UNIVERSITY*of* TASMANIA

EXPOSURE TO PASSIVE SMOKING IN CHILDHOOD AS A RISK FACTOR FOR POORER HEALTH AND WELLBEING ACROSS THE LIFE COURSE

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(Medical Studies)

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Declaration of Originality

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University. Ethics Approval No/s: H0014169, H0017161 and H0014432.

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Thesis Abstract

Background: Exposure to passive smoking in childhood, which mainly comes from parents, continues to be a concerning major public health issue many years after comprehensive global action on tobacco control was initiated. This thesis aimed to examine (1) the prevalence, determinants and the trend of maternal smoking during pregnancy; (2) hospital use among children associated with exposure to maternal smoking during pregnancy; (3) validity and reliability of a life course questionnaire on exposure to passive smoking during childhood and (4) the effect of exposure to passive smoke across childhood on cardiovascular function in adulthood. Previous studies in these areas had limitations related to measurement of exposure or outcomes, were cross-sectional, or did not have objectively measured outcomes. This thesis sought to overcome these limitations, adding new information in these areas that could be important for public health policy and practice.

Methods: Participants were drawn from three datasets, Tasmanian Conception to Community study (C2C), Childhood Determinants of Adult Health Study (CDAH) and Tasmanian Infant Health Study (THIS).

C2C is a de-identified linked dataset comprising perinatal, emergency department, and admitted patient databases collected between the period July 2008 to June 2014. Data on maternal smoking during pregnancy and other study factors were self-reported by mothers and collected by midwives as part of nationally mandated perinatal datasets. Emergency department presentations and admission into hospital through ED were from public emergency department data.

The CDAH study comprised of the 1985 Australian Schools Health and Fitness Survey (ASHFS) cohort aged 7- 15 years that were subsequently followed up in CDAH-1 (2004-06), CDAH-2 (2009-11) and CDAH-3 (2014 - 19). A range of validated measures of cardiovascular

structure and function were assessed by trained data collectors at face-to-face clinics around Australia. Data on passive smoking during childhood was collected with questionnaires in childhood and adulthood.

The TIHS included birth cohort between January 1988 to March 1990 that was followed up in 2015-16 for a pilot study of adult cardiovascular health. Measures of cardiovascular structure and function were taken in face-to-face clinics. Exposure to passive smoking during pregnancy and childhood was self-reported by mothers prospectively around the time of birth and shortly after.

Results: The first study examined the trends and determinants of maternal smoking during pregnancy, changes in maternal smoking during pregnancy between and within pregnancies and their determinants in Tasmania, Australia. Maternal smoking during pregnancy declined from 25.9% (2008) to 16.4% (2014). A cessation proportion of 35.1% was observed between index (first birth recorded in the dataset) and last pregnancy. Maternal alcohol consumption during pregnancy, living in a highly socioeconomically disadvantaged area or being an Aboriginal or Torres Strait Islander was associated with an increase in the prevalence of maternal smoking during pregnancy and continued smoking between pregnancies.

The second study evaluated the effect of exposure to passive smoking during pregnancy on ED presentations and admission into hospital through ED in exposed children up to 1-year and 5-years of age. Exposed children had 26% and 45% higher overall presentation to ED and admission into hospital through ED, respectively, compared to unexposed children at 5 years of age. Higher presentation and admission for respiratory, eye, ear, nose, and throat illnesses, systemic and parasitic infections and psychosocial/other presentations were observed above the level of the negative control outcome of poisoning or injuries in exposed children at 5 years. Similar results were obtained at 1 year. These effects had a dose-response relationship with

increased rates of presentation and admission associated with higher exposure to cigarettes per day.

The third study examined the reliability and validity of a retrospective questionnaire administered to middle-aged adults in CDAH phase 3 on prolonged exposure to tobacco smoke across childhood. The three measures of passive smoking derived from questions on other people smoking in the home (example. parents and siblings) included total household smoker (range: 0 to 5 smokers); cumulative years of exposure (range: 0 to 106 years) and severity of exposure index (range: 0 to 318). The three retrospective measures had good internal consistency and moderate agreement with childhood and adulthood factors in ASHFS and CDAH. The three measures were also significantly positively correlated with participant smoking and negatively with their lung function test. These results suggest that these measures are reliable and valid to measure prolonged passive smoke exposure from childhood to adulthood.

The fourth study illustrated the effect of exposure to passive smoking across childhood using the previously validated measures on cardiovascular function in adulthood. Greater exposure to passive smoking across childhood from the total number of smokers in the household was associated with an increase in central blood pressure. Worse left ventricular function as measured by global longitudinal strain was associated with greater cumulative years of exposure to passive smoke.

The fifth pilot study evaluated the effect of exposure to passive smoking during pregnancy and childhood on cardiovascular function in adulthood. There were significant increases in peripheral diastolic blood pressure and decreases in left ventricular function in children exposed to passive smoke at various time-points of exposure from pregnancy to adulthood.

Conclusion: The findings in this thesis suggest that exposure to passive smoking during pregnancy and childhood negatively impacts the health of offspring in childhood and into adulthood. Though exposure to maternal smoking during pregnancy is declining, more work needs to be done to reduce exposure and improve the cardiovascular health of children exposed to this risk factor early in life.

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Publications Arising from this Thesis

Journal article publications

1. Ezegbe, C., Neil, A. L., Magnussen, C. G., Chappell, K., Judd, F., Wagg, F., Gall, S. Maternal smoking during pregnancy: Trends and determinants in the conception to community study. *Birth*. 2020; doi: 10.1111/birt.12515

2. Ezegbe, C., Neil, A. L., Magnussen, C. G., Chappell, K., Judd, F., Wagg, F., Gall, S. Maternal Smoking in Pregnancy and Child's Hospital Use up to 5 Years of Age in a Data Linkage Birth Cohort. *Hospital Pediatrics*. 2021; 11 (1) 8-16; doi: 10.1542/hpeds.2020-0150.

3. Ezegbe, C., Magnussen, C. G., Neil, A. L., Buscot M. J., Dwyer, T., Venn, A., Gall, S. Reliability and validity of a life course passive smoke exposure questionnaire in an Australian cohort from childhood to adulthood. *Journal of Preventive Medicine and Public Health*. 2021;54(2): 153-159. doi: https://doi.org/10.3961/jpmph.20.559

Published abstracts

1. Ezegbe, C., Magnussen, C. G., Neil, A. L., Dwyer, T., Venn, A., Sharman, J.E., Gall, S. A Prospective Examination of Exposure to Passive smoking in Pregnancy, Infancy and Childhood, and Adult Blood pressure in the Tasmanian Infant Health Study. No 117 https://www.hbprca.com.au/wp-content/uploads/2019/11/HBPRCA-abstracts-2018-ASM.pdf

2. Ezegbe, C., Neil, A. L., Magnussen, C. G., Chappell, K., Judd, F., Gall, S. Maternal Smoking in Pregnancy and Hospital use up to 5 Years of Age in a Data Linkage Birth Cohort. *Emergency Medicine Australasia* (2020) 32(S1), 25 https://onlinelibrary.wiley.com/doi/epdf/10.1111/1742-6723.13474

3. Ezegbe, C., Magnussen, C. G., Neil, A. L., Buscot M. J., Marwick, T., Dwyer, T., Venn, A., Gall, S. Childhood Passive Smoke Exposure is Associated with Subclinical Left

Ventricular Dysfunction in Adulthood - Childhood Determinants of Adult Health Study. *Circulation.* 2020;142: A15431

https://www.ahajournals.org/doi/abs/10.1161/circ.142.suppl_3.15431?af=R

This abstract was used in media release to promote American Heart Association (AHA) conference in November 2020. Other news outlets (link below) reported on the findings. The impact on the community went further, generating 38,888,278 media impressions as well as 211,944 views on American Heart Association social media channels between 9th November 2020 and of 13th of January 2021. (Letter from AHA media team (before references))

a. https://newsroom.heart.org/news/children-exposed-to-tobacco-smoke-at-home-have-worse-heart-function-as-adults

b. https://www.healio.com/news/cardiology/20201119/childhood-smoke-exposure-reduces-lv-function

c. https://conferences.medicom-publishers.com/2020/11/17/children-exposed-to-tobacco-smoke-have-worse-heart-function-as-adults/

d. https://www.physiciansweekly.com/aha-2020-children-exposed-to-tobacco-smoke-have-worse-heart-function-as-adults/

Accepted abstracts

1. World Congress of Epidemiology, 3 - 6 September 2021 at the Melbourne Convention and Exhibition Centre, Melbourne, Australia. 'Childhood passive smoking is associated with adult blood pressure: Childhood Determinants of Adult Health study'

2. World Congress of Epidemiology, 3 - 6 September 2021 at the Melbourne Convention and Exhibition Centre, Melbourne, Australia. 'Reliability and validity of a life-course passive smoking questionnaire: Childhood Determinants of Adult Health study'

Scientific Presentations Arising from this Thesis

Oral presentations

1. Joint High Blood Pressure Research Council of Australia, Australian Atherosclerosis Society and Australian Vascular Biology Society Annual Scientific Meeting 2018, Glenelg, Adelaide, Australia. **November 2018**. 'A Prospective Examination of Exposure to Passive smoking in Pregnancy, Infancy and Childhood, and Adult Blood pressure in the Tasmanian Infant Health Study' https://www.hbprca.com.au/wp-content/uploads/2019/11/HBPRCA-abstracts-2018-ASM.pdf

2. 10th year anniversary of the Population Health Research Network. 'Researchable Linked Dataset- PhD Student Perspective: Exposure to Parental smoking in Childhood as a Risk factor for Poorer health and Wellbeing across the Life course' **September 2019.**

3. 36th Australasian College of Emergency Medicine Annual Scientific Meeting 2019, Hobart, Tasmania, Australia. **November 2019**. 'Maternal Smoking in Pregnancy and Hospital use up to 5 Years of Age in a Data Linkage Birth Cohort' https://onlinelibrary.wiley.com/doi/epdf/10.1111/1742-6723.13474

4. American Heart Association Scientific Sessions 2020. 'Childhood Passive Smoke Exposure is Associated with Subclinical Left Ventricular Dysfunction in Adulthood - Childhood Determinants of Adult Health Study' (virtual). **November 2020.**

Abbreviations list

Acronym	Definition
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukemia
ANOVA	One-way analysis of variance
ASHFS	Australian Schools Health and Fitness Survey
AUD	Australian dollar
C2C	Conception to community study
CDAH	Childhood Determinants of Adult Health
CYE	Cumulative years of exposure
DRG	Diagnosis Related Groups
ED	Emergency department
FCTC	Framework Convention on Tobacco Control
FEV1	Forced expiratory volume in 1 second
FMD	Flow-mediated dilatation
FVC	Forced vital capacity
GLS	Global longitudinal strain
GYTS	Global Youth Tobacco Survey
ICC	Intraclass correlation
ICU	Intensive care unit
IRR	Incidence rate ratio
IRSD	Index of Relative Socio-economic Disadvantage
LMICs	Low-income and middle-income countries
LOS	length of stay
MDC	Major diagnosis category
NPAPH	National Partnership Agreement on Preventive Health
NPDC	National Perinatal Data Collection
PM2.5	Particulate matter with diameter of 2.5 micrometres or less
PSDP	Passive smoking during pregnancy
PSDC	Passive smoking during childhood

SEI	Severity of exposure index
SCN	Special care nursery
SIDS	Sudden infant death syndrome
TIHS	Tasmanian Infant Health Study
THS	Total household smoker
TS	Thirdhand smoke
URG	Urgency Related Groups
WHO	World Health Organization

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CHAPTER 1: Introduction

1.1 Prelude

This thesis examines associations between passive smoking in children and the effects on their health from childhood to adulthood. Analyses presented within the thesis come from three different cohort studies with different designs and study populations. This introductory chapter contains historical context of smoking, definition and measurement of passive smoking, the prevalence and trend of exposure to passive smoking in children, adverse effects of passive smoking on children and the associated economic cost of exposure to passive smoking in children.

1.2 Historical context of tobacco smoking

Tobacco smoking is reported to have started as a ceremonial practice by native Americans in the United States more than 500 years ago. Subsequently, tobacco smoking spread to all other continents and became a worldwide epidemic .[1] Over time, adverse health effects attributable to tobacco started being observed. On January 11, 1964, the U.S. Surgeon General's Office released the first landmark report on the health consequences of tobacco smoking. The report had a large and immediate effect on the beliefs of the community that cigarettes were a risk factor for lung cancer and heart disease. [2] The awareness of other adverse health effects of cigarette smoking has continued to grow necessitating advocacy for establishment of programmes, actions, and policies to control tobacco smoking.

The World Health Organization (WHO) contributed immensely to the fight against tobacco smoking through the development of the Framework Convention on Tobacco Control (FCTC) in 1998. The FCTC later became a treaty ratified by 154 nations and led to major international collaboration on tobacco control.[1] The provisions of the treaty included a comprehensive ban

on tobacco advertising and placing of warning signs on cigarette packets using the main language of the country of sale. Globally, there was a significant increase in the implementation of demand-reduction measures of the WHO FCTC between 2007 and 2014, leading to a significant global decline in tobacco smoking. Countries with higher levels of implementation of FCTC measures had the highest levels of decline in tobacco smoking.[3]

A programme termed MPOWER by World Health Organization was developed in 2008 to reduce harm from tobacco through scaling up of some WHO FCTC provisions. But data on seven selected MPOWER control programmes implemented in countries around the globe and reported by the World Health Organization are not encouraging. Among countries of the world, only 32% collect periodic data of smoking for both adults and youths, around 24% have complete policies on smoke-free environments, around 10% have cessation programmes, 20% have warning labels on tobacco products, around 22% have mass media campaigns, 16% have advertising bans and 18% have taxation to reduce demand.[4] Many countries, especially among high-income countries including Australia, have achieved a reduction in smoking by the implementation of these control programmes.[5] Australia has implemented almost all of the proposed MPOWER components,[6]. Despite these progressive tobacco control policies, Australia have failed to meet the federally designated target for smoking prevalence set by The National Partnership Agreement on Preventive Health (NPAPH) of 10% by 2018.[7]

Despite all the harmful effects of tobacco smoke and efforts internationally to control tobacco smoking, tobacco has been, and continues to be, a lucrative business. The total value of tobacco retail sales in Australia in 2009 was AUD 12.17 billion.[8] But in 2014, tobacco product sales represented about 5% of total retail sales (AUD 280 billion) in Australia with up to 40,000 retail sales outlets for tobacco products across Australia.[8] This level of success has flowed from the initial almost undeterred growth achieved by tobacco companies between the 1950s to early

1990s. This growth was not only due to legitimate retail sales of tobacco but also criminal behaviour like racketeering and failing to disclose the harmful effects of tobacco.[9]

1.3 Prevalence of tobacco smoking

Worldwide, 22% of people aged 15 years and above smoke tobacco.[10] Eastern Europe has the highest prevalence of smokers (31%) and Africa, the lowest (13%), among persons 15 years and older.[11] In Australia, 13.8% or 2.6 million adults aged 18 years and above smoked daily during 2017-18, a decline from 23.8% in 1995.[12] Furthermore, in 2017-2018 1.9% of Australian children between 15 to 17 years smoked daily. Most smokers begin smoking during adolescence.[13] Though there has been a global decline in the prevalence of smoking, the number of daily smokers has increased due to population growth from 721 million (1980] to 967 million (2012).[14]

Within countries there is often variation in the prevalence of smoking by region, due to differences in social and demographic factors. For example, in Australia the highest prevalence of adult daily smokers in 2017-2018 was observed in Northern Territory (19.6%), while the lowest was in the Australian Capital Territory (10.6%). The prevalence of adult daily smokers in Tasmania, the focus of several cohorts in this thesis, was 16.4% (Figure 1-1).[12]

Even within regions, the prevalence of smoking may vary across sub-populations. In Tasmania, the highest smoking prevalence has been observed in the reproductive age group, 18 to 44 years, specifically 24.5% (18-24 years), 23.8% (25-34 years) and 28.7% (35-44 years).[15] Internationally, the prevalence of smoking in men (32%) is more than quadruple that of women (7%). Among Australian adults, men (16.5%) smoked more than women (11.1%), both genders smoking an average of 12.3 cigarettes per day.[12]

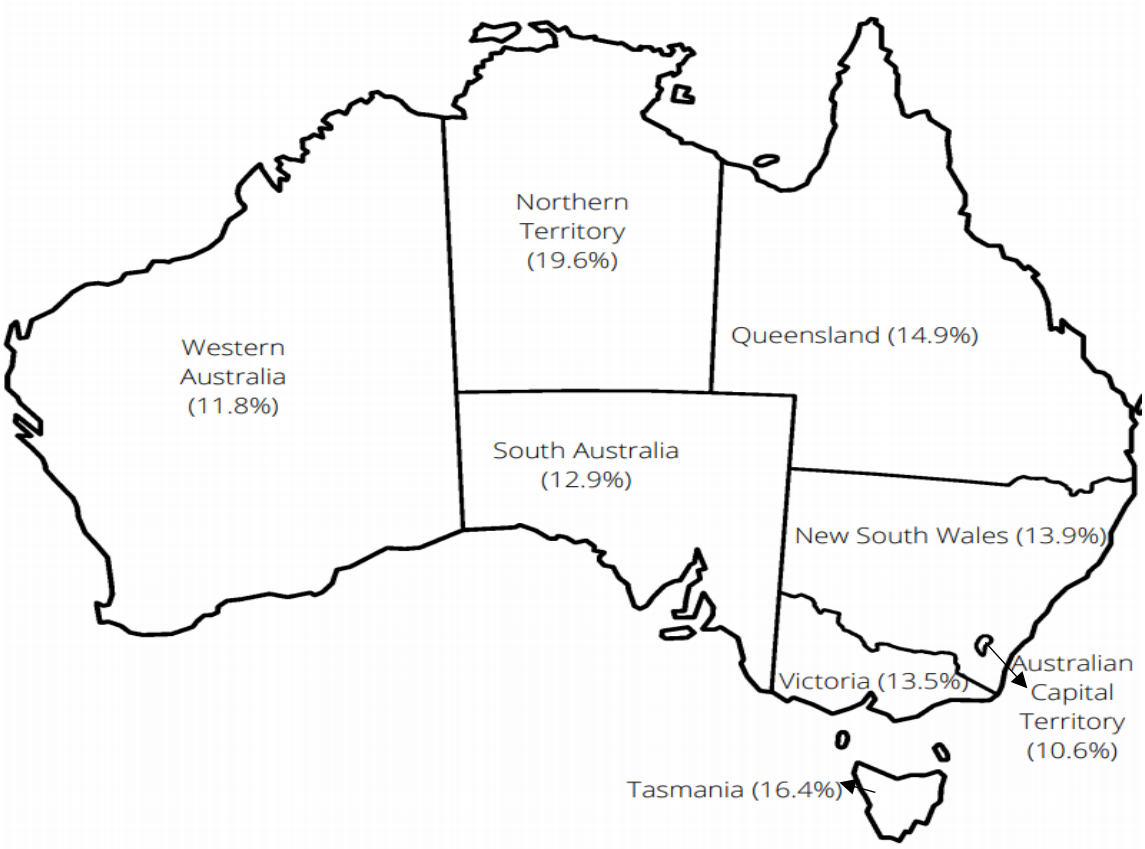

Figure 1-1 Prevalence of adult smokers (aged 18 years and over), Australia, 2017-2018

1.4 Passive smoking

Tobacco smoking is considered a large public health problem and is said to be a pandemic.[16] While active smoking is its own large problem, it has given rise to another pandemic, passive smoking; the inhalation of other people's tobacco smoke. Passive smoking has also been referred to as: second-hand smoking, or environmental tobacco smoke.[17] The inhaled smoke may be from the burning end of a tobacco product (side-stream smoke) or that breathed out by a smoker (mainstream smoke). [17] Side-stream smoke makes up around 85% of passive smoking exposure and is due to incomplete combustion, giving rise to greater concentrations of several chemicals found in tobacco than mainstream smoke.[18] Both adults and children may be affected by passive smoke. In this thesis, there is a focus on people exposed to passive smoke at different parts of their childhood including gestation.

Children may inhale tobacco smoke from smoking by their parents, other adults and may also be exposed in-utero through active maternal smoking or the mother's exposure to other adults smoking. These pathways serve as the two major sources through which children are exposed to passive smoke.[19] More than 70% of the source of passive smoking in children is from their parents.[20-22] In addition children may be exposed to thirdhand smoke, smoke that persists in the environment including on indoor surfaces, furniture, clothes, carpets, and other objects. thirdhand smoke accumulates over time and cannot be removed by ventilating rooms or by using fans or air conditioners.[23] While of increasing interest, thirdhand smoke is not examined in this thesis.

1.4.1 Components of tobacco smoke

Tobacco smoke contains at least 2,256 chemical compounds of which 98 of them are documented to be cancerous while many others have non-cancerous hazardous effect on health.[24] Nicotine is a major component of tobacco smoke with cotinine, a major proximate metabolite of nicotine, widely used as a quantitative biomarker of tobacco smoke exposure.[25] Cotinine has a relatively long half-life of 16 hours. Cotinine concentration thus reflects intake or exposure to tobacco smoke in the past few days. and can be measured from body fluids and samples including saliva, urine, blood and hair.[25] However, cotinine concentration in active smokers will depend on number of cigarettes smoked, smoking environment, and the time-lapse between smoking and collections specimen for testing.[26] Among passive smokers, cotinine concentration is determined by interactions with a smoker (e.g. cohabitation), duration of passive smoking and the time lapse between smoking and collections specimen for testing.[26] Cotinine measurement can be used to differentiate between active smoking and passive smoking. There are other possible biomarkers of nicotine including carbon monoxide,

thiocyanate and 4-aminobiphenyl—hemoglobin adduct, but cotinine is regarded as the best in terms of sensitivity and specificity.[25]

1.4.2 Measurement of passive smoking

Exposure to passive smoke may be measured through biomarkers and/or questionnaires, with biomarkers potentially used to validate self-reported exposure to passive smoking in questionnaires.[27] For example, measurement of cotinine in urine showed that using 30µg/L (same as ng/mL) identified active smokers with a sensitivity and specificity of 94% and 98% compared with a questionnaire while 1.78µg/L (same as ng/mL) as an upper reference value for non-smokers exposed to tobacco smoking had a sensitivity of 40%.[26] Exposure to passive smoking at home was associated with higher urinary cotinine levels compared to exposure in a car.[28] For saliva cotinine measurement, cut off points of 10 ng/mL (sensitivity 96%, specificity 95%) for adult self-reported active smokers[29] and smoking pregnant women,[30] and 1.5 ng/mL (sensitivity 63%, specificity 71%) for passive smoking in pregnant women[30] have been proposed. The demarcating line for exposure to passive smoke is still unclear and made more difficult by the possible overlap between light smokers and non-smokers that are also heavily exposed to passive smoking.

Children exposed to parental smoke show much higher cotinine (measured in same laboratory with same method) levels than the non-smoking spouse of an adult smoker in their respective homes.[31] This finding implies that children will have higher cotinine concentration when experiencing similar exposure to an adult. A wide range of cotinine concentrations were found in newborn dried blood spots of children whose mothers were smokers during pregnancy. Results ranged from 0.3–165.7 ng/ mL equivalent of cotinine in plasma.[32] In 103 children aged 4 to 11 years, whose parents reported being exposed to passive smoking at home from any source, the urinary mean cotinine was 5.1 µg/L.[33] Also in children between the age of 4 and 15,

the geometric mean of their salivary cotinine concentration was 1.67 ng/mL when only one parent smoked at home and 2.46 ng/ml when both parents smoked at home.[34] The cotinine concentration in urine of children was significantly positively correlated with the number of cigarettes parents smoked and the number of smokers in the household.[35] Validity in measuring passive smoking exposure seems to lie on the measurement of cotinine in blood, saliva or urine.[25] Cotinine measurement in a body fluid has also proved to be accurate in validating self-reported smoking information in children.[28]

Environmental markers and monitoring also have a role in exposure measurement. Personal Aerosol Monitors can be used to measure the concentration of particulate matter pollution due to tobacco smoke (PM2.5) and sodium bisulphate-treated filter sampler for airborne nicotine.[36] Correlations between both methods were higher in environs with high-level passive smoke (Spearman's rank correlation coefficient 0.733) and indoors (Spearman's rank correlation coefficient 0.739).[36] Investigation with Personal Aerosol Monitors suggest that exposure level is proportional to the number of active smokers in the person's immediate environment.[37] On average, exposure level increases by approximately 30% for each added smoker in the environment but by approximately 50% if under a roof or covering.[37] Measurement of particulate matter and/or airborne nicotine concentration can be used to measure exposure of children to passive smoking.

Self-report of passive smoke exposure is the most widely used method of measuring passive smoking, especially in large populations, due to ease of administration and relative 'cost-effectiveness' compared to environmental monitoring and biological markers.[38] Additionally, self-reported questionnaires can more readily measure exposure over time, unlike biomarker methods of measurement, which reflect recent exposure only. [38] Most assessments of a child's exposure to maternal smoking during pregnancy is through self-report.[39] For exposure during childhood, parents are sometimes asked on behalf of young children, while adolescents can be

administered questionnaires directly.[38] The questions administered by researchers are diverse. This partly has led to questions about the reliability and validity of some of the questionnaires.[38] However, community-based studies involving large populations of more than 5,000 participants and using cotinine as a gold standard for validation of smoking status, have shown that self-reported questionnaire responses on smoking exposure is valid and reliable irrespective of the age, socioeconomic position or area of residence of the participants.[40] Self-reported questionnaire have been shown to be reliable for measurement of passive smoking exposure but fewer studies have examined the validity of these measures.[38] Of importance is that due its half-life of about 16 hours cotinine can only be used to validate short-term exposure.[25] There is no recognized way of validating questionnaire on prolonged exposure to passive smoking like exposure that spans from early childhood to adolescence. This thesis will explore the potential reliability and validity of a retrospective childhood passive smoking exposure questionnaire administered to adults.

1.4.3 Passive smoke exposure in children

Children, due to their dependency on adults, are more likely to be exposed to passive smoking compared to adults. Children between the ages of 3 and 11 years are reported to be the most exposed when compared to adolescents and adults.[41, 42] Children are also reported to be more susceptible than adults to the adverse effects of the exposure due to their physiological composition.[43] The potential for short-term harms associated with exposure to passive smoke during pregnancy are quite well known, including foetal growth restriction, preterm birth, low birth weight, and sudden infant death syndrome.[44]

There is limited recognition of the longer-term effects of exposure to passive smoke during pregnancy, infancy or childhood on health into later childhood or even adulthood. This situation has arisen, at least in part, because many studies have short follow up,[45, 46] and have

relied on self-report of health including symptoms or signs of disease, disease diagnoses and health service use. [46-48] [49, 50] Among existing studies on longer term impacts of passive smoking in childhood, validation of the measurement of childhood exposure to tobacco smoke used in the study was not reported.[51, 52] This thesis will examine some aspects of childhood exposure to passive smoking and its health effects while overcoming some of the limitations of previous studies.

1.5 Different periods of exposure of children to passive smoking

In this thesis, two periods of exposure to children will be discussed, exposure to passive smoking during pregnancy and exposure to passive smoking during childhood. There is no ambiguity about the period of pregnancy which spans from the time of conception to delivery. Childhood may include any period from birth to 18 years of age grouped as early childhood (birth to 8 years), middle childhood (8 to 12 years) and late childhood (12 to 18 years) or adolescence (10 to 18 years).[53]

Exposure of children to passive smoking during pregnancy or childhood is mainly parental.[20, 43] Thus, most existing studies only report exposure to passive smoke from parents, most commonly mothers only, thus excluding fathers and other adults.[54, 55] This situation may mean that the effects of passive smoke on health in children has been underestimated. This next section will discuss the prevalence and effects of passive smoke exposure during pregnancy and childhood.

1.5.1 Exposure to passive smoking during pregnancy

Exposure to passive smoking during pregnancy, independent of exposure after birth, has been associated with adverse effects in children.[56, 57] Exposure of children to smoke during pregnancy can be from maternal, paternal, or other household member smoking. Maternal

smoking during pregnancy has received much more attention than paternal smoking during pregnancy and, similarly, the harmful effects attributed to the exposure from mothers are more often reported.[58] Both maternal and paternal smoking are harmful to children independently but may work synergistically leading to worse outcome[59, 60] Only a few studies have included both parental and non-parental exposure in their analysis.[48] The adverse effects of exposure to passive smoking during pregnancy have been suggested to differ in some locations depending on the place of residence; urban or rural but with mixed results.[61]

1.5.1.1 Prevalence and trend of exposure to passive smoking during pregnancy

The estimated prevalence of maternal smoking during pregnancy has been estimated through meta-analysis to be 1.7% globally, ranging from 8.1% in Europe to 0.8% in Africa in peer-reviewed papers published as of 2016.[62] Among the pregnant women who smoked, 72·5% smoked daily and 27·5% occasionally.[62] In a separate study of low to middle-income countries, prevalence of maternal smoking ranged from 6% in Nigeria to 73% in Armenia in 2013 (2013).[63] In a group of European countries the prevalence ranged from 4.2 % in Iceland to 18.9 % in Croatia in 2012.[64] In the United States, the percentage of mothers who ever smoked cigarettes during pregnancy was 55.5% for white and 10.2% for Hispanic women between 1986 and 1992.[65] In Australia, 9.9% of all pregnant mothers smoked at some point during pregnancy in 2016 based on routinely collected administrative data collated in the National Perinatal Data Collection (NPDC).[66] In Tasmania, 12.9 % of pregnant women reported that they smoked or continued to smoke while pregnant in 2015, as compared with 12.8% in 2016 and 14.5% in 2017.[67]

In Australia, the NPDC does not include any data on paternal smoking during pregnancy.[66] Few studies have considered paternal smoking during pregnancy on the study of adverse effects of exposure to passive smoking during pregnancy on children. Most emphasis has been on

maternal smoking during pregnancy or maternal exposure to passive smoking during pregnancy without emphasis on if paternal smoking alone was the source.[68, 69] However, in low-income and middle-income countries (LMICs) maternal exposure to passive smoking during pregnancy is more prevalent than maternal smoking during pregnancy.[63] These studies show that data on paternal smoking during pregnancy is not collected routinely, especially at the population level or in national data collections.[58, 60, 70, 71] This is also the case for the national Australian data collection.[66] Most data on parental smoking during pregnancy are collected in retrospective questionnaires in surveys and, as a result, information on prevalence and trends over time is lacking.

A decline in maternal smoking during pregnancy over the years has been reported but mainly in grey literature, especially in Australia.[66, 67] The decline in maternal smoking in Australia seems not to be due to anti-tobacco legislation and laws.[72] Some women may give up smoking temporarily when they find out they are pregnant. For example, a preconception smoking prevalence of 12.5% fell to 2.3% after confirmation of pregnancy in Singapore.[73] More understanding of the trend of exposure to maternal smoking during pregnancy globally, in Australia is necessary.

1.5.1.2 Trends in passive smoke exposure during pregnancy

PubMed was searched for studies published on the trend of passive smoking during pregnancy using the advanced search (1.8 Appendix 1.A: Additional Methods**)**. Table 1-1 lists studies on the trend or changes in passive smoke exposure during pregnancy (maternal smoking). These studies were conducted across Asia/Pacific,[72, 74] Europe,[75-79] South America [80] and the North America.[81-89] Most studies have used self-report on smoking during pregnancy from mothers,[74-78, 80, 84, 86] with one validating smoking during pregnancy using cotinine measures.[76] There was no age limit to pregnant women included in most studies. Most studies used repeated cross-

sectional population-based surveys with a variety of data source, medical birth registry and national natality data. The predominant trend in most studies was a decline in passive smoke exposure during pregnancy with only one study from Finland reporting an increase in passive smoke exposure during pregnancy based on responses validated with cotinine measures.[76] The largest changes were seen in Sweden from 30.3% (1982) to 11.0% 2001[78] and Brazil from 35.7% (1982) to 21.0% (2000).[80] These large decreases were attributed to increasing family income and to decreases in some ethnic groups. Larger changes were seen in studies that covered the longer periods. No change (0%) was observed in Finland where the prevalence of the maternal smoking during pregnancy was reported at 15% from 1987 to 1997[79] and from 2000 to 2010.[77] The proposed reasons for the no reduction in Finland included increasing prevalence in teenage mothers balancing out decline in other age groups and persisting regional differences balancing out each other.

