Lung function and cardiovascular risk in young adults

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Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of ethical conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government’s Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

The CDAH study was approved by the Southern Tasmanian Health and Medical Research Ethics Committee. Ref H8152

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Abstract

Background
Associations between poor lung function (LF) and cardiovascular disease (CVD) have been reported in patients with chronic obstructive pulmonary disease and in population samples of older adults, including lifelong non-smokers. There are few studies of this association in young adults.

Common modifiable risk factors for poor LF and CVD that might explain the association include smoking, low levels of physical activity, low cardiorespiratory fitness (CRF) and obesity. Systemic inflammation indicated by markers such as C-reactive protein (CRP), might also be explanatory.

Aim
The aims of this study were: 1) to investigate the cross-sectional and longitudinal associations of modifiable CVD risk factors with adult LF and 2) to investigate cross-sectional associations of young adult LF with CRP and carotid artery structure and function as subclinical indicators of atherosclerosis.

Methods
Data for this study were obtained from sub-samples of 2,410 participants of the 1985 Australian Schools Health and Fitness Survey who had follow up health assessments between 2004-2006 when aged 26-36 years of age.

Data from at least 1,700 participants were used to investigate cross-sectional associations of smoking, CRF, adiposity and CRP with adult LF (forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Longitudinal data were also examined to determine the effects on adult LF of: childhood and parental smoking (in 278 daily and 1,515 never smokers respectively), poor childhood CRF and obesity (among approximately 600 participants with baseline data). Associations between adult lung function and ultrasound measures of carotid intima-media thickness (cIMT) and arterial elasticity were also assessed.

Results
Adult smokers had higher mean lung volumes than non-smokers. Among daily smokers, cumulative cigarette exposure and childhood smoking had significant independent negative effects on adult LF. Higher CRF was positively associated with LF and was independent of adiposity among females. Adiposity was negatively associated with LF. Adult fitness and adiposity were much more strongly associated with adult LF than were childhood measures.
Weak negative associations between CRP and adult LF were observed which were stronger in participants with greater than average adiposity. Lower FEV$_1$ and FVC in female never-smokers and lower FEV$_1$/FVC in ever-smoking males were associated with thicker cIMT, but the latter associations were confounded by cumulative smoke exposure. No independent associations between lung function and arterial elasticity were observed for males or females.

**Conclusion**

Overall, adiposity was more strongly associated with LF than either smoking, CRF or CRP. In these young adults, there was little evidence of an independent association between LF and subclinical atherosclerosis in males. However, a significant association between LF and cIMT was evident for female never smokers independent of other known CVD risk factors.
**Statement of contribution**

The data used in this study come from the Childhood Determinants of Adult Health (CDAH), a large national cohort of Australian adults who had originally participated in a study of Australian children in 1985 when they were aged between 7 and 15 years of age.

I have been involved in the CDAH study since May 2001. I was responsible for the day-to-day running of a pilot study, funded by the Australian Heart Foundation. The pilot study tested the feasibility of tracing and recruiting participants of the 1985 Australian Health and Fitness Survey for follow up measures. The results of the pilot study were used in the National Health and Medical Research Association grant application that provided funding for following up the full cohort, the CDAH study.

I assisted in the planning and management of the main CDAH study including: protocol and questionnaire development, grant and ethics applications, database development and data management including preparing data for matching with the National Death Index and the Australian Electoral Commission.

I also assisted in the preparation of study materials: including questionnaires, participant information leaflets and newsletters. I trained, managed and assisted volunteers and staff who traced and recruited study participants.

I was involved in data collection at the first Tasmanian clinics and helped train the study technicians at the first mainland clinic in Victoria. I also assisted with cleaning of all collected data and helped in the analysis and development of strategies to maximise participant response rates.

For this thesis, I was responsible for cleaning the lung function and physical fitness data and designed the research questions proposed.
Statement regarding published work contained in thesis

This thesis includes (or will include) three papers for which I am not the sole author. However, I have been the lead author in these papers, designed the research questions, cleaned and analysed the data, drafted the manuscript then revised it in response to the comments of my co-authors (four of whom were my PhD supervisors† or expert advisors‡). The contributions of each author are detailed below:

The paper reported in Chapter 5

Curry BA, Blizzard CL, Schmidt MD, Walters EH, Dwyer T, Venn AJ. Longitudinal associations of adiposity with adult lung function in the Childhood Determinants of Adult Health (CDAH) Study. Obesity 2011; 19(10):2069-75

BC cleaned the data and undertook all the analysis. Contributed to the interpretation of the results, drafted and then revised the manuscript in response to feedback from her co-authors.

