Offspring of people with Chronic Obstructive Pulmonary Disease (COPD): Intergenerational and life course influence on respiratory impairment

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Declaration

I declare that this thesis presents work carried out by myself and does not incorporate without acknowledgement any materials previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.



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Abstract

Familial associations in Chronic Obstructive Pulmonary Disease (COPD) are acknowledged, but rarely capitalised upon as opportunities for early identification of respiratory impairment or intervening in order to delay the impairment. With the exception of specific genetic forms of COPD there is limited research on offspring of people with COPD. Yet this group is more likely to be exposed to genetic, environmental and lifestyle-related factors throughout their life course that increase their risks for respiratory impairment. This research program explored intergenerational and life course influences on respiratory impairment in adult offspring of people with COPD.

Study I was a systematic review of evidence (n = 8 studies) for co-occurrence and risk of COPD in adult offspring where one or both parents had COPD. The pooled prevalence of COPD in adult offspring of people with COPD was 28.6% (95% CI=17.4-41.3%) which was higher than population-based estimates (14.5%); these offspring had 1.57 greater odds of having COPD (95%CI=1.29-1.93) compared with people without a parental history of COPD.

Using longitudinal life course data from the 1958 British Birth Cohort, Study II explored potential explanatory factors linking parental respiratory disease history and reduced lung health of offspring in mid-adulthood. The association between parent and offspring lung health was confirmed and partly mediated by a sequence of exposure to maternal and personal smoking, although 70% of the relationship remained unexplained by the life course factors examined.

Study III was designed as a pilot study undertaken in a non-COPD sample to investigate practical issues associated with 1) indirectly recruiting adult offspring through their parents (proband) and 2) collecting data on life course exposure to COPD risk factors through the "Story of My Life calendar". Five parent-offspring pairs were recruited over a two-month period, no major practical issues were identified with the recruitment method or data collection instrument.

Study IV was designed to examine the feasibility of using the piloted methodology to 1) recruit adult offspring of people with COPD through their parents (proband) over a one-year period and 2) provide contemporary data on lung health and related life course exposure in adult offspring of people with COPD. Over 12 months 840 people with COPD (proband) were successfully contacted. It was estimated that non-participation was mostly due to ineligibility (no offspring living locally, 65%). In those eligible, only 28 probands agreed to convey information about this study onto their offspring and five adult offspring were successfully recruited. The recruitment methodology was concluded as unfeasible and this study was unable to provide meaningful contemporary data on lung health for this population.

This research program confirmed adult offspring of people with COPD are at increased risk of developing lung impairment. Life course approaches have strong potential for determining contributory factors to the increased risk of respiratory impairment in adult offspring of people with COPD. Identification of individuals with a positive parental history of COPD should prompt primary care providers to consider if the individual may benefit from spirometry screening. Life course approaches may help to unravel the mechanisms behind respiratory impairment in offspring of people with COPD.

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List of abbreviations

CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COPD-X	Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in 1 second
FEV_6	Forced Expiratory Volume in 6 seconds
FVC	Forced Vital Capacity
GOLD	Global initiative for Obstructive Lung Disease
HREC	Human Research Ethics Committee
mMRC	modified Medical Research Council
OR	Odds Ratio
SC	Social Class
SES	Socio- Economic Status
SOMLc	Story Of My Life calendar

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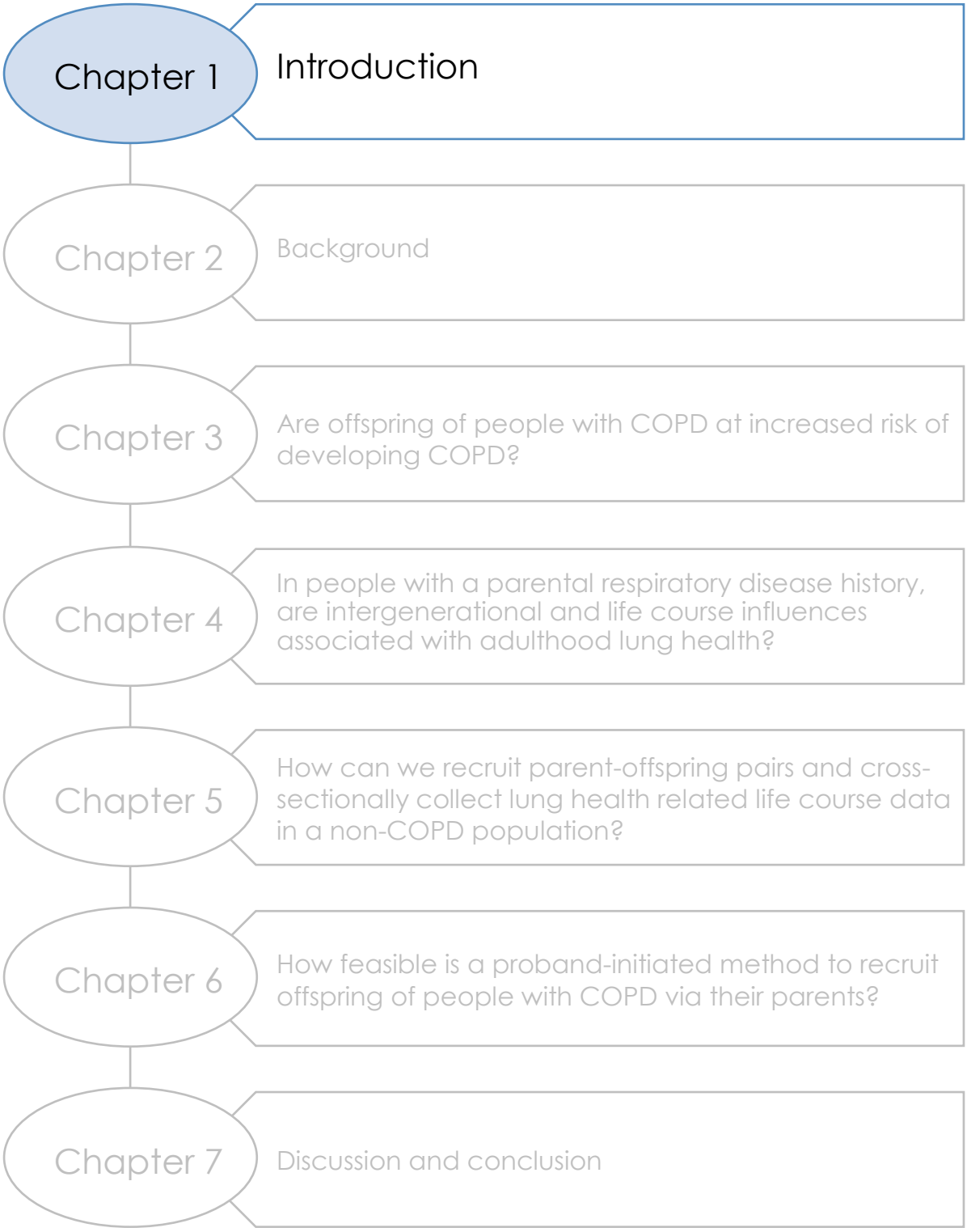
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Chapter 1
Introduction
Chapter 2
Background
Chapter 3
Are offspring of people with COPD at increased risk of developing COPD?
Chapter 4
In people with a parental respiratory disease history, are intergenerational and life course influences associated with adulthood lung health?
Chapter 5
How can we recruit parent-offspring pairs and cross-sectionally collect lung health related life course data in a non-COPD population?
Chapter 6
How feasible is a proband-initiated method to recruit offspring of people with COPD via their parents?
Chapter 7
Discussion and conclusion

1.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive condition characterised by inflammation and airflow limitation[1]. Worldwide it is estimated that 65 million people are affected by COPD and it will become the third leading cause of death by 2030[2]. One in seven Australians over the age of 40 have some form of COPD[3]. Distress with breathing (dyspnoea), chronic cough and sputum production are the most frequently reported symptoms of COPD[1]. Respiratory symptoms experienced by individuals with COPD have been reported to lead to work productivity loss[4], and creates a significant burden on the health care system[5, 6]. In 2011, COPD contributed to 43% (160,346 disability-adjusted life year) of the total burden of respiratory conditions in Australia [7].

Cigarette smoking is a well-recognised cause of COPD, but over 20% of people with COPD have never smoked[8], highlighting the importance of other COPD risk factors such as early life factors and environmental exposures[9]. Currently, the only robustly defined genetic risk factor for COPD is alpha-1 antitrypsin deficiency [1]. COPD is likely the result of a combination of gene-environment interactions and COPD risk factors may be present throughout different stages of a person's life course[10]. Parents and offspring not only share genes, but also typically share a living environment during the offspring's early life, both of these factors may increase the risk of offspring of people with COPD developing respiratory impairment in later life. While familial associations for COPD are acknowledged, with the exception of specific genetic forms of COPD, this association is rarely capitalised upon.

Limited research on the respiratory health in adult offspring of people with COPD has been conducted. An increase in our understanding of the respiratory health profile of adult offspring of people with COPD may present an opportunity to more effectively identify and intervene with those most at risk as early as possible in the trajectory of declining lung health[11]. A timely diagnosis combined with appropriate management can potentially reduce the burden of COPD[1]. Population based screening for COPD is controversial and not currently recommended[12], however active case finding in those with respiratory symptoms and/or exposed to risk factors is recommended [1]. The hypothesis of this thesis was that offspring of people with COPD are at increased

risk of developing respiratory impairment in adulthood due to intergenerational and life course influences.

1.2 Aims and Structure of this thesis

The overall aim of this research program was to explore intergenerational and life course influences on respiratory health in adult offspring of people with COPD and explore potential for case finding in this group. This thesis consists of seven chapters (Figure 1.1).

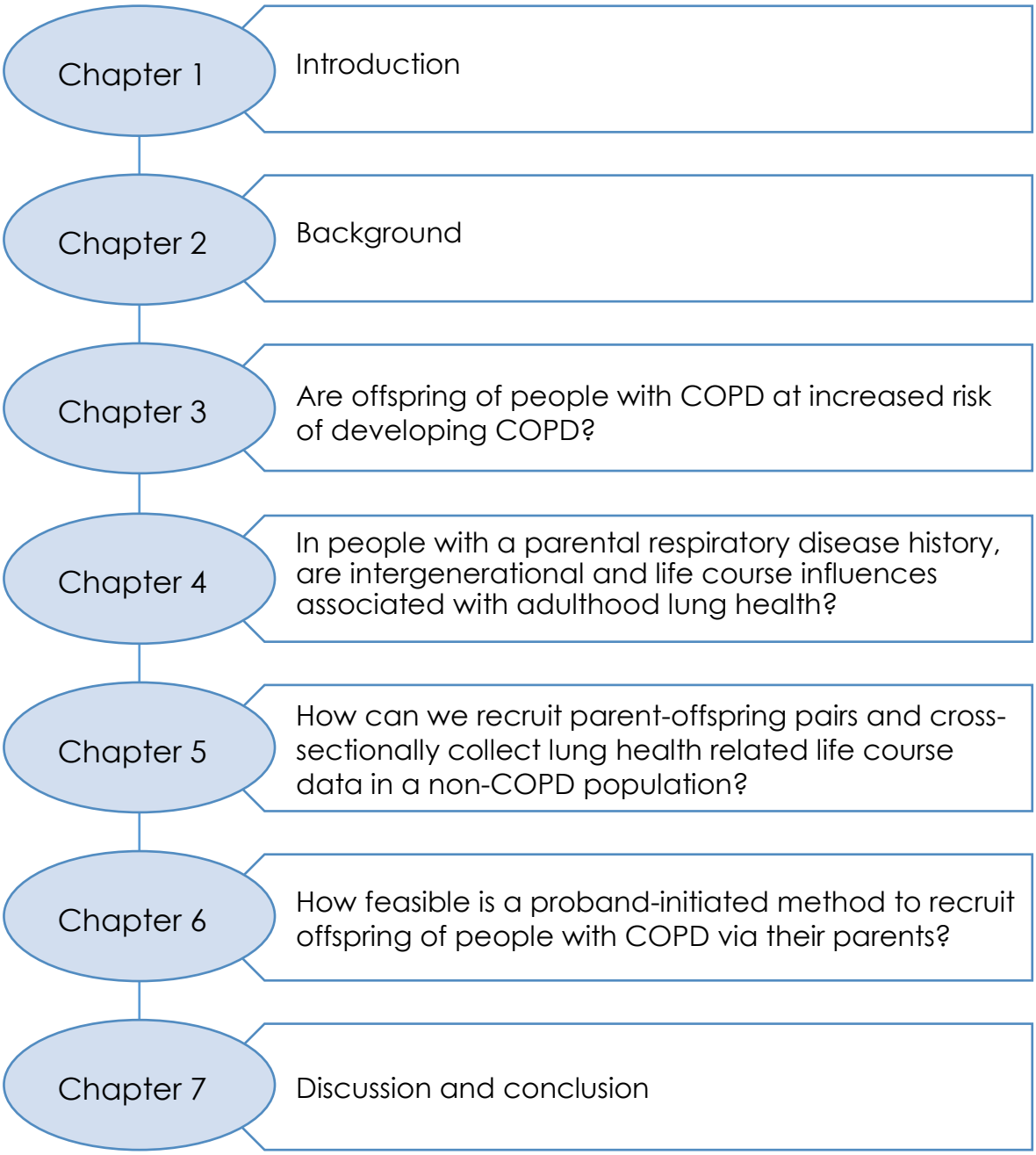


Figure 1.1 Outline of the flow of this thesis

Four original studies were undertaken within this research program and presented in Chapters 3-6:

- Study I (Chapter 3) was a systematic review with meta-analysis on the reported prevalence and risk estimates of COPD in offspring of people with COPD
- Study II (Chapter 4) used a life course approach to examine the influences of intergenerational and life course factors on the association between parental respiratory disease history and the lung health of cohort members in mid-adulthood using longitudinal data from the 1958 British birth cohort (National Child Development Study)
- Study III (Chapter 5) presents a pilot study conducted in a non-COPD sample in order to explore practical issues associated with 1) indirectly recruiting adult offspring through their parents (proband-initiated recruitment strategy) and 2) collecting data on life course exposure to COPD risk factors through the "Story of My Life calendar"
- Study IV (Chapter 6) explored the feasibility of COPD case finding using a proband-initiated recruitment strategy and accessing contemporary data on the respiratory health in adult offspring of people with COPD

1.3 Publications and presentations arising from work contained in this thesis

This thesis is submitted as a Thesis Containing Published Research in accordance with University of South Australia Academic Regulations for Higher Degrees by Research Clause 16.1.1.b.

Peer reviewed publication

Li, LSK., Paquet, C., Johnston, K., & Williams, M. T. (2017). "What are my chances of developing COPD if one of my parents has the disease?" A systematic review and meta-analysis of prevalence of co-occurrence of COPD diagnosis in parents and offspring. International journal of chronic obstructive pulmonary disease, *12*, 403-415.

Conference presentations (peer reviewed abstracts unless otherwise noted)

Study I:

Li, LSK., Paquet, C., Johnston, K., & Williams, M. 2016. "Prevalence of co-occurrence of COPD diagnosis in parents and offspring: Systematic Review". *Respirology*, *21*, 138. Thoracic Society of Australia and New Zealand Annual Scientific meeting, Perth, Australia. 1-5 April 2016. (Poster presentation).

Study II:

Li LSK, Williams MT, Johnston K, Frith P, Hypponen E & Paquet C 2018 (accepted). "Parental respiratory disease is associated with reduced offspring lung health at age 45 via pathway of maternal and personal smoking". Thoracic Society of Australia and New Zealand Annual Scientific Meeting. Adelaide, Australia. 24-27 March 2018. (Oral presentation).
(This abstract was selected as a Finalist for presentation in the South Australian and Northern Territory Thoracic Society of Australia and New Zealand Young Investigator Award. Adelaide, Australia. 14 November 2017).

Li LSK, Williams MT, Johnston K, Frith P, Hypponen E & Paquet C 2017. "Intergenerational and life course factors for lung health". South Australia State Population Health Conference in Adelaide Australia. Adelaide, Australia. 21 October 2017. (Oral presentation).

Study III:

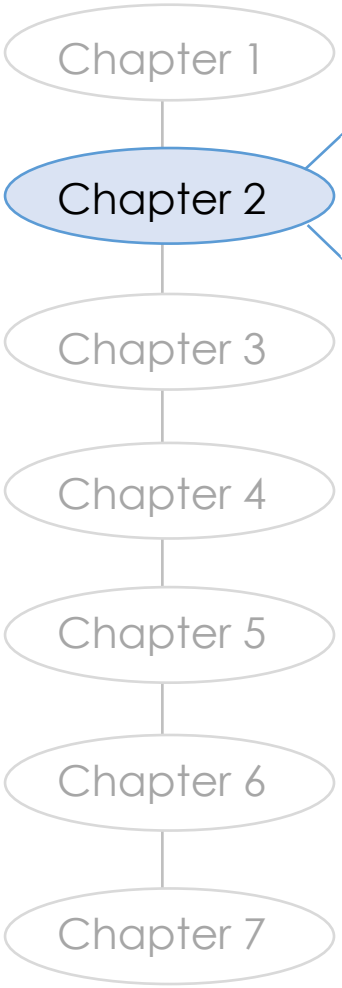
Li, LSK., Paquet, C., Johnston, K., Frith, P., & Williams, M. 2017. "A life history calendar to map lung health risk exposures: pilot study. *European Respiratory Journal*, vol 50, suppl 60, PA 1251). European Respiratory Society International Congress, Milan, Italy 9 – 13 September 2017. (Poster presentation).

Li, LSK., Paquet, C., Johnston, K., & Williams, M. T. 2017. "The story of your life and lung health: Pilot study of a life history approach". *Respirology,* Vol. 22, pp. 136). Thoracic Society of Australia and New Zealand Annual Scientific meeting, Canberra, Australia. 24-28 March 2017. (Poster presentation).

Study IV:

Li, LSK., Paquet, C., Johnston, K., Frith, P., & Williams, M 2018 (accepted). "Recruiting adult offspring of people with COPD to explore intergenerational lung health: feasibility study". Thoracic Society of Australia and New Zealand Annual Scientific Meeting. Adelaide, Australia. 24-27 March 2018. (Poster presentation).

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Li K, Johnston K, Paquet C, Williams MT 2016. "Respiratory health in adult children of people with Chronic Obstructive Pulmonary Disease". Physiotherapy Research Foundation Seeding Grant).



Background

This chapter provides essential background to the burden, common risk factors, diagnosis and management of chronic obstructive pulmonary disease (COPD). Section 2.1 outlines the evolution of the term COPD, current views on assessment, diagnosis and management of COPD. This is followed by the issues associated with timely identification of people with COPD through screening based on symptoms and risk factors. Section 2.2 summarises COPD risk factors and provides a rationale to consider offspring of people with COPD as a specific at-risk group taking into account the life course and intergenerational influences on lung function and COPD development. Section 2.3 discusses methods of collecting life course data relating to lung health and recruitment strategies suitable for intergenerational studies.

2.1 COPD

2.1.1 Evolution of the definition of COPD

Historically various terminologies have been used to describe respiratory symptoms of cough and dyspnoea [13, 14]. Figure 2.1 is a timeline of key events and publications related to the current definition of COPD. The Ciba guest symposium in 1959 was the first initiative to have an agreed definition of terminologies/ diagnoses and recommended use of the term "chronic non-specific lung disease" which included diagnoses previously classified as chronic bronchitis, asthma and emphysema[15]. However the term chronic non-specific lung disease was not widely adopted, with other expert committees continuing to use the terms chronic bronchitis, emphysema and asthma[16, 17].

In 1963, Williams and Seriff proposed the use of the term "chronic obstructive pulmonary disease" over the use of "emphysema"[18]. This new term was not widely adopted either, with the American College of Chest Physicians (ACCP) and American Thoracic Society (ATS) joint committee on pulmonary nomenclature in 1975 recommending that a more specific term such as chronic obstructive bronchitis or chronic obstructive emphysema to be used whenever possible[19]. In the same year, the World Health Organisation (WHO) memoranda made recommendations on the definition of chronic non-specific respiratory disease which included chronic bronchitis, generalised airways obstruction and emphysema[20].

In 1995, the ATS and European Thoracic Society independently published consensus statements each with a definition for COPD and a similar definition of chronic bronchitis and emphysema [21, 22]. While asthma was not included in the definition of COPD in this ATS statement, there was a non-proportional Venn diagram representing different phenotypes of COPD, acknowledging that some people with COPD will also have asthma[21]. A COPD guideline was published by the British Thoracic Society in 1997, wherein chronic bronchitis and emphysema were considered to be included within the COPD term, thus COPD was the only term defined in this guideline [23].

Timeline	Author	Chronic bronchitis	Emphysema	Asthma
400 B.C.	Hippocrates			Description of asthma
1679	Theophile Bonet[13]		Description of "voluminous lungs"	
1814	Charles Badham[14]	Description of bronchitis		
1821	Rene Laennac[37]	Invented stethoscope; Described a combination of CB and emphysema		
1837	William Stokes[25]	Description of CB		
1846	John Hutchinson *(invented spirometer)* [26]			
1860	Henry Salter[24]			Defined asthma
1934	Ronald Christie[27]		Description of emphysema	
1947	Tiffeneau and Pinelli *(led to the use of spirometry as a diagnostic tool)* [28]			
1959	CM Fletecter et al. *(bronchitis questionnaire)* [29]			
1959	CIBA guest symposium[15]	Used the term "Chronic non-specific lung disease"		
1961	WHO[16]	Used the term "Generalised airways obstruction" with separate defintions for CB and emphysema		
		Defined CB	Defined emphysema	
1962	ATS committee[17]	Defined CB	Defined emphysema	Defined asthma, asthmatic bronchitis
1963	Henry Williams & Nathan Seriff[18]	Defined the term "COPD"		
1965	William Briscoe[30]	Use the term "COPD" at the 9th Aspen emphysema conference		
	Bronchitis research committee of the MRC[31]	Defined "simple chronic bronchitis", "Chronic or recurrent mucopurulent bronchitis" and "chronic obstructive bronchitis"		
1975	ACCP and ATS joint committee[19]	Defined COPD (but discourage use of this term) with separate definitions for CB and emphysema		
		Defined CB	Defined emphysema	Defined asthma
1975	WHO[20]	"Chronic non-specific respiratory disease" with separate definition for each		
		Defined CB, chronic obstructive bronchitis	Defined emphysema	Defined asthma
1987	ATS [32]	Defined COPD with deparate defintions for CB and emphysema		
		Defined CB	Defined emphysema	Defined asthma
1995	ATS[21]	Defined COPD		
		Defined CB	Defined emphysema	
1995	ERS[22]	Defined COPD		
		Defined CB	Defined emphysema	
1995	TSANZ[38]	Defined COPD		
1997	BTS[23]	Defined COPD		
2001	GOLD[33]	Defined COPD (First to use FEV1/FVC < 0.7 cutoff)		
2003	LFA[39]	Defined COPD		
2004	ATS and ERS[34]	Defined COPD		
		Defined CB	Defined emphysema	
2006	GOLD[35]	Defined COPD		
2011	GOLD[35]	Defined COPD		
2015	GINA and GOLD[36]	Defined ACOS		
2018	GOLD[1]	Defined COPD		

Figure 2.1 Summary timeline of key events and definition of COPD

COPD = Chronic Obstructive Pulmonary Disease; CB = Chronic Bronchitis; WHO = World Health Organisation; ACCP = American College of Chest Physicians; ATS = American Thoracic Society; ERS = European Respiratory Society; BTS = British Thoracic Society; TSANZ = Thoracic Society of Australia & New Zealand; LFA = Lung Foundation Australia; GOLD = Global initiative for chronic Obstructive Lung Disease; GINA = Global Initiative for Asthma; ACOS = Asthma-COPD Overlap Syndrome; FEV_1/FVC = Forced Expiratory Volume in 1 second/ Forced Vital Capacity

Colour key: Grey = Specific definition related to chronic bronchitis; Blue = Specific definition related to emphysema; Red = Specific definition related to asthma; Purple = Term or definition includes chronic bronchitis +/- emphysema +/- asthma

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) began in 1997, when international COPD experts collaborated on an evidence-based report on the diagnosis, management and prevention of COPD[35]. The first GOLD report was published in 2001 and defined COPD as "a disease state characterised by airflow limitation that is not fully reversible"(p.1257), without using the terms chronic bronchitis and emphysema in the definition[33]. Since then, the GOLD document has been revised and updated regularly, with three major updates published in 2006, 2011 and 2017 [35]. The most recent 2018 version defined COPD as "a common preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"(p.4)[1]. While COPD is the terminology used currently, throughout this thesis both terms (chronic bronchitis and emphysema) will be used when referring to previous literature consistent with the terminology used within individual studies referenced.

2.1.2 Assessment and diagnosis of COPD

Presence of respiratory symptoms (e.g. chronic cough, dyspnoea) and risk factors (e.g. tobacco smoke, environmental exposure) are the key indicators for considering a diagnosis of COPD [1]. Two questionnaires are commonly used to assess respiratory symptoms. The Modified British Medical Research Council (mMRC) dyspnoea scale consists of five statements that allow the individual to grade exertion- related breathlessness on a scale [40]. The COPD Assessment Test (CAT) contains eight questions on respiratory symptoms, sleep and activity levels and is considered a valid and reliable tool for assessing health status impairment in COPD [41]. While these instruments provide an indication of an individual's symptom status and risk of having COPD, a definitive diagnosis of COPD is based on spirometry.

In the current GOLD guideline, a definitive diagnosis of COPD is made by spirometry, where the result of post-bronchodilator Forced Expiratory Volume in One second (FEV_1) over Forced Vital Capacity (FVC) is less than 0.7 ($FEV_1/FVC < 0.7$)[1]. There are debates within the respiratory clinical and research community regarding the use of the Lower Limit of Normal (LLN) rather than a fixed cut-off ratio as the spirometric definition of COPD[42]. The benefits of using the LLN is that it accounts for height,

age and ethnic background which can influence lung function. The use of a fix ratio for the diagnosis of COPD over the use of LLN is favoured by GOLD as the risk of misdiagnosis and over-treatment of COPD of using a fix ratio is limited[1]. To maintain consistency throughout the thesis, the spirometric definition of COPD is based on the fixed cut-off ratio ($FEV_1/FVC < 0.7$) as per the GOLD guideline.

The severity of airway obstruction can be ranked from GOLD grade 1 (mild) to GOLD grade 4 (very severe) depending on the post-bronchodilator FEV_1 value [1]. The term "stage" of COPD was used to classify the different severities in the 2001 and 2006 GOLD documents whereas the term "grade" was used in the two most recent updates[35]; throughout this thesis both terms will be used when referring to previous literature consistent with the terminology used within individual studies referenced.

People with COPD may experience episodes known as an exacerbation, when their respiratory symptoms worsen dramatically compared to their baseline symptoms. GOLD recommends formal assessment of symptoms with either the mMRC dyspnoea scale or the CAT to provide clinicians with information on the burden of symptoms and risk of exacerbation for individual patients, in addition to recording the number of exacerbations that resulted in hospitalisation within the last year (Figure 2.2) [1]. People with COPD can be classified into groups A to D based on their burden of symptoms and exacerbation history. Together, information on airflow limitation (Grade 1 to 4) with symptoms and exacerbation history (Groups A to D) can be used to guide treatment and management of COPD[1].

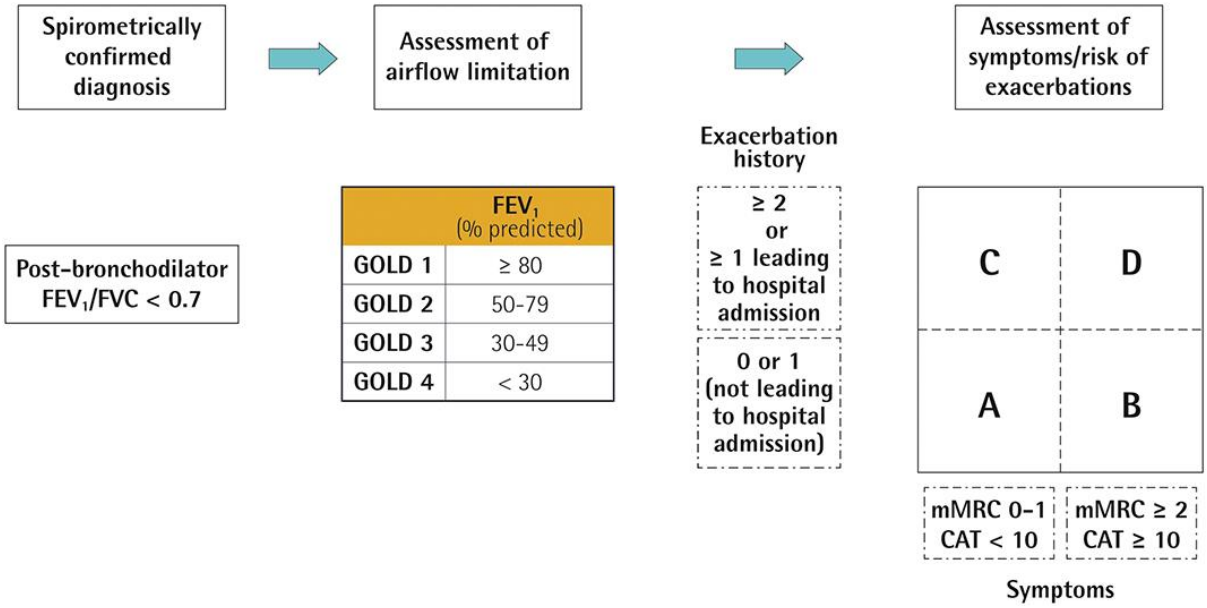


Figure 2.2 The GOLD COPD ABCD Assessment Tool

FEV1/FVC = Forced Expiratory Volume in 1 second/ Forced Vital Capacity; mMRC = modified Medical Research Council dyspnoea scale; CAT = COPD Assessment Test

(reproduced from [Global strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 report, Vogelmeier C et al., Respirology 2017; 575-601] with permission from John Wiley and Sons)

COPD is a complex disease with a high prevalence of comorbid conditions reported within this population[43]. Clinical features of COPD may overlap with other respiratory conditions [44]. The CIBA symposium in 1959 was an attempt by the medical community to clarify the definition and use of terms such as chronic bronchitis, asthma and emphysema[15]. Orie and colleagues proposed that the umbrella term "Chronic non-specific lung disease" should be used when describing asthma and COPD as they have common origins and are a result of host and environmental factors[45]. Characteristics that differentiate between asthma and COPD have since been recognised and led to distinct definitions for the two conditions[32, 46]. In recent years, there has been an increased interest in individuals with both asthma and COPD, known as Asthma-COPD Overlap Syndrome (ACOS) with a recent meta-analysis reporting approximately 27% of people with COPD also have asthma [48]. A joint project between the Global Initiative for Asthma and the Global Initiative for COPD defined Asthma-COPD overlap syndrome (ACOS) as "characterised by persistent airflow limitation with several features usually associated

with asthma and several features usually associated with COPD"[36]. This is an evolving and debated area[49, 50]. The focus of this thesis is on COPD and where possible the two conditions (COPD and asthma) will be distinguished.

2.1.3 Current views on management of COPD

Due to the progressive nature of COPD, the key focus of COPD management is to optimise physical function, prevent deterioration and reduce the risk of exacerbation [1]. Fletcher and Peto [51] first described the effects of smoking on the rate of decline in FEV_1 based on observations on 792 men aged between 30-59 years over eight years (Figure 2.3) and highlighted effects of smoking cessation on the rate of decline in FEV_1 in susceptible smokers[51].

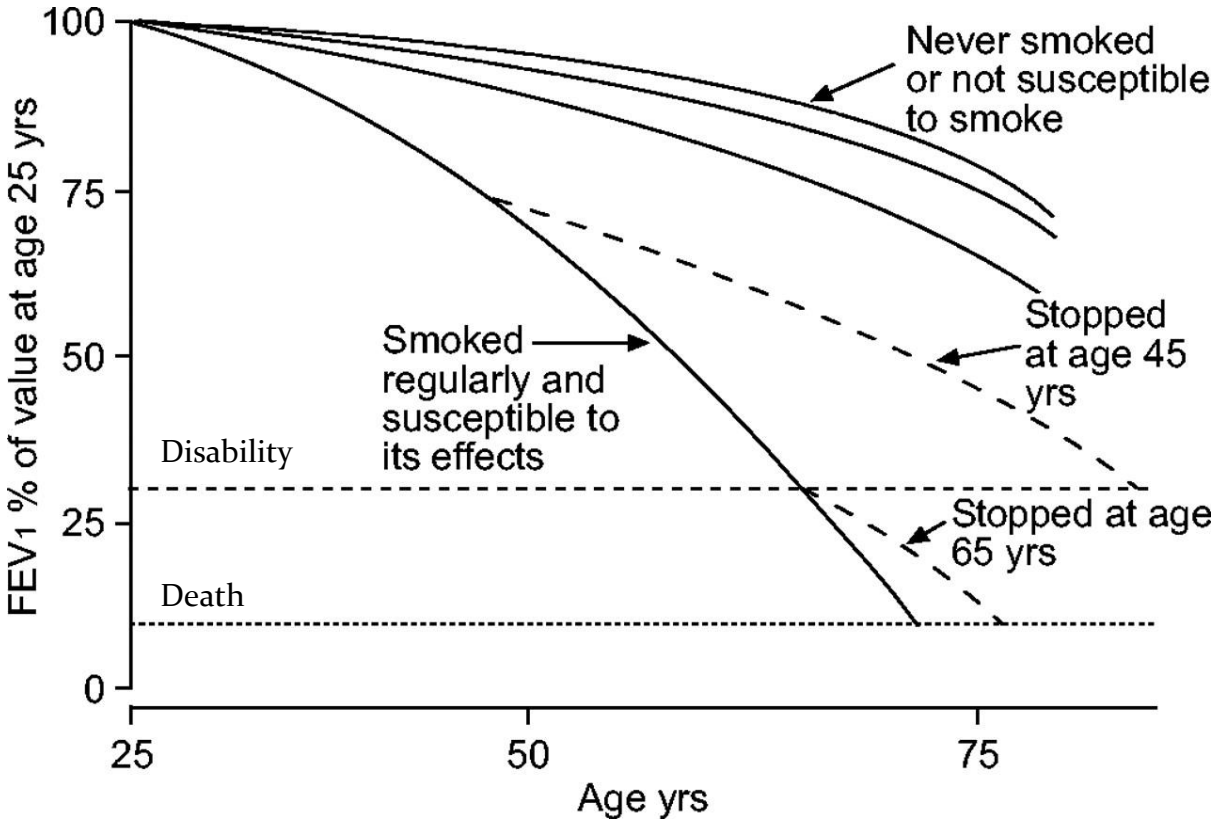


Figure 2.3 Rate of FEV1 decline over time in smokers and the potential effects of stopping smoking

(reproduced from [The natural history of chronic airflow obstruction, Fletcher C and Peto R, BMJ 1977;1: 1645-1948] with permission from BMJ Publishing Group Ltd.)

Current Australian clinical guidelines have several recommendations and strategies for preventing further deterioration in people with COPD[52]. Smoking cessation is a key early intervention as it reduces the rate of lung function decline [53] and there is high level evidence supporting the use of nicotine replacement therapy [54] and counselling in suitable cases [55]. Influenza vaccination [56], use of bronchodilators [57] and mucolytic agents [58] are also recommended to reduce the frequency of exacerbation and hospitalisation. The use of long-term oxygen therapy in appropriate patients has been shown to reduce mortality [59]. Non-pharmacological management such as physical activity and pulmonary rehabilitation are recommended for symptom control and optimisation of function in people with COPD [1, 60].

As COPD progresses, the individual will experience worsening symptoms [61-63]. Persistent, distressing breathlessness (dyspnoea) is one of the most disabling features of COPD, as it not only hinders an individual's ability to exercise and participate in physical activity but also affects their daily activities[64]. Symptoms of COPD have a wide spread of impact on the individual and may range from reduced quality of life to increased risk of exacerbation and influence on long- term disease prognosis[65]. Early treatment with pharmacological and non-pharmacological interventions such as self-management strategies can improve the individual's quality of life and reduce rate of lung function decline [66, 67]. A systematic review of 79 articles (that included 31 randomised controlled trials and 48 non-randomised controlled trials/ observational studies) concluded that intervention at early stages of COPD could assist with symptom control and decrease the rate of disease progression [68]. Hence early intervention and management is recommended and can optimise the quality of life of individuals with COPD.

2.1.4 Challenges in the timely diagnosis of COPD

While benefits of early diagnosis and management of COPD are clear, COPD is commonly under-diagnosed until the disease reaches an advanced stage. In the Australian cohort of the Burden of Lung Disease (BOLD) study, 5.2% of respondents who were 40 years or older reported having a previous diagnosis of COPD. However post-bronchodilator spirometry revealed that 14.5% of this sample had COPD GOLD

stage I or higher [3]. Similar statistics of high prevalence of undiagnosed COPD have also been reported in Spain [69], Norway [70] and Brazil [71].

While under-diagnosis of COPD might be common, concerns have also been raised about over or misdiagnosis of COPD. In a review of medical records of patients hospitalised for acute exacerbation of COPD, only 21% of these patients had spirometry performed within the past two years[72]. Similarly, Spero, Bayasi [73] found that spirometry results of patients who underwent spirometry during hospitalisation for a respiratory complaint and were coded as having COPD were not consistent with the GOLD criteria of COPD diagnosis in 30% (120/390). Of those with spirometry results inconsistent with COPD diagnosis, over 30% (39/120) were sent home with medications for COPD treatment[73]. This not only generates unnecessary cost for medications, but may also be accompanied by possible side effects[74, 75].

Currently spirometry is the gold standard in the diagnosis of COPD and is recommended in clinical guidelines for COPD [1, 52, 76]. In a study of 227 general practices in the UK, 44% reported spirometry was rarely or only used sometimes in the diagnosis of suspected COPD[77]. Similar conclusions of low spirometry usage was found in a national survey of general practices in Australia [78]. Previous qualitative studies have revealed common barriers to the use of spirometry, including lack of time [79], lack of accessibility or unfamiliarity with the spirometry equipment[80, 81] and physician scepticism about the relevance of the use of spirometry in the diagnosis and treatment of COPD [82]. The challenges of making a timely diagnosis are recognised with public health campaigns such as "World COPD Day" designed to raise awareness about COPD amongst the general public and recommendations within clinical guidelines for COPD case finding in primary care [52, 83].

2.1.5 Current recommendation for screening for COPD

Population-level screening for COPD is controversial. While results of the international population-based Burden of Obstructive Lung Disease (BOLD) study highlighted the high prevalence of undiagnosed COPD internationally[84], a systematic review by the US Preventive Services Task Force found no direct evidence of improved clinical outcomes with generalised population-based screening for COPD

and did not recommend screening in asymptomatic individuals [12]. It should be emphasised that the US Preventative Task Force recommendation on screening was focused on asymptomatic individuals. There might still be benefits in screening in people experiencing symptoms. However the presence of respiratory symptoms may not be consistently reported to clinicians due to poor recognition of respiratory symptoms or individuals may consider symptoms such as coughing or shortness of breath with exercise as a natural outcome of aging or reduced fitness levels [85]. The under-reporting of respiratory symptoms by patients was recognised and acknowledged in the 2018 GOLD report [1].

2.1.6 Common COPD case-finding strategies

Active case-finding through spirometry in at-risk groups such as those present with symptoms and/or risk factors is recommended by GOLD[1]. Individuals over age 40 with respiratory symptoms, who present with a history of risk factor exposure and/or a family history of COPD are the key indicators recommended by GOLD for investigating a diagnosis of COPD[1]. The Australian and New Zealand guidelines for the management for COPD (COPD-X) had similar recommendations on performing spirometry for at risk individuals over age 35, with a history of risk factor exposure and a strong family history of COPD[52]. Smokers are often the target group in COPD case-finding studies in the primary care setting [86, 87]. Apart from smokers, case-finding studies have also targeted individuals who may have been exposed to vapours, gases, dust or fumes in their occupation such as miners and farmers [88].

In a recent systematic review (n = 39 studies) by Haroon, Jordan [89] on the effectiveness of case finding strategies for COPD in primary care, age and smoking history were two of the most common inclusion criteria (used in 37 and 21 studies respectively) in the COPD case finding studies included. Interestingly, none of the 39 studies used family/parental history as inclusion or exclusion criteria[89]. The age inclusion ranged from 30 to 50 years with age over 40 as the most common inclusion criterion (>30yrs = 3 studies, >35yrs = 6 studies, >40yrs = 25 studies, >45yrs = 1 study, >50yrs = 2 studies). Overall any active case finding strategy resulted in identifying more new cases of COPD compared with usual care[89]. Studies that targeted high risk groups such as smokers and used a pre-screening questionnaire or handheld flow

meters appeared to achieve a higher yield of new COPD diagnoses compared with no pre-screening, however there were too few randomised controlled trials and the studies were heterogeneous in nature which limits the ability to conclude the effectiveness of different case-finding strategies[89].

Following the systematic review by Haroon, Jordan [89], Jordan, Adab [90] published the results of a cluster randomised controlled trial that targeted ever-smokers aged 40-79. An active case finding approach (mail screening questionnaires with reminders to reply, followed by invitation to attend spirometry in those with respiratory symptoms) was found to be more cost-effective and twice as effective compared with an opportunistic case finding approach (general practice staff handing out screening questionnaires during visit and those with respiratory symptoms invited to attend spirometry)[90]. Data from the cluster randomised controlled trial were used to develop the TargetCOPD risk score with an algorithm to predict risk of undiagnosed COPD, predictors of the score include age, smoking status, dyspnoea, prescription of salbutamol and antibiotics[91].

Key concepts: COPD is a debilitating chronic condition, the burden of COPD can be reduced by a timely diagnosis followed by appropriate management. Population based screening is not currently recommended however COPD case-finding in at risk groups is encouraged. Current COPD case finding strategies most commonly target individuals based on their age and smoking history.

2.2 Risk factors for development of COPD

In addition to cigarette smoking, various risk factors and exposures such as genetics and environmental exposures have been shown to play a significant role in the development of COPD [1, 9, 52]. In 2010, the American Thoracic Society published an official policy statement that comprehensively summarised risk factors for COPD[9]. They will be discussed below from a life course and intergenerational perspective.

2.2.1 Examination of risk factors for lung health from a life course perspective

Risk factors associated with later life lung health and COPD development may be present during different stages of a person's life. This can be illustrated by the graphical representation (Figure 2.4) by Postma, Bush [92] which presented COPD risk factors from a life course perspective.

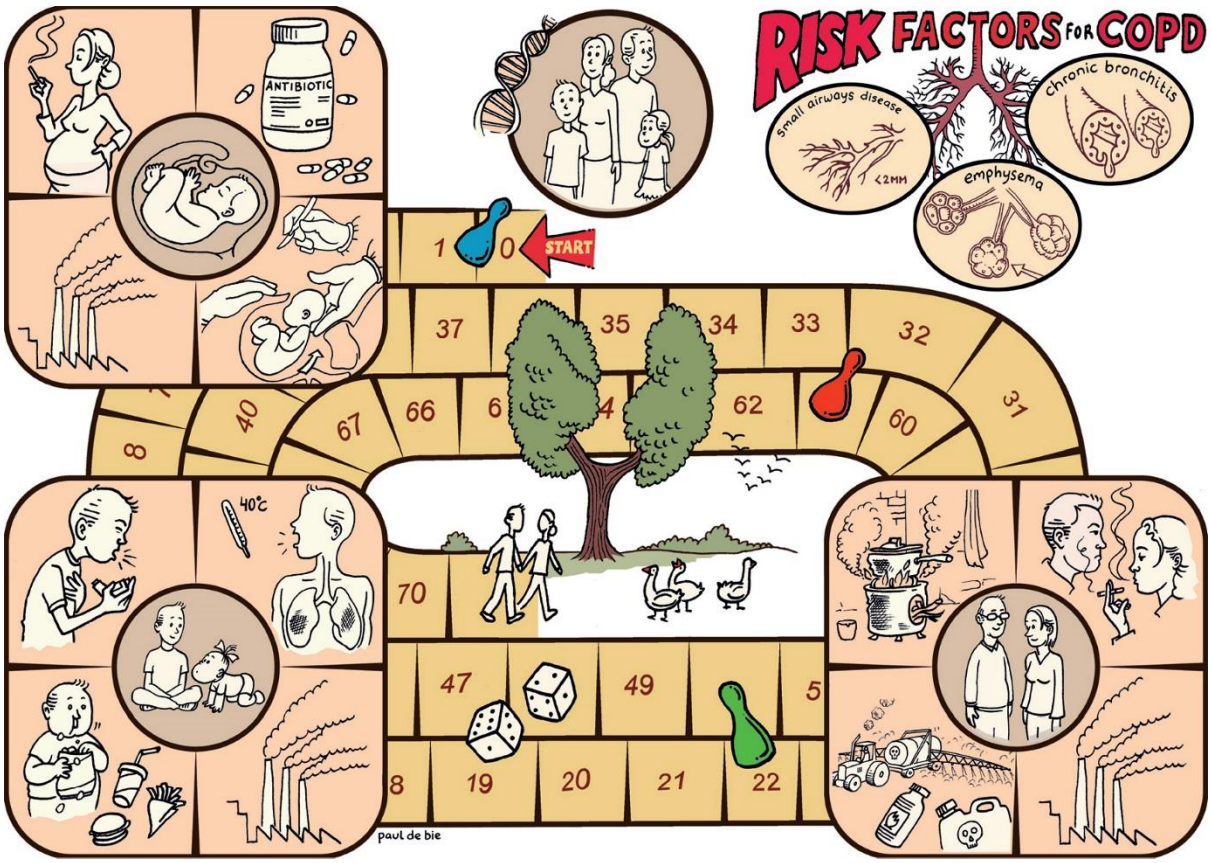


Figure 2.4 Graphical representation of risk factors for COPD across the life course
(Upper left corner = in-utero factors; Lower left corner = childhood factors; Lower right corner = adulthood factors) (Reprinted from The Lancet, vol 385, Postma, Bush & van den Berge, Risk factors and early origins of chronic obstructive pulmonary disease, p. 899-909, 2015 with permission from Elsevier)

A life course approach recognises that various exposures throughout life "independently, cumulatively and interactively influence health and disease"(p.778) [93]. A life course history approach to the development of COPD examines the contribution of both early life factors (e.g. childhood respiratory disease, prematurity and low birthweight[94, 95]) jointly with later life exposures and factors (e.g. smoking,

socioeconomic status, air quality[96]) to identify risk and protective processes across the lifespan.

Alpha-1-antitryspin deficiency is an established genetic risk factor for COPD development in non-smokers[97], however only about 3% of people with COPD have the deficiency [98, 99]. In-utero exposure to maternal smoking has a significant impact on the offspring's lung function in early adulthood [100]. Other early life factors can have long-term consequences on lung function and lung health[92, 95]. Longitudinal studies have found people with asthma may have accelerated lung function decline [101] and those with long standing asthma are more likely to have persistent airway obstruction [102]. Childhood pneumonia has been associated with increased risk of COPD and reduced adulthood lung function in adult smokers [103]. A recent systematic review by Kouzouna, Gilchrist [94] summarised evidence on the association between early life factors and reduced lung function in later life and concluded that low birth weight/ prematurity, parental history of respiratory allergy and/or asthma, respiratory symptoms in childhood and respiratory illness (early life respiratory infections, airway hyper-responsiveness, asthma and wheeze) were associated with lower FEV_1 in later childhood which may extend into adult life.

Lung function normally peaks in early adulthood followed by a natural decline with increasing age [104]. Analysis of longitudinal lung function data from the Tucson Children's Respiratory study identified a group of individuals with persistent low lung function trajectory since birth to the fourth decade which was associated with COPD [105]. Accelerated decline in lung function may lead to the presence of respiratory symptoms and disability [51, 106, 107]. Failure to achieve the maximally attained lung function in early adulthood has been reported as an important predictor of later life COPD diagnosis. Lange, Celli [108] identified four distinct lung function trajectories using longitudinal FEV_1 data from three cohort studies. Duffy, Weir [109] used data from Lange, Celli [108] to produce Figure 2.5 which summarises trajectories with maximally attained FEV_1, observed FEV_1 decline over time and the hypothetical trajectories. This figure highlights the current state of knowledge on the different lung function trajectories through the life course.

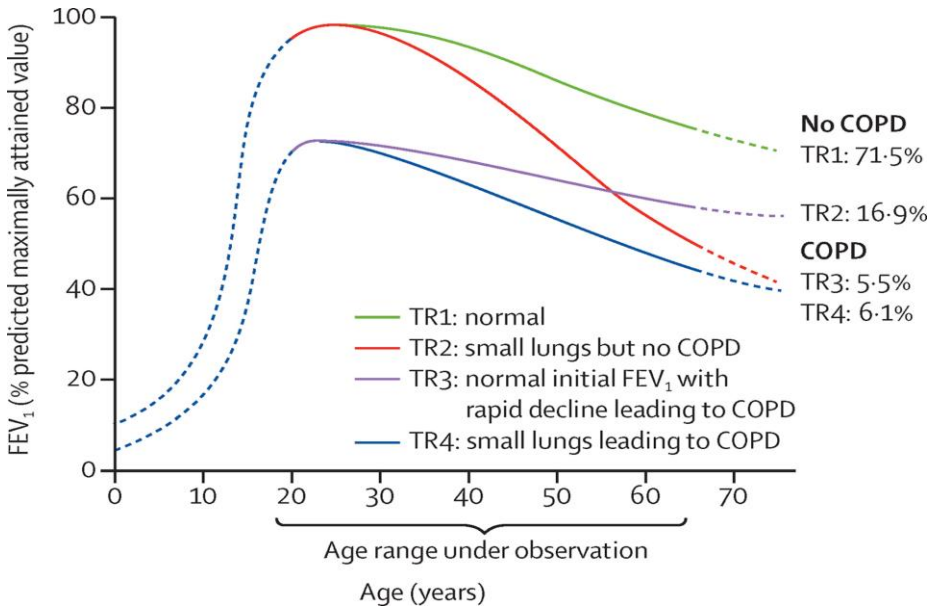


Figure 2.5 Four different FEV1 trajectories (TR) observed in the Framingham Offspring Cohort and the Copenhagen City Heart study.

TR = Trajectory; Solid lines represent observed changes, dash lines represent hypothetical trajectories. (Reprinted from The Lancet, vol 3, no 12, Duffy, Weir & Criner, The complex challenge of chronic obstructive pulmonary disease, p. 917-919, 2015, with permission from Elsevier.)

People who smoke have an accelerated lung function decline [110] and epidemiological evidence supports a causal relationship between smoking and COPD [111]. While smoking is a key risk factor for COPD, it is not the only cause of COPD. Data from 14 sites of the international Burden of Obstructive Lung Disease (BOLD) with a total of 10,000 subjects found that never smokers contributed to over 20% of all COPD cases [8].

Exposure to environmental factors across the lifespan have also been identified as risk factors for COPD. A meta-analysis (n = 11 epidemiological studies) conducted by Ryu, Sunwoo [112] on occupational exposure to vapour, gas, dust or fumes found individuals exposed had increased odds of developing COPD compared to those not exposed (pooled odds ratio [OR] = 1.43, 95%CI = 1.19-1.73). Exposure to biomass smoke as a result of combustion of solid fuels (e.g. wood, charcoal) for home heating or cooking concluded exposure to biomass smoke is a risk factor for COPD (meta-analysis n = 15 studies , pooled OR = 2.44, 95%CI = 1.90-3.33)[113]. A dose-response relationship between exposure to biomass smoke and COPD development has also been

reported[113]. Exposure to air pollution and passive smoke have also be associated with reduced pulmonary function and increase risk of COPD [114-118].

Furthermore, low socioeconomic status has been associated with increased risk of COPD[119]. The mechanism of the association is unclear as socioeconomic status is complex and may be linked with exposure or non-exposure to other risk factors such as smoking[120]. While individual risk factors for COPD are well recognized, the inter-relationships between these risk factors require further investigation as pathways to COPD development are complex [1]. Furthermore, a given individual may experience multiple factors over the life course for different duration, which in theory would increase their risk of developing COPD.

2.2.2 Adult offspring of people with COPD as an at-risk group

A family history of COPD is recommended as one of the indicators for considering a diagnosis of COPD in symptomatic individuals [1, 52]. Considering that the risk factors for COPD may be present in different stages of a person's life with a mixture of genetic, early life and environmental factors, adult offspring of people with COPD may present as a unique at risk group with greater chances of exposure to risk factors due to the shared genetics and living environment for a part of the offspring's life. A family history of COPD may be identified via two approaches: A descendant approach where individuals with diagnosed COPD and who have one or more adult offspring are identified. Or an antecedent approach where individuals self-report whether one or both of their parents had a diagnosis of COPD.

An early population- based study identified aggregation of chronic bronchitis and pulmonary function in individuals living within the same household [121]. A higher prevalence of children with asthma and bronchitis had a parent with a chronic lung condition living within the same household when compared with children living with parents without a chronic lung condition in a case control study [122]. Both studies commented that the association of household aggregation of lung function or condition was not explained by smoking habits. The shared home environment and the potential shared exposure to environmental risk factors such as passive smoke or biomass smoke may explain the familial aggregation of pulmonary function[9].

Adult offspring of people with COPD present as a unique at-risk group as they may have been exposed to more COPD related risk factors when living in the same environment as their parents especially during their early life. Any exposure to other risk factors in later life or the duration of exposures may further increase the adult offspring's risk of COPD development.

2.2.3 Potential pathways influencing the lung health in adult offspring of people with COPD

There are a number of theoretical models used in life course epidemiology which may be used to investigate the intergenerational and life course influences on lung function and COPD development[10]. The different models not only take into account the type of exposure but also its timing, "dose" and inter-relationship with other factors. Potential pathways from parental history to adulthood reduced lung health or COPD development may involve a combination of intergenerational influence and associations between risk factors across the life course (Figure 2.6).

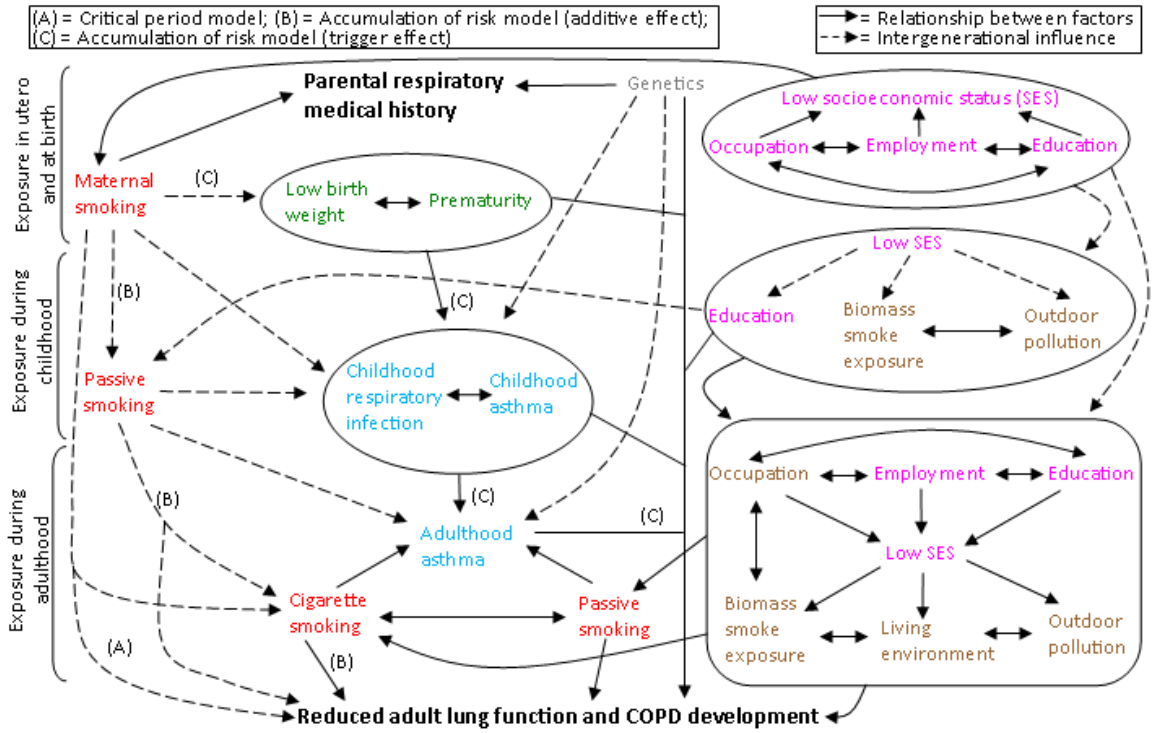


Figure 2.6 Proposed influence of intergenerational and life course factors on adulthood lung function and COPD development

Risk factors present at different stages of the life course were colour coded. Figure text colour key: red = smoking related factors; green = early life factors; grey = genetics; blue = respiratory illnesses; pink = related to their socioeconomic status; brown = environmental factors

The *critical period model* emphasises that exposure to a stimulus during a specific time period has a lifelong effect on an individual's physiology [123]. For example, being exposed to maternal smoking (Path A in Figure 2.6) during pregnancy or after birth can have deleterious effects on the offspring's lung structure and function [124]. Offspring of smoking mothers are more likely to have reduced intrauterine fetal growth and low birth weight [125, 126], which negatively impacts offspring's pulmonary function (FEV_1)[127]. These factors increase the risk of wheezing and asthma which are also associated with greater declines in lung function in later life [128, 129]. A longitudinal study that followed school children into adulthood found those who had childhood asthma or wheezy bronchitis had a more rapid decline in lung function and significantly lower FEV_1 at middle age compared to the control group [130]. Similarly, Tai, Tran [131] followed a cohort of Australian primary school children and reported that those with a history of severe asthma in childhood were associated with increased risk of developing COPD in middle age even in the absence of a smoking history. Therefore, being exposed to maternal smoking or respiratory illness in early life could affect the offspring's lung health and possible development of obstructive lung disease in later life.