Table 1-1 Studies on the trend of passive smoke exposure in children during pregnancy

Author/year	Country	Number of participants [year]	Study design	Cotinine measurement	Exposure measure	Study factors	Change in trend (Outcome)/ Annual change*	Study period [data points]
Li, 2018 [81]	United States	28,090	Cross-sectional (personal interview)	No cotinine measurement	Asked If biological mother smoked at any time during pregnancy	Family income, race, family head's education and marital status	From 24.6% to 10.7% / 0.5%	1985-2014 [>10 data points]
Reynolds, 2017 [75]	Ireland	42,509	Cross-sectional (self-reported interview)	No cotinine measurement	Asked during prenatal appointment if they smoked during the past week and quantity	Maternal age, multiparity, unemployment (maternal occupation), unplanned pregnancy, history of psychiatric problem, alcohol intake and illicit drug usage	From 14.3% to 10.9% / 0.9%	2011-2015 [5 data points]
Silveira, 2016 [80]	Brazil	5,909 [1982] 6,275 [2011]	Cross-sectional (self-reported [interview])	No cotinine measurement	Asked if at least one cigarette a day was consumed during any part of the pregnancy	Family income, ethnic group, maternal education, maternal age, parity, marital status	From 35.7% to 21.0% / 0.5%	1982-2011 [4 data points]
Mannisto, 2016 [76]	Finland	9,627	Retrospective cohort (Medical birth registry)	Cotinine measurement with serum samples	Asked to choose between 'non-smoking', 'ceased smoking during 1st trimester', 'continued	Maternal age, marital status, number of maternity visits, pre-pregnancy body mass index, socioeconomic	From 15.1% to 26.6% / 0.5% (increase)	1987-2011 [8 data points]

Author/year	Country	Number of participants [year]	Study design	Cotinine measurement	Exposure measure	Study factors	Change in trend (Outcome)/ Annual change*	Study period [data points]
					smoking after 1st trimester' or 'not known'	status and parity (nulliparous)		
Gilbert, 2014 [82]	Canada	27,034	Cross sectional (national longitudinal survey)	No cotinine measurement	Asked if smoked during pregnancy with child	Birth year of child, Maternal education, and maternal age	College/University degree: From 11.5% to 5.2% / 0.4% Less than secondary education: From 43.0% to 38.6% / 0.4%	1992/1996-2005/2008 [4 data points]
Ekblad, 2014 [77]	Nordic countries (Denmark, Finland, Norway, Sweden)	274,469-Denmark, 1,432,969: Finland, 637,752: Norway, 2,627,178: Sweden	Cross-sectional (Medical birth registry)	No cotinine measurement	Asked if smoked during 1st trimester and if continued smoking after 1st trimester	Maternal age, marital status, parity, socioeconomic position	Denmark: From 21% to 12% / 0.9% Finland: From 15% to 15% / 0% Norway: From 20% to 17% / 0.3% Sweden: From 17% to 12% / 0.6%	Denmark:2000-2010 Finland: 2000-2010 Norway: 2000-2009 Sweden: 2000-2008 [10 data points]
Mohsin, 2011 [74]	Australia (NSW)	258,485(1995/1997) 371,113	Cross-sectional	No cotinine measurement	Asked if they ever smoked during	Maternal age, English speaking background, aboriginal status,	From 21.0% to 13.5%	1995/1997 - 2005/2007

Author/year	Country	Number of participants [year]	Study design	Cotinine measurement	Exposure measure	Study factors	Change in trend (Outcome)/ Annual change*	Study period [data points]
		(2005/2007)	(self-reported interview)		their current pregnancy	socioeconomic position		[10 data points]
Moussa, 2009 [78]	Sweden	2,224,469	Cross-sectional (Medical birth registry)	No cotinine measurement	Asked if they smoked at least one cigarette per day at 1st antenatal visit	Maternal age, marital status, education level and country of origin	From 30.3% to 11.0%	1982-2001 [4 data points]
Ananth, 2005 [83]	United States	29,596,254	Cross-sectional (National natality and fetal mortality data)	No cotinine measurement	Asked if they smoked at any time during pregnancy	Maternal age, birth cohort	Whites: From 18.0% to 14.2% / 0.4% Blacks: From 14.0% to 10.2% / 0.4%	1990/1994 - 1995/1999 [10 data points]
Ventura, 2003 [84]	United States	3,526,855	Cross-sectional (birth certificates record)	No cotinine measurement	Asked if they used tobacco at any time during pregnancy and average number per day	Maternal age, live-birth order, marital status, race, maternal education, period (trimester) prenatal care commenced.	19.5% down to 12.2% / 0.7%	1989-2000 [5 data points]
Jaakkola, 2001 [79]	Finland	694,926	Cross-sectional	No cotinine measurement	Asked if they smoked during pregnancy	Maternal age, marital status, maternal education, maternal	From 15.0% to 15.0% / 0%	1987-1997 [>10 data points]

Author/year	Country	Number of participants [year]	Study design	Cotinine measurement	Exposure measure	Study factors	Change in trend (Outcome)/ Annual change*	Study period [data points]
			(Medical birth registry)			occupation, region of residence		
Ebrahim, 2000 [85]	United States	8,803 (Total) 712 (1987); 980 (1996)	Cross-sectional (Telephone survey)	No cotinine measurement	Asked if they smoke now (pregnancy)	Maternal age, marital status, maternal education, race and employment status	From 16.3% to 11.8% / 0.5%	1987-1996 [10 data point]
Land, 1993 [86]	United States	990,042	Cross-sectional (birth certificates record)	No cotinine measurement	Asked if they used tobacco at any time during pregnancy and average number per day	Race, maternal age, marital status	From 31.3% to 24.7%	1978 – 1990 [>10 data point]
Tong, 2013 [87]	United States	444,614	Cross-sectional (Self-reported questionnaire)	No cotinine measurement	Asked if they smoked 3months before pregnancy and during last 3 months of pregnancy	Smoking habit during pregnancy and after delivery, maternal age, race, maternal education and health insurance coverage	From 13.2% to 10.7% / 0.3%	2000 -2010 [>10 data point]
Brown, 2014 [88]	Canada	3745 (1995-2000), 5084 (2001-2005),	Cross-sectional (survey)	No cotinine measurement	Asked of smoking status during pregnancy	Maternal sociodemographic (Maternal age, marital status, education)	From 12.0% to 9.2% / 0.3%	2001/2002 – 2009/2010 [5 data points]

Author/year	Country	Number of participants [year]	Study design	Cotinine measurement	Exposure measure	Study factors	Change in trend (Outcome)/ Annual change*	Study period [data points]
		2900 (2006 - 2010)						
Hoff, 2012 [89]	United States	1,536,149 (Total), 1,255,562 (Whites) 237,596 (Blacks)	Cross-sectional (Medical birth registry-self reported)	No cotinine measurement	Asked of smoking hygiene during pregnancy	Race, Maternal age, marital status, trimester when prenatal care was started, educational attainment (years of education)	Overall: from 24.7% (1990) to 16.8% (2008) / 0.4%; Whites: from 25.6% (1990) to 18.2% (2008) / 0.4%; Blacks: from 21.5% (1990) to 12.6% (2008) / 0.5%	1990 – 2009 [>10 data points]
Havard, 2018 [72]	Australia	534,513	Cross-sectional (survey)	No cotinine measurement	Asked if smoked at any time during pregnancy. Changed in 2011 to smoke at any time in the 1st 20 weeks of pregnancy and at any time during second 20 weeks of pregnancy	Smoking ban in public places, tobacco tax, maternal age, parity, socioeconomic status	From 17.1% to 10.6% / 0.8%	2003 – 2011 [>10 data points]

*Change per year across study data point period

Overall, there was generally a decline in passive smoke exposure during pregnancy among, although results were not validated with cotinine most of the time. The annualized decrease of passive smoke exposure during pregnancy was between 0 to 1% per annum except for one study that reported an increase.[76] No peer- reviewed studies on passive smoke exposure trends during pregnancy were identified in Asia and Africa. The predominant data points or study year range covered by each study on passive smoke exposure trend during pregnancy was 10 or more.

1.5.1.3 Changes in exposure to passive smoking within and between pregnancy

Maternal smoking cessation during pregnancy has been reported to be 20.6% (Spain),[90] 54.9% (USA)[91] and 24.9% (Brazil)[92] among women who smoked during early pregnancy. Being highly educated, of high socioeconomic status, married, primiparous, and having adequate ante-natal care was associated with higher cessation rate of maternal smoking during pregnancy.[93] Therefore these aforementioned factors could potentially lead to higher cessation rate in some other places. Among the studies on cessation during pregnancy data on maternal smoking during pregnancy was retrospectively collected, [91] conducted with small samples[90]and in single centres.[92]

Maternal smoking cessation between first and second pregnancy has been reported to be 33.5%[94] in New South Wales, Australia while in Georgia, United States cessation has been reported at 31% for white women and 42% for black women.[95] Mothers were motivated to quit between pregnancies due to adverse events like gestational hypertension, large-for-gestational age baby and stillbirth in the first pregnancy.[94] However, these studies were conducted with reference to only the first and second pregnancy,[94, 95] and more than 20 years ago.[95] There is a need for further examination of changes in smoking within and between pregnancies as an

important indicator of the success of programs to protect children from passive smoke exposure, and to enhance the health of mothers.

1.5.1.4 Determinants of maternal smoking during pregnancy

Some studies have examined the individual level characteristics associated with smoking during pregnancy. A cohort study found smoking during pregnancy was associated with being in lower social class during childhood, exposure of the mother to parental smoking, depression, early smoking initiation, high smoking intensity, living with a smoker, no pregnancy planning and being a young mother (24 years or less).[96] Additionally, other studies found that low earners or being unemployed, low level of education,[97] being multiparous,[98] alcohol consumption and taking of illicit drugs[75] were associated with maternal smoking during pregnancy. Immigrants to western nations had lower prevalence of maternal smoking during pregnancy possibly reflecting the prevalence where they came from.[99] These reported studies were from Australia, New Zealand, and Norway but these factors are likely to have similar effect in other countries. Information about characteristics associated with smoking during pregnancy helps identify potential target groups for health promotion or other programs to reduce smoking during pregnancy.

1.5.1.5 Health adverse effects of exposure to passive smoking during pregnancy

The period of pregnancy is considered a critical point in a child's development. Exposure to unhealthy substances during this period makes children vulnerable to adverse health effects. Most of these health effects are not known to mothers, whether smokers or non-smokers,[100] and perhaps by association fathers. More adverse effects are being discovered. Some adverse effects might be temporary without immediate discernible disadvantage to children like the increase in haemoglobin level in newborns whose mothers smoked more than 6 cigarettes daily

in the last trimester of pregnancy.[101] However, many adverse effects may be lifelong across a broad number of body systems, from respiratory to gastrointestinal system.[102] This section will broadly examine the adverse health effects of exposure to passive smoking in children during pregnancy across infancy, childhood and into adolescence by body systems.

1.5.1.5.1 Respiratory health

Perhaps the most well recognised effects of exposure to passive smoke during pregnancy is on respiratory health. There was a significant relationship between maternal smoking during pregnancy and infant wheeze,[47, 48] and wheezing at 2 years,[46] at 1 to 4 years,[71] and at adolescence in studies with self-reported measurement of exposure and outcomes.[103] Apart from wheezing, exposed children were also prone to respiratory infections; respiratory syncytial virus, bronchiolitis, bronchitis, and pneumonia at 6 to 18 months of age.[57] Asthma was most strongly associated with maternal smoking during pregnancy,[56, 104, 105] although on the contrary, Harju and colleagues opined that asthma was most strongly associated with paternal smoking during pregnancy.[106] Female adolescents whose mothers smoked heavily during pregnancy have increased risk of asthma symptoms in adolescence.[107] Even if asthma does not develop, reduced forced expiratory volume in men exposed to smoking during pregnancy has been reported.[108] In-utero exposure to heavy smoking has been found to have a stronger adverse respiratory health effect at 21 years than postnatal environmental tobacco exposure.[57, 107] There is therefore substantial evidence that smoking during pregnancy has effects on the respiratory health of offspring in childhood, adolescence and into adulthood.

1.5.1.5.2 Cardiovascular health

Some early markers of cardiovascular dysfunction and some biomedical cardiovascular risk factors including cholesterol and blood pressure levels in offspring are associated with maternal smoking in pregnancy. In one longitudinal study of 616 children, having a mother that smoked during pregnancy was associated with lower high-density lipoprotein cholesterol at 8 years,[109]

while in another study 0.12 mmol/l per 10-year increase in cholesterol levels in exposed children aged 5 to 19 years were observed.[110] Children aged 8-years whose mothers smoked during pregnancy had a 2.9 mmHg increase in systolic blood pressure,[111] while another study reported a 1.43 mmHg higher diastolic blood pressure in 6 year olds.[112] One study using data from the Nurses Health Study examined the effect of exposure to maternal smoking during pregnancy on blood pressure in adult age. They found there was an association with adult hypertension,[113] but the diagnosis of hypertension was self-reported.[113]

More recently, some investigators have shown that there may be effects of exposure to maternal smoking during pregnancy on the structure and function of the cardiovascular system. Studies including a meta-analysis have shown being exposed to smoking during pregnancy increases the risk of having a congenital heart defect in infancy.[114, 115] But some detrimental epigenetic modifications associated with cardiometabolic risk factors that persists into adolescence independent of postnatal smoke exposure have been reported.[116] Parental smoking during pregnancy was associated with 1.01% higher fractional shortening, 18.8μm higher carotid intima–media thickness, 15% lower arterial distensibility among children (5 to 6 years) born after exposure during pregnancy.[117, 118] There are no studies on the effect of exposure to passive smoking during pregnancy on cardiovascular structure and function in mid to late adulthood. There is a need to examine more cardiovascular outcome measures in adult age.

1.5.1.5.3 Other body systems

There are other non-respiratory adverse effects due to exposure to passive smoking during pregnancy. There is sufficient evidence to infer a causal relationship between maternal active smoking during pregnancy and foetal growth restriction and low birth weight.[119 120] Maternal smoking during pregnancy is a risk factor for childhood obesity.[121-124] A dose-response association was observed between pregnancy smoking exposure, short stature and obesity[125,

[126] in offspring of mothers who smoked least 10 cigarettes per day during pregnancy compared with those exposed to less cigarettes per day or none at all.

Exposure to passive smoking during pregnancy may also affect neurological functions. Maternal prenatal smoking was accompanied by a 3.3-point deficit in their children's intellectual abilities.[127] Children exposed to passive smoking during pregnancy also perform less well than their classmates not exposed in mathematics,[128] specifically arithmetic, and in spelling tasks.[129] High nicotine exposure of more than 17 mg per day (20 or more cigarettes) during pregnancy has a negative association with reading performance in school-age children between 7 to 9 years even after adjusting for social class and other covariates.[130] These decrements in offspring academic performance has been suggested to continue into adolescence.[131] Children of mothers who smoked throughout pregnancy had significantly elevated levels of hyperactivity and inattention.[132-135] other neurological problems in children relating to movement and eating has been reported due to exposure to maternal smoking pregnancy.[136]

There is also evidence of effects of smoking during pregnancy on infections with relatively low exposure levels associated with an increased risk of acute otitis media within the first year of life.[137] Maternal active smoking in the first trimester of pregnancy was significantly associated with an increased prevalence of dental caries in children after adjusting for household income.[138, 139] A meta-analysis which included results from the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children produced a statistically significant association between paternal smoking during pregnancy and acute lymphoblastic leukaemia (ALL).[140] Another meta-analysis found an association between exposure to maternal smoking during pregnancy with non-Hodgkin lymphoma.[55] Smoking during pregnancy therefore has effects on a wide range of health outcomes and body systems in children.

1.5.1.5.4 Health service use

Data on health service use including costs are quite limited. Due to illnesses during the first six months after the birth, parents of children exposed to passive smoking during pregnancy and within six months after birth had to go often for physician consultations either at the physician's offices or home visits.[141] No studies have been done to assess any relationship between exposure to passive smoking during pregnancy and emergency department presentations in children. There are also no reports on physician visits or emergency department presentations later in childhood beyond 6 months of age.

Higher hospitalization or admission rates have been reported in children exposed to smoking during pregnancy[142-147] than in children without exposure. But most reports were based on admissions into hospital for respiratory illnesses[142-144] or other individual illnesses, e.g. gastroenteritis.[146] Some of these studies had low response proportions,[145, 146] relied on self-reported symptoms or diagnosed disease and admission into hospital[142, 145, 147] and were conducted over 10 years ago.[145-147] The dose of maternal smoking during pregnancy was not available in most studies[142, 143, 145, 146] and so data was analysed with the response being 'no' or 'yes' without any dose-response relationship. In some of the studies, hospitalization as the outcome was measured before two years of age.[145-147] There is a need for further research considering a broader range of illnesses associated with exposure to smoke during pregnancy as there may be underestimated effects.

1.5.1.5.5 Healthcare cost of exposure to passive smoking during pregnancy

Given the range of potential health effects of smoking during pregnancy it is reasonable to assume that it is associated with higher heath care costs. Just as the number of known adverse effects of exposure to passive smoking during pregnancy is growing, the associated healthcare cost will increase due to excess use of healthcare. Children exposed to tobacco smoke in-utero experienced an excess of 7.4% hospital presentations costing over 2.1 million US dollars within

the first year of life.[148] The additional healthcare costs for children in the first year of life per smoking pregnant mother was between $1142 to $1358.[149] Understanding more about health service use attributable to exposure to passive smoke may be informative for estimating the direct costs. Reducing passive smoking exposure during pregnancy may lead to cost savings. A 1 percentage point drop in maternal smoking during pregnancy has been associated with cost-savings of about $572 million in paediatric healthcare at 7 years of age.[150]

1.5.2 Exposure to passive smoking during childhood

Despite tobacco control measures, Daly et al demonstrated that community education strategies and public policies were not enough to protect infants and children from passive smoke exposure.[151] Further, children not exposed during pregnancy are not immune to exposure shortly after birth or even later on during their childhood. At times, some mothers who did not smoke during antenatal care took up smoking after delivery before their children were 7 months of age.[152] Locations where exposure occur and age during exposure is also varied. Studies of children under 12 months of age reported 10% were exposed at home, 6% exposed in a car, 0% in childcare, 22% at a friend or relative's home, 18% in a shopping centre, and 8% each in a restaurant and an outdoor location.[151] Infants with siblings are at higher risk of being exposed than infants with no siblings.[153] Households with children aged 14 years and below compared to childless households were more likely to be smoking household .[154] The diversity of the locations and age of exposure may mean that while parental exposure appears to be the most important, other individuals also play a role in the exposure of children. This makes the inclusion of non-parental exposure in the analysis of adverse effects, where available, a commendable idea.[155]

1.5.2.1 Prevalence and trend of exposure to passive smoking during childhood

Some surveys have reported on exposure to passive smoke in early childhood. In Taiwan, 62% of 18-month-old children lived in a household with a minimum of one smoker in 2005.[156] In the United States, the prevalence of homes adopting smoke-free home rules has increased from 43.0% in 1992-1993 to 83.0% in 2010-2011 in response to comprehensive smoke-free laws that prohibit tobacco smoking in all indoor public places and workplaces.[157] But the prevalence in US of exposure to passive smoking during childhood in children aged 3 to 11 years was 40.6% and 33.8% in adolescents aged 12 to 19 years.[158] Globally, 40% of children, 0–14 years, were exposed to second-hand smoke in 2004.[159] Also, worldwide, 12.5% of never-smoking children between 13 to 15 years were susceptible to passive smoking though in Europe it was as high as 29.8%.[160] Sometimes, the prevalence of exposure to passive smoking in children is indirectly measured. A survey of parents with infants showed that parental smoking (both or any) rate was 28.9% with fathers having a slightly higher rate than mothers.[161] These numbers are still relatively high which raises questions about the normalization of smoking around children.

The prevalence of exposure to passive smoking during childhood differs in many places and so does the trend. In Wales (UK), children aged 10-11 years were surveyed in 2007 and 2014 Reductions in exposure were observed across venues, exposure in the family vehicle falling from 18% in 2007 to 9% in 2014 and at home from 20.7% in 2007 to 9.6% in 2014.[162] In Australia, the proportion of households where children were exposed to tobacco smoke dropped from 31% to 3.7% from 1995 to 2013.[163]

The Centers for Disease Control and Prevention, a United States government agency and researchers around the world use data from Global Youth Tobacco Survey (GYTS) to publish prevalence and trends in passive smoke exposure among school children.[164] GYTS is a school-based survey of students aged 13–15 years of age and funded by the Canadian Public Health

Association, National Cancer Institute, United Nations Children Emergency Fund, and the World Health Organization.[164] These surveys and reports take time and are available over a range of years. This may affect how frequent researchers can examine trends in exposure to passive smoke during pregnancy and childhood. Studies on the trend of exposure to parental or passive smoking during childhood from 0 years to 18 years seems to be limited both in peer-reviewed articles and grey literature and the reporting pattern seem to be diverse. There is a need to understand the various locations, modes of measurement and degree of the exposure to passive smoking during childhood globally.

1.5.2.2 Trends in passive smoke exposure during childhood

PubMed was searched for studies published on the trend of exposure to passive smoking during childhood using the advanced search (1.8 Appendix 1.A: Additional Methods). Table 1-2 contains studies on passive smoke exposure trend during childhood. The range of studies conducted to examine changes in exposure to passive smoke in childhood included Europe,[34, 165, 166] Asia,[167, 168] and North America.[169, 170] Most studies used self-report from parents on their smoking behaviour at home,[165, 168-170] with two administering the questionnaire to children [166, 167] or validating exposure using cotinine measurement in the children.[34, 166] The age range of children included in the studies ranged from the post-natal period up to 18 years, with all the studies using repeated cross-sectional population-based surveys. Across all the studies there was a substantial reduction in exposure to passive smoke during childhood over time. The largest changes were seen in Japan from 2001 (36.8%) to 2010 (14.4%)[168] and Germany from 2003-2006 (23.9%) to 2009-2012 (6.6%).[165] The reasons for these large decreases were identified as a decline in parental smoking over time with mothers giving up smoking contributing to the greater proportion of the decline. A study in United States reported the smallest change during the study period where the prevalence of exposure to passive smoke during childhood decreased from 14.3% in 1998 to 13.8% in 2004.[170] The proposed reasons

for the smaller reduction in passive smoking during childhood in the USA study included an increase in the number of black people (mothers or any other household member) who smoked around their children or allowed smokers around their children. All studies except one [166] examined exposure at home/indoors. There are fewer studies of exposure to passive smoke during childhood than in pregnancy.

Summarily, passive smoke exposure during childhood is declining. There has been a decrease in children being exposed to passive smoke in childhood with the annual change ranging from 0.2% to 4.1% per annum across data collected between 1992 to 2014. There are fewer studies of exposure to passive smoke exposure during childhood compared to exposure during pregnancy. No peer-reviewed studies on passive smoke exposure trends during childhood were identified in Australia/Pacific and Africa.

Table 1-2 Studies on the trend of passive smoke exposure in children during childhood

Author/ year	Country	Number of participants [year] (age range)	Study design	Cotinine measurement	Exposure measure/ exposure location	Study factors	Change in trend (Outcome) / Annual change*	Study period [data points]
Lam, 2016 [167]	Vietnam	14,637 [2007] 3,430 [2011] (Age: 13-15 years)	Cross sectional (survey with questionnaire)	No cotinine measurement	Children asked if parents smoked at home in their presence in the past 7 days / Home	Parent's occupation, parent's education, gender, weekly spending money, parental smoking status	From 58.5% to 47.1% /1.6%	2007-2014 [2 data points]
Kuntz, 2016 [165]	Germany	6,680 (Age: 0 -6years)	Cross-sectional (survey) and cohort (earlier respondents invited again with new ones)	No cotinine measurement	Parents were asked about their smoking behaviour and if anyone was allowed to smoke in the presence of their child/Home	Socioeconomic status (parental education, occupational status and income), parental smoking behaviour	From 23.9% to 6.6% /1.9%	2003/2006-2009/2012 [2 data points]
Saito, 2015 [168]	Japan	41,833 [2001] 32,120 [2010] (6month old infants)	Cross sectional (survey using questionnaire)	No cotinine measurement	Parents were asked if they smoked and if it is indoors/Home	Household income, parental education level	From 36.8% to 14.4% /2.5%	2001-2010 [2 data points]

Author/ year	Country	Number of participants [year] (age range)	Study design	Cotinine measurement	Exposure measure/ exposure location	Study factors	Change in trend (Outcome) / Annual change*	Study period [data points]
Jarvis, 2009 [34]	United Kingdom	2,569 [1996] 695 [2007] (4-15 years)	Cross-sectional (survey-interview)	Cotinine checked with saliva	Parents were asked if anyone smoke inside their house or flat on most days/Home	Parental smoking habit	From 29.0% to 26.0% /0.3%	1996-2007 [9 data points]
Soliman, 2004 [169]	United States	4,418 families [1992] 11,183 families [2000] (families with children below 18 years)	Cross-sectional (questionnaire)	No cotinine measurement	Parents were asked the number of days someone smoked at home per week/ Home	Regions, race/ethnicity, mother's education, attitude towards environmental tobacco smoke	From 35.6% to 25.1% /1.3%	1992-2000 [2 data points]
Liang, 2011 [170]	United States	12,318 mothers were used in the analysis [Infants]	Cross-sectional (questionnaire)	No cotinine measurement	Mothers were asked about how many hours a day on average their baby was in the same room with someone who is	Race, maternal age, maternal education, marital status, preterm birth (<37weeks), infant sex, current maternal smoking status	From 14.3% to 13.8%/ 0.2%	1998-2004 [7 data points]

Author/ year	Country	Number of participants [year] (age range)	Study design	Cotinine measurement	Exposure measure/ exposure location	Study factors	Change in trend (Outcome) / Annual change*	Study period [data points]
					smoking/Home			
Holliday, 2009 [166]	United Kingdom	1611 [2007] 1605 [2008] (10-11years)	Cross-sectional (Self-report - questionnaire)	Cotinine measurement with saliva	Home, public places, car and someone's home	Age, family influence scale, current smoking status	'Exposure everyday': From 24.6% to 20.5% / 4.1% 'Exposure sometimes': From 63.1% to 60.1% /3%	2007-2008 [2 data points]

*Change per year across study data point period

1.5.2.3 Determinants of exposure to passive smoking during childhood

Various factors are associated with children who are exposed to passive smoking. Most of the exposure to passive smoke in children occurs from parents, with exposure inversely related to socioeconomic status.[43] A study that used cotinine validation found higher exposure levels in children from less advantaged backgrounds, during winter, on Mondays, in girls, and in smaller families with smokers.[171] Additional predictors identified are being a firstborn, presence of other household smokers and parental smoking status.[156] On occasions, determinants to exposure of children during childhood are examined in terms of parental characteristics. Children are more likely to be exposed if their parents were younger (24 years or less), had less education, employed in poor paying jobs and were raised in low earning families.[161] These findings are consistent with a meta-analysis that found exposure at home during childhood was associated with having parents who are smokers, of low education level and low socioeconomic position.[172]

1.5.2.4 Health effects of exposure to passive smoke during childhood

Though exposure to passive smoking during pregnancy and during childhood can act synergistically to cause health problems for the child,[173] there are many adverse health effects that have been associated with exposure to tobacco smoke during childhood only. These adverse health effects cover almost all systems of the body. Sometimes in reported studies, it is not clear if consideration was given to exposure to passive smoking during childhood independently by adjusting for any effect due to exposure to passive smoking during pregnancy. However, in some studies that adjusted for exposure to passive smoking during pregnancy, it was obvious that exposure to passive smoking during childhood independently harmed the health of children.[138, 139] These effects will be explored further without discrimination on whether the exposure was parental, non-parental or both.

Most of the adverse effects associated with passive smoking exposure during childhood seem to manifest in childhood. Whether these effects occur in adult age is unclear.

1.5.2.4.1 Respiratory health

Evidence of a strong effect between exposure to passive smoking during childhood and development of various respiratory problems have been documented. Children exposed to passive smoke during childhood had higher colonization with pathogenic bacteria in their middle nasal meatus compared to unexposed children at a mean age of 5 years,[51] leading to a higher risk of upper and lower respiratory tract infections including pneumonia and bronchiolitis.[155, 174] Exposed children tended to develop more active tuberculosis infection as children or adults.[175] These respiratory infections were also usually more severe in children who were exposed.[176] Exposure to passive smoking during childhood measured with cotinine has been associated with increased IgE[177, 178] and asthma in childhood before 18 years of age.[176, 178, 179] Asthma presentations are mostly of increased severity in children exposed to passive smoking during childhood.[180] When exposure is not associated with overt disease, wheezing[49, 181] and reductions in forced expiratory volume at 1 second (FEV1s) has been reported in school aged children between 6 to 19 years in a systematic review and case control analysis.[182] In conclusion, a range of respiratory ailments has been attributed to exposure to passive smoking during childhood.

1.5.2.4.2 Cardiovascular health

Although exposure to passive smoking has been associated with various diseases in children and adults, it is mainly cardiovascular diseases in adulthood that are responsible for the premature deaths among persons exposed to passive smoking after years of exposure.[159, 183] These cardiovascular effects may begin to be seen in childhood but may also persist into adulthood.

Compared to the preschool children of parents who do not smoke, preschool children aged 5 years of parents who smoked had a 1 mmHg higher systolic blood pressure.[184, 185] Similar effects have been observed in older persons. In 26-year-old males who were exposed to passive smoking for a short time in their young adult age, a 13 mmHg increase in peripheral and central systolic blood pressures was observed.[186] Similarly, lower aortic elasticity and lower brachial flow-mediated dilatation (FMD) has been shown in children between 8 to 11 years of age[187, 188] and adults aged 28 to 45 years[189] exposed to tobacco smoke in childhood. Exposure to environmental tobacco smoke during childhood has also been linked to increased carotid intima-media thickness and subclinical markers of atherosclerosis with these effects leading to long term damage to vascular function at adult age in their thirties and forties, [52, 190-192] and also to faster ageing of their blood vessels.[52] In most of the existing studies, exposure to parental smoking was the independent variable without considering other possible sources of exposure during childhood, [52, 184, 185, 189, 191] the analysis was cross-sectional [185, 193] and the response sample was small.[192] There are surprisingly few studies of the effects of passive smoke exposure in childhood on cardiovascular health into adulthood. Future studies that include other sources of passive smoke exposure with longitudinal designs would add to our understanding of the association between childhood passive smoke exposure and adult cardiovascular health.

1.5.2.4.3 Other body systems

Adverse effects of passive smoking during childhood on other body systems have been reported. Exposure to passive smoke during infancy is very likely to lead to weight and height growth reduction in the first four months of life.[194] Weight gain during the first 6 months of life in children who weighed less than 2500 g at birth and were exposed to maternal smoking postpartum was slower even if they are exclusively breastfed.[195] Another study found that parental smoking remains associated with low stature in their children at 5years of age.[196] At 6.5 years of age and above, there was associated with higher body mass index and greater odds

of overweight or obesity due to exposure after birth.[197, 198] Children exposed to parental smoking at preschool age showed persistent lower height-for-age from childhood to adolescence[199] and motor impairment including balance and strength at 7 to 9 years.[200]

Infections and degenerative changes associated with exposure to passive smoke during childhood have been suggested. Postnatal second-hand smoke exposure was independently associated with dental caries, with a significant positive exposure-response relationship.[138, 139] Middle ear disease (infections, hearing impairment and surgery due to middle ear disease) have been observed more in children exposed to parental smoking.[201] Other adverse effect associated with children exposed compared to unexposed children include habitual snoring,[50, 202] high C-reactive protein.[203]

Other adverse effects of passive smoking during childhood include cognitive and psychosocial development and cancers. Lower non-verbal reasoning skills due to exposure in childhood has been reported between the ages of 4 to 6 years.[204] Exposure to passive smoking during childhood between the age of 7 to 11 years has been associated with a lower cognitive score in overweight or obese children.[205] Children exposed to maternal postnatal smoking had slightly increased behavioural problems (externalizing and internalizing behaviours) at 6.5 years of age [197] and Attention deficit hyperactive disorder at below 18 years of age .[206] Exposure to passive smoking during childhood independently was associated with a higher odd (OR = 1.24, 95% CI: 1.03, 1.48) of developing nasopharyngeal cancer.[207] Also the risk of childhood acute lymphoblastic leukemia (ALL) and myeloid leukemia (AML) was increased in children below 15 years of age exposed to passive smoking during childhood.[208] Hence, adverse health effect after many body systems has been associated with exposure to passive smoking during childhood.

