733 (82.49)	856 (81.14)	1140 (81.22)	1547 (82.27)	1644 (81.50)
Yes	753 (15.12)	82 (16.67)	127 (17.86)	156 (17.51)	199 (18.86)	263 (18.78)	333 (17.73)	373 (18.50)
Mother's smoking during 1st trimester								
None	4347 (87.35)	426 (86.57)	604 (84.66)	753 (84.68)	883 (83.72)	1178 (83.98)	1602 (85.22)	1707 (84.65)
<=10 cigarettes daily	410 (8.23)	45 (9.09)	72 (10.09)	90 (10.10)	109 (10.32)	139 (9.90)	179 (9.5)	197 (9.78)
11+ cigarettes daily	220 (4.42)	21 (4.33)	37 (5.24)	46 (5.22)	63 (5.96)	86 (6.13)	99 (5.28)	112 (5.57)

VARIABLES	Baseline at Age 0-1 year n (%)	Loss to follow-up at Age 2-3 year n (%)	Loss to follow-up at Age 4-5 year n (%)	Loss to follow-up at Age 6-7 year n (%)	Loss to follow-up at Age 8-9 year n (%)	Loss to follow-up at Age 10-11 year n (%)	Loss to follow-up at Age 12-13 year n (%)	Loss to follow-up at Age 14-15 year n (%)
Antidepressant medication during pregnancy								
No	4870 (97.86)	484 (98.30)	700 (98.16)	879 (98.83)	1031 (97.67)	1371 (97.71)	1838 (97.76)	1958 (97.08)
Yes	107 (2.14)	8 (1.70)	13 (1.84)	10 (1.17)	24 (2.31)	32 (2.29)	42 (2.24)	59 (2.92)
Antibiotic medication during pregnancy								
No	4452 (89.46)	440 (89.53)	636 (89.19)	789 (88.78)	950 (89.98)	1253 (89.32)	1684 (89.57)	1810 (89.76)
Yes	525 (10.54)	52 (10.47)	77 (10.81)	100 (11.22)	105 (10.02)	150 (10.68)	196 (10.43)	207 (10.24)
CONTROL VARIABLES								
Child Health Issues								
Birth weight								
Normal (2,500–3,999)	4071 (81.79)	399 (81.05)	587 (82.35)	733 (82.49)	881 (83.46)	1175 (83.71)	1559 (82.92)	1667 (82.67)
Low (<2,500)	279 (5.61)	50 (10.25)	50 (7.03)	62 (6.96)	77 (7.29)	89 (6.36)	115 (6.1)	126 (6.25)
High (>=4,000)	627 (12.59)	43 (8.7)	76 (10.62)	94 (10.55)	97 (9.26)	139 (9.93)	206 (10.97)	224 (11.09)
Immunisation status of children								
Up to date	4516 (90.74)	415 (84.31)	615 (86.20)	790 (88.87)	943 (89.38)	1244 (88.68)	1670 (88.82)	1799 (89.22)
Not up to date	461 (9.26)	77 (15.69)	98 (13.80)	99 (11.13)	112 (10.62)	159 (11.32)	210 (11.18)	218 (10.78)
Breastfed children up to 6 months								
Yes	2328 (46.78)	185 (37.61)	260 (36.42)	322 (36.24)	395 (37.45)	526 (37.49)	722 (38.41)	779 (38.60)
No	2649 (53.22)	307 (62.39)	453 (63.58)	567 (63.76)	660 (62.55)	877 (62.51)	1158 (61.59)	1238 (61.40)
Mother's sleep quality in the year of childbirth								
Very good/Fairly good	3478 (69.89)	342 (69.56)	500 (70.08)	619 (69.61)	739 (69.98)	987 (70.34)	1323 (70.36)	1417 (70.24)
Fairly bad	1118 (22.46)	113 (22.96)	153 (21.52)	195 (21.89)	220 (20.87)	301 (21.49)	404 (21.5)	437 (21.67)
Very bad	381 (7.66)	37 (7.48)	60 (8.40)	75 (8.5)	96 (9.15)	115 (8.17)	153 (8.14)	163 (8.09)

APPENDIX B

Longitudinal prevalence of wheezing, asthma, and eczema (tabular data of Figure 2, Paper 2)

Table B-1: Prevalence of wheezing by age group and sex

Age Group	All	Male	Female
0-1	16.5%	18.6%	14.2%
2-3	26.0%	28.0%	23.8%
4-5	20.0%	21.3%	18.7%
6-7	18.6%	19.8%	17.4%
8-9	12.8%	14.7%	10.8%
10-11	11.3%	12.0%	10.6%
12-13	9.3%	10.4%	8.0%
14-15	7.3%	7.67%	7.03%

Table B-2: Prevalence of having ever diagnosed with asthma by age group and sex

Age Group	All	Male	Female
2-3	14.4%	17.3%	11.5%
4-5	21.6%	24.5%	18.7%
6-7	26.3%	28.9%	22.9%
8-9	27.0%	29.6%	23.8%
10-11	30.5%	33.0%	26.8%
12-13	31.5%	33.5%	28.1%
14-15	32.3%	33.6%	29.8%