LB† provided statistical expertise and provided comments on the manuscript.

MS† provided statistical support and provided comments on the manuscript.

EHW‡ provided respiratory and clinical expertise and provided comments on the manuscript.

TD was responsible for the conception of the CDAH and provided comments on the manuscript.

AV† was involved in the conception of the CDAH study and the acquisition of data. She also provided assistance with data interpretation and revisions of the manuscript.

Chapter 6 was written as a paper for submission to a peer-reviewed journal

Curry BA, Blizzard L, Walters EH, Dwyer T, Venn A

The contribution of adiposity to the association between C-reactive protein and lung function in young adults.

BC cleaned the data and undertook all the analysis. Contributed to the interpretation of the results, drafted then revised the manuscript in response to feedback from her co-authors.

LB† provided statistical expertise and provided comments on the manuscript.

EHW‡ provided respiratory and clinical expertise and provided comments on the manuscript.
TD was responsible for the conception of the CDAH study and provided comments on the manuscript.

AV† was involved in the conception of the CDAH study and the acquisition of data. She also provided assistance with data interpretation and revisions of the manuscript.

Chapter 7 was written as a paper for submission to a peer-reviewed journal

Curry BA, Blizzard L, Magnussen C, Walters EH, Dwyer T, Venn A

Lung function and vascular structure and function in young adults.

BC cleaned the data and undertook all the analysis. Contributed to the interpretation of the results, drafted then revised the manuscript in response to feedback from her co-authors.

LB† provided statistical expertise.

CM was responsible for data collection, provided assistance with data interpretation and provided comments on the manuscript.

EHW‡ provided respiratory and clinical expertise and provided comments on the manuscript.

TD was responsible for the conception of CDAH study and provided comments on the manuscript.

AV† was involved in the conception of the CDAH study and the acquisition of data. She also provided assistance with data interpretation and revisions of the manuscript.

Signed: 

Date: 

Alison Venn, Primary supervisor
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• All the other Menzies’ staff and students, who have supported, encouraged me over the last few years.

• My friends and family, particularly Heather and Rose, my two beautiful girls, who are looking forward to spending a lot more time doing ‘fun stuff’ with their mum.

I am also very grateful to Ruby Menzies’ and her family for the additional financial support that supplemented my Australian Postgraduate Scholarship.

I also appreciate the time, effort and the constructive criticism of Associate Professor Bob Hancox and Dr Charlotte Bolton who examined this work.
# Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>AEC</td>
<td>Australian Electoral Commission</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities</td>
</tr>
<tr>
<td>ASHFS</td>
<td>Australian Schools Health and Fitness Survey</td>
</tr>
<tr>
<td>β</td>
<td>Beta, regression coefficient</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CARDIA</td>
<td>Coronary Artery Risk Development In young adults</td>
</tr>
<tr>
<td>Cd</td>
<td>Carotid distensibility</td>
</tr>
<tr>
<td>CDAH</td>
<td>Childhood Determinants of Adult Health</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>cIMT</td>
<td>Caroid intima media thickness</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRF</td>
<td>Cardiorespiratory Fitness</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>ECHRS</td>
<td>European Cancer and Heart Risk Study</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>Mean forced expiratory flow between 25% and 75% of FVC</td>
</tr>
<tr>
<td>FER</td>
<td>Forced expiratory ratio</td>
</tr>
</tbody>
</table>
### Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass (Lean body mass)</td>
</tr>
<tr>
<td>FMI</td>
<td>Fat mass index</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>HDL-c</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IMT</td>
<td>Intima media thickness</td>
</tr>
<tr>
<td>LBM</td>
<td>Lean body mass</td>
</tr>
<tr>
<td>LDL-c</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MEF</td>
<td>Maximal mid expiratory flow</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>PDAY</td>
<td>Pathobiological Disease Indicators of Atherosclerosis Risk</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PWC&lt;sub&gt;170&lt;/sub&gt;</td>
<td>Physical work capacity at a heart rate of 170 beats per minute</td>
</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SI</td>
<td>Stiffness index</td>
</tr>
<tr>
<td>TChDLr</td>
<td>Ratio of total cholesterol to HDL-c</td>
</tr>
<tr>
<td>US, or USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Maximum oxygen uptake</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YEM</td>
<td>Young's elastic modulus</td>
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</tbody>
</table>
Chapter 1: Background
1.1 Introduction