1.5.2.4.4 Healthcare service use

There have been some studies that have explored health care use or costs associated with passive smoke exposure during childhood. In a group of German children aged 9 -11 years old, the total average costs per child for physician visits, physical therapy and hospital treatment due to passive smoke exposure during childhood was €87 per annum when the exposure occurred on their home balcony and €144 when it occurred indoors at home.[209] The effect at population level will be considerable. In the United States, exposure in children between 3 – 14 years led to additional costs for emergency department visits of $215.1 million, $77.1 million, and $62.9 million in 2000, 2005 and 2010 respectively.[210] In children and adolescents, attention deficit hyperactivity disorder gave rise to the highest cost ($7.8 million) compared to respiratory infections, middle ear disease and asthma in terms of in and outpatient care, general practice visits, emergency department visits and prescriptions.[211] A greater understanding of the cost of passive smoke exposure to society will be useful for prevention purposes including advocacy to increase funding for smoking cessation services.

1.6 Biological mechanisms for the adverse effects of passive smoking

The main toxic compounds found in tobacco smoke include nicotine and nicotine products, ammonia, amines and nitrosamines, aromatic amines, and oxidants.[212] These compounds probably act synergistically to bring about the adverse health effects attributed to passive smoking.[43] Nicotine is suggested to be responsible for the effects of passive smoke on the respiratory system.[213] Prenatal exposure to cigarette smoke has been found to cause different adverse effects through inflammation including increases in c-reactive protein, IgE, and eosinophils.[178] Exposure to passive smoke during childhood has also been associated with many other adverse effects through markers of immune system functioning including an increase in white blood cell count, decrease in neutrophils, increase in IgE, IgA, IgG and IgM, decrease in cytotoxic T-cell activity and decrease response to TRL stimulation.[178] These

mechanisms, whether through exposure during pregnancy or exposure during childhood, are pro-inflammatory, immunosuppressive, encourage infections and promote tissue damage.[178] Atherosclerosis is mediated through reduced nitric oxide bioavailability, elevated levels of inflammatory cytokines, reduction in high-density lipoprotein and increase in low-density lipoprotein. Thrombosis is mediated through increased thromboxane levels in serum and increase in fibrinogen levels in blood.[214] One of the most carcinogenic of the toxic compounds found in passive tobacco smoke is NNK [4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone] which through *HPRT* (hypoxanthine-guanine phosphoribosyl transferase) and *p53* mutation leads to cancers.[215, 216] These inflammatory and immunological factors may impact cardiovascular health including through the development of atherosclerosis and thrombosis.[214]

1.7 Summary

Adverse effects due to exposure to passive smoking during pregnancy and/or childhood are extensive and affect almost all systems of the body. Although the prevalence of passive smoke exposure in children is declining, population growth means that a significant number of children are still affected with substantial public health and economic consequences.

There remain some gaps in our understanding of passive smoke exposure in children and its longer-term effects. We need to understand contemporary trends and prevalence of passive smoke exposure, including factors associated with passive smoke exposure. This is because as the population changes, the factors associated with this behaviour could also be changing. If we know about trends and factors associated with passive smoking, including through maternal smoking during pregnancy, then we can be more efficient in the planning and implementation of interventions to decrease maternal smoking during pregnancy and exposure to other forms of passive smoke in children.

While we know a great deal about some of the health effects of passive smoke exposure in children, such as respiratory diseases, we know comparatively little in terms of other aspects of health, health service use and long-term impacts on cardiovascular diseases. These results are important because they will help us to fully understand the effects of exposure to passive smoking during childhood. This understanding would allow us to update information in awareness programmes targeted towards reduction of exposure of children to tobacco smoke. Similarly, while there are many studies that have looked at effects of exposure to passive smoke in childhood on health effects during the childhood or adolescent period, there are less studies that have followed people into adulthood. These types of studies are needed because they increase our understanding of longer-term effects including whether these persist as people age. This information could be of use to motivate smokers to quit to protect their children, but also to assist in preventative health efforts for children and adolescents.

There is also a need to be able to measure exposure to passive smoke across longer periods of childhood in a valid and reliable way. At present the measurement of passive smoke exposure in childhood is limited because there are few instruments.

Advances in the measurement of cardiovascular structure and function may allow us to discover subtle changes in body systems due to exposure to passive smoking during pregnancy or childhood. These advances include more nuanced understanding of blood pressure, such as through central rather than peripheral blood pressures, or through examining the structure and function of the heart with advanced echocardiography.[217, 218] Discovery of these subtle changes could also serve as a tool to inform interventions to promote smoking cessation among adults of reproductive age and in adults living with children. They may also assist with managing the prevention of cardiovascular disease in people who have been exposed to passive smoke as children.

1.8 Appendix 1.A: Additional Methods

PubMed was searched for studies published on the trend of passive smoking using the advanced search. The search was designed to identify relevant articles on the trend or changes in exposure of children to passive smoke using their title. The search was done in two categories. One for passive smoke exposure during pregnancy (first search) and another for passive smoke exposure in children from after birth to adolescence (second search). For the first search, a combination of these keywords was used: "passive smoking", "passive smoke", "secondhand smoking","secondhand smoke", "tobacco smoke", "involuntary smoke", "smoking", "smoke" AND "change", "changes", "trend", "trends" , "increase"," decrease", "reduction", "time" AND "mother", "mothers" , "maternal", " paternal" , "parental", "pregnant", "pregnancy". The second search used these keywords**:** "passive smoking", "passive smoke", "secondhand smoking", "secondhand smoke", "tobacco smoke", "involuntary smoke", "smoking", "smoke" AND "child", "children", "infant", "infants", "toddler", "toddlers" AND "change", "changes", "trend", "trends", "increase", "decrease", "reduction", "time". For analysis, articles on changes to maternal smoking during pregnancy will be referred to as passive smoke exposure trend during pregnancy while articles on changes to passive smoke exposure in childhood will be referred to as passive smoke exposure trend during childhood.

Articles needed to have the proportion (in percentage) of those exposed to passive smoke during pregnancy and childhood at baseline and endpoint. No limit was set for time or period each study will cover or when publication occurred. However, articles needed to be in English. Studies assessing associations with disease and interventions were excluded. Articles on smoking cessation during pregnancy, point prevalence (not trend) of passive smoke exposure during childhood and during pregnancy, validation of point prevalence with cotinine and letter to the editor were also excluded. A few did not have full text.

Relevant information was extracted from all the included articles. From all the included articles, the information on the author, year of publication, country (where the study was done), study period/ data points, number of participants/ age range, study design, cotinine measurement, exposure measurement, study factors and change in trend/annual change were extracted.

CHAPTER 2: Research questions and hypotheses

This thesis will address research questions Chapters 4 to 8, based on the underlying hypotheses.

Chapter 4: Maternal smoking during pregnancy: trends and determinants in the conception to community study

Question 1. What is the prevalence, trend, and determinants of maternal smoking during pregnancy and change in maternal smoking between pregnancies in Tasmania between 2008 and 2014? Maternal smoking during pregnancy is expected to have decreased over time in Tasmania, with mothers who are older and of higher socioeconomic status less likely to smoke during pregnancy.

Chapter 5: Maternal smoking in pregnancy and child's hospital use up to 5 years of age in a data linkage birth cohort.

Question 2. *Are emergency department presentations and hospital admissions through emergency department increased for respiratory illnesses and non-respiratory illnesses in the first five years of life in children exposed to maternal smoking during pregnancy in Tasmania?* Emergency department presentations and admissions into hospital through emergency department for respiratory and non-respiratory illnesses are expected to be more within the first five years of life in children exposed to maternal smoking during pregnancy compared to those that are not exposed.

Chapter 6: Reliability and validity of a life course passive smoke exposure questionnaire in a cohort from childhood to adulthood

Question 3. *Are retrospective measures of exposure to passive smoking across childhood in Childhood Determinants of Adult Health Study Phase 3 follow-up, reliable and valid?* Retrospective questionnaire measures of passive smoke exposure in Childhood Determinants

of Adult Health Study Phase 3 follow-up are expected to be valid and reliable for the measurement of prolonged exposure to passive smoking.

Chapter 7: Prolonged childhood exposure to passive smoke is associated with subclinical cardiovascular dysfunction.

Question 4. *What impact does prolonged passive smoke exposure in childhood have on adult cardiovascular (CV) health?*

Higher exposure to passive smoking during childhood will be independently associated with markers of subclinical dysfunction in cardiovascular structure and function in adulthood.

Chapter 8: Associations between exposure to passive smoking in early life and cardiovascular health in adulthood

Question 5. *Are there particularly vulnerable periods in early life (during pregnancy and childhood) when exposure to passive smoke exposure has the greatest impact on adult cardiovascular health?*

Adults with the poorest markers of subclinical cardiovascular dysfunction in structure and function in adulthood will be characterised by early and prolonged passive smoke exposure across the early life-course (during pregnancy and childhood)

CHAPTER 3: Overview of methods

3.1 Prelude

This chapter describes the data sources for this thesis including study participants, the variables in the data and the study setting for the various studies. The outcome measures, covariates, other study factors and statistical analyses peculiar to each of the separate chapters of this thesis are described in the methodology section of each chapter.

3.2 Study populations

The study populations were obtained from three different datasets, Conception to Community Study (C2C), Childhood Determinants of Adult Health Study (CDAH) and Tasmanian Infant Health Study (TIHS).

3.2.1 Conception to Community Study (C2C)

Participants: Tasmanian government and other institutions collect routine administrative data that are compiled by the Tasmanian Department of Health into Perinatal, Public Emergency Department, and Public Admitted Patient datasets. The Conception to Community (C2C) Study, is a long-term multi-sectoral program that has linked the de-identified version of these datasets in the C2C Database to establish a research program to help improve maternal and child health and development in Tasmania. Linkage was undertaken by the Tasmanian Data Linkage Unit using the separation principle that makes it impossible for researchers and unauthorized persons to access any identifying information.[219] Participants, children born during the period 2008-09 to 2013-14 and their mothers were identified through the Perinatal Dataset. The Perinatal Dataset included within the C2C Database contains information on Tasmanian

women presenting for public and private sector antenatal care and/or childbirth. The C2C database comprised 37,120 children and 27,532 mothers (See Figure 3-1).

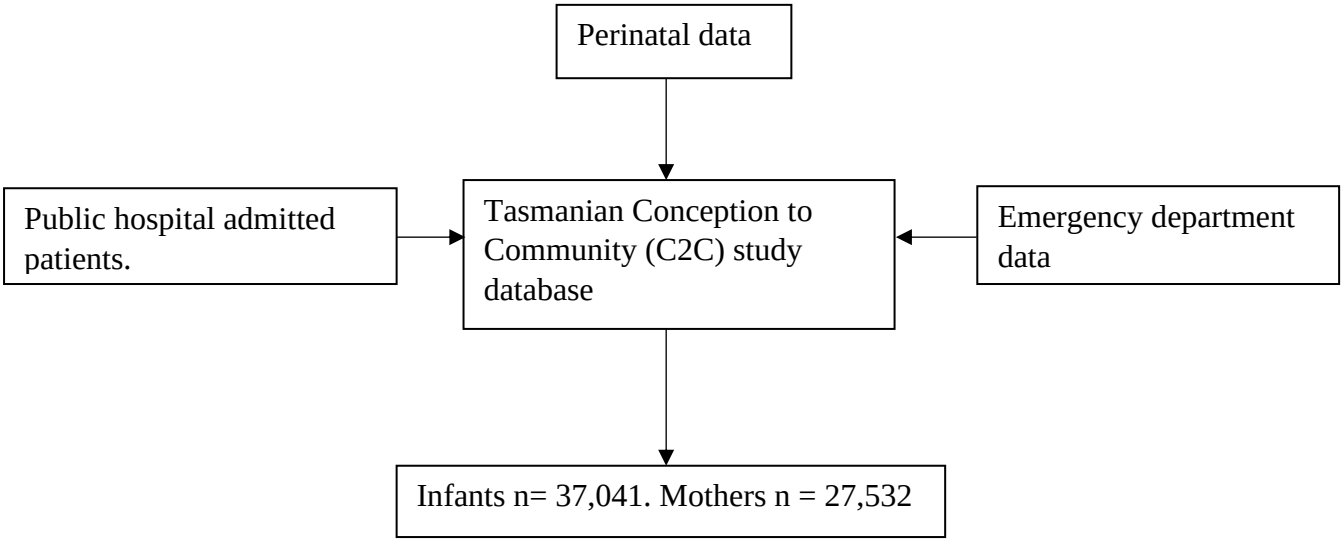

Figure 3-1 Flowchart of Tasmanian Conception to community study

Measurements: The Perinatal dataset included mothers details: age, country of birth, indigenous status, marital status, SA2, hospital code, estimated date of confinement, is this pregnancy the result of assisted reproductive technology?, intended place of birth, intending to breastfeed, plurality, gestation at the first antenatal visit, the total number of antenatal visits, height, weight, antenatal testing, pre-pregnancy conditions, did the mother smoke at all during the first half (≤ 20 weeks) of pregnancy?, did the mother smoke at all during the second half (≥ 20 weeks) of pregnancy?, did the mother consume alcohol during the pregnancy?, did the mother smoke marijuana during the pregnancy?, did the mother use other recreational drugs during the pregnancy?, vitamin supplements, date of admission (in which birth occurs), admitted patient election status, transfer of patient prior to delivery, obstetric complications, labour and delivery, the onset of labour, method of induction, indication for induction of labour,

augmentation of labour, analgesia during labour, labour & delivery complications, perineal status, indication of caesarean section, was the caesarean section a) Elective or emergency b) Primary or repeat, anaesthesia for delivery

Baby variables included day, month & year of birth, presentation at birth, mode of birth, indigenous status (baby), birth status, Apgar score, cord pH, gestational age at birth, weight, length, head circumference, sex, birth order, the actual place of birth, resuscitation at birth, medical admission to special care nursery/intensive care unit (SCN/ICU), congenital abnormalities, discharge status, the reason for the transfer of baby.

Public hospital emergency department dataset included age at the presentation –months, triage level, mode of arrival, discharge destination, admission ward, admission speciality, referral reason, length of stay in the emergency department, separation mode, referred to on separation, clinical variables, urgency related group, primary diagnosis, and major Diagnosis Category (MDC). The Public Hospital Admitted Patient dataset included: Admission date, type of admission, source of admission, source of referral, admission facility (Campus), admission ward, admission speciality, care type at admission, patient classification at admission, length of stay (LOS), same-day admission (yes or No), number of leave days, transferred from hospital, Barthel index of on admission, referral reason, discharge related variables, separation date, separation mode, referred to on separation, referred to hospital, referral Reason, readmission within 28 days, Barthel index of on discharge, clinical Variables, episode DRG, primary diagnosis, additional diagnoses, principal procedure, additional procedures and major diagnosis category (MDC). This dataset was used for the studies in chapters 4 and 5 of this thesis.

3.2.2 Childhood Determinants of Adult Health Study (CDAH)

The CDAH study is a longitudinal cohort study that began with a cohort that participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS). Since then, three follow-ups of the original cohort have been carried out as CDAH. ASHFS cohort was followed up as CDAH-1 study between 2004 and 2006 with a total of 3,967 (questionnaire only, questionnaire and clinic, questionnaire and pathology) participants (aged 26 – 36 years), CDAH-2 between 2009 and 2011 with 3,038 (questionnaire) participants (aged 31 – 41 years) while CDAH-3 was between 2015 and 2019 with 2,083 (questionnaire only, questionnaire and clinic) participants (36 to 49 years). The aim was to determine how childhood risk factors contribute to the development of cardio-metabolic diseases in adulthood. This study has aided immensely the study of the origins of heart disease, diabetes, and mental health.

Australian Schools Health and Fitness Survey (ASHFS)

The original 8,498 participants of ASHFS were selected from 109 schools Australia-wide. They were between the age of 7 and 15 years. A two-staged random sampling was used to make the selection of participants. Stage one was based on high enrolment numbers while stage two selected children in each school based on age and sex stratification. Schools that had less than 200 students were excluded. A total of 121 schools were selected but 109 of them accepted to participate. The expected sample was 500 for each gender in each of the age categories. The distribution of the 109 schools is illustrated in Figure 3-2.

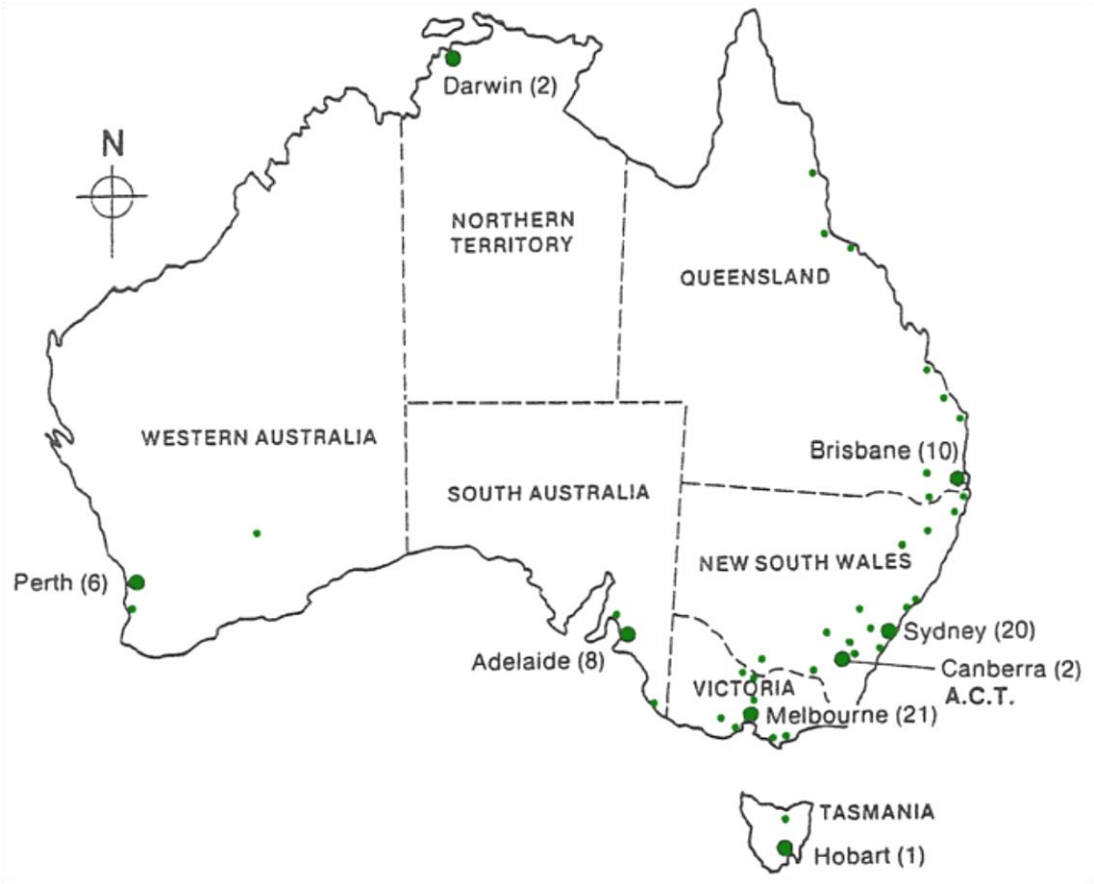

Figure 3-2 The distribution of schools that participated in the Australian School Health and Fitness Survey, 1985.

Measurements: At the beginning, the participants had physical measures that included anthropometry (height, weight, waist circumference), blood pressure and physical fitness (short/long run, sit-ups). A 36-item supervised questionnaire on demographics, sports participation, diet, smoking, and health was administered at children between 9 to 15 years while those aged 7 and 8 were left out due to age. A 24-hour food record was obtained from children aged 10 to 15 years. A blood sample was taken for fasting blood sugar and cardiorespiratory fitness tests were administered on children aged 9,12 and 15 years. More details of the measures collected at baseline (ASHFS) and in CDAH-1 can be found here.[220]

Childhood Determinants of Adult Health Study phase 1 (CDAH-1)

From the 8,498 participants of ASHFS, 6,840 were traced using school and family networks, the Australian Electoral Commission, and the Australian National Death Index. Eventually,

5,170 of them enrolled for CDAH-1 study. A total of 2,384 filled the questionnaire and attended the clinics, 1,397 filled the questionnaire only, 25 came for clinic only, 186 for pathology and questionnaire, 6 for pathology only and 1,171 only enrolled and 1 enrolled in error (See Figure 3-3)

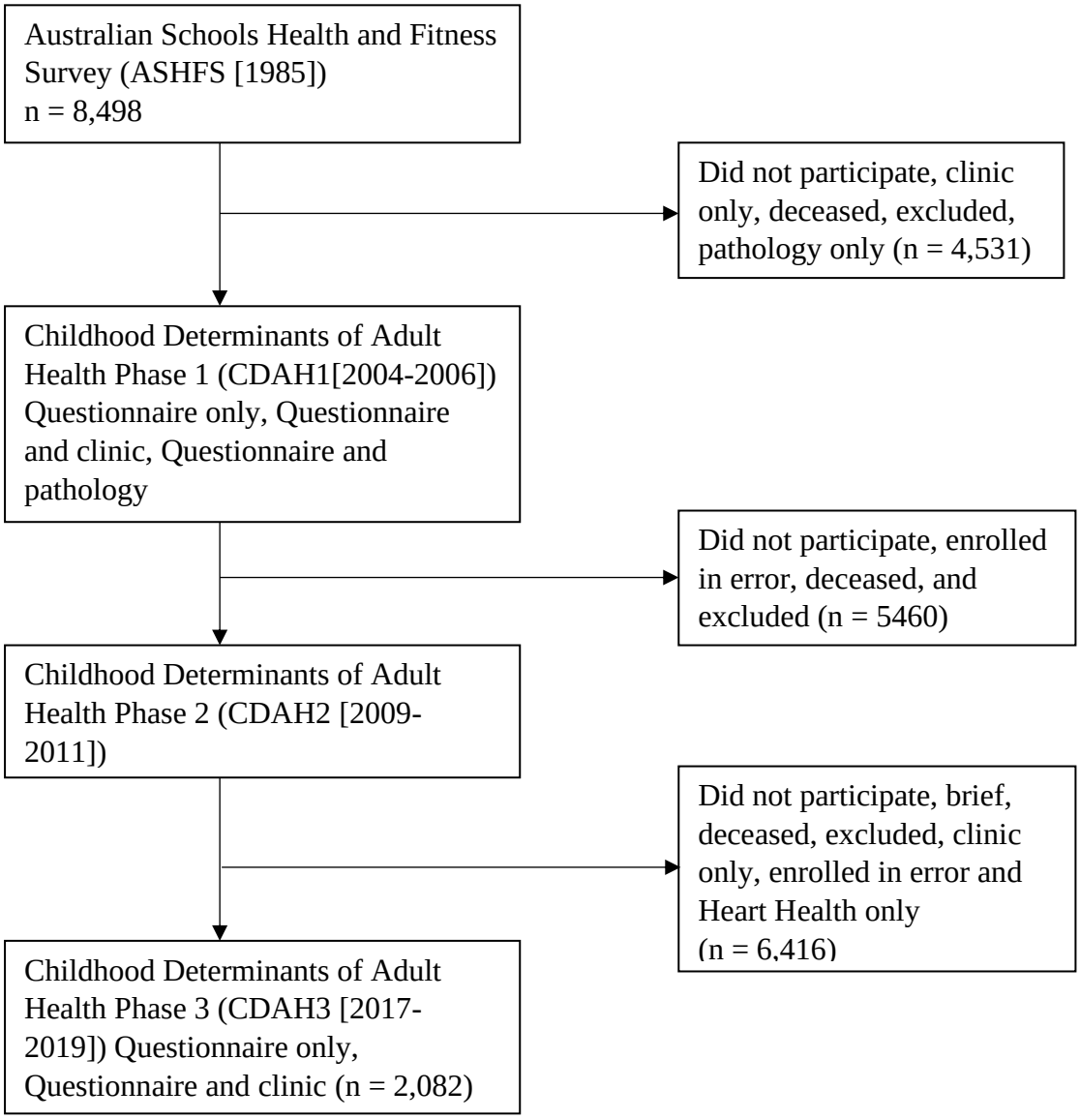

Figure 3-3 Flowchart of Childhood Determinants of Adult Health Study

Measurements: This included anthropometry (height, weight, girths, skin folds), physical activity (questionnaire and pedometer), diet, smoking, alcohol, fitness, blood pressure, lung function, fasting blood glucose and biochemistry (glucose, insulin, total cholesterol, HDL and LDL-cholesterol, triglycerides, C-reactive protein, sex-hormone binding globulin, total testosterone), and ultrasound measures of carotid intima-media thickness. Information on demographic characteristics was also collected. They include marital status, education, employment, self-reported health status (SF-12), medication use, family history of heart

disease and diabetes, self-reported birth weight, social support, personality type, menstrual characteristics (women). More details of these measures can be found here.[220] This dataset was used for the studies in chapters 6 and 7 of this thesis.

Childhood Determinants of Adult Health Study phase 2 (CDAH-2)

Out of the original 1985 cohort, 1,789 completed the full questionnaire, 1 enrolled in error, 5,333 did not participate, 12 were deceased, 114 excluded and 1,249 completed the short questionnaire.

Measurements: Questionnaires collected information on marital status, participants' highest level of education, occupation, employment status, living arrangements (parental home, cohabiting with a partner) and the number of children. Data was collected on alcohol consumption, physical activity using the International Physical Activity Questionnaire (IPAQ), smoking, diet, and social support.

Childhood Determinants of Adult Health Study phase 3 (CDAH-3)

From the original ASHFS cohort, 1,554 attended to clinics and full questionnaire, 528 to full questionnaire only, 12 to brief and brief2 questionnaire, 8 to brief questionnaire and heart health, 29 to brief2 questionnaire, 26 to brief questionnaire, 13 to clinic only, 972 to heart health only, 1 enrolled in error, 25 were deceased, 241 were excluded, and 5,089 did not participate.

Measurements: Questionnaires similar to that of CDAH-2 collected information on marital status, number of biological children, self-report of health status, occupation, employment status, the highest level of education, family history of stroke, cardiovascular disease or diabetes, alcohol consumption, smoking history from childhood, sleep pattern, menstrual and contraceptive history (women). Clinics for anthropometry (height/weight, waist & hip

measurement, skinfold measurement), pedometer measurement, ultrasonography, blood pressure measurement and pathology (blood glucose and lipid profile).

It is estimated that passive smoking have resulted in 603, 000 premature deaths in children, men and women.[159] However, it is mainly cardiovascular diseases in adulthood that is responsible for the premature deaths among persons exposed to passive smoking as adults after years of exposure.[159, 183] The development of cardiovascular diseases is gradual spanning many years.[221] This makes it necessary to detect subclinical cardiovascular become it becomes clinical. The CDAH study has information on a number of potentially relevant pre-clinical markers of cardiovascular disease. Examining all of these is beyond the scope of one PhD thesis. In choosing the particular outcome measures for analyses in this thesis, consideration was given to the following: (1) potential novelty of outcome measures in terms of previous analyses with the dataset with previous analyses predominantly on carotid intima media thickness; and (2) the potential to compare findings between the CDAH study and the TIHS study (see below for a description of the TIHS). Both the CDAH study and the TIHS had newer measures of cardiac structure and function, as well as comprehensive blood pressure measures, hence, in this thesis I studied markers of early markers of cardiovascular disease in adulthood which include blood pressure (central and peripheral)[222, 223] and left ventricular global longitudinal strain. [224, 225]

3.2.3 Tasmanian Infant Health Study (TIHS)

Participants: The Tasmanian Infant Health Study was conducted between January 1988 and March 1990. The birth cohort was established to identify the causes of sudden infant death syndrome (SIDS). A weighted scoring system was used to select infants at higher risk of SIDS for possible participation in an infant health study.[226, 227] Six major obstetric hospitals in the state of Tasmania contributed participants which included 3110 infants, representing

approximately 20% of all live births in Tasmania. More than 84 % of the 3110 infants participated in hospital and home interviews through their mothers.[227] In southern Tasmania, the mothers of 1,435 infants participated out of 1500 who were eligible. During 1st, 5th, and 11th week postpartum, information was collected through hospital interview, home visit, and telephone interview, respectively.

Measurements: birth weight, sex, the season of birth, height, head circumference, triceps, subscapular skinfold thicknesses, mother's age, duration of the second stage of labour, sociodemographic, type of infant feeding, sleep position, usual sleep pattern, infant illness and health service attendance maternal nutrition, alcohol and parental smoking practice during pregnancy and immunization history.

The TIHS cohort were followed-up in 1996-97 at age 8 (Southern Blood Pressure Study [443 participants] and Southern HDL-Cholesterol Study [446 participants]), and in 2004-05 at age 16 (Tasmanian-Bone (T-Bone 1) Study [415 participants]), and in 2013-14 at age 25 (Tasmanian-Bone (T-Bone 2) Study [280 participants]). A further follow-up in 2015-16 of participants for a pilot study in this thesis at age 27 was done with participants who were part of the 1996-97 Southern Blood Pressure Study or Southern HDL-Cholesterol Study (both were mutually exclusive). One hundred and fifty-five participants responded, with data collected used for the study in chapter 8 of this thesis (See Figure 3-4). As stated earlier specific cardiovascular outcome measures were studied in these participants as these measures were novel with regard to their association with passive smoking, were available in both CDAH and the TIHS and have been suggested as early markers of cardiovascular disease.

3.3 Ethical considerations

The University of Tasmania Health and Medical Human Research Ethics Committee approved the foundational C2C study (H0014169) and associated studies within this thesis (H0017161).

The University of Tasmania Health and Medical Human Research Ethics Committee approved the study and participants provided written informed consent for the studies from CDAH.The University of Tasmania Health and Medical Human Research Ethics Committee approved the TIHS study in this thesis (H0014432) and written informed consent was obtained from the participants.

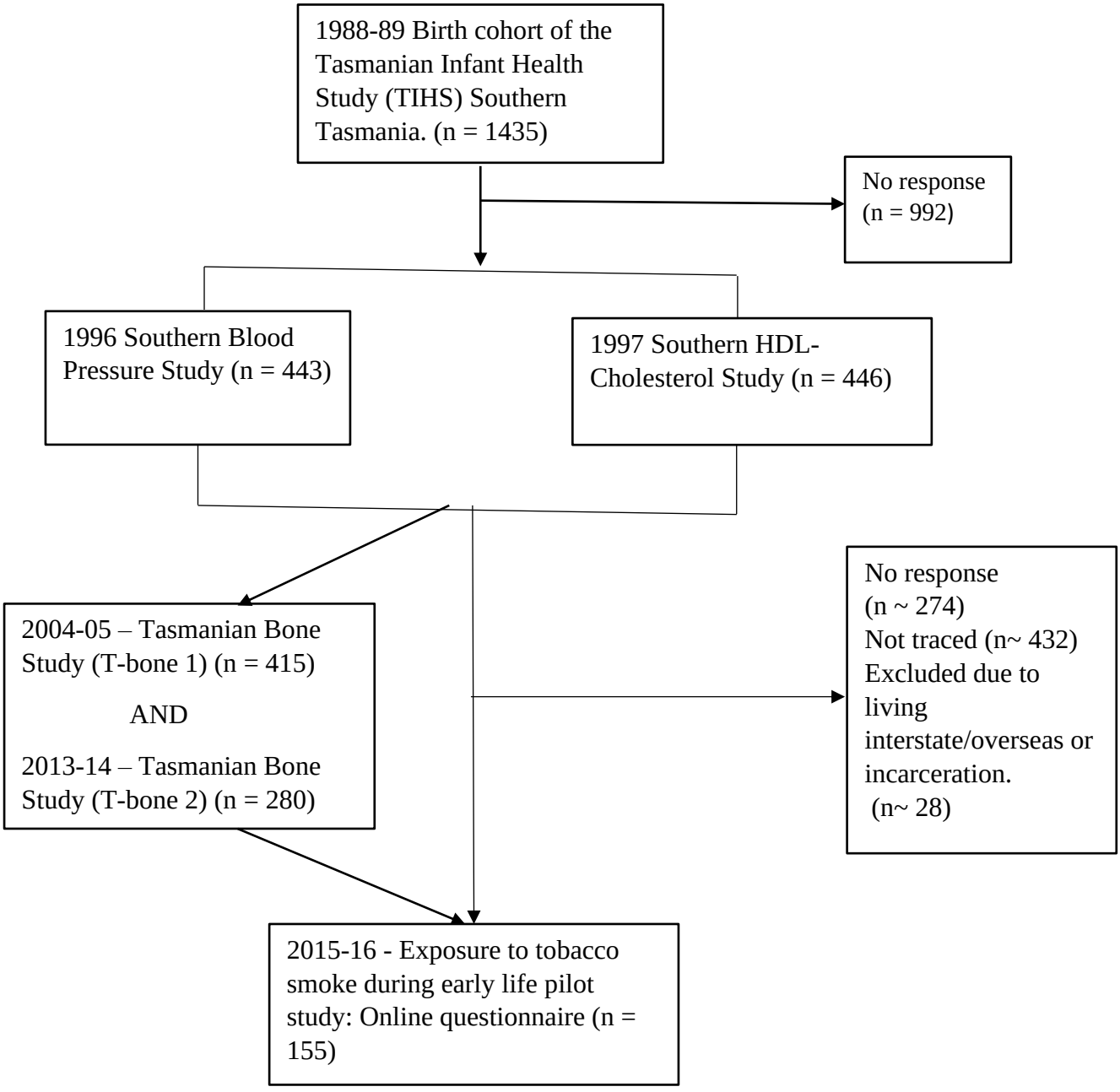

Figure 3-4 Flowchart of followed-up Tasmanian Infant Health Study participants

CHAPTER 4: Maternal Smoking During Pregnancy: Trends and Determinants in The Conception to Community Study

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Statement about this chapter: This chapter has some variation from the published version as analysis of change between index and subsequent pregnancy (as a sensitivity analysis) was included in the main results and the two tables reporting this analysis placed in the Appendix 4.A and cross-referenced.