Table B-3 Prevalence of ongoing asthma by age group and sex

Age Group	All	Male	Female
2-3	11.7%	13.6%	9.7%
4-5	13.4%	15.9%	12.7%
6-7	15.3%	16.8%	13.8%
8-9	15.3%	16.8%	13.7%
10-11	15.4%	17.0%	13.7%
12-13	14.8%	15.3%	14.3%
14-15	13.6%	13.46%	13.7%

Table B-4 Prevalence of eczema by age group and sex

Age Group	All	Male	Female
0-1	14.7%	15.3%	14.0%
2-3	17.8%	18.5%	17.0%
4-5	14.7%	14.8%	14.6%
6-7	13.2%	12.1%	14.3%
8-9	12.7%	10.9%	14.6%
10-11	11.4%	9.8%	13.2%
12-13	10.0%	8.1%	12.0%
14-15	9.5%	7.0%	12.1%

APPENDIX C

Sex segregated analysis tables on the risk of experiencing wheezing, asthma or eczema among children

Table C-1: The risk of experiencing wheezing among male children based on the incidence of maternal asthma, other morbidities, and maternal health behaviours during pregnancy

Maternal health, risk factors, and medications during pregnancy	**Age 0-1** OR (95% CI) N = 4977	**Age 2-3** OR (95% CI) N = 4485	**Age 4-5** OR (95% CI) N = 4264	**Age 6-7** OR (95% CI) N = 4088	**Age 8-9** OR (95% CI) N = 3922	**Age 10-11** OR (95% CI) N = 3574	**Age 12-13** OR (95% CI) N = 3097	**Age 14-15** OR (95% CI) N = 2960
Had asthma								
No								
Yes	1.50 (1.03-2.18)*	1.93 (1.35-2.76)**	1.77 (1.20-2.63)*	2.07 (1.35-3.18)*	1.97 (1.23-3.18)**	3.28 (2.01-5.34)**	1.56 (0 .78 -3.11)	1.13 (0.49-2.61)
Gestational age at birth								
On time (37-41 weeks, ref.)								
Early (36 weeks or less)	1.25 (0.78-1.99)	1.54 (0.97-2.45)†	1.50 (0.90-2.48)	1.96 (1.19-3.23) †	1.26 (0.67-2.36)	1.03 (0.41-2.63)	0.35 (0.11-1.09) †	1.15 (0.47-2.85)
Late (42 weeks or more)	0.77 (0.43-1.36)	.92 (0.56-1.51)	1.34 (0.78-2.31)	1.33 (0.77-2.27)	1.59 (0.87-2.91)	1.31 (0.59-2.89)	1.63 (0.76-3.52)	1.46 (0.58-3.67)
Pre-pregnancy obesity								
Healthy weight								
Underweight	0.38 (0.23-0.63)**	0.76 (0.50-1.16)	0.60 (0.36-.99)	0.72 (0.45-1.15)	0.69 (0.39-1.23)	0.64 (0.31-1.28)	1.32 (0.66-2.62)	0.55 (0.23-1.36)
Overweight	1.06 (0.77-1.45)	1.66 (1.26-2.20)**	0.98 (0.72-1.36)	1 (0.71-1.41)	1.04 (0.71-1.52)	0.93 (0.56-1.53)	2.08 (1.21-3.58) †	1.29 (0.70-2.39)
Obesity	0.97 (0.68-1.38)	1.56 (1.14-2.15)†	1.23 (0.86-1.75)	1.03 (0.70-1.51)	0.99 (0.64-1.53)	1.24 (0.77-2.01)	1 (0.53-1.91)	0.97 (0.50-1.90)
Not known	1.66 (1.22-2.24)*	1.52 (1.11-2.07)†	1.41 (1-2)†	1.46 (1.01-2.10)*	1.19 (0.80-1.77)	1.23 (0.73-2.05)	1.47 (0.81-2.67)*	1.81 (0.95-3.43)†
Smoking during 1st trimester								
None (ref.)								
<=10 cigarettes daily	1.75 (1.19-2.57)*	1.50 (1.04-2.18)*	1.40 (0.92-2.14)	1.31 (0.83-2.08)	1.24 (0.75-2.06)	0.96 (0 .47 -1.95)	1.74 (0. 89 -3.41)	1.45 (0.61-3.45)
11+ cigarettes daily	1.37 (0.83-2.25)	1.28 (0.76-2.16)	1.99(1.1-3.60)*	2.71 (1.51-4.85)*	1.33 (0.66-2.69)	1.10 (0.48-2.54)	0.73 (0.23-2.29)	1.72 (0.58-5.07)*
Antibiotic medication								
No								
Yes	1.39 (0.98-1.96) †	1.33 (0.95-1.87) †	1.25 (0.83-1.86)	1.14 (0.75-1.73)	1.32 (0.85-2.07)	1.19 (0.65-2.19)	1.37 (0.68-2.75)	0.68 (0.27-1.68)
Anti-depressant medication								
No								
Yes	1.70 (0.84-3.44)	2.08 (1.10-3.94)*	0.99 (0.47-2.07)	1.07 (0.50-2.32)	0.38 (0.12-1.18) †	1.80 (0.66-4.86)	2.09 (0.65-6.73)	-