On the other hand, the *accumulation of risk model* hypothesises that exposure to different risk factors at different stages in life can have an *additive effect* [123]. Smoking is the main risk factor for COPD; family environment and parents' level of disapproval for smoking can greatly influence their offspring's personal smoking behaviour [132]. Offspring of parents who currently smoke are two to three times more likely to start smoking at a young age compared with children of non-smoking parents [133]. An individual who was exposed to maternal smoking, passive smoking and personal smoking (Path B in Figure 2.6) is predicted to have a higher risk of developing COPD compared to another individual with a similar life course who was exposed to maternal and passive smoking but did not smoke themselves [134].

The *accumulation of risk model* also postulates that early life exposure can have a *trigger effect* and shape the trajectory of one's life [123]. Maternal smoking [128], prematurity [135], low birth weight [126], childhood respiratory infection [136] and childhood asthma [129] have all been shown to have separate impact on the offspring's

lung function and increase the risk of development of COPD in later life. However these risk factors are also associated with each other. For instance, maternal smoking (Path C in Figure 2.6) is associated with prematurity and low birth weight [137]; prematurity increases the risk of childhood respiratory illness [138]; having the history of respiratory illness as a child is associated with the development of asthma [139] and greater lung function decline in individuals with asthma has been associated with COPD [129]. This model demonstrates the risk factors can act sequentially, similar to a pathway, where one leads to another and eventually to developing or not developing COPD.

Key concepts: COPD development is complex and relatively few studies have investigated inter-relationship of exposures to COPD risk factors leading to COPD development. Identification of individuals with exposure to multiple risk factors may allow early identification and intervention in those most at risk. Exposure to risk factors during different stages of life may explain lung function trajectory deviations. Life course approaches are an appropriate approach to investigate lung health in adult offspring of people with COPD. Theoretical models may be used to investigate respiratory health in parent-offspring pairs and the intergenerational and life course influences that affect the association.

The prevalence and risk of developing COPD in adult offspring of people with COPD is not well described, Study I (Chapter 3) presents a systematic review and meta-analysis to investigate the lung health in this specific population. The association of reduced lung health in parent-offspring is also investigated in Study II (Chapter 4) taking into account exposure of intergenerational and life course factors.

To explore the association between parents with COPD and the lung health in their adult offspring requires examination of both intergenerational and life course exposures associated with lung health. The next section will discuss methods of collecting these intergenerational life course data.

2.3 Methods of collecting and examining intergenerational life course data regarding lung health

A life course approach appears ideally suited to investigate these complex intergenerational and life course influences on development of COPD as it allows the researcher to isolate exposure to specific or multiple risk factors and if relevant the length of the exposure. Previous studies have collected life course data either in a longitudinal cohort study design (prospective or retrospective) or using a life history calendar (retrospectively) in a cross-sectional study design. Examples of each type of studies are provided below.

2.3.1 Longitudinal cohort studies that have examined intergenerational and/ or life course lung health

Table 2.1 is a summary of key longitudinal cohort studies that have examined intergenerational and/or life course lung function and/or COPD development. The Framingham Heart Studies were able to recruit the original cohort's second (children) and the third (grandchildren) generation to participate in the study creating a rich pool of intergenerational life course data [140-142]. Givelber, Couropmitree [143] used spirometry data collected from the original Framingham cohort and the offspring cohort during their adulthood (mean age 53-54yrs) to demonstrate familial aggregation of pulmonary function. The Busselton Health Study recruited adults living in the Busselton area of Western Australia via electoral roll information and children through schools [144]. This cohort underwent health examinations and comprehensive surveys every three years [145]. A study on 468 nuclear families within the Busselton study found evidence of genetic determinants explaining familial aggregation of lung function [146].

Table 2.1 Key longitudinal cohort studies that examined intergenerational and life course factors on lung function/ COPD development

Name[#] (Country)	Year when study commenced	Cohort age at recruitment	No. of follow up and year of actual/ plan completion of most recent follow up*	Sample size when study commenced	Was the main intent of the original study respiratory related? *	Key intergenerational OR life course lung function findings
Busselton Health Study (AU)[144, 145]	1966	>18yrs, and school children	12th follow up on original cohort concluded in 1995	3,539	No (Focused on cardiovascular health)	Intergenerational [146]
European Community Respiratory Health Survey (ECRHS) (25 countries)[147]	1990	20-44yrs	2nd follow up concluded in 2012	137,619	Yes (Asthma distribution and health care given for asthma)	Intergenerational [148] Life course [149, 150] Intergenerational and life course[151]
Framingham Heart Study (US) (original cohort)[140]	1948	30-62yrs	31st follow up concluded in 2014	5,209	No (Focused on cardiovascular health)	Intergenerational [143]
The offspring study (offspring of Framingham cohort)[141]	1971	12-60yrs	8th follow up concluded in 2014	5,124		
Third Generation Cohort (offspring of offspring cohort)[142]	2002	>20yrs	2nd follow up schedule to conclude in 2019	4,095		
Swiss study on Air Pollution And Lung Disease In Adults (SAPALDIA) (Switzerland) [152-154]	1991	18-60yrs	2nd follow up concluded in 2011	9,651	Yes (Air pollution and respiratory health)	Life course [150]

[#]Studies ordered alphabetically

*Based on data from the individual study's website, or information from published studies if site information was not up-to-date

The European Community Respiratory Health Survey (ECRHS) collected information on respiratory health and lung function data from 56 sites in 25 countries mostly within Europe but also in Canada, United States of America and Australia [147, 155]. Maternal smoking (especially during pregnancy) was associated with reduced cohort FEV_1/FVC ratio and increased the cohort's odds of experiencing respiratory symptoms including cough and phlegm (OR = 1.32, 95%CI= 1.11-1.57), with consistent results between geographic centres[148]. Self-recall of early life serious respiratory infection before five years of age and ever being hospitalised for a lung disease before two years of age were associated with lower level of lung function in adulthood and increased odds of report of persistent wheeze (OR = 1.31, 95%CI = 1.02-1.66; OR = 2.24, 95%CI = 1.40-3.57 respectively)[149]. Early life risk factors including maternal asthma, paternal asthma, childhood asthma, childhood respiratory infections were individually associated with COPD. The odds of developing COPD in individuals exposed to three or more early life risk factors (Men: OR = 6.32, 95%CI=2.35-16.98; Women: OR = 7.16; 95%CI= 2.75-18.64) were comparable to the impact of current smokers who smoked more than 20 cigarettes daily (Men: OR = 3.70, 95%CI=2.05-6.69; Women: OR = 3.82; 95%CI= 2.04-7.13)[151]. A more recent study known as Respiratory Health In Northern Europe, Spain and Australia (RHINESSA) investigate the offspring and parents of participants from the ECRHS cohort with an aim to assess lung health through the lifespan and across generations[156]. There will likely be future publications that examine international and life course factors on lung function/ COPD development using data from this study.

Another large national cohort study with a specific respiratory focus was the Swiss study on Air Pollution And Lung Disease In Adults (SAPALDIA)[152]. Dratva, Zemp [150] used data from these two European cohorts and identified that early life exposures such as the season an individual was born, maternal age and maternal smoking were associated with more rapid decline of lung function in later life.

In the studies discussed above, participants were recruited based on specific locations and usually after childhood (Table 2.1). Another type of cohort studies, birth cohort studies, recruit participants born in a specific period of time and allow collection of early childhood factors[157]. Table 2.2 is a summary of key birth cohort

Table 2.2 Key birth cohort studies that examined intergenerational or life course factors on lung function/ COPD development

Name[#] (Country)	Year when study commenced	Cohort age at recruitment	No. of follow up and year of actual/ plan completion of most recent follow up*	Sample size when study commenced	Was the main intent of the original study respiratory related? *	Key intergenerational OR Life course lung function findings
Aberdeen WHEASE cohort (UK) [158]	1964	10-14yrs	Completed 4th follow up in 2014 (58-64yrs)	2,511	Yes (Investigation of respiratory symptoms – random sample of 20% of larger Aberdeen Child Development Study)	Life course [159]
Dunedin Multidisciplinary Health and Development study (NZ) [160]	1972	0yrs	13th follow up scheduled to conclude in 2019 (45yrs)	1,037	No (Nature, prevalence and factors associated with development and health problems)	Life course [161]
Dutch famine birth cohort study (Hunger winter study) (Netherlands) [162, 163]	First publication in 1947	Traced and interviewed at age 43	1995-1996 (50-58yrs)	5,425	No (Focused on the effects of poor maternal nutrition during pregnancy)	Intergeneration (critical period exposure) [164]
Melbourne Epidemiological Study of Childhood Asthma (AU) [129]	1964	7yrs	7th follow up concluded in 2007 (50yrs)	479	Yes (Prevalence and natural history of asthma and wheezy bronchitis)	Life course [131]

Name[#] (Country)	Year when study commenced	Cohort age at recruitment	No. of follow up and year of actual/ plan completion of most recent follow up*	Sample size when study commenced	Was the main intent of the original study respiratory related? *	Key intergenerational OR Life course lung function findings
National Child Development Study (1958 British Birth Cohort) (UK)[165]	1958	0yrs	10th follow up scheduled to commence in 2018 (60yrs)	17,638	No (Social and obstetric factors linked to stillbirth and neonatal death)	Life course [166, 167]
National survey of Health and Development (1946 birth cohort) (UK) [168]	1946	0yrs	23rd follow up concluded in 2011 (60-64yrs)	16,695	No (National fertility rate, obstetric medical and midwifery services)	Life course [169]
Tasmanian Longitudinal Health Study (AU)[170]	1968	7yrs	6th follow up concluded in 2016 (55yrs)	8,583	Yes (Prevalence and natural history of asthma in childhood)	Life course [171]
Tucson Children's Respiratory Study (US) [172]	1980	0yrs	13th follow up concluded in 2012 (32yrs)	1,246	Yes (Explore early life origins of asthma)	Life course [173, 174]

[#]Studies ordered alphabetically

*Based on data from the individual study's website, or information from published studies if site information was not up-to-date

studies that have examined intergenerational and or life course factors on lung function or COPD development. The main advantage of birth cohort studies is that early life risk factors are collected prospectively.

An example of a birth cohort study is the Dutch famine birth cohort. Food supply to the north-western parts of The Netherlands was blocked between October 1944 and May 1945 during the war which resulted in widespread starvation. The Dutch famine birth cohort included individuals born in three clinics in Amsterdam between 1944 and 1946 [175]. The effects of exposure to the famine on the pregnancy and long term consequences of exposure to famine at different stages of pregnancy on later life health has been examined [163, 176, 177]. Exposure to famine during the mid or early gestation period was associated with increased prevalence of respiratory symptoms and obstructive airways disease at age 50, highlighting the adverse effects of in-utero and early childhood exposure on later life lung health [164].

Four key birth cohort studies with a strong asthma focus were identified. The Melbourne Epidemiological Study of Childhood Asthma and the Tasmanian Longitudinal Health Study both recruited participants at age seven with an aim to determine the prevalence and natural history of asthma. Cohort members were in their 50's in the most recent follow up [129, 170]. Cohort members of the Tasmanian Longitudinal Health Study with lower lung function at age seven were at increased risk of COPD and asthma-COPD overlap syndrome (ACOS) at age 45 [171]. Similarly, in the Melbourne Epidemiological Study of Childhood Asthma, childhood severe asthma was found to be a significant predictor of COPD at age 50 [131]. Similar results were reported in the Aberdeen WHEASE (What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically) cohort where childhood asthma was associated with increased risk of COPD (OR = 6.37, 95%CI = 3.73 – 10.90) in the fifth decade[159].

The Tucson Children's Respiratory Study included a cohort of healthy infants born in 1980-1984 and cohort members were most recently followed up at 32 years[178]. The aim was to investigate a variety of potential risk factors, early life acute lower respiratory tract illness and later life development of chronic lung disorders[172]. A

subgroup of the cohort had their pulmonary function measured shortly after birth; worse lung function in early infancy was associated with low lung function at age 22[173]. Similar to findings in the ECRHS data by Dharmage, Erbas [149], cohort members in the Tucson Children's Respiratory Study with early life radiologically ascertained pneumonia had lower lung function in adulthood (at 26 years) and increased risk for asthma (OR = 1.95, 95%CI = 1.11-3.44) and wheeze (OR = 1.94, 95%CI = 1.28-2.95) (at 29 years) [174].

Life course data from three other birth cohort studies that did not originally have a specific respiratory focus have also led to investigations on the influence early life factors on later life lung function. The Dunedin Multidisciplinary Health and Development study was a prospective birth cohort that measured cohort lung function at age 9 to 38. Childhood asthma that persisted to adulthood was associated with airflow obstruction at 38 years [161]. In the National Child Development Study (1958 Birth Cohort) childhood pneumonia was associated with increased cough and phlegm symptoms at age 23[167], however it was not was associated with the rate of lung function decline between 35 and 45 years [166]. Analysis of the National Survey of Health and Development (1946 Birth Cohort) indicated that personal smoking can modify the effects of early life adversity (infant respiratory infections and home overcrowding) on lung function at age 43 [169].

To investigate the potential pathways to explore respiratory impairment in adult offspring of people with COPD, longitudinal cohort studies appear ideal as they contain valuable sources of life course data with data collected prospectively at different stages of the participant's life which minimises recall bias[179]. None of the studies presented in Tables 1 and 2 had an original intent to investigate intergenerational lung health. On the other hand, there were a few cohort studies that had a specific focus on asthma and respiratory health. Although prospective longitudinal studies that recruited adults have examined early life factors on later life lung health, data on early life factors were collected based on retrospective recall through standalone questions [149]. Alternatively, birth cohort studies that recruited infants since birth or during childhood provided a broad range of comprehensive data

across the life course that allowed examination of early life and later life factors on later life lung health with a lower risk of recall bias.

Data from birth cohort studies from different countries have allowed researchers to examine exposures across the life course and the long term health outcome such as the development of chronic diseases[180, 181]. Birth cohort studies are ideal sources of intergenerational life course data since they not only contain data on the cohort across their life span, but may also contain richer data on the parents as data are typically collected from parents during the birth cohort's early life and childhood years. While longitudinal birth cohort studies are expensive to conduct, they provide valuable information for a broad range of research questions and can provide evidence for policy makers [182, 183].

The UK has a strong history of conducting birth cohort studies with four currently ongoing national birth cohorts, with cohort members born in 1946 (National Survey of Health and Development), 1958 (National Child Development Study), 1970 (1970 British Birth Cohort) and 2000-2002 (UK Millennium Cohort Study). The 1946, 1958 and 1970 British Birth Cohort included all births that took place during a week in that year throughout England, Wales and Scotland [165, 168, 184]. The UK Millennium Cohort included all births between September 2000 and January 2002 in the UK [185]. Cohort members from each of the four birth cohorts were followed up, with ongoing data collection even for the oldest birth cohort up until the present[186]. Each of the UK birth cohort studies collect a wide range of life course data around social circumstances and health outcomes. For instance, the association between childhood factors on later life adulthood health outcomes has been examined and compared between the 1958 and 1970 British birth cohorts [187]. Researchers have used data collected from the 1958 birth cohort to examine the natural history of asthma[188] and influence of early life factors on adult lung function[189]. However none of these studies have used a life course approach to examine associations between parental and adult offspring lung health and examining influences of life course factors on the association.

Key concepts: While data from longitudinal studies have been used to examine familial aggregation of pulmonary function and the association between early life factors on lung health in adulthood or COPD development, there appears to be limited studies that used these longitudinal data to examine the association between parental respiratory diseases, such as COPD, with offspring adulthood lung health and the crucial factors that could mediate the pathway.

A life course approach was used in Study II (Chapter 4) to explore potential life course factors which could explain the association between parental history and reduced lung health in offspring using data from the 1958 British Birth Cohort.

While longitudinal cohort studies provide valuable data on intergenerational and life course factors, there are limitations of conducting secondary analysis. Firstly, access to raw data from these longitudinal data may be limited and costly. Attrition and missing data may also be problematic in longitudinal cohort studies with multiple waves of data collection across the life course. Finally, the original aims and scope of studies may lead to variations in the way data were collected and coded which limits the research questions that can be answered[190]. In addition to interrogating data collected from existing longitudinal cohort studies, there is a need for primary data collection in the investigation in the respiratory impairment in adult offspring of people with COPD. The following two sections will discuss potential ways to collect life course data retrospectively and strategies to recruit two generations of participants.

2.3.2 Life history calendar (retrospective)

Life history calendars have been used as tools to retrospectively collect information regarding life course events and circumstances in cross-sectional studies[191]. The life history calendar can be administered through a semi-structured interview in a paper and pencil format, over the phone or through a computer-assisted telephone interview [192-194]. A typical life history calendar contains columns that represent time (e.g. month, year) and rows that are relevant to specific data that the researchers wanted to collect (e.g. place of residence, education)[194]. This allows researchers to collect data

on timing of specific events (e.g. marriage, birth of children) and also duration of events (e.g. number of years in school, number of years living with a smoker). The sequence of events or timing of exposures may provide data for researcher to study effects of critical period exposure or accumulation of risk on their lung function trajectory.

Although the life history calendar is based on self-reported data, a review by Glasner and Van der Vaart [195] found this method to be beneficial in improving the accuracy of life course data collected retrospectively and that visualisation of the calendar increased the completeness of data. Data collected by life history calendars may be as accurate as medical record data. For example data collected on the use of oral contraceptives over time through the life history calendar method was found to be 90% accurate when compared with physician records[196]. Accuracy of retrospective life course information recall may be improved through anchoring it with significant life events. This was demonstrated in the lower odds of recall errors of residential mobility around the time of child birth when self-reported residential mobility data were compared with historical registry records[197]. Data collected using a life history calendar provided a more complete picture on participant's occupational and contraceptive history than data collected using a questionnaire [198, 199]. Strategies such as incorporating landmark events to the calendar as anchors and interviewer training improved the completeness and quality of data collected through the life history calendar [200, 201].

Researchers have used the life history calendar for a variety of reasons such as to examine the role of economic uncertainty on age at first childbirth[202], identify patterns of drug use[203], investigate the genetic and environmental influence of psychoactive substance use in twins[204], explore phases of disability using a mixed-methods approach[205] and identify pain management treatment and outcome trajectories to facilitate communication and management[206]. The life course history calendar method was found to be economical in a study that collect comprehensive life course data in 1,261 Australian older adults (60-64 years)[207], that allowed examination of potential pathways from childhood circumstances through to later life well-being [208].

Key concepts: The life history calendar method seems to be a feasible way to collect a broad range of life course data. It appears that no existing life history calendar has been designed or used to specifically collect data relevant to risk factor exposure for lung health.

A life history calendar ("The Story Of My Life calendar") was designed as part of this research program with a focus on collecting data on exposures relevant to lung health across the lifespan. The procedure and acceptability of using this instrument in a general population was piloted and discussed in Study III (Chapter 5), followed by application of the instrument on people with COPD and their adult offspring in Study IV (Chapter 6).

2.3.3 Recruitment approaches for dyads of parents and offspring

In order to ensure reliable and complete intergenerational life course data are collected, it is essential to recruit parent-offspring pairs to complete the life history calendar separately. Using the life history calendar method may facilitate recall of intergenerational and early life information, however it does not guarantee recall of all these data, therefore it is important to also collect these data from the parent's perspective to create a more complete intergenerational and life course picture of the offspring. Dyads of parents and offspring may be identified and recruited using the antecedent (individuals self-report whether one or both of their parents had a diagnosis of COPD) or descendant (individuals with diagnosed COPD with one or more adult offspring) approach.

An antecedent direct approach has been used to recruit individuals with specific family history in intervention studies[209]. The main issue with using this approach to recruit dyads of people with a positive parental history of COPD and their parents is around the accuracy of self-reported positive parental history of COPD. When Morris, Johnson [210] asked COPD patients an open-ended question on their understanding of their illness, only 7% of COPD patients (compared to 19% of patients with congestive heart failure) accurately described the pathophysiology of their condition. When COPD patients were asked if the statement "the amount of air that can be blown out quickly (the FEV1) is reduced in people with COPD" was true or false, 40% of COPD patients provided an incorrect answer [211]. The limited understanding of COPD

patients about their condition, together with the challenges in a timely diagnosis of COPD [72, 73] may lead to questions on the accuracy of their offspring in reporting a correct parental history of COPD.

Within the genetics literature, previous studies that have recruited parents and their offspring typically first identify a person with a specific condition (proband). The researcher then uses a direct or indirect approach to recruit family members or offspring into the study through a descendant approach (Figure 2.7).

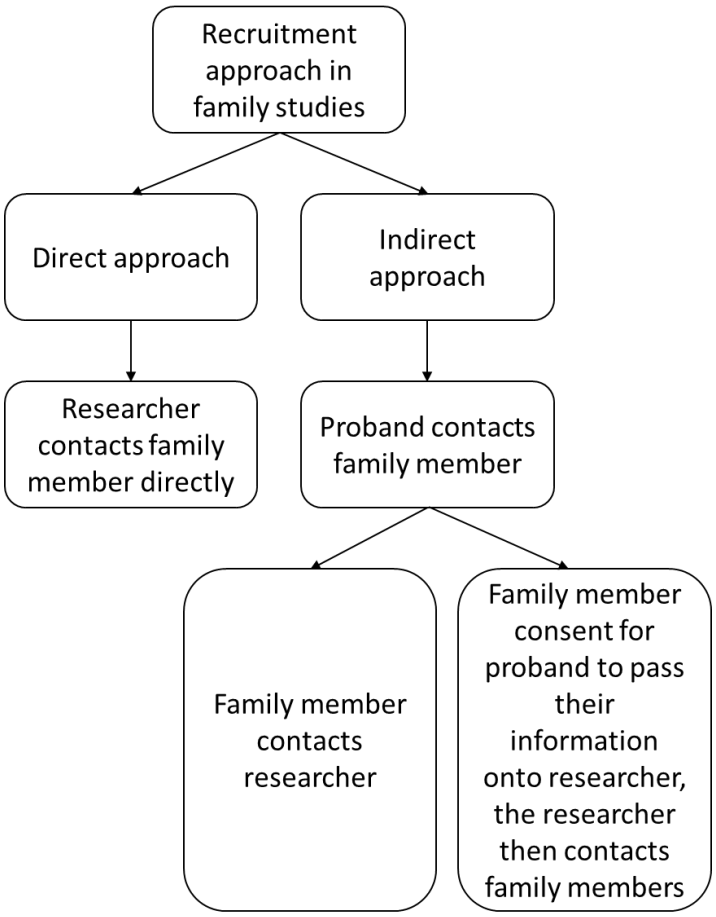


Figure 2.7 Summary of descendent recruitment approaches to recruit members of family into studies

A descendent direct approach refers to the researcher approaching the family member of a proband directly in order to recruit them into the study[212]. Although there are obvious advantages of direct contact with potential participants, there are ethical issues around breaching confidentiality, psychological and actual harms to the person

approached[212]. Considering in the case of offspring of people with COPD, potential issues may include offspring who were unaware of their parents' medical history, issues around privacy (i.e. how were the contact details of offspring gathered) and psychological harms (anxiety /distress) arising from screening or diagnosis of offspring of people with COPD.

An indirect approach is led by proband (person with a specific condition) who approaches family members and passes information onto them in order to recruit them into the study. In this approach, the researcher has no direct contact with the family member until the family member contacts the researcher, or after the family member verbally provides consent for the proband to provide contact details to the researcher. The indirect approach, also known as proband-initiated recruitment, may appear less efficient when compared with the direct approach method. In a mail survey (498 survey respondents) that focused on understanding the attitude and perspectives of probands with colorectal cancer and their first degree relatives (siblings and children age over 40) who had previously been involved in a colon cancer risk counselling study [213], the indirect approach appeared to be the more favourable method of contact. Where 79% of proband preferred to be the person initially contacting their relatives, and to be the person to provide their relatives about the research study with the researcher's contact details (78%) [213]. A lower percentage of probands (41%) were willing to provide their relative's contact details onto the researcher (i.e. direct approach) without first discussing it with their relatives [213]. While the indirect approach seem to be more preferable and would minimise some of the potential ethical issues faced in the direct approach, there could still be ethical issues around potential risk of coercion of offspring to participate by parents.

This proband-initiated recruitment strategy has been used in case-finding or screening studies, where health professionals approach people with a diagnosed or known health condition that has a familial/genetic component (i.e. the proband) and invite them to recruit their family members for screening[213]. Previous studies that have used this recruitment strategy in people with different health conditions report recruitment rates ranging from 9% (genetic testing relatives of people with breast cancer in the Bahamas) to 66% (relatives of people with Crohn's disease in the UK) [214, 215]. The

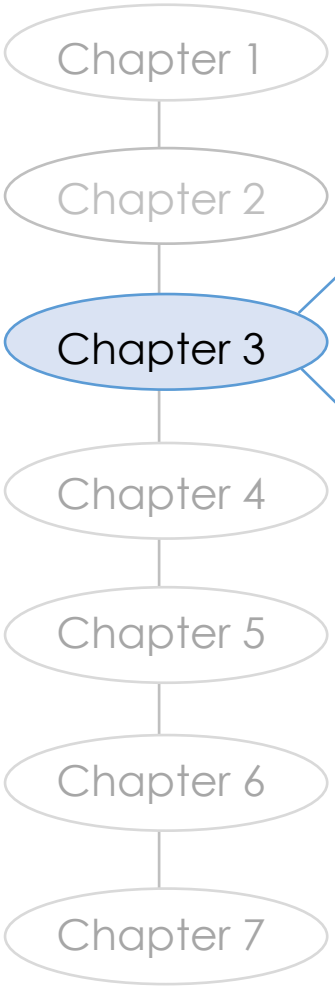
varied uptake rate may reflect the nature of the condition. While previous studies have recruited family members of people with COPD into research studies to examine their lung health, the methodology of how researchers approached family members and invited them into the studies was not reported [216, 217].

Key concepts: While the indirect recruitment approach seems to be preferable and would minimise some of the potential ethical issues, it is unknown whether practical or logistic issues may arise when using this strategy for recruiting offspring of people with COPD.

Study III (Chapter 5) presents a pilot study that investigates the practicalities of using a proband-initiated recruitment strategy to recruit pairs of parents and adult offspring in a general population. The feasibility of the recruitment strategy for adult offspring of people with COPD through their COPD parents is explored in Study IV (Chapter 6).

2.4 Chapter summary

This chapter provided general background on COPD and the challenges of timely diagnosis of COPD. Using a life course approach in the examination of intergenerational lung health, offspring of people with COPD may represent a specific at-risk group with potential exposure to intergenerational and life course factors that may alter their lung function trajectory. Potential primary and secondary life course data collection methods were discussed to lay a foundation for the investigation of respiratory health in offspring of people with COPD.



Study I : Systematic review

Are offspring of people with COPD at increased risk of developing COPD?

Intergenerational associations in COPD are well recognised and may result from genetic, gene-environment or exposure to life course factors. Consequently, adult offspring of parents with COPD may be at greater risk of developing COPD. Apart from studies examining specific genes or genetic forms of COPD, the prevalence of COPD in adult offspring of people with COPD is not well reported in the literature. The aim of this chapter was to review the prevalence of co-occurrence of COPD in adult offspring where one or both parents had COPD.

Conference presentation and publication related to this chapter

Data in this chapter was presented as poster at the 2016 Thoracic Society of Australia and New Zealand conference in Perth Australia (Li, LSK., Paquet, C., Johnston, K., & Williams, M. (2016). Prevalence Of Co-occurrence Of COPD Diagnosis In Parents And Offspring: Systematic Review. *Respirology*, *21*, 138.) Refer to Appendix A.1 for the submitted abstract.

An edited version of this chapter has been published (Li, LSK., Paquet, C., Johnston, K., & Williams, M. T. (2017). "What are my chances of developing COPD if one of my parents has the disease?" A systematic review and meta-analysis of prevalence of co-occurrence of COPD diagnosis in parents and offspring. *International journal of chronic obstructive pulmonary disease*, *12*, 403-415). Refer to Appendix A.2 for the published version and statement of authorship.

3.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common treatable condition [218], yet it is estimated to become the third leading cause of death by 2030 [219]. Globally, the prevalence of COPD in the general population is estimated to be between 9-10%[220]. Although COPD is a progressive disease, early intervention strategies such as optimising medication, exercise and pulmonary rehabilitation have been shown to reduce the rate of disease progression and improve symptom control [60, 68, 221-223]. As highlighted in Chapter 2.2, not all COPD cases can be explained by smoking[9]. While there are identified inherited forms of COPD such as alpha-1-antitrpsin deficiency[224], environmental lifetime exposure to smoke or pollution [113, 117] has been shown to increase a person's risk of COPD. Additionally early life factors such as low birth weight, prematurity, nutrition, childhood respiratory illness and exposure to passive smoking have been associated with reduced lung function in later life [94, 130, 148, 225, 226].

Familial or intergenerational associations for chronic respiratory disease have been observed with increased risk of chronic bronchitis in people with relatives and family members with bronchitis [227, 228], strong associations of increased respiratory symptoms or conditions among twins [134], individuals living in the same household [121] and more recently wheezing, asthma and lung cancer [225, 229]. While genetic factors such as alpha-1-antitrpsin deficiency explain familial aggregation of COPD, less than 3% of people with COPD have this deficiency [98]. Intergenerational associations overlap with some of the risk factors associated with the development of COPD including smoking behaviour of parents and offspring[132], educational achievement[230], lung function[146] and health such as asthma[231] and lung cancer[229]. Concepts, knowledge and behaviours about health can be transmitted from one generation to the next[232]. Thus offspring of people with COPD are considered as an at-risk group for the development of COPD, as they may be exposed to a greater number of these intergenerational factors which could trigger or have a cumulative effect that shapes the trajectory of lung health[123].

Apart from studies that focus on associations between genetic forms of COPD, specific genes and lung function in families [233, 234], there seems to be little direct data concerning the likelihood or risk of COPD in offspring of parents with COPD. It is hypothesised that offspring of people with COPD through exposure to intergenerational and life course factors will have higher rates or increased risk of COPD compared to people without a parental history of COPD. The overall aim of this systematic review was to collate the published evidence for co-occurrence and risk of COPD in adult children (offspring) where one or both parents had COPD.

There were two objectives for this review:

1) To report the prevalence of COPD in offspring of people with COPD and /or prevalence of a positive parental history of COPD in people with COPD.

2) To report the strength of the association between parental and offspring COPD status.

3.2 Methods

This review was designed and reported according to current recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[235]. The review protocol was registered with Prospero (an international prospective register of systematic reviews) with protocol registration number: CRD42015025228.

3.2.1 Search strategy

Electronic databases including Medline, CINAHL, EMBASE, SCOPUS and Cochrane Library were systematically searched from inception to mid-September 2015. Key search terms were adapted from previous systematic reviews on COPD [68, 222] and the effects of family history [225, 229]. An example of the search terms used in Medline is presented in Table 3.1. Two researchers independently performed the systematic search following a prospectively planned search protocol that was developed with the aid of an academic librarian.

Table 3.1 Search strategy

Database	Search terms
Medline Embase CINAHL SCOPUS Cochrane library	"COPD" OR exp "pulmonary disease, chronic obstructive" OR "emphysema" OR "chronic bronchitis$" OR "obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "COAD" AND "familial aggregation" OR "familial risk" OR "familial transmission" OR "heredity" OR "adult child" OR "intergenerational" OR "inheritance" OR "family adj3 history" OR "parental adj3 COPD"OR "adult child$" OR "adult son$" OR "adult daughter$" or "offspring"

3.2.2 Inclusion and exclusion criteria

Studies were eligible for inclusion, if data were reported for the prevalence of COPD (chronic bronchitis and/or emphysema either through self-reported, physician diagnosed, spirometry diagnosed or symptom profile) in either parents or offspring of people with COPD. No year or language limits were set.

Studies were excluded if they: 1) did not define family history or specifically report offspring/parent within first degree relative groups (due to possible inclusions of other family members such as siblings); 2) reported specific lung function parameters without a COPD classification definition; 3) if COPD (emphysema/chronic bronchitis) was combined with other respiratory conditions; 4) if data were limited to familial investigation of known genetic variations of COPD (alpha-1-antitrypsin deficiency) and 5) studies of participants from specific occupations/ living environment (e.g. coal miners, coke oven workers or living close to asbestos factory etc.).

3.2.3 Screening of studies

Two reviewers independently screened the title and abstract of citations returned from searches (KL and MTW or CP or KJ). The list of articles for full-text screening was compared between the two reviewers with disagreements resolved through discussion. Full-texts of studies were reviewed by two independent reviewers for inclusion or exclusion into this review (KL and MTW). Reasons for exclusion were recorded and discrepancies discussed until consensus was reached. The reference list of relevant articles was searched and citation tracking was performed to retrieve any potential additional citations.

All non-English publications were screened by a native speaker of the language assisted by one member of the research team (KL). A checklist of questions was provided to assist in determining whether the study met the inclusion criteria of this review.

3.2.4 Appraisal of methodological bias

The ten-item Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data was used[236] with interpretations specific to the review question (Appendix A.3). Two independent reviewers (KL, MTW or CP, KJ) appraised the methodology of included studies; a third reviewer was consulted when consensus was not reached through discussion. The checklist was completed for the non-English publication by a native speaker of the language together with a member of the research team (KL) who had appraised other included studies. No studies were excluded on the basis of the methodological bias.

3.2.5 Data extraction

Using a predetermined data extraction template and process, two reviewers (KL and CP) independently extracted data from included studies with disagreements resolved by consensus. For each study, the following data were extracted: publication details (title, authors, year of publication), study method (country of research, study design) , participant flow (whether it was a report on offspring of people with COPD (descendent approach), or people with COPD reporting on parental history of COPD(antecedent approach)), prevalence, total number of index cases and sample size, parents and offspring characteristics (demographics, method of COPD diagnosis, severity of COPD, prevalence of COPD), odds ratio (if reported) and covariates used (if any) to adjust the prevalence and/or odds ratio estimates.

3.2.6 Data analysis

A narrative approach was used to summarise results in terms of study design, participant characteristics and COPD diagnosis. Studies were collated and analysed separately for two possible approaches for exploring associations between parents with COPD and their offspring: 1) Studies that considered people with confirmed COPD and the prevalence of COPD in their offspring (descendent approach) and 2) studies

that considered prevalence of positive parental history of COPD in people with confirmed COPD (antecedent approach). Where odds ratios were not reported in the study and sufficient data were reported, the odds ratio was calculated. To analyse the effect of positive parental history of COPD on their offspring, the pooled prevalence and odds ratio were calculated and forest plots were created using MedCalc for Windows, version 15.11.4 (MedCalc Software, Ostend, Belgium). I^2 statistics were used to assess heterogeneity of the studies included in the review. The random effects model was used due to the high level of heterogeneity between included studies.

3.3 Results

3.3.1 Search results

Figure 3.1 presents the search results. The database search identified 3382 potential citations. After removal of duplicates, the title and abstract of 2464 articles were screened. A total of 129 full-text articles were reviewed, including 18 non-English articles (13 Chinese, 1 Greek, 1 Czech, 1 Afrikaans, 1 Russian and 1 Japanese). Of those, 122 were excluded (see flowchart for reasons for exclusions). An additional study was identified through citation tracking. A total of eight studies were eligible for inclusion within the review.

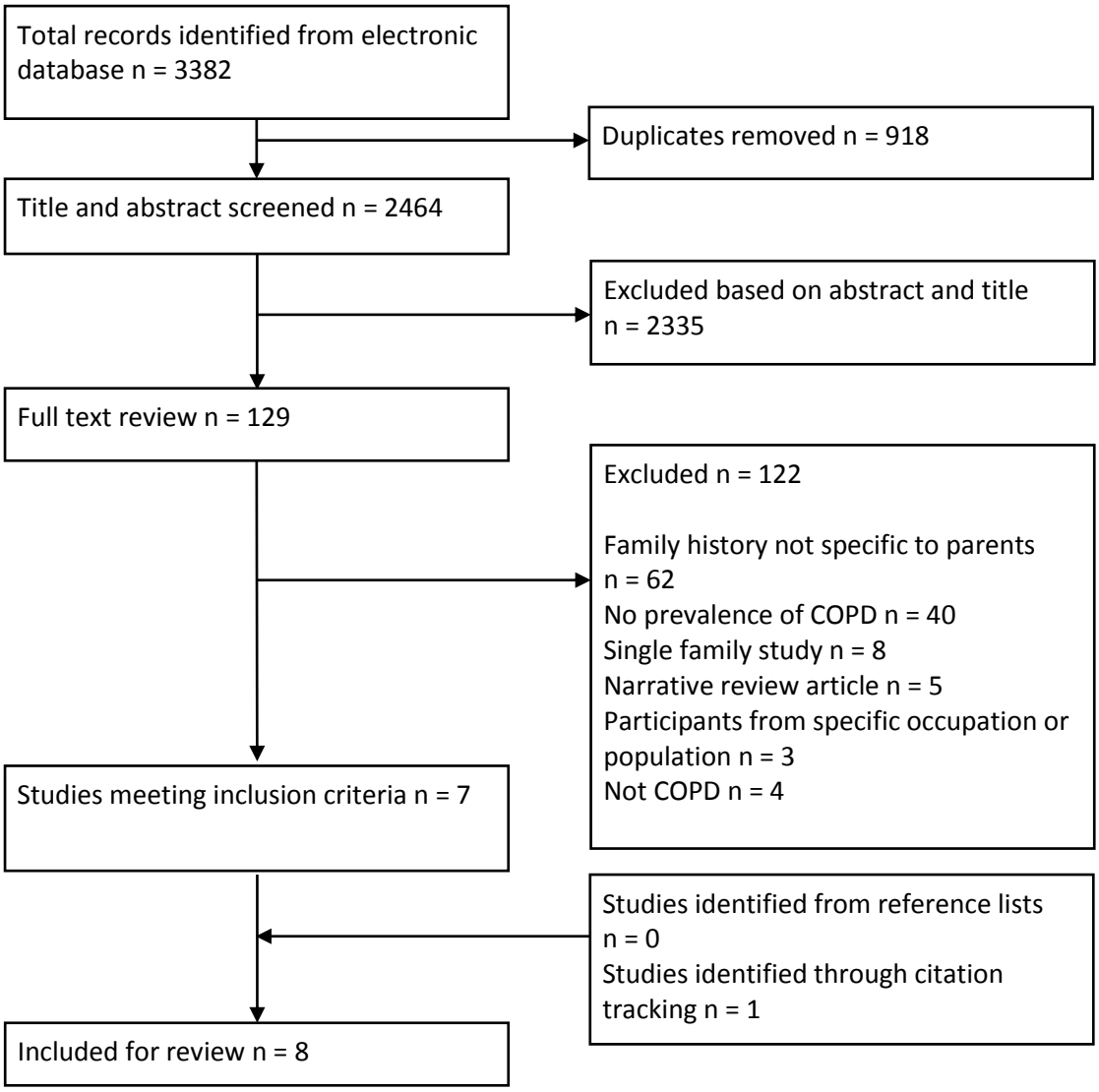


Figure 3.1 Flow chart for identifying studies

The search for the systematic review was completed in mid-September 2015. A re-run of the search protocol in December 2017 identified 743 new records published since 2015, but no new studies met the inclusion criteria for this systematic review.

3.3.2 Methodological quality assessment

Overall the studies in this review had variable risk of bias when appraised using the prevalence critical appraisal checklist (results presented in Appendix A.4). It should be emphasised that none of the studies included in this review were primarily designed as prevalence studies. Of the eight studies, the study by Zoller et al[237] had the lowest risk of bias, while Khoury et al [238] and Mostovoi[239] had the highest risk of bias

with reviewers considering most of the items on the checklist were either not reported or unclear. Three of the oldest studies [238-240] included in this review did not provide sufficient details on the representativeness and recruitment strategy for the study sample. None of the studies reported a calculation to justify their sample size; three of the studies[237, 240, 241] had adequate power based on a sample size analysis[236]. Seven of the eight included studies used objective and standard criteria for the measurement for COPD, however it was unclear in most studies whether COPD was measured reliably in parents and offspring.

3.3.3 Study characteristics

All included studies were observational in design. There were three studies that reported on the prevalence of COPD in offspring of people with COPD (descendent approach Table 3.2) with a total of 204 cases and 161 controls in two case-control studies[216, 238] and 5054 participants in a cross-sectional study[240]. There were five studies that reported on the prevalence of a parental history of COPD in people with COPD (antecedent approach Table 3.3), with 1545 cases and 1995 controls in four case-control studies[217, 239, 241, 242] and 80214 participants in a cohort study [237].

Table 3.2 Summary of studies reporting on COPD prevalence in offspring of people with COPD (descendent approach)

Author, Year	Higgins et al 1975 **[240]**	Khoury et al 1985 **[238]**	Amra et al 2015 **[216]**
County of data collection	United States	United States	Iran
Study design	Cross-sectional	Case-control	Case-control
Total number of index cases	5054+	150 cases 107 controls	54 cases 54 control
Cases/ control; Cohort	Residents of Tecumseh between 1962-1965	Cases: COPD Control: non-pulmonary patient	Case: offspring of people with severe COPD Control: Match in age, sex and height
Demographics of parents	Not reported	Not reported	Not reported
Diagnosis of parents	Chronic bronchitis (symptoms)	COPD (medical records)	COPD (medical records)
COPD Severity of parents	Not reported	Not reported	Severe (based on GOLD)
Demographics of offspring (COPD)	50.3% male Male age (years): <16 n=1779; 16-39 n=660; 40+ n=105 Female age (years): <16 n=1779; 16-39 n=621; 40+ n=110	(offspring of COPD parents) 44.8% male Mean age 27.4 years	(offspring of COPD parents) 65.8% male Mean age 34.3 years
Diagnosis of offspring	Chronic bronchitis (symptoms)	Chronic bronchitis (symptoms) Airway obstruction*	Abnormal pulmonary function#
Prevalence of COPD in offspring of people with COPD	Male: 17.3% (16-39 years) 16.7% (40+ years) Female: 6.6% (16-39 years) 8.3% (40+ years)	14.9% (with chronic bronchitis) 6% (with airway obstruction)	0%
Severity of offspring	Not reported	Not reported	Not applicable
Odds ratio	Number of offspring in each age category with parental history and OR not reported (unable to calculate OR)	OR = 2.1 (reported)(chronic bronchitis) OR = 6.4 (reported)(airway obstruction)	Number of parents in matched offspring control group and OR not reported (unable to calculate OR)

COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity
+ original study had 9226 study subjects in total, there were 5054 offspring participants with one or more parent assessed; * (FEV_1 less than 68% of FVC); # (FEV_1/FVC <0.7)

Table 3.3 Summary of studies reporting prevalence of parental history of COPD in people with COPD (antecedent approach)

Author Year	Mostovoi 1987**[239]**	Silverman et al 1998 **[217]**	McCloskey et al 2001 **[242]**	Hersh et al 2011**[241]**	Zoller et al 2015 **[237]**
County of data collection	Ukraine	United States	United Kingdom	United States	Sweden
Study design	Case-control	Case-control	Case-control	Case-control	Cohort study
Total number of index cases	530 cases 760 controls	44 cases 20 controls	150 cases 439 controls	821 cases 776 controls	80,214
Cases/ control; Cohort	Case: chronic bronchitis Control: healthy persons	Case: severe early onset COPD Control: current or ex-smokers	Case: severe COPD Control: matched for age, sex and smoking	Case: COPD GOLD stage II or higher Control: smokers	Cohort: Swedish-born adoptees born between 1932-2004
Demographics of parents	Not reported	Not reported	(parents who underwent spirometry) 23.7% male mean age: 75.9 ± 9.8 years	Not reported	Not reported
Diagnosis of parents	Chronic bronchitis (self-report by offspring)	Chronic bronchitis, emphysema or COPD (self-reported by offspring)	COPD (spirometry and self-reported by offspring)	COPD (self-reported by offspring)	COPD (medical records) ICD7-10 codes
COPD Severity of parents	Not reported	Not reported	Not reported	Not reported	Not reported
Demographics of offspring (COPD)	Not reported	20.4% male Mean age: 47.2 ± 5.6 years; Mean pack year: 38.8 ± 22.5	46% male Mean age: 52.3 ± 6.9 years	51.8% male Mean age: 64.2 ± 8.4 years, Mean pack year: 53.2 ± 26.3	49.8% male in total population 43% male with COPD events

Author Year	Mostovoi 1987[239]	Silverman et al 1998 [217]	McCloskey et al 2001 [242]	Hersh et al 2011[241]	Zoller et al 2015 [237]
Diagnosis of offspring	Chronic bronchitis (Chest x-ray, clinical information)	COPD (spirometry GOLD)	COPD (spirometry GOLD)	COPD (spirometry GOLD)	COPD (medical records) ICD7-10 codes
Prevalence of positive parental COPD history in people with COPD	14.5%	58%	44% (spirometry performed on living parents n=38) (self-reported) Male offspring: Mother with COPD 32% Father with COPD 37% Female offspring: Mother with COPD 29% Father with COPD 33%	43%	14.3% (biological parents) 11.7% (adoptive parents)
Severity of offspring	Not reported	Severe	Severe	GOLD stage II or higher	Not reported
Odds ratio	OR = 1.95 (Crude calculated)	OR = 7.9 (95%CI 2.0-30.9) (reported) unadjusted	(no control group for parents, unable to calculate OR)	OR = 1.69 (Crude calculated) OR = 1.68 (95%CI 1.32-2.13) (fully adjusted*)	OR = 1.41 (crude biological parents, calculated) OR = 1.21 (crude adoptive parents, calculated)

COPD: Chronic Obstructive Pulmonary Disease; ICD: International Statistical Classification of Diseases and Related Health Problems; GOLD: Global Initiative for Chronic Obstructive Lung Disease; OR: Odds Ratio; CI: Confidence Interval

*includes demographic covariates, parental history of COPD, parental history of smoking, childhood environmental tobacco smoke exposure

3.3.4 Prevalence of COPD in offspring of parents with COPD (descendent approach)

The prevalence of COPD in offspring of one or more parents with a diagnosis of COPD ranged from 0% to 17.3% in studies that used a descendent approach (Table 3.2). Studies that used the antecedent approach reported prevalence estimates ranging from 11.7% to 58% in people with COPD with a parental history of COPD (Table 3.3).

3.3.5 Pooled prevalence estimate

A pooled prevalence of COPD in offspring of people with COPD was unable to be calculated amongst the three studies employing the descendent approach (Table 3.2), as the prevalence of COPD in offspring of people with COPD was reported in different age groups in one study[240] and one study essentially excluded offspring with respiratory conditions[216].

The calculated pooled prevalence of people with COPD with a positive parental history of COPD (antecedent approach) was 28.6% (random effects model, 95%CI 17.4-41.3%) (Table 3.3, Figure 3.2). One study[237] provided prevalence of COPD in both biological and adoptive parents of people with COPD (both were included in the pooled prevalence calculation). Evidence of heterogeneity between studies was present (I^2=98.8%, p<0.0001). The study by Silverman et al. (1998)[217] included a very specific group of participants (people with severe, early-onset COPD). Where the pooled prevalence was calculated excluding Silverman et al (1998)[217] the prevalence of people with COPD with a positive parental history of COPD was 24.0% (random effects model, 95%CI 13.2-36.8%, I^2=99.0%, p<0.0001).

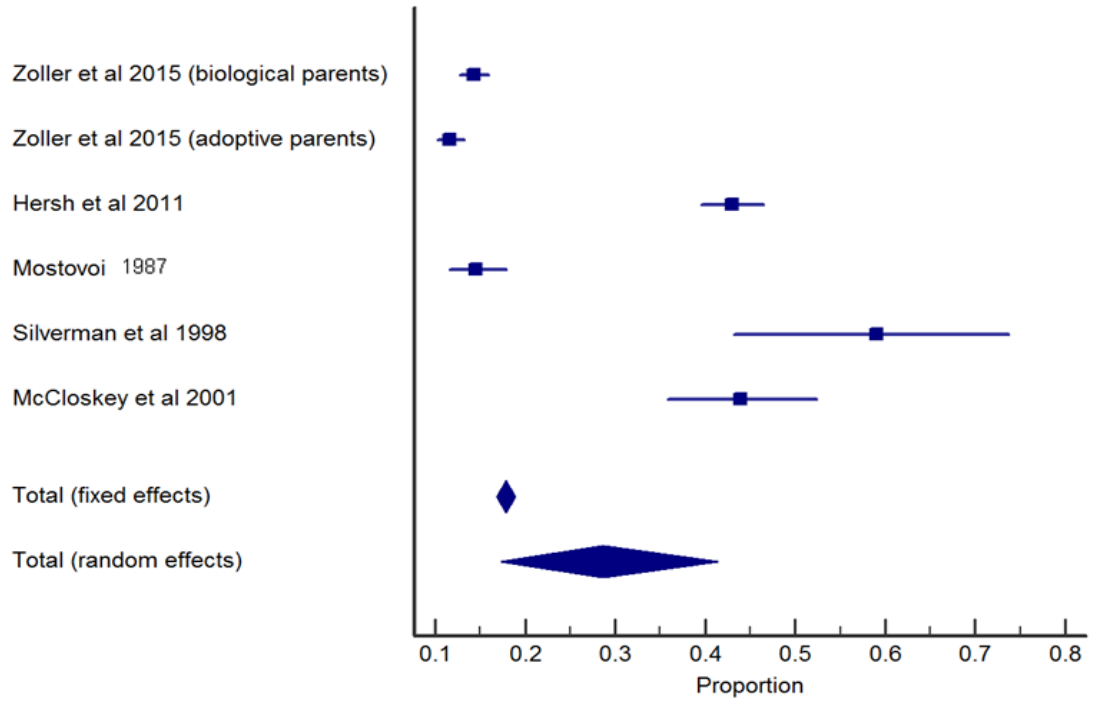


Figure 3.2 Pooled prevalence of people with COPD with positive parental COPD history

3.3.6 Pooled odds ratio

Of the eight included studies, three studies [217, 238, 241] reported an odds ratio (of the increased likelihood of offspring of people with COPD to develop COPD) and two other studies reported enough information to calculate comparable odds ratios. [237, 239]. Three studies [216, 240, 242] did not provide sufficient information for an odds ratio calculation. Meta-analysis of crude odds ratio from five studies indicated that offspring of people with COPD had 57% higher odds of having COPD compared to people without a parental history of COPD (random-effects model, pooled OR = 1.57, 95%CI 1.29-1.93, p<0.001) (Figure 3.3). Evidence of heterogeneity between studies was present (I^2=72%, p=0.0029). When the study by Silverman et al. (1998)[217], which only included people with severe early-onset COPD, was excluded from the pooled analysis, the heterogeneity decreased (I^2=66%, p=0.0198) and offspring of people with COPD had 50% higher odds of having COPD compared to people without a parental history of COPD (random-effects model, pooled OR = 1.50, 95%CI 1.26-1.77).

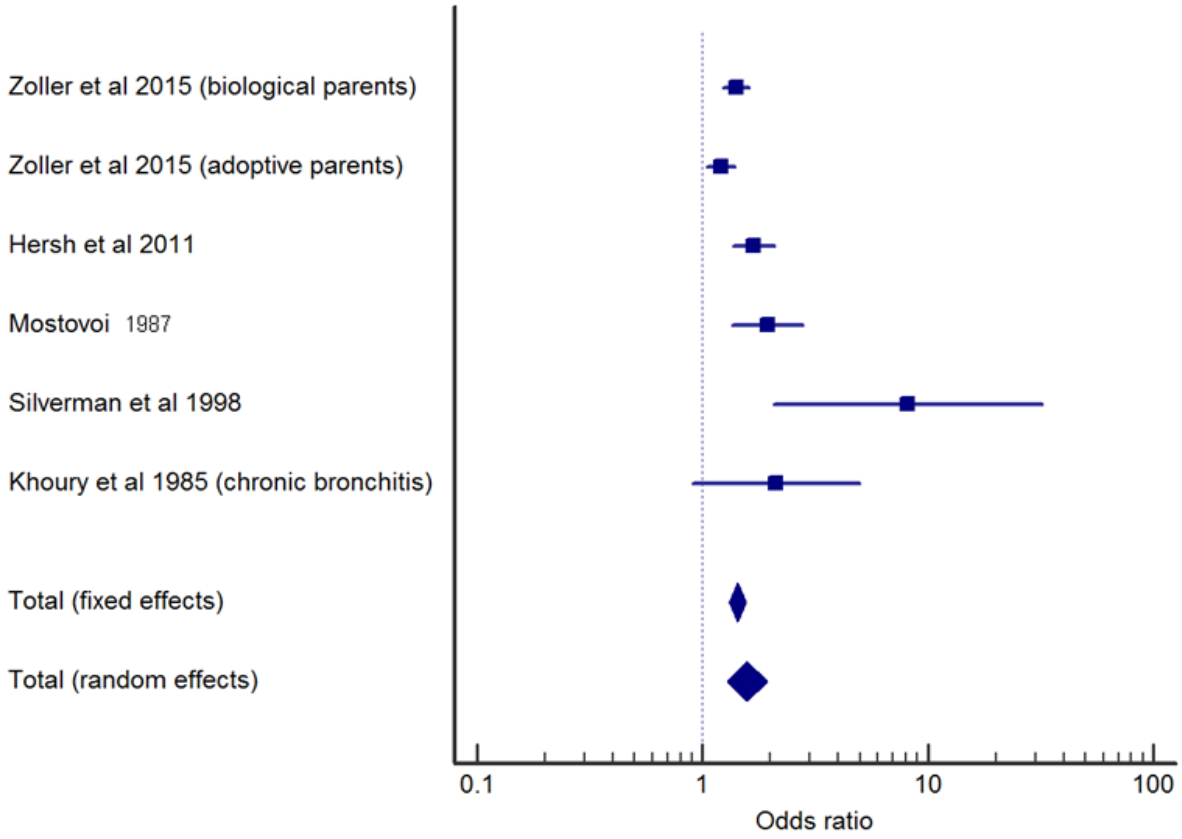


Figure 3.3 Summary effects of positive parental COPD history on offspring COPD (unweighted)

3.4 Discussion

It is well recognised and accepted that family history of chronic respiratory disease is a risk factor for COPD development[243]. Rather than broader family groups, this review specifically focus upon co-occurrence of COPD in parents and offspring as there are specific in-utero parental influences and the pair are more likely to cohabitate during critical periods of time where lifestyle and behavioural exposures might be subject to intergenerational influences. In this review, the pooled prevalence of people with COPD and a positive parental history of COPD was 28.6% and offspring of people with COPD had 1.57 times greater odds of having COPD compared to people without a parental history of COPD. While there is evidence to support familial associations in lung function decline in parent and offspring pairs[244], this review identified a paucity of studies which provided or enabled an estimate of the prevalence of COPD in offspring of people with COPD to be obtained.