4.1 Abstract

Background

Despite earlier declines, maternal smoking during pregnancy continues to be a public health problem. We examined trends and factors associated with maternal smoking during and between pregnancy over six years.

Methods

Participants were 27,532 pregnant women in Tasmanian public hospitals whose smoking status was gathered by midwives during perinatal care between July 2008 to June 2014. Generalized linear modelling was used to examine the trends in prevalence of maternal smoking over time and factors associated with change in smoking status both within and between pregnancies.

Results

Smoking during pregnancy decreased from 25.9% in 2008 to 16.4% in 2014 (57.9% decline). Multivariable regression analysis suggested that maternal alcohol consumption during pregnancy, living in a highly socioeconomically disadvantaged area and being an Aboriginal or Torres Strait Islander significantly increased the risk of maternal smoking during pregnancy. Being older, married or in a defacto relationship, and intending to breastfeed were associated with reduced risk of smoking during pregnancy. Between index (first birth recorded in dataset) and last pregnancy, 35.1% of smokers quit but 5.1% of non-smokers started smoking. Only 8.1% of mothers who smoked during the first half of pregnancy quit by the second half.

Conclusion

Maternal smoking during pregnancy is decreasing. To sustain the decline, preventive efforts must address the role of social determinants of health (e.g. mothers who drink alcohol, live in highly disadvantaged areas, are younger and single) among women who smoke during pregnancy.

4.2 Introduction

Maternal smoking during pregnancy is associated with poor birth outcomes, including increasing the likelihood of having a stillbirth by 20–30% and the risk of infant mortality by 40%. [228] Accurate assessment of maternal smoking during pregnancy and associated factors is necessary to provide support for quitting at the individual level, but also to quantify prevalence to plan, implement and evaluate interventions at the population level. In high and middle income countries such as Australia,[74] Ireland [75] and Brazil, [80] maternal smoking during pregnancy is routinely collected during antenatal care allowing national monitoring and reporting.

National reporting systems suggest that smoking during pregnancy is declining. For example, the proportion of mothers smoking during pregnancy has fallen in Australia, from 14.6% in 2009 to 11.0% in 2014, [66] in Sweden from 30.3% in 1982 to 11.0% in 2001[78] and in Brazil from 35.7% in 1982 to 21.0% in 2000.[80] No changes have been observed in some countries, such as Finland (15.0% in 1987 and 15.0% in 2010).[77] Ongoing population-level monitoring of maternal smoking during pregnancy remains critical even in the face of declining prevalence, as identifying the strategies that may be contributing to reductions in smoking could be implemented in other regions. In addition, examining the factors associated with maternal smoking during pregnancy can identify vulnerable groups who could be a focus of individual- or population-level interventions.

A range of factors are associated with smoking during pregnancy including younger age, [96-98] socioeconomic status, [96, 97] being multiparous,[98] exposure to parental smoking and living with a smoker [96], depression [96] and a lower intention to breastfeed.[229] These studies have limitations including a focus on groups with low prevalence of smoking during pregnancy, [98] low response proportion[229] and a focus on first pregnancies.[96] Changes in smoking status between pregnancies may demonstrate deficiencies or strengths in antenatal and primary care, as well

as wider tobacco control strategies. There are surprisingly limited data on how smoking status changes either within or between pregnancies. In one study in New South Wales Australia, of 22,761 women recorded as smokers during their first pregnancy, 33.5% quit by their second pregnancy.[94] This change appeared to be influenced by adverse events in the first pregnancy like gestational hypertension, large-for-gestational age baby and stillbirth.[94] Other studies have demonstrated similar proportions of women quitting between pregnancies ranging from 24.9% [230] [231] to 42.0% [95] [230] in different samples of women. There is also wide variation in the cessation of smoking during pregnancy. Cessation has been reported to range from 20.6%[90] to 54.9% [91] [92] among women who smoked during early pregnancy. These studies have also suffered from limitations including small samples;[90] single centres;[92] or data on maternal smoking during pregnancy collected retrospectively.[91] The aims of this study were to use a Tasmanian state-wide perinatal data set to: (1) investigate trends in smoking during pregnancy over time; (2) examine characteristics associated with smoking status during pregnancy; (3) examine changes in smoking status between and within pregnancies.

4.3 Methods

4.3.1 Participants

Data were obtained from the Conception to Community (C2C) study, a multi-sectoral (public perinatal, emergency department and admitted patients) de-identified linked database in Tasmania, Australia (population ~ 500,000). Our data are owned by the Tasmanian Department of Health and the data linkage was executed by the Tasmanian Data Linkage Unit following best practice protocols to maintain privacy and confidentiality. Best practice protocols involve the separation principle; the segregation of identifying information from clinical data, encryption of stored data and storage in a standalone server with no internet connectivity.[219]

The C2C study was developed to assist in monitoring maternal and child health in Tasmania. The database covers all births in Tasmania from July 2008 to June 2014.

4.3.2 Maternal smoking status during pregnancy and change in smoking status

In Tasmania, antenatal visits are advised at 7-12, 12-14, 18-22, 26-28, 32, 34, 36, 38, 40, and 41weeks gestation. Through the public system, women usually attend a general practitioner for the first visit and are seen by midwives at subsequent visits.[232] Maternal smoking status is recorded as part of mandatory national perinatal data collection by midwives and other birth attendants. The guidelines recommend that the smoking items be completed following birth so that information from across the pregnancy is recorded in the medical record. [233]

The questions on smoking changed during the period of the C2C study. From July 2008 to June 2010, women were asked at any antenatal visit "How much do you smoke?" with possible responses of "none", "≤10 per day" or ">10/day" and were categorized as "non-smoker" for those indicating "none" and "smoker" for those indicating "≤10 per day" or ">10/day". In 2010, the question asked of pregnant women was standardised across Australia, with responses to be obtained in both the first half (first twenty weeks) and last half (after twenty weeks) of pregnancy. From July 2010 to June 2014 the questions asked were "Did the mother smoke at all during the first half (<20 weeks) of the pregnancy" and "Did the mother smoke at all during the second half (≥ 20 weeks) of the pregnancy" with possible responses of "no" or "yes. These data allowed us to classify women as 'non-smokers', 'smoker' and 'missing' consistently over time. Across the entire study period, women who reported smoking in either the first or second half of pregnancy or who smoked ≥1 cigarette during pregnancy were classified as smokers.

We examined changes in smoking between index and last pregnancies (e.g. most recent pregnancy per participant) for all participants in C2C from 2007-08 to 2013-14 to encompass the range of change between pregnancies. As the C2C study was established with reference to

births, mothers may be in the dataset more than once. The data collection did not include the birth or pregnancy order for mothers. We therefore define the first pregnancy by each participant recorded in the C2C dataset as the 'index pregnancy' and the final pregnancy in the dataset as 'last pregnancy'. The same pattern in classification of change in smoking status was used for index and last pregnancy within the dataset. Mothers who smoked during index and last pregnancy and mothers who did not smoke during both periods were classified as "remained a smoker" and "remained a non-smoker", respectively. A smoker in an index pregnancy that quit in their last pregnancy were classified as "changed to non-smoker" while mothers who did not smoke in an index pregnancy, but smoked in their last pregnancy, were classified as "changed to smoker".

Cessation during pregnancy was examined for women who gave birth from July 2010 to June 2014. Smokers in the first 20 weeks who did not smoke in the second 20 weeks were classified as "changed to non-smoker", while smokers in first and second 20 weeks were "remained a smoker". Non-smokers in first 20 weeks who did not smoke in the second 20 weeks were classified as "remained a non-smoker", while if they started smoking in the second 20 weeks, they were classified as "changed to smoker".

4.3.3 Maternal characteristics

Maternal characteristics are gathered from mothers during scheduled antenatal appointments. Measures include maternal alcohol consumption ('Yes' or 'No'), maternal age classified into five categories '< 20 years', '20-24', '25-29', '30- 34' and 'above 34' years. Marital status was only available from 2010 and was categorized into 'single/never married', 'married/defacto' or 'other' (separated, divorced, or widowed). Index of Relative Socio-economic Disadvantage (IRSD), is a socioeconomic index based on area of residence (SEIFA) created by Australia Bureau of Statistics and measures relative disadvantage at area level based on social and

economic conditions.[234] Participants were separated into quartiles using IRSD score ('highly disadvantaged', 'moderately disadvantaged', 'mildly disadvantaged', 'least disadvantaged'). Maternal ethnic status was defined as 'Non-Aboriginal and Non-Torres Strait Islander' or 'Aboriginal and/or Torres Strait Islander'. Mother's intentions on feeding were categorized into 'formula' and 'breastfeeding'. These characteristics were mostly constant between pregnancies.

4.3.4 Statistical Analyses

Mothers may have more than one birth within the C2C dataset, which influenced the methods of analysis. General characteristics of the mothers in C2C were explored using all pregnancies in the dataset (e.g. individual mothers may appear more than once). There were missing data on smoking status, particularly in the records from public hospitals between July 2010 and June 2014. There were also missing data on marital status, as this variable was not available before 2010 in any hospital and was missing until 2013 in some private hospitals. Small proportions of data on birthweight, ethnic status, and drinking alcohol in pregnancy were also missing. Investigations revealed that the missing smoking data was a data entry issue, and we confirmed the data were missing at random. Subsequently, multiple imputation using chained equations was performed to account for the missing data. Maternal age at birth, year of birth, any previous record of smoking in the hospital data, state decile of IRSD score, gestational age, birthweight, hospital, marital status, ethnic status, assisted reproduction, intention to breastfeed, type of record (electronic or paper), and mother's insurance status (public or private patient) were used for the imputations. Ten imputed datasets were created.

The trend in smoking status over time was explored graphically by plotting the percentage of mothers smoking for each year over the 6-year study period using all pregnancies for all mothers. Generalised linear models with a Poisson family and log link were used to examine

the maternal factors associated with smoking during pregnancy using the imputed dataset. These analyses used smoking status in all pregnancies clustered on maternal identifier to account for women who had given birth more than once.

We examined the change in smoking status between (1) index and last pregnancy in women who gave birth at least twice and (2) within pregnancy (between first and second twenty weeks) for women who gave birth after July 2010. We used generalised linear models to examine the maternal factors from the index birth associated with change in smoking between pregnancies the index and last pregnancy. We separately compared (1) non-smoking mothers who started smoking between pregnancies to those that remained non-smoking and (2) smoking mothers who quit smoking to those that remained smoking. We examined maternal characteristics from the index birth rather than changes in characteristics as there was minimal change in these factors between pregnancies (e.g. socioeconomic status or marital status – data not shown). Examining change of predictors on change in outcomes can be problematic for interpretation. We also used a generalised linear model to examine the maternal factors associated with quitting smoking by second 20 weeks of pregnancy compared to continuing smoking in that period. An analysis for non-smokers in first 20 weeks of pregnancy who started smoking during the second 20 weeks of pregnancy was not done due to low numbers. All analysis was done using Stata 15 and p-value of < 0.05 was considered statistically significant.

4.5 Results

There were 27,532 women who gave birth at least once from July 2008 to June 2014 and 37,041 infants born (Table 4-1). There was a significant change over time in the pattern of missing data on maternal smoking status during pregnancy. The prevalence of missing data on maternal smoking during pregnancy increased from 0.9% in pre-July 2010 to 12.2% post July 2010. Most of the mothers were between the age 25 to 34 years, were married or in a

defacto relationship, non-Aboriginal and/or Torres Strait Islander, did not take alcohol during pregnancy, and intended to breastfeed their baby. Over the study period, the overall prevalence of smoking during pregnancy decreased from 25.9% of pregnancies in 2007-08 to 16.4% in 2013-14 though the rate of decline was gradual between 2010-11 and 2013-14 (Figure 4-1).

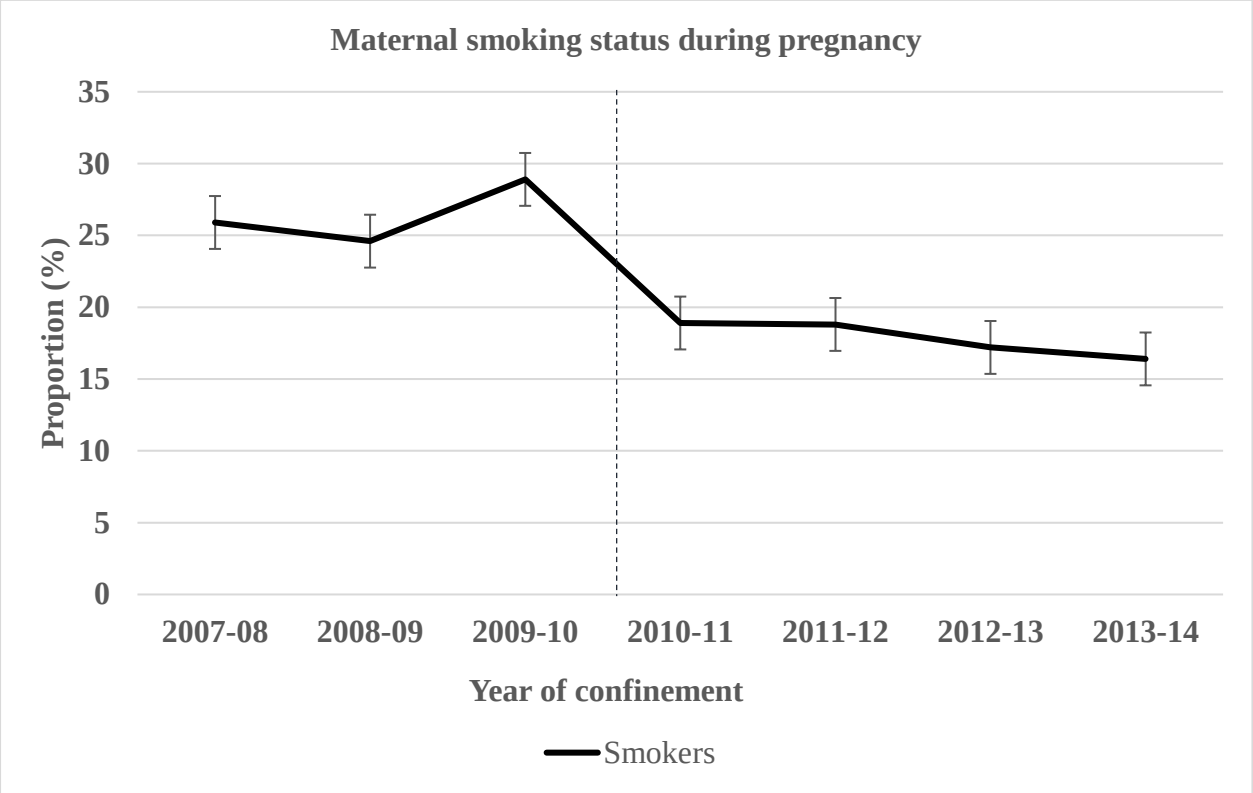
Women who drank alcohol during pregnancy were more likely to smoke during pregnancy compared with women who did not drink alcohol (Table 4-2). Married or defacto pregnant women were less likely than single mothers to smoke during pregnancy. Compared with women below 20 years, pregnant women aged 25-29, 30-34 and above 34 years were less likely to smoke. Living in a highly disadvantaged socioeconomic area and or being an Aboriginal and Torres strait islander was associated with increased risk of smoking during pregnancy. Mothers who intended to breastfeed were less likely to smoke during pregnancy than those who intended to formula feed.

A total of 8,376 women gave birth at least two times during the C2C study. Among smokers in their index pregnancy, 35.3% of women changed to a non-smoker by their last pregnancy (Table 4-3). Only 8.5% of women who were non-smokers in their index pregnancy changed to a smoker in their last pregnancy (Table 4-3). Results were consistent when examined using the first and subsequent pregnancy (Appendix 4.A Table 4-7).

Living in a mildly, moderately, and highly disadvantaged area, drinking alcohol during pregnancy and being an Aboriginal and/or Torres Strait Islander was associated with an increased likelihood of transitioning from a non-smoker in the index pregnancy to a smoker in the last pregnancy (Table 4-4). Pregnant women aged 20 years or older, who were married/defacto, or intended to breastfeed had a reduced likelihood of changing from a non-smoker in index pregnancy to smoker in their last pregnancy. Living in a moderately or highly

disadvantaged area or being an Aboriginal and/or Torres Strait Islander was associated with reduced likelihood of changing from a smoker to a non-smoker in their last pregnancy (Table 4-4). Mothers aged above 25 years, who were married, or intended to breastfeed had increased rate of changing from smoker in index pregnancy to non-smoker in their last pregnancy. Drinking alcohol during pregnancy increased the risk of both changing from a smoker to non-smoker and non-smoker to smoker between index and last pregnancies but higher for the later. Similar pattern was observed between index and subsequent pregnancy (Appendix 4.A. Table 4-8).

Cessation of smoking in the second 20 weeks of pregnancy was observed in 8.1% of women who reported smoking in the first 20 weeks (Table 4-5). Almost all (more than 99% with the exclusion of missing data) non-smokers in early pregnancy remained non-smokers throughout their pregnancy. Residing in a mildly, moderately, or highly disadvantaged area, or being above 20 years of age was associated with reduced likelihood of quitting smoking between the first and second 20 weeks of pregnancy. Being married/defacto and intending to breastfeed increased the likelihood of quitting during pregnancy (Table 4-6 , n=3,280).



----- represents when question on smoking status changed.

Figure 4-1 Maternal smoking during pregnancy in Tasmania, 2007-08 – 2013-14

Table 4-1 General characteristics of the pregnant women during pregnancy in Tasmania, 2008-09 to 2013-14

Maternal characteristics	n (%)
Self-reported smoking status (July 2008 – June 2010)	12,693 (100.0)
Non-smoker	9,468 (74.6)
≤ 10 cigarettes per day	1,829 (14.4)
> 10 cigarettes per day	1,287 (10.1)
Missing	109 (0.9)
Self-reported smoking status (July 2010 – June 2014)	24,348 (100.0)
Non-smoker	17,328 (71.2)
Smoker	4, 053 (16.7)
< 20 weeks	3,280
≥ 20 weeks	3,391
Missing	2,967 (12.2)
Maternal age	37,041 (100.0)
< 20 years	2,251 (6.1)
20-24 years	6,922 (18.7)
25-29 years	10,764 (29.1)
30- 34 years	10,252 (27.7)
> 34 years	6,852 (18.5)
Maternal marital status §*	19,944 (100.0)
Single/Never married	5,069 (25.4)
Married	14,646 (73.4)
Other ^	229 (1.2)

Maternal characteristics	**n (%)**
Area-level Socioeconomic position †*	37,025 (100.0)
Least disadvantaged	8,720 (23.6)
Mildly disadvantaged	9,058 (24.5)
Moderately disadvantaged	9,908 (26.8)
Highly disadvantaged	9,339 (25.2)
Maternal alcohol consumption during pregnancy*	37,041 (100.0)
No	32,202 (87.7)
Yes	4,495 (12.3)
Ethnic status*	36,609 (100.0)
Non- Aboriginal and Torres Strait Islander	34,925 (95.4)
Aboriginal and Torres Strait Islander	1,684 (4.6)
Intended feeding choice*	37,041 (100.0)
Formula	2,728 (7.9)
Breastfeeding	31,843 (92.1)

§ For Post July 2010 period

^ Separated, Divorced, Widowed

† Index of Relative Socio-economic Disadvantage (IRSD) score

* Missing data: Maternal marital status, n = 4,404; Area-level socioeconomic position, n = 16; Maternal alcohol consumption during pregnancy = 344; Ethnic status, n = 432; Intended feeding choice = 2,470.

Table 4-2 Factors associated with smoking during pregnancy in Tasmania, 2007-08 to 2013-14

	n	Maternal smoking during pregnancy in C2C database* (n = 37,041)
Characteristic		**Adjusted IRR† (95% CI)**
Maternal alcohol consumption during pregnancy		
No	32,202	Reference
Yes	4,495	**1.81 (1.70 - 1.93)**
Maternal marital status		
Single/ Never married	5,069	Reference
Married	14,646	**0.52 (0.48 - 0.57)**
Other^	229	0.91 (0.65 - 1.25)
Maternal age group		
< 20years	2,251	Reference
20-24 years	6,922	1.00 (0.94 - 1.06)
25-29 years	10,764	**0.78 (0.73 - 0.84)**
30- 34 years	10,252	**0.58 (0.53 - 0.63)**
Above 34 years	6,852	**0.57 (0.52 - 0.63)**
Area-level Socioeconomic status		
Least disadvantaged	8,720	Reference
Mildly disadvantaged	9,058	**1.57 (1.44 - 1.72)**
Moderately disadvantaged	9,908	**2.18 (1.97 - 2.41)**
Highly disadvantaged	9,339	**2.63 (2.42 - 2.86)**
Ethnic status		

Non-Aboriginal and Torres Strait Islander	34,925	Reference
Aboriginal and Torres Strait Islander	1,684	**1.44 (1.34 - 1.54)**
Intended feeding choice		
Formula	2,728	Reference
Breastfeeding	31,843	**0.64 (0.60, 0.67)**
Year of confinement		
2007-08	3,286	Reference
2008-09	6,372	0.95 (0.89 - 1.02)
2009-10	6,132	0.96 (0.89 - 1.03)
2010-11	6,322	**0.76 (0.70 - 0.83)**
2011-12	5,944	**0.76 (0.69 - 0.83)**
2012-13	6,022	**0.74 (0.67 - 0.80)**
2013-14	2,963	**0.70 (0.63 - 0.78)**

*** Reference category is 'non-smoking' during last pregnancy in C2C database**

Values in bold p-value < 0.05

^ Separated, Divorced, Widowed

† Adjusted for Maternal alcohol consumption during pregnancy, Maternal marital status, Maternal age group, Area-level Socioeconomic status, Ethnic status, Intended feeding choice and Year of confinement

Table 4-3 Smoking status between index and last pregnancies in Tasmania, 2007-08 to 2013-14

Maternal smoking during pregnancy		
Index pregnancy	**Last pregnancy**	**n (%)**
Non-smoker	Smoker	12,221 (8.5)
	Non-smoker	130,944 (91.5)
Smoker	Smoker	34,683 (64.7)
	Non-smoker	18,887 (35.3)

Table 4-4 Factors associated with change of smoking status between index and last pregnancies in Tasmania, 2007-08 to 2013-14

	Change in maternal smoking between index and last pregnancies	
	Changed to smoker† (n = 13,007)	**Changed to non-smoker § (n = 4,870)**
	Adjusted IRR (95% CI) **	**Adjusted IRR (95% CI)** **
Area-level Socioeconomic status		
Least disadvantaged	Reference	Reference
Mildly disadvantaged	**1.61 (1.29 - 2.00)**	0.89 (0.76 - 1.05)
Moderately disadvantaged	**2.32 (1.88 - 2.86)**	**0.80 (0.69 - 0.94)**
Highly disadvantaged	**2.82 (2.30 - 3.48)**	**0.64 (0.55 - 0.75)**
Maternal age group		
< 20years	Reference	Reference
20-24 years	**0.78 (0.64 - 0.97)**	1.15 (0.95 - 1.41)
25-29 years	**0.40 (0.32 - 0.50)**	**1.24 (1.01 - 1.51)**
30- 34 years	**0.28 (0.23 - 0.37)**	**1.38 (1.12 - 1.71)**

	Change in maternal smoking between index and last pregnancies	
	Changed to smoker† (n = 13,007)	**Changed to non-smoker § (n = 4,870)**
	Adjusted IRR (95% CI) **	**Adjusted IRR (95% CI) ****
Above 34 years	**0.31 (0.24 - 0.41)**	**1.34 (1.05 - 1.71)**
Maternal alcohol consumption during pregnancy		
No	Reference	Reference
Yes	**2.93 (2.52 - 3.41)**	**1.20 (1.08 - 1.34)**
Ethnic status		
Non-Aboriginal and Torres Strait Islander	Reference	Reference
Aboriginal and Torres Strait Islander	**1.41 (1.12 - 1.78)**	**0.71 (0.58 - 0.87)**
Maternal marital status		
Single/ Never married	Reference	Reference

	Change in maternal smoking between index and last pregnancies	
	Changed to smoker† (n = 13,007)	**Changed to non-smoker § (n = 4,870)**
	Adjusted IRR (95% CI) **	**Adjusted IRR (95% CI) ****
Married	**0.74 (0.63 - 0.87)**	**1.38 (1.22 - 1.57)**
Other^	1.14 (0.56 - 2.36)	1.07 (0.58 - 1.97)
Intended feeding choice		
Formula	Reference	Reference
Breastfeeding	**0.64 (0.53 - 0.78)**	**1.75 (1.46 - 2.09)**

† Reference category: remained a non-smoker

§ Reference category: remained a smoker

^ Separated, Divorced, Widowed

* Bold p-value < 0.05

** Adjusted for Maternal alcohol consumption during pregnancy, Maternal marital status, Maternal age group, Area-level Socioeconomic status, Intended feeding choice and Ethnic status

Table 4-5 Changes in smoking status within a pregnancy among women in Tasmania, 2007-08 to 2013-14

Maternal smoking during pregnancy (C2C)		
First 20 weeks of pregnancy (n)	**Second 20 weeks of pregnancy**	**n (%)**
Smoker (3,280)	Smoker	3,014 (91.9)
	Non-smoker	266 (8.1)
	Missing	0 (0.0)
Non-smoker (13,536)	Smoker	1 (0.01)
	Non-smoker	1,892 (14.0)
	Missing	11,643 (86.0)

Table 4-6 Factors associated with change in smoking status between early and late pregnancy period in an index pregnancy in Tasmania, 2007-08 to 2013-14

	Change in maternal smoking between early and late pregnancy period†	
	n	**Changed to non-smoker**** **Adjusted IRR (95% CI)**
Area-level Socioeconomic status		
Least disadvantaged	268	Reference
Mildly disadvantaged	571	**0.62 (0.40 - 0.98)**
Moderately disadvantaged	997	**0.58 (0.38 - 0.87)**
Highly disadvantaged	1,444	**0.54 (0.36 - 0.81)**
Maternal age group		
< 20years	423	Reference
20-24 years	1,056	**0.54 (0.36 - 0.80)**
25-29 years	898	**0.54 (0.36 - 0.81)**
30- 34 years	557	**0.53 (0.34 - 0.83)**
Above 34 years	346	**0.47 (0.27 - 0.80)**
Maternal alcohol consumption during pregnancy		
No	2,836	Reference
Yes	415	0.73 (0.47 - 1.14)
Ethnic status		
Non-Aboriginal and Torres Strait Islander	2,879	Reference
Aboriginal and Torres Strait Islander	367	0.69 (0.43 - 1.10)

	Change in maternal smoking between early and late pregnancy period†	
	n	**Changed to non-smoker** Adjusted IRR (95% CI)**
Maternal marital status		
Single/ Never married	1,562	Reference
Married	1,661	**1.34 (1.02 - 1.76)**
Other ^	50	1.59 (0.64 - 3.96)
Intended feeding choice		
Formula	535	Reference
Breastfeeding	2,393	**2.38 (1.48 - 3.81)**

† Reference category: remained a smoker throughout pregnancy

^ Separated, Divorced, Widowed

* Bold p-value < 0.05

** Adjusted for Maternal alcohol consumption during pregnancy, Maternal marital status, Maternal age group, Area-level Socioeconomic status, Intended feeding choice and Ethnic status

4.6 Discussion

We aimed to examine the trends, determinants, and changes in smoking during and between pregnancies. There was a gradual decrease in the prevalence of smoking during pregnancy in Tasmania over the 6-year period. Around 35.3% of women quit smoking between index and last pregnancies but less than 9.0% quit during pregnancy.

Smoking among pregnant women in Tasmania has decreased by 8.8% over the 6 years from 2007-08 to 2013-14. This is in line with, but of greater magnitude than, the national trend, where maternal smoking during pregnancy fell by 3.6%, from 14.6% to 11.0% between 2009 and 2014, noting the lower base. [66] The decline in maternal smoking during pregnancy has also been observed in some other states in Australia (New South Wales) and in other countries (Ireland, Brazil and United States). [74, 75, 80, 81] Declines have also been observed in subgroups with known high prevalence including Aboriginal and Torres Strait Islanders in Australia [235] and immigrants in Sweden.[78]

In Australia, the reductions in smoking during pregnancy may, at least in part, be attributed to national tobacco control efforts including plain packaging, comprehensive mass media advertising ban and tax increases.[236] These initiatives have been associated with a reduction in the daily smoking rate among adults 18 years and older (16.1% in 2011-12 to 14.5% in 2014-15).[237] For reproductive aged females and males (18 to 44 years) smoking rates reduced from 28.2% in 2001 to 16.3% in 2014-15. [237] The reduced prevalence of smoking during pregnancy may also reflect more targeted programs such as the 'Quit for you, Quit for two' campaign launched during the study period. [238]

The factors associated with smoking during pregnancy were like those reported elsewhere. Drinking alcohol during pregnancy was associated with smoking during pregnancy, as reported by others. [239] Smoking and alcohol during pregnancy may act synergistically to harm the health

of the child.[240] Living in an area of greater socioeconomic disadvantage was associated with maternal smoking during pregnancy, which is supported by earlier studies in Australia [74, 241] and elsewhere. [242] The disparity in smoking levels during pregnancy between women living in areas with different socioeconomic status suggests the need for targeting smoking prevention programs. Policies that promote economic justice to help reduce the stressors of poverty and inequality are also likely to be important. The finding that married women, and older women, and those who intended to breastfeed their baby were less likely to smoke during pregnancy is consistent with other findings.[242, 243] Women in Australia are giving birth at older ages. The average age of pregnant mothers in Australia was 29.8 years in 2006 and 30.5 years in 2016, and there was also an increase in the proportion of women above 35 years and a decrease in women below 25 years who gave birth over this period.[66] A combination of older women giving birth and older women smoking less could be another factor contributing to the downward trend in smoking during pregnancy. Younger women, unmarried women, women who drink alcohol and mothers who live in socioeconomically disadvantaged areas are potential targets for initiatives aimed at further reducing the smoking rate during pregnancy.

Smoking status tracks strongly between pregnancies. Almost two thirds (64.7%) of smokers remained smokers from index pregnancy to the last pregnancy i.e. less than one third gave up smoking, and a high proportion of non-smokers remained non-smokers (91.5%) in their next pregnancy. The factors associated with changing smoking status from to smoker to non-smoker between pregnancies were largely consistent with those that predicted smoking during pregnancy cross-sectionally. This may have some policy implications in terms of specifying target groups to increase smoking cessation after pregnancy and beyond, such as younger mothers and those facing disadvantage.