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-2: The risk of experiencing wheezing among female children based on the incidence of maternal asthma, other morbidities, and maternal health behaviours during pregnancy

Maternal health, risk factors, and medications during pregnancy	Age 0-1 OR (95% CI) N = 4977	Age 2-3 OR (95% CI) N = 4485	Age 4-5 OR (95% CI) N = 4264	Age 6-7 OR (95% CI) N = 4088	Age 8-9 OR (95% CI) N = 3922	Age 10-11 OR (95% CI) N = 3574	Age 12-13 OR (95% CI) N = 3097	Age 14-15 OR (95% CI) N = 2960
Had asthma								
No								
Yes	1.46 (0.95-2.24)†	1.73 (1.14-2.65)*	1.15 (0.70-1.91)	1.59 (0.96-2.66)†	1.80 (1.03-3.15)*	1.72 (0.92-3.21)†	1.67 (0.81-3.46)	1.48 (0.69-3.15)
Gestational age at birth								
On time (37-41 weeks, ref.)								
Early (36 weeks or less)	1.53 (0.92-2.57)	1.55 (0.90-2.67)	1.23 (0.67-2.26)	1.04 (0.47-2.28)	0.82 (0.38-1.75)	0.50 (0.18-1.37)	0.70 (0.15-2.94)	1.04 (0.24-4.41)
Late (42 weeks or more)	0.46 (0.23-0.93)*	1.06 (0.62-1.83)	1.89 (1.03-3.50)*	0.84 (0.38-1.77)	0.41 (0.16-1.06)†	1.10 (0.48-2.56)	0.84 (0.23-3.15)	0.55 (0.15-2.03)
Pre-pregnancy obesity								
Healthy weight								
Underweight	1.22 (0.76-1.97)	1.05 (0.70-1.58)	1.31 (0.81-2.11)	0.84 (0.49-1.45)	1.05 (0.56-1.96)	1.42 (0.72-2.82)	0.88 (0.36-2.13)	0.63 (0.19-2.07)
Overweight	1.40 (0.98-1.98)†	1.18 (0.85-1.60)	1.30 (0.93-1.84)	1.06 (0.73-1.54)	1.58 (1.01-2.49)*	1.47 (0.88-2.46)	0.90 (0.47-1.73)	1.32 (0.70-2.49)
Obesity	1.55 (1.03-2.33)*	1.24 (0.88-1.74)	1.47 (1.01-2.17)†	1.45 (0.97-2.16)†	1.70 (1.03-2.79)*	2.20 (1.29-3.73)**	2.14 (1.09-4.20)*	1.73 (0.87-3.43)
Not known	1.37 (0.96-1.96)†	1.58 (1.14-2.17)**	1.28 (0.86-1.90)	1.30 (0.87-1.95)	1.22 (0.76-1.98)	1.78 (1.03-3.06)*	2.14 (1.13-4.06)*	1.93 (0.98-3.80)*
Smoking during 1st trimester								
None (ref.)								
<=10 cigarettes daily	1.45 (0.92-2.27)	1.58 (1.05-2.38)*	1.37 (0.86-2.18)	1.95 (1.20-3.15)**	1.47 (0.78-2.75)	1.09 (0.54-2.18)	0.69 (0.25-1.92)	0.89 (0.36-2.35)
11+ cigarettes daily	1.33 (0.75-2.36)	2.31 (1.38-3.89)**	1.68 (0.96-2.94)†	1.35 (0.71-2.55)	1.42 (0.66-3.06)	2.13 (1-4.55)*	1.55 (0.53-4.49)	3.5 (1.43-8.79)**
Antibiotic medication								
No								
Yes	1.16 (0.80-1.67)	1.47 (1.06-2.06)*	1.74 (0.79-1.78)	1.18 (0.87-1.55)	0.88 (0.55-1.47)	1.40 (0.86-2.27)	0.90 (0.43-1.86)	1.43 (0.74-2.76)
Anti-depressant medication								
No								
Yes	0.87 (0.36-2.09)	1.65 (0.77-3.52)	1.19 (0.53-3.11)	1.29 (0.65-2.11)	1.18 (0.42-3.36)	1.39 (0.49-4)	0.77 (0.16-3.64)	2.36 (0.75-7.50)

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-3: The risk of having ever been diagnosed with asthma among male children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy (cumulative effect over age)