Given the number of studies screened for this review, it was unexpected and surprising that only eight studies could be included as they reported both parental and offspring

prevalence of COPD prevalence (with three specifically reporting prevalence of COPD in offspring of people with COPD[216, 238, 240]). Of the 122 out of 129 studies excluded after reviewing full version of the paper, the majority were excluded for two main reasons. The first reason (51%) was that despite reporting data for family history of COPD in people with COPD, studies were excluded as they did not define family history as parental history[245, 246] or reported a pooled analysis of family history that included a mixture of, or restricted to siblings, parents, offspring, first degree relatives [247, 248]. The second reason (33%) concerned studies that reported on the prevalence of a combination of respiratory problems[249] or on measures of lung function in offspring of people with COPD[250, 251] rather than the prevalence of COPD. Lower values for pulmonary function for offspring of COPD probands compared to reference or non-COPD probands have been reported [143, 250, 252], but in the absence of a categorising offspring into presence or absence of COPD and provision of sufficient information in order to calculate COPD prevalence within offspring, these studies were excluded from this review.

It should be noted that none of the studies screened for inclusion or ultimately included within the review were designed for the primary aim of determining prevalence of co-occurrence of COPD in parents and offspring. While this finding is of interest in its own right, it should not be interpreted as a criticism or limitation of previous studies. Of the studies included in this review, one study intended to determine strength of association of risk factors of COPD[238], two studies examined genetic influence on COPD development[217, 239], two studies examined the patterns of familial aggregation[237, 240] and two studies examined pathological changes in probands of people with severe COPD[216, 242].

These variations in original intent of the studies included in this review resulted in differences in study design, source and nature of participants and classification of COPD. Of the eight included studies, there were six case-control studies, one cross-sectional and one cohort study. The index cases in the six case-control studies varied from people with chronic bronchitis[239] to people with severe early-onset COPD[217] whereas the control group varied from matched individuals[216] to smokers[241]. Only one study[242] directly assessed both parents and offspring with spirometry, however

of the 150 cases there were only 38 living parents. Apart from two older studies (published in 1975[240] and 1987[239]) that used a symptom-based measure of chronic bronchitis as a classification for COPD in offspring, all other studies employed spirometry in order to classify COPD in offspring. Parental COPD history was self-reported by participants in all but one antecedent studies[217, 239, 241, 242], with the remaining study using medical records to identify COPD in parents and offspring [237]. High prevalence of undiagnosed COPD has been reported worldwide [69, 71] thus identifying COPD by self-report or medical record screening may be an underestimation and not reveal the true prevalence of positive parental COPD history. McCloskey et al[242] demonstrated this discrepancy between self-reported positive parental COPD history (29-37%) and parents with a spirometry diagnosis of COPD (44%).

Three of the eight studies used a descendent approach [216, 238, 240] and reported a wide range of COPD prevalence (0-17.3%) in offspring of people with COPD. Amra et al. [37] represents an outlier within this group as none of the offspring (n=54 cases, means age 34.3 years) met spirometric criteria for COPD (FEV_1/FVC <0.7). While the relative young mean age of offspring may have played a part in this finding, it is more likely that the exclusion criteria applied to offspring cases (smokers, employed in high risk jobs for the respiratory system or had a pulmonary disease) biased the case group towards those with lower risk profile for COPD. The other two studies reported prevalence to range between 6 and 17.3% [238, 240] which was higher than contemporaneous published prevalence estimates of COPD in the general population (4%) for comparable age group (25-44 years)[253].

Across five studies that used the antecedent approach [217, 237, 239, 241, 242] between 11.7 - 58% of people with COPD reported a positive parental history. No comparable reviews or population-based data were found to compare these estimates of parental history of COPD, however the prevalence of COPD (in parents of people with COPD) appears higher when compared to contemporaneous estimates of prevalence of COPD in the general population (9-10%)[220]. The studies that recruited participants with moderate to severe COPD reported a relatively higher positive parental history of COPD (43-58%)[217, 241, 242] and all three studies alluded the increased risk of COPD

in families was likely to be as a result of genetic factors. Although there are ongoing genome-wide association studies exploring genotypes of COPD, there remains unanswered questions around COPD heritability and susceptibility due to the complex nature of the disease[254]. Another possible explanation for the higher prevalence of positive parental COPD history reported by participants with more severe COPD may relate to an increased awareness of respiratory problems in their immediate family and greater vigilance or likelihood of reporting [255]. The wide range of prevalence of co-occurrence of COPD in parents and their offspring is likely also a reflection of the specific study samples that may not be representative of the general population.

The findings of this review confirm that offspring of people with COPD are a specific at-risk group. The risk of developing COPD in people with a parental history of COPD (OR=1.57) was comparable to those exposed to passive smoking (OR= 1.48)[117], maternal smoking (OR=1.7)[256] and childhood pneumonia (OR=1.4)[103]. The magnitude of effect of having a parental history of COPD was lower when compared with the effects of personal smoking in the development of COPD (OR=6.3)[257]. Early identification of those at risk of developing COPD is commonly based on modifiable behaviours such as smoking or symptom profiles. Smokers are a common target population in COPD case finding studies[258, 259] as smoking cessation is a well-recognised early intervention that slows the progression of the disease[53]. Offspring of people with COPD may provide a similar opportunity for early identification case finding. By capitalising on the increased prevalence and risk of developing COPD in adult children of people with confirmed COPD, health practitioners working with people with COPD could use opportunistic screening of adult offspring to enable early intervention strategies such as smoking cessation, physical activity, appropriate pharmacologic support and pulmonary rehabilitation to reduce the rate of lung function decline, improve symptom control and improve the quality of life[60, 260, 261].

3.4.1 Limitations

This review included studies that were published over a forty year period (1975-2015). The two oldest studies included in this review both reported on the prevalence of

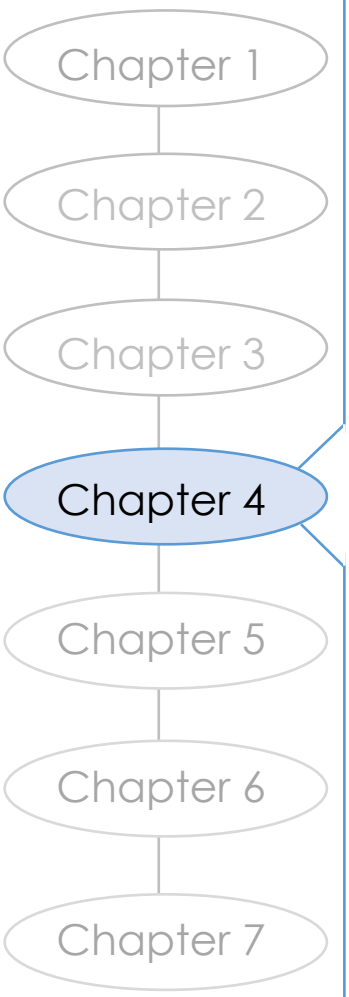
COPD in offspring of people with COPD[238, 240] and unsurprisingly the diagnostic criteria used over 30 years ago differed from the current gold standard [218]. Although both studies reported performing lung function testing on the offspring and assessed chronic bronchitis symptoms, one study[240] reported only on the prevalence of chronic bronchitis in the offspring and the other study[238] used a slightly different definition of airway obstruction compared to the current standard. While the presence of respiratory symptoms may indicate underlying impaired lung function, it is not possible to determine whether participants had irreversible airway obstruction solely based on their symptom profile. Hence it is difficult to determine whether this is a true representation, over or under estimation of the prevalence. With close to half of the studies included in this review published over 20 years ago, the reported prevalence of co-occurrence of COPD may differ compared to the present day due to changes in lifestyle, increased in education and health promotion on the health consequences of smoking[262].

A critical appraisal checklist for studies reporting on prevalence data was used even though the included studies were not specifically designed to report prevalence. This checklist[236] was chosen as information on prevalence was the main focus of this review. While no studies were excluded from the review based on the quality of the study appraised using this checklist, modifications and clarification point were required to adapt the checklist to determine the representativeness of the study sample and interpretation of the results specific to the review question.

Meta-analysis was performed despite significant heterogeneity amongst the studies. Only eight studies met the inclusion criteria of this review, highlighting the limited available literature that reported on the co-occurrence of COPD diagnosis in parents and offspring. The pooled prevalence and odds ratio calculated provides a summary of the available evidence on the prevalence and odds of COPD development in offspring of people with COPD but may not be generalizable due to the heterogeneity and limited populations of the included studies.

3.5 Conclusion

While familial associations with COPD are generally well recognised, results of this review indicate that there were few studies that specifically reported on the co-occurrence of COPD diagnosis in parents and offspring. Nevertheless, findings of this study indicate that offspring of people with COPD are at increased risk of developing COPD and screening of this at-risk group may lead to opportunities to capitalise on familial links and promote early identification and intervention.



Study II : 1958 Study

In people with a parental respiratory disease history, are intergenerational and life course influences associated with adulthood lung health?

The increased risk of adult offspring of people with COPD in developing COPD may result from a combination of genetic susceptibility and exposure to risk factors throughout life. In this chapter, a life-course approach was used to investigate factors contributing to the relationship between parental respiratory disease history and reduced lung health (presence of respiratory symptoms and airway obstruction) in adulthood using data from the 1958 British Birth Cohort Study. Path analysis was used to investigate the mediating role of life-course factors in the relationship between parental respiratory disease history and reduced lung health, adjusting for gender, asthma and recent chest infection.

Conference presentations related to this chapter

Data in this study was reported at an oral presentation at the 2017 South Australia State Population Health Conference in Adelaide Australia (Li LSK, Williams MT, Johnston K, Frith P, Hypponen E, Paquet C. Intergenerational and life course factors for lung health. October 21 2017, Adelaide Australia). Refer to Appendix B.1 for the submitted abstract.

An abstract of this study has been accepted for an oral presentation at the upcoming 2018 Thoracic Society of Australia and NZ Annual Scientific Meeting in Adelaide Australia (Li LSK, Williams MT, Johnston K, Frith P, Hypponen E, Paquet C. Parental respiratory disease is associated with reduced offspring lung health at age 45 via pathway of maternal and personal smoking). Refer to Appendix B.2 for the submitted abstract.

4.1 Introduction

The systematic review (Chapter 3) concluded that adult offspring of people with COPD are at increased risk of developing COPD compared with people without a parental history. Exposure to risk factors at different life stages may have long-term influences on an individual's lung health. Parents and their offspring typically live in a shared environment during the early years of the offspring's life, which may explain the increased risk of developing COPD in offspring of people with COPD.

Early life exposures including in-utero and during childhood, to parental and environmental risk factors for lung health may shape the offspring's lung health trajectory [92]. Factors such as maternal smoking and low birth weight can have deleterious effects on the offspring's lung structure, influencing their maximally attained lung function and adult lung function [100, 124, 263]. Parents and their socio-economic situation may also shape and influence their offspring's behaviour and occupational choices or opportunities which may alter the lung function trajectory [264, 265]. Therefore adult offspring of people with COPD may present as a unique at-risk group with a number of potential pathways that could explain why people with a parental history of COPD are at increased risk of reduced lung health.

Longitudinal data on risk factor exposures throughout the life course provide an opportunity to explore complex inter-relationships between parental respiratory disease history, life course factors and the cohort member's adult respiratory health status. The association between early life lung function or childhood asthma with adulthood lung function or risk of developing COPD has been well reported in previous studies[92, 105, 131, 171], However these previous studies have mostly focused on single risk factors (e.g. low lung function, asthma) and have used spirometry results as the sole measure of lung health. Development of COPD is likely a result of the complex interaction of risk factors[1], with individuals with reduced lung function commonly reporting respiratory symptoms having a major impact on their quality of life [65, 266].

To our knowledge, no previous studies have investigated the relationship between parental respiratory disease history and reduced adulthood lung health using a

combination of spirometry results and respiratory symptoms as an outcome measure within the National Child Development Study (1958 birth cohort). Participants in the 1958 cohort study were systematically recruited at birth around England, Scotland and Wales and provided a representative sample of individuals born in Britain in 1958[165]. Compared with the 1958 cohort, Australian longitudinal cohorts tend to have a smaller sample size at study commencement and fewer numbers of follow ups (Table 2.2). Together these factors makes the 1958 birth cohort a unique dataset appropriate for the life course approach planned for this study.

It should be emphasised that while the focus of this thesis is on COPD, it is acknowledged that asthma is a risk factor for COPD development and may also co-exist in approximately 27% of people with COPD [9, 36, 48]. The aim of this study was to use a life course approach to investigate the relationship and contributing life course factors between parental respiratory disease history and incidence of airway obstruction with respiratory symptoms in adulthood (controlling for asthma) in the 1958 birth cohort.

There were two objectives for this study:

1) To report the prevalence of airway obstruction with respiratory symptoms in 1958 cohort members with a positive parental respiratory disease history

2) To report on the relationship between parental respiratory disease history and the incidence of airway obstruction with respiratory symptoms in adulthood accounting for lifetime history of asthma, and life course factors that contributed to this relationship

4.2 Methods

4.2.1 Study population

The National Child Development Study (1958 cohort) began as a study on perinatal mortality that examined factors associated with stillbirth and infant mortality [165]. The initial assessment included 17,414 births occurring during a specific week of 1958 in England, Scotland and Wales[165]. Up until 2013, nine sweeps of data collection were completed with data on education, health, social and economic circumstances

collected from the cohort throughout their childhood, teenage years, early and mid-adulthood [165, 267]. Biomedical data were collected from 9,377 cohort members when they were 45 years old from a largely representative sample of the original cohort [268, 269]. Approval from relevant ethics committee and consent from participants were obtained for each sweep of data collection [270]. Permission for the research team to access these data was granted (Appendix B.3).

4.2.2 Primary exposure: Parental respiratory disease history

Data on parental respiratory disease history were collected from the cohort member's mother in the first three sweeps. If the mother was not available, data were collected from the father or mother-figure. Participants were considered to have a positive parental respiratory disease history if the participant's mother had a respiratory illness during pregnancy, or if either parent in the household had any respiratory medical history when the cohort member was 11 and 16 years. Data were only available at the level of systems (e.g. respiratory, cardiovascular) rather than specific conditions.

4.2.3 Outcome: Airway obstruction with respiratory symptoms

The outcome for this study was airway obstruction with respiratory symptoms, which was operationalised as the presence of (1) airway obstruction defined using the following criteria: ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) <0.7 at 45 years old and (2) any respiratory symptoms (cough, phlegm, shortness of breath or wheeze) at 42 years old, as reported by participants. Spirometry was performed using the Vitalograph Micro spirometer (Vitalograph, Maids Moreton, UK) by trained nurses in accordance to the American Thoracic Society guidelines in standing position without nose clips[271]. A small number of cohort participants (n = 36) used a bronchodilator within one hour of performing spirometry. At least three satisfactory measures were obtained when the cohort was 45 year old and the highest technically satisfactory values for forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were used. The ratio of FEV1/FVC < 0.7 was used to define airway obstruction [1].

Data on respiratory symptoms were collected based on the Medical Research Council questionnaire [29]. Cohort members were asked "Do you usually cough first thing in

the morning in the winter?", "Do you usually bring up phlegm from your chest first thing in the morning in winter?", "Do you get short of breath walking with other people of your own age on level ground?" and "Have you ever had wheezy or whistling in the chest at any time in the past?". Cohort participants were considered to have respiratory symptoms if they reported experiencing one or more of the respiratory symptoms at the 42 year old sweep. Respiratory symptoms data were not collected when the cohort participant completed spirometry assessments at the 45 year old sweep, hence symptom data were taken from the previous sweep (42 years of age). The temporality of the symptom measures in relation to the spirometry results is consistent with evidence that respiratory symptoms are often present prior to a diagnosis of COPD [272].

4.2.4 Life course factors

In order to assess the contribution of life course factors in the relationship between parental respiratory disease history and airway obstruction with respiratory symptoms in adult offspring, a range of life course factors were investigated based on established COPD risk factors identified from the literature [1, 9, 94]. Figure 4.1 represents a summary of life course factors with data available from the 1958 cohort. Life course factors were operationalised with respect to their life period (in utero/ at birth, childhood, adulthood) or a combination thereof and duration of exposure to test for critical period and cumulative exposure effects. They are described below according to the life period they cover.



Figure 4.1 Summary of life course factors investigated in this study, including timing of primary exposure (parental respiratory disease history) and outcome (airway obstruction and respiratory symptoms)

In utero/ at birth

Data on maternal smoking status at four months of pregnancy were collected in 1958. Cohort member's birth weight and gestational age were collected by the midwife in charge of the delivery. Birth weight was converted from pounds to kilograms, and low birth weight was defined as a birth weight of <2.5kg [273]. Preterm birth was defined as less than 37 weeks gestation age [274].

Childhood factors (0-16 years)

Passive smoke exposure: Exposure to passive smoke during childhood was considered present based on maternal smoking status (when mother was four months pregnant) or if either parent smoked when the cohort participant was 16 years. No data on parental smoking status were collected at the 7 and 11 years old sweep.

Childhood respiratory illness: Data on whether the cohort participant ever had pneumonia were collected from the cohort's mother or father when the cohort member was seven years old.

Adulthood factors (23-45 years)

Passive smoke exposure: Exposure to passive smoke during adulthood was considered present if the cohort participant reported living with any smoker at 23, 33 or 42 years old.

Biomass exposure: Exposure to biomass during adulthood was considered present if the cohort participant reported using paraffin or solid fuel as the heating source at home at 33 years old. This information was not available at other sweeps of data collection.

Smoking status: The cohort participant's smoking status (current/ non-smoker) was collected when they were 23, 33 and 42 years old. To minimise bias resulting from missing information on smoking status, data for smoking status needed to be available in at least two of the three sweeps for the individual to be included in the study sample. Three adulthood smoking status categories were created: persistent smoker (current smoker based on available data), ever smoker (mixture of current/non-smoker based on available data), and never smoker (non-smoker based on available data).

Occupational exposure: Participants' occupations were originally coded according to the Standard Classification of Occupations and were recoded into the International Standard Classification of Occupations (ISCO-88)[275]. Based on previous research on occupation with exposure to dust, gases and fumes which have been linked with greater COPD risk [276, 277], three researchers (KL, CP and KJ) discussed and categorised the list of ISCO-88 occupations expressed at the 3-digit level into either minimal or potential occupation exposure to dust, gases and fume. A variable on ever or never occupational exposure was derived based on the cohort member's occupation at 33 and 42 years old.

Lifetime factors

Social class: Social class information was derived from the occupation of the male head of the household at the time of the participants' birth (or imputed from 7 years if data were unavailable at birth; n=207), and the participant's own occupation in early adulthood (23 years, or imputed from 16 years if data were unavailable at 23; n=560))

and middle life (42 years, or imputed from 33 years if data were unavailable at 42; n=655)). Missing social class information was imputed with data from the previous sweep in accordance to previous studies[278]. Occupations were coded using the Registrar General's social class system as: I - professional occupation, II – managerial and technical occupations, IIIN – skill occupations (non-manual), IIIM – skilled occupations (manual), IV – partly skilled occupations and V – unskilled occupations. The categories were collapsed into four social class (SC) categories: SC1 - professional/managerial (I and II), SC2 - unskilled non-manual (IIIN), SC3 - skilled manual (IIIM) and SC4 - unskilled manual (IV and V) for analysis based on prior work on these data [279].

4.2.5 Covariates

Childhood asthma: Data on the cohort member's respiratory medical history were collected throughout all sweeps of data collection. As consensus on differential diagnosis between asthma and wheezy bronchitis in children appears not to have been clearly established at the time when the data were collected [280], the cohort member was considered to have childhood asthma if they reported yes to "ever asthma or bronchitis" at ages 7, 11 or 16.

Adulthood onset asthma: It was considered present if they reported no to asthma or bronchitis at 7, 11 or 16 but answered yes to "ever asthma" at age 33 or 42 [281]. Data on "ever asthma or bronchitis" were available from the 23 year old sweep, however the data were not included in our definition of adulthood onset asthma, because it was not possible to differentiate between the number of participants who had asthma and those who had bronchitis at that time point.

Recent chest infection: At the biomedical sweep (45 years), cohort members self-reported presence of any respiratory infection in the past three weeks.

Cohort's mother's marital status in 1958: Marital status was self-reported by the mother in 1958 and was recoded into single (if the mother was separated, divorced, widowed or unmarried) or married (if the mother was in a stable union, married or twice married).

Cohort's mother's age in 1958: Mother's age at last birthday was self-reported by the mother in 1958 and was recorded in years.

4.2.6 Statistical analysis

All variables were treated as categorical variables (binary or ordinal) with the exception of maternal age (years) which was treated as continuous. Difference in characteristics between cohort members with or without airway obstruction and respiratory symptoms were tested using chi-square test (categorical variables) or independent sample t-test (continuous variables). Descriptive statistics and between group comparison were conducted in SPSS (version 21, IBM Armonk, NY).

In order to test whether parental respiratory disease history was related to airway obstruction with respiratory symptoms and the life course factors potentially involved in this relationship, we conducted path analysis using the MPlus software (version 8.0, Muthen & Muthen, Los Angeles, CA). This method allowed both direct and indirect (or mediated) effects between an exposure (parental respiratory disease history) and an outcome measure (airway obstruction with respiratory symptom) to be assessed (Figure 4.2). Using this model, the total effect (i.e. direct and indirect) of parental respiratory disease history on airway obstruction with respiratory symptoms in cohort members was tested (Figure 4.2*a*, path *c*). The marginal effects were calculated to provide an indication of the effect size using estimate from probit regression[282].

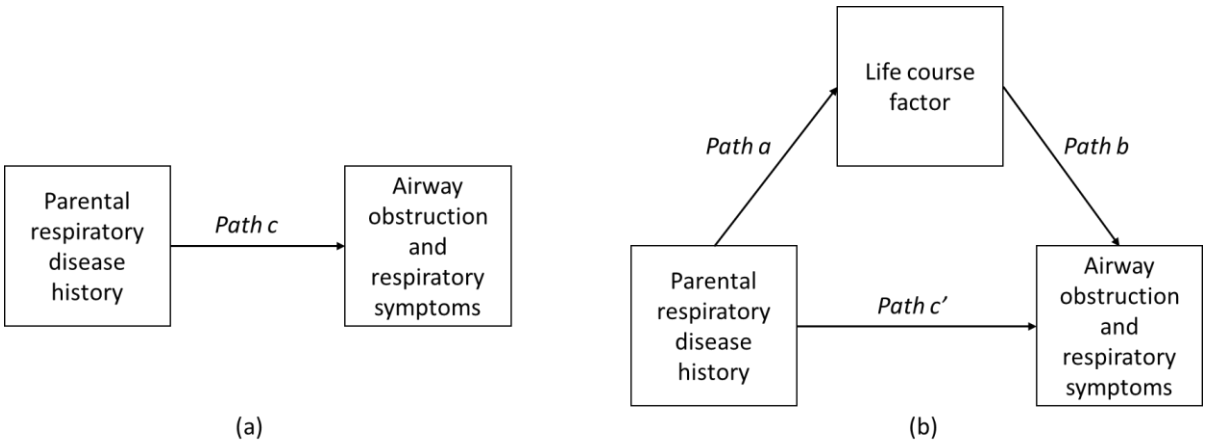


Figure 4.2 (a) Total association between parental respiratory disease history and airway obstruction and respiratory symptoms. (b) Indirect (path a and b) and direct (path c') associations between parental respiratory disease history and airway obstruction and respiratory symptoms through life course factors.

Individual life course factors were separately added in the same model to establish if they satisfied criteria for mediation as per Baron and Kenny [283]: (1) whether parental history was related to the life course factor (Figure 4.2*b*, path *a*), and (2) whether the individual life course factors was related to airway obstruction with respiratory symptom (Figure 4.2b, path *b*) while accounting for parental respiratory disease history. Paths *b* and *c* were adjusted for participant's gender, history of asthma and recent chest infection as these factors may have an impact on an individual's lung function [101, 284, 285] and life course factors. Path *a* was tested adjusting for parental-related covariates (cohort's mother's age and marital status in 1958) as these factors may influence their parenting style and exposure to life course factors [286]. A summary of pathways tested from parental respiratory disease history through life course factors to adulthood airway obstruction and respiratory symptoms is presented in Figure 4.3.

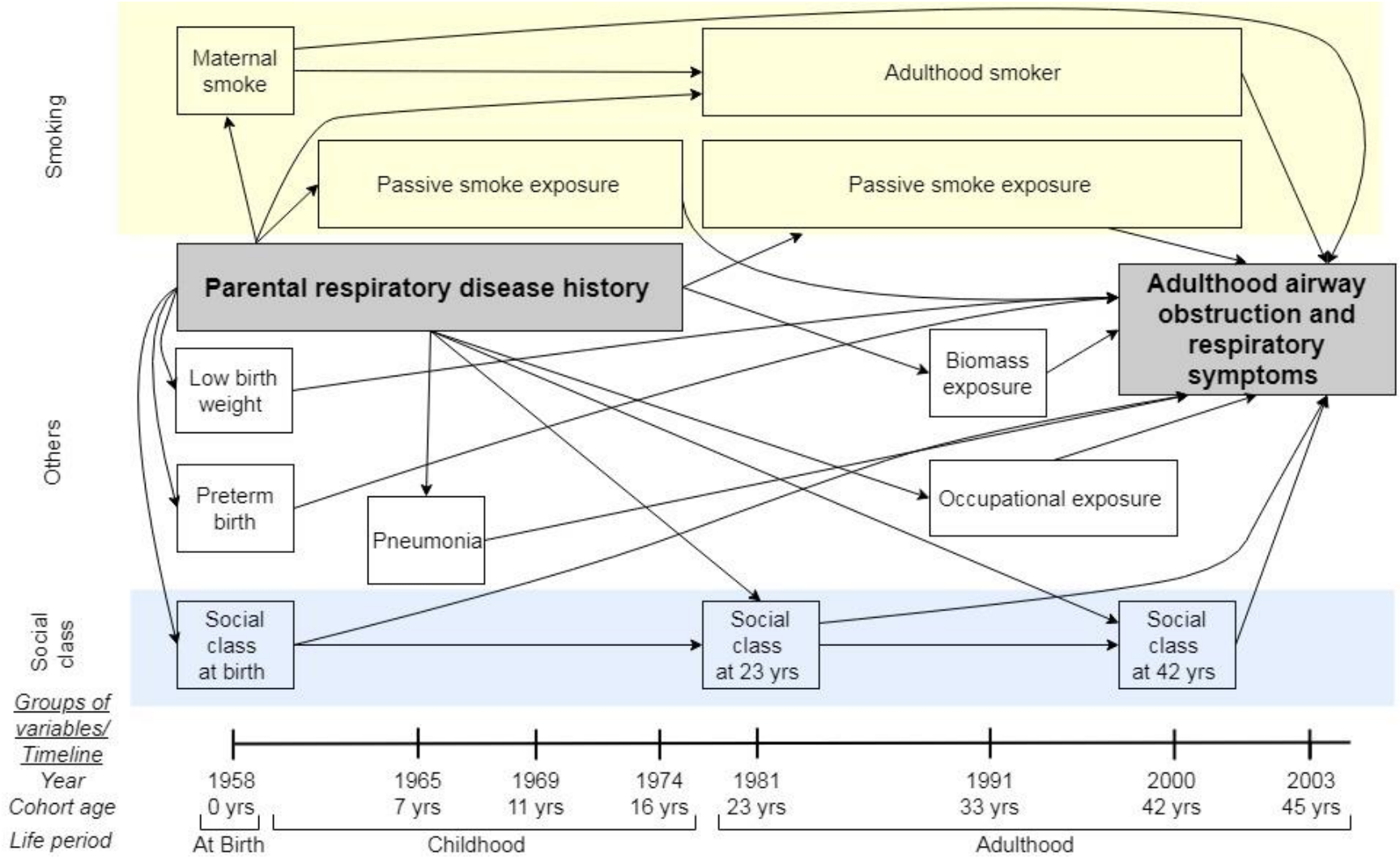


Figure 4.3 A summary of pathways tested, from parental respiratory disease history through life course factors to adulthood airway obstruction and respiratory symptoms.

Background yellow and blue shade indicate similar factors that were modelled as a chronological sequence if they met the criteria for mediation.

Life factors that met the criteria for mediation were incrementally added into a single model, with the exception of life course factors of the same nature (e.g. social class or smoking trajectories), which were modelled as a chronological sequence of events. When appropriate, correlation between other interrelated variables (e.g. maternal smoking and social class at birth) was specified in the model. The indirect effects (specific to a given life factor or a combination thereof) were tested using the product of paths *a* and *b* using the MODEL INDIRECT command in MPlus [287]. The direct, total indirect (i.e. indirect effect for all mediators included) and specific indirect effects from parental respiratory disease history to outcome through the life course factors were evaluated with bootstrapped confidence interval (bootstrap = 1000). The proportion of the total effect mediated was calculated for both total and specific indirect effects. This measure is used as a measure of effect size for mediation and has been shown to perform well in samples > 500 [288]. Missingness for variables with less than 5% missing was considered small and not imputed[289]. Variables with greater than 5% missing data were imputed to maximise the analytical sample 10 times using the multiple imputation function in the Mplus software (version 8.0). Analyses were conducted on the resulting 10 imputed datasets. Relationships with binary outcomes were estimated with weighted least squares parameter estimates (WLSMV) estimator, which uses probit regression [287, 290]. Ordinal mediators (e.g. smoker status = never/ ever/ persistent) were treated as a continuous latent response variable by default in MPLUS to allow calculation of indirect effects [291]. Model fit was assessed using the root-mean-square error of approximation (RMSEA), Comparative Fit Index (CFI) and Tucker-Lewis index (TLI) with cut-off values of RMSEA < 0.06, CFI > 0.95 and TLI > 0.95 indicating good model fit [292]. Statistical significance was set at $p < 0.05$.

4.3 Results

4.3.1 Study sample

Of the original 1958 cohort (n = 17,414), 9,377 participated in the biomedical assessment at 45 years, with lung function data available for 9,090 individuals and data on presence/ absence of respiratory symptoms (at 42 years old) available in 8,804

individuals. Of these, parental respiratory disease history data was available in 7,298 individuals, with different proportion of missing data in the life course variables of interest (Figure 4.4).

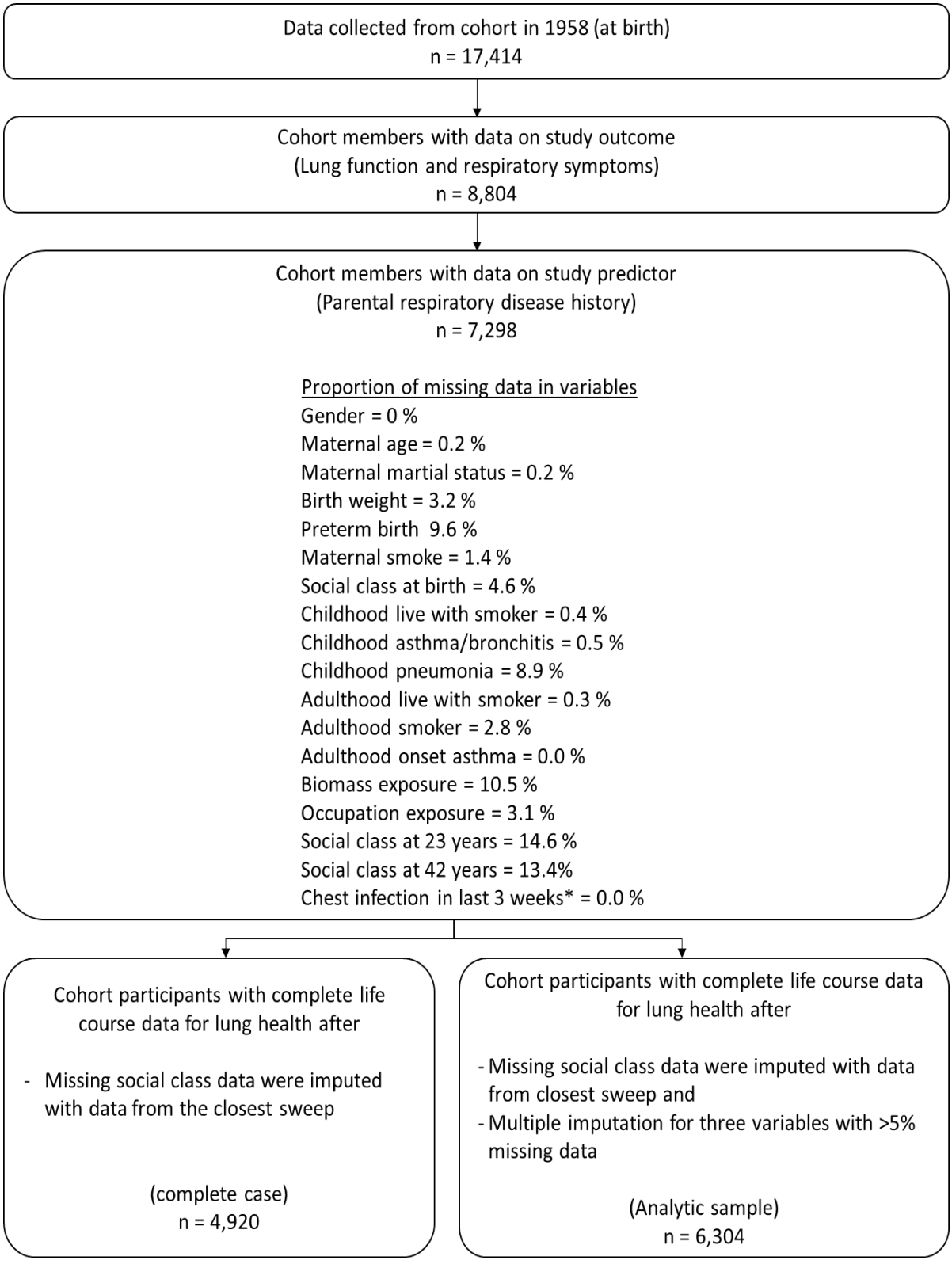


Figure 4.4 Flow chart showing sample selection

*Refers to last three weeks prior to undertaking spirometry

Social class variables had a high proportion of missing data and after imputation using data from the closest sweep, the complete case sample size was 4,920. Three variables (preterm birth, childhood pneumonia, biomass exposure) had greater than 5% missing data and were therefore imputed using multiple imputation. To maximise the analytic sample, analyses were conducted on the imputed data set, which included 6,304 cohort members.

4.3.2 Prevalence of airway obstruction with respiratory symptoms and positive parental history of respiratory disease

In the final analytic sample, 3.7% of cohort had a parental respiratory disease history and 6.3% of participants had airway obstruction with respiratory symptoms. Of the participants with airway obstruction and respiratory symptoms, 6.6% had a positive parental respiratory disease history. Characteristics of the study sample are summarised in Table 4.1.

Table 4.1 Characteristics of the studied sample

Cohort member characteristics	Total n = 6,304	No AO/ respiratory symptoms n = 5,909	AO and respiratory symptoms n = 395	P value#
Gender n(%)				
Male	3085 (48.9%)	2891 (48.9%)	194 (49.1%)	0.98
Female	3219 (51.1%)	3018 (51.1%)	201 (50.9%)	
Positive parental respiratory disease history n(%)	232 (3.7%)	206 (3.5%)	26 (6.6%)	< 0.01
One parent with respiratory history n	226	200	26	
Both with respiratory history n	6	6	-	
Mother's age at birth (years) Mean +/- SD (age range)	27.5 +/- 5.6 (15 – 46)	27.5 +/- 5.5 (15 – 46)	27.2 +/- 5.7 (17 - 45)	0.30
In utero/ at birth				
Low birth weight n(%)	327 (5.2%)	300 (5.1%)	27 (6.8%)	0.13
Born preterm' n(%)	235 (3.7%)	219 (3.7%)	16 (4.1%)	0.83
Mother smoking during pregnancy n(%)	2013 (31.9%)	1860 (31.5%)	153 (38.7%)	< 0.001
Social class at birth n(%)				
SC1	1226 (19.4%)	1161 (19.6%)	65 (16.5%)	0.21
SC2	631 (10.0%)	592 (10.0%)	39 (9.9%)	
SC3	3154 (50.0%)	2958 (50.1%)	196 (49.6%)	
SC4	1293 (20.5%)	1198 (20.3%)	95 (24.1%)	

Cohort member characteristics	Total n = 6,304	No AO/ respiratory symptoms n = 5909	AO and respiratory symptoms n = 395	P value#
Childhood (0-16 years)				
Passive smoke exposure n(%)	5884 (93.3%)	5521 (93.4%)	363 (91.9%)	0.28
Had asthma n(%)	1417 (22.5%)	1268 (21.5%)	149 (37.7%)	< 0.001
Had pneumonia' n(%)	280 (4.4%)	248 (4.2%)	32 (8.1%)	< 0.001
Adulthood (23-45 years old)				
Passive smoke exposure n(%)	3527 (55.9%)	3259 (55.2%)	268 (67.8%)	< 0.001
Smoker in adulthood n(%)				
Never	3801 (60.3%)	3667 (62.1%)	134 (33.9%)	< 0.001
Ever	1347 (21.4%)	1266 (21.4%)	81 (20.5%)	
Persistent	1156 (18.3%)	976 (16.5%)	180 (45.6%)	
Adult onset asthma n(%)	398 (6.3%)	322 (5.4%)	76 (19.2%)	< 0.001
Biomass Exposure' n(%)	779 (12.4%)	709 (12.0%)	70 (17.7%)	< 0.001
Ever occupational exposure	1929 (30.6%)	1781 (30.1%)	148 (37.5%)	< 0.001
Social class at 23 years n(%)				
SC1	1031 (16.4%)	989 (16.7%)	42 (10.6%)	< 0.001
SC2	2328 (36.9%)	2198 (37.2%)	130 (32.9%)	
SC3	1649 (26.2%)	1522 (25.8%)	127 (32.2%)	
SC4	1296 (20.6%)	1200 (20.3%)	96 (24.3%)	
Social class at 42 years n(%)				
SC1	2566 (40.7%)	2447 (41.4%)	119 (30.1%)	< 0.001
SC2	1531 (24.3%)	1438 (24.3%)	93 (23.5%)	
SC3	1206 (19.1%)	1110 (18.8%)	96 (24.3%)	
SC4	1001 (15.9%)	914 (15.5%)	87 (22.0%)	
Chest infection last 3 weeks prior to lung function test n(%)	576 (9.1%)	524 (8.9%)	52 (13.2%)	< 0.001
Has respiratory symptoms at 42 years n(%)	1795 (28.5%)	1400 (23.7%)	395 (100%)	< 0.001
Airflow obstruction at 45 years n(%)	925 (14.7%)	530 (9%)	395 (100%)	< 0.001

AO = airway obstruction; SC = social class (SC1 = professional/managerial; SC2 = unskilled non-manual; SC3 = skilled manual; SC4 = unskilled manual); SD = standard deviation; 'based on mean of ten imputed datasets; #calculated by Chi square or independent sample t-test as appropriate

4.3.3 Association between parental respiratory disease history and outcome (path c)

Parental respiratory disease history was significantly associated with airway obstruction and respiratory symptoms at 45 years of age after adjusting for gender, history of asthma (childhood or adult onset) and recent chest infection (estimate = 0.268, 95%CI = 0.035 - 0.501, p = 0.024).

To evaluate the strength of the association between parental respiratory disease history and cohort airway obstruction and respiratory symptoms, the difference in the marginal effects was calculated in two hypothetical scenarios. When the effects of other factors were kept constant, individuals with adulthood onset asthma and parental respiratory disease history had a higher probability (male: 9.2%; female: 9.0%) of airway obstruction and respiratory symptoms in adulthood compared to those without a parental respiratory disease history. In a second scenario, in individuals without any history of asthma or recent chest infection, those with a parental respiratory disease history had 3.8% (male) and 3.7% (female) higher probability of having airway obstruction and respiratory symptoms in adulthood compared to those without a parental respiratory disease history.

To allow comparison of the results in this study with results in the systematic review (Chapter 3), logistic regression was used estimate the association between parental respiratory disease history and cohort airway obstruction and respiratory symptoms in the 1958 cohort. Cohort participants with a parental respiratory disease history had 68% higher odds of having airway obstruction and respiratory symptoms (OR = 1.68, 95%CI 1.07 - 2.65, p = 0.026) after adjusting for gender, history of asthma (childhood or adult onset) and recent chest infection.

4.3.5 Associations between parental respiratory disease history, individual life course factors and outcome (path a and path b)

Results for associations between parental respiratory disease history and individual life course factors (path a) are presented in Table 4.2.

Table 4.2 Results of individual associations between (1) parental history and life course factors and (2) life course factors and airway obstruction with respiratory symptoms.

Life period	Life course factors	Parental history predicting life course factors ^ (Path a) Estimate (95%CI)	Life course factors predicting airway obstruction with respiratory symptoms+ (Path b) Estimate (95%CI)
In utero/ birth	Maternal smoking	0.289 (0.120,0.458)**	0.082 (0.019,0.145)*
	Low birth weight	0.371 (0.142,0.600)**	0.046 (-0.058,0.150)
	Preterm birth	0.105 (-0.234,0.444)	0.024 (-0.103,0.151)
	SC at birth	0.320 (0.185,0.455)***	0.059 (0.004,0.114)*
Childhood	Passive smoke exposure	-0.148 (-0.391,0.095)	-0.041 (-0.137,0.055)
	Pneumonia	0.056 (-0.258 ,0.370)	0.106 (-0.002,0.214)
Adulthood	Passive smoke exposure	0.165 (-0.004,0.334)	0.146 (0.083,0.209)***
	Adulthood smoker	0.184 (0.019,0.349)*	0.386 (0.333,0.439)***
	Biomass exposure	0.097 (-0.121,0.315)	0.106 (0.026,0.186)*
	Occupation exposure	0.264 (0.090,0.438)**	0.106 (0.039,0.173)**
	SC at 23 years	0.253 (0.124,0.382)***	0.104 (0.053,0.155)***
	SC at 42 years	0.281 (0.130,0.432)***	0.137 (0.084,0.190)***

SC = Social Class; ^adjusted for maternal age, mother's marital status at 1958; + adjusted for gender, childhood and adulthood onset asthma and recent chest infection; *p<0.05; ** p< 0.01; *** p<0.001
CI = confidence interval (bootstrap=1000)

Parental respiratory disease history was positively associated with the cohort member being exposed to maternal smoking, born with low birth weight, adulthood smoker, exposed to vapour, gas, dust or fumes through their occupation, lower social class at birth, 23 and 42 years.

Results of analyses testing life course factors as predictors of airway obstruction with respiratory symptoms (path b) are also reported in Table 4.2. After accounting for parental respiratory disease history, exposure to maternal smoking, living with or being a smoker during adulthood, use of biomass as home heating source in adulthood, occupational exposure to vapour, gas, dust or fumes, lower social class at birth, 23 and 42 were positively associated with airway obstruction with respiratory symptoms.

4.3.4 Complete model: Indirect effects of parental respiratory disease history and outcome through life course factors

Life course factors that satisfied the criteria for mediation testing were added incrementally in a single model. Firstly, maternal smoking and adulthood smoking were modelled as a sequence (Model 1). Model 1 had good model fit based on the RMSEA and CFI values, the TLI value was marginally below the cut-off of good model fit. The total indirect effect from parental respiratory disease history to cohort airway obstruction and respiratory symptoms was significant (p=0.015). However, the only significant specific indirect path was through the sequence of maternal to adulthood smoking (p= 0.014).

Occupational exposure was added in Model 2, with correlation between occupation and adulthood smoking specified in the model. The total (p=0.020) and total indirect effects (p=0.013) from parental respiratory disease history to adulthood airway obstruction and respiratory symptoms were significant in this model. The specific indirect effects through the maternal-adulthood smoking sequence remained significant (p=0.014), but the specific indirect effect through occupation was not (p=0.512). This model also had poor model fit. Occupational exposure was therefore not retained in subsequent models.

In Model 3, the sequence of social class variables were added to Model 1, with correlation between smoking and social class variables of the same time period specified in the model. As for the previous models, the total indirect effect (p=0.006) and the specific indirect path through the smoking sequence (p=0.007) were statistically significant. However, the specific indirect effect through individual social class and social class trajectories were not significant. Model fit of this model improved compared to Model 2 however only one of the three model fit indices met the criteria of good model fit. Given that no other life course factors satisfied the criteria for mediation testing, Model 1 was therefore considered as the final model. The three model results are summarised in Table 4.3.

Table 4.3 Total, total indirect and specific indirect effects through life course factors

	Model 1 (smoking variables only) Estimate (95%CI)	Model 2 (Model 1 + occupation) Estimate (95%CI)	Model 3 (Model 1+ social class variables) Estimate (95%CI)
Total effect	0.307 (0.050,0.564)*	0.309 (0.050,0.568)*	0.309 (0.047,0.565)*
Total indirect effect	0.092 (0.018,0.166)*	0.122 (0.038,0.206)*	0.108 (0.032,0.184)**
Specific indirect			
Maternal smoke	0.016 (-0.008,0.040)	0.016 (-0.008,0.040)	0.010 (-0.014,0.034)
Adulthood smoking	0.066 (-0.005,0.137)	0.066 (-0.003,0.135)	0.061 (-0.008,0.130)
Maternal smoke → adulthood smoking	0.009 (0.001,0.017)*	0.009 (0.001,0.017)*	0.013 (0.003,0.023)**
Occupational exposure	-	0.007 (-0.015,0.029)	-
SC at birth	-	-	0.013 (-0.011,0.037)
SC at 23	-	-	-0.003 (-0.015,0.009)
SC at 42	-	-	0.010 (-0.004,0.024)
SC at 0 →SC at 23	-	-	-0.002 (-0.010,0.006)
SC at 23 → SC at 42	-	-	0.004 (-0.002,0.010)
SC at 0→ SC at 23→ SC at 42	-	-	0.003 (-0.001,0.007)
Fit indices			
RMSEA	0.014	0.080	0.048
CFI	0.975	0.508	0.594
TLI	0.940	-0.115	0.768

*p < 0.05; **p<0.01; SC = Social Class; CI = Confidence Interval; RMSEA = Root-Mean-Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index
adjusted for gender, childhood and adulthood onset asthma and recent chest infection

The final model explained 30% of the effect of parental respiratory disease history on cohort airway obstruction and respiratory symptoms. The proportion mediated by the sequence of maternal smoking to adulthood smoking was 3%. Figure 4.5 presents results from model 1 (in black) and also presents all life course factors tested but for which no evidence of mediation was found (in grey). The final model was re-run on the complete case sample, resulting in similar interpretation of mediation effects (data not shown).

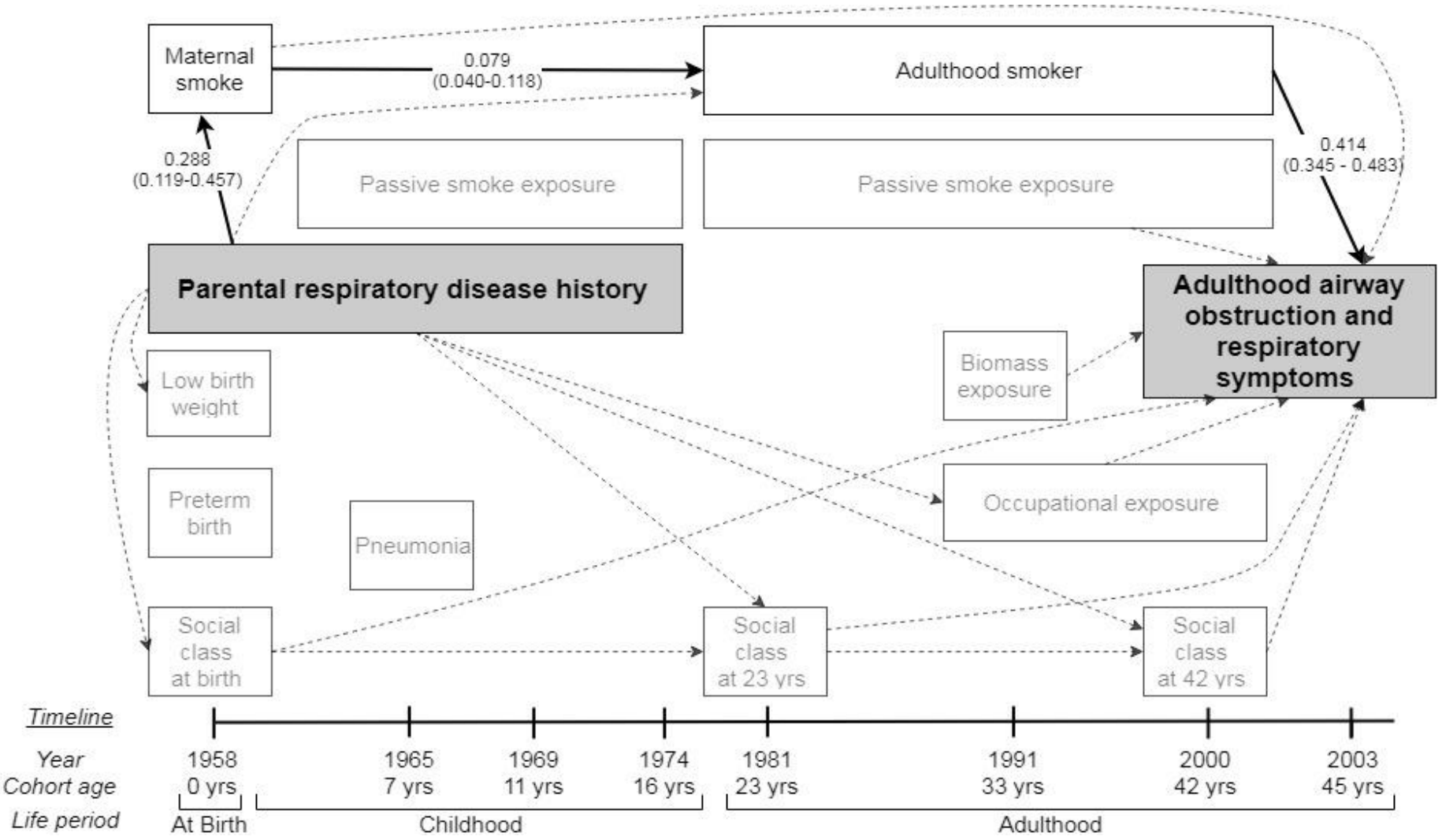


Figure 4.5 Final model with solid black arrows indicating significant pathway from parental respiratory disease history to adulthood airway obstruction and respiratory symptoms (adjusted for gender, history of asthma and recent chest infection).

Dotted grey arrows represent significant associations but non-significant mediating pathway. Values are unstandardized path estimate (95%CI), only significant pathway values shown.

4.4 Discussion

The aim of this analysis was to use a life course approach to investigate factors contributing to the relationship between parental respiratory disease history and airway obstruction with respiratory symptoms in adulthood using data from the 1958 British birth cohort study. The prevalence of cohort participants with airway obstruction and respiratory symptoms in adulthood and a positive parental respiratory disease history was 6.6%. The analysis found a significant association between parental respiratory disease history and the presence of airway obstruction with respiratory symptoms in offspring. The strength of the association using data from the 1958 cohort (OR = 1.68, 95%CI = 1.07-2.65, p = 0.026) was comparable to the results in the systematic review (Chapter 3, pooled OR = 1.57, 95%CI = 1.29-1.93, p< 0.001). The relationship was mediated by an accumulation of smoking exposure (maternal smoker to adulthood smoker) rather than through one specific factor, suggesting the complex nature of the inter-relationships between intergenerational and life course influence and the cohort's lung health[293].

4.4.1 Life course factors mediating the relationship of parent-offspring lung health

The significant pathway from parental respiratory disease history through maternal smoking and adulthood smoking to cohort airway obstruction and respiratory symptoms in adulthood was biologically plausible. Exposure to maternal smoking during pregnancy has been reported to have long-term consequences on the offspring's lung health [124], with increased risk of presence of respiratory symptoms and reduced lung function in adulthood [148]. The relationship between smoking, accelerated lung function decline and development of COPD has been well studied [110, 111]. Results of this analysis indicate that from parental respiratory disease history, two smoking factors (maternal smoking to adulthood smoking) contributed to the relationship between parental respiratory disease history and adulthood airway obstruction and respiratory symptoms, rather than an individual smoking factor.

Intergenerational transmission of smoking behaviour is likely multifactorial. Family based association analyses in a genome wide association study identified that the

presence of α-nicotinic acetylcholine receptor (CHRNA3/5) is significantly associated with lung function and COPD development[294]. Genetic and twin studies indicate that the transmission of smoking behaviour from parent to offspring is likely influenced by the interaction between genes and environment [295, 296]. Parental smoking behaviour had been shown to have an influence on their adolescent offspring's initiation of smoking [297]. In addition to social learning of the parent's smoking behaviour, implicit attitudes towards smoking may also be transmitted from parents onto their offspring [298]. This was also reflected in studies that examined the influence on the parent's lifetime smoking trajectory (e.g. never smoker, smoked but quitted, started smoking at an early age and were persistent smokers) on the risk of their adolescent child's initiation of smoking [299, 300]. Following initiation of smoking, individuals may have different trajectories of smoking from their adolescent years through to their adulthood years. Individuals who start smoking at a young age and persist into early adulthood (31 years) are more likely to have parents who smoked and positive smoking –related beliefs (i.e. low perceived consequences of smoking)[301].

4.4.2 Life course factors that did not mediate the relationship of parent-offspring lung health

Similar to findings from previous studies, the current study found a significant association between adulthood passive smoke exposure and cohort airway obstruction and respiratory symptom [117, 118], but adulthood passive smoke exposure was not associated with parental respiratory disease history. This may reflect temporal changes in smoking prevalence in the wider population between the cohort's early life (cohort age = 2 years, UK prevalence of smoking in 1960 = 70% male and 40% females) compared to their early adulthood (cohort age = 24 years, UK prevalence of smoking in 1982 = 38% male and 33% females) [302-304]. With over 90% of the study sample ever exposed to passive smoking during their childhood and no significant difference between those with airway obstruction and respiratory symptoms compared to those without, it was unlikely that childhood passive smoke exposure would contribute to the relationship between parental respiratory disease history and airway obstruction and respiratory symptoms in this cohort.

Consistent with results from previous studies, socioeconomic status in childhood [305] and adulthood [306] were found to be associated with adulthood lung health. The accumulation of socioeconomic disadvantage over the life course had been associated with reduced health outcomes [307]. In an analysis of cross-sectional data on spirometry and wealth scores of adults over 40 years from 11 countries, poverty was a strong predictor of chronic airflow obstruction [119]. It has been suggested that a combination of socioeconomic status measures at multiple time points may be more informative than single measures, with reduced risk of over or under-adjustment of later life socioeconomic status and associated risk factors [308]. Hence the effect of the social class sequence on the relationship between parental respiratory disease history and cohort airway obstruction and respiratory symptoms was investigated in this study.

Due to the high proportion of missing social class data across the three selected time points, missing social class data were imputed from the closest sweep of data collection as described in previous studies that examined the effects of life course social class trajectory in the 1958 cohort [278, 309]. A plausible explanation of the non-significant specific indirect path through the social class sequence in model 3 may be due to the strong association between smoking and social class [119, 310, 311]. The association between smoking and social class variables was taken into account in Model 3 and was found to improve model fit. Post-hoc analyses testing the indirect effect of social class variables alone, or without accounting for the correlation between smoking and social class measures revealed that the specific indirect path through social class trajectories was statistically significant but the model fit was sub-optimal (results not shown). Collectively, these results suggest that social class is not likely to contribute further to the relationship between parental history and adult lung health once their relationship with smoking variables have been considered.