Cardiovascular disease (CVD) and chronic respiratory disease are two of the biggest killers and causes of disease in Australia today. These diseases are a considerable burden to the community and affect around 1 in 6 Australians. The Australian Institute of Health and Welfare’s report on “Australia’s Health 2010”\(^1\) reported that an estimated 4.3 million Australians (19.5\%) were affected by CVD or chronic respiratory disease, and 34\% of all deaths were attributable to these conditions. Figure 8-1 below shows how the burden of CVD and chronic lung disease compares with other major disease groups in the Australian population.

Figure 8-1: Projected burden of disease for major causes of morbidity in Australia in 2010.

Although the 2011 report on CVD in Australia\(^2\) does not report chronic respiratory disease as a significant co-morbid condition, CVD is the leading cause of death for those with chronic respiratory disease. In addition to having a higher risk of developing CVD and having CVD events such as heart attack and stroke\(^3\) these patients are also more likely to have poor outcomes after such events.\(^4\) However, even in the absence of overt lung disease, lung function appears to be negatively associated with CVD, cardiovascular mortality and all-cause mortality.\(^5\)\(^\text{-7}\) Despite more than 30 years of research, the reasons for these associations have not yet been established.
1.2 Lung function

Lung (or pulmonary) function relates to all aspects of the lungs. It includes: the mechanics of breathing, measures of the volumes that may be contained within lungs, the rate of airflow during inhalation and exhalation, differences between the expected lung volumes and those predicted from age and height measures, the effects of challenge by stimulants, respiratory muscle strength, chest wall compliance and the efficient delivery of oxygenated blood to the tissues. Most of these functions are measured using simple breathing tests.

The most common measures of lung function used in epidemiological studies are spirometric measures of forced maximal inspiration and expiration. The following definitions of these indices were extracted from ‘The Spirometry handbook’⁸ (with permission from the Australian lung foundation).

Forced Vital Capacity (FVC) is the maximum volume of air that can be exhaled, or inspired during a forced manoeuvre.

Forced Expired Volume in one second (FEV₁) is the volume expired in the first second of maximal expiration after a maximal inspiration. It is a useful measure of how quickly full lungs can be emptied.

FEV₁/FVC or FER is the FEV₁ expressed as a percentage of FVC and gives a clinically useful index of airflow limitation.

FEF_{25-75} is the average expired flow over the middle half of the FVC. It is regarded as a more sensitive measure of small airways narrowing than FEV₁ but has a wide range of normality, and is less reproducible than FEV₁.

The FER is one of the indices used by clinicians to identify individuals who may have airflow limitation. If the FEV₁ is reduced, and FVC is unaffected, the FER will decrease, suggesting there is an obstruction to air flow, possibly due to COPD or asthma. Alternatively, if the FEV₁ and the FVC are both reduced and the FER remains above 80%, the patient may have restricted pulmonary function.

Modern spirometers used to measure these forced expiratory volumes include small table-top devices, linked to computers with software that print out spirometric tracings and provide information on the result compared to reference (predicted) values for lung function. Given a trained operator and guidance to the participant, FEV₁ and FVC are very reproducible. Guidelines for measurement⁹ and assessment¹⁰ of spirometry have been prescribed by the American and European Respiratory Societies.
1.2.1 Reference values

Forced expiratory lung function measures are often expressed as ‘per cent predicted values’. These are a measure of the lung function of an individual compared to what might be expected given the participants age and height compared to ‘normal’ volumes obtained from a reference population sample of never smoking adults. The most important determinants used to generate ‘normal’ values are sex, age and height. Per cent predicted values are however problematic, as the ‘normal values’ obtained may differ depending on the source of the population sample used to generate them. The ethnicity of the study population should therefore be considered when selecting the reference equations. The reference equations generated from the Third National Health and Nutritional Examination Survey (NHANES III),\textsuperscript{11} which include data from both adults and children, are the recommended standard for interpreting lung function from the US population. Until very recently there have been no recommended reference measures for the Australian population.