Maternal health, Risk factors, and medications during pregnancy	**Age 2-3**	**Age 4-5**	**Age 6-7**	**Age 8-9**	**Age 10-11**	**Age 12-13**	**Age 14-15**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N = 4485	N = 4264	N = 4088	N = 3922	N = 3574	N = 3097	N = 2960
Had Asthma							
No							
Yes	2.76 (1.86-4.11)**	2.75 (1.86-4.07)**	2.69 (1.81-3.98)**	2.87 (1.93-4.28)**	3.04 (1.98-4.67)**	2.66 (1.69-4.18)**	2.35 (1.46-3.79)**
Gestational age at birth							
On time (37-41 weeks, ref.)							
Early (36 weeks or less)	2.16 (1.25-3.72)**	2.10 (1.30-3.40)**	1.65 (1.02-2.65)*	1.62 (0.98-2.66)*	1.15 (0.68-1.95)	0.83 (0.44-1.59)	0.90 (0.47-1.72)
Late (42 weeks or more)	1.07 (0.61-1.85)	1.08 (0.62-1.88)	0.79 (0.46-1.34)	0.79 (0.46-1.34)	0.83 (0.47-1.47)	1.13 (0.61-2.07)	1.07 (0.58-1.98)
Pre-pregnancy obesity							
Healthy weight							
Underweight	1.06 (0.66-1.71)	0.88 (0.57-1.36)	0.99 (0.66-1.48)	1.02 (0.69-1.5)	1.00 (0.67-1.49)	1.03 (0.66-1.61)	1.10 (0.7-1.7)
Overweight	1.3 (0.91-1.84)	1.15 (0.84-1.58)	1.36 (1.02-1.82)	1.32 (0.99-1.77)	1.19 (0.87-1.61)	1.08 (0.77-1.51)	1.20 (0.85-1.7)
Obesity	1.65 (1.13-2.41)*	1.45 (1.03-2.04)*	1.34 (0.97-1.86)†	1.38 (1.00-1.91)*	1.23 (0.87-1.74)	0.9 (0.62-1.3)	1.00 (0.69-1.44)
Not known	1.64 (1.14-2.36)	1.54 (1.11-2.14)	1.42 (1.02-1.96)*	1.46 (1.05-2.02)*	1.61 (1.13-2.28)**	1.65 (1.12-2.43)	1.44 (0.96-2.14)†
Smoking during 1st trimester							
None (ref.)							
<=10 cigarettes daily	1.02 (0.66-1.59)	1.01 (0.67-1.53)	1.16 (0.77-1.74)	1.06 (0.70-1.61)	1.25 (0.81-1.95)	1.08 (0.66-1.75)	1.03 (0.63-1.71)
11+ cigarettes daily	1.59 (0.89-2.84)	1.86 (1.07-3.22)*	1.54 (0.89-2.68)	1.26 (0.69-2.28)	1.52 (0.82-2.81)	1.4 (0.7-2.81)	1.51 (0.77-2.97)
Antibiotic medication							
No							
Yes	1.04 (0.69-1.58)	1.03 (0.71-1.51)	1.20 (0.81-1.76)	1.38 (0.95-1.99)†	1.28 (0.86-1.88)	1.12 (0.73-1.73)	1.00 (0.64-1.54)
Anti-depressant medication							
No							
Yes	0.73 (0.28-1.92)	1.09 (0.50-2.38)	1.29 (0.64-2.6)	1.00 (0.43-2.32)	1.37 (0.58-3.23)	1.18 (0.44-3.13)	0.45 (0.11-1.77)

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-4: The risk of having ever been diagnosed with asthma among female children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy (cumulative effect over age)

Maternal health, Risk factors, and medications during pregnancy	**Age 2-3**	**Age 4-5**	**Age 6-7**	**Age 8-9**	**Age 10-11**	**Age 12-13**	**Age 14-15**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N = 4485	N = 4264	N = 4088	N = 3922	N = 3574	N = 3097	N = 2960
Had Asthma							
No							
Yes	1.77 (1.1-2.86)*	2.01 (1.31-3.10)**	2.45 (1.57-3.81)**	1.98 (1.30-3.01)**	2.29 (1.46-3.59)**	3.42 (2.06-5.69)**	2.83 (1.73-4.62)**
Gestational age at birth							
On time (37-41 weeks, ref.)							
Early (36 weeks or less)	0.60 (0.26-1.37)	0.62 (0.32-1.20)	0.5 (0.25-0.97)*	0.93 (0.5-1.75)	0.99 (0.50-1.99)	0.76 (0.36-1.59)	0.82 (0.41-1.65)
Late (42 weeks or more)	0.34 (0.12-0.93)*	0.90 (0.48-1.70)	1.01 (0.53-1.89)	0.88 (0.48-1.60)	0.84 (0.43-1.64)	1.05 (0.50-2.21)	0.92 (0.46-1.81)
Pre-pregnancy obesity							
Healthy weight							
Underweight	0.87 (0.50-1.52)	0.80 (0.49-1.31)	0.74 (0.46-1.2)	0.68 (0.41-1.10)	0.61 (0.36-1.02)†	0.62 (0.36-1.05)†	0.68 (0.39-1.18)
Overweight	1.47 (0.99-2.17)*	1.50 (1.08-2.10)*	1.2 (0.87-1.65)	1.25 (0.91-1.71)	1.42 (1.02-1.96)*	1.43 (1.01-2.02)*	1.25 (0.88-1.78)
Obesity	1.47 (0.93-2.31)†	1.55 (1.07-2.24)*	1.52 (1.05-2.2)*	1.51 (1.06-2.14)*	1.72 (1.19-2.48)**	1.73 (1.16-2.59)**	1.61 (1.06-2.43)*
Not known	1.11 (0.72-1.71)	1.11 (0.76-1.62)	1.32 (0.91-1.9)	1.25 (0.87-1.78)	1.67 (1.14-2.44)**	1.59 (1.05-2.41)*	1.91 (1.27-2.87)**
Smoking during 1st trimester							
None (ref.)							
<=10 cigarettes daily	1.18 (0.68-2.04)	0.80 (0.49-1.33)	0.9 (0.54-1.49)	0.87 (0.53-1.43)	0.89 (0.52-1.54)	0.92 (0.52-1.63)	0.69 (0.35-1.35)
11+ cigarettes daily	1.73 (0.95-3.17)†	1.82 (1.03-3.20)*	1.87 (1.05-3.31)*	1.88 (1.05-3.35)*	1.83 (0.97-3.45)†	1.68 (0.85-3.31)	2.00 (0.97-4.12)*
Antibiotic medication							
No							
Yes	1.43 (0.96-2.15)†	1.12 (0.77-1.62)	1.18 (0.82-1.71)	1.00 (0.70-1.43)	1.10 (0.76-1.60)	0.92 (0.60-1.41)	1.09 (0.71-1.67)
Anti-depressant medication							
No							
Yes	1.06 (0.42-2.65)	1.57 (0.72-3.46)	2.43 (1.13-5.24)*	1.73 (0.79-3.80)	1.65 (0.75-3.61)	1.45 (0.56-3.75)	0.68 (0.26-1.82)