A similar pattern of sub-optimal model fit was observed when occupational exposure was included into Model 2. This could potentially be explained by the derivation of social class variable which was based on the cohort's occupation in adulthood. The association between occupation exposure and chronic respiratory disease has been well documented within the 1958 cohort and in other populations [281, 312]. Data from

the British Household Panel Survey found parents' occupation status had a strong influence on their children's attainment showing constrained intergenerational occupation mobility in Britain in 1990s [313, 314].

Exposure to biomass was significantly associated with cohort airway obstruction and respiratory symptom as reported in previous literature[113, 315]. Not surprisingly, parental respiratory disease history was not associated with household biomass exposure in adulthood as parents and cohort members were unlikely to be living in the same household when this data was collected. The association between biomass exposure and COPD development has been reported to have a dose-response relationship, so that longer exposure duration with poor indoor ventilation was associated with greater decline of lung function[316]. Although use of biomass fuel has been linked with economic development of countries[317, 318], it has been argued that beyond cost, the choice of using biomass fuel can also be linked to lifestyle and cultural factors [319]. Therefore although biomass exposure was only available at one sweep when the cohort were 33 years, it was included in the analysis.

Unlike results from previous studies, this study did not find associations between early life factors and cohort airway obstruction with respiratory symptoms[94]. Low birth weight was associated with worse adult lung function and having COPD as the cause of mortality in a historical cohort study[320]. However a recent meta-analysis reported a strong association between low birthweight and adulthood restrictive impairment (59.4mL higher FVC in adulthood per kg increase in birth weight) rather than airflow obstruction [321]. Previous studies that investigated effects of preterm birth on lung health either measured the participant's lung function in their childhood to early adulthood years (5-31 years) or in older adults (60-80 years)[322]. The different life stage of when the 1958 cohort (45 years) had their lung function measured compared with previous studies may explain the lack of significant association. Additionally preterm birth and childhood pneumonia were imputed with multiple imputation to maximise the sample size, it is possible that results might differ if data were complete.

4.4.3 What has changed over the life course of the 1958 cohort?

In this analysis, tobacco smoking played an important role in the association between parental respiratory disease history and adulthood airway obstruction and respiratory symptom. During the lifetime of the 1958 cohort, there have been major changes in public policies with legislation progressively introduced to reduce and minimise exposures to factors known to impact on lung health[323]. The UK legislative changes commencing with banning cigarette advertisements on television (1960s), warnings on cigarette packages (1970s), banning smoking on public transport (1980s-90s) and most recently smoking bans in enclosed public places including workplaces (2006-07) [303, 324]. Regulations around occupational exposure to substances hazardous to health (1980s) and personal protective equipment (1990s) were also introduced [325]. Hence, the results would be likely to differ if the same analysis was conducted on life course data from a British cohort born in the 21st century.

However, approximately one third of the world's population (57 countries) are not protected by at least one of the World Health Organisation best-practice tobacco control measures [326]. In countries with tobacco control policies, levels of compliance and law enforcement have been reported to vary, with greater challenges experienced in middle- and low- income countries [326, 327]. Opportunities for biomass exposure are also higher in developing countries with higher prevalence of households using solid fuel with limited ventilation[328]. Therefore, results of this study may still apply in some low or middle-income countries where the majority of the world's population lives in an environment with suboptimal tobacco control and access to effective health care services[329]. While this study has concentrated on exploring the contribution of exposure to life factors on the relationship between parental respiratory disease history and the incidence of airway obstruction with respiratory symptoms, future studies should incorporate findings from ongoing genome wide association studies to explain the association between parent and offspring lung health.

4.4.4 Strengths and limitations

The strength of this study was the availability of a range of life course information collected at multiple time points from a large sample of participants, which allowed the exploration of various life course factors and their mediation role in the relationship between parental respiratory disease history and cohort airway obstruction and respiratory symptoms. A comprehensive list of life course factors selected from current consensus and evidence on COPD risk factors were examined in this study [1, 9, 94]. While there was sample attrition (50%) within the 1958 cohort from when the study first started to when they were at age 45 years, the 45 year sample is considered broadly representative of the surviving 1958 cohort[269]. The analytic sample was not significantly different to the 45 year old sample (Appendix B. 4).

Under-diagnosis of COPD is common [69, 70], and this may explain the relatively high proportion of cohort members with airway obstruction and respiratory symptoms (6.3%) in this analysis compared to the reported population estimate for COPD in the UK (2.2% in 2003) [330]. Those meeting the criteria of airway obstruction and respiratory symptoms at 45 years are likely to represent individuals with early changes and likely to have worse lung function trajectory as COPD is commonly diagnosed in the fifth or sixth decade [84]. If this analysis was repeated with post-bronchodilator spirometry and respiratory symptom data collected when the cohort members were in their sixth decade, it is possible that the correlations and mediators that mediate the relationship between parental respiratory disease history and cohort reduce lung health may differ.

The analyses conducted were limited to the data available. Of the cohort members with data on their lung function and respiratory symptoms, only 7,298 (91.8%) had data on parental respiratory disease history. As parental history was the main exposure of this study, this variable was not imputed although it had greater than 5% missing data[289, 331]. Beyond reduction of sample size, the nature of missing data (missing completely at random, missing at random or missing not at random) were unclear and may have introduced bias.

It should be emphasized that data on the primary exposure measure of parental respiratory disease history were collected across three sweeps (cohort age 0 - 16yrs). It may be argued that there were temporality issues when assessing associations between parental respiratory disease history and cohort early life factors. The duration of parental respiratory disease history was 11 years or longer (i.e. onset before cohort age 5) in half of those who reported a positive parental respiratory disease history at the third sweep of data collection (Appendix B.5). With consideration of the progressive natural history of chronic respiratory disease, there is a time lag between the initiation of the disease process to the time that the person receiving a clinical diagnosis [10]. Those 50% of parents who reported a shorter duration of respiratory disease history were likely to with have experienced respiratory symptoms which progressively worsened over time that eventually led to a clinical diagnosis. For mediation testing purposes, one direction had to be imposed to test for mediation. Thus although data on parental respiratory disease history data were collected cross-sectionally representing a snap shot of the parents' respiratory health at one time point during the cohort's early life, it was used as primary exposure in this study as those who reported a positive respiratory disease history likely represent those who have a respiratory disease that has progressed over time.

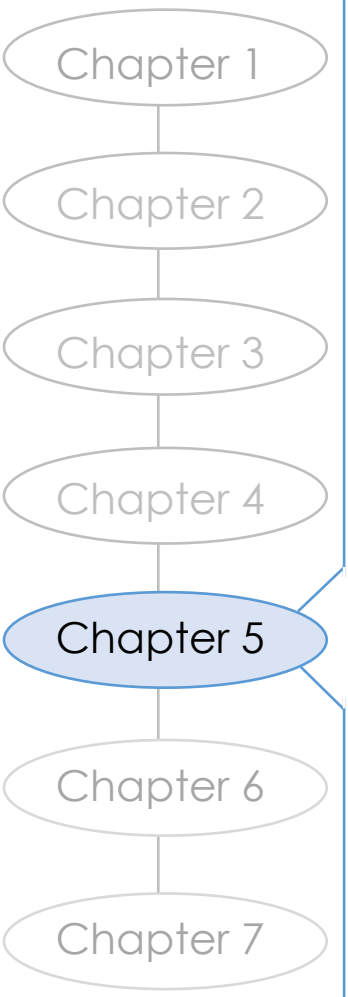
Parental respiratory disease history was self-reported and only available up until the third sweep when the 1958 cohort was 16 years old. Based on the maternal age when the 1958 cohort was born, parental respiratory disease history data were only available up until the mothers were in their mid-forties. It is likely that the self-reported positive parental respiratory disease history (3.7%) may be an under-estimate, as it does not capture parental respiratory disease history at an age when COPD may be more readily diagnosed with spirometry [84, 332].

Consistent with the GOLD guideline, a fixed ratio cut-off was used in this study to categorise cohort members' lung function as either "normal" or "reduced". Analysis of lung function data as a categorical, as opposed to a continuous variable, may have limited the statistical power. Post-bronchodilator spirometry data were not consistently available, hence this study was unable to specifically assess presence of COPD. The use of pre-bronchodilator lung function in analysis of data from other

longitudinal cohort studies indicates this measure can still provide meaningful insight into the participant's lung function[333]. Classification of cohort members using the definition of COPD upon Lower Limit of Normal values calculated using reference equations from the Global Lung Function Initiative may reduce the risk of under or over diagnosis of COPD of this analytic sample. It is possible that occupational exposure may have been misclassified. Future studies should use a validated Job Exposure Matrix to classify potential occupational exposure to minimise the risk of misclassification of potential occupational exposure. Some COPD risk factors (e.g. biomass exposure in childhood or outdoor air pollution) were not explored as data were not available. Finally, results of this study was adjusted for asthma history and this may been an over-adjustment as estimates for the coexistence of COPD and asthma as the prevalence of ACOS have been reported to range between 15 and 55% in epidemiological studies[36]. However results from post-hoc analysis of the final model without adjusting for asthma was similar to the final model (Appendix B.6).

4.5 Conclusion

Results of this analysis confirmed the central role of maternal smoking and personal smoking in the development of cohort airway obstruction and respiratory symptoms in adulthood, but these factors only explained 30% of the relationship between parental respiratory disease history and cohort airway obstruction and respiratory symptoms. A large proportion of the relationship between parental respiratory disease history and offspring airway obstruction and respiratory symptoms remains unexplained by life course factors explored in this study. Routine assessment of parental history of respiratory disease in primary care may provide an opportunity for clinicians to identify individuals at increased risk of reduced lung health in the long term.



Study III : Pilot study

How can we recruit parent-offspring pairs and cross-sectionally collect lung health related life course data in a non-COPD population?

While the 1958 British Birth Cohort study dataset provided a wide range of intergenerational life course data collected longitudinally, the original study was not intended to examine intergenerational lung health. This restricted analysis to data that were available. Cross-sectionally recruiting and collecting life course data from dyads of parents and offspring may be an alternative way to explore intergenerational lung health.

The aim of this chapter was to pilot a strategy of recruiting adult offspring through initial contact with a parent (proband) and to assess the acceptability of the "Story Of My Life calendar". The "Story Of My Life calendar" was an instrument designed by the research team with an aim to capture exposures relevant to lung health that may be present at different stages in life.

Conference presentations related to this study

Data in this chapter were presented in a poster at the 2017 Thoracic Society of Australia and New Zealand conference in Canberra Australia (Li, LSK., Paquet, C., Johnston, K., & Williams, M. T. (2017). The story of your life and lung health: Pilot study of a life history approach. *Respirology,* Vol. 22, pp. 136). Refer to Appendix C.1 for the submitted abstract.

Data in this chapter were presented as a poster at the 2017 European Respiratory Society International Congress in Milan Italy (Li, LSK., Paquet, C., Johnston, K., Frith, P., & Williams, M. (2017). A life history calendar to map lung health risk exposures: pilot study. *European Respiratory Journal*, vol 50, suppl 60, PA 1251). Refer to Appendix C.2 for the submitted abstract.

5.1 Introduction

Retrospective analysis of the current literature (Chapter 3) and data from the 1958 birth cohort (Chapter 4) are limited by secondary analysis of data not necessary collected for examining intergenerational COPD. In the previous chapter, it was found that maternal smoking and personal smoking only explained 30% of the relationship between a positive parental respiratory disease history and reduced lung health in offspring (presence of respiratory symptoms and airway obstruction). Collecting cross-sectional primary data about life course history may help to fill in the gaps unanswered through secondary analysis and allow the researcher to have greater control over data availability and interpretation of data. Additionally this is may be a more efficient way to collect life course data. Prospective assessment of intergenerational COPD will need both a recruitment strategy and a life course history data collection instrument.

Recruitment of parents and their offspring to examine intergenerational influences such as genetic and or lifestyle variables on health are more common in longitudinal cohort studies such as the Framingham Heart Study[141]. Participants within the cohort studies were the first point of contact and their offspring were recruited into subsequent studies [141, 160]. This proband-initiated recruitment strategy has also been used in case-finding or screening studies, where health professionals approach people with a health condition that has a familial/genetic component (i.e. the proband) and invite them to recruit their family members for screening[213]. However depending on the nature of the medical conditions, varied uptake rates have been reported [214, 215]. We are unaware of studies that have used this recruitment strategy to recruit adult offspring of people with COPD for screening or to investigate intergenerational lung health.

Life history calendars have been used as a data collection method to retrospectively collect longitudinal life course data in a cross-sectional manner[192, 194]. Researchers can create and modify life history calendars to collect data based on their research aims. This method has been reported to improve recall of events and reliably collect data on family structure, employment, medical events or behaviour patterns over a person's life course [195, 334, 335]. To date this data collection method has not been

trialled specifically to map life course exposures relevant to lung health or COPD development.

This Pilot study primarily aimed to:

1) Investigate the practicalities of a recruitment process (proband-initiated recruitment strategy) that recruited pairs of parents (proband group) and their adult offspring (offspring group) through the parent in a general population and

2) Assess the acceptability of using a life history data collection instrument ("Story Of My Life calendar" [SOMLc]) to collect life course information relevant to lung health.

The secondary aim was to test run data management from the SOMLc, through creating variables and descriptively summarise life course risk factor exposure relevant to lung health. Results of this study were intended to provide a foundation, prior to undertaking a Feasibility study in people with COPD and their offspring, using the proposed methodology to recruit offspring of people with COPD and to collect data across their life course.

5.2 Methods

Design: This was a descriptive observational study. Ethical approval was obtained prior to study commencement from the University of South Australia Human Research Ethics Committee (HREC) (ID no. 0000035431) (Appendix C.3).

5.2.1 Participants

Participants were recruited from a single university-based teaching clinic (University of South Australia, City East Campus) that provides podiatry services to members of the community. Approximately 40% of the clinic patients were over 60 years of age and thus likely to have a range of chronic health conditions which could include COPD. The intent of this study was to pilot the recruitment strategy and life history instrument with older adults similar in age to the intended population to be recruited in the Feasibility study (people with confirmed COPD).

Two groups of participants were recruited: (1) proband group and (2) offspring group. Proband was defined as individuals approached by the research personnel directly

during recruitment (i.e. the first point of contact). Offspring were defined as both biological and non-biological adult offspring of the proband. For the proband group, participants were eligible if they were aged 60 years or older. For the offspring group, participants were eligible if they were adult children (aged 18 years or over) of the proband group. In both groups, participants were ineligible for the study if they had a cognitive impairment or insufficient English language to provide informed consent and complete assessments. This was determined by the research personnel through interaction with the participants.

All eligible persons who consented to participate were included in the study regardless of whether their parent or offspring agreed to participate.

5.2.2 Recruitment

The recruitment protocol was based on a previous study that used a proband-initiated recruitment strategy[336]. The research personnel (KL) attended a university-based podiatry clinic on four occasions between May and June 2016. The research personnel systematically approached individuals in the clinic waiting area, spoke with them about the study, and checked for interest and eligibility. An information sheet about the study was given to eligible individuals who indicated interest (Appendix C.4) and an information package was also provided if proband parents indicated willingness to convey information onto their adult children (Appendix C.5). Contact details of potential proband participants were recorded where possible. A follow up phone call was made to potential participants (probands) approximately one week after they had received the information sheet about the study. If the potential proband participant indicated interest, they were asked whether they had conveyed information onto their offspring. The number of proband approached, proband who indicated interest, contact received from adult offspring and reasons for decline were recorded.

Due to ethical issues around privacy and dependent relationship between parent and offspring, the research personnel was not given permission from the University of South Australia HREC to directly contact offspring even if the parent volunteered to provide the research personnel with their offspring contact details. Offspring of

proband participants contacted the research personnel to indicate interest in the study.

5.2.3 Study procedure and data collection

Both groups followed the same study procedure (summarised in Figure 5.1). Once an individual participant (proband or offspring) provided verbal consent to participate in the study, an appointment (face-to-face or telephone) was scheduled and a copy of the SOMLc memory aid (step one of SOMLc, Appendix C.6) was provided to the participant. Participants were encouraged to complete the SOMLc memory aid prior to attending the appointment.

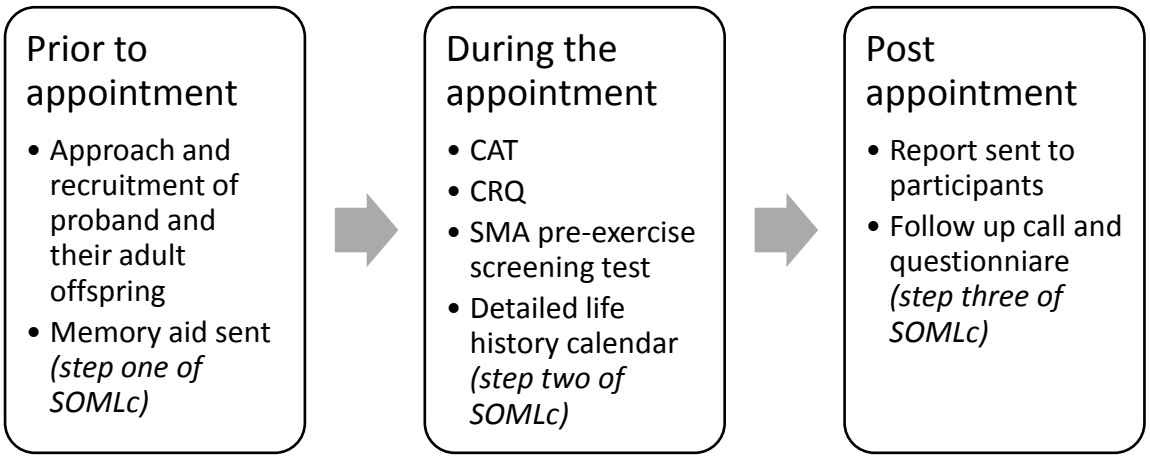


Figure 5.1 Summary of study procedure
SOMLc = Story Of My Life calendar; CAT = COPD Assessment Test; CRQ = Chronic Respiratory disease Questionnaire; SMA = Sports Medicine Australia

Prior to appointment

The Story Of My Life calendar (SOMLc) was designed and developed by the research team to collect data on exposures relevant to lung health across the lifespan. The structure of the SOMLc was based on the methods described in a study that aimed to retrospectively collect data related to social and health circumstances from birth throughout adulthood[207]. The SOMLc was structured into four life course stages (early life, school life, life after school and life after work) based on previous chronic disease epidemiology research[123] each covering established COPD risk factors identified from the literature[9,

94]. The SOMLc was designed to be completed in three steps (self- completed memory aid, detailed life history calendar, follow up call and questionnaire).

Step one of SOMLc: The self-completed memory aid was provided to participants one week prior to their scheduled appointment. The intent of the memory aid was to prepare participants for the sort of questions that the research personnel would ask when completing the SOMLc during the face-to-face appointment. This memory aid contained standard questions specific to different life stages (e.g. when were you born, where did you live, did you have any lung problems, when did you start paid work) to anchor life course events (Table 5.1).

Table 5.1 Summary of questions in memory aid and in detailed life history calendar specific to different life stages (step one and two of SOMLc)

Life stages	Factors of interest	Questions asked in the memory aid (Step one of SOMLc)	Examples of questions asked in face-to-face appointment to complete detail life history calendar (Step two of SOMLc)
Early life	Age	When were you born?	I see you were born in [year], so you are [age] this year?
	Birth weight	What was your birth weight?	(if unfilled) Did you miss out this question?
	Born preterm	Were you born early?	
School life	Highest level of education	How many years of schooling have you completed?	How old were you when you first started school? Is that [number of years] years in [primary/high] school?
		When did you start school? When did you finish school?	(if their place of residence had changed whether they went to the same primary or secondary/ high school)
		What is your highest level of school based attainment/ qualification achieved?	And you finish with [qualification] in [year]?
Life after school	Highest level of education	Any further education? (if yes, details)	Did you do any studies afterwards such as, diploma or certificate? (If yes, details)
	Occupational exposure	When did you start paid work?	Is [job/role] your first job? What was your main role in this job?
		Please list the jobs that you have worked in for over 1 year	How long where you in this job for? What did you do after your left [job]? (Continue until current job or retirement)
			(If retired) Did you do any volunteer and or unpaid work after retirement? (follow up with details on role and duration)
			Do you consider any of the places that you have worked in as smoky or dusty? (if yes, details)
Other personal	Offspring early life details	If you are married, when did you get married?	
		How many children do you have? Were any of them born early? What was their weight at birth?	
		Did your child have any lung problems when he/she was young?	(If yes, details)

	Factors of interest	Questions asked in the memory aid (Step one of SOMLc)	Examples of questions asked in face-to-face appointment to complete detail life history calendar (Step two of SOMLc)
Other personal	Personal smoking history	Have you ever smoked? (if yes, details)	(if current/ex-smoker) You wrote here you started smoking at [age]? And you have smoked for [number of years]? How much did/do you smoke on average? (if have quit smoking) So you stopped smoking in [year or age] and have not smoked since? (if never smoker) You have never smoked is that correct?
(asked in all life stages)	Living environment (Exposure to passive smoking Environmental exposure Biomass exposure)	Where did you live? Have you ever lived with someone who smokes? (if yes, for how long)	Do you remember which suburb your family lived in when you were born? Were you living in the same house until you started school? (continue until current place of residence) Who did you live with when you live in (suburb)? Were they smokers? Then when you living in (suburb), was it still with (person)? (continue until current place of residence) Do you remember what was the main heating and cooking source in (suburb)? Was it electric, gas, kerosene etc.? And then in the (suburb)? (continue until current place of residence) Looking back at all the places you have lived in, do you consider any of the places that you have lived in as polluted, for example close to industries, factories or busy roads?
	History of respiratory illness	Did you have any lung problems?	I note you wrote here you had (lung problem) here? (if yes, details) Do you recall any other bad episodes?
	Physical activity	Did you regularly participate in sports of fitness programmes?	I see you played sports in (primary/high school), what sports did you play? How regular did you play (sport/exercise)? Did you continued playing (sport/ exercise) when you started (post school life)?

SOMLc = Story Of My Life calendar

During the appointment

Upon attending the scheduled appointment, a timer was set once the participant had settled. The research personnel (KL) first explained the purpose, procedure, benefit and risk of the study to the participant. Participants were asked if they had any questions and informed written consent was then obtained (Appendix C.7). Participants were then instructed to complete three health questionnaires (COPD Assessment Test, Chronic Respiratory Questionnaire and Sports Medicine Australia Pre-exercising Screening Questionnaire) sequentially.

The COPD Assessment Test (CAT) was used to assessed the participant's current lung health, with eight items on respiratory symptoms, sleep and activity levels (Appendix C.8) [337]. Each item consist of two statements on the two ends of a scale ranging from zero (e.g. "I never cough") to five (e.g. "I cough all the time"), participants marks on the scale that best describe them currently. The score of each item was added to compute the total CAT score. Based on recommendations from the COPD Assessment Test user guide [338], participants with a score greater than 10 were encouraged to take their test result to their doctor to seek advice about their respiratory symptoms.

The Chronic Respiratory Questionnaire (CRQ) (self-administered version) was used as a measure of respiratory related quality of life. This questionnaire contains 20 items across four domains (dyspnoea, fatigue, emotional function and mastery) through a seven-point modified Likert scale (Appendix C.9) [339]. The total score for each domain were calculated (score of questions in that domain divided by number of questions answered), a higher score represents better health related quality of life in that domain. The CRQ has been reported to be a reliable and valid tool for the measurement of health related quality of life in people with chronic respiratory disease[340].

The Sports Medicine Australia (SMA) Pre-exercise Screening Questionnaire was used to assess the overall health status of participants and collect information on their comorbidities. This instrument consist of 17

questions that identify the presence of common medical conditions (Appendix C.10) [341]. The participant's answer was used to summarise their health status.

The research personnel recorded the time required to complete each questionnaire and checked for any missing answers. The research personnel then used guiding questions to complete the participant's detailed version of life history calendar (Step two of SOMLc, described below).

Step two of SOMLc: During the appointment, a detailed life history calendar was completed by the participant facilitated by the research personnel. The research personnel (KL) used the answers provided by the participant in the memory aid to populate a blank (A3 size) paper calendar template (Appendix C.11). The columns on the template represented year/ participant's age and the rows represented life course data of interest (e.g. living environment, education, occupation, lung health). Using a lists of guiding questions, the research personnel clarified information from the memory aid and obtained more detailed information on different aspects of their life and recorded it on the calendar template directly see Table 5.1 for examples of guiding questions.

The structure of guiding questions was the same for all participants, however the order of the guiding questions was flexible and amended if the participant indicated difficulty in recalling specific life history information or if they volunteered information in a reversed/mixed chronological order. As the participant provided life history information, the research personnel recorded it on the calendar template to allow the participant to visualise and clarify if required. Upon completion of the life history calendar, the participant was asked if there was anything that they wished to change or add that might have had an influence of their lung health. The research personnel then completed a final checklist (Table 5.2) in the presence of the participant to ensure all relevant data were obtained.

Table 5.2 Checklist completed after completion of the life history calendar (Step two of SOMLc)

Life course factor	Participant's answer	
Asthma	Yes/ No	
Passive smoke exposure	Throughout life? Yes/ No During childhood? Yes/ No	
Biomass smoke exposure	Yes/ No	
Outdoor pollution	Throughout life? Yes/ No During childhood? Yes/ No	
Personal cigarette smoking	Yes/ No	
Occupational exposure	Yes/ No	
	Participant's own	Participant's parent
Occupation Highest education		
	Participant's own	Participant's offspring
Birth weight		
Preterm birth	Yes/ No	Yes/ No
Childhood respiratory illness	Yes/ No	Yes/ No

The research personnel then concluded the appointment and explained to the participant that a summary of their life history report (Figure 5.2) would be posted/ emailed to them with a copy of their CAT results approximately a week later. All participants received a 25 dollar gift-card at the end of the appointment as honoraria.

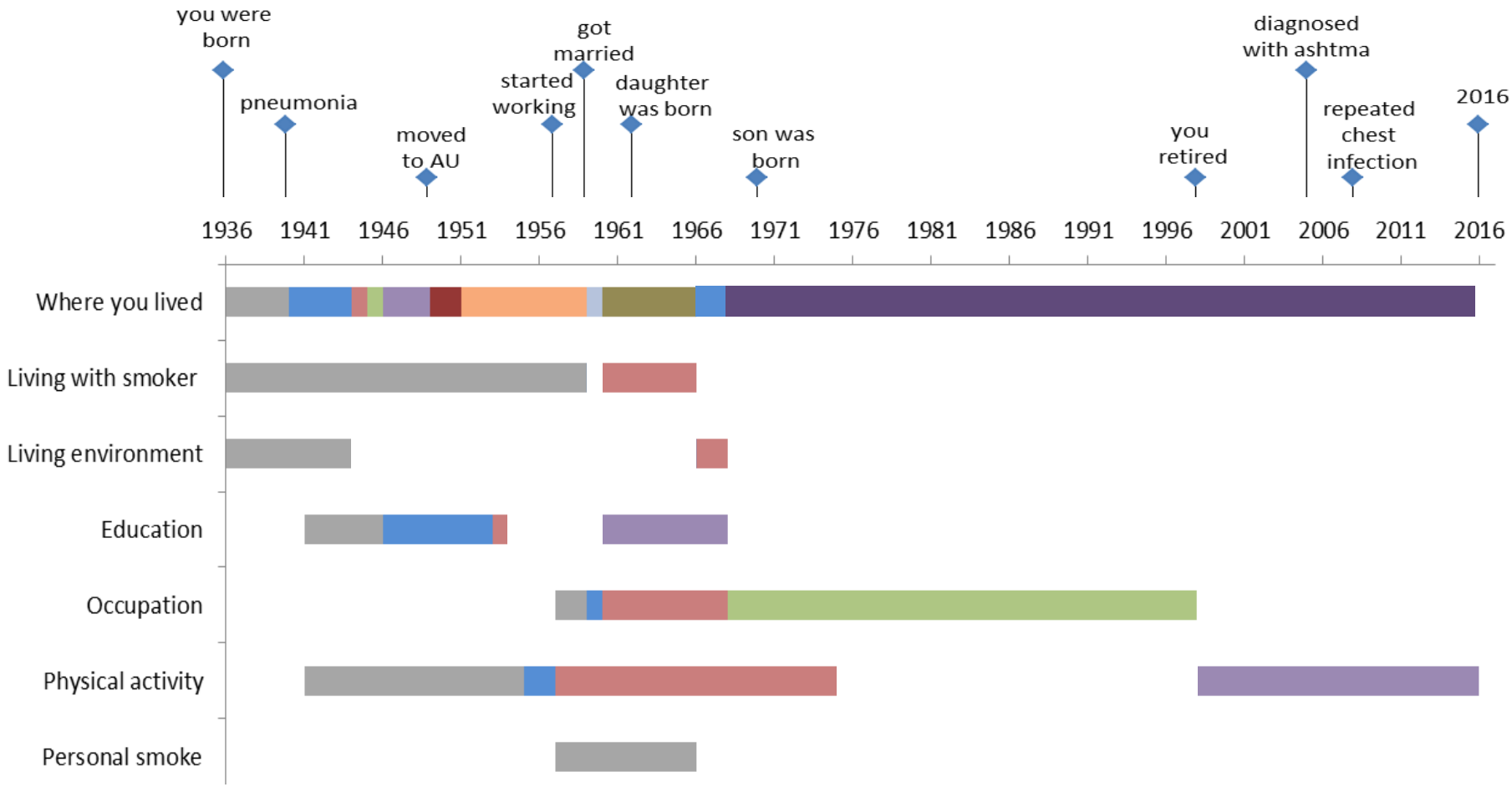


Figure 5.2 Sample graphical representation of a participant's life history report (step three of SOMLc)

*Note: each row represents an aspect of their life with different colours representing a change (e.g. a change in where they lived). The graph was accompanied by a descriptive summary (not shown here)

Post appointment follow up

Approximately two weeks after the initial study appointment, the research personnel (KL) made a follow up phone call to check if the participant had received the report. The CAT results were explained to individual participants verbally based on recommendations from the COPD Assessment Test user guide[338]. Participants who had a CAT score of greater than 10 were asked if they had taken any action in relation to this information (e.g. made an appointment or plan to see their doctor). The interviewer then asked participants to provide comments using a list of structured guiding questions to obtain general and specific comments of the SOMLc instrument (step 3 of SOMLc).

> **Step 3 of SOMLc:** Within the week of the face-to-face appointment, each participant received a copy of their life history report which contained a descriptive summary and graphical representation of their life history (Figure 5.2). The research personnel made a follow up phone call to the participant and used a list of nine questions designed to obtain feedback on the accuracy of data collected (questions 2-4), acceptability of the SOMLc (questions 5-6) and any general feedback (question 7-9) (Table 5.3). If the participant reported inaccuracies/ additional information required on their life history calendar, the research personnel recorded the details and asked if the participant would like to receive an updated copy of their calendar.

Table 5.3 Post appointment follow up phone call (step 3 of SOMLc)

Questions asked
1. Can I check that you have received and had time to read the summary of the report?
2. Do you feel that the calendar is an accurate description of your life? If no, could you talk me through which parts are not right, need changing?
3. Were there any periods of your life that you felt were missing from the calendar? Or big life events that were not covered?
4. Would you like to add or change any information in your calendar?
5. How easy or difficult did you find it to complete the memory aid (posted to you before the appointment)? Did it help you prepare for the appointment?
6. How easy or difficult did you find completing the detailed life history calendar with the researcher during the appointment? Were there any questions that you were unsure or could be asked in a clearer way?
7. Overall, were there any questions you felt uncomfortable answering?
8. In general, do you have any suggestions to make the Story Of My Life calendar more user-friendly? What changes should we make before we use this again?
9. Any other comments about the study or the report?

5.2.4 Analyses

Aim 1: Investigate the practicalities of a recruitment process that recruited pairs of parents and their adult offspring through the parent (proband-initiated recruitment strategy)

Proband response rate was calculated based on the number of probands consenting to participate out of the number of eligible probands approached. Offspring response rate was calculated from the number of offspring who approached the research personnel and number of probands that accepted the invitation to convey the information package onto their offspring. Reasons volunteered by participants (e.g. reasons for declining to join the study or for not conveying the information package) were collated into categories and frequencies reported.

Aim 2: Assess the acceptability of using a life history data collection instrument ("Story Of My Life calendar" [SOMLc]) and life course data collected

Response rate and feedback on the SOMLc

Data on the acceptability of the SOMLc were summarised and descriptively reported (Table 5.4). Return rate of the memory aid, completion rate and time taken to complete step one and two of the SOMLc were calculated. Feedback obtained from participants were presented in counts or collated into relevant categories.

Table 5.4 Summary of data collection and management for acceptability of the SOMLc instrument

Instrument	Data collected	Data analysis
SOMLc (step 1) Memory aid	Number of participants who brought the memory aid to the appointment Time required to complete it (minutes) Number of completed answers	Proportion of return rate (%) Mean completion time (minutes) Completion rate category (<50% completed, 50 – 90% completed, > 90% completed)
SOMLc (step 2) Detailed life history calendar	Time required to complete (minutes)	Mean completion time (minutes)
SOMLc (step 3) Post appointment follow up call	Participant feedback Accuracy of life history report Reasons for changes if required Ease or difficulty of the SOMLc General comments	Mean number of changes made in the life history reports Reasons of the changes categorised Clarity and acceptability of the SOMLc categorised

Consistency of SOMLc responses between participant pairs

Life history report data collected from proband-offspring or husband-wife pairs were compared during the time period where the pair cohabitated. Discrepancies between the pair were presented based on the category of discordant life course information in count and percentage (if information was collected once from each participant e.g. birth weight) or in number of pairs of discordant information and mean number of discrepancies per discordant pair (if information was collected more than once from each participant e.g. place of residence throughout life).

Secondary aim: Pilot managing data collected from SOMLc

Variables representing individual life course data in different life periods (if relevant) were created. All life course data collected from the SOMLc were treated as a categorical variable (e.g. asthma yes/no) and where appropriate, a continuous variable (e.g. duration of smoking). Each occupation reported by the participant was classified into one of the eight categories using the Australian and New Zealand Standard Classification of Occupations (Version 1.2) [342]. Physical activity in different life periods were classified as mostly active or not mostly active, where mostly active was defined as the participant participated in sports or regular structured physically activity at least 50% of that time period. Counts and percentages are presented for categorical variables, means and standard deviations are presented for continuous variables.

5.3 Results

5.3.1 Participant characteristics

A total of 31 participants completed the study with 26 in the proband group and five in the offspring group. A summary of participant characteristics is presented in Table 5.5.

Table 5.5 Participant characteristics

	Proband group (n = 26)	Offspring group (n = 5)
Age (years, mean ± SD, range)	76.3 ± 6.8 (62-90)	51.2 ± 4.9 (44-56)
Gender	Male: 9; Female: 17	Male: 1; Female: 4
CRQ domain score (mean± SD, range) (possible range = 1 - 7)		
Dyspnoea	6.59 ± 0.54 (5.00-7.00)	6.45 ± 0.44 (6.00-7.00)
Fatigue	5.42 ± 0.98 (3.25-7.00)	5.30 ± 0.65 (4.50-6.00)
Emotional	5.85 ± 0.78 (3.71-7.00)	5.37 ± 1.08 (4.00-6.71)
Mastery	6.60 ± 0.66 (5.00-7.00)	5.85 ± 1.56 (3.50-7.00)
CAT		
Numeric score (mean ± SD , range) (possible range = 0 - 40)	8.2 ± 5.0 (1-19)	8.0 ± 6.0 (2-18)
Score category (>10) n(%)	7 (26.9%)	1 (20%)
Self-reported health conditions*		
Cardiovascular n(%)	9 (34.6%)	0
Diabetes n(%)	7 (26.9%)	0
Liver, kidney or thyroid disorders n(%)	6 (23.1%)	1 (20.0%)
Respiratory disease n(%)	1 (3.8%)	0

SD: Standard Deviation; CRQ: Chronic Respiratory Questionnaire; CAT: COPD Assessment Test
*Summarised and collated from results from the Sports Medicine Australia (SMA) pre-exercise screening questionnaire

There were more female than male participants in both the proband group (65% female) and the offspring group (80% female). The mean CAT score was similar in both groups. Of the eight participants with a CAT score >10 (indicating they were experiencing respiratory symptoms), two reported that their doctor was previously aware of their respiratory health status, three participants had or planned to informed their doctor of their CAT results and three participants (with no previous respiratory medical history) reported they did not plan to take action on their CAT results. The proband group had more self-reported health conditions compared to the offspring group, with only one proband participant with a self-reporting a respiratory condition.

5.3.2 Aim 1: Practicalities of a recruitment process that recruited pairs of parents and their adult offspring through the parent (proband-initiated recruitment strategy)

Recruitment occurred over two months (May and June 2016). Participant flow through the study is presented in Figure 5.3.

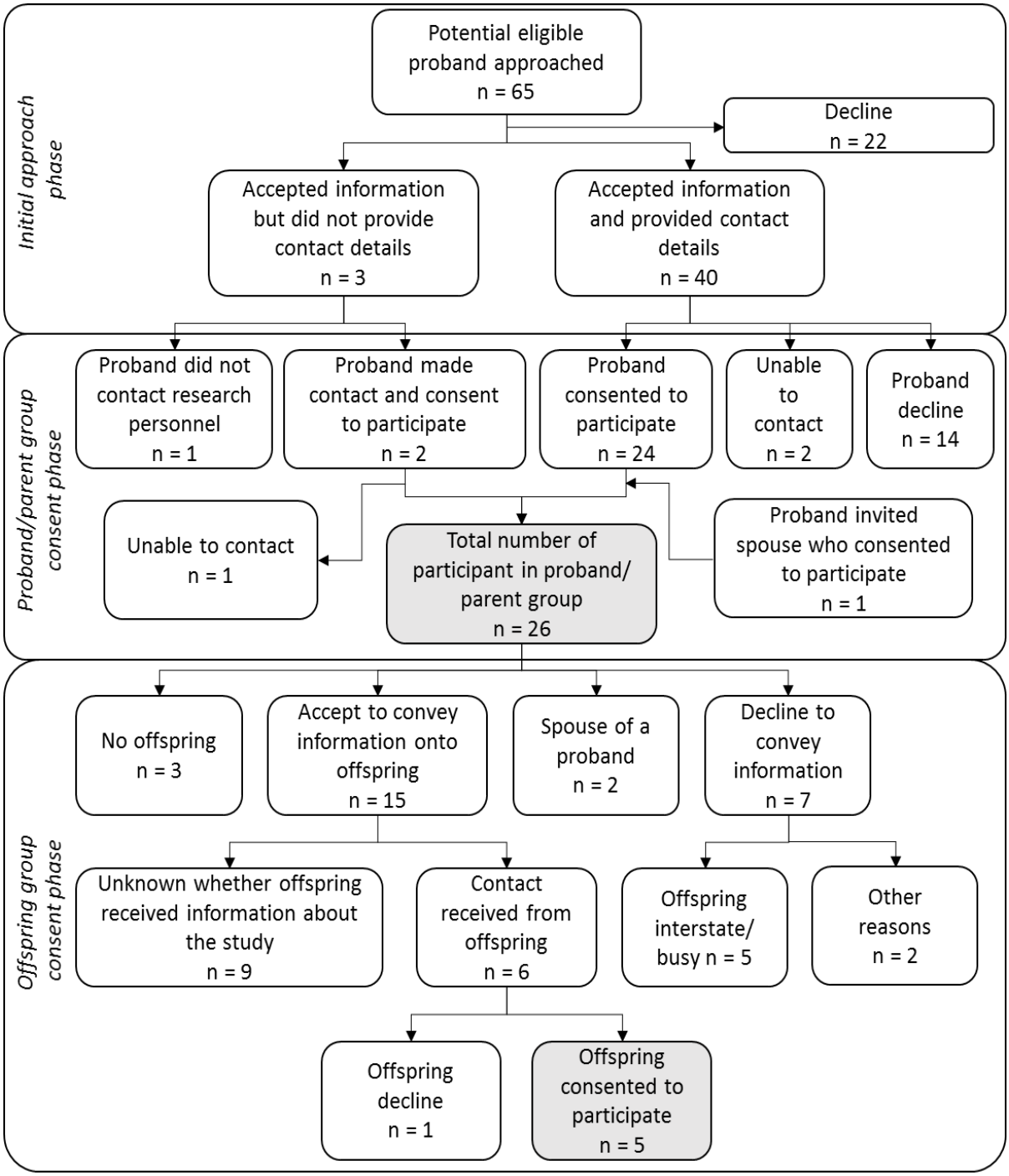


Figure 5.3 Proband-initiated recruitment results

Of the 65 proband participants approached in person, 22 declined, three accepted the information package but did not provide contact details and 40 participants accepted the information package and provided their own contact details. Of these 40, 25 participants and one spouse (not directly approached by research personnel)

consented to participate and were included in the proband/ parent group (response rate = 26/65 = 40%).

Of the 26 participants in the proband/parent group, 15 conveyed information about the study onto their adult offspring, six of the offspring returned the accept/decline form with five offspring consenting to participate (response rate = 5/15 = 33%). The reasons for declining to convey information onto adult offspring were geographic location (offspring lived interstate) (n = 3), parents and their offspring were not in contact (n = 1), the parent's perception that their offspring are too busy (n = 1) or would not be interested (n = 2).

5.3.3 Aim 2: The acceptability of using a life history data collection instrument ("Story Of My Life calendar" [SOMLc])

Part one of SOMLc: Memory aid (self-completed)

The SOMLc memory aid was posted/emailed to all participants prior to the appointment and participants invited to completed or at least review the questions in preparation for the appointment. Table 5.6 presents SOMLc memory aid completion time and rates.

Table 5.6 Self-completed SOMLc memory aid completion time and rate

	Proband group (n = 26)	Offspring group (n = 5)
Brought it to the appointment? n(%)	24 (92.3%)	4 (80%)
Mostly completed?* n(%)	23 (95.8%)	5 (100%)
Time to complete questionnaire (mins; median [IQR])	25.0 (24)	15 (2)

*missing answers to three or less questions (<10% missing); IQR = interquartile range

Almost all participants (n=28 [90%]) brought the SOMLc memory aid to the appointment, with the majority of participants completing most of the memory aid. One proband participant brought a blank SOMLc memory aid accompanied with a page of narrative of their early life history and another proband participant completed the memory aid supplemented with an additional page outlining family medical history. One offspring participant completed the appointment over the phone and emailed the memory aid to the research personnel after the appointment was

completed. Mean completion time for the self-reported SOMLc memory aid was 28.0 ± 22.7 minutes (range 10-130 minutes). One participant reported the completion time was 130 minutes due to not completing the questionnaire in one sitting.

Part two of SOMLc: Detailed life history calendar (researcher assisted)

The mean total appointment time was 57.0 ± 15.5 minutes (range 30-95 minutes) which included obtaining consent and completion of all instruments used in the study. For the detailed life history calendar (part 2 of SOMLc), the proband group took approximately 10 minutes longer to complete it compared to the offspring group (proband mean: 39.0 ± 10.3, range: 23 – 63 minutes; offspring mean: 29.8 ± 10.7, range: 18 - 41 minutes). Except for one participant who completed the appointment over the phone, all other participants completed the appointment in person.

The ability to recall early life history, specifically birth weight, gestational age at birth and childhood respiratory illness varied between the two groups (Table 5.7). Overall, more parents were able to recall their offspring's birth weight and gestational age compared to offspring recalling their own birth weight and gestational age. All participants were able to provide information on other life course exposures such as passive smoke, biomass or occupational exposure throughout all stages of their life course.

Table 5.7 Ability to recall early life information

Ability to recall information	Proband group (n = 26) n(%)	Offspring group (n = 5) n(%)
Birth weight	12 (46%)	4 (80%)
Preterm birth*	21 (81%)	5 (100%)
Childhood respiratory illness	26 (100%)	5 (100%)
(participant was a parent)	(n = 23)	(n = 3)
Offspring birth weight	18 (78%)	3 (100%)
Offspring preterm birth*	22 (96%)	3 (100%)
Offspring childhood respiratory illness	22 (96%)	3 (100%)

*preterm birth defined as born < 38 weeks

Step 3: Post appointment telephone follow-up (participant feedback)

The majority of participants (97%) indicated that the individualised report was an accurate description of their life course history (Table 5.8). Eleven participants noted some aspect of the report to be inaccurate (n= 8). Four proband participants reported

life events were missing in the report. The number of minor corrections made in the life history calendar per participant ranged between one to three changes. Four participants reported a life event missing in their report related to either personal events or non-respiratory related medical history. One participant considered that their life history report was inaccurate, however in response to further questioning was unable to provide any specific feedback or corrections to improve the accuracy of their report.

Table 5.8 Participant feedback on acceptability of the SOMLc instrument

	Proband group (n = 26) n(%)	Offspring group (n = 5) n(%)
Found memory aid helpful to prepare for interview	20 (77%)	5 (100%)
Found questions uncomfortable	0 (0%)	0 (0%)
Felt the report was accurate or mostly accurate	25 (96%)	5 (100%)
Want to make corrections to the report	10 (39%)	1 (20%)
Reason for corrections	(n=10)	(n=1)
Incorrect details of specific life events	4 (40%)	1 (100%)
Incorrect recall of home heating source	1 (10%)	0 (0%)
Incorrect passive smoke exposure history	1 (10%)	0 (0%)
Incorrect physical activity history	1 (10%)	0 (0%)
Missing information in report	3 (30%)	0 (0%)
Life events missing from the report	4 (15%)	0 (0%)

With the exception of one participant, participants did not report difficulties concerning the interpretation of the questions and format of the self-completed memory aid. The majority (86%) of participants who completed the memory aid prior to the researcher-assisted detailed life history calendar indicated that the memory aid was a useful tool to help them prepare for appointment. None of the participants reported concerns or issues with the structure or content of the detailed life history calendar. No participants indicated or reported feeling uncomfortable with any of the life history questions and no suggestions were provided by participants to increase the clarity of questions.

Consistency of SOMLc responses between participant pairs

Data were compared for similarities and differences within participant pairs (five parent and offspring pairs; two husband and wife pairs) during periods of cohabitation (Table 5.9).

Table 5.9 Pairs of participants with discordant information

	Parent/offspring pair (n = 5)	Husband/wife pair (n = 2)
Birth weight n(%)	2 (50%) *out of 4 pairs, as 1 pair both unable to recall	-
Preterm birth n(%)	0 (0%)	-
Childhood respiratory illness history n(%)	1 (20%)	-
Place of residence No. of discordant pair (no. of discrepancies per no. of discordant pair)	3 (2.7)	2 (5.0)
Passive smoke exposure No. of discordant pair (no. of discrepancies per no. of discordant pair)	2 (1.0)	0 (0.0)
Biomass exposure No. of discordant pair (no. of discrepancies per no. of discordant pair)	4 (1.0)	1 (2.0)

Two parent and offspring pairs provided a similar responses when asked about the offspring participant's birth weight (minor discrepancy of two ounces difference) and in one pair both participants were unable recall the information. One pair of parent and offspring had a consistent one year difference on when they lived in a certain place. Another husband and wife pair reported the same order of places that they have lived in, however there were eight inconsistencies with regards to the length of time they spent living in each of the houses. In addition to the different recall of duration spent in the houses, there were also four inconsistencies in the recall of four house's heating and/or cooking source that resulted in a difference of estimated length of biomass exposure by 15 years during the time they lived together.

Life course data collected through the SOMLc

Participants were born in various countries with half of the participants (n=16) born within Australia. Half of the proband group (n=13) were born in Europe, twelve of them lived in Europe in their early life (during World War II), of those seven were from the UK. Of the offspring group (all born post-war), three were born in Australia, one in Papua New Guinea and one in the UK.

Overall, the offspring group had a higher level of education and were mostly employed in non-manual work compared to the proband group (Table 5.10). When the

participant's education and occupation were compared with their parents (between generations), there was a similar pattern of intergenerational upward social mobility. Approximately 23% of the participants did not know or was unsure of how many years of schooling their parents experienced. Within the proband group, 81% of proband's mothers were not in paid employment (i.e. housewife/ did not work) whereas all mothers in the offspring group were in the paid workforce.

Table 5.10 Life course information on education and occupation

	Proband group (n = 26)	Offspring group (n = 5)
Participant's total number of years of schooling (years ± SD, range)	12.4 ± 4.3 (5-23)	16.4 ± 4.1 (11-22)
Occupation (if multiple, the category that spend the most time in; n(%)		
Managers	2 (7.7%)	1 (20%)
Professionals	7 (26.9%)	1 (20%)
Technicians and trades workers	3 (11.5%)	0
Community and personal service workers	1 (3.8%)	2 (40%)
Clerical and administrative workers	8 (30.8%)	0
Sales workers	3 (11.5%)	0
Labourers	2 (7.7%)	1 (20%)
Parent's total number of years of schooling (years ± SD, range)	9.1 ± 3.3 (5-15)	11.0 ± 2.8 (9-15)
Participant did not know	6 (23.1%)	1 (20%)
Father's occupation n(%)		
Managers	3 (11.5%)	0
Professionals	6 (23.1%)	2 (40%)
Technicians and trades workers	9 (34.6%)	2 (40%)
Community and personal service workers	1 (3.8%)	1 (20%)
Clerical and administrative workers	1 (3.8%)	0
Sales workers	1(3.8%)	0
Labourers	5 (19.2%)	0
Mother's occupation n(%)		
Professionals	0	1 (20%)
Community and personal service workers	1 (3.8%)	1 (20%)
Sales workers	2 (7.7%)	3 (60%)
Labourers	2 (7.7%)	0
(mother didn't work)	21 (80.8%)	0

SD = Standard Deviation

Life course exposures relevant to lung health for the proband and offspring group are summarised in Table 5.11.

Table 5.11 Life course risk factor exposure relevant to lung health

Life course exposure	Proband group (n = 26)	Offspring group (n = 5)
Birth weight (kg , mean ±SD , range)	3.0 ± 0.6 (1.4 - 3.6)	3.3 ± 2.9 (3.0 - 3.7)
Was born preterm*	0	0
Had childhood respiratory illness n(%)	5 (19.2%)	1 (20%)
Had asthma n(%)	3 (11.5%)	1 (20%)
During childhood	0	0
During adulthood	3 (11.5%)	1 (20%)
Lived with one or more smokers (passive smoke exposure) n(%)	26 (100%)	4 (80%)
One or both parent smoked (during childhood)	22 (84.6%)	4 (80%)
Exposure to passive smoke during childhood	25 (96%)	4 (80%)
Length of exposure (years, mean ± SD, range)	30.5 ± 18.3 (2 - 77)	26.3 ± 15.4 (6 - 41)
Used biomass/ derivative of biomass fuel within household n(%)	21 (80.8%)	4 (80%)
Length of exposure (years, mean ± SD, range)	26.3 ± 13.3 (8 - 60)	13.8 ± 8.2 (5 - 24)
Flued heating fuel (combustion, wood, coal) n(%)	15 (71.4%)	1 (25%)
Likely flued heating fuel (open fire, turf, peat) n(%)	3 (14.3%)	2 (50%)
Unflued heating fuel (kerosene) n(%)	3 (14.3%)	1 (25%)
Lived in a polluted area n(%)	9 (35%)	2 (40%)
Length of exposure (years, mean ± SD, range)	17.0 ± 13.0 (2 - 41)	27.0 ±14.1 (17 - 37)
Occupational exposure (dust, gases, fumes, smoke, asbestos) n(%)	16 (62%)	4 (80%)
Length of exposure (years, mean ± SD, range)	9.4 ± 9.4 (1 - 37)	7.8 ± 7.4 (1 - 16)
Exposure to passive smoke n(%)	13 (50%)	2 (40%)
Exposure to dust n(%)	1 (3.8%)	1 (20%)
Exposure to gases/chemicals n(%)	1 (3.8%)	0
Exposure to asbestos n(%)	0	1 (20%)
Exposure to passive smoke and gases/chemicals n(%)	1 (3.8%)	0
Smoking status Current smoker n(%)	2 (7.7%)	1 (20%)
Former smoker n(%)	14 (53.8%)	3 (60%)
Never smoker n(%)	10 (38.5%)	1 (20%)
Physical activity# during life course		
Active form of transport during school years n(%)	23 (88.5%)	4 (80%)
Mostly active during school years n(%)	20 (76.9%)	4 (80%)
Mostly active during work life/ adulthood n(%)	9 (34.6%)	2 (40%)
Physically active now (within last year) n(%)	18 (69.2%)	4 (80%)

*****preterm birth defined as born < 38 weeks; # defined as the participant participated in sports or regular structured physical activity (at least 50% of that time period), does not include occupational physical load/ household work/ gardening/ walking as means of transport

A similar proportion of probands and offspring reported having a respiratory illness during their childhood (19% and 20% respectively). With the exception of one participant from the offspring group, all participants in this study reported being exposed to passive smoke at some point in their life, with the majority exposed to passive smoking during their childhood. Only three participants were current smokers (proband group: 2; offspring group: 1) and 65% of all participants were ex-smokers. Use of biomass or derivatives of biomass (wood, coal, kerosene, peat or turf) as the residential heating /cooking sources was reported in 80% of participants was consistent with reports of the common source of energy consumption used for domestic heating in the UK during the corresponding time period[343]. A small proportion of the proband (14%) and offspring (25%) group were never exposed to unflued biomass heating sources. Less than half (39%) of all participants considered that they have resided in an area that was polluted (i.e. close to industries, factories or main/ busy roads), although 65% of all participants considered their work environment involved exposures that could have influenced their respiratory health.

Both parent and offspring groups reported similar involvement in physical activity during school and work life. An active form of transport (walking / cycling) during the school years was reported in 88% of proband and 80% of offspring. Seventy-seven percent of proband and 80% of offspring participants reported engaging in regular structured physical activity/ exercise during their school life. A higher proportion of participants in the offspring group were physically active during their work life and within the last year compared to the proband group.

5.4 Discussion

The key findings of this Pilot study were: 1) A proband –initiated strategy to recruit pairs of parents and their adult offspring through the parent was achievable, but despite comparatively high response rates in proband, this resulted in a low number of participating proband/ offspring pairs. 2) The life history instrument (SOMLc) was acceptable based on participant feedback regarding ease of use, accuracy and time taken to complete both the memory aid (self-completed) and the detailed life history calendar (researcher-assisted). Data collected from the SOMLc were summarised and generated into variables that could be operationalised for analysis.

5.4.1 Was proband-initiated recruitment strategy practical?

The proband-initiated recruitment strategy appeared feasible with a fair proband and offspring response rate (40% and 33% respectively) compared to other studies using a similar recruitment protocol. This recruitment protocol was based on an intervention study in offspring of diabetic and control (non-diabetic) patients (response rate 13.5% and 15.4%)[336]. The difference in offspring response rate may be explained by the different study nature. This was an observational study and only required one visit by the offspring participant whereas the intervention study by Nishigaki, Ota [336] required four visits for data collection.

Using a similar recruitment strategy, a higher response rate (66%) was reported in a study that required first degree relatives of proband with Crohn's disease to complete a questionnaire, where first degree relatives included parents, siblings or children over 18 years[214]. In contrast, a lower response rate (9%) was seen in female relatives (sisters, mothers and daughter) of known breast cancer gene mutation carriers using a similar strategy to recruit relatives to undergo genetic testing [215]. In addition to the study design and nature of the health condition, response rate in proband-initiated recruitment may also be affected by gender, race, ethnicity and cultural norms[344].

This study was not given permission by the University of South Australia HREC to directly contact offspring unless the offspring contacted the researcher and indicated interest in the study. This was due to ethical issues around breaching confidentiality and potential of psychological harm to offspring participants. Without direct contact with offspring of proband participants, we were unable to investigate if non-response from the offspring was due to lack of knowledge of the study (i.e. did not receive information from their parent) or disinterest, non-availability limiting participation in the study.