In recent years, international collaborators have attempted to develop better reference ranges, particularly for children.\textsuperscript{12} Combined data from four surveys, with 3598 participants in total, and statistical modelling techniques, that allow for inter-subject variation between individuals of the same age and height, have been used to generate new reference ranges from early childhood through adulthood for FEV\textsubscript{1}, FVC and FEF\textsubscript{25-75}. This new model of evaluating the lung function of individuals’ allows generation of either a per cent predicted value or a z-score comparison (an indicator of the difference from the reference mean/median value for any given age and height). A recent Australian study has evaluated the reference equations and look up tables used to generate these new estimates and has concluded that they are applicable the contemporary Australian population.\textsuperscript{13} Unfortunately, the study results came too late to incorporate into the analytical methods of this thesis.

1.2.2 Determinants of lung function

Lung function measured at any time-point is the product of genetic expression, age, height and a continuum of lifetime exposures such as intrauterine growth retardation, childhood respiratory infections, living conditions (including exposure to smoke in the home) and nutrition that may affect the growth and development of the lungs during childhood. In addition, adult exposures: smoking cigarettes, recurrent infections, and a variety of environmental and occupational factors such as air allergens and mineral or organic dusts also adversely affect adult lung function and may result in a faster rate of lung function decline or may cause chronic respiratory diseases. It has been suggested that lung function may be an indicator of an individual’s overall health status.\textsuperscript{14}
Lung function data from a number of large population based cohort surveillance studies have been used to investigate changes in lung function over the life-course. The idealised growth, plateau and decline of lung function across the lifespan (as originally published by Speizer and Tager in 1979\textsuperscript{15}), and the periods of exposure to factors that adversely affect lung function is presented in Figure 1-2.

During childhood and adolescence, lung growth is faster in females than males. Female lung function also peaks earlier, usually in the late teens, while male lung volumes continue to grow into the mid to late 20s.\textsuperscript{16} After the age of around 35, there is a gradual age-related decline in lung function associated mainly with a loss of elasticity.\textsuperscript{16}

Figure 1-2: Lung function across the lifespan

Reprinted with the permission of the American Thoracic Society. Eisner et al.\textsuperscript{17}
1.2.3 Chronic respiratory disease

Excluding lung cancer, the most common chronic respiratory diseases are asthma and chronic obstructive airways disease (COPD) (Figure 1-3). Others include sleep apnoea (associated with obesity) and pneumoconiosis (a restrictive condition where deposits of mineral or organic dust in the airways leads to inflammation, scarring and loss of lung parenchyma and elasticity). Most of these conditions are preventable.18

Figure 1-3: The burden of chronic respiratory disease in Australia, by cause, as a proportion of the total, by sex and according to fatal or non-fatal outcomes.

From AIHW report ‘Chronic respiratory diseases in Australia. Their prevalence, consequences and prevention’19

Asthma and COPD are both associated with airway obstruction, but they have quite different aetiologies. Asthma affects the young (mostly males in childhood and females in adulthood) but rarely causes death. Airway obstruction occurs when large airway calibre is reduced as a consequence of spasm of bronchial smooth muscle (bronchospasm), brought on by allergy or physical stress, e.g. exercise or cold air. Such bronchospasm is temporary and may be reversed with medication. In contrast, COPD is a chronic inflammatory condition in which the bronchial mucosa is swollen and inflamed and produces excess volumes of mucus, which may block the airways. Airway obstruction associated with COPD is not reversible. In addition there may also be some destruction of lung parenchyma and additional loss of elasticity secondary to inflammation and scarring. COPD is most prevalent in adults over 40 years of age.