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-5: The risk of having ongoing asthma among male children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	Age 2-3 OR (95% CI) N = 4485	Age 4-5 OR (95% CI) N = 4264	Age 6-7 OR (95% CI) N = 4088	Age 8-9 OR (95% CI) N = 3922	Age 10-11 OR (95% CI) N = 3574	Age 12-13 OR (95% CI) N = 3097	Age 14-15 OR (95% CI) N = 2960
Had asthma							
No							
Yes	3.17 (2.10-4.77)**	4.09 (2.76-6.08)**	3.29 (2.17-5.00)**	3.66 (2.36-5.68)**	3.66 (2.36-5.68)**	3.17 (1.93-5.21)**	1.99 (1.14-3.48)*
Gestational age at birth							
On time (37-41 weeks, ref.)							
Early (36 weeks or less)	2.01 (1.07-3.76)*	2.04 (1.19-3.52)*	1.55 (0.91-2.64)	0.67 (0.31-1.44)	0.67 (0.31-1.44)	0.81 (0.33-1.95)	0.96 (0.36-2.53)
Late (42 weeks or more)	1.18 (0.65-2.14)	1.35 (0.72-2.53)	1.30 (0.71-2.38)	1.48 (0.74-2.94)	1.48 (0.74-2.94)	1.19 (0.56-2.56)	2.07 (0.99-4.33)*
Pre-pregnancy obesity							
Healthy weight							
Underweight	0.71 (0.39-1.28)	0.74 (0.43-1.27)	1.08 (0.66-1.76)	0.89 (0.52-1.51)	0.89 (0.52-1.51)	1.38 (0.80-2.37)	1.05 (0.56-1.94)
Overweight	1.31 (0.90-1.91)	1.04 (0.72-1.50)	1.17 (0.81-1.67)	1.21 (0.83-1.78)	1.21 (0.83-1.78)	1.47 (0.95-2.27)†	1.08 (0.65-1.78)
Obesity	1.56 (1.03-2.37)*	1.35 (0.92-2.00)	1.34 (0.90-2.00)	1.12 (0.73-1.73)	1.12 (0.73-1.73)	0.88 (0.54-1.44)	1.05 (0.63-1.74)
Not known	1.67 (1.13-2.49)*	1.30 (0.88-1.90)	1.43 (0.97-2.11)	1.74 (1.14-2.65)*	1.74 (1.14-2.65)*	1.12 (0.66-1.91)	1.13 (0.66-1.93)
Smoking during 1st trimester							
None (ref.)							
<=10 cigarettes daily	0.93 (0.56-1.54)	0.99 (0.60-1.63)	0.90 (0.53-1.53)	1.22 (0.67-2.24)	1.22 (0.67-2.24)	1.31 (0.69-2.47)	1.01 (0.49-2.07)
11+ cigarettes daily	1.54 (0.82-2.91)	1.82 (0.96-3.46)†	1.61 (0.84-3.06)	2.07 (1.02-4.21)*	2.07 (1.02-4.21)*	1.56 (0.70-3.47)	1.57 (0.63-3.90)
Antibiotic medication							
No	1.00 (0.62-1.6)	1.02 (0.66-1.57)	1.25 (0.81-1.94)	1.39 (0.90-2.15)	1.39 (0.90-2.15)	1.08 (0.65-1.79)	1.05 (0.62-1.77)
Yes							
Anti-depressant medication							
No	0.75 (0.27-2.12)	1.05 (0.44-2.52)	1.65 (0.77-3.53)	1.12 (0.38-3.31)	1.12 (0.38-3.31)	0.57 (0.13-2.47)	0.82 (0.13-5.10)
Yes	3.17 (2.10-4.77)**	4.09 (2.76-6.08)**	3.29 (2.17-5.00)**	3.66 (2.36-5.68)**	3.66 (2.36-5.68)**	3.17 (1.93-5.21)**	1.99 (1.14-3.48)*