5.4.2 Acceptability of the life history instrument

Feedback from participants about the SOMLc instrument was positive, with no concerns on the three-step SOMLc process (memory aid, detailed life history calendar, post-appointment report and call). The process adopted in this study was based on methods reported by Kendig, Byles [207] in their study that collected life course data

from older adults (60-64 years) using a similar memory aid as a strategy to reduce the length of the interview. The memory aid was designed to prompt participants to recall and record specific years of events or location that would assist them in completing the detailed life history calendar during the appointment. The proband group on average spent twice as long to complete the questionnaire compared to the offspring group with a wider range of self-reported completion time. This is likely due to the proband group having a longer life course (i.e. were older) compared to the offspring group. Due to the small sample size, no statistical analysis was performed to measure the association between the use of the memory aid and length of time to complete the life history calendar during the appointment. Of participants who completed the memory aid, the majority considered it a useful way to help prepare for the appointment as they were prepared for the sort of questions that the interview will be focused on, suggesting participants valued the memory aid.

The detailed life history calendar provided valuable data on the participant's life history exposure relevant to lung health in a relatively short completion time (mean: 37.5 ± 10.8 minutes). This time was less than the initial predicted time of one hour. The length of time used to gather extensive life course exposure relevant to lung health was considered acceptable with minimal risk of participant fatigue. Peel and Wilson [345] conducted interviews to collect life course health data and falls history on 378 participants consisting of cases (aged over 65 who were hospitalised for a fall-related hip fracture) and controls (matched with sex, age and postcode); the mean time to complete the interview was 73 minutes (range: 30 minutes to 3 hours). Despite the longer interview time compared with this study, only 1% of the interviews' quality was recorded to have been negatively impacted by participant fatigue[345].

Participants in the current study were able to recall most of the life course information of interest to this study. Recall of early life information (specifically birth weight) was challenging for some participants, with some participants reporting they looked up childhood health records to seek this information. It was interesting to see the discrepancies of results when life course information was compared between pairs of participants. Previous studies compared maternal recall of offspring birth weight and gestation age with medical records and considered maternal recall to be accurate for

epidemiological use[346, 347]. Since more participants were able to recall their offspring's early life information compared with recalling their own information, having the parent's perspective on their offspring's early life history was valuable in the absence of access to medical records. Overall, data collected from the SOMLc appeared to have face validity when compared across generations showing upward mobility in terms of education and occupation which was consistent with societal trends [348].

The SOMLc appeared to have collected accurate data based on feedback from participants and the minor number of changes made to reports generated from this study. None of the participants provided any suggestions to improve the study protocol or the content of the life history instrument. Participants reported feeling comfortable with questions asked in the SOMLc, with some participants volunteering additional information in the follow-up call on personal events or medical history that they considered appropriate to be included in the life history calendar.

5.4.3 Data collected from the SOMLc relevant to lung health exposure

With the exception of occupational exposure, similar proportions of participants in the proband and offspring group reported ever exposure to lung health related risk factors. Similar to the 1958 study (Chapter 4) where 93% of cohort members lived with smokers during their childhood, the majority of participants within this local sample (proband group:96%, offspring group: 80%) reported exposure to passive smoke during their childhood. Using the SOMLc, the lengths of exposure (in years) to different risk factors were also calculated and were generally shorter in the offspring group. While this may be explained by the shorter life course of offspring participants, the reduced lengths of exposures may also be caused by increased awareness as a result of public health campaigns and emerging knowledge of latent effects of specific environmental and occupational exposures that led to changes in legislation that coincides with the offspring participant's early adulthood years [349, 350]. The timing and influence of social and public policy on exposures during a person's life course was identified as an important consideration for planning the Feasibility study analysis.

Recruitment occurred within a university-based teaching podiatry clinic where a high proportion of all clinic patients were female. This was reflected in the study sample with more female than male proband participants. More proband participants were born overseas (48%) when compared with the national estimate (28%) for all age groups [351], the higher proportion in this sample may be explained by probands mostly born during or soon after the end of World War II when there was an increase in immigration to Australia[352]. The relatively high proportion of participants that reported ever using biomass fuels for residential heating or cooking appears consistent with the reports of the common source of energy consumption used for domestic heating in the UK during the corresponding time period[343]. Since the cost for health service in the teaching clinic is lower than private clinics, it is likely to attract predominantly people from lower socioeconomic backgrounds which may explain the higher prevalence of cardiovascular disease (35%) compared to population based estimates (26%)[353]. There was also a higher proportion of participants reporting the presence of respiratory symptoms (26% vs 14.5%)[3] which may indicate self- selection of participants, where participants may have decided to participate as they perceived themselves to have poorer lung health compared to their peers.

From a case-finding point of view, the CAT score indicated eight participants (proband group = 7; offspring group = 1) were experiencing respiratory symptoms. The life course exposure histories of the eight participants with a CAT score > 10 (indicating they experience respiratory symptoms) were similar when compared with other participants in the respective groups. This was highly likely to be the result of the small sample size, with only one participant in the offspring group meeting the CAT ≥ 10 cut-off. The intent of the larger planned Feasibility study is to allow further comparison and statistical analysis of any relationship between life course exposure and the participant's lung health status.

5.4.4 Considerations for the planned Feasibility study

Proband recruitment strategy

The low uptake rate of proband-offspring pairs in this Pilot study might reflect the specific topic of lung health. Proband participants approached in the Feasibility study may have been more interested in the study if they did have a chronic lung condition

such as COPD. Through interviews with people with COPD, the central theme identified by Lindqvist and Hallberg [354] was "feelings of guilt due to self-inflicted disease"(p.460) as COPD is commonly associated with smoking habits of individuals. Probands approached in the Feasibility study may be reluctant to participate or convey information onto their offspring as there may be associated feelings of guilt about having a "self- inflicted disease"[354].

In this study, common reasons that probands declined to convey study information onto their offspring was because their offspring lived interstate or were perceived by the proband to be too busy. Minimising the need for the offspring participant to physically attend an appointment may potentially increase the willingness of the proband to convey information onto their offspring. One offspring participant successfully completed the SOMLc interview by phone, suggesting the SOMLc interview could potentially be conducted over the phone or electronically to eliminate travel time and reduce total time commitment required from the offspring participant. As the intent in the Feasibility study was to objectively measure the offspring participant's lung function, it is not practical to eliminate the need of the participant attend a face-to-face appointment, but it would be possible to reduce the length of time of the appointment by completing parts of the interview over the phone or online.

The use of a convenient sample in this Pilot study may have influenced the response rate obtained in this study. Patients at the university-based podiatry clinic may have been more familiar with the university environment therefore more amenable to participating in this research study. Thus the high proband response rate in this Pilot study may not be translated to the Feasibility study where potential participants will be recruited from a hospital/clinic environment and invited to participate in a research study in a different (university) setting.

SOMLc

There were individual variations in the way that the memory aid was perceived and used in this Pilot study. Feedback from participants indicated they valued the memory aid as a useful tool to prepare them for the interview, hence for the Feasibility study,

the research personnel will continue to encourage participants to complete the memory aid and add any further information that they perceive as important in preparation for the interview. The level of precision of details of data collected in the SOMLc depended on the participant's ability to recall details regarding different aspects of their life. It is acknowledged the SOMLc may have missed some information such as short term (less than 1 year) acute exposures that could have an impact on their long term lung health.

The SOMLc provided a large amount of valuable life course data. While no statistical analysis was conducted in this study due to the small sample size, the data provide a basis to plan the analysis for the Feasibility study. Similar categories of variables of lung health related risk factors that were examined in the 1958 study (Chapter 4) can also be examined using data collected from the SOMLc. Life course factors can also be operationalised with respect to the timing of the event for example in-utero/ at birth, childhood and adulthood in a similar fashion. Depending on the nature of the life course factor, the SOMLc would provide sufficient data to allow analysis specific to a life course period (e.g. ever or never exposure to passive smoke during childhood), as a cumulative lifetime exposure expressed using categorical (e.g. lifetime never, ever or persistent exposure to passive smoke) or continuous (the total number of years a person was exposed to passive smoke) measures.

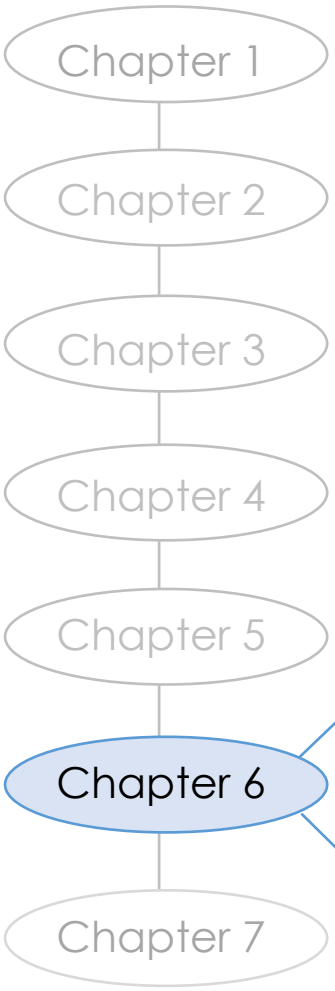
Minor revisions to SOMLc questions: When analysing the SOMLc data, the research team found two questions that could be worded differently or clarified in the Feasibility study. A potential way to overcome the low rate of recall of the participant's own birth weight may be to rephrase the question and ask participants if they were small, average or large at birth rather than ask for a specific birth weight. The research personnel only asked about the participant's home heating and cooking source in the Pilot study but did not consider the ventilation method. Flued or un-flued sources should be clarified in the Feasibility study as better ventilation within the household may lead to biomass exposure having a lower impact on lung health [316].

As expected in this Pilot study, there were a number of limitations. This was a single clinic Pilot study. Rather than people with COPD, older people in general were

recruited. Proband were eligible to be accepted into the proband group, even if they had no adult offspring or declined to convey information onto their offspring. This approach was chosen in order to maximise sample size and data collection on the acceptability of the SOMLc. Due to ethical requirements, researchers were unable to contact potential offspring participants directly unless the offspring had contacted the research personnel, limiting the understanding of non-response or non-participation of offspring of the proband group. While attempts were made to compare consistencies of data provided in pairs of participants, it was restricted to the small number of available pairs of participants within this study. With the lack of access to medical records or electoral roll, life course information collected was unable to be cross validated.

5.5 Conclusion

There appear to be no major practical issues with the indirect proband-initiated recruitment strategy and the life history data collection instrument (SOMLc) was an acceptable tool to collect lung health related life course information. The rate of participation of parent and offspring pairs was low. This may have been influenced by the lack of perceived benefits from participants as older adults in general were recruited rather than people with a chronic respiratory disease. Minor changes in the wordings when asking participants about their birth weight and a follow-up question on ventilation in the household where biomass fuel was used in the Feasibility study to allow more comprehensive COPD-related life course history data collection.



Study IV : Feasibility study

How feasible is a proband initiated method to recruit offspring of people with COPD via their parents?

Within a university- based teaching clinic setting, no major practical issues were identified when the proband-initiated recruitment method was piloted. The Story Of My Life calendar, an instrument designed to collect life course COPD related risk factors, was considered an acceptable tool for data collection based on completion time, participant feedback and similarities between data from proband-adult offspring pairs.

This study aimed to test the feasibility of using the piloted recruitment and data collection method to investigate lung health in adult offspring of parents diagnosed with COPD.

Conference presentation and publication related to this study

An abstract of this study has been accepted for presentation at the upcoming 2018 Thoracic Society of Australia and NZ Annual Scientific Meeting in Adelaide Australia (Li, LSK., Paquet, C., Johnston, K., Frith, P., & Williams, M. Recruiting adult offspring of people with COPD to explore intergenerational lung health: feasibility study). Refer to Appendix D.1 for the submitted abstract.

This study was funded by the Physiotherapy Research Foundation. An overview of this study was published in the Australian Physiotherapy Association InMotion magazine (April 2017 issue pp.40-41).

6.1 Introduction

Early diagnosis and management of COPD is recommended, however there are current challenges in the timely diagnosis of COPD. Population-level screening programs for COPD in asymptomatic individuals are not currently recommended[12], however active case-finding in at-risk groups is encouraged[1]. Case finding in the primary care setting has mostly targeted COPD at risk groups, such as individuals aged over 40 with a smoking history[89]. The systematic review (Chapter 3) and analysis of the 1958 study (Chapter 4) provided support for the hypothesis that offspring of people with COPD or a respiratory disease history have an increased risk of reduced adulthood lung health. The association may be explained by exposures to different COPD risk factors that may be present at different stages in a person's life.

This study was designed to examine the feasibility of using a descendent approach (identifying parents with COPD and recruiting their offspring) to provide contemporary data on the lung health in adult offspring of people with COPD. The three specific objectives of this study were to:

1. Explore the feasibility of recruiting pairs of parents and their adult offspring through parents with confirmed COPD (proband-initiated recruitment strategy)

2. Assess the respiratory health and respiratory risk profile of offspring of people with COPD

3. Explore any relationship between life course exposures on COPD risk in offspring of people with COPD

6.2 Methods

Design: This was a descriptive observational study.

Ethical approval was obtained prior to study commencement from the University of South Australia Human Research Ethics Committee (HREC) (ID no. 0000034888) and the Southern Adelaide Local Health Network HREC (application number: ORF 523.15 – HREC/15/SAC/515). Additional ethics amendment approvals were sought and obtained from both HRECs to expand from single to multiple sites for recruitment. Site specific approval was obtained from the Southern Adelaide Local Health Network HREC for

recruitment at the Repatriation General Hospital and Noarlunga GP Plus Super Clinic (reference number: SSA/16/SAC/329) and the Central Adelaide Local Health Network HREC for recruitment at the Hampstead Rehabilitation Centre (Reference number: SSA/17/RAH/241) for onsite recruitment (Appendix D.1).

An a priori criterion for this Feasibility study was determined prospectively at the project development stage. The criterion was successful recruitment of 60 pairs of COPD parent and adult offspring over a one-year period using the specified proband-initiated recruitment strategy. This sample estimate was set as the feasibility criteria as this sample size gives us power above 0.80 to detect medium to large effect sizes (f> 0.37) using ANOVAs with an alpha of 0.10, justified by the exploratory nature of the study.

6.2.1 Participants

Two groups of participants were recruited: (1) COPD parent group and (2) offspring group (i.e. adult offspring of people with COPD). Proband was defined as individuals approached by the research personnel directly during recruitment (i.e. the first point of contact).

For the COPD parent group, people with a spirometrically confirmed diagnosis of COPD and at least one adult child (biological or adopted) who currently lived in metropolitan Adelaide or were willing to travel to Noarlunga (approximately 30km south of the central business district of Adelaide) for the study appointment were eligible to be included. For the offspring group, participants were eligible if they were adult (aged 18 years or over) offspring of the proband group. In both groups, participants were ineligible for the study if they had a cognitive impairment or insufficient English language to provide informed consent and complete assessments. This was determined by the research personnel through interaction with the participants. Offspring participants were also excluded if any of the pulmonary function testing contraindications (within last eight weeks: abdominal, thoracic or eye surgery, pneumothorax, heart attack or chest pain; in last six weeks: lung infection; currently: haemoptysis, syncope, nausea or vomiting, or an intracranial aneurysm) applied to them[355].

The ideal situation was to only include a complete pair of parent and offspring. However this was a Feasibility study which aimed to: examine the feasibility of recruiting pairs of COPD parent and their adult offspring (aim 1), examine the lung health (aim 2) and explore any relationship between life course exposures on COPD risk in offspring of people with COPD (aim 3). If offspring wanted to participate, but the parent declined, the offspring was included in the study as his/her information could still contribute to the three aims of the study. However, if the parent wished to participate, but the offspring declined, the parent was not eligible to be included as data would not be available for the second and third aims of the study.

6.2.2 Recruitment

This Feasibility study used the proband-initiated recruitment strategy, which has been described in detail and piloted in the previous chapter (Chapter 5). Proband participants were identified and contacted via two strategies in this study over a one-year period (November 2016 – November 2017) at three public sites (Repatriation General Hospital, Hampstead Rehabilitation Centre, Noarlunga GP Plus Super Clinic) and two private clinics (Hutt Street General Practice, Respiratory PhysiO2). The two recruitment strategies were:

1) Postal recruitment: A mailing list was created by local clinic staff who identified people with spirometrically confirmed COPD through two clinic databases, and those who had attended the pulmonary rehabilitation or airway clearance program at three public sites. A letter of invitation containing a brief description of the aim and methods of this study was sent to individuals on the mailing list. Interested individuals were invited to contact the research personnel to seek further information about the study, either by post (reply slip with a reply paid envelope provided with each letter of invitation), phone or email (Appendix D.3). The eligibility of probands were confirmed when the research personnel spoke with the potential proband on the phone.

2) Face-to-face recruitment: On days when pulmonary rehabilitation program sessions were scheduled, KL or a trained research assistant enquired whether or not individuals (i.e. probands) attending the program were

interested in being involved or knowing more about this study. The research personnel confirmed the potential proband's eligibility. If the proband was interested and eligible, a letter of invitation (same letter as above) was provided and the individual was encouraged to contact the research personnel to seek further information.

In each of these two recruitment approaches, ethical considerations required that interested proband be invited to convey study information onto their adult offspring. The research personnel then awaited a response from adult offspring (by listed phone, email or return of an enclosed reply paid envelope) to indicate their willingness to participate in the study.

6.2.3 Study procedure and data collection instruments

Both groups of participants were invited to attend a single study appointment either at the City East Campus of the University of South Australia, located in Adelaide's Central Business District, or at the Noarlunga GP Plus Super Clinic, located approximately 30km south of the Central Business District of Adelaide. The same research personnel (KL) conducted all study appointments. A summary of the overall study procedure for the COPD parent group and the offspring group is presented in Figure 6.1. All participants received a 25 dollar gift-card upon completion of the study appointment as honoraria.

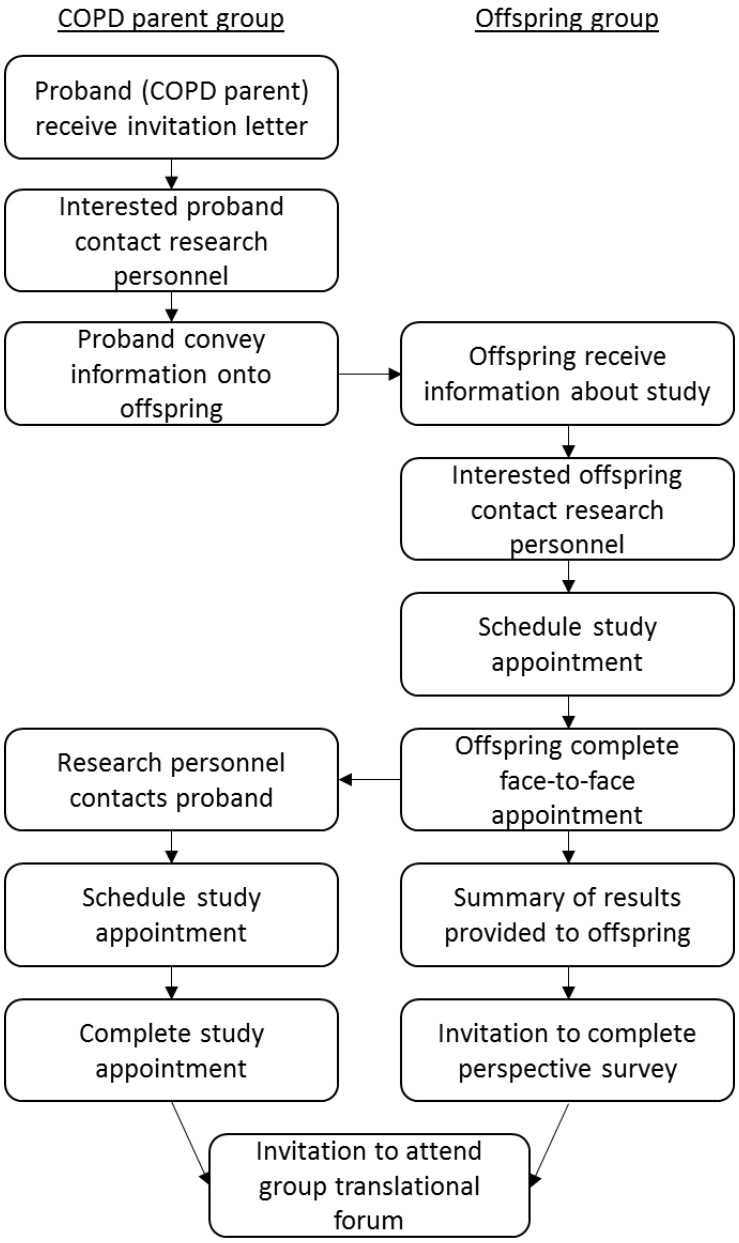


Figure 6.1 Summary of recruitment and overall study procedure

Note: the offspring participant has to complete the study appointment before the research personnel contacted the COPD parent regarding their interest of attending a study appointment

Data on the number of probands attempted to be contacted through the two recruitment strategies, number of COPD probands with confirmed eligibility, number of response received from probands, number of COPD parent willing to convey information onto their adult offspring and the number of response received from adult offspring were collated. Any comments volunteered by probands were recorded.

The study appointment procedure was overall similar for participants in both COPD parent and offspring group. Participants in the offspring group completed additional questionnaires during the appointment and were asked to complete a perspective survey following the appointment. Figure 6.2 outlines the study appointment processes.

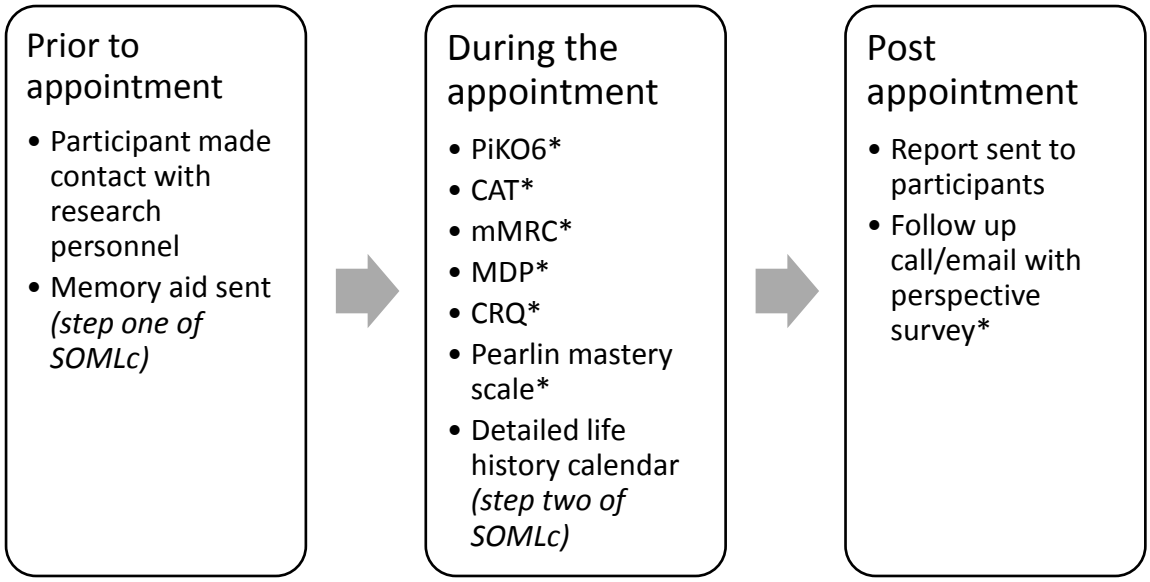


Figure 6.2 Summary of study procedure

SOMLc = Story Of My Life calendar; PiKO6 = Lung function measurement device; CAT = COPD Assessment Test; mMRC = modified Medical Research Council dyspnoea scale; MDP = Multidimensional Dyspnoea Profile; CRQ = Chronic Respiratory disease Questionnaire; * = only for participants in the offspring group

Participants in the offspring group

Once an individual participant provided verbal consent to participate in the study, an appointment was scheduled and a copy of the Story Of My Life calendar (SOMLc) memory aid (step one of SOMLc) was provided to the participant. Unlike the Pilot study, the HREC did not provide approval for the research personnel to ask participants to complete the memory aid prior to attending the appointment, as written consent was not obtained until attending the schedule interview. For this Feasibility study, the HREC permitted the research personnel to encourage participants to review the questions within the SOMLc memory aid prior to attending the appointment.

Step one of the SOMLc, the SOMLc process used in this Feasibility study included the first two steps of the SOMLc (Figure 6.2). The SOMLc process used in this Feasibility study included the first two steps of the SOMLc. All participants were provided with the memory aid (step one of SOMLc), a copy of the memory aid can be found in Appendix C.6.

On arrival of the scheduled appointment, a timer was set once the participant had settled. The research personnel (KL) first explained the purpose, procedure, benefit and risk of the study to the participant and obtained written informed consent. Participants were then screened for any contraindications for undergoing COPD screening through a checklist published by Lung Foundation Australia [355]. If none of the contraindications applied, a hand held expiratory flow meter (PiKO-6 [nSpire Health, Inc. Longmonth, CO, USA]) was used to collect data on Forced Expiratory Volume in 1 second (FEV_1) and Forced Expiratory Volume in 6 seconds (FEV_6) in accordance with the instructions published by Lung Foundation Australia [356]. The research personnel was trained by an experienced respiratory clinician in the use of the PiKO-6 equipment.

The PiKO-6 device was used to collect data on FEV_1, FEV_6 and FEV_1/FEV_6 ratio for COPD screening. The research personnel first demonstrated and explained the procedure according to the instructions published by Lung Foundation Australia[357]. Participants were provided with a new mouth piece, instructed to inhale maximally and then blow out as hard and as fast as possible through the mouth piece for at least six seconds. Participants were provided with feedback on their technique and were encouraged after each attempt. Participants completed the procedure at least three times. The best results were noted if the three test results were reproducible (FEV1 within 0.2L)[358]. The participant was allowed up to eight attempts with sufficient rest between each attempt. A lower FEV_1/FEV_6 ratio may indicate airway obstruction. Participants with FEV_1/FEV_6 <0.75 were encouraged to take their test result to their doctor for further investigation and management [356].

Participants were then instructed to sequentially complete six questionnaires:

The COPD Assessment Test (CAT) [41] was used to assess the participant's current lung health. The CAT contains eight items with a higher score indicating greater impact of respiratory symptoms on their wellbeing (Appendix C.8) [337]. As in the Pilot study (Chapter 5), participants with a score greater than 10 were encouraged to take their test result to their doctor to seek advice about their respiratory symptoms [338].

The modified Medical Research Council (mMRC) dyspnoea scale contains five statements that describe various degree of breathlessness with physical activities[359]. Participants were instructed to read through the statements and choose one that best describes them. Each statement was assigned a score with grades range from 0 (not impaired by breathlessness) to 4 (severe impairment due to breathlessness) [360]. A copy of the mMRC dyspnoea scale can be found in Appendix D.4.

The Multidimensional Dyspnoea Profile (MDP) was used to assess overall breathing discomfort (sensation and intensity) and participant's emotional responses through a four page questionnaire[361]. A copy of the MDP can be found in Appendix D.5. During the appointment, the research personnel read the standard script to the participant to explain the purpose of the questionnaire and the difference between unpleasantness or intensity of their breathing sensation. Participants were asked to rate the unpleasantness of their breathing sensation on a scale of 0 (pleasant/neutral) to 10 (unbearable) with a focus on the last two weeks. The second page contains five descriptors for the quality of their respiratory sensation (My breathing requires muscle work or effort; I am not getting enough air or I am smothering or I feel hunger for air; My chest and lungs feel tight or constricted; My breathing requires mental effort or concentration; I am breathing a lot). The first step was for the participant to decide if each of the descriptors did or did not apply to how their breathing felt during the past two weeks. The second step was for the participant to select one descriptor that most accurately described their breathing (if none of the descriptors applied to the participant in step one then the participant did not need to choose the best descriptor in step two). A

standard script was read to remind the participant of the difference between the unpleasantness or intensity of their breathing sensation, then participants were asked to rate the intensity of their breathing sensation on a scale of 0 (none) to 10 (as intense as I can imagine) for the same five descriptors. Participants could also volunteer other descriptors of their breathing sensation. Participants were then asked to rate on a scale of 0 (none) to 10 (the most I can imagine) five emotions evoked by their breathing sensation (depressed; anxious; frustrated; angry; afraid).

Frequencies or scores of the results in individual items of the MDP were reported. Two scores were calculated from the MDP for the participant's immediate perception (range = 0 - 60) and emotional response (range = 0 -50) with a lower score indicating less sensation/ emotion related to their breathlessness [361]. The MDP has been reported to be reliable and valid measurement tool in a range of people with breathless conditions[362].

The Chronic Respiratory Questionnaire (CRQ) (self-administered version) was used as a measure of respiratory related quality of life and was described in detail in Chapter 5. This questionnaire contains 20 items across four domains (dyspnoea, fatigue, emotional function and mastery); a higher score represents better health related quality of life in that domain [339]. A copy of the CRQ can be found in Appendix C.9.

The Pearlin's Mastery scale contains seven items and measures a person's sense of control (mastery) in general aspects of life. Participants were instructed to rate each item on a five-point scale ranging from strongly disagree to strongly agree[363]. A total score ranging from 7 to 35 was calculated with higher scores indicate greater levels of mastery. A copy of the scale can be found in Appendix D.6.

Step two of SOMLc was conducted in the same manner as in the Pilot study (Chapter 5), where the research personnel facilitated participants to complete the detailed life history calendar using a list of guiding questions. There were

minor revisions of the wordings to two questions as per recommendations from the Pilot study.

The research personnel recorded the time used to complete each questionnaire and checked for any missing answers.

Following the research appointment, the research personnel compiled all the results obtained from the screening test and questionnaires into a report for the respiratory physician on the research team, Professor Peter Frith, to review. An individual summary of the screening test and questionnaire results were posted/ emailed to each participant within one week of their research appointment (Appendix D.7). One of the research team members followed up with individual participants by telephone/ email (based on participant preference) after dissemination of these results to address any questions.

As per recommendations of the COPD assessment test (CAT) user guide[338] and the Lung Foundation Australia Position Paper for Use of COPD screening devices for targeted COPD case finding in community settings [356], participants who experienced symptoms (CAT score >10) or had Forced Expiratory Volume in 1 second (FEV_1) / Forced Expiratory Volume in 6 seconds (FEV_6) ratio less than 0.75 were advised and encouraged to consult their general practitioner for further investigation and management and to take a copy of the summary with them. All offspring participants received a copy of their SOMLc life history report as shown in Figure 5.2. However unlike in the Pilot study, the research personnel in the Feasibility study did not actively seek participant feedback on the accuracy of the report.

Around one month after the study appointment, offspring participants were invited to complete a perspective survey.

The perspective survey was designed to assist with the structure of the content of the translational forum (described below). The survey contains seven open ended questions (Table 6.1) on the offspring's perspective regarding intergenerational influence on their lung health, screening in offspring of parents with COPD and early interventions for lung health. This survey was

posted or emailed or completed over the phone based on preference of the participant. Follow up emails were sent every two weeks if the participant had not returned the survey. Data obtained were first transcribed, similar ideas or concepts were collated and the frequency of the concepts responded to the questions were reported.

Table 6.1 Perspective survey

Questions asked
1. What things do you think are important for good lung health? If possible, please provide at least three things in order of importance (1 = most important).
2. Do you think lung health can be improved? How?
3. Do you see any value in participating in a program which aims to improve lung health?
4. Who do you think would benefit the most from a lung health program? Why?
5. What sorts of things would encourage you to consider joining a lung health program? (e.g. specific program content, format [e.g. online, attending in person, in a group or individual sessions], length, location, are there specific things you would like to know about?)
6. Has the health of your parent(s) with COPD had an influence on your behaviour or thoughts about your own health? Could you tell us a little more about this?
7. Do you have any overall comments about this study? Or is there anything else you would like to tell us or make sure we discuss in the group meeting (translational forum)?

Participants in the COPD parent group

Participants were asked to complete the SOMLc following the same procedure as described for the offspring group. A copy of the memory aid (step one of SOMLc) was provided prior to the appointment. After obtaining informed consent, the research personnel guided the participant to complete the detailed version of the life history calendar. The research personnel then concluded the appointment and asked if the participant would like a summary of their life history report be posted/ emailed to them approximately a week later.

For all participants

An interactive translational forum was planned to be held for all study participants (COPD proband and adult offspring) by the whole study team at the end of the study. The purpose of the forum was to provide participants with information about lung health, a summary of the study results and provide an opportunity for participants to ask questions. The structure and content was planned to be guided response and

comments that offspring participants provide in the perspective survey. It was also intended to facilitate participants to contribute their thoughts and feedback on the study findings.

6.2.4 Data analyses

Aim 1: Explore the feasibility of recruiting offspring of people with confirmed COPD through their parents

The proportion of proband and offspring participants remaining after each recruitment stages were calculated as detailed in Table 6.2 [364].

Table 6.2 Equations for calculation of recruitment proportions at each stage

Recruitment proportions at each stage	Equations
Proportion of proband who declined due to non-eligibility among those who volunteered a reason	$= \frac{\text{no. of proband with confirmed non} - \text{eligibility (no adult offspring in metropolitian Adelaide)}}{\text{no. of COPD proband volunteered reason for decline}}$
Proportion of COPD proband eligible and interested among those who were successfully contacted	$= \frac{\text{no. of eligible and interested proband who made contact with research personnel}}{\text{no. of COPD proband successfully contacted}}$
Proportion of proband agreeing to convey information onto offspring among those eligible and interested	$= \frac{\text{no. of COPD proband agree to convey information onto their offspirng}}{\text{no. of eligible and interested proband who made contact with research personnel}}$
Proportion of offspring who contacted research personnel among those COPD proband that agree to convey information onto their offspring	$= \frac{\text{no. of offspring that made contact}}{\text{no. of COPD proband agree to convey information onto their offspring}}$
Proportion of offspring that participated among those who contacted research personnel	$= \frac{\text{no. of offspring that participated in the study}}{\text{no. of offspring who made contact}}$
Proportion of probands that participated among those who had offspring that participated	$= \frac{\text{no. of COPD proband that participated in the study}}{\text{no. of offspring who participated in the study}}$

Any reasons volunteered by participants at any stages of recruitment (e.g. reasons for declining to join the study or for not conveying the information package) were collated into categories and frequencies reported.

Aim 2: Assess the respiratory health and respiratory risk profile of offspring of people with COPD

Descriptive statistics were used to summarise the respiratory health (lung function measure, CAT, mMRC dyspnoea scale, CRQ domain score, MDP item and subdomain score, Pearlin's mastery scale) and respiratory risk profile (SOMLc) of the offspring group. Offspring participants were classified into four COPD risk groups based on their CAT score and lung function measure (Table 6.3).

Table 6.3 Classification of COPD risk groups

COPD risk groups	CAT score	Lung function measure (FEV_1/ FEV_6)
Experience respiratory symptoms and lung function changes	> 10	< 0.75
Experience respiratory symptoms but no lung function changes	> 10	> 0.75
Experience lung function changes but no/minimal respiratory symptoms	< 10	< 0.75
Experience no symptoms or lung function changes	< 10	> 0.75

CAT = COPD Assessment Test, FEV_1 = Forced Expiratory Volume in 1 second, FEV_6 = Forced Expiratory Volume in 6 seconds

Aim 3: Explore any relationship between life course exposure on COPD risk in offspring of people with COPD

Inferential statistics were planned to be used to explore any relationship between life course exposures and COPD risk in offspring of people with COPD. To do so, differences in patterns of lifetime risk/protective factors across four COPD risk groups (Table 6.3) were planned to be tested using ANOVAs or logistic regression adjusted for age.

6.3 Results

6.3.1 Participant characteristics

A total of eight participants completed the study with three in the COPD parent group and five in the offspring group. There were three COPD parent-offspring pairs of participants, with one father-son pair, one mother- son pair and one mother-daughter pair. The mean age of participants in the COPD parent group was 68 years (range = 67 – 71 years), and 48 years (range = 43 – 51 years) for participants in the offspring group. There were more female than male participants in both the COPD proband (67% female) and the offspring group (60% female).

6.3.2 Aim 1: Explore the feasibility of recruiting offspring of people with confirmed COPD through their parents

Results of the proband-initiated recruitment are presented in Figure 6.3. Through the two recruitment strategies, a total of 889 probands were initially contacted. Of those, 42 eligible probands made return contact with research personnel to gather more information about the study. A total of 28 COPD parents agreed to convey information about this study onto their adult offspring. Seven offspring contacted the research personnel, five attended the appointment and two completed the follow up survey. Parents of the offspring who had attended the appointment were contacted and three COPD parents attended the appointment, resulting in three COPD parent-offspring pairs of participants recruited in this study.

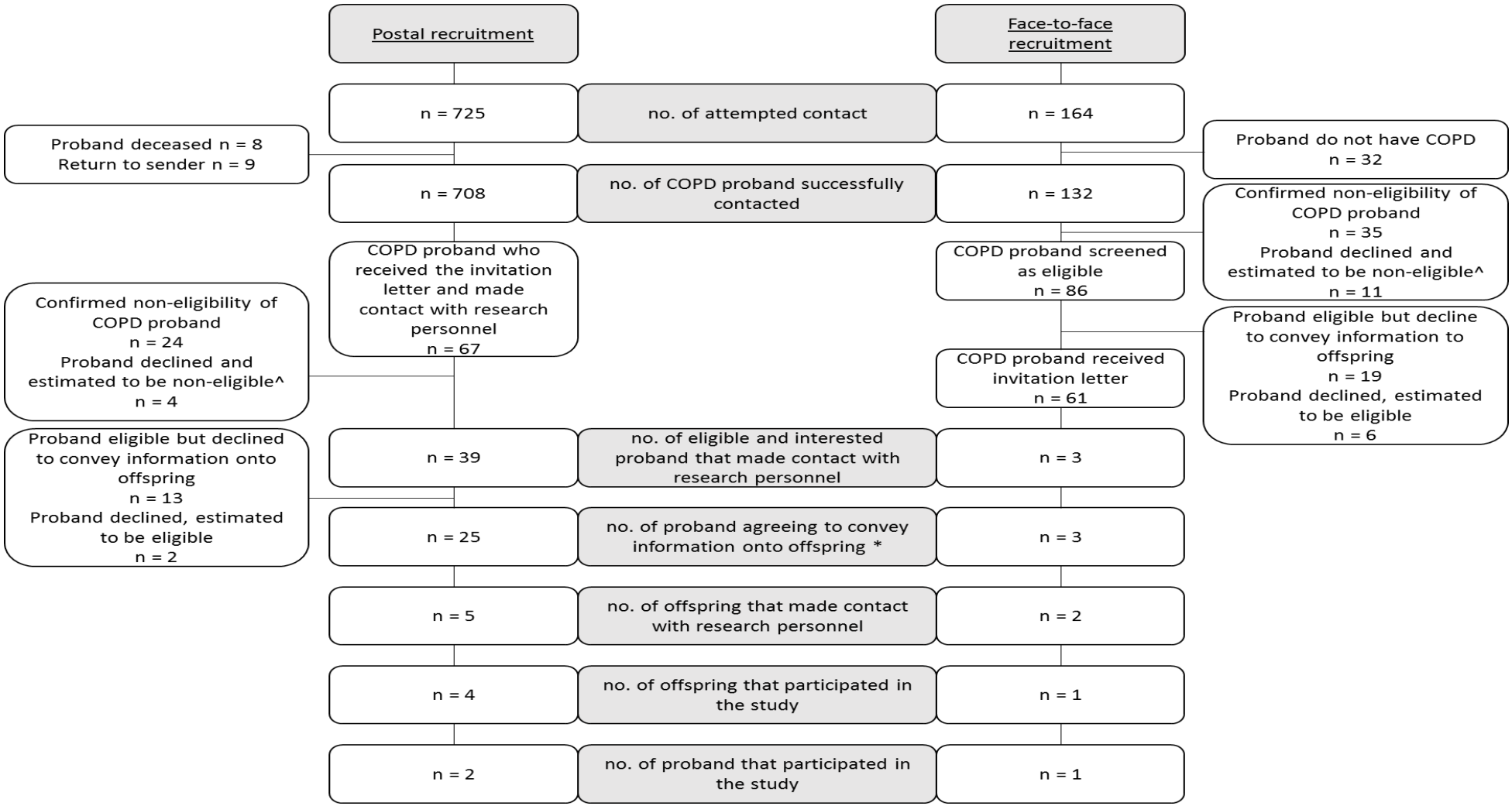


Figure 6.3 Proband-initiated recruitment results

^ This was estimated by multiplying the number of proband decline with unknown eligibility by the proportion of proband screened by research personnel and confirmed non-eligible; * Three offspring (face-to-face recruitment = 2; postal recruitment = 1) made direct contact with the research personnel after their parents received the invitation letter i.e. bypassed proband contacting the research personnel but implied that proband agree to convey information onto the adult offspring

The two recruitment strategies appeared to yield different recruitment rates at different stages of the recruitment process (Table 6.4). In both recruitment approaches, 65% of COPD probands who were screened by research personnel were non-eligible due to proband's adult offspring not living in Adelaide (postal recruitment n = 13; face-to-face recruitment n = 19), or proband did not have adult offspring (postal recruitment n = 11; face-to-face recruitment n = 14) or non-specified if proband had no adult children or that they did not live in Adelaide (face-to-face recruitment n = 2). A slightly higher proportion of COPD probands were eligible and interested in the study through postal recruitment. Overall in probands who were eligible, common reasons for declining to convey information onto their adult offspring include: proband's perception that their offspring were too busy (31%) or would not be interested in the study (31%), parent-offspring do not have good relationship (16%) and offspring has good lung health (9%).

Table 6.4 Proband and offspring recruitment proportions at each stage

Recruitment proportions at each stage	Postal recruitment proportion (%)	Face-to-face recruitment proportion (%)
Proportion of proband who declined due to non-eligibility among those who volunteered a reason	24 / 37 (65%)	35 / 54 (65%)
Proportion of COPD proband eligible and interested among those who were successfully contacted	39 / 708 (6%)	3 / 132 (2%)
Proportion of proband agreeing to convey information onto offspring among those eligible and interested *	25 / 39 (64%)	3 / 3 (100%)
Proportion of offspring who contacted research personnel among those COPD proband that agree to convey information onto their offspring	5 / 25 (20%)	2 / 3 (67%)
Proportion of offspring that participated among those who contacted the research personnel	4 / 5 (80%)	1 / 2 (50%)
Proportion of probands that participated among those who had offspring that participated	2 / 4 (50%)	1 / 1 (100%)

Note: Equations for calculation were presented in Table 6.2.
*Three offspring (face-to-face recruitment = 2; postal recruitment = 1) made direct contact with the research personnel after their parents received the invitation letter i.e. bypassed proband contacting the research personnel. For these cases, it was implied that the proband agreed to convey information onto the adult offspring

6.3.3 Aim 2: Assess the respiratory health and respiratory risk profile of offspring of people with COPD

Offspring participants were classified into four risk groups based on their CAT score and lung function measure. Three of the five participants in the offspring group had a CAT score >10 and/or a lung function measure of FEV_1/FEV_6 <0.75, and were therefore encouraged to make an appointment with their doctor for further investigation. A descriptive summary of the respiratory health in offspring of people with COPD categorised in the four risk groups is provided in Table 6.5. While no statistical analysis was performed due to the small sample size, it was interesting to note that the participant with symptoms only, had worse health-related quality of life based on the CRQ dyspnoea domain score, reported a higher grade in the mMRC dyspnoea score and had a higher MDP subdomain score in immediate perception and emotion response. The detailed Multidimensional Dyspnoea Profile of offspring participants based on their risk groups were presented in Table 6.6.

Table 6.5 Respiratory health in the offspring group

Measure	Offspring participants risk groups (n= 5)				All offspring participants
	Symptoms and spirometry changes (n = 1)	Only symptoms present (n = 1)	Only spirometry changes present (n = 1)	No symptoms/ spirometry changes (n = 2)	(n = 5)
Lung function measure					
FEV_1 (mean ± SD)	3.40	2.54	2.66	3.35 ± 1.6	3.06 ± 0.90
FEV_6 (mean ± SD)	4.65	3.33	3.70	4.25 ± 1.92	4.01 ± 1.09
FEV_1/FEV_6 (mean ± SD)	0.73	0.77	0.72	0.78 ± 0.01	0.76 ± 0.03
CAT					
Numeric score (mean ± SD, range) (possible range= 0 – 40)	10	15	5	7.5 ± 0.7 (7 – 8)	9 ± 3.8 (5 – 15)
mMRC dyspnoea scale					
Grade 0 n(%)	-	-	1 (100%)	1 (50%)	2 (40%)
Grade 1 n(%)	1 (100%)	-	-	1 (50%)	2 (40%)
Grade 2 n(%)	-	1 (100%)	-	-	1 (20%)
CRQ domain score (mean± SD, range) (possible range = 1 - 7)					
Dyspnoea	6.8	4.0	7.0	6.4 ± 0.2 (6.3 – 6.6)	6.13 ± 0.89 (4.0 – 7.0)
Fatigue	5.3	2.5	6.5	3.8 ± 0.0 (3.8 – 3.8)	4.35 ± 4.55 (2.5 – 6.5)
Emotional	5.7	4.0	6.3	4.8 ± 0.5 (4.4 – 5.1)	5.11 ± 0.93 (4.0 – 6.3)
Mastery	7.0	5.8	7.0	6.9 ± 0.2 (6.8 – 7.0)	4.70 ± 0.54 (5.8 – 7.0)
Pearlin's mastery scale					
Numeric score (mean ± SD , range) (possible range = 7-35)	31	23	27	21.0 ± 2.8 (19 – 23)	24.6 ± 4.6 (19 – 31)
MDP Subdomain scores					
Immediate perception (possible range = 0 – 60)	4	18	5	1.5 ± 0.7 (1 – 2)	6.0 ± 6.9 (1 – 18)
Emotional response (possible range = 0 – 50)	1	5	0	0	1.2 ± 2.2 (0 – 5)

CAT: COPD Assessment Test; SD: Standard Deviation; mMRC: modified Medical Research Council; CRQ: Chronic Respiratory Questionnaire; MDP: Multidimensional Dyspnoea Profile; FEV_1: Forced Expiratory Volume in 1 second; FEV_6: Forced Expiratory Volume in 6 seconds

Table 6.6 Multidimensional Dyspnoea Profile of offspring participants

MDP items	Offspring participants risk groups (n= 5)				
	Symptoms + spirometry changes (n = 1)	Only symptoms present (n = 1)	Only spirometry changes present (n = 1)	No symptoms / spirometry changes (n = 2)	All offspring participants (n = 5)
Unpleasantness of breathing (A1 scale) *(mean± SD, range)* (possible score = 0 – 10)	0	1	0	0	0.2 ± 0.4 (0 – 1)
If any of the phrases applies and describes how their breathing felt (SQ choice) (1 = does apply; - = does not apply)					
I am not getting enough air or I am smothering or I feel hunger for air	-	1	1	-	2 (40%)
My breathing requires mental effort or concentration	-	1	1	-	2 (40%)
I am breathing a lot	-	1	-	-	1 (20%)
The group that most accurately describes how their breathings felt (1 = does apply; - = does not apply)					
I am breathing a lot	1	-	-	1 (50%)	2 (40%)
I am not getting enough air or I am smothering or I feel hunger for air	-	1	-	-	1 (20%)
My breathing requires mental effort or concentration	-	-	1	-	1 (20%)
Intensity of breathing sensations (SQ scales) *(mean± SD, range)* (possible range = 0 – 10)					
My breathing requires muscle work or effort	1	1	2	0	0.8 ± 0.8 (0 – 2)
I am not getting enough air or I am smothering or I feel hunger for air	1	5	1	0.5 ± 0.7 (0 – 1)	1.6 ± 1.9 (0 – 5)
My chest and lungs feel tight or constricted	1	1	0	1.0 ± 1.4 (0 – 2)	0.8 ± 0.8 (0 – 2)
My breathing requires mental effort or concentration	0	5	2	0	1.4 ± 2.2 (0 – 5)
I am breathing a lot	1	5	0	0	1.2 ± 2.2 (0 – 5)
Emotions experienced when breathing doesn't feel normal (A2 scales) *(mean± SD, range)* (possible range = 0 – 10)					
Anxious	1	4	0	0	1.0 ± 1.7 (0 – 4)
Frustrated	0	1	0	0	0.2 ± 0.4 (0 – 1)

MDP: Multidimensional Dyspnoea Profile; SD: Standard Deviation

Comparing the MDP of offspring participants in the different risk groups, the offspring participant in the symptoms only group scored higher in all of the individual MDP items when compared with participants in the other risk groups. The two participants with no symptoms or spirometry changes scored lowest in all of the individual MDP items except for one item "my chest and lungs feel tight and constricted".

6.3.4 Aim 3: Explore any relationship between life course exposure on COPD risk in offspring of people with COPD

Respiratory risk profiles based on lung health-related life course exposure data were collected through the SOMLc. Table 6.7 summarises life course data collected from participants in both groups. As the proband-initiated recruitment strategy only recruited five participants in the offspring group, no inferential statistics were performed. Despite the small numbers, the proportion of participants exposed to COPD-related risk factors (including passive smoke and environmental exposures) appeared higher in the COPD parents group, with a relatively longer length of exposure compared to those in the offspring group.

Table 6.7 Respiratory risk profile of all participants

Life course exposure		Offspring group (n = 5)	COPD parents group (n = 3)
Able to own recall birthweight n(%)		3 (60%)	0 (0%)
Birth weight (kg , mean ±SD , range)		3.6 ± 1.1 (2.9 - 4.8)	-
If unable to recall, asked if they knew they were small, average or large at birth			
	Small n(%)	-	1 (33%)
	Average n(%)	2 (40%)	1 (33%)
	Large n(%)	-	-
	Cannot recall n(%)	-	1 (33%)
Was born preterm*	Yes n(%)	0 (0%)	0 (0%)
	No n(%)	4 (80%)	2 (67%)
	Don't know n(%)	1 (20%)	1 (33%)
Had childhood respiratory illness n(%)		2 (40%)	2 (67%)
Had asthma n(%)		0 (0%)	0 (0%)
Lived with one or more smokers (passive smoke exposure) n(%)		4 (80%)	3 (100%)
	One or both parent smoked	3 (60%)	3 (100%)
	Exposure to passive smoke (childhood)	3 (60%)	3 (100%)
	Length of exposure (mean ± SD, range)	26.0 ± 16.8 (2 – 39)	52.7 ± 23.1 (26 - 67)
Used biomass/ derivative of biomass fuel within household n(%)		3 (60%)	3 (100%)
	Length of exposure (mean ± SD, range)	11.7 ± 8.3 (5 - 21)	33.0 ± 22.3 (9 -53)
	Flued heating fuel n(%)	3 (60%)	3 (100%)
Lived in a polluted area n(%)		4 (80%)	3 (100%)
	Length of exposure (mean ± SD, range)	10.8 ± 5.1(4 - 16)	14.8 ± 20.2 (1-38)
Occupational exposure (dust, gases, fumes, smoke, asbestos) n(%)		3 (60%)	2 (67%)
	Length of exposure (mean ± SD, range)	8.7 ± 12.4 (1 - 23)	13.9 ± 21.8 (1 – 39)
	Exposure to passive smoke n(%)	2 (40%)	1 (33%)
	Exposure to gases/chemicals n(%)	-	1 (33%)
	Exposure to dust and gases n(%)	2 (20%)	-
Smoking status	Current smoker n(%)	2 (40%)	1 (33%)
	Former smoker n(%)	2 (40%)	2 (67%)
	Never smoker n(%)	1 (20%)	-
Physical activity# during life course			
	Active transport during school years n(%)	4 (80%)	3 (100%)
	Mostly active during school years n(%)	5 (100%)	2 (67%)
	Mostly active during work life/ adulthood n(%)	4 (80%)	1 (33%)
	Physically active (within last year) n(%)	3 (60%)	2 (67%)

*****preterm birth defined as born < 38 weeks [#] defined as the participant participated in sports or regular structured physical activity (at least 50% of that time period), does not include occupational physical load/ household work/ gardening/ walking as means of transport

Exposure to life course factors were presented based on the four offspring participants' respiratory risk groups in Table 6.8. The participant with both symptom and spirometry changes appeared to have been exposed to more life course risk factors compared with offspring participants in other risk groups.

Table 6.8 Offspring participant's respiratory profile based on risk groups

Life course exposures	Offspring participants risk groups (n= 5)				All offspring participants
	Symptom + spirometry changes (n = 1)	Only symptoms present (n = 1)	Only spirometry changes present (n= 1)	No symptom/ spirometry changes (n = 2)	(n = 5)
Had childhood respiratory illness (%)	-	100%	100%	-	40%
Lived with one or more smokers (passive smoke exposure) (%)	100%	100%	100%	50%	80%
Length of exposure* (yrs) (mean ± SD, range)	27	2	36	39	26.0 ± 16.8 (2 – 39)
Used biomass/ derivative of biomass fuel within household (%)	100%	-	100%	50%	60%
Length of exposure* (yrs) (mean ± SD, range)	21	-	5	9	11.7 ± 8.3 (5 – 21)
Lived in a polluted area (%)	100%	100%	-	100%	60%
Length of exposure*(yrs) (mean ± SD, range)	16	4	-	11.5 ± 2.1 (10 – 13)	10.8 ± 5.1 (4 – 16)
Occupational exposure (dust, gases, fumes, smoke, asbestos) (%)	100%	100%	100%	50%	60%
Length of exposure* (yrs) (mean ± SD, range)	23	-	2	1	8.7 ± 12.4 (1 – 23)
Smoking status					
Current smoker *(%)*	100%	-	-	50%	40%
Former smoker *(%)*	-	100%	100%	-	40%
Never smoker *(%)*	-	-	-	50%	20%

*length of exposure: mean and standard deviation only calculated for those who were ever exposed
yrs = years

The planned translational forum was cancelled at the end of the study due to the low number of participants, resulting in a high risk that participant anonymity could not be maintained when discussing study results in the forum. The lung health perspective survey, designed to guide the structure of the translational forum, was completed online by two of the five participants in the offspring group. Due to the small numbers, responses to the survey were unable to be collated and were presented as "direct quotes" in Table 6.9.

Table 6.9 Summary of participant's response to lung health perspective survey questions

Questions	Participant 1 response	Participant 2 response
1. What things do you think are important for good lung health?	1. Good air flow and production 2. Good lung capacity 3. -	1. Healthy lifestyle and general fitness 2. Environmental factors 3. Diet
2. What things do you think are important for good lung health?	Exercise, cease smoking	Yes, by changing lifestyle habits and changing environment
3. Do you see any value in participating in a program which aims to improve lung health?	Yes, to improve lung function	My lung health is good currently. There would be value if my lung health needed to be improved
4. Who do you think would benefit the most from a lung health program? Why?	People with mild chronic lung issues	Someone suffering respiratory problems
5. What sorts of things would encourage you to consider joining a lung health program?	Online (less than 15 minutes/ session)	If I was having problems with my lungs I think it would be beneficial
6. Has the health of your parent(s) with COPD had an influence on your behaviour or thoughts about your own health?	No. Have not given any thought that their COPD could affect me in any way	Yes it had made me aware of the damaging effects of smoking. I have a history of smoking too and need to take further care of my own health
7. Do you have any overall comments or things to discuss in the translational forum?	Interesting study	No overall comments

6.4 Discussion

The overall aim of this study was to assess the feasibility of recruitment through the proband-initiated strategy to investigate lung health in adult offspring of parents with

diagnosed COPD. Despite recruiting over a period of twelve months (November 2016 – November 2017) through five clinics and hospitals and two recruitment methods, the number of pair of participants recruited (n = 3) was lower than the a priori targeted sample size (n = 60). We therefore conclude that the piloted recruitment strategy was not feasible in recruiting adult offspring through their parents with diagnosed COPD. Due to the small sample size, this study was unable to robustly explore any associations between respiratory health, risk profile and life course exposure on COPD risk in offspring of people with COPD, nor assess the perspectives of participants, although preliminary data has been collected in these areas.

6.4.1 Differences between Pilot and Feasibility study

The proband-initiated recruitment strategy was trialled in the Pilot study (Chapter 5) where a two-month recruitment period resulted in successful recruitment of five parent-offspring pairs of participants. There were several differences between the Pilot study compared with this Feasibility study which may explain the difference in recruitment results. Firstly in the Pilot study, the research personnel only recruited through the face-to-face approach and obtained contact details for the proband (where possible) allowing follow up phone calls. In the Feasibility study, two recruitment approaches were used (postal and face-to-face recruitment) and no follow up calls were made to the proband due to concerns raised by the HREC.