An Australian Institute of Health and Welfare (AIHW) report on chronic respiratory disease, published in 2005,19 suggested that 3.1% of Australians had COPD of which 70% in males and 60% in females was attributable to tobacco smoke. These prevalence rates were estimated from mortality data,
hospital and GP usage data, disability claims and self-reported data for emphysema and bronchitis. However as the early stages of the disease are asymptomatic and often go undetected, or are mistaken for asthma, these figures are accepted as an underestimate of the burden of disease in the community.

An indication of how much the AIHW figures underestimate the prevalence of COPD was highlighted by a more recent report, prepared for the Australian Lung Federation, by Access Economics. The report used data from the National Health Survey 2007 and, symptom and spirometry, data from the Australian arm (n=541) of the international population-based Burden of Obstructive Lung disease initiative (BOLD). Figure 1-4 shows the prevalence rates for COPD according to age group. Overall the results indicate that an estimated 5.6% of Australians had obstructive airways disease, almost twice the prevalence reported by the AIHW.

Figure 1-4: Prevalence of Chronic obstructive pulmonary disease in the Australian population according to sex and age group

Source: Access Economics estimates of COPD prevalence based on data from the Burden of Obstructive lung disease (BOLD) study, and 2007 National Health survey data.

Although COPD does not generally manifest itself until the fourth decade of life, cohort studies of young adults have shown that those with early signs of lung function deficits (particularly smokers) have a greater likelihood of developing COPD in later life. If spirometry was used routinely in doctors’ surgeries, it may be possible to identify those with early signs of lung impairment and assist them to limit further lung function decline. The burden on the community that could be relieved by such screening and preventative action is potentially considerable.


1.3 Cardiovascular disease

CVD refers to any condition that affects the health of the circulatory system including acute coronary disease (myocardial infarction and cardiac death), chronic angina and stroke. Estimates from the 2007 National Survey of Mental Health and Well-being estimated that around 3.5 million Australians between the ages of 16 and 85 years had a chronic CVD condition. The prevalence of CVD in Australia according to age group is illustrated in Figure 1-5.

Figure 1-5: The Prevalence of CVD in Australia 2008-2009 according to age and sex

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Arteriosclerosis 1.3.1

The most common aetiology of CVD events is arteriosclerosis. Arteriosclerosis is the build-up of fat and cholesterol in the medial and intimal layers (smooth muscle cells and endothelium) of the arterial wall. Eventually these deposits become larger and initiate an inflammatory response ultimately becoming fibrous, calcified, plaques that reduce the vessel lumen (Figure 1-6). Plaques tend to occur more often in places where there is turbulent blood flow e.g. in the heart or at sites...
where arteries fork e.g. the bifurcation of the carotid artery. When plaques reach a critical size, the flow of blood along the vessel is restricted and the patient may experience angina pains because of a reduction in oxygen getting to the cardiac tissues. When the plaque completely occludes the vessel, or fragments distributing emboli through the circulation, the patient may experience either a myocardial infarction or a stroke.

**Figure 1-6: Atheromatous plaque development**

![Atheromatous plaque development](Modified from www.doctorsgates.blogspot.com)

Although CVD generally manifests itself in middle age or later, there is considerable evidence that the disease process begins in childhood. The Bogalusa Heart Study found evidence of atheromatous streaks in children as young as 4 years. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study investigated, and established, the association between cardiovascular risk factors and post mortem evidence of atherosclerosis in 15-34 year old victims of traumatic death. The PDAY scoring system, devised from an individual’s age, sex and a battery of modifiable CVD risk factors (obesity, hypertension, smoking, hyperglycaemia, low levels of high density lipoproteins (HDL-c and high LDL-c) pre-mortem has been shown to predict atherosclerosis in other post-mortem studies of young and middle aged adults.25,26
1.3.2 Non-invasive measures of atherosclerosis

In the past 20 years or so new technologies such as computerised tomography (CT), magnetic resonance imaging (MRI) and ultrasound have enabled detection of subclinical CVD in asymptomatic individuals using non-invasive techniques. Subclinical measures include, the combined thickness of the arterial endothelium and the medial layer (the intima medial thickness, or IMT), detection of arterial plaques, and deposition of minerals associated with arterial plaque development.