Only 8.1% of women who smoked were recorded as quitting within their pregnancy (between the first and last 20 weeks), which is lower than the 20.6% (Spain) to 54.9% (United States)

reported elsewhere. [90-92] There may be multiple reasons for this lower quit rate including the overall greater burden of socioeconomic disadvantage and high background levels of smoking in the state of Tasmania where the study was conducted. [244] The barriers to smoking cessation in disadvantaged smokers are complex and likely also operate in women who smoke during pregnancy within these groups.[245]

4.6.1 Strengths and Limitations

Our data set is large, containing data on 27,535 mothers over 6 years across the Australian state of Tasmania. The information on maternal smoking was collected as part of mandatory reporting for the national perinatal minimum dataset for every pregnancy irrespective of the place of delivery (e.g. public, private or home) or health professional attending the birth (e.g. midwife or obstetrician). Data are reported shortly after birth and so recall bias should be limited. Further, selection bias is not considered a factor either given that the dataset comprised all births in Tasmania, though findings may not be generalizable to other regions.

As information on maternal smoking during pregnancy was self-reported, reporting bias may have led to underestimation or overestimation of the prevalence of maternal smoking during pregnancy coupled with some missing data on maternal smoking. However, maternal self-report of smoking status has been found to be a valid measure of smoking status following concordance with cotinine analysis.[246] Change of questions in mid-2010 may have also affected the responses to questions as to whether a woman identified as a smoker. There were missing data on smoking status due to data collection issues with the change from a paper-based to electronic system. We were able to impute missing data, but we may have misclassified women. Area level socioeconomic position was used in our analysis and this may differ from true individual level socioeconomic position of the participants. We chose to analyse changes in smoking status between pregnancies using the first and last pregnancies in the database. The

alternative was to use the first and subsequent pregnancies. When analysed using the alternative method, the results did not differ, and that approach may have lost information for the approximately 1041 women that had 3 or more births.

4.7 Conclusions

The decrease in smoking during pregnancy in Tasmania signifies that preventive efforts are working but further efforts are needed to reduce disparities in smoking for some groups. It is hoped this trend can continue and targeting the social determinants of smoking may support this aim. The low proportion of women quitting during pregnancy suggests an urgent need for effective and acceptable treatments during pregnancy.

4.8 Appendix 4.A. Additional Results

Table 4-7 Smoking status between index and subsequent pregnancies in Tasmania, 2007-08 to 2013-14

Maternal smoking during pregnancy		
Index birth	**Subsequent birth**	**n (%)**
Non-smoker	Smoker	12,364 (9.2)
	Non-smoker	122,584 (90.8)
Smoker	Smoker	32,076 (65.0)
	Non-smoker	17,248 (35.0)

Table 4-8 Factors associated with change of smoking status between index and subsequent pregnancies in Tasmania, 2007-08 to 2013-14

	Change in maternal smoking between index and subsequent pregnancies	
	Changed to smoker† Adjusted IRR (95% CI) **	**Changed to non-smoker § Adjusted IRR (95% CI)** **
Area-level Socioeconomic status		
Least disadvantaged	Reference	Reference
Mildly disadvantaged	**1.60 (1.29, 1.98)**	0.87 (0.73, 1.03)
Moderately disadvantaged	**2.25 (1.83, 2.76)**	**0.82 (0.70, 0.97)**
Highly disadvantaged	**2.60 (2.12, 3.19)**	**0.62 (0.53, 0.73)**
Maternal age group		
< 20years	Reference	Reference
20-24 years	**0.76 (0.62, 0.93)**	1.21 (0.99, 1.49)
25-29 years	**0.42 (0.34, 0.52)**	**1.27 (1.03, 1.56)**
30- 34 years	**0.27 (0.21, 0.34)**	**1.43 (1.15, 1.78)**
Above 34 years	**0.30 (0.23, 0.40)**	**1.43 (1.11, 1.84)**
Maternal alcohol consumption during pregnancy		
No	Reference	Reference
Yes	**3.55 (3.08, 4.08)**	**1.18 (1.05, 1.32)**
Ethnic status		

	Change in maternal smoking between index and subsequent pregnancies	
	Changed to smoker† Adjusted IRR (95% CI) **	**Changed to non-smoker § Adjusted IRR (95% CI)** **
Non-Aboriginal and Torres Strait Islander	Reference	Reference
Aboriginal and Torres Strait Islander	**1.18 (.92, 1.52)**	**0.73 (0.59, 0.91)**
Maternal marital status		
Single/ Never married	Reference	Reference
Married	**0.73 (0.61, 0.88)**	**1.33 (1.16, 1.52)**
Other^	1.20 (0.52, 2.77)	0.99 (0.53, 1.83)
Type of Conception		
Not assisted	Reference	Reference
Assisted	**0.35 (0.21, 0.59)**	1.22 (0.89, 1.69)
Intended feeding choice		
Formula	Reference	Reference
Breastfeeding	**0.63 (0.53, 0.77)**	**1.65 (1.38, 1.97)**

† Reference category: remained a non-smoker.

§ Reference category: remained a smoker.

*** Bold p-value < 0.05**

****** Adjusted for Maternal alcohol consumption during pregnancy, Maternal marital

	Change in maternal smoking between index and subsequent pregnancies	
	Changed to smoker† **Adjusted IRR (95% CI) ****	**Changed to non-smoker §** **Adjusted IRR (95% CI)** **

status, Maternal age group, Area-level Socioeconomic status, Ethnic status, Type of Conception, Type of Conception, and Intended feeding choice.

^ Separated, divorced, widowed

CHAPTER 5: Maternal Smoking in Pregnancy and Child's Hospital Use up to 5 Years of Age in A Data Linkage Birth Cohort

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Link to published paper:
https://hosppeds.aappublications.org/content/11/1/8?ijkey=6462a26cd035d867929fda20a596ab74a593c8fe&keytype2=tf_ipsecsha

CHAPTER 6: Reliability and Validity of a Life Course Passive Smoke Exposure Questionnaire in a Cohort from Childhood to Adulthood

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This paper has been re-submitted with revisions on 25th January 2021.

6.1 Abstract

Background

Cotinine measurement can be used as a gold standard to validate questionnaires on recent exposure to passive smoking. No such gold standard exists for questionnaires on prolonged passive smoking exposure. We tested the reliability and validity of a questionnaire on life course passive smoke exposure using the demographics and health-related factors in a longitudinal cohort.

Methods

Participants comprised of the Childhood Determinants of Adult Health phase 3 (CDAH3) study (2014-2019, ages 36-49 years) cohort followed up after 34 years. Severity of exposure index; cumulative years of exposure and total household smokers were derived as 6-item scales (exposure to mother/father/ other household smokers) from questionnaire measuring prolonged passive smoking. Internal reliability and internal consistency were assessed with item-to-total correlation and Cronbach's alpha respectively. Convergent and divergent validity were examined using spearman's correlation and intraclass correlation (ICC).

Results

Total of 2082 participants responded with a mean age of 45 ± 2.5years and 55.2% were females. Cronbach's alpha for Severity of exposure index and Cumulative years of exposure was 0.70 and Total household smokers, 0.75 illustrating good internal consistency for each 6-item scale. There Item-to-total correlation ranged from r = 0.24 to r = 0.78 indicating strong to weak correlation. The three measures were weakly but significantly correlated with participant's own smoking status, Forced Expiratory Volume 1second, Forced Vital Capacity and Physical activity with correlation coefficient ranging from r = 0.01 to r = -0.06. Retrospective measures showed moderate agreement with Total household smokers 34 years earlier with ICC ranging from 0.58 to 0.62.

Conclusion

CDAH3 passive smoking exposure questionnaire is reliable and valid.

6.2 Introduction

Passive smoke exposure increases the risk of diseases including lower respiratory infections in infancy, lung and cervical cancer and stroke.[277] The frequency and duration of exposure to passive smoking influence its adverse effects.[278, 279] We have found that prospectively reported childhood measures of passive smoke exposure from parents were associated with greater carotid intima-media thickness [52] and increased risk of carotid atherosclerotic plaque.[191] There is increasing recognition of the importance of exposures across the life course from childhood to adulthood[280] but examining these relationships between exposure in childhood and health outcome in adulthood requires measurements of exposures over time. Existing questionnaires on passive smoking in children and adults measured short term exposure to passive smoking ranging from 24 hours to a few weeks.[281-284] There are some measures of passive smoking that have attempted to retrospectively capture prolonged passive smoke exposure across childhood with demonstrated reliability being mostly intra-rater reliability using repeated assessments in adulthood. Few researchers have examined validity of these measures possibly due to lack of gold standard.[38]

Among existing passive smoke exposure instruments, mostly developed for adult exposure, some have been shown to be reliable and valid. To examine reliability, the same questions on passive smoke exposure were asked of participants at different point in time. Similar existing instruments of passive smoke exposure in adults and children (asking parents on behalf of children) have found that they have good reliability.[281, 284] For passive smoke exposure questionnaires in adults, concurrent validity has been shown against information from smokers in their household, [285, 286] while construct validity has been shown through correlation with biomarkers like cotinine and environmental nicotine measurement.[282, 283, 287] Most of these questionnaires measured recent term exposure to passive smoking.[281-284] Validation of

questionnaire measurement of retrospective passive smoke exposure across childhood tantamount to lifetime exposure has not been undertaken.

The Childhood Determinants of Adult Health (CDAH) study is a follow-up of the cardiovascular health of people from the Australian Schools Health and Fitness Survey, which was a nationally representative cross-sectional study of the health and fitness of Australian school children in 1985. The aim of this study was to assess the reliability and validity of a retrospective childhood passive smoking questionnaire making use of the rich data on childhood and adulthood social, demographic, and health-related factors captured across the life course.

6.3 Methods

6.3.1 Study participants

Participants were from the Childhood Determinants of Adult Health (CDAH) study, a follow-up of the 8498 children, aged 7 -15 years, who participated in the Australian Schools Health and Fitness Survey (ASHFS) in 1985 after a two-staged random sampling first of schools and then of children within schools.[288] The response proportion in ASHFS was 67.5%. After the first follow up in 2004-6 (CDAH-1, response proportion 47%), subsequent follow up happened in 2009 – 2011 (CDAH-2, response proportion 36%) and 2015-2019 (CDAH-3, response proportion 25%). Institutional ethics approval were obtained from the Tasmania Health and Medical Human Research Ethics Committee and other relevant bodies for each follow up.

6.3.2 Study measures

Self-reported exposure to passive smoking

In the third follow-up of the CDAH study (CDAH-3), from 2014 to 2019, participants completed face to face assessments, along with questionnaires on health and lifestyle, diet and

physical activity when they were aged 36-49 years. Data on exposure to passive smoke during childhood was collected with a questionnaire including the number of household members who smoked (mother, father and other), environments where the exposure occurred (car and house), and the duration of the exposure for each household member (years). This was based on measures in adults in the literature. [289] Specific questions are included in Appendix 6.A.

The questionnaires were used to derive three passive smoke exposure variables described below based on an approach reported in adults in the literature.[289]

Total household smokers: This represents a sum of the total number of household members who were regular smokers, lived with the participant and smoked inside the house. Parental smoking in CDAH-3 was categorized as 'none', 'either parents smoked' and 'both parents smoked'.

Cumulative years of exposure: This was derived from summing the total number of years participants were exposed to passive smoke from each household member that he or she lived with. Cumulative years of exposure was also categorized into three categories (no exposure, 1 to 50 years and 51 years and above).

Severity of exposure index: Frequency of exposure inside the house from each household member were scored: 'Never'=1, 'Sometimes'=2 and 'Always'=3. An index of severity of exposure was calculated by multiplying the years of exposure from each household member by the frequency of the exposure and summing over all household members for each participant. [289] Severity of exposure index was also categorized into quartiles: no exposure, 1-30, 31 - 60 and >60.

Other measurements

A range of measurements in same participants taken in childhood at ASHFS, and during adult follow-ups (CDAH-1 and CDAH-3) were used to explore the reliability and validity of the retrospective passive smoke exposure questionnaire administered at CDAH-3.

Baseline – ASHFS in 1985

Measures included gender, age group (7-9 years, 10-12 years and 13-15 years), area-level socioeconomic status according to postcode of residence (quartiles of a continuous measure - high, medium-high, medium-low and low),[290] smoking experimentation in childhood (one, a few puffs, yes, < 10 in my life, yes, > 10 in my life), total household smokers and parental smoking categorized as 'none', 'either parents smoked' and 'both parents smoked' and lung function using a Vitalograph single-breath wedge spirometer to estimate forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).[291]

CDAH-1 in 2004-06

Lung function was measured at CDAH-1 using portable electronic spirometer and included FEV1 and FVC. [291] The mean of lung function measures was used as cut points for descriptive analyses.

CDAH-3 in 2014-19

Measures taken included physical activity level (low, moderate and high) from total minutes of physical activity per week using the International Physical Activity Questionnaire,[292] employment status (categories) and own smoking status (categories) in adulthood. Main occupation of participants were categorized into Skill level A, B and C. Skill level A for managers or administrators (e.g. magistrate, farm manager, general manager, director of nursing, school principal), professionals (e.g. scientists, doctors, registered nurses, teachers) and associated professionals (technicians, police officers, youth workers). Skill level B for tradespersons, advanced and intermediate clerical or service workers and skill level C for production or transport workers, elementary clerical or service workers, labourers, cleaners and those with no paid job.

6.3.3 Data analysis

We explored the descriptive summary statistics of the three derived passive smoking exposure measures according to their range, mean and standard deviation.

Reliability

We assessed internal reliability using item-to total correlation and Cronbach's alpha.[293] Internal reliability was tested by examining each component item-to-total correlation of the three retrospective passive smoking exposure variables using Pearson or Spearman's correlation. Component items for (1) total household smokers were maternal, paternal and any other household smoking status; (2) cumulative years of exposure were years of exposure from mother, father, and any other household member; and (3) severity of exposure index were cumulative exposure from mother, father and any other household member. We determined correlation coefficients <0.3 as weak, 0.3 - 0.5 as moderate and >0.5 as strong.[294] Subsequently, the three derived exposure variables with their component items was also tested using Cronbach's alpha and score of 0.7 deemed acceptable.[294]

We used intraclass correlation coefficient (ICC) to examine agreement in passive smoking exposures from childhood to adulthood. [295] We used one-way random-effects ICC to examine absolute agreement between the three retrospective derived measures of passive smoking and parental smoking from CDAH-3 with childhood (ASHFS) assessment of parental smoking and total number of smokers in their home. ICC <0.5 shows poor agreement, 0.5 to 0.75 shows moderate agreement; 0.75 to 0.9 shows good agreement and >0.9 shows excellent reliability/excellent agreement.[295]

Validity

As there is no gold standard for validating prolonged passive smoking questionnaires, we used a range of variables from ASHFS, CDAH-1 and CDAH-3 to examine aspects of construct

validity of the retrospective passive smoke exposure questionnaire. Tests included t-tests and one-way analysis of variance (ANOVA) to examine how passive smoke exposure varied by different childhood (e.g. socioeconomic status and smoking experimentation) and adulthood (e.g. employment and smoking status) characteristics, addressing aspects of convergent validity.

We also examined convergent validity of the three derived passive exposure variables and parental smoking in CDAH-3 with participants own smoking status at CDAH-3, lung function tests (FEV1 and FVC) from CDAH-1 and ASHFS using Spearman's or Pearson's correlation as appropriate based on the distribution of variables. Divergent validity was assessed with physical activity using Spearman's or Pearson's correlation on the premise that ordinary day to day physical activity would not be affected by being exposed to passive smoking in childhood. All analysis was conducted with Stata version 16 (StataCorp, TX, USA).

6.4 Results

There were 2,082 participants in CDAH3 (Figure 6-1). Total household smokers ranged from 0 to 5 household members; cumulative years of exposure ranged from 0 to 106 and severity of exposure ranged from 0 to 318 (Table 6-1).

6.4.1 Reliability

Internal reliability of derived exposure variables and the correlation of each item in the scale to the total derived variable is shown in Table 6-2. All component items demonstrated moderate to strong correlation ($r \geq 0.3$) with their constituent retrospective passive smoking variables (CDAH-3) except for cumulative exposure from another household smoker four ($r = 0.24$) and years of exposure from another household smoker four ($r = 0.24$). Coefficient of determination from correlation of each item to the total shows that 62% of the variance in severity of exposure

index is explained from cumulative exposure from participant's father while it was 61% from participants' mother. The Cronbach's alpha for severity of exposure index, cumulative years of exposure and total household smokers were >0.7 illustrating good internal consistency.

ICCs demonstrated mostly moderate agreement between the derived measures of passive smoking in CDAH-3 and parental smoking and total household smokers in ASHFS (Table 6-3). For example, the highest agreement was between retrospectively reported parental smoking in CDAH-3 and parental smoking in ASHFS (ICC 0.65, 95% CI 0.62, 0.68). There was lower agreement with less similar items, such as total household smokers assessed retrospectively with parental smoking in ASHFS (ICC 0.47, 95% CI 0.43, 0.51).

6.4.2 Construct Validity

As shown by the mean of the three derived measures of exposure according to childhood and adulthood factors (Table 6-4), demographics factors varied by exposure to passive smoking. Analyses repeated using non-parametric tests confirmed these results (data not shown).

There were weak but statistically significant positive correlations between retrospective passive smoking measures with participant's own smoking (CDAH-3) and weak, but significant, negative associations with lung function in adulthood (Table 6-5). In terms of divergent validity, the correlation of adult physical activity at CDAH-3 was weak (r = 0.01) for all retrospective passive smoking measures

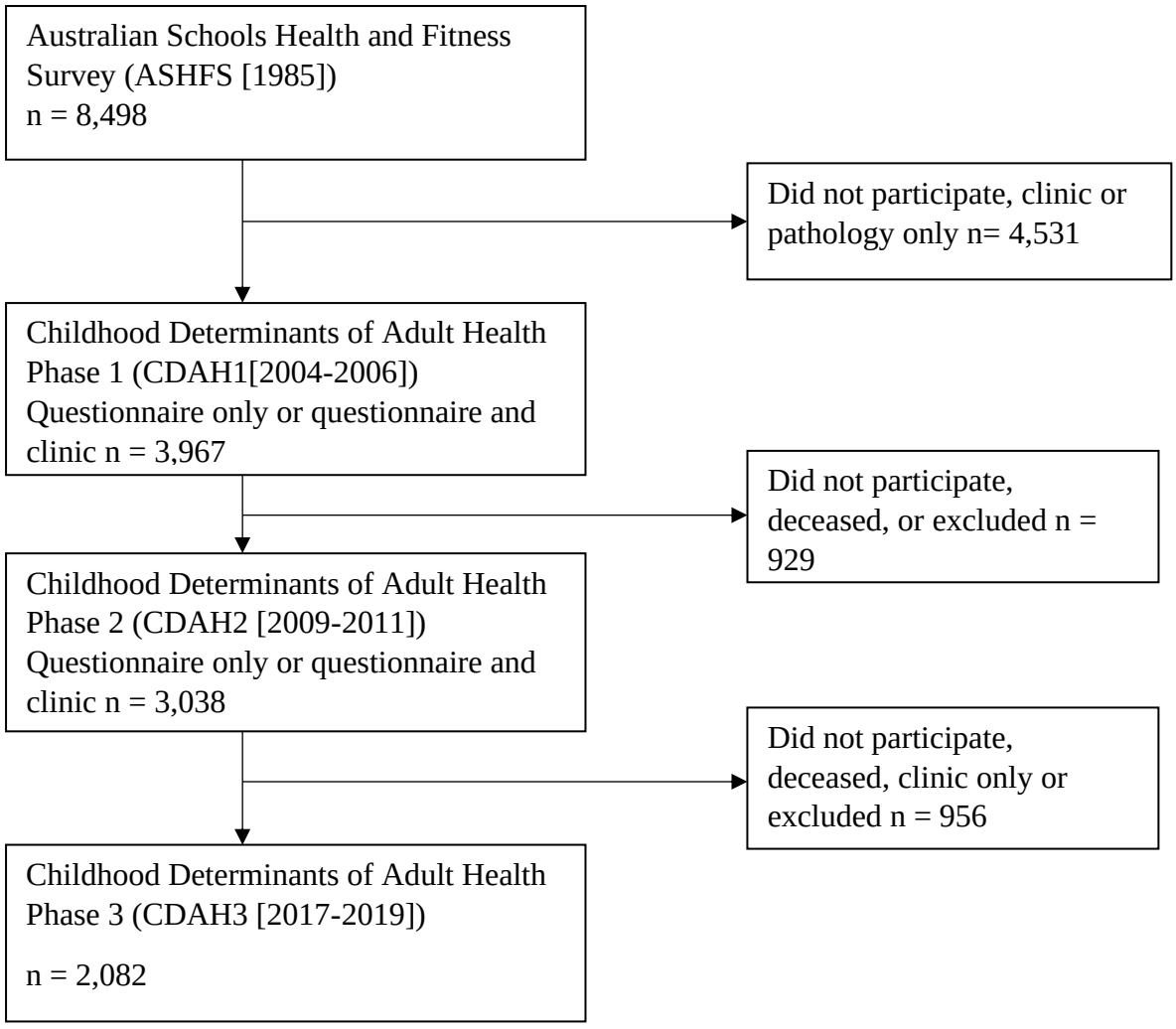


Figure 6-1 Flowchart of participants

Table 6-1 Distribution of derived passive smoking measures

	Descriptive statistics		
Derived measures of passive smoking	**n**	**Range**	**mean (SD)**
Total household smokers*	2,052	0 - 5	0.9 (1.0)
Cumulative years of exposure*	2,051	0 -106	10.5 (13.9)
Severity of exposure index*	2,051	0 - 318	24.4 (36.0)

*Missing data: Total household smokers, n = 31; Cumulative years of exposure, n = 32; Severity of exposure index, n = 32

Table 6-2 Item-to-total correlation (reliability) and Internal consistency of the derived passive smoke exposure variables

Derived exposure variable with constituent component	**Constituent components to derived exposure variables correlation ***	**Coefficient of determination †**	**Cronbach's alpha**
Severity of exposure index			0.70
Cumulative exposure from mother	0.78	0.61	
Cumulative exposure from father	0.79	0.62	
Cumulative exposure from another household smoker one	0.49	0.24	
Cumulative exposure from another household smoker two	0.44	0.19	
Cumulative exposure from another household smoker three	0.36	0.13	
Cumulative exposure from another household smoker four	0.24	0.10	
Cumulative years of exposure			0.70
Years of exposure from mother	0.74	0.55	
Years of exposure from father	0.76	0.58	
Years of exposure from another household smoker one	0.49	0.24	
Years of exposure from another household smoker two	0.49	0.24	
Years of exposure from another household smoker three	0.37	0.14	

Derived exposure variable with constituent component	**Constituent components to derived exposure variables correlation ***	**Coefficient of determination †**	**Cronbach's alpha**
Years of exposure from another household smoker four	0.24	0.10	
Total household smokers			0.75
Mother smokes	0.68	0.46	
Father smokes	0.71	0.50	
Other household member smokes	0.59	0.35	

*** Pearson or Spearman's correlation**

† Square of correlation coefficient

Table 6-3 Intraclass correlation of the CDAH3 measures of passive smoking with similar measures of passive smoking in ASHFS

	Prospective passive smoke exposure (ASHFS)			
	Total household smokers in ASHFS (1985)		**Parental smoking in ASHFS (1985)**	
Retrospective passive smoke exposure (CDAH-3)	**No of observations**	**ICC * 95% CI**	**No of observations**	**ICC * 95% CI**
Total household smokers	1603	0.58 (0.55, 0.61)	1613	0.47 (0.43, 0.51)
Cumulative years of exposure	1604	0.62 (0.59, 0.65)	1613	0.64 (0.61, 0.67)
Severity of exposure index	1604	0.59 (0.56, 0.62)	1613	0.54 (0.50, 0.57)
Parental smoking	1586	0.55 (0.52 0.59)	1596	0.65 (0.62, 0.68)

* Intraclass correlation coefficient

Table 6-4 Descriptive statistics and mean of derived Passive smoke exposure stratified by childhood and adult variables

		Derived measures of passive smoking		
	n (%)	**Total household smokers**	**Cumulative years of exposure**	**Severity of exposure index**
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
Childhood variables				
Sex †				
Male	924 (44.4)	0.9 (1.0)	10.1 (13.7)	22.9 (35.2)
Female	1139 (55.6)	0.9 (1.0)	10.9 (14.1)	25.5 (36.5)
p-value		0.320	0.186	0.112
Age group §				
7 to 9 years	639 (30.7)	0.8 (0.9)	9.1 (12.6)	19.6 (31.1)
10 to 12 years	725 (34.8)	0.9 (1.0)	10.0 (14.0)	23.3 (35.8)
13 to 15 years	718 (34.5)	1.0 (1.0)	12.4 (14.8)	29.7 (39.4)
p-value		**0.002**	**<0.001**	**<0.001**
Socioeconomic status *§				
High	449 (27.9)	0.9 (1.0)	10.1 (14.2)	23.6 (35.9)
Medium - high	454 (28.2)	0.9 (1.0)	10.2 (13.3)	23.3 (33.8)
Medium - low	606 (37.6)	1.0 (1.0)	11.7 (14.1)	27.6 (37.1)
Low	101 (6.3)	1.0 (1.0)	13.8 (17.4)	33.7 (48.5)
p-value		0.299	**0.035**	**0.012**
Smoking experimentation *§				
None	917 (55.9)	0.8 (0.9)	9.7 (13.8)	22.6 (36.0)
A few puffs	387 (23.6)	1.0 (1.0)	11.4 (13.5)	27.0 (35.9)
Yes, < 10 in my life	137 (8.3)	0.8 (0.9)	10.3 (12.4)	23.9 (32.2)
Yes, > 10 in my life	200 (12.2)	1.3 (1.2)	15.7 (16.1)	37.6 (41.7)
p-value		**<0.001**	**<0.001**	**<0.001**
Adult variables (CDAH-3)				

		Derived measures of passive smoking		
	n (%)	**Total household smokers**	**Cumulative years of exposure**	**Severity of exposure index**
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
Current employment status *§				
Not working	102 (4.9)	1.0 (1.0)	14.0 (19.2)	35.6 (52.0)
Studying	135 (6.5)	1.0 (1.0)	10.9 (13.0)	24.7 (32.7)
Working	1,841 (88.6)	0.9 (1.0)	10.3 (13.6)	23.7 (35.0)
p-value		0.162	**0.033**	**0.006**
Occupation *§				
Occupation type A	1,275 (62.2)	0.8 (0.9)	9.3 (12.7)	20.8 (31.9)
Occupation type B	473 (23.1)	1.0 (1.1)	12.3 (15.3)	29.4 (40.9)
Occupation type C	302 (14.7)	1.1 (1.1)	12.9 (15.8)	30.9 (41.7)
p-value		**<0.001**	**<0.001**	**<0.001**
Smoking status (Adult) *§				
Never	1,186 (60.4)	0.7 (0.9)	8.9 (13.3)	20.1 (33.4)
Former	137 (7.0)	1.4 (1.1)	18.7 (16.7)	45.8 (47.1)
Current	641 (32.6)	1.0 (1.0)	11.5 (13.7)	26.7 (35.6)
p-value		**<0.001**	**<0.001**	**<0.001**

Bold = p-value < 0.05

† t-test

§ The one-way analysis of variance (ANOVA)

*****Missing data: Socioeconomic status, n = 472; Smoking experimentation, n = 441; Current employment status, n = 4; Occupation, n = 32; Smoking status (Adult) = 118

Table 6-5 Convergent and divergent validity of the measures of passive smoking using CDAH-3 and CDAH-1

	Convergent validity						Divergent validity	
Retrospective passive smoke exposure (CDAH-3)	**Participant's smoking status ***		**Forced Expiratory Volume 1 second ****		**Forced Vital Capacity ****		**Physical activity category ***	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**	**r**	**P-value**
Total household smokers	0.15	<0.001	-0.06	0.032	-0.04	0.110	0.01	0.65
Cumulative years of exposure	0.13	<0.001	-0.05	0.054	-0.03	0.237	0.01	0.54
Severity of exposure index	0.14	<0.001	-0.06	0.019	-0.04	0.107	0.01	0.67
Parental smoking	0.13	<0.001	-0.05	0.064	-0.04	0.185	0.01	0.80

*** Spearman's correlation**

**** Pearson or Spearman's correlation**

6.5 Discussion

This study aimed to establish the reliability and validity of a retrospective questionnaire on prolonged passive smoking exposure in childhood. The three derived measures showed good internal consistency and moderate reliability with similar measures reported prospectively in childhood. The three retrospective measures were weakly but significantly correlated in the expected direction with a number of variables suggesting the instrument is valid. The passive smoke exposure questionnaire was therefore found to be reliable and valid in the measurement of prolonged passive smoke exposure.

The retrospective passive smoking measure was found to be reliable. The ICCs were broadly supported by findings in another study with a reference standard using answers from surrogates for the number of years exposed (ICC 0.89), number of smokers at home (ICC 0.79) and childhood exposure severity index (ICC 0.74). [289] While our ICCs were of smaller magnitude, this could reflect the difficulties measuring prolonged exposure with reference standards measured more than 30 years ago. Further, the prospective questions were referenced to the current behaviour within the household, whereas the retrospective questions were across all of childhood. Therefore, complete agreement would be unlikely given the dynamic nature of smoking behaviour over time.

The retrospective passive smoking measures were found to have reasonable validity. Some other investigators validated their self-reported questionnaires on passive smoking with airborne nicotine concentration [283] and cotinine in urine.[282] However, our measures were validated more indirectly with participant's own demographic and health-related factors which included lung function, physical activity, and participant's own smoking. We were validating prolonged passive smoke exposure instead of recent exposure and this cannot be done with cotinine and nicotine concentration measurement. There is no gold standard in measuring

prolonged passive smoke exposure as seen in the use of cotinine measurement in the validation of questionnaires on recent exposure to passive smoking.[282] Our reference standards for convergent validity were selected because they have been associated with sustained or prolonged passive smoking exposure, for example, decrease in lung function.[296] Also, exposure to parental smoking in childhood increased the risk of being current smoker in adulthood.[297]

6.5.1 Limitations

There is no 'gold standard' measure of prolonged passive smoke exposure that we could use to validate the instrument. Questions on passive smoking were asked differently for the two periods. In ASHFS participants were asked "Does your mother/father smoke at home?" while in CDAH3 they were asked "Was your mother/father ever a regular smoker". Although subtle, these differences in the questions may have affected recall of smoking status and therefore the assessments of reliability.

6.5.2 Strengths

Our sample is relatively large and contained a range of factors with which to validate the prolonged passive smoking exposure questionnaire. The cohort showed heterogeneity with regards to the passive smoke exposure and the variables used to examine validity.

6.6 Conclusion

There was evidence of reliability and validity for the passive smoking instrument suggesting it can be used to measure prolonged passive smoking. Our finding supports the use of exposure from different close contacts, years of exposure and the intensity of exposure to represent passive smoke exposure across childhood. These holistic data on this exposure will be useful to understand of the frequency, determinants, and outcomes of passive smoking exposure.

6.7 Appendix 6.A. Additional Methods

Questions asked in CDAH3 questionnaire include exposure to parental smoking as follows.

We are interested in your exposure to passive smoke during childhood.

16. How old were you when you moved out of home? ☐☐ years of age

Think about people you lived with up to this age.

17. Was your mother ever a regular smoker?

O Yes

O No --> **Skip to Question 18**

O Don't know --> **Skip to Question 18**

17a. Did you live with your mother most of the time? O Yes O No

17b. How many years during this time did your mother smoke? ☐☐

Did your mother smoke:

17c. Inside the house? O Never O Sometimes O Always

17d. Inside the car? O Never O Sometimes O Always

18. Was your father ever a regular smoker?

O Yes

O No --> **Skip to Question 19**

O Don't know --> **Skip to Question 19**

18a. Did you live with your father most of the time? O Yes O No

18b. How many years during this time did your father smoke? ☐☐

Did your father smoke:

18c. Inside the house? O Never O Sometimes O Always

18d. Inside the car? O Never O Sometimes O Always

Similarly, like for parents, questions on duration of smoking and whether the smoking was inside the house were administered regarding other household members as follows.