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-6: The risk of having ongoing asthma among female children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	Age 2-3 OR (95% CI) N = 4485	Age 4-5 OR (95% CI) N = 4264	Age 6-7 OR (95% CI) N = 4088	Age 8-9 OR (95% CI) N = 3922	Age 10-11 OR (95% CI) N = 3574	Age 12-13 OR (95% CI) N = 3097	Age 14-15 OR (95% CI) N = 2960
Had asthma							
No							
Yes	2.08 (1.27-3.41)**	2.68 (1.69-4.24)**	3.40 (2.14-5.39)**	2.83 (1.81-4.43)**	4.09 (2.55-6.56)**	3.38 (1.94-5.86)**	3.30 (1.88-5.82)**
Gestational age at birth							
On time (37-41 weeks, ref.)							
Early (36 weeks or less)	0.51 (0.20-1.31)	0.47 (0.20-1.12)†	0.41 (0.18-0.98)*	0.49 (0.18-1.31)	0.51 (0.17-1.60)	0.42 (0.12-1.50)	0.51 (0.16-1.60)
Late (42 weeks or more)	0.30 (0.09-0.95)*	0.68 (0.30-1.55)	1.13 (0.52-2.49)	0.72 (0.31-1.69)	1.12 (0.49-2.59)	1.09 (0.46-2.59)	0.78 (0.33-1.87)
Pre-pregnancy obesity							
Healthy weight							
Underweight	0.94 (0.52-1.71)	0.66 (0.34-1.27)	0.72 (0.39-1.35)	1.23 (0.70-2.15)	1.03 (0.54-1.99)	0.55 (0.26-1.18)	0.78 (0.39-1.57)
Overweight	1.47 (0.96-2.26)†	1.36 (0.92-2.02)	1.34 (0.90-1.98)	1.52 (1.02-2.28)*	1.46 (0.94-2.27)†	1.28 (0.80-2.05)	1.21 (0.76-1.93)
Obesity	1.51 (0.92-2.48)	1.41 (0.91-2.19)	1.80 (1.15-2.80)*	1.79 (1.15-2.80)*	1.53 (0.95-2.47)†	2.00 (1.19-3.35)**	1.69 (1.00-2.87)*
Not known	1.05 (0.66-1.67)	1.09 (0.71-1.69)	1.53 (0.99-2.38)*	1.66 (1.08-2.54)*	1.85 (1.15-2.99)	1.81 (1.10-2.98)*	1.57 (0.95-2.58)†
Smoking during 1st trimester							
None (ref.)							
<=10 cigarettes daily	0.98 (0.53-1.84)	0.87 (0.48-1.56)	1.05 (0.56-1.98)	1.26 (0.70-2.27)	1.26 (0.64-2.46)	1.15 (0.57-2.34)	0.50 (0.2-1.27)
11+ cigarettes daily	1.42 (0.73-2.77)	1.94 (1.04-3.61)	1.76 (0.91-3.43)†	1.75 (0.85-3.60)	1.51 (0.70-3.26)	1.37 (0.62-3.04)	1.62 (0.68-3.9)
Antibiotic medication							
No	1.55 (1.01-2.38)*	1.25 (0.81-1.92)	1.29 (0.84-1.96)	0.92 (0.60-1.43)	0.99 (0.61-1.59)	0.77 (0.43-1.38)	1.00 (0.55-1.81)
Yes							
Anti-depressant medication							
No	0.98 (0.38-2.51)	1.77 (0.69-4.55)	1.33 (0.52-3.41)	1.37 (0.52-3.59)	2.19 (0.86-5.58)	3.28 (1.23-8.71)	1.13 (0.36-3.5)
Yes	2.08 (1.27-3.41)**	2.68 (1.69-4.24)**	3.40 (2.14-5.39)**	2.83 (1.81-4.43)**	4.09 (2.55-6.56)**	3.38 (1.94-5.86)**	3.30 (1.88-5.82)**