Secondly in the Pilot study, 65 potential non-COPD older probands were approached in the university-based podiatry teaching clinic over two months. In the Feasibility study, the twelve-month recruitment period resulted in the research personnel approaching only 164 potential probands through face-to-face recruitment. The higher volume of approached potential probands in the Pilot study was likely due to the setting (university-based podiatry teaching clinic) where there were approximately between 20 to 30 patients scheduled for appointments on each planned recruitment date and overall good attendance rates. In the Feasibility study, potential probands were approached (face-to-face recruitment) in three hospital/ clinic pulmonary rehabilitation programs. The structure of the program at the recruitment sites guided the recruitment dates and opportunities for approaching potential probands. In two of the three hospital/clinic sites, the pulmonary rehabilitation program was structured

in blocks where approximately 12 new individuals started the program every six weeks with two classes scheduled on each planned recruitment date. In the third hospital/clinic site, the pulmonary rehabilitation program had rolling recruitment, where there were approximately two new individuals starting the program every two weeks in each class; there were four classes (three new classes and one maintenance class) scheduled on each planned recruitment date. While there were approximately between 20 to 40 patients scheduled in the pulmonary rehabilitation program classes per recruitment day, the proportion of non-attendance in pulmonary rehabilitation program was high. Thus the lower than expected volume of probands approached in the twelve-month period may be explained by various factors leading to non-attendance and non-completion in pulmonary rehabilitation programs such as issues with transport and exacerbations[365, 366].

Finally the considerably lower proportion of probands who were eligible and showed interested in this Feasibility study (face-to-face recruitment: 2%) compared to the Pilot study (40%) may be due to differences in the aim of the study and study population. The eligibility criteria of the Pilot study did not prevent probands from participating in the Pilot study if they had no offspring in Adelaide or declined to convey information onto their offspring. Next, the health status of the approached proband may have influenced on their willingness and interest in the study, where probands predominately had cardiovascular diseases in the Pilot study, whereas probands approached in this Feasibility study were a chronic lung disease population.

6.4.2 Why was a proband-initiated recruitment strategy not feasible in this study?

In this Feasibility study, common strategies used to improve recruitment to clinical trials such as amendment of inclusion criteria and trial extension were not used [367, 368]. Apart from increasing the number of recruitment sites, no adjustments were made to the original study protocol.

Rate-limiting steps observed

While a large number of potential COPD probands were identified and sent an invitation letter through post (postal recruitment), only a small proportion (9%) of

those COPD probands made contact with the research personnel. Previous intervention studies using a postal recruitment strategy for people with COPD listed within local pulmonary rehabilitation databases and general practitioner's patient database result in response rates between 22 and 28% [369, 370]. It should be emphasised that these studies used a direct approach (i.e. those receiving the letter were the target participant) [369, 370], whereas this study used an indirect approach (i.e. those receiving the letter were the proband of the target participant). We are unaware of previous studies that have used an indirect recruitment strategy to recruit offspring of people with COPD to examine their lung health and reported on the response rate.

Another important rate-limiting step of this proband-initiated recruitment strategy was the large proportion of probands (65% of screened) who did not meet the inclusion criteria. Over half of the proband that were not eligible for this study had at least one adult offspring, but their offspring resided interstate or overseas. This was unsurprising as Adelaide has the second highest net regional migration loss (net loss = 6,100 people in 2015-16) where people move to other regions within Australia [371]. Approximately three quarters of long distance residential moves occur between age 17-35, with life course transitions such as higher education entry, labour force entry, marriage and first child birth influencing short and long distance migration[372]. Combined with the relatively high unemployment rate in South Australia compared with other states such as New South Wales and Victoria [373], this may explain the high proportion of probands with adult offspring who resided interstate or overseas.

Challenges observed in this study

The most common reasons volunteered by COPD probands with adult offspring living within Adelaide, but who declined to convey information about this study onto them were the parent's perception that their offspring were too busy (31%) or would not be interested in the study (31%). COPD probands approached were approximately in their sixties and seventies and were grandparents if their adult offspring had children. Proband may have observed the reduction in discretionary time through their role as informal providers of childcare for their offspring's children. Data from the Longitudinal Study of Australian Children indicate that up to 37% of grandparents

were the sole provider of informal childcare for their (infant) grandchildren[374, 375]. Trends in Australian families have changed between 1980 and 2010: for example the proportion of lone parents and babies born outside of marriage have increased, parent's education level has increased and a larger proportion of mothers work in part-time or full-time employment[376]. These societal changes may underpin a perception that the proband's offspring were too busy or would not be interested in taking part in this study. The low proportion of probands interested and agreeing to convey information to their offspring may also be due to concerns about confidentiality and privacy.

Challenges associated with reaching recruitment targets have been well reported and recognised in health research studies [377, 378]. A review of clinical trials reported that approximately half of the trials failed to recruit the pre-specified target sample size [368, 377]. In clinical trials on individuals with respiratory conditions including asthma and COPD, approximately 60% of studies successfully achieved the predetermined recruitment target[379]. A recent Cochrane Review protocol published by Houghton, Dowling [380] further highlighted the need to explore factors impacting on recruitment in randomised controlled trials to facilitate trial participation rates. The proband-initiated recruitment strategy used in this study involves an extra layer of challenge in comparison to direct recruitment, as it was not only restricted by the proband-related barriers, but may be further restrained by offspring-related barriers. Moreover, this was an observational study which may potentially increase the difficulty of recruitment, as potential participants may not see any benefit from participation as compared to participating in intervention studies.

Potential influence of stigma on recruitment

Previous studies that have used a proband-initiated recruitment have reported a wide range of response rates[214, 215]. Trottier, Lunn [215] concluded that the low response rate (9%) in a breast cancer genetic testing in the Bahamas was likely the result of fear and stigma of shame and discrimination experienced by proband about their breast cancer genetic test results. A higher response rate (66%) using the same recruitment method was reported in recruiting relatives of people with Crohn's disease in the UK [214]. While people with Crohn's disease may also experience stigma associated with

their condition, the stigmas were mostly associated with the natural history of the disease and the impact of their symptoms [381, 382]. Although not explicitly stated by the COPD probands in this study, stigma associated with COPD may be a hidden reason for the low proportion of COPD proband that made contact with research personnel to gather more information about this study.

While COPD has a genetic component and has been associated with various risk factors[9], medical professionals and COPD patients commonly perceive it as a condition related to smoking [383]. Studies on experiences related to stigma in non-communicable respiratory diseases have mostly been reported in relation to lung cancer [384]. Feelings of guilt towards their family and sense of disapproval from family members were reported by patients who continue to smoke after receiving a cancer diagnosis. At the same time, family members of the newly diagnosed cancer patient who continue to smoke also reported a similar experience of guilt and censure[385]. In-depth interviews identified two opposite approaches used by lung cancer patients whose family members were smokers. Some chose to confront their family about their smoking behaviour while others chose to maintain harmony within the family and distance themselves from others' choice to smoke[386]. Experiences of stigma may also include elements of self-blame, embarrassment and not wanting to burden others which may have played a part in the low rate of probands indicating interest in this study [354, 387]. While these were not specifically parent-offspring intergenerational studies, similar issues may explain why some COPD probands declined to convey information about a lung health study onto their adult offspring.

COPD probands with adult offspring who were non-smokers may have been less likely to see relevance of this study for their own children. This was reflected in the results where only one of the five offspring participants had never smoked. Based on the offspring participant's respiratory symptoms and/or lung function measures, three of the five offspring participants (60%) in this sample were encouraged to make an appointment with their doctor for further investigations. This relatively high proportion of offspring participants with symptom and/or lung function changes may represent self-selection of participants, where only those offspring who were concerned about their lung health participated in this Feasibility study. Only two

offspring participants completed the perspective survey, the responses were diverse with regard to who would benefit from a lung health program and any intergenerational influences on their lung health.

6.4.3 Strengths and limitations

The main strength of this study was the a priori criterion for sample size and the multiple recruitment sites that provided a representative population of COPD patients who attended hospital or clinics in the central and southern parts of Adelaide. Two recruitment strategies were used, postal recruitment led to a broad reach of potential participants, while direct contact with proband during face-to-face recruitment provided valuable information on proband- related barriers that would assist future researchers who may wish to use this recruitment strategy.

The main limitations were the inability to systematically assess: 1) eligibility of proband and reasons for decline to participate (especially in postal recruitment) and 2) whether information was or was not conveyed onto the adult offspring. In order to meet the requirements of ethics approval and due to resource limitations, this study was limited to recruiting offspring participant who resided in Adelaide and were able to attend a face to face appointment to perform spirometry.

The overall proportion of offspring who made contact with research personnel in this study (25%) was comparable with response rate reported in previous COPD case-finding studies (13 - 31%) where participants responded to postal screening questionnaires and/or spirometry testing [3, 90]. However, overall only a small number of offspring participants participated, because few offspring received this information. Without follow up contact with the proband and/or the adult offspring, reasons for non-response due to ineligibility, lack of interest, not receiving the study information or other concerns about the study remain unknown. Another limitation was the chance of a proband being within the clinic database or attending the pulmonary rehabilitation program at more than one of the recruitment sites, thus they may have been approached repeatedly via postal and/or face-to-face recruitment.

6.4.4 What did this Feasibility study tell us?

- Future studies should continue examining lung health in adult offspring of people with COPD to provide local contemporary data on the respiratory health and risk profile in this specific high risk group of people
- One of the reasons why the proband-initiated approach used in this study was not feasible was due to COPD proband ineligibility and proband/parent-related barriers

- Potentially an indirect approach through COPD proband might yield a better response rate if the person was approached by their regular medical care providers such as their GP, as probands may see more relevance in this research study to them and their families

- Future studies should consider using a direct approach to identify and recruit adult offspring of people with COPD to reduced proband/parent- related barriers

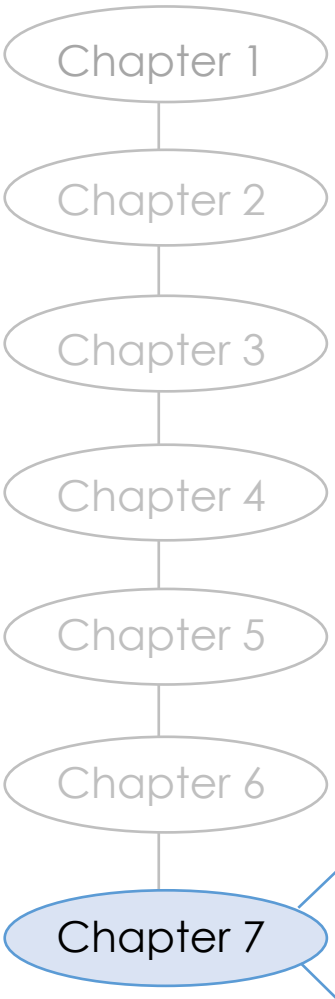
While directly approaching/recruiting adult offspring of people with COPD may yield higher response rate or provide insight into other barriers associated with investigating lung health in this group of people, researchers should be vigilant to ensure the recruited adult offspring does have a parent with COPD. A possible way to ensure the parent does have COPD may be through adult offspring asking their parent about their post-bronchodilator spirometry (FEV1/FVC ratio) results. While this strategy can ensure the eligibility of the participant (adult offspring of people with COPD), it may also be a barrier as not all COPD patients may know or have access to their spirometry results and will likely raise confidentiality issues.

Previous studies that have directly recruited adult offspring of people with a certain medical history have typically used a antecedent approach, for instance recruiting individuals with a family history of type II diabetes into lifestyle intervention studies [388] or individuals with a family history of depression for psycho-educational intervention[389]. Directly approaching adult offspring of people with COPD or people with a parental history of COPD would allow recruitment beyond hospitals and clinics. For instance, recruitment through social media may be an effective method to

reach this specific target population [390, 391]. The feasibility of directly recruiting adult offspring of people with COPD and possible methods to ensure the eligibility of the participants will need to be explored.

6.5 Conclusion

The proband-initiated recruitment strategy was not a feasible method to recruit pairs of parents and their adult offspring through parents with confirmed COPD. Only a small number of participants were recruited in this study, thus the respiratory health, respiratory risk profile and any relationship between life course exposures on COPD risk in offspring of people with COPD were only assessed descriptively. Local contemporary data on the lung health of adult offspring of people with COPD is of interest. Future studies should consider using an antecedent direct approach (i.e. identifying people with a parental history of COPD) to minimise parent- related barriers experienced in this study.



Discussion and conclusion

The overall aim of this research program was to explore intergenerational influences on respiratory health in offspring of people with COPD. A series of four studies were conducted. This chapter first summarises key findings across the four studies (Section 7.1). Section 7.2 discusses influence of public health policies in relation to the life course of participants, followed by how target participants were identified (Section 7.3). The clinical implications (Section 7.4) and future research directions (Section 7.5) in relation to examining respiratory health in adult offspring of people with COPD are then explored. Finally the strength and limitations (Section 7.6) of this thesis are discussed.

7.1 Overview of studies and key findings

This research program of four studies explored intergenerational influences on lung health in offspring of people with COPD. The systematic review and meta-analysis (Chapter 3) revealed only a scarce number of studies reported on the prevalence of co-occurrence of COPD in parents and offspring. Across these studies, it was estimated that offspring of people with COPD were at increased risk of developing COPD (pooled OR = 1.57, 95%CI = 1.29-1.93, p<0.001) compared with those without a parental history of COPD. This association was confirmed using life course data from the 1958 British birth cohort (Chapter 4), which also found that the combination of maternal and personal smoking explained 30% of the association, but a large proportion of the association remained unexplained by the life course factors examined.

In order to overcome limitations associated with use of secondary data, a Pilot study (Chapter 5) was conducted to trial a local proband-initiated recruitment strategy and a life course data collection tool (Story of My Life Calendar [SOMLc]) in a non-COPD population. No major practical issues were identified with the recruitment strategy and data collection tool in the Pilot study. However a proband-initiated recruitment strategy was found to be not a feasible method to recruit adult offspring of people with COPD through their parents with diagnosed COPD (Chapter 6). Thus only limited data were available to examine the influence of life course factors or respiratory health in a local prospectively recruited population. While the number of offspring participants in the Feasibility study was small, it is noteworthy that three of the five offspring participants showed respiratory symptoms (CAT score >10) and/ or lung function changes ($FEV_1/FEV_6 < 0.75$).

7.2 Life course of participants in relation to lung health-related public policies

This section describes the temporal and geographical context of the studies reviewed and undertaken in this research program to help compare and contextualise study results. The life course-related factors expected to explain the intergenerational effects would be shaped by societal and policy changes, which may have an impact on the intergenerational influence of respiratory health in adult offspring of people with

COPD. The background of the life course and timing of public health policies in the different studies are first described, followed by a discussion of specific exposure to COPD risk factors and relevance of the study findings.

7.2.1 Life course of participants and timing of lung health-related public health policies

In the four studies of this research program, participants were born over a wide range of birth years (1922-1977). This range would reflect differences in lifestyle, home and work environment and public policies which may represent different types or levels of exposure related to lung health development. Different labels have been created and used to describe individuals born in particular spans of time based on their generational characteristics, for example "Baby Boomers" refers to those born during the post-war economic growth era[392]. Definitions of generations may be influenced and impacted by multiple effects. The generation labels used in Table 7.1 are likely to be more relevant and applicable to Western countries. Generation labels and ranges of year of birth have been proposed (Table 7.1) which will be used for the purposes of this discussion [393-395].

Table 7.1 Definition of generations and year of birth

Generation Label	Birth year range
Silent generation	< 1945
Baby Boomers	1946-1964
Generation X	1965-1979
Generation Y	1980-1994

If we apply the generational labels to participants in four studies, we can explore the impact of various public health policies on the prevalence of COPD and reduced lung health. A summary of the approximate life course of participants across the four studies in this research program are presented in Figure 7.1. The coloured rows in the middle represent the life course of study participants (across all studies), starting with the year when participants were born (calculated based on participant mean age or

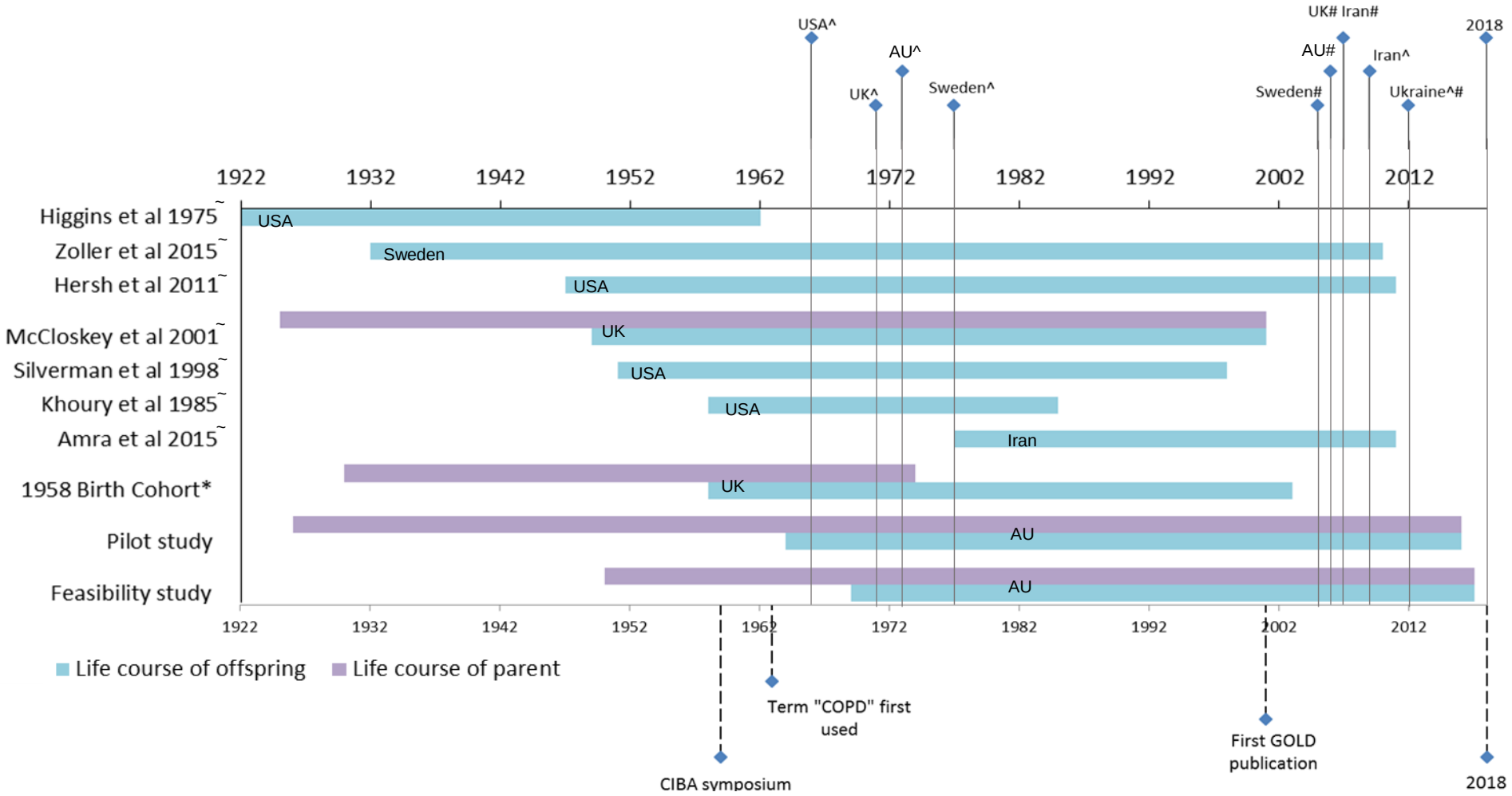


Figure 7.1 Life course of participants Chapters 3-6 (from birth to year of data collection)

Horizontal bars represent study participant's year of birth to year of data collection; Solid lines above the graph = key country specific tobacco control public health policies; ^ Government laws on compulsory warning displayed on cigarette packages; # National policy on smoking restrictions in work place and or public areas; Dashes below the graph = key events related to COPD terminology or definition; ~ Individual studies within the systematic review (Chapter 3); *Based on data on the mother's age only in the 1958 birth cohort

reported year of birth if available) through to the year of data collection (or the year of publication if not specified). With the exception of Mostovoĭ [239], seven studies included in the systematic review and meta-analysis (Chapter 3), reported age related data for parent and offspring.

The top part of the figure indicates a timeline of country-specific tobacco control public policies. Country of data collected are indicated for each study in the respective rows. Two key tobacco control policies are indicated in the timeline related to the year when governments enforced regulations on compulsory health warning messages on cigarette packages and national policy on smoking restriction in work place and/or public enclosed areas (Figure 7.1). Finally the bottom part of the graph represents a timeline highlighting key historic events related to when there was consensus around the definition and terminology of COPD.

The following section first discusses smoking-related exposures and public health initiatives on tobacco control. Next, the likely important future problems related to increase prevalence of preterm birth, asthma and exposures to pollution and biomass is discussed,

Smoking-related exposures

Since smoking is a key risk factor for COPD and smoking prevalence has changed over time[396, 397], exposure to smoking-related factors were compared across the four studies. In the context of offspring participant's life course, participants within the systematic review studies (Chapter 3) likely to represent the "worst case scenario" with potentially the highest level of tobacco exposure and least knowledge about the harmful effects of smoking.

Tobacco control public health initiatives varied between countries (top part of Figure 7.1). The US was the first country to implement regulation on health warning labels on cigarette packages in 1966 [398]. In the context of the four US studies' participant lifespan, one study was published prior to when health warning labels on cigarette packages were compulsory[240], in the other three studies offspring participants were aged 19[241], 15[217] and 8[238] in relation to this policy. To date, there is no national regulations around smoking in public places in the US, however individual states have

their own smoke-free laws on smoking restrictions in various public spaces[399]. For other studies within the systematic review (Chapter 3), offspring participants were in their early to mid- adulthood when the country specific tobacco control initiatives were in place in the UK [323], Sweden[398, 400] and Iran[401, 402]. While the study by Mostovoĭ [239] did not report on the age of participants (thus not included in Figure 7.1), this study was published 25 years prior to public health initiatives in tobacco control were enforced in Ukraine where data were collected for this study[403]. Thus it is unlikely that smoking-related public health policies would have had much effect on participants within studies that were included in the systematic review. Only three studies collected lung function data after the first global consensus document on COPD was published[216, 237, 241], which not only explains the inconsistencies in terminologies and lung function measures used within the included studies, but may have over- or under-estimated the prevalence of COPD.

In the 1958 study (Chapter 4), Pilot study (Chapter 5) and Feasibility study (Chapter 6), offspring participants were generally younger when the Australian and British governments first introduced policies around tobacco advertisements [323]. Parents were in their early adulthood (Feasibility study) and mid- adulthood (1958 study and Pilot study), offspring were seven and two years old in the 1958 and Pilot study, whereas those offspring in the Feasibility study were not born. When health warning on cigarette packages were introduced [323], offspring participants in the Feasibility study were three years old. When smoking was banned in public spaces and work places in 2006-2007 in Australia and the UK[324, 397], parent participants in all three studies were at least in their fifth decade and offspring participants were in their mid-adulthood.

While smoking or passive smoke exposure data on participants within the systematic review studies were unable to be extracted systematically, exposure to these factors were hypothetically the highest amongst the four studies within this research program based on the higher global smoking prevalence during that generation[302]. In the 1958, Pilot and Feasibility study (Chapter 4 – 6), data on levels of smoking-related exposures were able to be compared across offspring participants (Table 7.2).

Table 7.2 Offspring participant's smoking related exposure

Thesis Chapter Study name	Chapter 4 1958 study	Chapter 5 Pilot study	Chapter 6 Feasibility study
Sample size (n)	6,304	5	5
Mean age of offspring participant (years)	45	51	48
Generation label	Baby Boomer	Baby Boomer	Generation X
Exposure to passive smoke exposure during childhood (%)	93%	80%	60%
Smoking history			
Current smoker (%)	18%	20%	40%
Ever smoker (%)	21%	60%	40%
Never smoker (%)	60%	20%	20%

It should be highlighted that there were very small numbers of participants in the pilot and feasibility studies. While the numbers of offspring participants were small in the Pilot and Feasibility studies, the proportion of offspring participants exposed to passive smoke during their childhood appears to be in the expected direction. A lower proportion of Generation X offspring participants were exposed to passive smoke in childhood compared to Baby Boomers. On the other hand, it was surprising to see that there were a larger proportion of offspring participants who were current and ever smokers in the Pilot and Feasibility study in comparison with the 1958 study despite the trend of decline in smoking prevalence in the UK and Australia[302, 397]. Offspring participants were invited to participate in a "lung health" research study in the Pilot and Feasibility study, whereas participants in the 1958 study were recruited at birth and followed up over time. The more selective sample of parents and adult offspring interested in participating in a "lung health" research study may have resulted in a biased sample, when participants may have been smokers themselves with potential intergenerational transfer of smoking behaviour[404]. Together these may explain the larger proportion of offspring participants who were smokers in the Pilot and Feasibility study compared to a general population sample (1958 study).

Generation Xs were in their childhood during the early phases of public health policies implementation of tobacco control. Landmark reports were published by the Royal College of Physicians in the UK and the Surgeon General of the US in the 1960's on

smoking and health[323, 405, 406], this was followed by public policies on compulsory warning on cigarettes were enforced in Australia and UK in 1970's [397, 407]. Changes in people's attitudes about smoking and reduction in smoking prevalence occurred gradually over time[408]. Thus, depending on the individual parents, the levels of smoke exposure at home during the childhood years of Generation Xs may or may not be significantly different when compared to Baby Boomers in countries such as UK and Australia.

As demonstrated in Figure 7.1 different public health initiatives on tobacco control were implemented at different times by different countries [323], with westernised industrialised countries typically enacting policies earlier than non-western countries. It was not until 2003 when the World Health Organisation Framework Convention on Tobacco Control treaty was adopted in the World Health Assembly in response to the global tobacco epidemic, that principles and frameworks were provided for governments to implement tobacco control measures. This prompted more middle and lower income countries to implement these measures[409, 410]. In the 2017 report by the World Health Organization [326], approximately 63% of the world's population are protected by at least one tobacco control measures with a declining global smoking prevalence (21% in 2015) with the decline projected to continue to 2030. Early life exposure to maternal smoking will likely reduce for the future generations with reported decline in the prevalence of maternal smoking [411-413]. Therefore the influence of smoking-related health policies will likely have a greater impact on the pattern of smoke exposure in offspring of Generation Y in middle and lower income countries which implemented tobacco control measures for a shorter period of time.

Non-smoking-related exposures

Maternal health and prenatal care has improved in the last 20 years [414, 415], consequently offspring of Generation Ys are likely to have better health at birth compared to previous generations. However with medical advances, the prevalence of preterm birth has also increased, with approximately one in ten babies born preterm worldwide during 2010 [416]. The long term lung health outcomes of preterm babies who may or may not have been supported by modern intensive care technologies during their early life will require long term follow up studies [417-419].

Another important risk factor for COPD is chronic asthma. The prevalence of asthma appears to have increased between 1980's to 2000's in Australians including children and other ages [420, 421]. At the same time, novel therapies and medications for asthma have been developed[422]. National asthma strategies have also been developed and launched in Australia with an aim to prevent and improve asthma management[423]. Ongoing longitudinal studies are required to monitor how these strategies impacts on the risk of COPD developing in adult offspring of people with COPD.

A report published by the Forum of International Respiratory Societies [424] in 2017 highlighted the global burden of respiratory diseases including COPD and emphasised the importance of using prevention strategies to reduce the burden of respiratory disease. The harmful respiratory effects as a result of in-utero, childhood and long term exposure to environmental/ air pollution are well established [425, 426]. Over time there has been an increased awareness of specific environmental exposures in workplaces impacting worker's health[427, 428], accompanied by regulations to minimise occupational exposures and use of personal protection at work[325, 427, 429-432]. There have also been global initiatives to reduce indoor air pollution as a result of the use of solid biomass fuels for cooking in poorly ventilated households in low and middle income countries[433, 434]. Data from the Global Burden of Diseases Study indicate that air pollution in low and middle income countries has increased in the last 25 years and is predicted to increase burden of diseases, unless there are effective national strategies focused on the reduction of air pollution[435]. Fortunately countries such as India and China with high levels of outdoor air pollution recently proposed strategies to improve air quality aimed at reducing mortality attributable to air pollution [436-438].

Findings of this research program would be applicable to Generation Xs (currently in their 40s – 50s) in Western countries, as their levels of exposures to COPD risk factors were likely similar to exposures experienced by offspring participants included in this research program. However results of this research program cannot be generalised globally. Ongoing societal changes and public health initiatives should result in a reduction of exposure to modifiable COPD risk factors for Generation Ys and their

offspring. It is unclear if the reduction of COPD risk factor exposure would increase or decrease the risk of developing lung impairment in offspring of people with COPD. Use of a life course approach provided a way of unravelling mechanisms behind respiratory impairment in offspring of people with COPD. Additionally this approach positions the life course of participants relative to historical and contemporary events that may influence on exposures to risk factors.

7.3 Identification of adult offspring of people with COPD

The target population in this research program was adult offspring of people with COPD, that is people with a parental history of COPD. There were two underlying assumptions in this thesis. Firstly, everyone is an offspring and can either have a positive or negative parental history of COPD. Secondly, offspring share their parents' genes and typically live in the same environment for a period of time thus parent-offspring pairs may have shared exposures to different risk factors. Based on these two assumptions, two approaches were used to identify people with a parental history of COPD (antecedent approach) or adult offspring of people with COPD (descendent approach).

7.3.1 Antecedent approach (recruiting people with a parental history of COPD)

Antecedent approaches appears to be the more commonly used recruitment method to identify people with a parental history of COPD (five of the eight studies included in the systematic review [Chapter 3]). The importance of family history in health originates with Hippocrates and has since been adopted by physicians and researchers [439]. Identifying positive family history of diseases including cancer, cardiovascular disease and diabetes has been recognised as a promising and inexpensive tool for disease prevention and health promotion [440]. While parental history is included within the broader term of "family history", the term "family history" may also include history of their siblings, half-siblings, grandparents, aunts, uncles, nieces and nephews[440] whom are less likely to have a shared environment/ risk exposure for an extended period of time.

The systematic review and meta-analysis undertaken as part of this program of research indicated that individuals with a parental history of COPD are at increased risk of developing COPD[441]. The systematic search strategy was re-run in December 2017 to identify any new studies in the area. Despite the large volume of references (n = 743) published since the systematic review search was first conducted (2015), no new journal articles met the review inclusion criteria (reported on the prevalence of COPD in either parents or offspring of people with COPD). Several conference abstracts alluded to family history and prevalence or associations with offspring respiratory disease [442-446], but in the absence of full text versions of the studies, it could not be determined whether family history was restricted to parents or extended to siblings or first degree relatives. Amongst the new references identified with full text versions, there appears to be an assumption that "family history" does not need to be further defined within studies. Analyses of Japanese biobank data (n = 199,982) by Hirata, Kamatani [447] demonstrated significant associations between 46 diseases (including COPD) with a positive family history of the same disease, but the study did not provide a definition for family history. Similarly, in a systematic review and meta-analysis of 14 studies by Yang, Mao [448], family history (not defined) was concluded as a risk factor for COPD with a reported pooled odds ratio of 2.068 (95% CI = 1.466-2.918)[448]. In addition to English databases Yang, Mao [448] searched three Chinese databases. Where possible the original articles used in the calculation of the pooled odds ratio (n = 14) in the meta-analysis by Yang, Mao [448] were traced. Seven full text articles were retrieved and translated from Chinese, but none provided separate prevalence data on parental history of COPD.

This issue of whether different definitions of family history would have influenced risk estimates has been recognised in previous reviews on the impact of family history on diabetes [449] and asthma [231]. In a type II diabetes review of 11 studies, Harrison, Hindorff [449] reported that in the two studies where the family history also included other family members/ relatives, risk estimates were similar. The sensitivity, specificity, positive and negative predictive values appeared similar across ten studies that used various definitions of family history of asthma (mother only, father only, either parent, first degree relatives, not specified)[231]. While asthma is also caused by

a combination of genetic and environmental factors[450], unlike COPD, genetic factors explained a large proportion of the heritability or familial aggregation of asthma[451, 452]. While there is some evidence that use of a broader definition of family history or a narrower definition of parental history did not influence risk estimates in diabetes and asthma, it is unclear if this is translatable to COPD. The reported pooled odds ratio in the systematic review by Yang, Mao [448] (broader definition for family history) was higher when compared with the pooled odds ratio calculated in Chapter 3 when it was restricted to parental history of COPD (pooled OR = 2.068 and 1.57 respectively). Further studies and comparisons are required to investigate why a broader definition of positive family history of COPD lead to higher risk of COPD development.

7.3.2 Descendent approach (identifying parents with COPD and recruiting their offspring)

Relatively fewer cross-sectional studies have used a descendent approach to investigate lung health in adult offspring of people with COPD. The main benefit of using a descendent approach is that researchers can be confident that the participants, or at least one proband actually do have COPD, and may also reduce recall bias and self-selection[453]. Another benefit that is relevant to the life course approach is the opportunity to gather life course data from both in the parent-offspring pair, which can be used as a method of validation across data collected from the pair of participants.

This research program (Feasibility study, Chapter 6) attempted to use a descendent approach to recruit pairs of COPD parents and their offspring. However despite the Pilot study (Chapter 5) indicating there were no practical issues with the proband-initiated recruitment method in a non-COPD population, this recruitment strategy proved not to be feasible in identifying and recruiting adult offspring through their parents with diagnosed COPD. This was possibly due to their offspring's geographical location and parent- related barriers in relaying information onto their offspring.

In contrast to our findings, an indirect method to approach relatives of proband has been previously reported as an acceptable recruitment method to recruit family

members (not limited to offspring) in family studies[213]. Previous studies that have successfully used a descendent approach to recruit pairs of parents and offspring in the investigation of offspring lung health, typically recruiting the mother during pregnancy or recruiting the offspring at birth which allowed data collection from both parents and offspring [128, 454]. Secondary analysis of parent-offspring data collected from existing large population- based longitudinal studies such as the Framingham study[143] and the Busselton Health Study[146] may provide the best potential for intergenerational assessment in terms of time and resources. While this may be the most practical method for investigating intergenerational and life course factors influencing lung health in adult offspring of people with COPD through the descendent approach, limitations associated with secondary analysis such as missing data and variable of interest not available will remain a challenge for researchers.

The main consideration for future studies aiming to prospectively recruit adult offspring of people with COPD is to have appropriate measures in place to ensure the eligibility of the parent-offspring pair. The use of an antecedent or descendent approach would both result in the identification of adult offspring of people with COPD/ people with a parental history of COPD. Ability to directly approach offspring of people with COPD or people with a parental history of COPD may be the key to successful recruitment of this specific population in future studies.

7.4 Clinical implications and recommendations

Findings of this research program confirmed that adult offspring are at increased risk of developing lung impairment. Apart from genetic factors such as alpha-1-antitrypsin deficiency, parental history or family history is not commonly considered amongst "factors that would influence disease development and progression" (p. 8) [1] within the most recent 2018 GOLD report. However a "family history of COPD and/or childhood factors" is recommended as one of the key indicators for considering a diagnosis of COPD, together with the presence of respiratory symptoms, recurrent lower respiratory tract infections and history of risk factor exposure. Interestingly in the 2015 GOLD report, only "family history of COPD" but not "childhood factors" was listed along with other factors as one of the key indicators of considering a COPD diagnosis[218]. This is likely a result of the recent publications from large- population

based studies strengthening evidence on the impact of early life home overcrowding[169] and exposure to maternal smoking [455] on the offspring's lung function in middle age.

Recommendations for indications for spirometry in the Australian and New Zealand guideline for the management of COPD (COPD-x) remain the same between the June 2015 publication (version 2.42) and the most recent September 2017 guideline (version 2.52) [52]. Similar to the GOLD report, family history of COPD is not currently stated as a risk factor, but listed as one of the indications for spirometry "risk factors such as exposure to tobacco smoke, occupational dust and chemicals, and a strong family history of COPD"(p.24) [52]. A definition for "strong family history" was not provided within the COPD-x guideline which may be interpreted differently by clinicians. To minimise ambiguity, it is recommended that more precise terms like "parental history" to be used.

Routinely asking new patients about their family history is considered good clinical practice [456], however it is unclear if acknowledging the importance of family history translates to actions such as screening in primary care providers[457]. For people who report a parental history of COPD, it should prompt primary care providers to ask questions about any respiratory symptoms, respiratory illness history, smoking history and exposures to other COPD risk factors which would indicate those suitable for further spirometry screening.

For people with known parental history of COPD, health promotion strategies should aim at increasing their vigilance of the presence of any unexplained respiratory symptoms. The Australian Lung Foundation's Lung Health Checklist may be a useful tool to aid recognition of the presence of respiratory symptoms[458]. Although parental history of COPD and genetics remain as non-modifiable risk factors, efforts can be made to identify and reduce modifiable risk factors that may be part of the mechanisms underlying the intergenerational relationship. It is important to increase publics' awareness that while smoking is a risk factor for COPD, it is not the sole risk factor for COPD development. Resources such as the European Lung Foundation's

quiz on "Is your workplace affecting your breathing?" may help increase awareness of additional risk factors that may influence individual's lung health[428].

For people with diagnosed COPD with adult offspring, education sessions during pulmonary rehabilitation programs may provide an opportunity to spark a conversation between the parent and offspring. The Pulmonary Rehabilitation Toolkit developed by Lung Foundation Australia contains resources to assist health professionals provide evidence- based pulmonary rehabilitation programs[459]. A list of recommended educational topics is included in the toolkit with risk factors for respiratory disease currently included as one of the topics. The suggested content includes "smoking, sedentary lifestyle and behaviour change"[460]. Education sessions of pulmonary rehabilitation programs provide an ideal opportunity to reinforce that COPD risk factors go beyond cigarette smoking, but also includes environmental factors and childhood respiratory illnesses, and the potential implications of parents-offspring living in a shared environment for an extended period of time may prompt COPD parents and their offspring to start a discussion.

7.5 Future research directions

Several future research directions have emerged in this discussion.

- A more feasible method is required to recruit adult offspring of people with confirmed COPD in accordance with the Australian National Statement on Ethical Conduct in Human Research[461]. In the ethics application process for both the Pilot and Feasibility studies, the Human Research Ethics Committee (HREC) raised concerns around respecting potential participant's autonomy and minimising issues with coercion and pressure. Thus the researchers were not permitted to ask potential participants for contact details of their offspring or contact the offspring directly. In future studies, if the intention was to recruit parent-offspring dyads, these ethical issues will remain regardless of whether an antecedent or descendent approach was planned. That is, unless both parent and offspring have consented for their details to be included in databases or registries and to be contacted for future studies or researchers have independent direct contact with each member of the dyad, one or other of the

dyad would need to convey information to the other. Studies planning to recruit offspring of parent with a known medical condition (e.g. COPD) may need to focus on recruiting people with a self-reported parental history of COPD, through a direct antecedent approach. While this approach is consistent with best practice ethical conduct, it is recognised that there are also limitations associated with this recruitment approach (such as under/misdiagnosis of COPD in the parent which can affect an individual's perceived and actual eligibility).

- Contemporary data on the respiratory health and risk profile in adult offspring of people with COPD are required. This may provide evidence for using parental history of COPD as an opportunity to identify pre-symptomatic individuals susceptible to the development of COPD[11].
- The effectiveness of using parental history of COPD on its own and in combination with other factors (e.g. smoking and age) as a case finding strategy should be evaluated.
- With ongoing genome wide association studies and increase in population-wide biobanks, these will likely identify specific genes or gene-environmental factors with great potential in explaining susceptibility and gene-environment association [462-464]. Together with the move towards electronic health records and disease registries, these will provide large databanks available for analysis. A life course approach could be used when examining these data to unravel the mechanism explaining the increased risk of COPD in offspring of people with COPD.
- The long term lung health consequences of the use of electronic cigarettes (especially in younger populations) and those who use electronic cigarettes as a replacement/ alternative to smoking should be investigated.
- This research program has focused on risk factors for COPD. Physical activity and diet such as antioxidants have been associated with better lung function in smokers and lower risk of COPD [333, 465, 466]. Future research should explore how protective factors might mitigate the risk of COPD development in offspring of people with COPD.

- Researchers should capitalised on existing longitudinal cohorts with large amount of life course data. In future, research teams planning longitudinal studies that will collect biomedical data should incorporate pre and post bronchodilator spirometry. These data will be especially important as cohort members age.

7.6 Strength and limitations across four studies

The overall strength of this research program was the systematic approach and rigorous methodologies used to answer a range of research questions. Both primary and secondary research methods have resulted in an improved understanding of lung health of adult offspring of people with COPD. An overview of the current literature (Chapter 3) and analysis of secondary data from a large representative birth cohort (Chapter 4) provided evidence to support primary data collection in offspring of people with COPD. The recruitment and life course data collection instrument were first piloted in a non-COPD population (Chapter 5) and then assessed for feasibility in a COPD population (Chapter 6).

The use of a life course perspective approach to explore lung health in adult offspring of people with COPD not only allowed the examination of the contribution of different risk factors present at different time points for a person's life, but puts the individual's life course in perspective to potential impacts of contemporaneous world events (e.g. war, policy changes) and societal changes over the different generations which may be less understood in this area of study. The life history data collection instrument (SOMLc) developed and trialled in the Pilot and Feasibility study (Chapter 5 and 6) may be valuable for future research, as it is a simple tool that can assist researchers to better tie objective evidence obtained in cross-sectional studies with previous historical elements.

While the proband-initiated recruitment method proved not to be a feasible method to recruit adult offspring of people with COPD (Chapter 6), the study provided insight to why this recruitment strategy was not feasible (ineligibility of people with COPD, geographical location of offspring, parent-related barriers) which will be crucial points for consideration for future studies.

The main limitation of this thesis was the inconsistency in measures of lung health in both parents and offspring. As demonstrated in Figure 7.1, secondary analysis of data that were collected prior to a global consensus for a definition of COPD meant not all studies collected standardised spirometry data from parents and offspring, thus analysis was restricted to data that were available. While primary data collection was attempted in the Feasibility study, only screening spirometry was performed in accordance to the current recommendations from the Australian Lung Foundation[356]. Due to the small number of offspring participants recruited in the Feasibility study, observations on the respiratory health in offspring of people with COPD could not be generalised. The planned translational forum was not conducted and the low number of participants who responded to the perspective survey provided limited insight on the perspective of both parents and offspring on the issue.

7.7 Conclusion

Globally life expectancy has increased between 1990 and 2010, at the same time the numbers of healthy years lost to disability have also increased indicating more people are living with chronic conditions [467, 468]. The prevalence of COPD increases with age[84], which can indirectly increase the number of adult offspring of people with COPD.

Confirmation that offspring of people with COPD are at increased risk of developing lung impairment presents an opportunity to reduce the burden of COPD. Clinicians should use the knowledge of positive parental history of COPD as a prompt to consider if the individual is experiencing any respiratory symptoms and exposures to risk factors of COPD to determine suitability for further screening. Future case finding studies should include positive parental history of COPD.

Use of a life course approach allowed examination of factors linking parental respiratory disease history and reduced lung health of offspring in mid-adulthood. While exposure to maternal and personal smoking explained about 30% of the relationship between parent and offspring lung health, a large proportion of the relationship remains unexplained. Reduction of exposure to other modifiable risk factors along the life course is important and may influence the impact of a positive

parental history of COPD on the person. Preventing further exposure to COPD related risk factors, increase awareness of the presence of respiratory symptoms in individuals with a parental history of COPD are important strategies to reduce the burden of COPD.

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Appendix A: Systematic Review

A.1 Conference abstract

(Presented at the 2016 Thoracic Society of Australia and New Zealand conference)

Prevalence of co-occurrence of COPD diagnosis in parents and offspring: systematic review

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Introduction/Aim:
Intergenerational associations in COPD are well recognised and may result from genetic, gene-environment or exposure to life course factors. Consequently, children of parents with COPD pose a high risk group for development of COPD. We evaluated the reported prevalence of co-occurrence of COPD diagnosis in parents and offspring.

Method:
Five databases (Medline, Embase, Scopus, CINAHL, Cochrane library) were searched for original, human studies where prevalence of COPD was reported in both offspring (children) and one or both parents. Studies were excluded if COPD was not defined (spirometry, physician diagnosis, self-report or symptom profile), parents or offspring were not reported separately to first degree relatives, COPD was combined with other chronic respiratory conditions, familial studies of alpha-1-antitrypsin (AAT) deficiency or not published in English. Data extraction was completed by two independent reviewers. Where possible, the odds ratio was calculated if it was not reported.

Results:
Of 3382 citations, 134 full texts were reviewed to include seven studies (3 case-control, 2 cross-sectional, 2 cohort) reflecting prevalence of COPD in offspring of people with COPD (n = 3) or prevalence of people with COPD reporting positive parental history of COPD (n = 4). The prevalence of COPD in offspring of people with COPD ranged from 6.6% (female aged 16-39) to 17.3% (males aged 16-39). The prevalence of people with COPD with a parental history of COPD ranged from 11.7% (adoptees non biological parents) to 58% (in people with severe, early onset COPD (non AAT)). The unadjusted odds ratio of an offspring having COPD if they have a parental history of COPD ranged from 1.21 to 7.9.

Conclusion:
There were surprisingly few studies that specifically reported prevalence of COPD in offspring of parents with COPD, with the resultant wide range of prevalence of co-occurrence of COPD likely to reflect specific, non-representative study samples.

A.2 Published version of the systematic review and meta-analysis

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REVIEW

"What are my chances of developing COPD if one of my parents has the disease?" A systematic review and meta-analysis of prevalence of co-occurrence of COPD diagnosis in parents and offspring

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Introduction: Intergenerational associations in chronic obstructive pulmonary disease (COPD) have been well recognized and may result from genetic, gene environment, or exposure to life course factors. Consequently, adult offspring of parents with COPD may be at a greater risk of developing COPD. The aim of this study was to review the prevalence of co-occurrence of COPD in adult offspring with one or both parents having COPD independent of specific genetic variations.

Methods: In total, five databases were searched for original studies in which prevalence of COPD was reported in both offspring (children) and one or both parents. Studies were excluded if COPD was not clearly defined, COPD was linked to specific genetic variations, COPD was combined with other chronic respiratory conditions, or estimates included other first-degree relatives. Data extraction (ie, sample characteristics, prevalence of COPD, and odds ratio [OR] if reported) was completed by two independent reviewers. A meta-analysis of prevalence and OR was conducted, where possible.

Results: Of the 3,382 citations, 129 full texts were reviewed to include eight studies (six case–control, one cross-sectional, and one cohort) reflecting either prevalence of COPD in offspring of parents with COPD (descendent approach, n=3), which ranged from 0% to 17.3%, or prevalence of people with COPD reporting positive parental history of COPD (antecedent approach, n=5), for which the pooled prevalence was 28.6%. Offspring of people with COPD had 1.57 times greater odds (95% confidence interval = 1.29–1.93; $P<0.001$) of having COPD compared with people not having a parental history of COPD.

Conclusion: The prevalence of COPD in adult offspring of people with COPD is greater than population-based estimates, and the ORs indicate a higher risk in this group. This offers clinicians a potential strategy for opportunistic screening, early identification, and intervention in this at-risk group.

Keywords: COPD, intergenerational, prevalence, systematic review

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common condition and is estimated to become the third leading cause of death by 2030.[1,2] Globally, the prevalence of COPD has been estimated to be between 9% and 10%.[3] Although COPD is a progressive disease, early intervention strategies such as optimizing medication,

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exercise, and pulmonary rehabilitation have been shown to reduce the rate of disease progression and improve symptom control in people diagnosed with COPD.[4–8] The high prevalence of undiagnosed COPD has been reported internationally.[9,10] Underdiagnosis of COPD is problematic as symptoms of COPD may hinder an individual's daily activities.[11,12] Generalized population level screening for COPD is controversial and, currently, is not recommended for asymptomatic individuals as it is unclear whether early detection improves clinical outcomes.[13] Individuals may, however, present asymptomatic because of modification in activities that trigger symptoms.[14] Targeted case findings in the community and in primary care commonly focus on people with recognized COPD risk factors or exposures such as smokers and consider them as an at-risk population.[15,16]

Although cigarette smoking is a key risk factor for COPD development, not all COPD cases can be explained by smoking.[17] Lifetime exposure to smoke or pollution has been shown to increase a person's risk of developing COPD.[18,19] In addition, early life factors such as low birth weight, prematurity, nutrition, childhood respiratory illness, and exposure to passive smoking are associated with reduced lung function in later life.[20–24]

Familial or intergenerational associations for chronic respiratory disease have been observed with an increased risk of chronic bronchitis in people with family members having bronchitis.[25,26] Strong familial associations have been reported for increased respiratory symptoms or conditions including wheezing, asthma, and lung cancer among twins and individuals living in the same household.[23,27–29] Currently, although alpha-1-antitrypsin deficiency is the only robustly defined inherited form of COPD that can explain familial aggregation of COPD,[30] <3% of people with COPD have this deficiency.[31] Intergenerational associations overlap with the risk factors associated with the development of COPD, including smoking behavior of parents and offspring, educational achievement, lung function, and conditions or diseases such as asthma and lung cancer.[29,32–35] Concepts, knowledge, and behaviors about health can be transmitted from one generation to the next.[36] Thus, offspring of people with COPD are considered as an at-risk group for the development of COPD, as they may be exposed to a greater number of these intergenerational factors that could trigger or have a cumulative effect that shapes the trajectory of lung health.[37]

Apart from studies that focus on associations between genetic forms of COPD, specific genes, and lung function in families,[38,39] there seem to be little direct data concerning the likelihood or specific risk of COPD in offspring of parents with COPD. The odds of having COPD have been shown to be 1.7–2.7 times higher in people with family history of COPD (all first-degree relatives included) than in those without family history.[40,41] Adult offspring of people with COPD might present with a different risk profile as they are more likely to cohabitate during formative early life periods. It is hypothesized that offspring of people with COPD through exposure to intergenerational and life course factors will have higher rates or an increased risk of COPD compared with people without a parental history of COPD. The overall aim of this systematic review was to collate the reported evidence for co-occurrence and risk of COPD, especially in adult offspring with one or both parents having COPD independent of specific genetic variations.

The following were the two objectives of this review:

1. To report the prevalence of COPD in offspring of people with COPD and/or prevalence of a positive parental history of COPD in people with COPD.
2. To report the strength of the association between parental and offspring COPD status.

Methods

This review was designed and reported according to the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines, and the protocol was registered (PROSPERO no: CRD42015025228).[42]

Study selection

Electronic databases (ie, Medline, CINAHL, EMBASE, SCOPUS, and Cochrane Library) were systematically searched from inception to mid-September 2015. Search terms (Table 1) were adapted from previous systematic reviews on COPD and the effects of family history.[5,8,23,29] Two researchers independently performed the systematic search

Table 1 Search strategy

Databases	Search terms
Medline EMBASE CINAHL SCOPUS Cochrane library	"COPD" OR exp "pulmonary disease, chronic obstructive" OR "emphysema" OR "chronic bronchitis$" OR "obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "COAD" AND "familial aggregation" OR "familial risk" OR "familial transmission" OR "heredity" OR "adult child" OR "intergenerational" OR "inheritance" OR "family adj3 history" OR "parental adj3 COPD" OR "adult child$" OR "adult son$" OR "adult daughter$" or "offspring"

following a prospectively planned search protocol that was developed with the aid of an academic librarian.

Inclusion and exclusion criteria

Studies were included if data were reported or could be inferred for the prevalence of COPD, chronic bronchitis, and/or emphysema (through self-report, physician-diagnosed, spirometry-diagnosed, or symptom profile) in parents and adult offspring of people with COPD. No year or language limits were set for inclusion of studies in this review.

Studies were excluded: 1) if they did not define family history or specifically report offspring/parents within first-degree relative groups (due to possible inclusions of other family members such as siblings); 2) if they reported specific lung function parameters without a COPD classification definition; 3) if COPD, emphysema, or chronic bronchitis was combined with other respiratory conditions; 4) if data were limited to familial investigation of known genetic variations in COPD (alpha-1-antitrypsin deficiency); and 5) if studies were on participants from specific occupations/living environment (eg, coal miners, coke oven workers, and living close to asbestos factory).

Screening of studies

Two reviewers independently screened the titles and abstracts of citations returned from searches. Full texts of studies were reviewed by two independent reviewers for inclusion or exclusion. Reasons for excluding the studies were recorded, and discrepancies were discussed until consensus was reached. Reference lists of relevant articles were searched, and citation tracking was performed to retrieve any potential additional citations.

Data extraction and appraisal of methodological bias

By using a predetermined template (Table S1), two reviewers independently extracted data from the included studies with disagreements resolved by consensus. A ten-item methodological appraisal checklist for studies reporting prevalence data was used.[43] Interpretations specific to the review questions (Table S2) were used by two independent reviewers; when consensus was not reached, then a third reviewer was consulted. No studies were excluded on the basis of the methodological bias.

Data analysis

Study design, participant characteristics, and the method of COPD diagnosis were descriptively reported. Studies were collated and analyzed separately: 1) studies that considered people with confirmed COPD and the prevalence of COPD in their offspring (descendent approach); and 2) studies that considered prevalence of positive parental history of COPD in people with confirmed COPD (antecedent approach). If odds ratios (ORs) were not reported in the study but sufficient data were provided, then the ORs were calculated. The prevalence and ORs were compiled from the reported statistics or calculated when sufficient information was provided, the pooled prevalence and OR were calculated, and forest plots were created by using MedCalc for Windows, Version 15.11.4 (MedCalc Software, Ostend, Belgium). I^2 statistics were used to assess the heterogeneity of the studies. The random-effects model was used due to the high level of heterogeneity between the studies.

Results

Search results

One hundred and twenty-nine full-text articles were reviewed (including 18 non-English articles; Figure 1). Studies were excluded for two main reasons: first (51% of the excluded studies), despite reporting data for family history of COPD in people with COPD, studies either did not define family history as a parental history[44,45] or reported a pooled analysis of family history that included various combinations of siblings, parents, offspring, and first-degree relatives.[46,47] Second (33% of the excluded), studies reported on the prevalence of respiratory problems/symptoms or on measures of lung function in offspring of people with COPD without a reference to a COPD classification.[48–50]

Seven studies were included after full-text review, and one additional study was identified through citation tracking, resulting in a total of eight studies eligible for inclusion in this review.