19. Was any other household member (e.g. brother, sister) during this time a regular smoker?

O Yes

O No **--> Skip to Section F**

O Don't know **--> Skip to Section F**

		What was his/her relationship to you? e.g. older sister, younger brother	How many years during this time did he/she smoke?	Did they smoke inside the house?		
				Never	Sometimes	Always
19a	Smoker 1		☐☐	O	O	O
19b	Smoker 2		☐☐	O	O	O
19c	Smoker 3		☐☐	O	O	O
19d	Smoker 4		☐☐	O	O	O
19e	Smoker 5		☐☐	O	O	O
19f	Smoker 6		☐☐	O	O	O

CHAPTER 7: Prolonged Childhood Exposure to Passive Smoke is associated with Cardiovascular function in Mid-Adulthood

7.1 Abstract

Background

There are few studies of prolonged childhood passive smoke exposure on cardiovascular function. We examined the association between passive smoke exposure during childhood with cardiovascular function in adults.

Methods

Participants, aged 36-49 years, were from the third follow-up of the Childhood Determinants of Adult Health (CDAH) (2014-19). Validated retrospective measures of passive smoking in childhood (severity of exposure index [SEI, range: 0-318, mean 24.4 ± 36.0 SD], cumulative years of exposure [CYE, range: 0-106, mean 10.5 ± 13.9 SD], total household smokers [THS, range: 0-5, mean 0.9 ± 1.0 SD]) were from questionnaires. Measures of cardiovascular function included central and peripheral blood pressure and subclinical left ventricular dysfunction detected by global longitudinal strain (GLS). Analyses using linear and log binomial regression were adjusted for age, gender, childhood socioeconomic position, child and adult smoking status, and parental education level.

Results

Among 2,082 participants (mean age 45.1 ± 2.5 SD years, 55.6% females, 54.2% ever exposed to passive smoking in childhood), central systolic blood pressure increased by 0.64mmHg (95% CI 0.004, 1.27) per SD of severity of exposure index and by 0.75mmHg (95% CI 0.11, 1.40) for each household smoker in childhood. GLS decreased (βadjusted -0.13% 95% CI -0.25%, 0.0003%) per SD of cumulative years of exposure.

Conclusion

Prolonged childhood exposure to passive smoke exposure, independent of own smoking, was associated with higher adult central systolic blood pressure and lower GLS in mid-adulthood.

7.2 Introduction

Passive smoking is still prevalent in our communities and affects a diverse range of the population. A World Health Organisation summary of data from 192 countries showed that globally 40.0% of children, 33.0% of adult male non-smokers and 35.0 % of adult female non-smokers around the world were exposed to passive smoking.[159] Due to this level of exposure, passive smoke exposure in children accounted for 61.0% of total disability-adjusted life-years (DALYs) and 28.0% of premature deaths.[159] According to a systematic review, public smoking bans have reduced the extent of passive smoking at home in children through reduction in smoking in many regions, however, there has been an increase in a some places (e.g. Spain and Hong Kong).[298]

Development of cardiovascular diseases is a gradual process, that follows a constellation of pathways over many years.[221] As a result, most cardiovascular events occur in old age. The early life environment during childhood is recognised as an important factor in this pathway. The association between cardiovascular risk factors in childhood and cardiovascular structure and function in early adulthood may portray a level of susceptibility to premature cardiovascular diseases.[299, 300] One risk factor from childhood that appears to confer risk to cardiovascular health into adulthood is passive smoking. Compared with children not exposed to passive smoking, those exposed had thicker carotid intima-media thickness,[52, 192, 301] reduced flow-mediated dilatation of the brachial artery,[189] higher risk of carotid atherosclerotic plaque,[191] and a higher odds of atrial fibrillation[193] in studies with follow-up into adulthood. Blood pressure is also an important cardiovascular risk factor. Some studies restricted to childhood have found that exposed children have higher systolic and diastolic blood pressure than those not exposed.[185, 302] Similarly, a number of studies have shown that adults exposed to passive smoke more often have hypertension.[303, 304] However, no studies have examined the association of childhood passive smoke exposure on adult blood pressure.

One study has suggested passive smoke exposure in childhood is associated with cardiac health in adulthood. The authors reported that exposed children had increased left ventricular ejection fraction, left atrial volume index and reduced left ventricular global longitudinal strain (GLS) compared to children who were not exposed after outcomes were measures at 45 years of age and above.[305] This is supported by evidence in adults exposed to passive smoke who have higher mean left ventricular mass and lower right ventricular stroke volumes[306] and left atrial diameters than those not exposed.[307] Further examination of the association between passive smoke exposure in early life and cardiac function are warranted.

Most of the reported associations between childhood passive smoke exposure on markers of adult cardiovascular health remain independent after adjustment for adult gender, age and smoking status. However, these existing studies are limited by measurement of exposure to parental smoking only, [52, 185, 189, 191] self- reported outcomes, [193] cross-sectional analysis, [185, 193] low response sample proportion[192] or, in the case of blood pressure and cardiac structure or function, a limited number of studies.

Using data from the longitudinal Childhood Determinants of Adult Health (CDAH) study that seeks to understand the contribution of childhood risk factors on adult cardiovascular health, we aimed to examine the long-term association of prolonged passive smoking exposure during childhood on left ventricular dysfunction and blood pressure measured 34 years later in mid-adulthood.

7.3 Methods

Study participants

Participants were from the Childhood Determinants of Adult Health (CDAH) study. These participants were initially part of the Australian Schools Health and Fitness Survey (ASHFS) in 1985 which included 8498 children, aged 7 -15 years.[288] CDAH involved a follow up of this

cohort and this has been conducted three times. The first follow up was in 2004-6 (CDAH-1 [26-36 years]), while the second was in 2009 – 2011 (CDAH-2 [31-43 years]) and 2014-2019 (CDAH-3 [36-49 years]) was the third. In the most recent follow up (CDAH-3), a total of 2,082 members of the cohort participated. The Tasmania Health and Medical Human Research Ethics Committee approved the ASHFS and CDAH study and participants provided written informed consent.

Exposure to passive smoking during childhood

The CDAH-3 questionnaire asked participants to complete information on passive smoking exposure during childhood, retrospectively. This included the number of household smokers (mother, father, and other household members), venue of the exposure (car and house), and the duration in years when the exposure occurred. Subsequently, three measures of passive smoking were derived based on a suggested conceptual framework[289] and truncated to the age at which participants moved out of their parents' home. These measures were validated in chapter 6 of this thesis.

Severity of exposure index (SEI): Each participant answered questions on the years of exposure and the frequency of exposure to tobacco smoke inside their house from all regular smokers. The frequency 'Never', 'Sometimes' and 'Always' were scored as '1', '2' and'3' respectively. Severity of exposure index was derived by the multiplication of the years of exposure from each household smoker and frequency of exposure. The summation of all scores for each participant were termed severity of exposure index.

Cumulative years of exposure (CYE): This represents the total number of years of exposure to all household smokers.

Total household smokers (THS): This represents the total of household smokers participants lived in the same house with across their childhood.

Process of validation showed a moderate agreement between these three retrospective measures of passive smoking and participant's total household smokers in ASHFS with intraclass correlation coefficient of between 0.58 to 0.62 despite more than 34 years difference between when both data were collected.

Cardiovascular function

Outcome measures included left ventricular function and central and peripheral blood pressure.

Three readings of peripheral systolic and diastolic blood pressure were obtained from a Omron Hem 907 Digital Automatic Blood Pressure Monitor and appropriately sized Omron cuff according to participant's arm circumference. Participants had rested, were sitting comfortably for five minutes before these measures were taken from their right arm and with an interval of a minute between the three readings. The average of the three readings was used as the peripheral systolic and diastolic blood pressure for each participant. A SphygmoCor 8.1 device (AtCor Medical, Sydney, NSW) was used for central blood pressure after the measurement of peripheral blood pressure using the left arm. Central blood pressure predicts cardiovascular risk better,[223] though clinically peripheral blood pressure is used for treatment. Central systolic and peripheral systolic blood pressure varies in the same individual but central diastolic and peripheral diastolic blood pressure usually remain similar.[308] Blood pressure in childhood has been associated with preclinical markers of cardiovascular disease in adulthood.[222]

Siemens Acuson SC2000 ultrasound machine and 4V1c transducer was used for two-dimensional measurement of subclinical left ventricular dysfunction detected by global longitudinal strain (GLS) at high frame rates (50-70 fps). Participants were made comfortable on their left lateral side with the upper body slightly elevated and their left arm under their head which allowed the heart to be scanned in the correct plane. Subsequently, the two-dimensional measurement of GLS was processed with off-line software (Velocity Vector Imaging VB10D,

Siemens) through speckle-tracking analysis. GLS is the measurement of the shortening (systole) and lengthening (diastole) longitudinally of the myocardium of the right and left ventricle (more commonly measured) during cardiac cycle. The values are applied in systole and so the values are in the negative.[309] GLS was derived from the 4-chamber and 2-chamber views. Readings of -21.0% (-19.2% to -22.7%) is considered to be normal range with higher values being better.[310] There were multiple sonographers that took the echocardiography images in clinics, but a single experienced cardiac sonographer took all measurements from images. GLS has been suggested to relay early changes in systolic function and provide information on continuing risk of cardiovascular morbidity in the general population.[224, 225]

Confounding factors

A range of factors were considered as confounders because they are associated with exposure to tobacco smoke in childhood and cardiovascular health in adulthood.

Baseline – ASHFS in 1985

Baseline measures included gender (male and female), age, childhood socioeconomic status according to the relative disadvantage of their postcode of residence categorized into quartiles and childhood smoking. Childhood smoking was recorded based on the question "how many cigarettes have you smoked in the last 7 days?".

CDAH-1 in 2004-06

Measure includes parental education level based on three categories 1 for higher degree, post-graduate diploma, Bachelor's degree, 2 for undergraduate diploma, associate diploma, skilled and basic vocational training and 3 for secondary school only.

CDAH-3 in 2014-19

Measures included smoking status in adulthood categorized as smokers and non-smokers based on standard questions.

Statistical analysis

Linear regression was used to examine the association between passive smoking exposure and central and peripheral blood pressure and GLS. Log binomial regression was used to examine the association between passive smoke exposure variables and categories of left ventricular dysfunction (GLS). GLS of -18% was considered as the lower limit of normal and so -18% and above was used as cut off for the categorization.[310] The analyses were performed separately for each of the derived measures of childhood passive smoke exposure with SEI presented per standard deviation, CYE per standard deviation and THS per smoker in the household. There were no interactions were between passive smoking measures and other confounders. Two models are presented. Model 1 was adjusted for age and gender and model 2 for age, gender, childhood socioeconomic position, childhood smoking, adult smoking status, and parental education level. Ten imputations using chained equations with variables age, sex, state of residence in Australia, scholastic level assigned by school, waist circumference, height, weight, standing long jump (centimetre), and number of push-ups completed from childhood that had completed data were performed to replace data missing at random on childhood socioeconomic status, childhood smoking, parental education and adult smoking status.

Sensitivity analysis was performed comparing ASHFS sample to participants with outcome measures in CDAH-3 to identify if there were differences in terms of gender, age group, state of residence in Australia, waist circumference, height, weight and standing long jump range during childhood between both. All analyses were conducted with Stata version 16 (StataCorp, TX, USA) and P values < 0.05 were considered as statistically significant.

7.4 Results

There were 2,082 participants that participated in CDAH-3, but fewer than the total had readings for central and peripheral systolic and diastolic blood pressure and global longitudinal strain (Figure 7-1). Compared to those that did not participate in CDAH-3, participants were more often females than males, of medium-low socioeconomic position during childhood, and mostly non-smokers in adult age (Table 7-1). Severity of exposure index ranged from 0 – 318, cumulative years of exposure from 0 - 106 and total household smokers from 0 – 5. About 54.2% of participants were exposed to passive smoking across childhood.

Central systolic blood pressure was 0.64 mmHg (95% CI 0.004, 1.27) higher per standard deviation (SD) of SEI (Figure 7-2) independent of age, gender, childhood socioeconomic position, childhood smoking and adult smoking status and parental education level. Central systolic blood pressure was 0.66 mmHg (95% CI 0.04,1.27) higher per SD of CYE in exposed participants in model 1 but did not remain significant after further adjustment in model 2. There was a 0.75mmHg (95% CI 0.11, 1.40) higher central systolic blood pressure per smoker in the household in model 2. No relationship was observed between passive smoke exposure and central diastolic blood pressure per SD of SEI and CYE. However, central diastolic blood pressure was 0.57 mmHg (95% CI 0.07, 1.07) higher per smoker in the household in model 1 but not statistically significant in model 2.

There were no significant associations between peripheral systolic and diastolic blood pressure for SEI and CYE. While there was a significant increase in peripheral systolic blood pressure and diastolic blood pressure in model 1 per smoker in the household (Figure 7-3), the relationship was found to be non-significant in model 2.

GLS was associated with cumulative years of exposure to passive smoke but not significantly associated with SEI or THS (Figure 7-4). Of note is that the magnitude of the decrease in GLS

was same in model 1 (β -0.13% 95 CI -0.25, -0.002) and model 2 (β -0.13% 95 CI -0.25, 0.0003) per SD of CYE. Additionally, there was an increased risk of having GLS below -18% per THS. (Appendix 7.A Table 7-2).

Sensitivity analysis comparing participants with outcome measures in CDAH-3 and the rest of ASHFS sample did not show any proportional differences or difference in mean between both samples in terms of sex, age group, state of residence in Australia, waist circumference, height, weight and standing long jump range during childhood (Appendix 7.A Table 7-3).

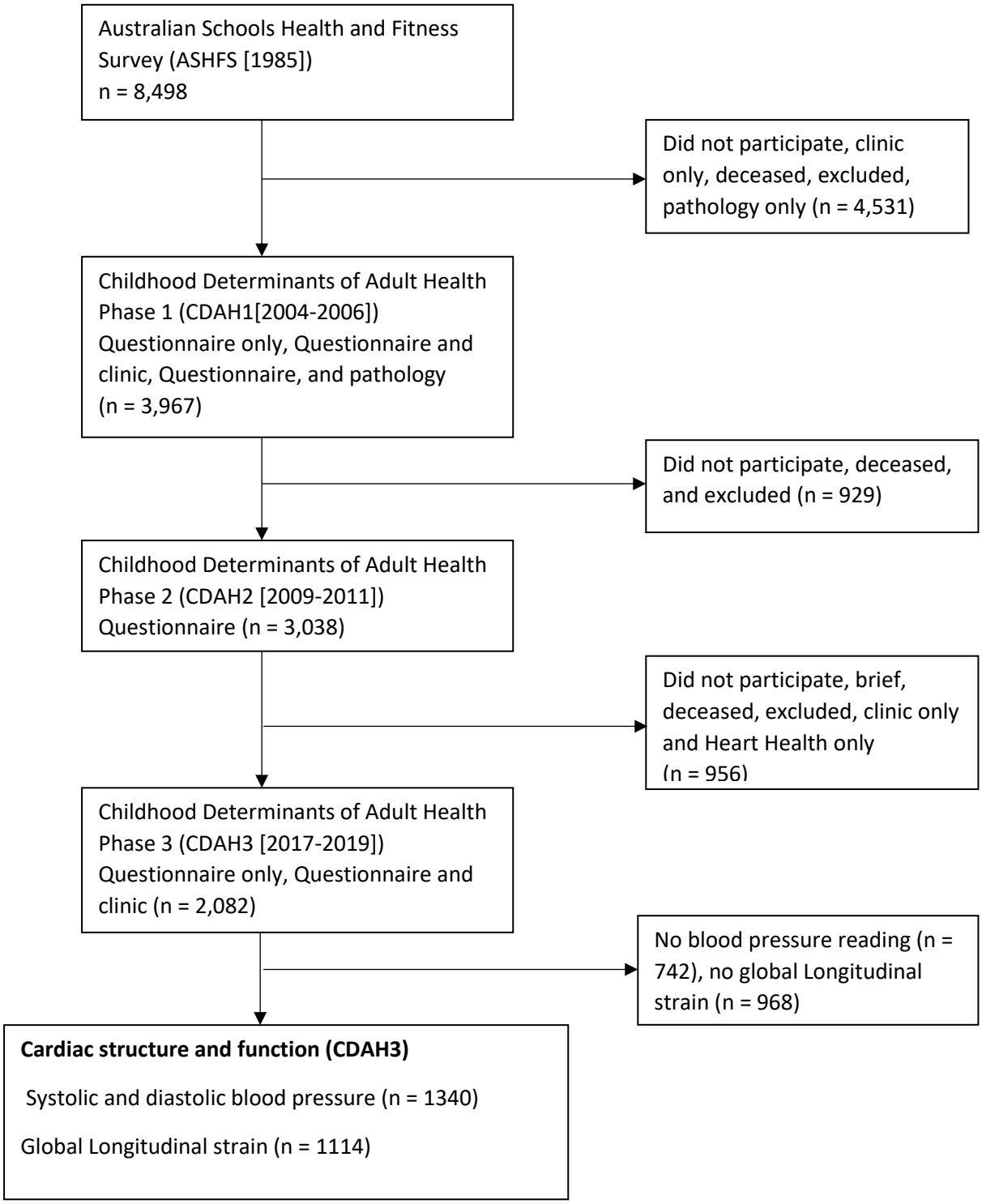


Figure 7-1 Flowchart of participants

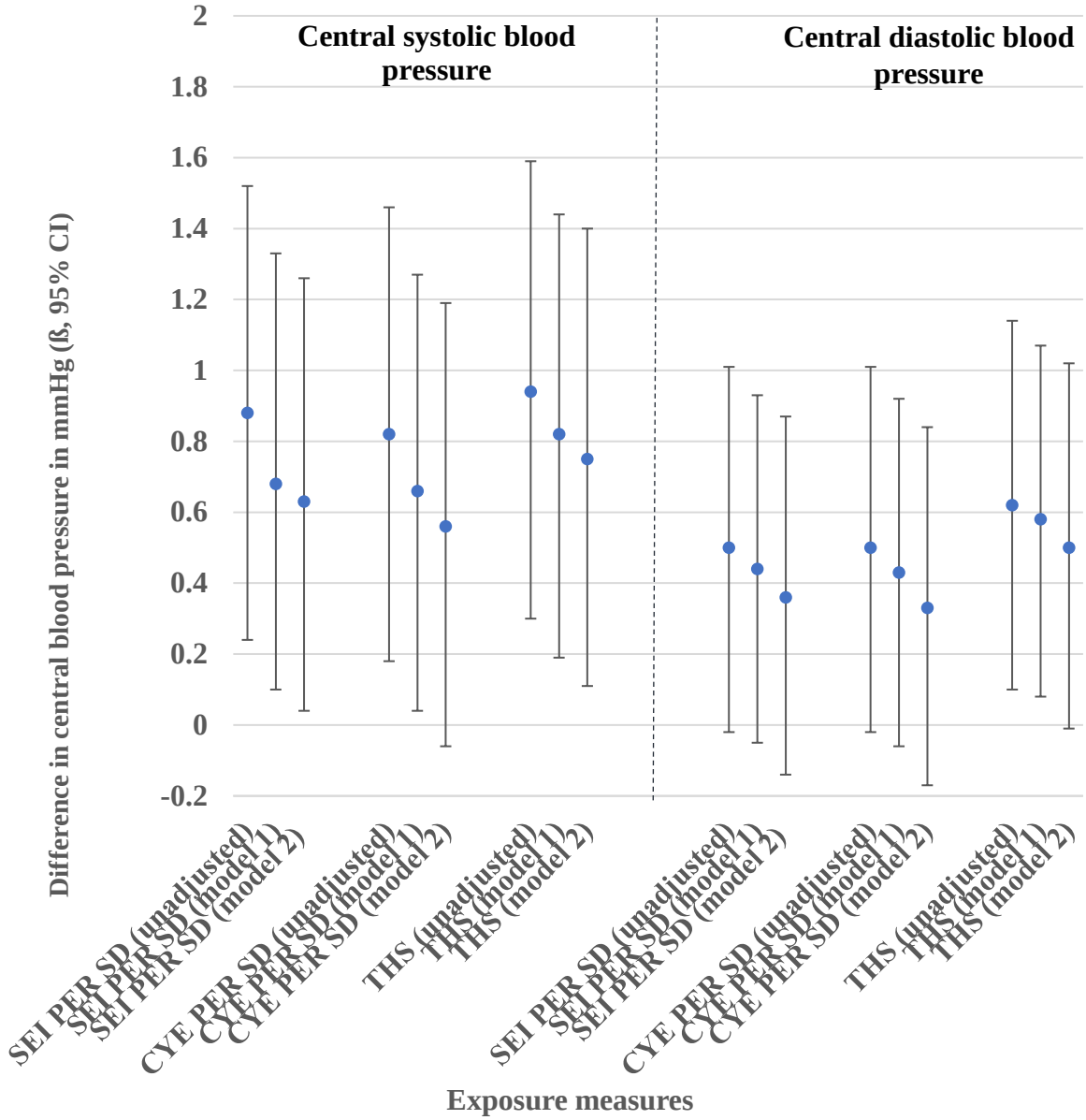
Table 7-1 General characteristics of the participants

Characteristics	**n**	**Mean / (%)**	**SD**
Age (years)	2,082	45.1	± 2.5
Sex			
Male	924	(44.4)	
Female	1,159	(55.6)	
Childhood characteristics			
Childhood smoking (mean number of cigarettes smoked) *	1,639	1.6	± 9.8
Childhood Socioeconomic position*			
High	449	(27.9)	
Medium-High	454	(28.2)	
Medium-low	606	(37.6)	
Low	101	(6.3)	
Passive smoking measurement in childhood			
Severity of exposure index* (range: 0 - 318)	2,051	24.4	± 36.0
Cumulative years of exposure*(range: 0 - 106)	2,051	10.5	± 13.9
Total household smokers* (range: 0-5)	2,052	0.9	± 1.0
Adulthood characteristics			
Adult smoking status*			
Non-smoker	1,206	(60.7)	
Smoker	780	(39.3)	

Characteristics	n	Mean / (%)	SD
Adult blood pressure measurement* (mmHg)			
Central systolic blood pressure	1,340	108.0	± 11.8
Central diastolic blood pressure	1,340	75.5	± 9.5
Peripheral systolic blood pressure	1,340	119.0	± 12.9
Peripheral diastolic blood pressure	1,340	74.7	± 9.4
Global longitudinal strain* (%)	1,114	20.2	± 2.3

* Missing data: Childhood smoking, n = 443; Childhood Socioeconomic position, n = 472; Severity of exposure index = 31; Cumulative years of exposure, n = 31; Total household smokers, n = 30; Adult smoking status, n = 96; Adult blood pressure measurement, n = 742; Global longitudinal strain, n = 968.

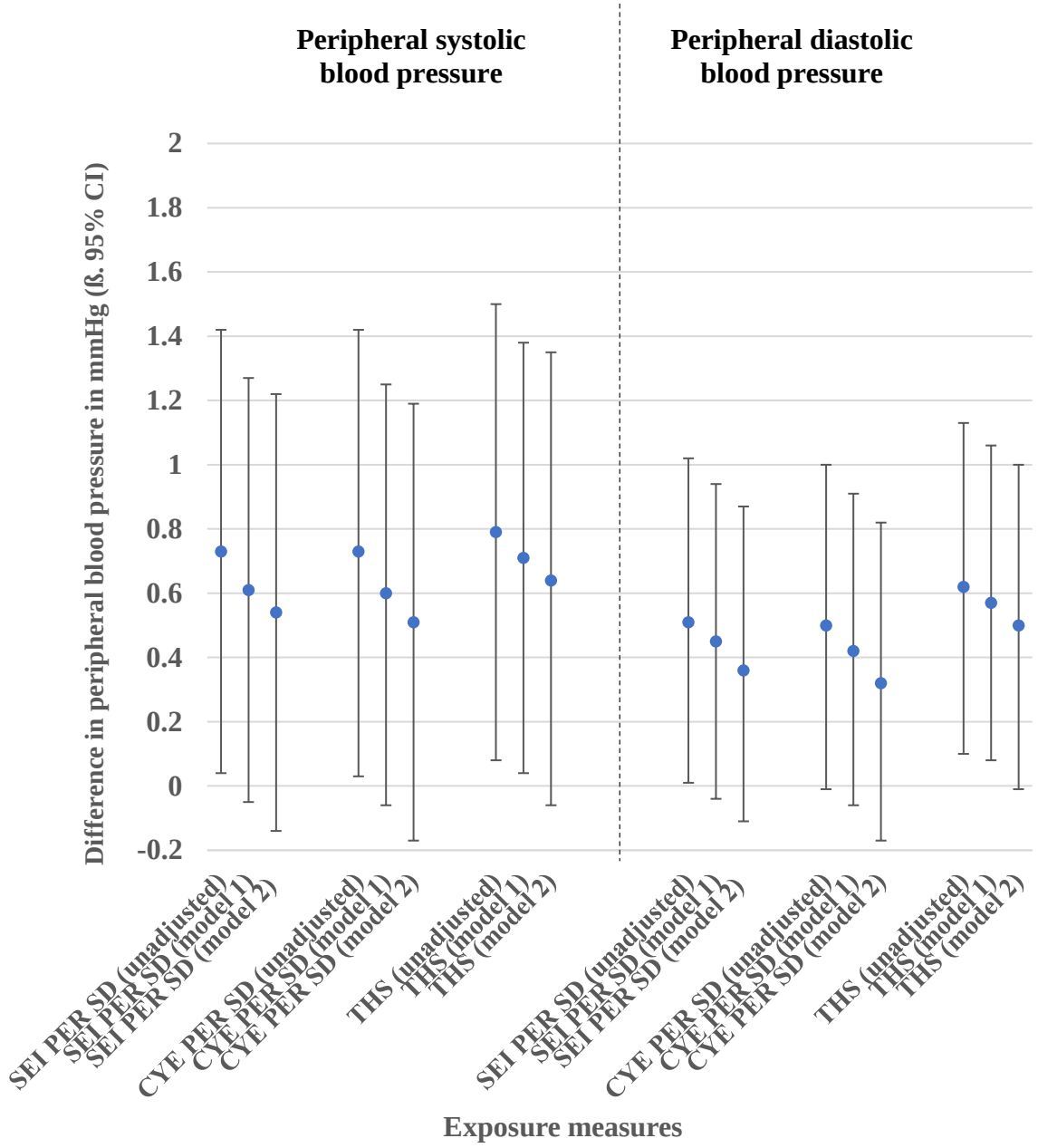
Figure 7-2 Relationship between central systolic and diastolic blood pressure at adult age with passive smoke exposure in childhood



SEI: Severity of exposure index
CYE: Cumulative years of exposure
THS: Total household smokers

Model 1: Adjusted for age and gender
Model 2: Adjusted for age, gender, childhood socioeconomic position, childhood smoking and adult smoking status and parental (maternal) education level

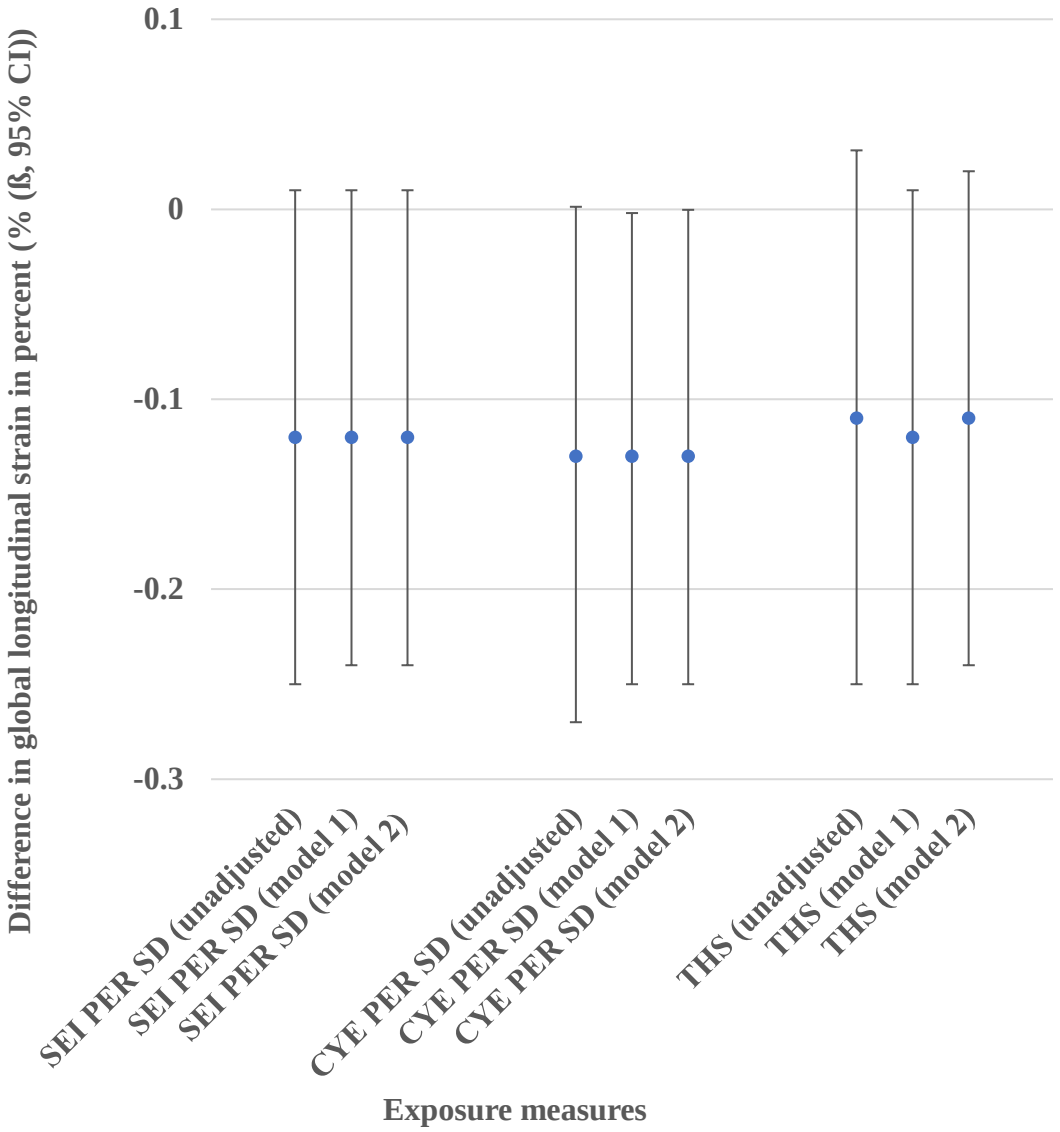
Figure 7-3 Relationship between peripheral systolic and diastolic blood pressure at adult age with passive smoke exposure in childhood



SEI: Severity of exposure index
CYE: Cumulative years of exposure
THS: Total household smokers

Model 1: Adjusted for age and gender
Model 2: Adjusted for age, gender, childhood socioeconomic position, childhood smoking and adult smoking status and parental (maternal) education level.

Figure 7-4 Relationship between global longitudinal strain at adult age with passive smoke exposure in childhood



SEI: Severity of exposure index
CYE: Cumulative years of exposure
THS: Total household smokers

Model 1: Adjusted for age and gender
Model 2: Adjusted for age, gender, childhood socioeconomic position, childhood smoking and adult smoking status and parental (maternal) education level.

7.5 Discussion

This aims of this study were to assess the association of prolonged passive smoking exposure during childhood on cardiovascular function in adulthood. The results indicate that exposure to passive smoke during childhood was associated with higher levels of central systolic and diastolic blood pressure, peripheral systolic and diastolic blood pressure, and lower levels of left ventricular function estimated by global longitudinal strain. This association observed for blood pressure depended on the severity of the exposure and number of smokers within participants household, while the association observed for GLS depended on cumulative years of exposure. Our findings provide support that passive smoking exposure during childhood might lead to long term changes in cardiovascular function into adulthood.