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-7: The risk of experiencing eczema among male children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	**Age 0-1** OR (95% CI) N = 4977	**Age 2-3** OR (95% CI) N = 4485	**Age 4-5** OR (95% CI) N = 4264	**Age 6-7** OR (95% CI) N = 4088	**Age 8-9** OR (95% CI) N = 3922	**Age 10-11** OR (95% CI) N = 3574	**Age 12-13** OR (95% CI) N = 3097	**Age 14-15** OR (95% CI) N = 2960
Had asthma								
No								
Yes	1.46 (0.96-2.21)	1.13 (0.73-1.75)	1.33 (0.83-2.13)	2.08 (1.29-3.36)**	1.76 (1.05-2.96)*	2.19 (1.24-3.84)**	1.16 (0.58-2.34)	0.93 (0.41-2.09)
Gestational age at birth								
On time (37-41 weeks, ref.)								
Early (36 weeks or less)	0.64 (0.36-1.13)	0.98 (0.56-1.71)	1.21 (0.67-2.19)	1.39 (0.75-2.56)	1.36 (0.68-2.73)	0.70 (0.28-1.77)	1.31 (0.51-3.35)	0.85 (0.29-2.44)
Late (42 weeks or more)	0.57 (0.30-1.09)	0.65 (0.34-1.23)	0.27 (0.09-0.78)*	0.73 (0.34-1.58)	0.97 (0.47-2.00)	0.62 (0.25-1.57)	0.53 (0.15-1.86)	0.85 (0.31-2.35)
Pre-pregnancy obesity								
Healthy weight								
Underweight	0.91 (0.59-1.39)	0.53 (0.34-0.84)**	0.44 (0.26-0.75)**	0.69 (0.39-1.20)	0.64 (0.34-1.21)	0.97 (0.51-1.85)	0.80 (0.39-1.65)	1.09 (0.53-2.25)
Overweight	1.21 (0.88-1.66)	1.04 (0.76-1.41)	0.95 (0.67-1.34)	0.91 (0.62-1.36)	1.15 (0.75-1.75)	1.12 (0.70-1.79)	0.84 (0.48-1.48)	0.72 (0.37-1.41)
Obesity	1.05 (0.72-1.51)	1.09 (0.77-1.54)	1.06 (0.71-1.58)	1.05 (0.68-1.61)	1.42 (0.90-2.24)	0.94 (0.54-1.62)	0.77 (0.42-1.41)	1.6 (0.88-2.9)
Not known	1.19 (0.85-1.65)	0.92 (0.65-1.3)	1.06 (0.72-1.56)	0.97 (0.63-1.50)	0.95 (0.59-1.53)	1.10 (0.62-1.95)	1.24 (0.67-2.31)	1.02 (0.49-2.11)
Smoking during 1st trimester								
None (ref.)								
Occasional/<10 daily	1.16 (0.73-1.85)	1.32 (0.87-2.01)	1.29 (0.79-2.12)	0.92 (0.50-1.70)	0.67 (0.34-1.31)	0.98 (0.45-2.14)	0.70 (0.30-1.63)	0.64 (0.22-1.82)
11+ daily	0.54 (0.24-1.22)	0.98 (0.51-1.88)	0.84 (0.38-1.89)	1.30 (0.55-3.06)	0.51 (0.17-1.52)	0.70 (0.17-2.86)	1.17 (0.22-6.26)	1.52 (0.47-4.97)
Antibiotic medication								
No								
Yes	0.86 (0.58-1.28)	1.01 (0.69-1.48)	0.95 (0.62-1.44)	0.98 (0.60-1.59)	1.52 (0.95-2.42)†	0.90 (0.50-1.62)	1.77 (0.96-3.26)†	1.38 (0.79-2.43)
Anti-depressant medication								
No								
Yes	0.69 (0.28-1.71)	1.84 (0.93-3.62)†	1.28 (0.55-2.97)	1.04 (0.42-2.56)	0.37 (0.08-1.72)	1.03 (0.30-3.48)	1.99 (0.56-7.12)	0.91 (0.11-7.82)

Notes: †: p<0.05 & >0.01; *: p<0.01 & >0.001; **: p<0.001; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Table C-8: The risk of experiencing eczema among female children based on the incidence of maternal asthma, other morbidities, and health behaviours during pregnancy