Study characteristics

All the included studies were observational in design. Of the eight studies, three studies reported on the prevalence of COPD in offspring of people with COPD (descendent approach, Table 2), with a total of 204 cases and 161 controls in two case–control studies and 5,054 participants in a cross-sectional study,[51–53] and five studies reported on the prevalence of a parental history of COPD in people with COPD (antecedent approach, Table 3), with 1,545 cases and 1,995 controls in four case–control studies and 80,214 participants in a cohort study.[54–58] None of the studies included in this review were primarily designed as prevalence studies, and all the studies included had a variable risk of bias when appraised using the prevalence appraisal checklist (Table S2).[43]

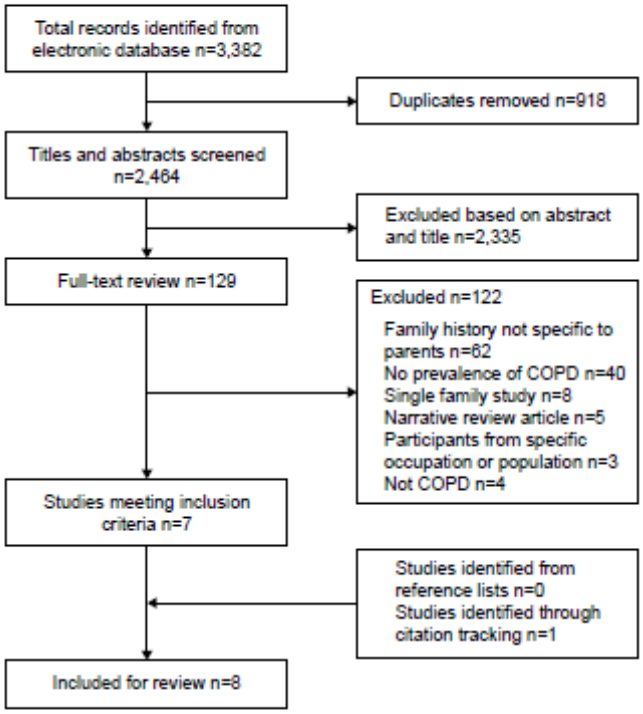


Figure 1 Flow chart for identification of studies.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 2 Summary of studies reporting on COPD prevalence in offspring of people with COPD (descendent approach)

	Higgins and Keller,[53] 1975	Khoury et al,[51] 1985	Amra et al,[52] 2015
Country of data collection	US	US	Iran
Study design	Cross-sectional	Case–control	Case–control
Total number of index cases	5,054[a]	150 cases, 107 controls	54 cases, 54 controls
Case/control cohort	Residents of Tecumseh between 1962 and 1965	Cases: COPD Control: nonpulmonary patient	Cases: offspring of people with severe COPD Controls: matched in age, sex, and height
Demographics of parents	Not reported	Not reported	Not reported
Diagnosis of parents	Chronic bronchitis (symptoms)	COPD (medical records)	COPD (medical records)
COPD severity of parents	Not reported	Not reported	Severe (based on GOLD)
Demographics of offspring (COPD)	50.3% male Male, age (years): <16, n=1,779; age =16–39, n=660; age =40+, n=105 Female, age (years): <16, n=1,779; age =16–39, n=621; age =40+, n=110	Offspring of COPD parents 44.8% male Mean age =27.4 years	Offspring of COPD parents 65.8% male Mean age =34.3 years
Diagnosis of offspring	Chronic bronchitis (symptoms)	Chronic bronchitis (symptoms) Airway obstruction[b]	Abnormal pulmonary function[c]
Prevalence of COPD in offspring of people with COPD	Male: 17.3% (16–39 years); 16.7% (40+ years) Female: 6.6% (16–39 years); 8.3% (40+ years)	14.9% (with chronic bronchitis) 6% (with airway obstruction)	0%
Severity of offspring	Not reported	Not reported	Not applicable
OR	Number of offspring in each age category with parental history and OR not reported (unable to calculate OR)	OR =2.1 (reported chronic bronchitis) OR =6.4 (reported airway obstruction)	Number of parents in matched offspring control group and OR not reported (unable to calculate OR)

Notes: [a]Original study had 9,226 subjects in total, there were 5,054 offspring participants with one or more parent assessed; [b]FEV_1 <68% of FVC; [c]FEV_1/FVC <0.7.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio.

Table 3 Summary of studies reporting prevalence of parental history of COPD in people with COPD (antecedent approach)

	Mostovoĭ,[54] 1987	Silverman et al,[55] 1998	McCloskey et al,[56] 2001	Hersh et al,[57] 2011	Zöller et al,[58] 2015
Country of data collection	Ukraine	US	UK	US	Sweden
Study design	Case–control	Case–control	Case–control	Case–control	Cohort study
Total number of index cases	530 cases, 760 controls	44 cases, 20 controls	150 cases, 439 controls	821 cases, 776 controls	80,214
Case/control cohort	Case: chronic bronchitis Control: healthy persons	Case: severe early onset COPD Control: current or ex-smokers	Case: severe COPD Control: matched for age, sex, and smoking	Case: COPD GOLD Stage II or higher Control: smokers	Cohort: Swedish-born adoptees born between 1932 and 2004
Demographics of parents	Not reported	Not reported	Parents who underwent spirometry 23.7% male Mean age: 75.9±9.8 years	Not reported	Not reported
Diagnosis of parents	Chronic bronchitis (self-reported by offspring)	Chronic bronchitis, emphysema or COPD (self-reported by offspring)	COPD (spirometry and self-reported by offspring)	COPD (self-reported by offspring)	COPD (medical records) ICD7-10 codes
COPD Severity of parents	Not reported	Not reported	Not reported	Not reported	Not reported
Demographics of offspring (COPD)	Not reported	20.4% male Mean age: 47.2±5.6 years; Mean pack-years: 38.8±22.5	46% male Mean age: 52.3±6.9 years	51.8% male Mean age: 64.2±8.4 years, Mean pack-years: 53.2±26.3	49.8% male in total population 43% male with COPD events
Diagnosis of offspring	Chronic bronchitis (Chest x-ray, clinical information)	COPD (spirometry)	COPD (spirometry GOLD)	COPD (spirometry GOLD)	COPD (medical records) ICD7-10 codes
Prevalence of positive parental COPD history in people with COPD	14.5%	58%	44% (spirometry performed on living parents n=38) (self-reported) Male offspring: mother with COPD 32%; father with COPD 37%; Female offspring: mother with COPD 29%; father with COPD 33%	43%	14.3% (biological parents) 11.7% (adoptive parents)
Severity of offspring	Not reported	Severe	Severe	GOLD Stage II or higher	Not reported
Odds ratio	OR =1.95 (crude calculated)	OR =7.9 (95% CI =2.0–30.9) (reported; unadjusted)	No control group for parents, unable to calculate OR	OR =1.69 (crude, calculated) OR =1.68 (95% CI =1.32–2.13; fully adjusted[a])	OR =1.41 (crude calculated, biological parents) OR =1.21 (crude calculated, adoptive parents)

Note: [a]Includes demographic covariates, parental history of COPD, parental history of smoking, and childhood environmental tobacco smoke exposure.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICD, International Statistical Classification of Diseases and Related Health Problems; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio.

Prevalence

The prevalence of COPD in offspring of one or more parents with a diagnosis of COPD ranged from 0% to 17.3% in studies that used a descendent approach (Table 2). Studies that used the antecedent approach reported prevalence estimates ranging from 11.7% to 58% in people with COPD with a parental history of COPD (Table 3).

Pooled prevalence estimate

A pooled prevalence of COPD in offspring of people with COPD could not be calculated across the three studies that employed the descendent approach (Table 2), as one study reported prevalence of COPD in offspring for different age groups and a second study essentially excluded offspring with respiratory conditions.[52,53]

The calculated pooled prevalence of people with COPD with a positive parental history of COPD (antecedent approach) was 28.6% (random-effects model, 95% confidence interval [CI] =17.4–41.3; Table 3, Figure 2). One study provided prevalence of COPD in both biological and adoptive parents of people with COPD (both included in the

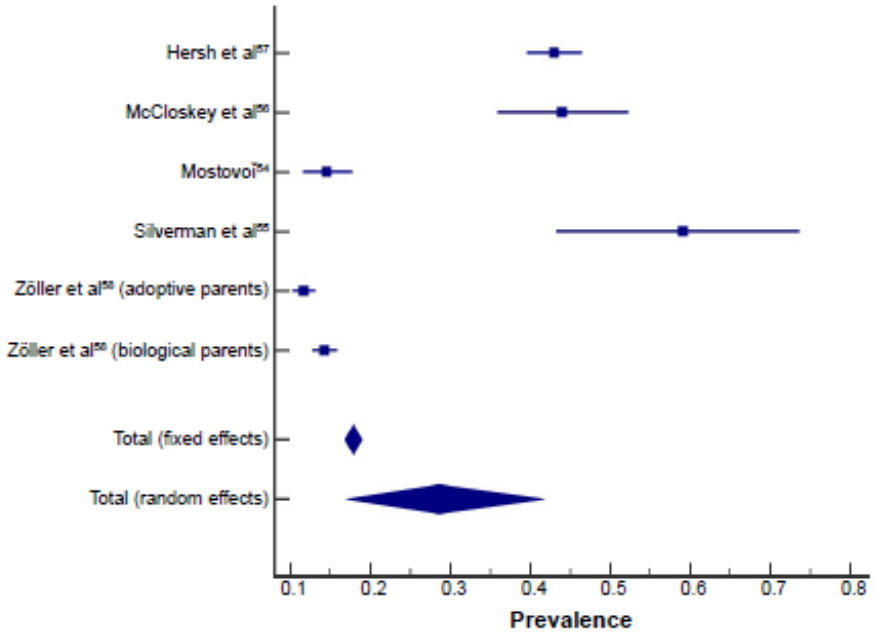


Figure 2 Pooled prevalence of people with COPD with positive parental COPD history.
Abbreviation: COPD, chronic obstructive pulmonary disease.

pooled prevalence calculation).[58] Evidence of heterogeneity between the studies was found (I^2=98.8%; P<0.0001). A study by Silverman et al (1998) included a specific group of participants (severe early-onset COPD).[55] When excluding Silverman et al (1998), the prevalence of people with COPD with a positive parental history of COPD was 24.0% (random-effects model, 95% CI =13.2–36.8; I^2=99.0%; P<0.0001).[55]

Pooled OR

Of the eight included studies, three studies reported an OR (of the increased likelihood of offspring of people with COPD to develop COPD),[51,55,57] two studies reported enough information to calculate comparable ORs,[54,58] and three studies did not provide sufficient information for OR calculation.[52,53,56] A study by Khoury et al reported the prevalence of chronic bronchitis and airway obstruction in the offspring of people with COPD.[51] However, this study defined airway obstruction (forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] <68%) differently from the conventional ratio used for COPD diagnosis (FEV_1/FVC <70%).[1] To maintain consistency across diagnosis methods through the studies, only the data on chronic bronchitis from the study by Khoury et al were used in the pooled analysis.[51]

Meta-analysis of crude OR from five studies indicated that offspring of people with COPD had 57% higher odds of having COPD compared with people without a parental history of COPD (random-effects model, pooled OR =1.57; 95% CI =1.29–1.93; P<0.001; Figure 3). Evidence of heterogeneity between studies was found (I^2=72%; P=0.0029). When the study by Silverman et al (in severe early-onset COPD) was excluded from the pooled analysis,[55] the heterogeneity decreased (I^2=66%; P=0.0198), and offspring of people with COPD had 50% higher odds of having COPD compared with people without a parental history of COPD (random-effects model, pooled OR =1.50; 95% CI =1.26–1.77).

Discussion

This review specifically focused on the co-occurrence of COPD in parents and offspring. The pooled prevalence of people with COPD and a positive parental history of COPD was 28.6%, and offspring of people with COPD had 1.57 times greater odds of having COPD compared with people without a parental history of COPD. Although there is evidence to support familial associations in lung function decline in parent and offspring pairs,[59] this review identified a paucity of studies (especially recent publications) that provided or enabled an estimate of the prevalence of COPD, especially in offspring of people with COPD, to be obtained.

Due to the inconsistencies in the definition of family history and reporting of outcome measures, only a small

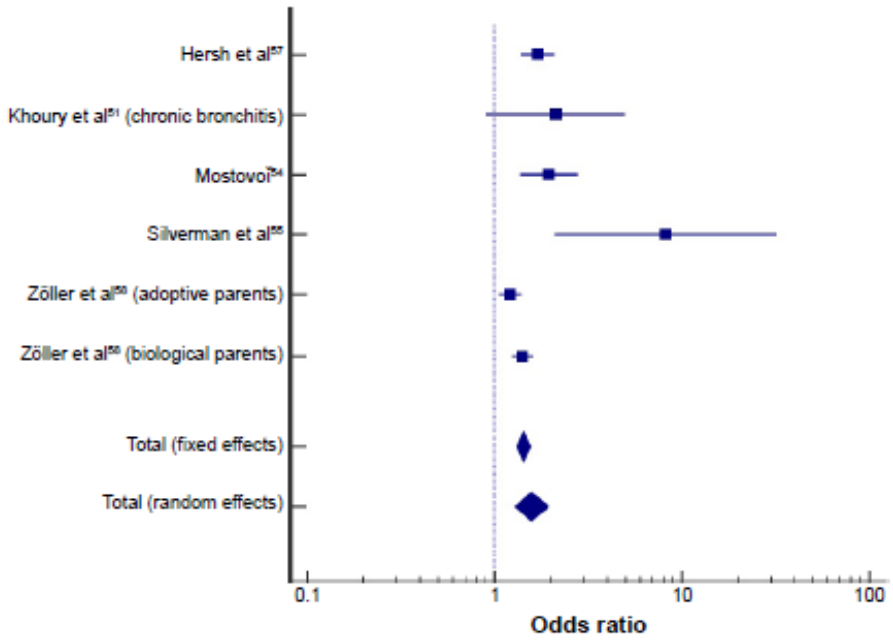


Figure 3 Summary of effects of positive parental COPD history on offspring COPD (unweighted).
Abbreviation: COPD, chronic obstructive pulmonary disease.

number of studies met the inclusion criteria of this review. Lower values for pulmonary function in offspring of COPD probands compared with reference or non-COPD probands have been reported,[49,60,61] but in the absence of categorizing offspring with or without COPD or sufficient information to calculate COPD prevalence within offspring, these studies were excluded.

Variation in the original intent of the included studies resulted in differences in study design, source and nature of participants, and classification of COPD. Index cases in the case–control studies varied from people with chronic bronchitis to people with severe early-onset COPD,[54,55] whereas index cases in the control groups varied from matched individuals to smokers.[52,57] Apart from two older studies (published in 1975 and 1987), all other studies employed spirometry to classify COPD in offspring;[53,54] only one study directly assessed both parents and offspring with spirometry.[56] Parental COPD history was self-reported by participants in all but one of the antecedent studies,[54–57] with the remaining study using medical records to identify COPD in parents and offspring.[58] High prevalence of undiagnosed COPD has been reported worldwide;[10,62] thus, identifying COPD by self-report or medical record screening may be an underestimation and not reveal the true prevalence of positive parental COPD history.[11,59]

Three of the eight studies used a descendent approach and reported a wide range of COPD prevalence (0%–17.3%) in offspring of people with COPD.[51–53] Amra et al represent an outlier within this group as none of the offspring (n=54) met spirometric criteria for COPD ($FEV_1/FVC < 0.7$).[52] However, young mean age of offspring (34.3 years) and exclusion criteria applied to offspring cases (smokers, employed in high-risk jobs for the respiratory system, or had a pulmonary disease) biased the case group toward including only those with lower risk profile for COPD. The other two studies reported prevalence ranging between 6% and 17.3% which was higher than contemporaneous published prevalence estimates of COPD in the general population for a comparable age-group (4% in 25–44 years).[51,53,63]

Across five studies that used the antecedent approach, between 11.7% and 58.0% of people with COPD reported a positive parental history.[54–58] No comparable reviews or population-based data were found to compare these estimates of parental history of COPD; however, this prevalence appears high when compared to the estimate of prevalence of COPD in the general population (9%–10%).[3] Studies that recruited participants with moderate-to-severe COPD reported a relatively higher positive parental history of COPD (43%–58%) and alluded that the increased risk of COPD in families was likely to be the result of genetic factors.[55–57] Although there are ongoing studies on genome-wide association exploring genotypes of COPD, there remain unanswered questions on COPD heritability and susceptibility.[64]

Another possible explanation for the higher prevalence of positive parental COPD history reported by participants with more severe COPD may be an increased awareness of respiratory problems in their immediate family and greater vigilance or likelihood of reporting.[65]

The risk of developing COPD in people with a parental history of COPD (OR =1.57) was comparable to those exposed to passive smoking (OR =1.48), maternal smoking (OR =1.7), and childhood pneumonia (OR =1.4) and lower compared with the effects of personal smoking in the development of COPD (OR =6.3).[18,66–68] Further epidemiological studies are required to promote understanding of the mechanism of interactions between various risk factors and differentiate shared lifestyle factors from true genetic risk in parents with COPD and their adult offspring.

Early identification of those at a risk of developing COPD is commonly based on modifiable behavior such as smoking or symptom profiles. Smokers are a common target population in COPD case-finding studies as smoking cessation is a well-recognized early intervention that slows the progression of the disease.[16,69,70] As universal screening of asymptomatic individuals for COPD is not recommended,[13] offspring of people with COPD may be considered as an at-risk group due to their shared genetic and environment factors, which presents an opportunity for case finding. By capitalizing on the increased prevalence and the risk of developing COPD in adult offspring of people with confirmed COPD, health practitioners working with people with COPD could use opportunistic screening of adult offspring to enable early lifestyle intervention strategies such as smoking cessation, physical activity, appropriate pharmacologic support, and pulmonary rehabilitation to reduce the rate of lung function decline, improve symptom control, and improve quality of life.[7,71,72]

Limitations

This review included studies that were published over a 40-year period (1975–2015). The two oldest studies included in this review reported on the prevalence of COPD in offspring of people with COPD, and unsurprisingly the diagnostic criteria used differed from the current standard.[1,51,53] Diagnostic criteria and terminology for COPD have changed over time.[73] As no time limit was set for the systematic search strategy, studies were eligible for inclusion in this review if participants were classified as having emphysema, chronic bronchitis, or COPD. The prevalence of co-occurrence of COPD reported in this review may differ from the present day due to changes in the definition of COPD, lifestyle, and increased education and health promotion on the health consequences of smoking.[74]

A critical appraisal checklist for studies reporting on prevalence data was used even though the included studies were not specifically designed to report prevalence.[43] As no studies were excluded from the review, modifications were required to adapt the checklist to determine the representativeness of the study sample and interpretation of the results specific to the review question.

Meta-analysis was performed despite significant heterogeneity among the studies. The pooled prevalence and OR calculated provided a summary of the available evidence but may not be generalizable due to the heterogeneity and limited populations of the included studies.

Conclusion

Although familial associations with COPD have been generally well recognized, the results of this review indicate that there were few studies that specifically reported on the co-occurrence of COPD diagnosis in both parents and offspring. Nevertheless, the findings of this review indicate that offspring of people with COPD are at an increased risk of developing COPD. Targeted screening in this at-risk group (adult offspring of people with COPD) may lead to opportunities to capitalize on familial links and promote early identification and intervention.

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Author contributions

All the authors (LSKL, CP, KJ, and MTW) contributed substantially to the study design, data collection, data analysis and interpretation, and the writing and critical revision of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Name of candidate: Lok Sze Katrina Li (KL)

KL contributed to the conception and design of the study, search strategy development, data collection, data extraction, data analysis, interpretation and drafted the manuscript under the supervision of CP, KJ and MTW.
I hereby certify that this statement of contribution to the above-named paper is correct.

Signed: ..... Date: 27 / 2 / 2018

Author 2: Catherine Paquet (CP)

CP contributed to the conception and design of the study, search strategy development, data collection, data extraction, data analysis, interpretation, supervised KL's work and critically reviewed the manuscript.
I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.

Signed: ..... Date: 27/02/2018

Author 3: Kylie Johnston (KJ)

KJ contributed to the conception and design of the study, search strategy development, data collection, data extraction, data analysis, interpretation, supervised KL's work and critically reviewed the manuscript.

I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.

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Author 4: Marie Williams (MTW)

MTW contributed to the conception and design of the study, search strategy development, data collection, data extraction, data analysis, interpretation, supervised KL's work and critically reviewed the manuscript.

I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.

Signed: M T Williams Date: 28/2/2018

A.3 Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data

	Yes	No	Unclear	NA
1. Was the sample representative of the target population?				
2. Were the study participants recruited in an appropriate way?				
3. Was the sample size adequate?				
a) Did the authors conduct a sample size calculate to determine an adequate sample size?				
b) Using the calculation Catherine did (10% prevalence, 2.5 % precision), did the study have adequate sample size?				
4. Were the study subjects and the setting described in detail?				
a) Did the study provide sufficient details on the subjects (age, sex, smoking status etc.)?				
b) Did the study provide sufficient details on the setting (community, primary care, hospital, database registry)?				
5. Was the data analysis conducted with sufficient coverage of the identified sample?				
a) Did the authors describe the reasons for non-response and compare persons in the study to those not in the study, particularly with regards to their socio-demographic characteristics?				
b) Could the not-responders have led to an underestimate of prevalence of the disease or condition under investigation?				
c) If reasons for non-response appear to be unrelated to the outcome measure and the characteristics of non-responders are comparable to those in the study, the researchers may be able to justify a more modest response rate				
6. Were objective, standard criteria used for the measurement of the condition?				
a) In parents?				
b) In offspring?				
7. Was the condition measured reliably?				
a) In parents?				
b) In offspring?				
8. Was there appropriate statistical analysis?				
9. Are all important confounding factors/subgroups/differences identified and accounted for?				
a) For prevalence?				
b) For odds ratio?				
10. Were subgroups identified using objective criteria?				
a) For prevalence?				
b) For odds ratio?				

A.4 Methodology quality assessment of included studies

	Higgins et al. 1975[240]	Khoury et al. 1985[238]	Mostovoi 1987[239]	Silverman et al. 1998[217]	McCloskey et al. 2001[242]	Hersh et al. 2011[241]	Amra et al. 2015[216]	Zoller et al. 2015[237]
1. Was the sample representative of the target population?	Unclear	Unclear	Unclear	Yes	Yes	No	No	Yes
2. Were study participants recruited in an appropriate way?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes
3. Was the sample size adequate?								
Did the authors conduct a sample size calculate to determine an adequate sample size?	No	No	No	No	No	No	No	No
Estimating an expected prevalence of 10% with 2.5% precision*, did the study have adequate sample size?	Yes	No	No	No	No	Yes	No	Yes
4. Were the study subjects and the setting described in detail?								
Did the study provide sufficient details on the subjects?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Did the study provide sufficient details on the setting	Yes	Yes	No	Yes	Yes	No	Unclear	Yes
5. Was the data analysis conducted with sufficient coverage of the identified sample?								
Did the authors describe the reasons for non-response and compare persons in the study to those not in the study, particularly with regards to their socio-demographic characteristics?	Yes	No	No	Yes	Yes	Yes	No	yes

	Higgins et al. 1975[240]	Khoury et al. 1985[238]	Mostovoi 1987[239]	Silverman et al. 1998[217]	McCloskey et al. 2001[242]	Hersh et al. 2011[241]	Amra et al. 2015[216]	Zoller et al. 2015[237]
Could the not-responders have led to an underestimate of prevalence of the disease or condition under investigation?	No	Unclear	Unclear	No	No	Yes	Yes	No
If reasons for non-response appear to be unrelated to the outcome measure and the characteristics of non-responders are comparable to those in the study, the researchers may be able to justify a more modest response rate	Unclear	Unclear	N/A	N/A	N/A	Unclear	Unclear	Unclear
6. Were objective, standard criteria used for the measurement of the condition?								
Parents?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Offspring?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the condition measured reliably?								
Parents?	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Offspring?	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes
8. Was there appropriate statistical analysis?	No	Yes	Unclear	Yes	Yes	No	No	Yes
9. Are all important confounding factors/ subgroups/ differences identified and accounted for?								
Prevalence?	Yes	No	No	Unclear	Yes	No	Unclear	No
Odds ratio?	N/A	No	N/A	Yes	Yes	Yes	N/A	No
10. Were subpopulations identified using objective criteria?								
Prevalence?	Yes	No	No	No	No	No	N/A	Yes
Odds ratio?	N/A	No	N/A	yes	Yes	Yes	N/A	Yes

N/A: Not Applicable; *calculated using the formula suggested in the Joanna Briggs Institute reviewers' manual[236]

Appendix B: 1958 Study

B.1 Conference abstract

(Presented at the 2017 Public Health Association of Australia, South Australia State Population Health Conference)

Title: Intergenerational and life course factors for lung health
Author/s: LSK Li, MT Williams, K Johnston, P Frith, E Hypponen, C Paquet
ABSTRACT TEXT
Introduction: Familial aggregation of chronic lung conditions may result from a combination of genetic susceptibility and exposure to risk factors throughout life. We used a life-course approach to investigate life-course factors contributing to the relationship between parental respiratory history and Reduced Lung Health (RLH) in adulthood. Methods: 1958 British Birth Cohort participants (n=6938) were characterised in terms of RLH (presence of respiratory symptoms at 42yrs and airway obstruction [FEV1/FVC<0.7 at 45yrs]), and parental history of respiratory disease (offspring age 0,11,16). Life-course factors evaluated were maternal smoking (0yrs), passive smoking (16,23,33,42yrs), social class (0,7,16,23,33,42yrs), respiratory illness (7,11,16,23,33,42yrs), smoking status (16,23,33,42yrs), and occupation exposure to dust or fumes (33,42yrs), which were operationalised for life periods (at birth, childhood [7,11,16yrs], adulthood [23,33,42yrs]) and/or as cumulative lifetime exposure. Path analysis was used to investigate the mediating role of life-course factors in the relationship between parental respiratory disease history and RLH, while adjusting for gender, physical health and asthma history. Results: Within this cohort, 3.3% had a parental respiratory history and 6.1% of offspring had RLH. Parental respiratory history was positively associated with RLH (p=0.033). Maternal smoking, social class (0yrs, 42yrs, lifetime) and occupational exposure were the only factors related to both parental history and RLH. Model fit and mediating pathway testing indicated that, of those, maternal smoking, and social class (42yrs, lifetime) jointly mediated 23% of the parental history-RLH relationship. Conclusion: An association between parental respiratory history and offspring RLH at 45yrs was jointly mediated by maternal smoking and social class indicators, but not by common risk factors like personal smoking history, suggesting the complex inter-relationship between intergenerational and life-course influence on offspring lung health. Implications for policy and/or practice: Beyond smoking history, assessing patient's parental history of respiratory disease may provide an opportunity for early diagnosis and intervention.

B.2 Conference abstract

(Accepted for the 2018 Thoracic Society of Australia and New Zealand conference)

Parental respiratory disease is associated with reduced offspring lung health at age 45 via pathway of maternal and personal smoking

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Introduction:
Familial aggregation of chronic lung conditions may result from a combination of genetic susceptibility and exposure to risk factors throughout life. We used a life-course approach to investigate factors contributing to the relationship between parental respiratory disease history and Reduced Lung Health (RLH) in adulthood using data from the 1958 British Birth Cohort Study.

Methods:
Cohort participants (n=6304) were characterised in terms of RLH (presence of respiratory symptoms at 42yrs and airway obstruction [FEV1/FVC<0.7 at 45yrs]) and parental history of respiratory disease (at offspring age 0,11,16yrs).
Life-course factors evaluated were maternal smoking (0yrs), living with smoker (16,23,33,42yrs), social class (0,7,16,23,33,42yrs), respiratory illness (7,11,16,23,33,42yrs), smoking status (23,33,42yrs), and occupational exposure to dust or fumes (33,42yrs), operationalised for life periods (birth, childhood [7,11,16yrs], adulthood [23,33,42yrs]). Path analysis was used to investigate the mediating role of life-course factors in the relationship between parental respiratory disease history and RLH, adjusting for gender, asthma and recent chest infection.

Results:
Within this cohort, 3.7% had a parental respiratory history and 6.3% of offspring had RLH. Parental respiratory history was positively associated with RLH (p=0.023). Maternal smoking during pregnancy, personal smoking in adulthood, social class (0, 23 and 42yrs) and occupational exposure to dust or fumes were the only factors related to both parental history and RLH. Mediating pathway testing indicated that the sequence through maternal and adulthood smoking contributed most to model fit (indirect effect p=0.015), explaining 30% of the parental history-RLH relationship.

Conclusion:
An association between parental history of respiratory disease and offspring RLH at 45yrs was partly mediated by a sequence of exposure to maternal smoking and being a smoker during their adulthood. A large proportion of the relationship between parental history-RLH remains unexplained by smoking, suggesting that assessing parental history of respiratory disease may provide insights into earlier diagnosis and intervention.

Grant Support:
Australian Government Research Training Program Scholarship (LSK Li)

B.3 Approval to access data

Li, Lok Sze Katrina - liyly041

From: UK Data Service Helpdesk <help@ukdataservice.ac.uk>
Sent: Wednesday, 16 March 2016 1:50 AM
To: Li, Lok Sze Katrina - liyly041
Subject: RE: NCDS Special Licence application - Katrina Li - Project 91545

Dear Katrina,

This is to let you know that we have now received permission to release the NCDS special licence data to you, and the data are now available for download.

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2. Click on the relevant usage/project title, and the study number(s) should be displayed.

3. Click on the download button next to each study number.

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Please note that the special licence data above must only be used for the project specified in your application. In addition, if any of the information you have given in your application changes, for example if you move institutions, you must notify the UK Data Archive/UK Data Service in writing otherwise you may be breaching the terms and conditions of the special licence.

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Best wishes,

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B.4 Characteristics of those with valid lung function test results with those included in the analytic sample

		Sample that participated in 45 year biomedical sweep with valid lung function results (n = 9089)	Analytic sample in the chapter (n = 6304)	P value*
Gender				
	Male	4521 (49.7%)	3085 (48.9%)	0.3290
	Female	4568 (50.3%)	3219 (51.1%)	
Maternal smoke				
	No	5764 (63.4%)	44291 (68.1%)	0.6990
	Yes	2736 (30.1%)	2013 (31.9%)	
	Missing	589 (6.5%)	-	
Childhood asthma				
	No	6938 (76.3%)	4887 (77.5%)	0.3802
	Yes	1949 (21.4%)	1417 (22.5%)	
	Missing	202 (2.2%)	-	
Adulthood onset asthma				
	No	8513 (93.7%)	5906 (93.7%)	1.0000
	Yes	575 (6.3%)	398 (6.3%)	
	Missing	1 (0.0%)	-	
Occupational exposure				
	No	6061 (66.7%)	4375 (69.4%)	0.7928
	Yes	2647 (29.1%)	1929 (30.6%)	
	Missing	381 (4.2%)	-	
Live with smoker in adulthood				
	No	4120 (45.3%)	2777 (44.1%)	0.0862
	Yes	4937 (54.5%)	3527 (55.9%)	
	Missing	32 (0.4%)	-	
SC at 42 years				
	SC 1	3359 (37.0%)	2463 (39.1%)	0.4914
	SC 2	1619 (17.8%)	1240 (19.7%)	0.4062
	SC 3	1488 (16.4%)	1092 (17.3%)	0.6663
	SC 4	1133 (12.5%)	854 (13.5%)	0.7498
	Missing	1490 (16.4%)	655 (10.4%)	-
Personal smoking at 42 years				
	Never smoker	4030 (44.3%)	2965 (47.0%)	0.1447
	Ex- smoker	2661 (29.3%)	1909 (30.3%)	0.8950
	Current smoker	2112 (23.2%)	1429 (22.7%)	0.0630
	Missing	286 (3.1%)	1 (0.0%)	-
Lung function (mean ± SD)				
	FEV_1	3.23 ± 0.87	3.25 ± 1.05	0.1980
	FVC	4.19 ± 1.06	4.21 ± 1.05	0.2479

SC = social class (SC1 = professional/managerial; SC2 = unskilled non-manual; SC3 = skilled manual; SC4 = unskilled manual); SD = standard deviation; FEV_1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vial Capacity; *calculated by difference in proportion test or independent sample T-test as appropriate

B.5 Summary of raw data of cohort age in relation to onset of parental respiratory disease

Cohort age in relation to onset of parental respiratory illness									Total no. of parental respiratory history
Cohort age	Pre-birth/ at birth n (%)	1 yrs n (%)	1-4 yrs n (%)	5-6 yrs n (%)	7-10 yrs n (%)	11-14 yrs n (%)	15-16 yrs n (%)	Unknown n (%)	
Mother reported positive respiratory disease history									
Sweep 0	12 (100%)	-	-	-	-	-	-	-	12
Sweep 2	20 (41%)	3 (6%)	5 (10%)	6 (12%)	15 (31%)	-	-	-	49
Sweep 3	31 (61%)			11 (22%)		5 (10%)	3 (6%)	1 (2%)	51
Father reported positive respiratory disease history									
Sweep 0	-	-	-	-	-	-	-	-	-
Sweep 2	(not an option)	30 (36%)	3 (4%)	4 (5%)	7 (8%)	-	-	39 (47%)	83
Sweep 3	34 (44%)			20 (26%)		13 (17%)	7 (9%)	4 (5%)	78
Total parental (mother + father) positive respiratory disease history									
Sweep 0 - 3	138 (51%)			63 (23%)		18 (7%)	10 (4%)	44 (16%)	273

Yrs = years

Note: This table contains a summary of the raw data extracted from sweep 0 (cohort age 0), sweep 2 (cohort age 11) and sweep 3 (cohort age 16). The total number of parents with respiratory disease history includes over-lap across different sweeps, duplicates were removed in the final analysis presented in Chapter 4 (1958 study). The sole purpose of this appendix is to demonstrate the onset of parental respiratory disease mostly occur during the cohort member's early life.

B.6 Complete case sample (n=4,920)

Table of cohort member characteristics

Cohort member characteristics	Total N = 4,920	No AO/ respiratory symptoms n = 4,625	AO and respiratory symptoms n = 295	P value#
Gender n(%)				
Male	2377 (48.3%)	2238 (48.4%)	139 (47.1%)	0.672
Female	2543 (51.7%)	2387 (51.6%)	156 (52.9%)	
Positive parental respiratory disease history n(%)	163 (3.3%)	146 (3.2%)	17 (5.8%)	0.024
One parent with respiratory history n	160	143	17	
Both with respiratory history n	3	3	-	
Mother's age at birth (years)	27.6 +/- 5.5	27.6 +/- 5.5	27.4 +/- 5.5	0.526
Mean +/- SD (age range)	16- 46	16 - 46	17 - 43	
In utero/ at birth				
Low birth weight n(%)	237 (4.8%)	219 (4.7%)	18 (6.1%)	0.288
Born preterm' n(%)	170 (3.5%)	157 (3.4%)	13 (4.4%)	0.356
Mother smoking during pregnancy n(%)	1529 (31.1%)	1415 (30.6%)	114 (38.6%)	0.004
Social class at birth n(%)				
SC1	989 (20.1%)	938 (20.3%)	51 (17.3%)	0.528
SC2	515 (10.5%)	480 (10.4%)	35 (11.9%)	
SC3	2459 (50.0%)	2312 (50.0%)	147 (49.8%)	
SC4	957 (19.5%)	895 (19.4%)	62 (21.0%)	
Childhood (0-16 years)				
Passive smoke exposure n(%)	4616 (93.8%)	4346 (94.0%)	270 (91.5%)	0.091
Had asthma n(%)	1127 (22.9%)	1016 (22.0%)	111 (37.6%)	0.000
Had pneumonia' n(%)	215 (4.4%)	193 (4.2%)	22 (7.5%)	0.007
Adulthood (23-45 years old)				
Passive smoke exposure n(%)	2714 (55.2%)	2516 (54.4%)	198 (67.1%)	0.000
Smoker in adulthood n(%)				
Never	3002 (61.0%)	2896 (62.6%)	106 (35.9%)	0.000
Ever	1080 (22.0%)	1021 (22.1%)	59 (20.0%)	
Persistent	838 (17.0%)	708 (15.3%)	130 (44.1%)	
Adult onset asthma n(%)	306 (6.2%)	248 (5.4%)	58 (19.7%)	0.000
Biomass Exposure' n(%)	629 (12.8%)	574 (12.4%)	55 (18.6%)	0.002
Ever occupation exposure	1518 (30.9%)	1408 (30.4%)	110 (37.3%)	0.014
Social class at 23 years n(%)				
SC1	842 (17.1%)	811 (17.5%)	61 (10.5%)	0.000
SC2	1857 (37.7%)	1760 (38.1%)	97 (32.9%)	
SC3	1249 (25.4%)	1150 (24.9%)	99 (33.6%)	
SC4	972 (19.8%)	904 (19.5%)	68 (23.1%)	

Cohort member characteristics	Total N = 4,920	No AO/ respiratory symptoms n = 4,625	AO and respiratory symptoms n = 295	P value#
Social class at 42 years n(%)				
SC1	2011 (40.9%)	1930 (41.7%)	81 (27.5%)	0.000
SC2	1221 (24.8%)	1144 (24.7%)	77 (26.1%)	
SC3	907 (18.4%)	836 (18.1%)	71 (24.1%)	
SC4	781 (15.9%)	715 (15.5%)	66 (22.4%)	
Chest infect last 3 weeks prior to lung function test n(%)	441 (9.0%)	405 (8.8%)	36 (12.2%)	0.045
Has respiratory symptoms at 42 years n(%)	1342 (27.3%)	1047 (22.6%)	295 (100%)	0.000
Airflow obstruction at 45 years n(%)	714 (14.5%)	419 (9.1%)	295 (100%)	0.000

AO = airway obstruction; SC = social class (SC1 = professional/managerial; SC2 = unskilled non-manual; SC3 = skilled manual; SC4 = unskilled manual); SD = standard deviation
'based on mean of ten imputed datasets
#calculated by Chi square or independent sample t-test as appropriate

Complete case analysis of final model

	(Base model) (parental history → cohort lung health) Estimate (95% CI)	Model 1 (smoking variables only) Estimate (95%CI)
Total effect	0.221 (-0.067 , 0.509)	0.250 (-0.066,0.566)
Total indirect effect	- - -	0.072 (-0.016,0.160)
Specific indirect Maternal smoke	-	0.019 (-0.01 , 0.048)
Adulthood smoking	-	0.044 (-0.038,0.126)
Maternal smoke → adulthood smoking	-	0.010* (0.002,0.018)
Fit indices		
RMSEA	-	0.013
CFI	-	0.978
TLI	-	0.947

*p < 0.05; **p<0.01; SC = Social Class; CI = Confidence Interval; RMSEA = Root-Mean-Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index
adjusted for gender, childhood and adulthood onset asthma and recent chest infection

Appendix C: Pilot study

C.1 Conference abstract

(Presented at the 2017 Thoracic Society of Australia and New Zealand conference)

The story of your life and lung health: pilot study of a life history approach

LSK Li[1],C Paquet[2],K Johnston[1],MT Williams[3]

[1]School of Health Sciences, International Centre for Allied Health Evidence, Sansom Institute for Health Research, University of South Australia, SA 5000
[2]School of Health Sciences, Centre for Population Health Research, Sansom Institute for Health Research, University of South Australia, SA 5000
[3]School of Health Sciences, Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health research, University of South Australia, SA 5000

Introduction/Aim:
Adult lung health is likely to be a result of intergenerational combinations of genetics, environmental exposures and lifestyle factors across the lifespan. This pilot study aimed to assess acceptability of a life history instrument designed to capture life course related risk factors for lung disease in parents and offspring.

Methods:
Proband participants (>60years) likely to have a range of chronic health conditions were recruited from a single university-based health clinic and provided with an information package to pass on to their adult children. Participants were asked to complete a life history questionnaire as a memory aid in preparation for a single appointment, during which a researcher gathered more detail on key life events; family/cohabitation structure, potential lung disease risk exposures (e.g. smoking, occupation). One week following the assessment, participants were provided with a copy of their completed life history report and asked to provide feedback on the accuracy of their report, the life history instrument and the study process. Paired data were compared.

Results:
Thirty-one participants (proband group n=26, mean age 76.3years; offspring group n=5, mean age 51.2years) completed the study, with five parent-offspring pairs and two husband-wife pairs. The mean time to complete the life history calendar during the appointment was 37.5±10.8 minutes. The life history questionnaire was considered as a useful preparation tool by 86% of participants and 97% of participants considered the report to be an accurate description of their life. Eleven participants noted minor inaccuracies in their report (e.g. incorrect year or suburb of residence). No participants reported feeling uncomfortable using the life history instrument. Most discrepancies identified in data provided by pairs of participants were categorised as temporal and/or geographic variations.

Conclusion:
The life history instrument appeared acceptable to collect relevant environment and life course information relevant to lung health.

C.2 Conference abstract

(Presented at the 2017 European Respiratory Society international congress)

A life history calendar to map lung health risk exposures: pilot study

LSK Li[1],C Paquet[2],K Johnston[1], P Frith, MT Williams[3]

[1]School of Health Sciences, International Centre for Allied Health Evidence, Sansom Institute for Health Research, University of South Australia, SA 5000
[2]School of Health Sciences, Centre for Population Health Research, Sansom Institute for Health Research, University of South Australia, SA 5000
[3]School of Health Sciences, Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health research, University of South Australia, SA 5000

Introduction:
Exposure to various factors over a person's life course may have an impact on their long term lung health. This study aimed to pilot an instrument designed to map life course exposures relevant to lung health over the lifespan of parents and offspring.

Methods:
Proband participants (>60y) were recruited from a single university-based health clinic and were given an information package to pass on to their adult offspring. At a single appointment, participants completed an interviewer-assisted life history calendar designed to capture exposures to risk factors relevant to lung health (birth weight, prematurity, childhood respiratory illness, asthma, exposure to passive/personal smoking, environmental/occupational exposure). One week after receiving an individualised life history report, feedback on the accuracy was sought via a phone call. Time to complete, perceived accuracy, and consistency between proband and adult offspring pairs were analysed descriptively.

Results:
31 participants (proband n=26, mean age 76y, response rate 40%; offspring n=5, mean age 51y, response rate 33%) completed the study. Time to complete the life history calendar differed between proband (mean: 39 ± 10, range: 23 – 63min) and offspring groups (mean: 30 ± 11, range: 18 – 41min). 97% of participants perceived their report to be accurate. Few discrepancies existed between the five parent/offspring pairs (birth weight n=3, and for different points of their life: place of residence n=3, passive smoke exposure n=2, biomass exposure n=4).

Conclusion:
All participants were able to provide details across their lives on exposures relevant to lung health. The instrument appears to be an appropriate tool to collect life history data.

C.3 Ethics approval

Li, Lok Sze Katrina - liyly041

From: no_reply@unisa.edu.au
Sent: Monday, 23 May 2016 8:23 AM
To: humanethics@unisa.edu.au; Li, Lok Sze Katrina - liyly041; Marie Williams
Subject: Human Ethics: Application approved

Dear Applicant

Re: Ethics protocol "The story of your life and lung health: a pilot study" (Application ID: 0000035431)

Thank you for submitting your ethics protocol for consideration. Your protocol has been considered by the E2 Committee Review Group.

I am pleased to advise that your protocol has been granted ethics approval and meets the requirements of the National Statement on Ethical Conduct in Human Research.

Please note that the E2 Committee Review Group's decision will be reported to the next meeting of the Human Research Ethics Committee for endorsement.

Please regard this email as formal notification of approval.

Ethics approval is always made on the basis of a number of conditions detailed at http://www.unisa.edu.au/res/forms/docs/humanresearchethics_conditions.doc; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at http://www.unisa.edu.au/res/ethics/default.asp

Please note, if your project is a clinical trial you are required to register it in a publicly accessible trials registry prior to enrolment of the first participant (e.g. Australian New Zealand Clinical Trials Registry http://www.anzctr.org.au/) as a condition of ethics approval.

Best wishes for your research.

Executive Officer
UniSA's Human Research Ethics Committee
CRICOS provider number 00121B

This is an automated email and cannot be replied to. Please direct your query to humanethics@unisa.edu.au.

Li, Lok Sze Katrina - liyly041

From: Human Ethics <humanethics@unisa.edu.au>
Sent: Friday, 8 July 2016 10:52 AM
To: Li, Lok Sze Katrina - liyly041
Cc: Marie Williams; Kylie Johnston; Catherine Paquet
Subject: RE: Amendment Request - Ethics Protocol 0000035431-Approved
Attachments: HREC conditions.pdf

Dear Katrina,

Re: Ethics Protocol 0000035431 The story of my life and lung health: a pilot study

Thank you for submitting an ethics protocol amendment request. I am pleased to advise that the Chairperson of the University's Human Research Ethics Committee has assessed and **approved** your request to send all participants a copy of their COPD Assessment Test results with a simple explanation of what the results mean. For participants who had a high score in this test, the researchers will encourage them to take the test results to their GP and seek advice about any respiratory symptoms that they may be experiencing. (as detailed in your email dated 6/7/2016).

Please regard this email as formal notification of approval.

Ethics approval is always made on the basis of a number of conditions detailed in the attachment; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at http://www.unisa.edu.au/res/ethics/default.asp .

Best wishes for your research.

Kind regards,

Liz

Elizabeth Collins | Ethics and Biosafety Officer | Research and Innovation Services
University of South Australia | Mawson Lakes Campus | Mawson Lakes SA 5095
Ph: +61 8 8302 3723 | Fax: +61 8 8302 3723 | Email: Liz.Collins@unisa.edu.au

University of South Australia

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University of South Australia

C.4 Information sheet for probands

Research Study: **The story of your life and lung health**

Researchers: Miss Katrina Li, A Prof Marie Williams, Dr Kylie Johnston, Dr Catherine Paquet, Prof Peter Frith

Purpose of this study

Apart from smoking, there are many other factors during a person's life that can have an impact on lung health such as being born early, having lung problems as a child or where you work. This study will trial a way to collect information relevant to lung health through different stages of one's life. It is called the "**Story of My Life**" calendar. We are interested in testing this method on **pairs of parents and adult children**. This will allows us to improve this method before it is used in a larger study.

Invitation to join the study

We would like to recruit **pairs of parents and adult children to join this study**. You are invited to join this study if you:

(1) are aged 60 years or older, AND

(2) have one or more adult children living in Adelaide

People with or without lung conditions are all welcome to participate. You may join the study regardless of whether your offspring also joins. Please note priority will be given to pairs of parents and adult children.

If you are interested in joining this study, please pass the information package onto your adult children. Your adult children will be asked to return a reply-slip indicating whether they would like to know more about the study.

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way. Also, you may withdraw from the study at any time after you have started.

What is involved if I join this study?

You will be invited to attend an appointment at the podiatry clinic at the University of South Australia (based at City East Campus, Frome Road, Adelaide).

Before the appointment: You will complete a "Story of My Life" calendar questionnaire (30 mins max)

During the appointment: You will complete three questionnaires about your health and complete the "Story of My Life" calendar interview with a researcher) (1.5 hours max)

After the appointment (one week later): You will receive a copy of your completed "Story of My Life" calendar by post. A researcher will telephone you to gain your comments or suggestions to help us improve the use of the "Story of my Life" calendar (15 mins max).

Possible benefits and risks of being in this study

There are no costs associated with participating in this research project. Each participant will be reimbursed $25 for the time taken to participate in this research project.

There will not be any direct benefits to you from joining this study. Results from this study will be used to improve the "Story of my Life" calendar questionnaire and interview process before it is used in a larger study. The risks associated with participation in this study are low. Responding to questions about health, and life experiences may possibly raise questions or concerns for some people. If this did happen, researchers would encourage you to contact your usual general practitioner to discuss any specific questions or concerns.

Your privacy: All personal information will remain confidential and no information which could lead to identification of any individual will be released. All study information will be securely stored (in locked School Office) at the University of South Australia for 15 years. The research will be conducted according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research 2007.

This project has been approved by the University of South Australia's Human Research Ethics Committee. If you have any ethical concerns about the project or questions about your rights as a participant please contact the Executive Officer of this Committee, Tel: 8302 3118; email: vicki.allen@unisa.edu.au

Thank you for your time and for consideration to participate in this study

Contact the researchers:

Miss Katrina Li (8302 1284 or email: lok_sze_katrina.li@mymail.unisa.edu.au)
A Prof Marie Williams (8302 1153 or email: marie.williams@unisa.edu.au)

University of South Australia

C.5 Information sheet for adult offspring

Research Study: **The story of your life and lung health**

Researchers: Miss Katrina Li, Associate Professor Marie Williams, Dr Kylie Johnston, Dr Catherine Paquet, Professor Peter Frith

Purpose of this study

There are many factors during a person's life that can have an impact on lung health such as being born early, having lung problems as a child, being exposed to smoke or where you work. This study will trial a way to collect information relevant to lung health through different stages of one's life. It is called the **"Story of My Life"** calendar. We are interested in testing this method on **pairs of parents and adult children**. This will allows us to improve this method before it is used in a larger study.

Invitation to join the study

People aged 60 years or over are the first contact point for this study, so you will have received this study information via one of your parents. You can be involved if you are 18 years of age or over. People with or without lung conditions are all welcome to participate. You may join the study regardless of whether your parent also joins.

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way. Also, you may withdraw from the study at any time after you have started.

What is involved if I join this study?

You will be invited to attend an appointment at the podiatry clinic at the University of South Australia (based at City East Campus, Frome Road, Adelaide).

Before the appointment: You will have the opportunity to see and fill in the "Story of My Life" calendar questionnaire (30 mins max)
During the appointment: You will complete three questionnaires about your health and a researcher will work through the "Story of My Life" calendar with you (1.5 hours max)
After the appointment (one week later): You will receive a copy of your completed "Story of My Life" calendar by post. A researcher will telephone you to gain your comments or suggestions to help us improve the use of the "Story of my Life" calendar (15 mins max).

Possible benefits and risks of being in this study

There are no costs associated with participating in this research project. Each participant will be reimbursed $25 for the time taken to participate in this research project.

There will not be any direct benefits to you from joining this study. Results from this study will be used to improve the "Story of my Life" calendar questionnaire and interview process before it is used in a larger study. The risks associated with participation in this study are

low. Responding to questions about health, and life experiences may possibly raise questions or concerns for some people. If this did happen, researchers would encourage you to contact your usual general practitioner to discuss any specific questions or concerns.

Your privacy: All personal information will remain confidential and no information which could lead to identification of any individual will be released. All study information will be securely stored (in locked School Office) at the University of South Australia for 15 years. The research will be conducted according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research 2007.

This project has been approved by the University of South Australia's Human Research Ethics Committee. If you have any ethical concerns about the project or questions about your rights as a participant please contact the Executive Officer of this Committee, Tel: 8302 3118; email: vicki.allen@unisa.edu.au

Thank you for your time and for consideration to participate in this study

We have enclosed a reply paid envelope and a response option.

If you WOULD LIKE to hear more about or participate in this study please tick the "Please contact me about this study" option and provide a phone number and preferred time for us to contact you. Or you could contact Ms Katrina Li on the number provided below.

If you would NOT like to known more or participate in this study, it would be helpful if you could tick the "I would NOT like to know more or participate in this study" option.

Contact the researchers:
Miss Katrina Li (8302 1284 or email: lok_sze_katrina.li@mymail.unisa.edu.au)
A Prof Marie Williams (8302 1153 or email: marie.williams@unisa.edu.au)

REPLY SLIP: Please send back in enclosed reply paid envelope (no stamp required)

Study Title: **The story of your life and lung health**

☐ Please contact me about this study

☐ I would NOT like to know more or participate in this study

My parent's name: _____

My Name: _____

Telephone number: _____

Email address: _____

C.6 The Story of My Life calendar (self-completed)

Story Of My Life calendar questionnaire

Where and whom we live with during our lives may have an influence on our health and our behaviours. The purpose of this questionnaire is to help us learn more about factors during your life that may have influenced your lung health.
In this Story of My Life calendar questionnaire you will be asked to write down some information about various phases of your life. Please complete this before your appointment and bring it to your appointment.
We will use the information you provided here, step through each phase of your life and fill in further details during the appointment.

Early life Before you started school	School life Kindergarten to high school	Life after school Working life	Life after work Retirement

Instructions: Please work through the list of questions and provide an answer. Try to complete the questionnaire. If you cannot remember or don't know an answer to a question, please write – Cannot recall.

Where possible, try to complete the Story of My Life calendar questionnaire in one go.

Please record the time you start doing this questionnaire: _____

Early life

When were you born? (in year) _____

What was your birth weight? _____

Were you born early? (i.e. premature) _____

Where did you live when you were born? (suburb/town/city) _____

Where did you live mostly before you started school? (suburb/town/city) _____

Whom did you live with? (mother /father/grandparents/brothers and sisters/ other (please specify)) _____

_____

Did you have any lung problems as a child? (e.g. chest infections, asthma, pneumonia) _____

If yes, what lung problems did you have? _____

Were you hospitalised for this? _____

School life

How many years of schooling have you completed?

What is your highest level of school based attainment/qualification achieved?

	Kindergarten/ preschool	Primary	High school
When did you start school?			
Where did you **mostly** go to school? (suburb/town/city)			
When did you leave/finish school?			
Where did you **mostly** live during this time? (suburb/town /city)			
Did you regularly participate in sports or fitness programmes?			
Did you have any lung problems when you were in school?			
If yes, what lung problems did you have?			
Were you hospitalised for this?			

Life after school

Which of the following best describes what you did when you left school? (please tick the box)

1. Further education (university, TAFE, trade school etc.) □
2. Paid apprenticeship □
3. Military service □
4. Entered the paid workforce □
5. Home maker (married or provided care to relative) □

Further education

If you did further education after high school, what did you study? _____

Where did you do it? _____

When did you start? _____

When did you finish? _____

Where did you **mostly** live during this time? _____

_____

Work

When did you start paid work? _____

Please list the jobs that you have worked in for over 1 year.
*you do not have to list these in the order in which you were employed

_____

_____

_____

Where did you live during this time? _____

_____

_____

Personal

If you are married, when did you get married? _____

Where did you live during this time? _____

_____

Did you have any lung problems after you have finished school? _____

If yes, what lung problems did you have? _____

Were you hospitalised for this? _____

Have you ever smoked? _____

If yes, when did you start smoking? _____

How much did/ do you smoke?(average cigarettes/pipes per day) _____

For how long? _____

Do/have you ever lived with someone who smokes? _____

If yes, for how long? _____

Do you think your parents have any health issues? _____

Do you think you have any health issues? _____

Have your doctor told you that you have any health issues? _____

Have you ever seen a doctor for any health issues? _____

_____

_____

For parents only

How many children do you have? _____

Were any of your children born early? _____

What was your child/children's weight at birth? _____

Did you child have any lung problems when he/she was young? E.g. asthma, pneumonia, chest infections etc. _____

Please record the time you finished this questionnaire:

Thank you for completing the questionnaire!

Please remember to bring it along to your schedule appointment

C.7 Consent form for Pilot study

UniSA Research and Innovation Services

Human Research Ethics Committee
CONSENT FORM

This project has been approved by the University of South Australia's Human Research Ethics Committee. If you have any ethical concerns about the project or questions about your rights as a participant please contact the Executive Officer of this Committee, Tel: +61 8 8302 3118; Email: humanethics@unisa.edu.au

SECTION 1: CONTACT AND PROJECT DETAILS

Researcher's Full Name:	Ms Katrina Li, Associate Professor Marie Williams, Dr Kylie Johnston, Dr Catherine Paquet, Professor Peter Frith
Contact Details:	Phone: 8302 1284 email: lok_sze_katrina.li@mymail.unisa.edu.au
Supervisor's Full Name:	Associate Professor Marie Williams
Contact Details:	Phone: 8302 1153 email: marie.williams@unisa.edu.au
Protocol Number:	Application ID: 0000035431
Project Title:	The story of your life and lung health

SECTION 2: CERTIFICATION

Participant Certification

In signing this form, I confirm that:

- I have read the Participant Information Sheet and the nature and purpose of the research project has been explained to me. I understand and agree to take part.
- I understand the purpose of the research project and my involvement in it.
- I understand that I may withdraw from the research project at any stage and that this will not affect my status now or in the future.
- I understand that while information gained during the study may be published, I will not be identified and my personal results will remain confidential, unless required by law.
- I understand the statement in the information sheet concerning payment to me for taking part in the study.
- I understand that my data will be stored in electronic or paper format. All study information will be securely stored (in locked School Office or secure server space) at the University of South Australia for 15 years.

[NOTE: Participants under the age of 18 normally require parental consent to be involved in research. If appropriate, the consent form should allow for those under the age of 18 to agree to their involvement and for a parent to give consent.]

Participant Signature	Printed Name	Date

Researcher Certification

I have explained the study to subject and consider that he/she understands what is involved.