Systolic blood pressure in adulthood was comparatively higher in those exposed to passive smoke during childhood. This finding is supported by a meta-analysis that showed significant increases in systolic blood pressure (pooled coefficient (mmHg) = 0.26; 95% CI: 0.12 to 0.39) in children and adolescents due to passive smoking.[302] The magnitude of the increase in blood pressure in the current study was higher than reported in that analysis. By extrapolation, our findings show that having four household smokers could result in a 3.3 mmHg (central systolic) or 2.8 mmHg (peripheral systolic) increase in blood pressure. In people with cardiovascular risk factors or diseases, central blood pressure has been reported to be significantly higher than peripheral blood pressure compared to healthy people.[308] Cardiovascular risk factors including blood pressure track from childhood to adulthood.[300] While at this stage most participants have not developed hypertension, it has been found that adults exposed to parental smoking in childhood have a 55% higher risk of developing hypertension.[311] To put this in context, each 1 mmHg increase in systolic blood pressure is associated with an 0.8% (male) and 1.2% (female) increase in the risk of cardiovascular diseases namely coronary heart disease, peripheral artery

disease, cerebrovascular events and heart failure.[312] Therefore, the increase in blood pressure associated with exposure to passive smoke in childhood is potentially clinically significant.

Central and peripheral diastolic blood pressure were also increased in the exposed compared to the unexposed group. This is contrary to the finding in a meta-analysis that suggested exposure to passive smoking in childhood did not have any significant effect on diastolic blood pressure.[302] However, our study supports a similar finding of higher diastolic blood pressure in younger children at age 7.5 years due to passive smoking.[185] The number of household smokers participants were exposed to could have been responsible for these difference because our findings were based on total household smokers as opposed to parental smoking. This increase along with the increase in systolic blood pressure may likely be detrimental to cardiovascular health. However, the observed increase in both central and peripheral (0.57 mmHg per THS [model 1]) diastolic blood pressure was lower than the observed increases in the corresponding systolic pressure. Sustained lower increase in diastolic pressure (or higher increase in systolic blood pressure) could result in higher pulse pressure. Higher pulse pressure more than other components of blood pressure has been associated with new-onset atrial fibrillation.[313] Of note is that a higher odds for atrial fibrillation has been observed in children exposed to passive smoking in childhood.[193]

We found that exposure to passive smoking in childhood is associated with adult left ventricular function measured by reduced GLS, as reported by one other study.[305] A similar result has been found in active smokers.[314] This could have some clinical implications as each 1% decrease in GLS has been reported to be associated with 12% higher risk of cardiovascular morbidity and mortality in low-risk general population.[225] As GLS measures left ventricular (LV) longitudinal contraction of the heart, reduction in GLS may be due to an effect of passive smoke exposure on LV myocardial fibres. It could also be due to increase in weight of the LV after prolonged exposure to passive smoking, which was observed in rats.[315] Similarly, the

combination of increase in LV weight and reduced GLS was observed in individuals exposed to biomass fuel for more than 6 months, a fuel that emits a smoke with similar chemical components as seen in tobacco smoke.[316] GLS is considered an initial marker of subclinical cardiac dysfunction and more reliable than 2D ejection fraction in determining left ventricular function.[317] Therefore, a reduction in GLS in our participants may be a marker of subclinical cardiovascular dysfunction that may be associated with vulnerability to developing overt cardiovascular disease later in life.

Our study findings were based on three different conceptual frameworks of measurement of passive smoking and the effect estimates for each exposure measure on the observed outcomes was all similar. However, the findings suggest that total household smoker are a good measure of passive smoking exposure compared to the other more complex measures of exposure. Other studies on adverse effects of passive smoke exposure had similar findings.[52] Any reduction in the number of smokers in a household with children is a positive step with associated positive health benefits in the short and long term. However, that does not diminish the benefits of not smoking inside a room with children, so called 'hygienic smoking', even if the smoker did not quit. Some other studies with non-cardiovascular outcomes have also suggested promoting reducing exposure to children by smoking outside.[246] Nonetheless, we would encourage wherever possible, that researchers capture as many alternative passive smoking exposures including retrospectively.

The limitations include that we could not look at dose-response effect of passive smoking exposure in terms of the number of cigarettes usually smoked in the household, by household members, or in the vicinity of the child because data were not available. There was also no measure of third-hand smoking and of early life exposure (e.g., pre- and post-natal exposure, early childhood). The severity of exposure index is more about duration than frequency, so does not wholly represent intensity of the exposure. This may be responsible for the small

observed effect in some of our outcomes. However, the ability to reliably capture such information, even prospectively, is questionable unless gathered directly from the smoker. There were also some missing data on passive smoking. Fewer participants had detailed sonography (e.g. GLS) due to logistical issues compared with central and peripheral blood pressure. Although there were few differences in participants with and without these measures within the sample followed-up, this could still introduce bias within our results adjusted for limited covariates.

The strengths of the study include that we were able to look at three alternative measures of passive smoking exposure. These validated measures of passive smoking spanned over many years across childhood. We have a comprehensive set of measures of cardiovascular function assessed in adulthood by trained data collectors providing novel associations between childhood passive smoke exposure and adult cardiovascular health.

7.6 Conclusion

There was evidence that passive smoke exposure in children is detrimental to cardiovascular function into adulthood. Interventions to prevent such exposure should continue to be supported by governments, healthcare professionals and the community.

7.7 Appendix 7.A. Additional Results

Table 7-2 Global Longitudinal strain according to exposure to passive smoking in childhood

	Global Longitudinal strain* (n = 1,110)					
	unadjusted† RR (95% CI) (n = 1,110)	**P-value**	**Adjusted† RR (95% CI) Model 1 (n = 1,110)**	**P-value**	**Adjusted†† RR (95% CI) Model 2 (n = 1,085)**	**P-value**
Severity of exposure index (per SD of exposure)	1.08 (0.96, 1.23)	0.209	1.10 (0.97, 1.23)	0.126	1.08 (0.95, 1.22)	0.225
Cumulative years of exposure (per SD of exposure)	1.10 (0.97, 1.24)	0.149	1.10 (0.98, 1.24)	0.101	1.09 (0.96, 1.23)	0.180
Total household smokers in childhood (per smoker)	**1.14 (1.00, 1.30)**	**0.042**	**1.16 (1.03, 1.31)**	**0.015**	**1.15 (1.01, 1.31)**	**0.030**

§ Bold p-value < 0.05 * Categorized as below 18% or from 18% and above

† Adjusted for age and gender.

†† Adjusted for age, gender, childhood socioeconomic position, childhood smoking and adult smoking status and parental (maternal) education level

Table 7-3 Differences in characteristics between participants with study outcome measures and all participants at baseline

	Central and peripheral blood pressure		Global longitudinal strain	
Characteristics	**Yes n (%) / mean ± SD**	**No n (%)/ mean ± SD**	**Yes n (%)/ mean ± SD**	**No n (%)/ mean ± SD**
Sex				
Male	623 (46.5)	3,680 (51.5)	531 (47.7)	3,773 (51.2)
Female	717 (53.5)	3,469 (48.5)	583 (52.3)	3,603 (48.8)
Age group				
7 to 9 years	402 (30.0)	2,503 (35.0)	334 (30.0)	2,571 (34.9)
10 to 12 years	478 (35.7)	2,464 (34.5)	381 (34.2)	2,562 (34.7)
13 to 15 years	460 (34.3)	2,182 (30.5)	399 (35.8)	2,243 (30.4)
Participant's state				
ACT	40 (3.0)	134 (1.9)	30 (2.7)	144 (2.0)
New South Wales	410 (30.6)	2,546 (35.6)	323 (29.0)	2,633 (35.7)
Victoria	332 (24.8)	1,790 (25.0)	309 (27.7)	1,813 (24.6)
Queensland	281 (21.0)	1,208 (16.9)	185 (16.6)	1,305 (17.7)

	Central and peripheral blood pressure		**Global longitudinal strain**	
Characteristics	**Yes n (%) / mean ± SD**	**No n (%)/ mean ± SD**	**Yes n (%)/ mean ± SD**	**No n (%)/ mean ± SD**
South Australia	114 (8.5)	590 (8.3)	109 (9.8)	595 (8.1)
West Australia	130 (9.7)	570 (8.0)	131 (11.8)	569 (7.7)
Tasmania	17 (1.3)	152 (2.1)	14 (1.26)	155 (2.1)
Northern Territory	16 (1.2)	159 (2.2)	13 (1.2)	162 (2.2)
Waist circumference	63.1 ± 7.9	63.7 ± 8.8	63.3 ± 7.9	63.6 ± 8.7
Height	147.4 ± 15.6	145.5 ± 15.4	147.7 ± 15.7	145.5 ± 15.4
Weight	40.2 ± 12.8	39.8 ± 13.1	40.6 ± 13.0	39.8 ± 13.0
Jump	147.1 ± 30.6	142.6 ± 28.6	147.1 ± 30.6	142.6 ± 28.6

CHAPTER 8: Associations between Exposure to Passive Smoking in Early Life and Cardiovascular function in Adulthood

8.1 Abstract

Background

We examined the association of passive smoke exposure during pregnancy, the postnatal period and childhood on cardiovascular function in young adults.

Methods

We analysed data on 96 participants (female: 41.8%, mean age: 27.0 years [SD:0.7]) from the Tasmanian Infant Health Study birth cohort (established 1988-90). Exposure to smoking during pregnancy, the postnatal period, childhood, and early adulthood was self-reported by mothers and children. The relationship between exposure at each period and cumulative exposures with cardiovascular function at 26-28 years was assessed using multivariable linear regression, adjusting for sex, maternal age at birth and infant feeding choice and duration of breastfeeding depending on the outcome.

Results

Exposure to maternal smoking during pregnancy was associated with significantly greater peripheral diastolic blood pressure (β= 3.8 mmHg, 95% CI 0.6, 7.0) in adulthood compared to no exposure. Cumulative exposure to passive smoke over time was associated with a significant decrease in global longitudinal strain (β= -0.4%, 95% CI -0.7, - 0.01) on unadjusted analysis only.

Conclusion

Exposure to tobacco smoke in-utero adversely associates with peripheral diastolic blood pressure in young adulthoods.

8.2 Introduction

Evidence suggests that many children are exposed to passive smoke during pregnancy, infancy, and childhood. A meta-analysis of 295 studies worldwide estimated that 52·9% of pregnant women smoked daily during pregnancy between 1985 and 2016.[62] In childhood, 40% of children globally are estimated to be exposed to passive smoking.[159] There are many potential health effects of this exposure including immediate effects through risk of premature birth [318] and a higher risk of respiratory infections during childhood.[318] There is increasing evidence of longer term effects including early signs of cardiovascular disease in children [118] and adults up to 20 years after the exposure. [189, 190] A greater understanding of the longer-term effects of early life exposure to passive smoking will assist with health policy and promotion efforts, such as inclusion of longer-term effects in awareness campaign messages to reduce children's exposure to passive smoking.

A small number of prospective studies have examined the effects of exposure to passive smoke during gestation, infancy and childhood on the structure and function of the cardiovascular system in children and adults.[52, 112, 118, 189-191] Maternal smoking of 10 or more cigarettes per day during pregnancy was associated with a higher fractional shortening of the left ventricle (the degree of shortening of the left ventricular diameter between end-diastole and end-systole) in childhood. [112] Children exposed to maternal smoking throughout pregnancy have also been found to have higher markers of atherosclerosis,[190] thicker carotid intima media thickness (CIMT) and lower arterial distensibility at 5 years of age [118] and, in a retrospective study among preterm children, higher systolic and diastolic blood pressure in 8 year olds.[184] We previously reported that maternal and paternal smoking exposure during childhood and adolescence is associated with thicker carotid intima media thickness,[52] reduced flow-mediated dilatation of the brachial artery[189] and higher risk of carotid atherosclerotic plaque[191] in young adults

independent of classical risk factors such as blood pressure and body mass index in childhood and adulthood.

Exposure to passive smoking may affect later cardiovascular health adult through its effects on childhood or adult body mass index (BMI). Although babies exposed to smoking during pregnancy are, on average, smaller, they are prone to developing obesity in childhood compared to those that are not exposed.[59] It is possible that BMI could partly explain poorer cardiovascular health in individuals exposed to passive smoke across the life course. As this is a potential target to ameliorate the effects of exposure to passive smoke, it should be examined as a potential mediator in studies of passive smoke exposure and cardiovascular health.

We had an opportunity to conduct detailed cardiac echocardiography and other cardiovascular measures in a pilot study of participants from the Tasmania Infant Health Study (TIHS), which was seminal to the identification of Sudden Infant Death Syndrome.[227] The aim of this prospective cohort analysis was to examine the influence of passive exposure to tobacco smoke during pregnancy, the postnatal period and childhood, individually and cumulatively, on cardiovascular function in young adults.

8.3 Methods

Participants were randomly selected from the TIHS, a birth cohort established between January 1988 and March 1990 in Southern Tasmania. In the TIHS, 1435 mothers of eligible infants were interviewed in hospital after delivery and during the postnatal period, with the children later followed up in the 1996 Southern Blood Pressure Study, 1997 Southern High density lipoprotein (HDL)-Cholesterol Study (childhood) and 2004-2005 Tasmanian Bone Study (T-Bone 1) (adolescence) (

Figure 8-1). Individuals who participated in either the 1996 or the 1997 follow up studies (N= 889) formed the basis of our eligible sample. In 2015-16 (adulthood), 429 (48%) members of

the cohort were traced using telephone numbers, electoral roll, and Facebook as a last resort. They were invited to participate in a cardiovascular function assessment with 155 (17% of the eligible sample) providing some data of which 110 (12% of eligible sample) attended clinics. Among the participants, 96 (11%) had full data available. We did not attempt contacting 432 (49%) members of the cohort and 28 (3%) were excluded due to living interstate/overseas, death or incarceration. The Tasmanian Health and Medical Human Research Ethics Committee approved the study (H0014432).

8.3.1 Measurement of passive smoke exposure

Baseline interviews at the hospital (fourth day after birth) and home (from fifth post-natal week) were conducted by research assistants using structured questionnaires adapted to the different settings. A sample of 100 mothers from the same cohort had urinary cotinine (a major metabolite and biomarker of nicotine) assays performed. Concordance with self-reported exposure levels showed that maternal self-reports of smoking in this cohort are reliable.[319]

Maternal smoking during pregnancy was based on responses to a question from the hospital interview: 'How much did you smoke during pregnancy?' Answers were obtained for the first, second and third trimesters as 'nil', '1-10', '11-20', '21-40' and 'above 41' cigarettes per day. Participants were classified as 'No', if not exposed and 'Yes', if exposed in any trimester during pregnancy.

Maternal exposure to passive smoke during pregnancy was based on responses to two questions from the hospital interview: **'**During pregnancy, did you live with people who smoked cigarettes or a pipe? (Yes/No) and 'On average, during pregnancy, how many cigarettes were smoked each day in your presence at home (including visitors)? Responses were not classified by trimesters. Participants were classified as 'No' if they were not exposed or 'Yes' if exposed to tobacco smoke of any other adult.

Maternal smoking during postnatal period was based on responses to two questions from the home interview: 'How many cigarettes do you smoke per day?' (responses: 'nil', '1-10', '11-20', '21-40' and 'above 41' cigarettes per day) and 'How often do you smoke in the same room as the infant?' (responses: 'usually', 'sometimes' and 'never'). Participants were classified as 'No' if not exposed and 'Yes' if exposed at all during the postnatal period through maternal smoking.

Maternal exposure to passive smoke during the postnatal period was based on responses to two questions during the home interview: 'How many other adults in the house smoke?' and 'How many cigarettes do other resident adults in your house smoke, in total, per day? (responses: 'nil', '1–10', '11–20', '21–40' and 'above 41' cigarettes per day). We classified this exposure into two categories of exposure, 'Yes' if exposed to at least one active smoker or 'No' if not exposed.

Exposure to passive smoke in childhood was based on responses to the questions 'How many cigarettes does child's mother smoke per day? (responses: 'nil', '1–10', '11–20', '21–40' and 'above 41' cigarettes per day) and 'How many cigarettes do other adults (excluding mother) in your household smoke, in total, per day? (responses: 'nil', '1–10', '11–20', '21–40' and 'above 41' cigarettes per day) asked during the 1996 Southern Blood Pressure Study and the 1997 Southern HDL-Cholesterol study. Responses were classified into two categories, 'Yes' if exposed by mother/principal carer or any other adult and 'No' if not exposed by either.

Cumulative exposure across all periods was calculated by combining variables indicating exposure to passive smoke at each time-point: maternal smoking during pregnancy or maternal exposure to passive smoking during pregnancy; maternal smoking in the postnatal period or maternal exposure to passive smoking during the postnatal period, childhood, adolescent and adulthood. This resulted in a score from 0 to 5 across the periods of exposure, pregnancy, postnatal period, childhood, adolescence, and adulthood. An alternative cumulative variable

was also derived with 8 time point exposure. The time points included maternal smoking during pregnancy, maternal exposure to passive smoke during pregnancy, maternal smoking during postnatal period, maternal exposure to passive smoke during the postnatal period, exposure to passive smoke in childhood through mother, exposure to passive smoke in childhood through other adults, exposure during adolescence and adulthood. Hence the period of pregnancy, postnatal period and childhood contributed double points depending on whether our participants were exposed by their mother and any other adult in their household.

8.3.2 Measurement of outcomes

Clinics were conducted at Menzies Institute of Medical Research, Hobart, Tasmania. A trained technician blinded to exposure to passive smoke used a Philips Ie33 ultrasound (Philips Medical Systems) to conduct resting echocardiography. A variable-frequency phased array transducer was used for the two-dimensional examinations while a matrix array probe was used for the three-dimensional examinations. After obtaining consent, participants were made comfortable lying down in a left lateral position with head propped up in a lounge. Electrodes were attached to the chest for the measurements. Measures included global longitudinal strain (higher values are better).

Brachial oscillometry measurements were taken using Mobil-O-Graph and Omron HEM907 Digital Automatic Blood Pressure Monitor. Participants were seated then fitted for the correct sized cuff on the left arm. Blood pressure was taken over a period of 5 minutes using the Omron HEM907. Omron HEM907 measures included peripheral systolic and diastolic blood pressure.

8.3.3 Measurement of covariates

A range of covariates were explored from the pre- and postnatal periods including sex, maternal alcohol consumption during pregnancy, maternal age at birth, infant feeding choice at birth, duration of breastfeeding and total household income at birth (Table 8-1). Data were obtained

during the baseline interviews. Participant's adult body mass index (BMI) were derived from their weight and height and considered as a mediator. Adulthood BMI was categorized as normal/underweight (<18.5 and 18.5- 24.99kg/m^2), overweight (25-29.99kg/m^2) or obese (>30kg/m^2).

8.3.4 Statistical analysis

Stata version 15.1 (StataCorp LLC) was used for analysis. We performed multivariable linear regression to examine the association between the passive exposure variables and outcome variables. We present unadjusted models and models adjusted for potential confounding factors based on purposeful model building.[320] For outcomes where there was evidence of an effect of passive smoke exposure, we additionally examined the potential influence of birth weight, childhood, or adult BMI in adjusted models. We handled missing data using multiple imputation by chained equations and imputed three out of the six exposure variables given missing data and all the outcome variables that had missing data (Table 8-1). Maternal smoking during pregnancy, maternal exposure to passive smoke during pregnancy, sex, maternal age at birth, birth weight and infant feeding choice were used for the imputation, and 30 imputations undertaken. We compared the adjusted coefficients of 5-time point categorization of cumulative exposure measure with an alternative 8-time point categorization with similar result. Comparison of the original 1988-1990 TIHS participants and the present participants of our study was performed with chi-square.

8.4 Results

Most of our participants were male, born at term (37 weeks and above), and weighed more than 2,500 grams at birth (Table 8-1). Most mothers of our participants were 26 years of age or older. Compared to participants in the larger TIHS sample, those included in the current study were more often female (43% vs 31%), more often low birthweight (30% vs 21%), were less often

exposed to maternal smoking during pregnancy (38% vs 51%) and during the post-natal period (38% vs 51%).

Exposure to passive smoking during pregnancy, the post-natal and childhood periods

Nearly half of all participants were exposed to passive tobacco smoke during pregnancy through either their mother (38.7%) or another adult (45.8%) (Table 8-1). Only 14% of participants were not exposed to any tobacco smoke indoors from pregnancy and birth to early adulthood.

Relationship between cardiac structure and function and passive smoke exposure

Global longitudinal strain (GLS)

Those exposed to passive smoking during pregnancy, the postnatal and childhood periods had lower GLS, in general, than those not exposed (Table 8-2). The effect was only statistically significant for the unadjusted cumulative exposure model with a reduction in GLS per unit of exposure (β= -0.4% 95 CI -0.7, -0.01).

Peripheral systolic and diastolic blood pressure

In unadjusted analysis, there was evidence of a significant association between maternal smoking during pregnancy and increased peripheral diastolic blood pressure (β= 4.3 mmHg 95% CI 1.0, 7.6) (Table 8-3), which remained in the adjusted model (β = 3.8 mmHg 95% CI 0.6, 7.0).

Role of birth weight and body mass index in associations

Among both, only adult BMI was identified as a potential mediator of the associations between passive smoke exposure and peripheral blood pressures. Peripheral diastolic pressure was reduced from 3.8 mmHg (95% CI 0.6, 7.0) to 3.0 mmHg (95% CI 0.3, 6.4) when adult BMI was added to the adjusted model (Table 8-3 and Appendix 8.A Table 8-4).

Sensitivity analyses

Following multiple imputation for missing data (30 imputations) the results for all cardiovascular function outcomes did not change significantly (Appendix 8.A Table 8-5 and Table 8-6).

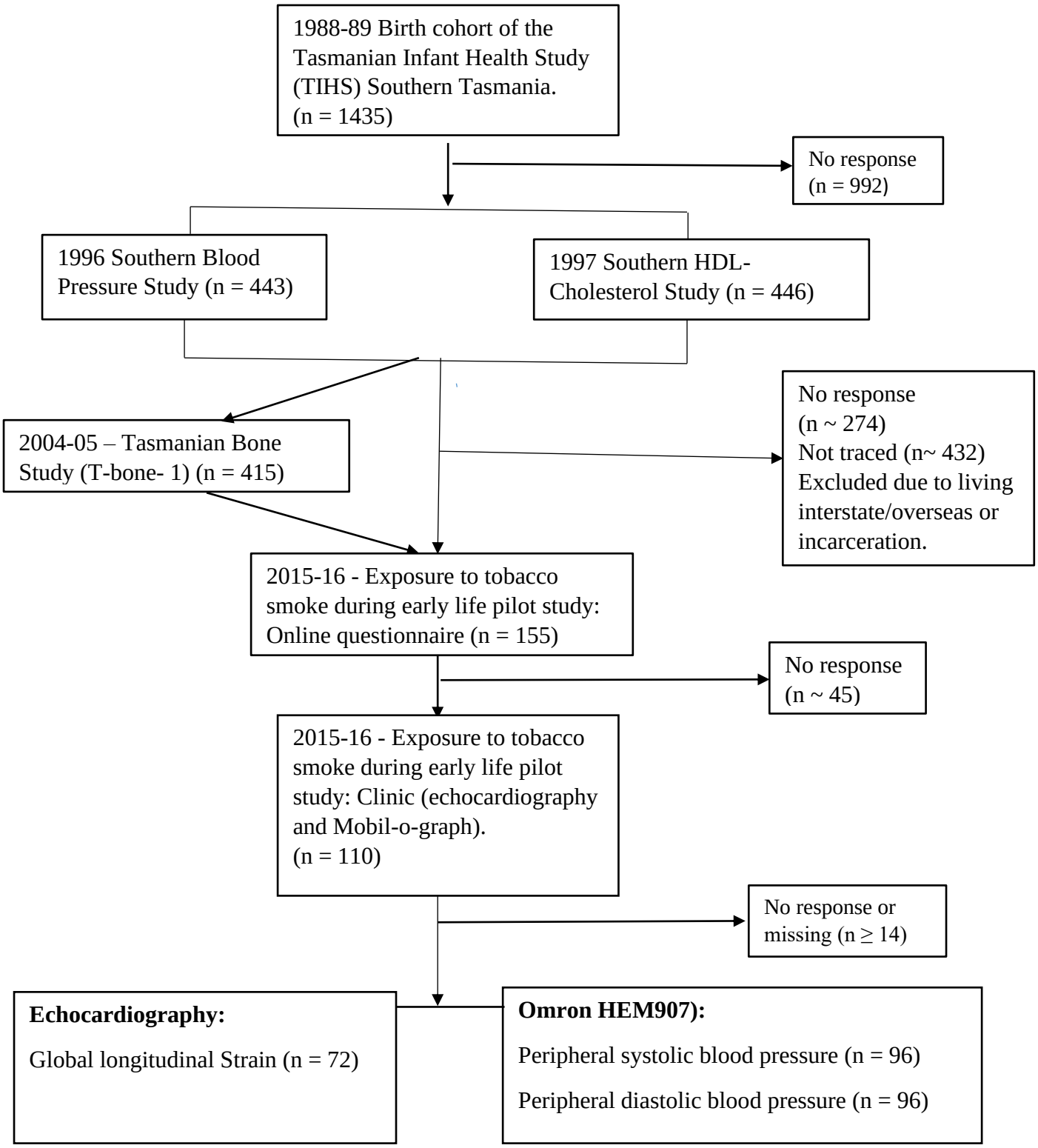


Figure 8-1 Flowchart of study participants

Table 8-1 General characteristics of participants

Characteristics	n	Mean / (%)	SD
Age (years)	155	27.09	0.7
Sex			
Male	88	(56.8)	
Female	67	(43.2)	
Childhood characteristics			
Birthweight			
<2500g	47	(30.3)	
≥ 2500g	108	(69.7)	
Gestational weeks at birth			
Less than 37 weeks	43	(27.7)	
37 weeks and above	112	(72.3)	
Mother's age at birth (years)		27.0	4.7
< 25 years	65	(41.9)	
≥ 26 years	90	(58.1)	
Family income level at birth* (AUD)			
Low (≤AUD 500 per fortnight)	53	(39.8)	
Mid (AUD501 to 750 per fortnight)	56	(42.1)	
High (> AUD 750 per fortnight)	24	(18.1)	
Infant feeding choice			
Formula milk	44	(28.4)	
Breast milk and formula milk	111	(71.6)	
Duration of breastfeeding* (days)			
Not breastfed	36	(25.0)	

Characteristics	n	Mean / (%)	SD
1 to 90 days	108	(75.0)	
Exposure to maternal alcohol intake during pregnancy			
None	88	(56.8)	
Some trimesters	28	(18.1)	
All trimesters	39	(25.1)	
Exposure to passive smoke			
Maternal smoking during pregnancy			
No	95	(61.3)	
Yes	60	(38.7)	
Maternal exposure to passive smoke during pregnancy			
No	84	(54.2)	
Yes	71	(45.8)	
Maternal smoking during postnatal period *			
No	97	(67.8)	
Yes	46	(32.2)	
Maternal exposure to passive smoke during postnatal period *			
No	81	(56.3)	
Yes	63	(43.7)	
Exposure to passive smoke in childhood*			
No	104	(69.3)	

Characteristics	n	Mean / (%)	SD
Yes	46	(30.7)	
Cumulative exposure across all periods (per unit exposure)			
0	22	(14.2)	
1	33	(21.3)	
2	14	(9.0)	
3	32	(20.7)	
4	42	(27.1)	
5	12	(7.7)	
Global longitudinal strain (peak) (%) - Left ventricle*	72	18.7	± 2.5
Peripheral systolic blood pressure (mmHg)*	96	119.7	± 11.0
Peripheral diastolic blood pressure (mmHg)*	96	73.6	± 8.2

***Missing data: Family income level at birth, n= 22; Duration of breastfeeding, n = 11; Maternal smoking during post-natal period, n= 12; Maternal exposure to passive smoke during post-natal period, n= 11; Exposure to passive smoke in childhood, n= 5; Global longitudinal strain, n= 83; Peripheral systolic blood pressure, n= 59; Peripheral diastolic blood pressure, n= 59.

Table 8-2 Relationship between cardiovascular measures (GLS) and passive smoke exposure during pregnancy and early life

Exposure to passive smoking	**Global Longitudinal Strain (%)**	
	Unadjusted	**Adjusted***
	β (95% CI)	**β (95% CI)**
Maternal smoking during pregnancy		
No	Reference	Reference
Yes	-0.8 (-1.9, 0.4)	0.1 (-1.1, 1.2)
Maternal exposure to passive smoke during pregnancy		
No	Reference	Reference
Yes	- 0.4 (-1.6, 0.7)	-0.03 (-1.1, 1.0)
Maternal smoking during post-natal period		
No	Reference	Reference
Yes	-0.6 (-1.9, 0.8)	0.1 (-1.1, 1.4)
Maternal exposure to passive smoke during post-natal period		
No	Reference	Reference
Yes	-0.6 (-1.8, 0.7)	- 0.2 (-1.3, 0.9)
Exposure to passive smoke in childhood		
No	Reference	Reference
Yes	-1.2 (-2.4, 0.03)	-0.5 (-1.7, 0.6)
Cumulative exposure across all periods		
Per unit of exposure	**-0.4 (-0.7, - 0.01)**	-0.2 (-0.5, 0.2)

Bolded values are p<0.05

Exposure to passive smoking	Global Longitudinal Strain (%)	
	Unadjusted	Adjusted*
	β (95% CI)	β (95% CI)

***Adjusted for sex, maternal age at birth and infant feeding choice**

Table 8-3 Association of passive smoke exposure with peripheral systolic and diastolic blood pressure

Exposure to passive smoke	**Peripheral systolic blood pressure (mmHg)**		**Peripheral diastolic blood pressure (mmHg)**	
	Unadjusted β (95% CI)	**Adjusted* β (95% CI)**	**Unadjusted β (95% CI)**	**Adjusted** β (95% CI)**
Maternal smoking during pregnancy				
No	Reference	Reference	Reference	Reference
Yes	4.4 (-0.1, 8.9)	2.6 (-1.6, 6.8)	**4.3 (1.0, 7.6)**	**3.8 (0.6, 7.0)**
Maternal exposure to passive smoke during pregnancy				
No	Reference	Reference	Reference	Reference
Yes	-0.4 (-4.9, 4.1)	0.1 (-3.9, 4.1)	0.5 (-2.8, 3.8)	0.7 (-2.6, 3.9)
Maternal smoking during post-natal period				
No	Reference	Reference	Reference	Reference
Yes	1.3 (-3.5, 6.1)	-0.4 (-4.8, 4.0)	2.4 (-1.1, 5.9)	1.9 (-1.5, 5.3)

Maternal exposure to passive smoke during post-natal period				
No	Reference	Reference	Reference	Reference
Yes	-1.9 (-6.5, 2.7)	-1.8 (-5.9, 2.3)	0.2 (-3.3, 3.6)	0.2 (-3.1, 3.5)
Exposure to passive smoke in childhood				
No	Reference	Reference	Reference	Reference
Yes	-1.1 (-5.7, 3.5)	-2.4 (-6.4, 1.7)	1.6 (-1.8, 5.1)	1.3 (-2.0, 4.6)
Cumulative exposure across all periods				
Per unit exposure	-0.2 (-1.2, 0.8)	-0.4 (-0.2, 1.4)	0.3 (-0.4, 1.0)	0.3 (-0.4, 1.0)

Bolded values are p<0.05

***Adjusted for sex and maternal age at birth.**

****Adjusted for sex**

8.5 Discussion

We examined whether exposure to tobacco smoke during pregnancy and early in life influenced cardiovascular function in young adults. Our findings suggest that exposure to passive tobacco smoke during pregnancy and early life had negative effects on some aspects of the cardiovascular system of young adults. Exposure to maternal smoking during pregnancy was associated with increased central and peripheral diastolic, and to a lesser extent systolic blood

pressure, as well as elevated total peripheral vascular resistance in adulthood. However, there was a substantial decrease in GLS associated with cumulative exposure to passive smoke.

Maternal smoking during pregnancy was associated with a potentially clinically significant increase in peripheral diastolic blood pressure (3.8 mmHg), in adulthood. To put this in context, a 3 mmHg reduction in diastolic blood pressure is estimated to lead to reduction of stroke by approximately a third.[321] Our results are supported by a retrospective study of maternal smoking in pregnancy with follow-up of children at 8 years of age.[111] That study found an increase of 2.9 mmHg in peripheral systolic blood pressure and 0.9 mmHg in peripheral diastolic blood pressure associated with exposure during pregnancy after adjusting for current weight, instrument used, birthweight ratio for gestation, singleton or multiple pregnancy status and social class. [111] Our study found similar changes in peripheral diastolic blood pressure associated with exposure to passive smoke during pregnancy. As individuals tend to maintain their position in the overall blood pressure distribution overtime, [322] people exposed to maternal smoking during pregnancy may be at higher risk of developing hypertension later in life.