Maternal health, Risk factors, and medications during pregnancy	**Age 0-1** OR (95% CI) N = 4977	**Age 2-3** OR (95% CI) N = 4485	**Age 4-5** OR (95% CI) N = 4264	**Age 6-7** OR (95% CI) N = 4088	**Age 8-9** OR (95% CI) N = 3922	**Age 10-11** OR (95% CI) N = 3574	**Age 12-13** OR (95% CI) N = 3097	**Age 14-15** OR (95% CI) N = 2960
Had asthma								
No								
Yes	1.46 (0.96-2.21)	1.28 (0.82-2.01)	1.62 (0.99-2.66)*	2.08 (1.29-3.36)*	1.11 (0.67-1.85)	1.03 (0.58-1.83)	2.15 (1.21-3.83)	1.95 (1.08-3.51)*
Gestational age at birth								
On time (37-41 weeks, ref.)								
Early (36 weeks or less)	0.64 (0.36-1.13)	0.70 (0.38-1.30)	0.61 (0.28-1.32)	1.39 (0.75-2.56)	0.47 (0.16-1.36)	0.68 (0.22-2.13)	0.24 (0.07-0.78)†	0.60 (0.17-2.18)
Late (42 weeks or more)	0.57 (0.30-1.09)	0.60 (0.30-1.21)	0.75 (0.36-1.56)	0.73 (0.34-1.58)	0.89 (0.44-1.82)	0.62 (0.29-1.33)	0.52 (0.18-1.52)	1.03 (0.43-2.45)
Pre-pregnancy obesity								
Healthy weight								
Underweight	0.91 (0.59-1.39)	0.86 (0.54-1.37)	1.07 (0.64-1.77)	0.69 (0.39-1.20)	0.79 (0.45-1.4)	1.37 (0.75-2.5)	1.07 (0.51-2.22)	0.62 (0.30-1.29)
Overweight	1.21 (0.88-1.66)	0.97 (0.70-1.35)	1.19 (0.82-1.73)	0.91 (0.62-1.36)	1.18 (0.82-1.71)	1.52 (1.00-2.31)*	1.81 (1.13-2.93)	1.10 (0.68-1.78)
Obesity	1.05 (0.72-1.51)	1.23 (0.85-1.77)	1.39 (0.93-2.09)	1.05 (0.68-1.61)*	1.19 (0.77-1.82)	1.62 (0.99-2.63)*	1.80 (1.00-3.24)	2.03 (1.22-3.36)**
Not known	1.19 (0.85-1.65)	0.95 (0.67-1.36)	1.42 (0.95-2.14)	0.97 (0.63-1.50)	0.97 (0.61-1.54)	1.16 (0.69-1.97)	1.85 (1.05-3.26)	1.09 (0.60-1.96)
Smoking during 1st trimester								
None (ref.)								
Occasional/<10 daily	1.16 (0.73-1.85)	1.02 (0.61-1.69)	0.97 (0.55-1.71)	0.92 (0.50-1.70)	0.96 (0.52-1.76)	0.65 (0.31-1.35)	0.50 (0.18-1.43)	0.49 (0.18-1.36)
11+ daily	0.54 (0.24-1.22)	0.87 (0.44-1.73)	0.61 (0.29-1.30)	1.30 (0.55-3.06)	1.18 (0.52-2.67)	0.75 (0.28-1.98)	1.07 (0.40-2.90)	0.88 (0.34-2.24)
Antibiotic medication								
No								
Yes	0.86 (0.58-1.28)	1.04 (0.70-1.53)	1.08 (0.71-1.64)	0.98 (0.60-1.59)*	1.13 (0.73-1.75)	1.47 (0.92-2.34)	0.76 (0.38-1.55)	1.31 (0.72-2.38)
Anti-depressant medication								
No								
Yes	0.69 (0.28-1.71)	1.47 (0.59-3.67)	1.37 (0.58-3.22)	1.04 (0.42-2.56)	1.7 (0.71-4.1)	0.94 (0.33-2.71)	0.40 (0.08-2.03)†	0.40 (0.09-1.78)

Notes: †: $p<0.05$ & >0.01; *: $p<0.01$ & >0.001; **: $p<0.001$; the regression models were adjusted for several covariates outlined in 'Control variables' sub-section of 'Methods' section.

Appendix D: A media coverage from the thesis findings

Brisbane Today 14°/23°

The Courier Mail

Lifestyle

Stress in pregnancy could leave babies with chronic health problems

Psychological distress during pregnancy results in increased odds of chronic health conditions and lower health scores in babies, Queensland researchers have found.

Felicity Ripper Unfollow

@felicity_ripper less than 2 min read September 14, 2021 - 12:00AM

More could be done to improve the mental and physical health of pregnant women according to a new report which found poor health in mums increased the likelihood of their babies having chronic health conditions.

The study published today by researcher Kabir Ahmad from the University of Southern Queensland found poor general health of the mother in the year after childbirth was also associated with higher odds of poor health in infants and adolescents across their general health and physical health.

Psychological distress during pregnancy also resulted in increased odds of chronic health conditions and lower physical health scores in babies.

"These study findings emphasise the importance of improving maternal physical and mental health and promoting a healthy lifestyle during pregnancy or in the year after childbirth to improve child health," the report stated.

"These results have policy implications for undertaking preventive measures to improve maternal health and create awareness of the importance of a healthy lifestyle during pregnancy to reduce poor health outcomes in their offspring."

Researchers used data from the Longitudinal Study of Australian Children, a major study following the development of 10,000 children and families from all parts of the country.

The weblink of the online edition news is as follows:

https://www.couriermail.com.au/lifestyle/stress-in-pregnancy-could-leave-babies-with-chronic-health-problems/news-story/bfa44ddf1338def1f84a5a69f6ddf78f

Figure D2: Print media coverage of the research findings of this thesis in the Courier Mail, published on 14 September 2021.

COURIERMAIL.COM.AU TUESDAY SEPTEMBER 14 2021

Pregnant stress a problem for later

FELICITY RIPPER

MORE could be done to improve the mental and physical health of pregnant women according to a new report which found poor health in mums increased the likelihood of their babies having chronic health conditions.

The study published by researcher Kabir Ahmad from the University of Southern Queensland found poor general health of the mother in the year after childbirth was also associated with higher odds of poor health in infants and adolescents across their general health and physical health.

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"These study findings emphasise the importance of improving maternal physical and mental health and promoting a healthy lifestyle during pregnancy or in the year after childbirth to improve child health," the report stated.

"These results have policy implications for undertaking preventive measures to improve maternal health and create awareness of the importance of a healthy lifestyle during pregnancy to reduce poor health outcomes in their offspring."

Researchers used data from the Longitudinal Study of Australian Children, a major study following the development of 10,000 children and families from all parts of the country.

Figure D1: Online media coverage of the research findings of this thesis in the Courier Mail, published on 14 September 2021.