Researcher Signature	Printed Name	Date

C.8 COPD Assessment Test

Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

COPD Assessment Test and the CAT logo is a trade mark of the GlaxoSmithKline group of companies.
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Last Updated: February 24, 2012

C.9 Chronic Respiratory Questionnaire

My Flintbox Public Home My Projects My Groups Licenses

Receipt for Order #11492
Order placed

Order Details

Order Order #11492
Order Date Oct 31, 2013 6:06 PM
Offering Price $ 150.00
Offering Handling Fee $ 0.00
Project Chronic Respiratory Questionnaire (CRQ)
Offered By McMaster University
Contact Information None

Cart

	Quantity	Price	Sub Total
CRQ-SAS for use in an Academic Research study Agreed Licenses: CRQ-SAS Academic Research license agreement (Revision: 1) Oct 31, 2013 6:06 PM	1	150.00	150.00
Total			150.00 USD

Components

Component	Download
CRQ-SAS for use in an Academic Research study	Download

Address Information

Billing Address Judy Barnes
City East Campus, Health Sciences
Centenary lvl 8-Reception
Cnr Frome Rd & North Tce
SA 5000
Adelaide, South Australia
Australia 5000
Phone: +61 8 8302 1213
Fax: +61 8 8302 2853

Shipping Address Judy Barnes
City East Campus, Health Sciences
Centenary lvl 8-Reception
Cnr Frome Rd & North Tce
SA 5000
Adelaide, South Australia
Australia 5000
Phone: +61 8 8302 1213
Fax: +61 8 8302 2853

Payment Details

Payment Type Credit Card - Visa

First Name on Card Judy
Last Name on Card Barnes
Card Number XXXXXXXXXXXX2961
Card Expiration Date Dec 1, 2015

Payment Status Paid

Delivery Information

No Delivery Information

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McMaster University
Canada

Chronic Respiratory Questionnaire

Self-Administered Standardized Format (CRQ-SAS)

First Administration

CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date ☐☐ DAY ☐☐ MONTH ☐☐☐☐ YEAR

CHRONIC RESPIRATORY QUESTIONNAIRE -SAS- FIRST ADMINISTRATION 1(10)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue on the next page.

CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date ☐☐ DAY ☐☐ MONTH ☐☐☐☐ YEAR

CRQ-SAS- 1ST ADMINISTRATION 2(10)

Below is a list of activities which make some people with lung problems feel short of breath.

For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1 Feeling emotional such as angry or upset	1	2	3	4	5	6	7	8
2 Taking care of your basic needs (bathing, showering, eating or dressing)	1	2	3	4	5	6	7	8
3 Walking	1	2	3	4	5	6	7	8
4 Performing chores (such as housework, shopping groceries)	1	2	3	4	5	6	7	8
5 Participating in social activities	1	2	3	4	5	6	7	8

Please continue to the next page.

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Date ☐☐ DAY ☐☐ MONTH ☐☐☐☐ YEAR

CRQ-SAS- 1ST ADMINISTRATION 3(10)

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

1.	All of the time	☐
2.	Most of the time	☐
3.	A good bit of the time	☐
4.	Some of the time	☐
5.	A little of the time	☐
6.	Hardly any of the time	☐
7.	None of the time	☐

(Place an "x" in one box only)

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

1.	All of the time	☐
2.	Most of the time	☐
3.	A good bit of the time	☐
4.	Some of the time	☐
5.	A little of the time	☐
6.	Hardly any of the time	☐
7.	None of the time	☐

(Place an "x" in one box only)

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 4(10)

8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS?**

1. Extremely tired ☐
2. Very tired ☐
3. Quite a bit of tiredness ☐
4. Moderately tired ☐
5. Somewhat tired ☐
6. A little tired ☐
7. Not at all tired ☐

(Place an "x" in one box only)

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

(Place an "x" in one box only)

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 5(10)

10. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

(Place an "x" in one box only)

11. How much energy have you had in the **LAST 2 WEEKS**?

1. No energy at all ☐
2. A little energy ☐
3. Some energy ☐
4. Moderately energetic ☐
5. Quite a bit of energy ☐
6. Very energetic ☐
7. Full of energy ☐

(Place an "x" in one box only)

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 6(10)

12. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

(Place an "x" in one box only)

13. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

(Place an "x" in one box only)

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 7(10)

14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

(Place an "x" in one box only)

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

(Place an "x" in one box only)

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 8(10)

16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐ (Place an "x" in one box only)
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐ (Place an "x" in one box only)
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date ☐☐ DAY ☐☐ MONTH ☐☐☐☐ YEAR

CRQ-SAS- 1ST ADMINISTRATION 9(10)

18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1. Very dissatisfied, unhappy most of the time ☐
2. Generally dissatisfied, unhappy ☐
3. Somewhat dissatisfied, unhappy ☐
4. Generally satisfied, pleased ☐
5. Happy most of the time ☐
6. Very happy most of the time ☐
7. Extremely happy, could not be more satisfied or pleased ☐

(Place an "x" in one box only)

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

(Place an "x" in one box only)

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDIZED ACTIVITIES - "CRQ-SAS"

Date DAY MONTH YEAR

CRQ-SAS- 1ST ADMINISTRATION 10(10)

20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐ (Place an "x" in one box only)
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

THANK YOU

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C.10 Sports Medicine Australia (SMA) Pre-exercise screening

Pre-exercise screening system 2005
Sports Medicine Australia (SMA) - Stage 1 questionnaire

Name | Age | Gender M F
Address | Phone | Date

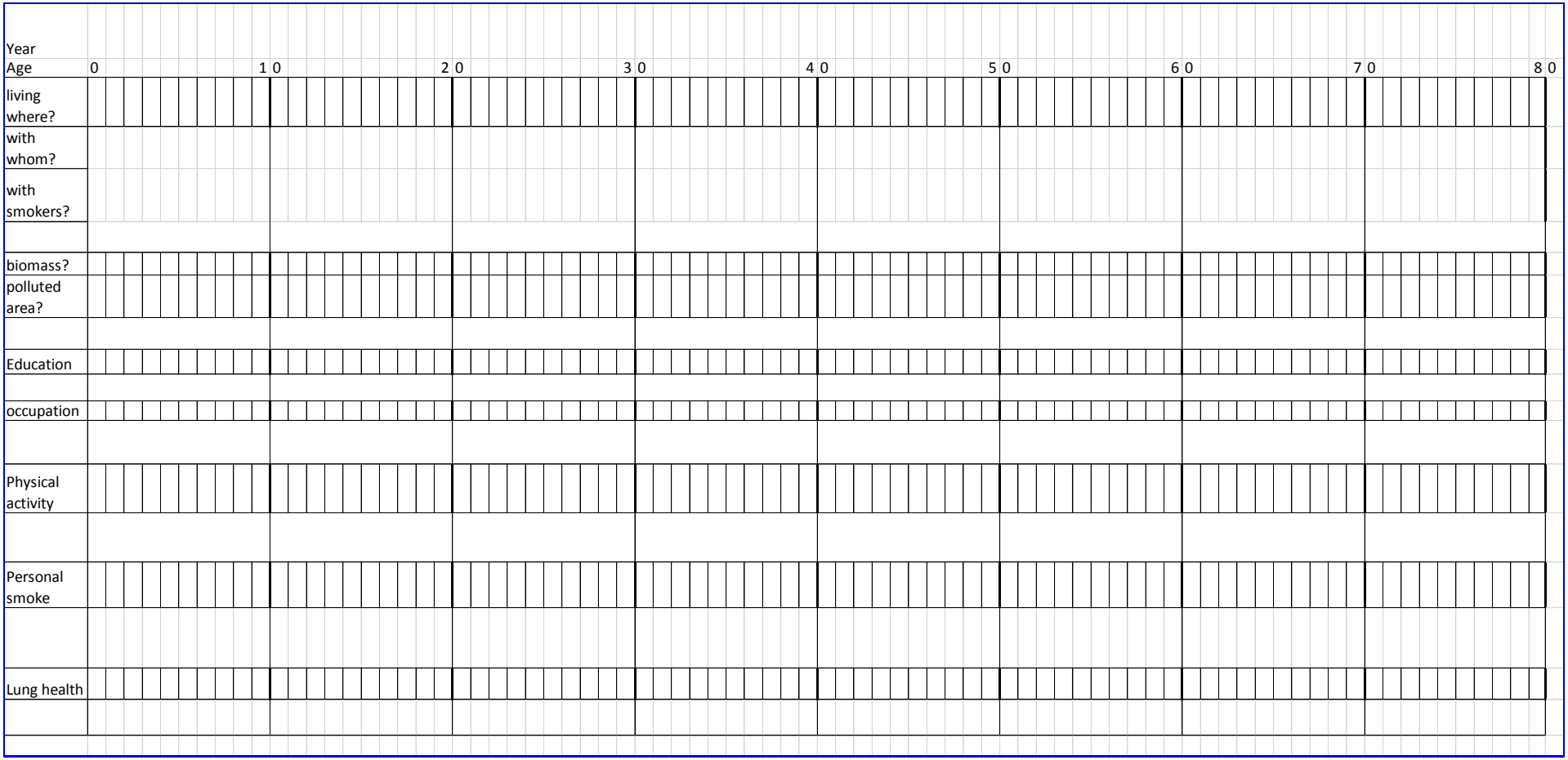
1	Have you ever had a heart attack, coronary revascularisation surgery or a stroke ?	No	Yes
2	Has your doctor ever told you that you have heart trouble or vascular disease ?	No	Yes
3	Has your doctor ever told you that you have a heart murmur ?	No	Yes
4	Do you ever suffer from pains in your chest, especially with exercise ?	No	Yes
5	Do you ever get pains in your calves, buttocks or at the back of your legs during exercise which are not due to soreness or stiffness ?	No	Yes
6	Do you ever feel faint or have spells of severe dizziness, particularly with exercise ?	No	Yes
7	Do you experience swelling or accumulation of fluid about the ankles ?	No	Yes
8	Do you ever get the feeling that your heart is suddenly beating faster, racing or skipping beats, either at rest or during exercise ?	No	Yes
9	Do you have chronic obstructive pulmonary disease, interstitial lung disease, or cystic fibrosis?	No	Yes
10	Have you ever had an attack of shortness of breath that developed when you were not doing anything strenuous, at any time in the last 12 months ?	No	Yes
11	Have you ever had an attack of shortness of breath that developed after you stopped exercising, at any time in the last 12 months ?	No	Yes
12	Have you ever been woken at night by an attack of shortness of breath, at any time in the last 12 months ?	No	Yes
13	Do you have diabetes [IDDM or NIDDM] ? If so, do you have trouble controlling your diabetes?	No	Yes
14	Do you have any ulcerated wounds or cuts on your feet that do not seem to heal?	No	Yes
15	Do you have any liver, kidney or thyroid disorders?	No	Yes
16	Do you experience unusual fatigue or shortness of breath with usual activities?	No	Yes
17	Is there any other physical reason or medical condition, or are you taking any medication(s) which could prevent you from undertaking an exercise program, or that you are concerned about? #	No	Yes

NOTES:

Some of these conditions might include a history of blood clotting, osteoporosis, bone fractures or serious musculoskeletal disorders, or if they have recently lost a large amount of body mass without trying to. Other types of conditions might include psychiatric disorders, later-stage pregnancy or those with a history of health problems during pregnancy. Those people taking medication(s) for medical conditions listed may also need medical clearance.

Also, if any one or more of the risk factors [below] are extreme then the health and fitness professional should use professional judgement as to whether medical clearance may be required.

C.11 Template for SOMLc



Note: The template was printed on A3 size paper for all participant appointments.

Appendix D: Feasibility study

D.1 Conference abstract

(Accepted for the 2018 Thoracic Society of Australia and New Zealand conference)

Recruiting adult offspring of people with COPD to explore intergenerational lung health: feasibility study

LSK Li[1], C Paquet[2], K Johnston[1],P Frith[1], MT Williams[3]

[1]School of Health Sciences, Sansom Institute for Health Research, University of South Australia, SA 5000
[2] School of Health Sciences, Centre for Population Health Research, Sansom Institute for Health Research, University of South Australia, SA 5000
[3] School of Health Sciences, Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health research, University of South Australia, SA 5000

Introduction/Aim:
Parental history of COPD increases the likelihood of the same condition occurring in their adult offspring. Despite this, familial associations have not generally been a focus of early examination of lung health. Proband-initiated recruitment is a screening/case-finding strategy used to recruit family members of people with conditions that have well-known genetic components. This study aimed to test the feasibility of using this recruitment method to investigate lung health in adult offspring of parents diagnosed with COPD.

Methods:
People with confirmed COPD (proband) were identified and contacted by mail from four hospital/clinic databases or face-to-face during a pulmonary rehabilitation program. Ethical considerations required that interested probands be invited to pass on study information to their adult offspring, who if interested, could then contact the researchers. Any comments volunteered by potential participants were recorded.

Results:
645 proband were contacted through mail (n= 546) or face-to-face (n=99), resulting in four offspring recruited (1% offspring response rate).
Fifty-eight (11%) proband invited by mail made contact with the researcher; 16 agreed to pass information on to their adult offspring and four offspring consented to participate.
Of those approached face-to-face, forty-one (41%) eligible proband indicated interest in the study. One contacted the researcher regarding passing information onto their adult offspring, who later declined to participate.
Common reasons that proband (n=74) declined to pass information onto their offspring include: offspring lives interstate/overseas (39%), no offspring (28%), perception that their offspring are too busy (14%) or would not be interested (7%).

Conclusion:
Low recruitment of adult offspring by contacting people with diagnosed COPD indicate that this process was not feasible to investigate offspring exposures and lung health. Some known parent-related barriers were identified that include possible low prioritisation of lung health as an issue but offspring-related barriers remain unknown.

Grant Support:
Australian Government Research Training Program (LSK Li); Physiotherapy Research Foundation seeding grant.

D.2 Ethical approval

Approval from Southern Adelaide Local Health Network (SALHN) HREC

Office for Research

Flinders Medical Centre / The Flats F6/F8
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

Final approval for ethics application

You are reminded that this letter constitutes **ethical** approval only. **Ethics approval is one aspect of the research governance process**.
You must not commence this research project at any SA Health sites listed in the application until a Site Specific Assessment (SSA), or Access Request for data or tissue form has been authorised by the Chief Executive or delegate of each site.

18 July 2016

Dr Marie Williams
School of Health Sciences
University of South Australia
GPO Box 2471
ADELAIDE SA 5001

Dear Dr Williams

The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) have reviewed and provided ethical approval for this application which appears to meet the requirements of the *National Statement on Ethical Conduct in Human Research.*

Application Number: OFR # 523.15 - HREC/15/SAC/515

Title: Lung health in adult children of people with Chronic Obstructive Pulmonary Disease

Chief investigator: Dr Marie Williams

Approval Date: 13 July 2016

Approval Period: 13 July 2016 to 13 July 2020

Public health sites approved under this application:

- Flinders Medical Centre
- Repatriation General Hospital

The below documents have been reviewed and approved:

- General Research Application form v4 dated 15th June 2016
- Head of Department Support Letter – Dr Jeff Bowden
- Head of Department Support Letter – Professor Roger Eston dated 01 April 2016
- Participant Information Sheet/Consent Form (for COPD Patients v6 dated 15 June 2016
- Participant Information Sheet/Consent Form (for adult children) v6 dated 15 June 2016
- Investigator Confirmation – Katrina Li dated 19 February 2016
- Investigator Confirmation – Kylie Johnston dated 18 February 2016
- Investigator Confirmation – Peter Frith dated 19 February 2016
- Investigator Confirmation – Catherine Paquet dated 17 February 2016
- Investigator Confirmation – Marie Williams dated 18 February 2016
- Chronic Respiratory Questionnaire v1 dated 17 February 2016
- Clinical Data Collection form v1 dated 17 February 2016
- Perspective Survey v2 dated 15 June 2016
- Life History Guiding Question (part 1) v1 dated 17 February 2016
- Life History Questionnaire (self-version) v1 dated 17 February 2016

- Modified Medical Research Council Dyspnoea Scale v1 dated 17 February 2016
- Multidimensional Dyspnoea Profile v1 dated 17 February 2016
- Response to Reviewers Comments dated 15 June 2016
- Sample Results Letter v2 dated 15 June 2016
- Invitation to Participate in a Research Project v4 dated 15 June 2016

TERMS AND CONDITIONS OF ETHICAL APPROVAL
As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions:

1. The approval only covers the science and ethics component of the application. A SSA will need to be submitted and authorised before this research project can commence at any of the approved sites identified in the application.
2. If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
3. Compliance with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
4. To immediately report to SAC HREC anything that may change the ethical or scientific integrity of the project.
5. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.
6. Submit an annual report on each anniversary of the date of final approval and in the correct template from the SAC HREC website.
7. Confidentiality of research participants MUST be maintained at all times.
8. A copy of the signed consent form must be given to the participant unless the project is an audit.
9. Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
10. All requests for access to medical records at any SALHN site must be accompanied by this approval email.
11. To regularly review the SAC HREC website and comply with all submission requirements, as they change from time to time.
12. Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable) Please refer to the relevant committee link on the SALHN intranet for further information.

Kind Regards

[redacted]

Paula Davies
Manager, Office for Research

Approval from University of South Australia HREC

Li, Lok Sze Katrina - liyly041

From: no_reply@unisa.edu.au
Sent: Wednesday, 10 August 2016 10:29 AM
To: Li, Lok Sze Katrina - liyly041; Marie Williams; humanethics@unisa.edu.au
Subject: Human Ethics: Application approved

Dear Applicant

Re: Ethics protocol "Lung health in adult children of people with Chronic Obstructive Pulmonary Disease" (Application ID: 0000034888)

Thank you for submitting your ethics protocol for consideration. Your protocol has been considered by the E1 Committee Review Group.

I am pleased to advise that your protocol has been granted ethics approval and meets the requirements of the National Statement on Ethical Conduct in Human Research. Please note that the E1 Committee Review Group's decision will be reported to the next meeting of the Human Research Ethics Committee for endorsement.

Please regard this email as formal notification of approval.

Ethics approval is always made on the basis of a number of conditions detailed at http://www.unisa.edu.au/res/forms/docs/humanresearchethics_conditions.doc; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at http://www.unisa.edu.au/res/ethics/default.asp

Please note, if your project is a clinical trial you are required to register it in a publicly accessible trials registry prior to enrolment of the first participant (e.g. Australian New Zealand Clinical Trials Registry http://www.anzctr.org.au/) as a condition of ethics approval.

Best wishes for your research.

Executive Officer
UniSA's Human Research Ethics Committee CRICOS provider number 00121B

This is an automated email and cannot be replied to. Please direct your query to humanethics@unisa.edu.au.

1

Amendment approval from University of South Australia HREC



Wed 14/12/2016 9:09 AM

Human Ethics <humanethics@unisa.edu.au>

RE: ethics amendment request - ethics protocol:0000034888-Approved

To ☐ Li, Lok Sze Katrina - liyly041

Cc ☐ Marie Williams; ☐ Kylie Johnston; ☐ Catherine Paquet; ☐ Peter Frith

Follow up. Start by Wednesday, 14 December 2016. Due by Wednesday, 14 December 2016.

Message HREC conditions.pdf

Dear Katrina,

Re: Ethics Protocol 0000034888 "Lung health in adult children of people with Chronic Obstructive Pulmonary Disease"

Thank you for submitting an ethics protocol amendment request. I am pleased to advise that the Chairperson of the University's Human Research Ethics Committee has assessed and **approved** your request to extend the recruitment field for this project, outside of the approved Repatriation General Hospital, include offices of GPs and physiotherapists. (as detailed in your email dated 8 Dec 2016).

Please regard this email as formal notification of approval.

The Human Ethics Unit would like to suggest that consideration be given to offering cash to participants, to the maximum of $25, to cover parking in the City precinct. This might be more attractive to participants. However, please consult the School account manager as the gift cards might be easier in terms of School accounting processes. If the gift cards are more practicable for accounting purposes then please continue using the gift cards. Either way, $25 is considered a reasonable amount.

Ethics approval is always made on the basis of a number of conditions detailed in the attachment; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at http://www.unisa.edu.au/res/ethics/default.asp .

Best wishes for your research.

Kind regards,

Liz

Elizabeth Collins | Ethics and Biosafety Officer | Research and Innovation Services
University of South Australia | Mawson Lakes Campus | Mawson Lakes SA 5095
Ph: +61 8 8302 3723 | Fax: +61 8 8302 3723 | Email: Liz.Collins@unisa.edu.au

University of South Australia

Amendment approval from SALHN HREC

Office for Research

Flinders Medical Centre
Ward 6C, Room 6A219
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

Amendment to ethics application approved

You are reminded that this letter constitutes ethical approval only for this amendment. If you are waiting on Site Specific Assessment (SSA) authorisation for your study, you must not commence this research project at any public Health site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

23 May 2017

Dr Marie Williams
School of Health Sciences,
University of South Australia
GPO Box 2471,
Adelaide, SA 5001

Dear Dr Williams

The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) have reviewed and provided ethical approval for this amendment which appears to meet the requirements of the *National Statement on Ethical Conduct in Human Research.*

Application Number: OFR 523.15 - HREC/15/SAC/515

Title: Lung health in adult children of people with Chronic Obstructive Pulmonary Disease

Chief Investigator: Dr Marie Williams

This amendment approval does not alter the current SAC HREC approval period for the study: 13/07/2016 to 13/07/2020

Public health sites approved under this application:

- Flinders Medical Centre
- Repatriation General Hospital
- Noarlunga GP Plus Super Clinic
- Hampstead Rehabilitation Clinic

The below documents have been reviewed and approved:

- Project amendment form – addition of sites – dated 12 May 2017
- General research application form v5 dated 12 May 2017
- Participant Information Sheet and consent form- adult children v7 dated 12 May 2017
- Participant Information Sheet and consent form- adults v7 dated 12 May 2017
- Invitation to participate in a research project for Southern Adelaide Local Health Network v5 dated 12 May 2017

Noted

- Participant Information Sheet and consent forms – Hampstead Rehabilitation Centre v7 dated 12 May 2017
- Invitation to participate in a research project for Royal Adelaide Hospital v5 dated 12 May 2017

TERMS AND CONDITIONS OF ETHICAL APPROVAL

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions:

1. The approval covers the ethics component of the application. Please submit a copy of the approved amendment to the local RGO for acknowledgement
2. If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
3. Compliance with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
4. To immediately report to SAC HREC anything that may change the ethical or scientific integrity of the project.
5. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.
6. Submit an annual report on each anniversary of the date of final approval and in the correct template from the SAC HREC website.
7. Confidentiality of research participants MUST be maintained at all times.
8. A copy of the signed consent form must be given to the participant unless the project is an audit.
9. Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
10. All requests for access to medical records at any SALHN site must be accompanied by this approval email.
11. To regularly review the SAC HREC website and comply with all submission requ rements, as they change from time to time.
12. Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable) Please refer to the relevant committee link on the SALHN intranet for further information.
13. Researchers are reminded that all advertisements/flyers need to be approved by the committee, and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contact should be coordinated through the FMC media unit.

Yours sincerely

[redacted]

A/Professor Bernadette Richards
Chair, SAC HREC

Site specific approval for Repatriation General Hospital

Office for Research

Flinders Medical Centre
Ward 6C, Room 6A219
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

20 October 2016

Professor Peter Frith
Respiratory Medicine
Repatriation General Hospital
DAW PARK SA 5042

Dear Professor Frith

HREC reference number:	HREC/15/SAC/515 **523.15**
SSA reference number:	SSA/16/SAC/329
Project title:	Lung health in adult children of people with Chronic Obstructive Pulmonary Disease
Ethics approval:	13 July 2016 to 13 July 2020
Site:	Repatriation General Hospital and Flinders Medical Centre
Subject:	Site Specific Assessment Review

Thank you for submitting an application for authorisation of this project.

On the basis of the information provided in your Site Specific Assessment submission, I am pleased to inform you that authorisation has been granted for this study to commence.

This authorisation is based on the following documents:

Site Specific Assessment AU/12/C7E723 dated 03 August 2016

Participant Information Sheet/Consent form for COPD Patients v6.0 dated 15 June 2016

Participant Information Sheet/Consent form for Adult Children v6.0 dated 15 June 2016

Peter Frith, Principal Investigator CV

HREC reviewed documents listed on the approval letter are accepted as part of the site authorisation.

The SSA reference number should be quoted in any correspondence about this matter.

If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

Should you have any queries about the consideration of your Site Specific Assessment form, please contact Dawn Jennifer on 8204 6453.

Yours sincerely

[redacted]

Professor Villis Marshall
Director, Office for Research

Site specific approval for Noarlunga GP Plus Super Clinic

Wed 9/08/2017 9:39 AM

Creaser, Damian (Health) <Damian.Creaser@sa.gov.au>

RE: SSA submission for recruitment at Noarlunga (SAC HREC study 523.15)

To Li, Lok Sze Katrina - liyly041

Follow up. Start by Wednesday, 9 August 2017. Due by Wednesday, 9 August 2017.
You replied to this message on 9/08/2017 9:46 AM.

Action Items + Get more apps

Good morning Katrina

The Office for Research has reviewed and acknowledged the following documents on behalf of SALHN Governance and GP Plus Super Clinic Noarlunga is now authorised as a study site. The following documents can now be incorporated in your study:

- study_introduction_letter for Noarlunga v5 120517.docx
- participant info sheet (G1) v7 120517 for Noarlunga.docx

For your information I have clarified the process and any future update to site won't need a new SSA and can be dealt with on the OfR Project Amendment Form.

Kind regards

Damian

Damian Creaser

Office for Research
Corporate Services
Southern Adelaide Local Health Network
Ward 6C, Room 219, Flinders Medical Centre

Tel: (08) 8204 6285
Email: damian.creaser@sa.gov.au

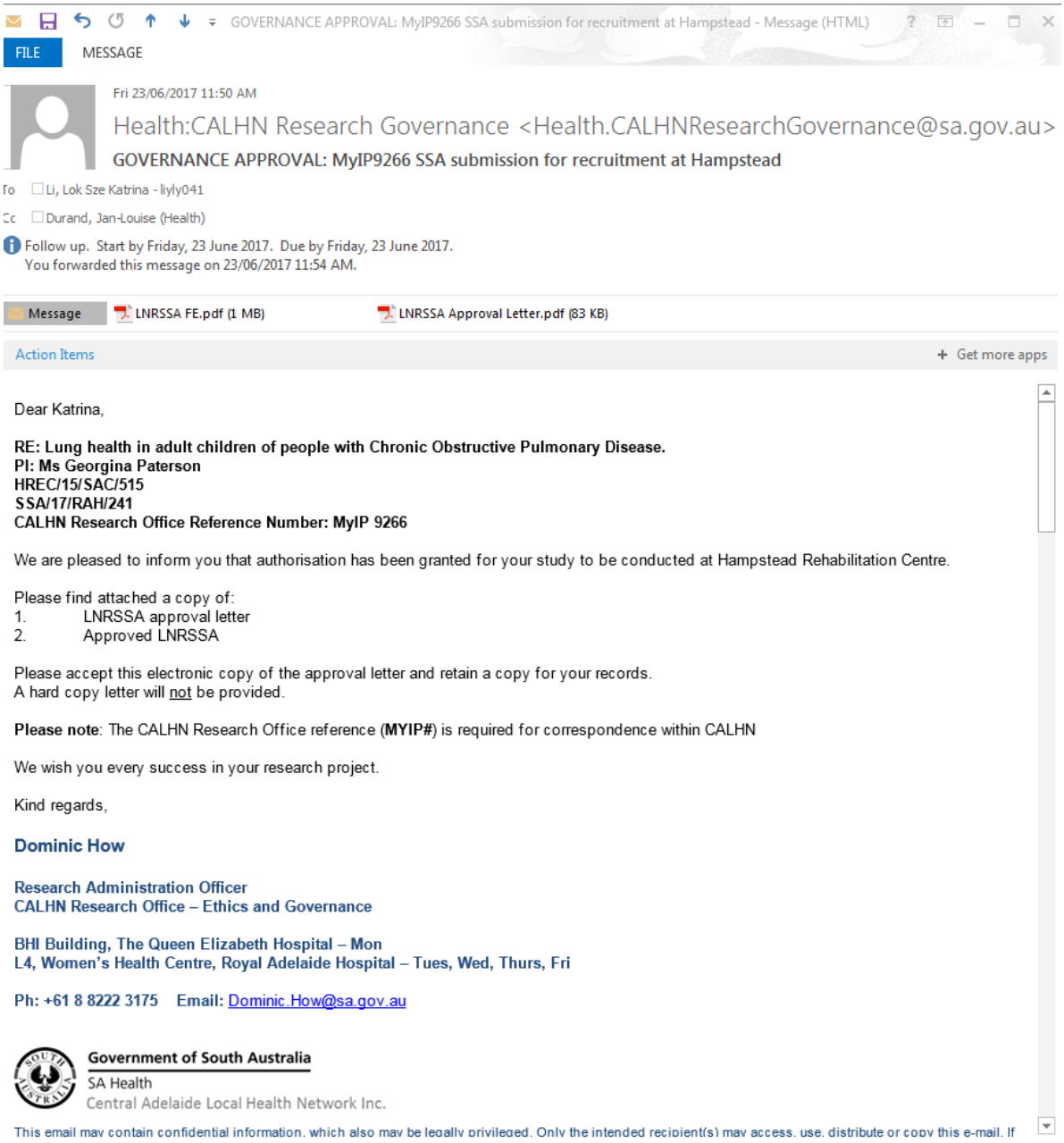
Web: www.sahealth.sa.gov.au/SALHNresearch

Southern Adelaide Local Health Network
Office for Research

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Site specific approval for Hampstead Rehabilitation Centre



GOVERNANCE APPROVAL: MyIP9266 SSA submission for recruitment at Hampstead - Message (HTML)

FILE MESSAGE

Fri 23/06/2017 11:50 AM

Health:CALHN Research Governance <Health.CALHNResearchGovernance@sa.gov.au>

GOVERNANCE APPROVAL: MyIP9266 SSA submission for recruitment at Hampstead

To Li, Lok Sze Katrina - liyly041

Cc Durand, Jan-Louise (Health)

Follow up. Start by Friday, 23 June 2017. Due by Friday, 23 June 2017.
You forwarded this message on 23/06/2017 11:54 AM.

Message LNRSSA FE.pdf (1 MB) LNRSSA Approval Letter.pdf (83 KB)

Action Items + Get more apps

Dear Katrina,

RE: Lung health in adult children of people with Chronic Obstructive Pulmonary Disease.
PI: Ms Georgina Paterson
HREC/15/SAC/515
SSA/17/RAH/241
CALHN Research Office Reference Number: MyIP 9266

We are pleased to inform you that authorisation has been granted for your study to be conducted at Hampstead Rehabilitation Centre.

Please find attached a copy of:
1. LNRSSA approval letter
2. Approved LNRSSA

Please accept this electronic copy of the approval letter and retain a copy for your records.
A hard copy letter will not be provided.

Please note: The CALHN Research Office reference (**MYIP#**) is required for correspondence within CALHN

We wish you every success in your research project.

Kind regards,

Dominic How

Research Administration Officer
CALHN Research Office – Ethics and Governance

BHI Building, The Queen Elizabeth Hospital – Mon
L4, Women's Health Centre, Royal Adelaide Hospital – Tues, Wed, Thurs, Fri

Ph: +61 8 8222 3175 Email: Dominic.How@sa.gov.au

Government of South Australia
SA Health
Central Adelaide Local Health Network Inc.

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D.3 Invitation letter

Repatriation General Hospital

Invitation to participate in a research project

University of South Australia

Dear Sir/Madam,

I am writing to tell you about a study on **Lung health in adult children of people with Chronic Obstructive Pulmonary Disease (COPD)** being conducted by researchers from the Repatriation General Hospital and the University of South Australia. You have received this letter because you were referred to the Pulmonary Rehabilitation program at the Repatriation General Hospital or you were listed within the research database at the Repatriation General Hospital and provided permission to be contacted for future studies.

This study is about the lung health of adult children of people with COPD. Children where one or both parents have COPD may have an increased risk of developing COPD because of genetics, environmental and behavioural influences. We are interested in talking to **parent-child pairs** to see whether the pair's life history has any influence on lung health.

Participation in this study is voluntary, your decision to participate or not participate in this study will have no effect on your medical care in any way. If you and your adult child decide to join this study, it will involve

- As a **parent with COPD** you will be invited to attend one appointment (about 1 hour max) to complete a survey about your life history and answer questions about any lung symptoms that you may have.
- As an **adult child of a parent with COPD** you will be invited to attend an appointment (about1.5 hours max). This session will involve a simple breathing test (max of three deep breath and blowing out), completing a life history questionnaire and surveys about whether you experience any respiratory symptoms

If you are interested in participating in this study, please return the attached reply slip in the reply paid envelope to obtain more information about this study. Alternatively you can contact Katrina for information about this study at any time on 08 8302 1284 or lok_sze_katrina.li@mymail.unisa.edu.au

Thank you for your time and consideration.

Yours sincerely,

[redacted]

Dr Jeff Bowden
Head, Respiratory and Sleep Services
Southern Adelaide Local Health Network

Noarlunga GP Plus Super Clinic

GP plus Super Clinic

University of South Australia

Invitation to participate in a research project

Dear Sir/Madam,

I am writing to tell you about a study on **Lung health in adult children of people with Chronic Obstructive Pulmonary Disease (COPD)** being conducted by researchers from the Southern Adelaide LHN and the University of South Australia. You have received this letter because you have attended the airway clearance or pulmonary rehabilitation program at the Noarlunga GP Plus Super Clinic.

This study is about the lung health of adult children of people with COPD. Children where one or both parents have COPD **may** have an increased risk of developing COPD because of genetics, environmental and behavioural influences. We are interested in talking to **parent-child pairs** to see whether the pair's life history has any influence on lung health. Your children do not need to have any lung problems to take part in this study.

Participation in this study is voluntary, your decision to participate or not participate in this study will have no effect on your medical care in any way. If you **and** your adult child decide to join this study, it will involve

- **As a parent with COPD** you will be invited to attend one appointment (about 1 hour max) to complete a survey about your life history and answer questions about any lung symptoms that you may have.
- **As an adult child of a parent with COPD** you will be invited to attend an appointment (about1.5 hours max). This session will involve a simple breathing test (max of three deep breath and blowing out), completing a life history questionnaire and surveys about whether you experience any respiratory symptoms

If you are interested in participating in this study, please return the attached reply slip in the reply paid envelope to obtain more information about this study. Alternatively you can contact Katrina for information about this study at any time on 08 8302 1284 or lok_sze_katrina.li@mymail.unisa.edu.au

Thank you for your time and consideration.
Yours sincerely,

[redacted]

Dr Jeff Bowden
Head, Respiratory and Sleep Services
Southern Adelaide Local Health Network

Hampstead Rehabilitation Centre

Government of South Australia
SA Health

University of South Australia

Invitation to participate in a research project

Dear Sir/Madam,

I am writing to tell you about a study on **Lung health in adult children of people with Chronic Obstructive Pulmonary Disease (COPD)** being conducted by researchers from the Royal Adelaide Hospital and the University of South Australia. You have received this letter because you have attended the pulmonary rehabilitation program at the Hampstead Rehabilitation Centre.

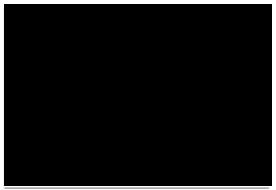
This study is about the lung health of adult children of people with COPD. Children where one or both parents have COPD **may** have an increased risk of developing COPD because of genetics, environmental and behavioural influences. We are interested in talking to **parent-child pairs** to see whether the pair's life history has any influence on lung health. Your children do not need to have any lung problems to take part in this study.

Participation in this study is voluntary, your decision to participate or not participate in this study will have no effect on your medical care in any way. If you **and** your adult child decide to join this study, it will involve

- **As a parent with COPD** you will be invited to attend one appointment (about 1 hour max) to complete a survey about your life history and answer questions about any lung symptoms that you may have.
- **As an adult child of a parent with COPD** you will be invited to attend an appointment (about 1.5 hours max). This session will involve a simple breathing test (max of three deep breath and blowing out), completing a life history questionnaire and surveys about whether you experience any respiratory symptoms

If you are interested in participating in this study, please return the attached reply slip in the reply paid envelope to obtain more information about this study. Alternatively you can contact Katrina for information about this study at any time on 08 8302 1284 or lok_sze_katrina.li@mymail.unisa.edu.au

Thank you for your time and consideration.
Yours sincerely,



Dr Ral Antic
Director, Department of Thoracic Medicine
Royal Adelaide Hospital

Generic letter for private clinics

University of South Australia

Invitation to participate in a research project

Dear Sir/Madam,

I am writing to tell you about a study on **Lung health in adult children of people with Chronic Obstructive Pulmonary Disease (COPD)** that you may be interested in joining. The study is being conducted by researchers from the University of South Australia. This study is about the lung health of adult children of people with COPD. Children where one or both parents have COPD **may** have an increased risk of developing COPD because of genetics, environmental and behavioural influences. We are interested in talking to **parent-child pairs** to see whether the pair's life history has any influence on lung health.

Participation in this study is **voluntary**, your decision to participate or not participate in this study will have no effect on your medical care in any way. If you **and** your adult child decide to join this study, it will involve

- **As a parent with COPD** you will be invited to attend one appointment (about 1 hour max) to complete a survey about your life history and answer questions about any lung symptoms that you may have.
- **As an adult child of a parent with COPD** they will be invited to attend an appointment (about 1.5 hours max). This session will involve a simple breathing test (max of three deep breath and blowing out), completing a life history questionnaire and surveys about whether they experience any respiratory symptoms.

If you are interested in participating in this study, please return the attached reply slip in the reply paid envelope to obtain more information about this study. Alternatively you can contact Katrina for information about this study at any time on 08 8302 1284 or lok_sze_katrina.li@mymail.unisa.edu.au

Thank you for your time and consideration.

Yours sincerely,

[redacted]

Professor Peter Frith
MB BS, FRACP
Professor Respiratory Medicine

Reply slip accompanying all invitation letters

REPLY SLIP: Please send back in enclosed reply paid envelope (no stamp required)

Study Title: Lung health in offspring of people with Chronic Obstructive Pulmonary Disease (COPD)

My Name: _____

My phone number: _____

My address: _____

_____

☐ Please send me further information about the study
☐ I consent to a follow up phone call for information about this study

D.4 modified Medical Research Council dyspnoea scale

Modified Medical Research Council Scale for breathlessness

I'm going to ask you to read the following statements.

While all of these statements might be true for you, which one best describes you?

Circle the grade that best describes.

MRC Grade	**Severity of Breathing Difficulty**
Grade 0	"I only get breathless with strenuous exercise"
Grade 1	"I get short of breath when hurrying on the level or walking up a slight hill"
Grade 2	"I walk slower than people of the same age on the level because of breathlessness" or "I have to stop for breath when walking at my own pace on the level"
Grade 3	"I stop for breath after walking about 100 yards or after a few minutes on the level"
Grade 4	"I am too breathless to leave the house" or "I am breathless when dressing"

D.5 Multidimensional Dyspnoea Profile

Multidimensional Dyspnea Profile page 1 of 4 name/code_____date&time

MULTIDIMENSIONAL DYSPNEA PROFILE
©2011 R.B.Banzett

Script for first time use:

The purpose of this questionnaire is to help us understand how your breathing feels.
There are no right or wrong answers. We want to know what you tell us about your own breathing.

On this page we ask you to tell us how unpleasant your breathing feels. On a later page we will ask you about the intensity or strength of your breathing sensations. The distinction between these two aspects of breathing sensation might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases.

A1 Scale

Use this scale to rate the **unpleasantness or discomfort** of your breathing sensations, how **bad** your breathing feels [felt].

Please focus on the period when_____

← ←		0	1	2	3	4	5	6	7	8	9	10
PLEASANT		NEUTRAL										UNBEARABLE

MDPv7.doc saved 1/11/2014 6:42:00 AM

Multidimensional Dyspnea Profile page 2 of 4 name/code_____date&time
SQ choice

Below are phrases or terms arranged in groups of similar meaning.
Step 1: Check each group that describes how your breathing feels [felt] during _____(indicate focus period).
Step 2: Please also mark *one* group that most accurately describes how your breathing feels [felt].

If *ANY* term in the group applies, choose that group.	**Step 1** DOES NOT APPLY	**Step 1** DOES APPLY	**Step 2** MOST ACCURATELY DESCRIBES
My breathing requires muscle work ***or*** effort			
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air			
My chest and lungs feel tight ***or*** constricted			
My breathing requires mental effort ***or*** concentration			
I am breathing a lot			

MDPv7.doc saved 1/11/2014 6:42:00 AM

Multidimensional Dyspnea Profile page 3 of 4 name/code_____date&time
SQ Scales

Use these scales to rate the intensity of the breathing sensations you feel [felt] (like the loudness of sound, regardless of whether the sensation is pleasant or unpleasant; for example a sensation could be intense without being unpleasant.)

Please focus on the period when _____

If ANY term in the group applies, rate that group.	**NONE**										AS INTENSE AS I CAN IMAGINE
My breathing requires muscle work ***or*** effort	0	1	2	3	4	5	6	7	8	9	10
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air	0	1	2	3	4	5	6	7	8	9	10
My chest and lungs feel tight ***or*** constricted	0	1	2	3	4	5	6	7	8	9	10
My breathing requires mental effort ***or*** concentration	0	1	2	3	4	5	6	7	8	9	10
I am breathing a lot	0	1	2	3	4	5	6	7	8	9	10
Other*	0	1	2	3	4	5	6	7	8	9	10

*If you need to, you can add additional descriptions of your breathing sensations.

MDPv7.doc saved 1/11/2014 6:42:00 AM

Multidimensional Dyspnea Profile page 4 of 4 name/code_____date&time
A2 Scales

When your breathing doesn't feel normal, you may experience emotions or 'feelings'. Using the scales below, please tell us about how your breathing sensations made you feel – rate zero for any emotion you did not feel.

Please focus on feelings during the period when _____.

	NONE										THE MOST I CAN IMAGINE
Depressed	0	1	2	3	4	5	6	7	8	9	10
Anxious	0	1	2	3	4	5	6	7	8	9	10
Frustrated	0	1	2	3	4	5	6	7	8	9	10
Angry	0	1	2	3	4	5	6	7	8	9	10
Afraid	0	1	2	3	4	5	6	7	8	9	10
Other?	0	1	2	3	4	5	6	7	8	9	10

MDPv7.doc saved 1/11/2014 6:42:00 AM

D.6 Pearlin Mastery Scale

Pearlin mastery scale

On a scale of 1 – 5, with 1 being strongly agree and 5 being strongly disagree, how would you rate the follow statements.

1. I have little control over the things that happen to me.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

2. There is really no way I can solve some of the problems I have.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

3. There is little I can do to change many of the important things in my life.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

4. I often feel helpless in dealing with the problems of life.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

5. Sometimes I feel that I am being pushed around in life.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

6. What happens to me in the future mostly depends on me.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

7. I can do just about anything I really set my mind to do.

1	2	3	4	5
Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

D.7 Results letter template

Lung health in adult children of people with Chronic Obstructive Pulmonary Disease
MT Williams, K Li, K Johnston, C Paquet, P Frith
University of South Australia and Repatriation General Hospital

Dear _(insert name)_,
Thank you again for participating in this study.
The aim of this study was to explore the life history and lung health of adult children of people with COPD. While we won't know the final results of the overall study until ____, we would like to provide some information about your own lung health. Once the study has been completed, we will invite you to attend a group information and feedback session to provide you with a summary of the overall results and what we think these results mean and give you some general information about lung health.
Summary of your results

Measure (specific assessment)	Your result	What the number means (Score/scale range)
Respiratory symptoms (COPD assessment test)		Lower score reflects less symptoms (0-40)
Impact of breathlessness (modified Medical Research Council scale)		Lower score reflects less breathlessness (0-4)
Sensation of breathlessness (Multidimensional Dyspnoea Profile: Immediate perception Emotional Response)		Immediate perception is the sensation you feel Emotional Response is the emotion you feel A lower score means less sensation /emotion
Quality of life (Chronic Respiratory Questionnaire)		Higher score reflects better lung health related quality of life (Dyspnoea domain: 1-8; Fatigue: 1-7; Emotional function: 1-7; Mastery: 1-7)
Lung function measure (FEV_1/FEV_6 =)		A score of greater than 0.75 suggests NO increased risk of obstructive lung disease

From your results (use one of the following)
You reported no or minimal respiratory symptoms and the lung function measure did not suggest that you have an increased risk of obstructive lung disease.
You reported no or minimal respiratory symptoms but your lung function measure suggests that you might be at risk of obstructive lung disease. It would be a good idea to make an appointment to see your doctor (GP and if, relevant your lung specialist) for further investigation and management. We suggest you take this letter when you have these appointments.

You reported experiencing some respiratory symptoms but your lung function measure did not suggest that you have an increased risk of obstructive lung disease. It would be a good idea to make an appointment to see your doctor (GP and if relevant, your lung specialist) to seek advice about your respiratory symptoms. We suggest you take this letter when you have these appointments.
You reported experiencing some respiratory symptoms and the lung function measure suggests that you might be at risk of obstructive lung disease. It would be a good idea to make an appointment to see your doctor (GP and if, relevant your lung specialist) for further investigation and management. We suggest you take this letter when you have these appointments.

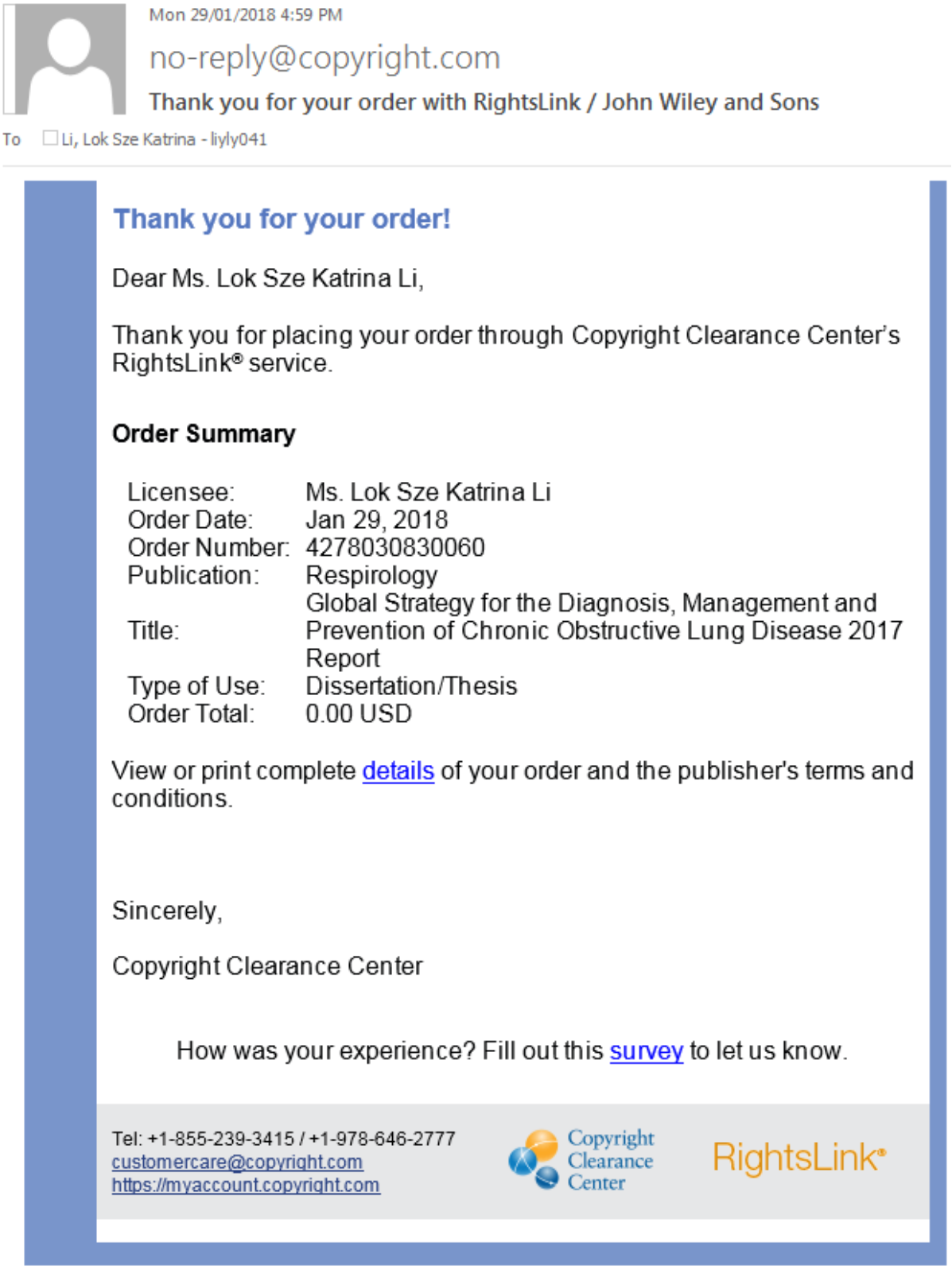
We are grateful for your participation in this study. We will shortly be in touch by phone to answer any questions you have about this report and give you an opportunity to make any comments about the study. You will also be invited to complete a short survey where we would like to hear your views about growing up as a child of a person with a lung condition and whether health checks or health programs would be useful.

Sign_____
Date_____

Prof Peter Frith	Dr Marie Williams	Ms Katrina Li	Dr Kylie Johnston	Dr Catherine Paquet
Respiratory physician	Physiotherapist	Physiotherapist	Physiotherapist	Epidemiologist

Appendix E: Permission for figures

Permission for Figure 2.2



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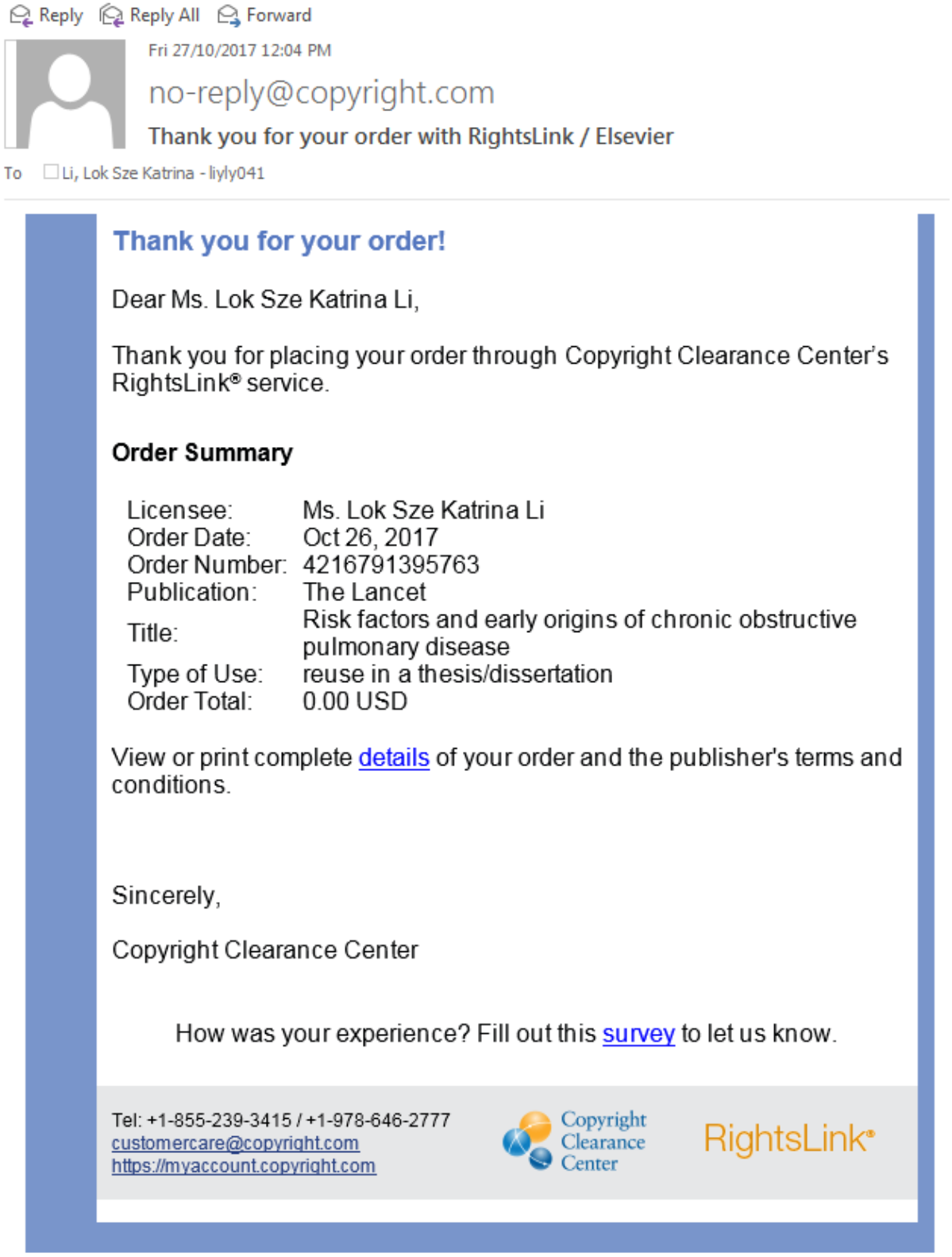
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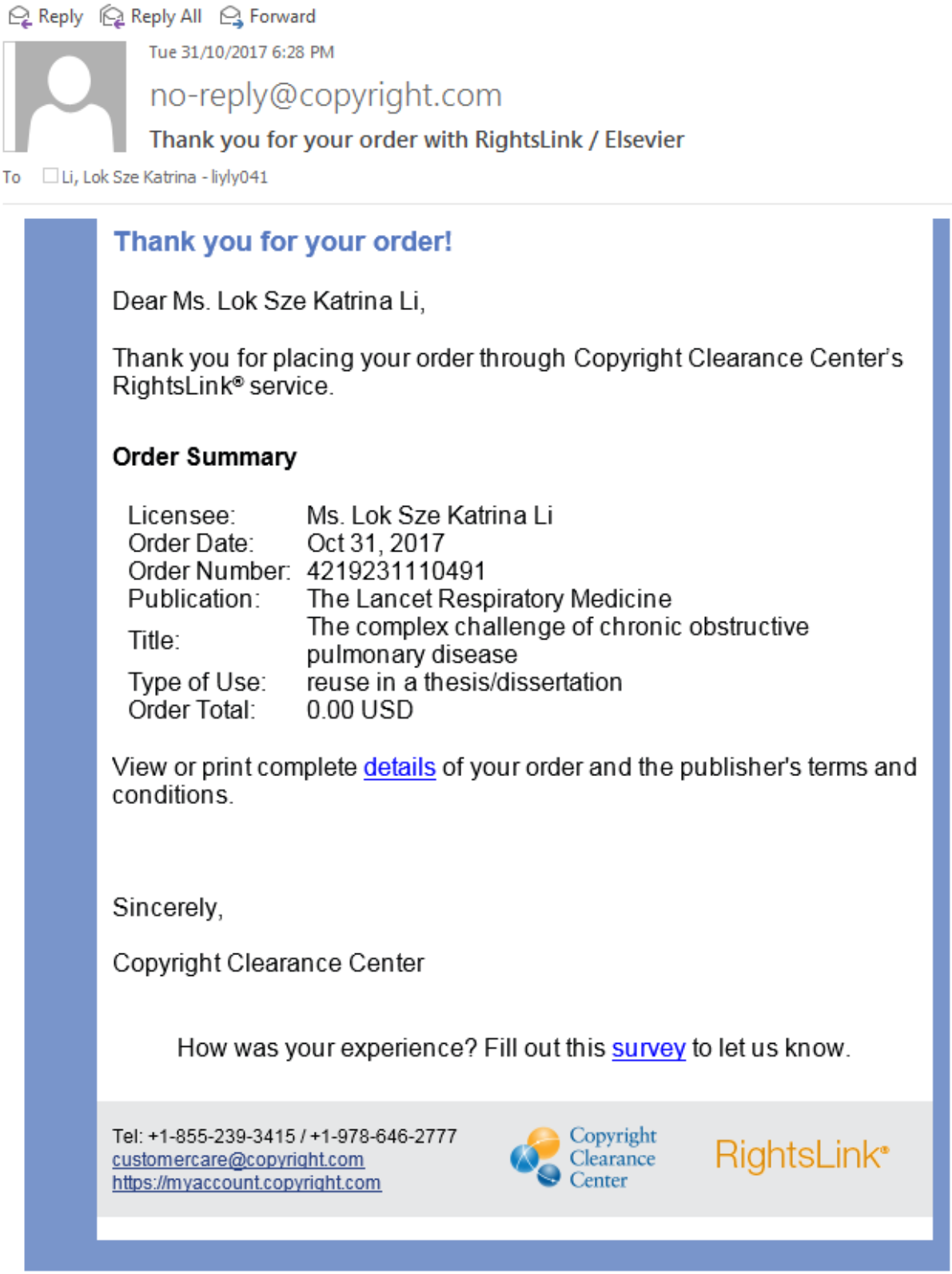
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