There were small effects of exposure to passive smoke during pregnancy and early life on some other measures of cardiovascular function. Our finding of a reduction in GLS of 0.4% (unadjusted) and 0.5% due to cumulative exposure to passive smoke and exposure in childhood is potentially important. A reduction of 1% in GLS magnitude has been reported to be associated with a 11.3% rise in cardiovascular mortality[323] and lower GLS has been suggested as a predictor of cardiovascular events in healthy people.[224] Further examination of these effects in a larger study with greater statistical power are warranted.

There have been some suggestions of the pathway that could account for the effect of exposure to passive smoke exposure during pregnancy and early life on cardiovascular structure and function. Exposure to environmental tobacco smoke, confirmed by serum cotinine

concentrations, has been found to impair the functioning of the endothelial lining of cardiac chambers and vessels in a dose-dependent manner. [324] This impairment may lead to an increase in arterial resistance and a decrease in the diameter of the ascending aorta.[325] It is possible that vascular stiffness with attendant reduced distensibility as a result of exposure to passive smoke could lead to an increase in total vascular resistance[308] and an increase in blood pressure. People who are exposed to tobacco smoke during pregnancy tend to be smaller at birth but are more likely to be obese as they get older.[59] Obesity predisposes people to structural alteration of their small arteries [326] and is a risk factor for hypertension and a range of cardiovascular outcomes.[327] However, our study showed that adjusting for adult BMI only reduced the magnitude of the increase in peripheral diastolic pressure among those exposed to maternal smoking during pregnancy by a small amount. Therefore, the inter-relationship between exposure to maternal smoking during pregnancy and blood pressure appears complex. Indeed, it has also been suggested exposure to tobacco smoke in early life leads to long-lasting "reprogramming" of infant blood pressure control mechanisms.[328] Our study suggests the potential for this reprogramming to lead to increases in blood pressure that may be of clinical significance.

Exposure to passive smoke during pregnancy appeared more detrimental than exposure in other periods in terms of the association with on cardiovascular function. It is therefore possible that this is a sensitive period for exposure. Clinical guidelines recommend using antenatal visits to help every pregnant mother to quit using options suitable to her needs. It is also recommended to continue monitoring at every visit. [329] Presently, in Australia, only one in four women who reported smoking during the early part of their pregnancy quit smoking during their pregnancy.[66] Our study suggests that ongoing smoking during pregnancy will likely lead to negative impacts on the cardiovascular function of their children later in life through both direct and indirect mechanisms.

Limitations

We were limited by the small sample size in this pilot study. Further, participants were young people at an age when cardiovascular disease does not commonly manifest minimising our ability to detect differences. There were significant differences between participants included in the current study and the full TIHS sample.

Strengths

This is a prospective study that used data on passive smoke exposure at several time points and with a long follow up period. Echocardiography allowed us to evaluate subtle changes in cardiovascular function. Together these capabilities allowed us to examine whether any observed effect on cardiac structure and function was due to cumulative exposure or exposure to passive smoke at particular period in time. Although the sample was small there was heterogeneity in the exposure, outcomes, and covariates.

8.6 Conclusion

This study observed that exposure to smoking during pregnancy and early life lead to subtle negative effects on cardiovascular health in adulthood. Smoking during pregnancy appeared particularly detrimental, necessitating a focus on measures to help pregnant women to quit smoking.

8.7 Appendix 8.A. Additional Results

Table 8-4 Relationship between Central and peripheral systolic and diastolic blood pressure, and passive smoke exposure during pregnancy and early life with Body mass index added to the adjusted model

Exposure to passive smoking	Peripheral systolic blood pressure	Peripheral diastolic blood pressure
	Adjusted*	**Adjusted****
	β (95% CI)	**β (95% CI)**
Maternal smoking during pregnancy		
No	Reference	Reference
Yes	1.6 (-2.8, 5.9)	**3.0 (0.3, 6.4)**
Maternal exposure to passive smoke during pregnancy		
No	Reference	Reference
Yes	-0.6 (-4.6, 3.5)	0.01 (-3.2, 3.2)
Maternal smoking during post-natal period		
No	Reference	Reference
Yes	- 1.2 (-5.6, 3.3)	1.4 (-2.1, 4.9)
Maternal exposure to passive smoke during post-natal period		
No	Reference	Reference
Yes	-2.3 (-6.5, 1.8)	-0.3 (-3.6, 3.0)
Exposure to passive smoke in childhood		
No	Reference	Reference
Yes	-3.2 (-7.3, 0.9)	0.7 (-2.7, 4.0)
Cumulative exposure across all periods		
Per unit exposure	-1.0 (-2.3, 0.2)	0.1 (-1.0, 1.1)

***Adjusted for sex, maternal age at birth and adult body mass index**

**** Adjusted for sex and adult body mass index**

Table 8-5 Association using multiple imputation of missing data for Global longitudinal strain.

Exposure to passive smoking	**Global longitudinal strain (%)**	
	Unadjusted β (95% CI)	**Adjusted* β (95% CI)**
Maternal smoking during pregnancy		
No	Reference	Reference
Yes	-0.48 (-1.58, 0.61)	0.22 (-0.85, 1.30)
Maternal exposure to passive smoke during pregnancy		
No	Reference	Reference
Yes	-0.31 (-1.49, 0.85)	-0.15 (-1.25, 0.93)
Maternal smoking during post-natal period		
No	Reference	Reference
Yes	-0.38 (-1.54, 0.76)	0.25 (-0.86, 1.36)
Maternal exposure to passive smoke during post-natal period		
No	Reference	Reference
Yes	-0.31 (-1.55, 0.92)	-0.25 (-1.40, 0.90)
Exposure to passive smoke in childhood		
No	Reference	Reference
Yes	-1.02 (-2.11, 0.05)	-0.37 (-1.44, 0.69)
Cumulative exposure across all periods		
Per unit exposure	-0.15 (-0.38, 0.07)	-0.06 (-0.29, 0.15)

Exposure to passive smoking	Global longitudinal strain (%)	
	Unadjusted β (95% CI)	Adjusted* β (95% CI)

Bolded values are p<0.05

***Adjusted for sex, maternal age at birth and infant feeding choice.**

Table 8-6 Association using multiple imputation of missing data for peripheral systolic and diastolic blood pressure.

Exposure to passive smoke	**Peripheral systolic blood pressure**		**Peripheral diastolic blood pressure**	
	Unadjusted β (95% CI)	**Adjusted* β (95% CI)**	**Unadjusted β (95% CI)**	**Adjusted** β (95% CI)**
Maternal smoking during pregnancy				
No	Reference	Reference	**Reference**	**Reference**
Yes	4.1 (-0.3, 8.4)	2.5 (-1.6, 6.7)	**4.2 (0.9, 7.5)**	**3.9 (0.6, 7.1)**
Maternal exposure to passive smoke during pregnancy				
No	Reference	Reference	Reference	Reference
Yes	0.1 (-4.1, 4.3)	-0.3 (-4.2, 3.6)	0.2 (-3.0, 3.4)	0.2 (-2.9, 3.3)
Maternal smoking during post-natal period				
No	Reference	Reference	Reference	Reference
Yes	0.5 (-4.2, 5.2)	-0.6 (-5.1, 3.9)	2.1 (-1.6, 5.7)	1.9 (-1.7, 5.5)
Maternal exposure to passive smoke during post-natal period				

No	Reference	Reference	Reference	Reference
Yes	-2.0 (-6.1, 2.1)	-2.0 (-5.8, 1.9)	-0.1 (-3.3, 3.0)	0.04 (-3.1, 3.2)
Exposure to passive smoke in childhood				
No	Reference	Reference	Reference	Reference
Yes	-0.4 (-4.7, 3.9)	-2.3 (-6.3, 1.7)	1.4 (-1.9, 4.7)	0.9 (-2.3, 4.1)
Cumulative exposure across all periods				
Per unit exposure	-0.1 (-1.0, 0.7)	-0.4 (-1.2, 0.5)	0.3 (-0.4, 1.0)	0.3 (-0.4, 0.9)

Bolded values are p < 0.05.

***Adjusted for sex and maternal age at birth.**

****Adjusted for sex**

CHAPTER 9: Summary, implications, and future directions

9.1 Introduction

Exposure to passive smoking during pregnancy and passive smoking during childhood remain huge public health issues more than 20 years into the 21st century. Peer-reviewed studies have reported declines in passive smoking exposure during pregnancy[75, 86] and childhood[167, 169] including in Australia. And that this decline has been very gradual over the years from 1978 to 2015, with no change in exposure to passive smoking during pregnancy reported for some years in some places like Finland.[79]

Children are particularly vulnerable to the adverse health effects associated with exposure to passive smoking, and the number of reported adverse effects through to adulthood is growing. However, awareness of the 'newer' reported adverse effects, e.g. on cardiovascular health, does not seem to be growing among caregivers. For example, one study that evaluated maternal knowledge of adverse effects of maternal smoking on mothers and children included lung and cardiovascular effects in mothers but only considered lung effects in children.[330] More healthcare resources will presumably be required to tackle the expected differential increase in poor healthcare resource use in children exposed to passive smoking during pregnancy and childhood, however studies on healthcare resource use in childhood and adulthood is limited.

Most studies have been conducted on exposure to passive smoking during pregnancy than for passive smoking during childhood, which may give the impression that exposure during both periods are disproportionately harmful. This paucity of studies on childhood exposure to passive smoking could also indicate that there is limited data available on exposure to passive smoking during childhood. There are also no validated questionnaires on the measurement of prolonged passive smoke exposure in childhood.

This thesis has sought to address the knowledge gaps raised above by examining (1) the prevalence, determinants and trends of exposure to passive smoking during pregnancy, (2) impacts on emergency department (ED) presentations and admission into hospital through ED due to exposure to passive smoking during pregnancy, (3) the validity and reliability of a life course questionnaire on exposure to passive smoking during childhood and (4) the association with cardiovascular function due to exposure to life course passive smoking during pregnancy and passive smoking during childhood. The gaps were addressed using three data sources namely Conception to Community Study, Childhood Determinants of Adult Health Study and Tasmanian Infant Health Study. This chapter provides a summary of the findings of these studies as well as a discussion of the implications and future directions based on the findings.

9.2 Summary of findings

Chapter 4 examined the trends, determinants, and changes in maternal smoking during and between pregnancies in Tasmania, Australia. A 57.9% decline (25.9% in 2008 to 16.4% in 2014) was observed over six years. The quit rate between index (first birth recorded in dataset) and last pregnancy, was 35.1% while the quit rate between the first half and the second half of pregnancy was 8.1%. Unfortunately, 5.1% of non-smokers began smoking between their index and last pregnancy. The risk of smoking during pregnancy (passive smoking during pregnancy) was significantly higher if there was associated maternal alcohol consumption during pregnancy, the mother lived in a highly socioeconomically disadvantaged area or was Aboriginal or Torres Strait Islander, while being older (25 years and above) or married reduced the risk of smoking during pregnancy. These determinants had a similar association in terms of likelihood of changing from non-smoker to smoker between index and last pregnancy (and subsequent pregnancy when used as an alternative to last pregnancy).

Chapter 5 evaluated the association of exposure to passive smoking during pregnancy on ED presentations and admission into hospital through ED for a number of disease categories in exposed children compared to those not exposed at 1- and 5-years, in Tasmania, Australia. At five years of age, exposed children had 26% higher overall presentation to ED and 45% higher overall admissions into hospital through ED compared to unexposed children. Greater health service utilisation was therefore associated with being exposed to passive smoking during pregnancy. Among the disease categories assessed, there was higher rates of ED presentation and hospital admissions for respiratory; eye, ear, nose, and throat illnesses; systemic and parasitic infections and psychosocial/other presentations in exposed children. There was an associated dose response relationship between the reported number of cigarettes per day smoked by the mother (none, <10 per day and ≥10 per day) for both overall ED presentation and admission through ED in almost all major disease categories.

Chapter 6 examined the reliability and validity of a retrospective questionnaire on prolonged passive smoking exposure from childhood in Australian children using three measures of passive smoking exposure derived from the CDAH questionnaire: total household smokers, cumulative years of exposure, and severity of exposure. The number of total household smokers ranged from 0 to 5 (mean 0.9 SD 1.0); cumulative years of exposure ranged from 0 to 106 years (mean 10.5 SD 13.9) and severity of exposure ranged from 0 to 318 (mean 24.4 SD 36.0). The three derived retrospective measures demonstrated reliability through having good internal consistency and moderate agreement with a similar measure in childhood. The retrospective measures were also associated with a range of participant characteristics in the expected direction, including participant smoking and measures of lung function, suggesting convergent validity. These combined findings suggest that these measures are reliable and valid to measure prolonged passive smoke exposure in childhood from questions asked up to two decades later. This instrument (questionnaire) could fill the gap of a lack of a validated measure

for prolonged exposure to passive smoking during childhood. The derived measures were subsequently used as exposure measures in Chapter 7.

Chapter 7 assessed the association of exposure to passive smoking during childhood on cardiovascular function in adulthood. The outcomes of interest considered as markers of subclinical cardiovascular disease were central and peripheral blood pressures (systolic and diastolic), and left ventricular dysfunction measured by global longitudinal strain (GLS). Central systolic and diastolic pressure were significantly higher in participants who were exposed compared to unexposed participants. Peripheral systolic and diastolic blood pressures were associated with total household smokers but only in the minimally adjusted analysis. GLS was significantly decreased in exposed participants compared to the unexposed in terms of cumulative years of exposure to passive smoke during childhood. GLS and central blood pressure may be considered early markers of cardiovascular disease and were adversely affected in those exposed to higher levels of passive smoke during childhood. These findings could have long term implications for these people's health.

Chapter 8 was a pilot study that assessed the effect of exposure to passive smoking during pregnancy and childhood on cardiovascular health in adulthood. The measures of passive smoke exposure in this study were maternal smoking during pregnancy, maternal exposure to passive smoke during pregnancy, maternal smoking during postnatal period, maternal exposure to passive smoke during the postnatal period, exposure to passive smoke in childhood, and cumulative exposure across all periods. There was an increase in peripheral diastolic blood pressure in participants exposed to passive smoking during pregnancy alone compared to the unexposed. However, the association between passive smoke exposure with peripheral systolic blood pressure had effect sizes comparable to those for diastolic blood pressure and were not statistically significant. Significantly lower left ventricular function as measured by global longitudinal strain was observed in those exposed to both passive smoking during pregnancy

and passive smoking during childhood. This result is generally concordant with the results in Chapter 7, supporting the finding that exposure to passive smoking during childhood negatively affects a range of markers of cardiovascular health into adulthood.

9.3 Implications

The findings in this thesis have implications for policy and practice in public health and clinical care, as well as research. Though many sections of this thesis treated exposure to passive smoking during pregnancy and during childhood as different entities they are interrelated phenomena, a situation which has implications for how the findings may be translated into improvements in health for children and adults.

9.3.1 Greater knowledge on the magnitude and impact of passive smoke exposure in childhood

This thesis illustrates prevalence of maternal smoking during pregnancy is still high in Tasmania compared to other states in Australian affecting 16. 4% in 2013-14. As a state, Tasmania may observe more long terms effects of exposure to passive smoking than other states in Australia. I have shown that the adverse effects of exposure to passive smoking during pregnancy and passive smoking during childhood may start within the first year after birth but may also be apparent many years after the exposure occurred in adulthood. Effects in adulthood could also be complicated by continued exposure to passive smoking during childhood, and from direct exposure from own smoking.

Adverse effects on the cardiovascular system may be subtle as assessed in the studies undertaken during young to mid adulthood in this thesis. But it is possible that the problems identified could progress to become overt clinical cardiovascular conditions later in life reflecting increased risk thereof. Similarly, the lower GLS suggesting left ventricular

dysfunction and higher central systolic blood pressure observed after exposure in childhood may be an early sign of disease. Of importance is there is evidence of tracking of blood pressure levels across life.[322] Overt cardiovascular diseases may have consequent effects on morbidity and mortality. Adverse effects due to passive smoking during adulthood has been suggested to be life-long, especially for the risk of developing cardiovascular diseases.[331] One can also postulate that higher presentations to ED and admissions through ED for respiratory and non-respiratory diseases observed at 5 years could also occur later in life when participants are in their 20s and 30s, particularly if the associations found were the result of epigenetic modifications,[264, 265] that cannot be expected to be modified at older age. In summary, I found considerable evidence that exposure to passive smoke in either pregnancy or childhood was associated with a range of poorer health outcomes that span childhood to early adulthood, including but not limited to cardiovascular disease and respiratory illness.

9.3.2 Need for innovation in interventions to reduce passive smoke exposure in children

From the findings in this thesis, it is clear that existing programs to prevent exposure of children to passive smoking especially during pregnancy are not fully effective. Thus, newer interventions are needed, or old interventions requires changes to make them more effective.

Smoking during pregnancy is a key touch point for reducing exposure. I saw that if women did not quit during an 'early' pregnancy (noting I could not clearly identify the first pregnancy) then they were very unlikely to quit for subsequent pregnancies. There are examples of innovative interventions to increase smoking cessation among women who are pregnant in Tasmania, in Australia that the findings in this thesis support their implementation. These innovative interventions were not yet operational during the study period (period data covered).

In the state of Tasmania, a pilot program to test the use of carbon monoxide monitoring in pregnant women during antenatal care was undertaken between July 2018 to June 2019. This

program was based on a UK initiative that reported to give women who are motivated to quit extra leverage to quit. The program also offers midwives an extra opportunity to discuss cessation with pregnant smokers.[332] The evaluation report of the pilot project of the 'Antenatal Carbon Monoxide Monitoring in Tasmania' showed that this approach is helping detect women exposed to smoking (either by their own active smoking or others smoking around them) and led to an 8-fold increase in the number of smokers who are referred to cessation services (10%, 2016; 80%, 2018/19).[333] There is a need for the Tasmanian Government to fully fund and roll out this pilot across the Tasmanian Health Service to enhance smoking cessation rate during pregnancy and protect children from exposure during pregnancy and beyond. Reduced resource use among children within 5 years of life will have considerable economic benefit.

Another positive aspect of this pilot project is that it used a different set of questions to collect data on maternal smoking during pregnancy compared with questions used for National perinatal Data Collection. The project staff have advocated assimilation of the questions in future data collection to improve consistency.[333] The questions asks "Do you smoke?" and pregnant women were to answer, 'never smoked', 'no', 'quit in the last 12 months', 'recently quit (before 1st visit)', 'yes' and 'not known'. These options would provide more valuable data to measure women who quit before and during pregnancy and evaluate interventions that work in reducing smoking.

Other interventions that are of interest to address smoking during pregnancy and after delivery include:

The Quit for You, Quit for Two mobile phone application which may be useful in helping pregnant women and those planning to have children to quit. This phone App has tips on how to tackle craving, exercises to help maintain abstinence, shows weekly progress of baby's development and savings made by not smoking.[334] But whether this App is effective is not

known and an evaluation is required. There are no studies on their effectiveness. A study on the quality and content of free smoking cessation Apps available in Australia showed that most were of low quality in terms of usability, engagement with users, artistic appearance and nature of information available.[335] In a world now increasingly embracing Apps, there is a need to improve and promote any App that could effectively and efficiently reduce exposure of children to passive smoking.

Family-based interventions can also help both the mother and their partner to quit smoking. Quit Together, a telephone counselling program, that has been implemented in Romania shows that couple counselling is effective in aiding parents quit during pregnancy,[336, 337] and could be useful in maintaining abstinence during the postnatal period.[337] Couple-based interventions could include discussions on smoking hygiene at home. Extension of smoke-free areas to public housing or apartment buildings, especially where there are children, has been recommended by the National Preventative Health Taskforce to protect more children during their childhood.[338] The findings in this thesis supports implementation of this recommendation.

9.3.3 Public and stakeholder's awareness on broader health effects of passive smoke exposure in children

There seems to be a lack of public and stakeholder's awareness of the longer term and broader range of the effects of childhood exposure to passive smoking. In most studies, the 'traditional' adverse effects include respiratory illnesses like upper respiratory tract infections and asthma. More studies are needed on the awareness of the populace on the broader range of side effects and to update resources with the full range of side effects as there were limited studies on resource use and cardiovascular effects after exposure to passive smoking during childhood. Inclusion of these 'newer' adverse effects and their impact in awareness programmes could enhance quit attempts. Publicly available information about adverse effects of smoking during

pregnancy and passive smoke exposure in children should be updated to include a wider range of diseases. Resources that should be updated include Australian Government Department of Health website,[339] Royal Australian College of General Practitioners cessation guide for health professionals[273] and The Royal Children's Hospital, Melbourne website.[340]

9.4 Future directions

As already highlighted, exposure to passive smoking during pregnancy and to passive smoking during childhood is declining globally but there is no safe level of exposure. There are more studies reporting the trend for exposure to passive smoking during pregnancy compared to exposure to passive smoking during childhood. Nevertheless, exposure to passive smoking during pregnancy and passive smoking during childhood independently led to adverse health effects in children in the studies within this thesis. The imbalanced investigation may mean that interventions geared towards the prevention of exposure to passive smoking in children may also be skewed more towards exposure to passive smoking during pregnancy. This situation needs to be addressed, with potential future directions described below.

9.4.1 Further validation and use of retrospective passive smoke exposure questionnaire

This thesis highlighted the reliability and validity of a life course questionnaire utilised for examination of the adverse health effects due to exposure to passive smoking during childhood. This thesis therefore suggests a new way to assess passive smoke exposure in childhood retrospectively. Researchers are encouraged to use this measure and continue to test its reliability and validity in other samples. The findings that a valid and reliable recall 'estimate' of childhood exposure might be useful for subsequent cardiovascular risk prediction among adults.

9.4.2 Measurement of passive smoke exposure in children

Data on maternal smoking during pregnancy is routinely collected and reported in Australia.[66] It would be useful to expand data collection to include maternal exposure to passive smoking during pregnancy and delineate the source of the exposure, e.g. paternal smoking or otherwise. In this way other potential sources of exposure could be recorded. The implication of the limited current measurement is that the adverse health effects associated with maternal smoking during pregnancy are likely underestimated, but also there is a missed opportunity to be able to intervene to help reduce exposure at household level. Professional cessation support counselling has been shown to work better with the involvement of the pregnant mother's social support network.[341]

There should be better collection of data on of exposure to passive smoking during childhood in more health care settings and in research studies. Improvements may include considering different stages of childhood (e.g. early childhood, middle childhood, and adolescence). National guidelines in US recommend screening for exposure to tobacco smoke in children during all paediatric consultations, but almost half of the children presenting in emergency departments are not screened, even when they present with tobacco-smoke exposure related illness.[342] This thesis shows that collecting such data in the ED where many children are presenting could be important in determining resource use. Having such data would offer the opportunity to intervene to reduce parental exposure. It could also be possible to collect and routinely report data on passive smoke exposure of children from different health care settings including ED and immunisation clinics.

9.4.3 Holistic interventions to reduce passive smoke exposure in children

Maternal smoking during pregnancy is declining in Tasmania. This is good news as Tasmania has had the second highest prevalence in Australia for almost a decade.[343] But an increasing

population may mean that the absolute number of children exposed will still be large over the years and the change in prevalence little. We will need to continue to make sure interventions, including the Antenatal Carbon Monoxide Monitoring program, are effective, scaled up and well-funded. Intervention to aid pregnant women to quit smoking should include long term follow-up and support. One systematic review showed that 43% of women who quit smoking during pregnancy restart smoking at 6 months postpartum.[344]

Holistic interventions to support mothers to engage in healthy lifestyles during their pregnancy could be useful. Other health behaviours like drinking alcohol during pregnancy were associated with maternal smoking during pregnancy in this thesis. Under Action Area 3 of Tasmanian Tobacco Control Plan, "reduce smoking by high prevalence groups",[15] pregnant women, middle-aged males, young people, Aboriginal and Torres Strait Islander peoples, people experiencing mental ill-health and people from low socio-economic areas were listed as special priority groups. People with children should be added to increase the focus on protecting children against exposure to passive smoking. As mentioned earlier, involvement of a pregnant mothers support network improves cessation results. [341] Possibly, families or parents with other associated adverse health behaviours like alcoholism can be added too. Change in prevalence of exposure to passive smoking during childhood will likely have a positive impact on exposure to passive smoking during pregnancy and vice versa If there are subsequent pregnancies and births.

Through historical data this thesis has shown that a significant number of children were being exposed to tobacco smoke across their childhood, although recent data suggests exposure is now much reduced. Multi-faceted interventions targeted at preventing passive smoke exposure to children to assist further decline after the reported decline in exposure of children at home in Australia fell from 19.7% in 2001 to just 2.1% in 2019. Of note is that the proportion of smokers not planning to quit has not changed in the last ten years.[345] Programs with a multi-

level approach including community (e.g. schools), healthcare (e.g. infant immunisation clinics and emergency departments) settings could have positive results. A Cochrane review has showed some decrease in exposure to passive smoking achieved across these three settings.[346] Specific interventions to address exposure of children through these settings were not included in the Tasmanian Tobacco Control Plan.[15] More needs to be done to ensure that health care professionals across settings have the skills to deliver smoking cessation advice. Research has shown that healthcare professionals including general practitioners, obstetricians, midwives are good at the assessment of smoking among pregnant women but less often provide practical quitting support, such as prescribing NRT for pregnant women.[347] Proper implementation of multi-faceted interventions is needed to reduce exposure of children to passive smoking.

9.4.4 Costs of exposure to passive smoke in childhood

This thesis uncovered a hidden burden of disease in children below five years due to exposure to passive smoking during pregnancy. According to the findings, there were higher presentations to ED for a wide range of non-respiratory and respiratory diseases and conditions and higher admission into hospital through ED associated with passive smoke exposure during pregnancy. Exposed children therefore require higher levels of healthcare resources. Thus, there could be potential "cost savings" through reduced service use if we can eliminate or minimise exposure to maternal smoking during pregnancy. Apart from higher rates of ED presentations and hospital admissions identified in this thesis, exposed children have elsewhere been identified as spending more days in hospital.[348] For example, children exposed to passive smoking during pregnancy were reported to have spent more days in hospital within their first five years of life with a higher adjusted mean cost difference of £462 if exposed to up to 20 cigarettes per day during pregnancy compared to children not exposed.[348] These findings will

be conservative as they do not include costs after these children are above five years of age, they also do not include indirect costs.

Studies undertaken from a societal perspective that have assessed the indirect costs of exposure to passive smoke during pregnancy and childhood suggests the cost is substantial. Children exposed to passive smoke during childhood spend 1.5 days more per year being absent from school compared to unexposed children, and absence from work for their caregivers costs the economy an estimated $227 million per year.[349] Another study estimated that attention deficit hyperactivity disorder -associated with passive smoke exposure costs the US educational system between $2.90 to $9.23 billion.[350] There is a need for detailed analysis of the direct and indirect costs associated with passive smoke exposure in children accounting for a wide range of health effects. These data will be useful for advocacy efforts to ensure continued investment in programs to reduce smoking, particularly among children.

9.4.5 Data linkage to increase efficiencies in research

This study highlights the usefulness of data linkage which can convert routinely collected data into a longitudinal data. This data linkage provides researchers with access to data on many factors that may influence health over a life course. A limitation of this type of research is that there are a number of factors that cannot be examined as exposures or confounders because they are not collected during routine data collection processes. This situation suggests the potential benefits of linking other non-health datasets to access other relevant data, such as community services or education datasets.

The possibility of linking the very large administrative Tasmanian Infant Health Study to state-wide public hospital and death records should be explored. Such linkage could aid in studying more possible adverse effects of passive smoke exposure including those outside of the healthcare setting.

9.4.*6* Longer follow-up studies of children exposed to passive smoke in childhood

Longer follow up studies of the ongoing effects of passive smoke exposure in childhood on health into older age may be helpful to determine if the identified increase or differential in presentations and admissions due to exposure to passive smoking during pregnancy remained or got worse. This thesis also showed different results for the 1-year and 5-years old which suggests the potential trajectory of health service use within the participants and between disease categories. This trajectory in terms of admissions could worsen with age as suggested by this thesis including spending more days in hospital admission as suggested by other researchers.[348] Increased hospitalization or associated higher death rate in adult age could also be evaluated through follow-up studies depending on the availability of data. Follow up studies may be beneficial to strategic health planning in Tasmania. However, the present findings still have direct relevance to the Tasmanian healthcare system and for Tasmanians in terms of data collection, service utilization, planning of service delivery and in the training of healthcare professionals.

9.4.7 Threshold of exposure at which adverse effects are observed

This thesis looked at health outcomes that span the severity of potential outcomes ranging from subclinical processes, e.g. cardiac structure measured by echocardiography, through to illnesses requiring hospital admission. In the examination of adverse health effects, hospital record of presentation and admission for an illness can help circumvent recall bias that may occur with a questionnaire though it may skew severity as only people with advanced disease will go to hospital. For subclinical dysfunctions, technology now offers us the chance to detect this with a new level of precision. A subclinical diagnosis could aid discovery of at what age range adverse effect starts becoming apparent and examination of if modifying lifestyle could slow the progression to clinical disease. We also looked at a range of ways of quantifying

exposure to passive smoke from 'simple' measures of a mother ever smoking during pregnancy, through to complex combinations of years of exposure by many individuals. Most studies of passive smoke exposure do not examine the number of cigarettes, maybe due to the difficulty in measuring this accurately. I attempted to overcome this by having a range of exposure measures. Researchers should develop proxies to the measurement of dose of exposure with whatever information available in their data. Expansion of the measurement of exposure could include the severity of exposure, cumulative years of exposure, total household smokers as used in this thesis. This will give researchers the leverage to further suggest that these adverse effects depend on the number of persons exposed to (total household smokers), the number of years the exposure occurred (cumulative years of exposure) or on if the exposure occurs while in the same room with a smoker (severity of exposure index).

9.5 Conclusion

The fight against exposure of children to passive smoking during pregnancy and passive smoking during childhood is an important public health issue to protect the next generation and the generation after next. Continued improvement in data collection (including historical data) and increased awareness of the adverse health effects associated with the passive smoke is needed. Both are veritable tools in this fight. Like the success achieved in the decline of exposure to passive smoking during pregnancy, success can be achieved in terms of prevention of these adverse health effects associated with exposure to passive smoking during pregnancy and passive smoking during childhood.

It is the following published article:
Ezegbe, C., Neil, A. L., Magnussen, C. G., Chappell, K., Judd, F., Wagg, F., Gall, S., 2021. Maternal smoking during pregnancy: trends and determinants in the conception to community study, Birth, 48(1), 76-85

It is the following published article:
Ezegbe, C., Neil, A. L., Magnussen, C. G., Chappell, K., Judd, F., Wagg, F., Gall, S., 2021. Maternal smoking in pregnancy and child's hospital use up to 5 years of age in a data linkage birth cohort, Hospital pediatrics, 11(1), 8-16

Letter from AHA media team

Vincent Ezegbe

From: Joanna Carr <Joanna.Carr@heart.org>
Sent: Wednesday, 13 January 2021 1:47 AM
To: Vincent Ezegbe
Cc: Denise Kuo; David Rivera; Michelle Kirkwood; Karen Astle; Bridgette McNeill; Joanna Carr; Cathy Lewis; William Westmoreland; Heather Goodell; Mariell Jessup; Greg Donaldson; Suzanne Grant; Maggie Francis
Subject: AHA News Coverage Report: American Heart Association's Scientific Sessions 2020/Ezegbe
Attachments: Ezegbe SS Coverage Report.xlsx

Dear Dr. Ezegbe,

Thank you, again, for working with our media relations team to promote your important research. Attached is a media coverage report and the link to the news release for your study "Children exposed to tobacco smoke at home have worse heart function as adults" which was published November 9, 2020 and presented at the virtual American Heart Association's Scientific Sessions 2020.

As detailed in the report, the news release generated ***38,888,278*** media impressions as well as ***211,944*** views on American Heart Association social media channels.

Please note that media impressions are mentions of your study in consumer and trade media in print publications, online, or broadcast media (TV and radio). It does not include citations in peer-reviewed scientific journals.

Thank you for your time and assistance in allowing us to promote your research. Please contact us if you have any questions or if we can be of assistance in the future.

Best regards,
The American Heart Association's Communications & Media Relations Team

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