Measures such as the IMT have been associated with myocardial infarction, stroke, and cardiac death across a wide age range. Carotid IMT (cIMT) has also been shown to be associated with significant CVD risk factors in living asymptomatic young adults. In 2008 the American Society of Echocardiography published a review of the evidence and recommended that ultrasound cIMT measures may be a useful means to classify patients (particularly asymptomatic patients) according to risk of a future CVD event.37

Atherosclerosis is also associated with reduced arterial elasticity (and conversely increased arterial stiffness), which affects a vessel’s ability to respond to circulatory volume changes. Arterial elasticity and stiffness measures, determined from changes in artery diameter and blood pressure (which is increased as arterial elasticity decreases), may be obtained using a number of methods. Magnetic resonance imaging, ultrasonography, analysis of arterial pulse wave forms and measurement of the speed with which the pulse wave travels along the length of an artery provide different measures of arterial function. In 2006 the European Cardiology Society published a review of the different methodologies and recommended PWV as the gold standard measure in clinical practice. A meta-analysis of many studies of aortic PWV concluded that it is a strong predictor of CVD events and all-cause mortality, particularly in those with higher baseline CV risk.41

Obtaining ultrasound images of arteries requires more skilled technicians than measuring PWV, however one advantage of measuring local arterial elasticity using ultrasound (rather than PWV) is that cIMT may also be determined from the same ultrasound images. This allows calculation of the Young’s Elastic Modulus (YEM). The YEM provides information about the stiffness of the artery taking into consideration the thickness of the arterial wall, which also contributes to arterial stiffness. Carotid femoral PWV and carotid stiffness measures have been reported to provide similar estimates in normal subjects without hypertension or diabetes. In young adults, carotid elasticity measures have been associated with other known CVD risk factors, including the metabolic syndrome. These observations indicate that such subclinical measures of early atherosclerotic changes are an
appropriate outcome measure to determine the early signs of atherosclerosis in young adults otherwise free of overt CVD.

1.1 Evidence for the association between lung function and CVD

1.1.1 Mortality

The majority of studies which have investigated the association between pulmonary function and CVD have focused on clinical endpoints and outcomes such as myocardial infarction, stroke or cardiac death.

The association between lung function and cardiovascular mortality was first reported by Higgins and Keller in 1970. As smoking was already an established risk factor for both CVD and poor lung function, and no adjustment for smoking status was included in the analysis, it was suggested that the associations may have been attributable to cigarette smoke exposure. Since then a number of longitudinal studies have observed significant associations between all-cause cardiovascular mortality and baseline FEV₁, FVC, and the rate of FEV₁ decline during follow up, independently of smoking status. However, associations between lung function and CVD mortality have not been consistent across all studies after adjustment for other CVD risk factors.

In Australia, the 20 year follow up of the Busselton population surveys of 751 males and 940 females, aged 25 to 79 at baseline estimated that a one litre lower mean baseline FEV₁ increased the risk of death by 43% for males and 60% for females (Table 1-1). The associations were stronger for females than males, particularly current smoking females. However, associations between mean FEV₁ and rate of decline in FEV₁ did not reach statistical significance for CVD outcomes.

For all but never smoking males, the observed associations between average FEV₁ and all-cause mortality were similar to results observed in a Norwegian study of working males and from the USA’s first National Health and Nutritional Examination Survey (NHANES-1). In these studies a 10% decline in per cent predicted FEV₁ was associated with an increased likelihood of death of 10 to 15 per cent.

Most other studies have compared the mortality rates of the top and bottom quarters (or fifths) of lung function. The mortality risk across fifths of FEV₁ for the smoking and never smoking participants of the original Renfrew and Paisley survey of 15,000 are presented in Figure 1-7. The observed 15-year mortality rates for males were 15%, 28% and 48% respectively for lifelong non-smokers, those who smoked more than 20 cigarettes per day and smokers with poor lung function. The comparator figures for females were 10%, 17%, and 29%.
The relative risk of all-cause mortality, across fifths of FEV₁, for smokers compared to never smokers was 1.95 (95%CI, 1.62 to 2.35) to 1.27 (95%CI, 1.05 to 1.54). The trend for cardiac death was similar and the relative risk of ischaemic heart disease (IHD) 1.79 (95%CI 1.29 to 2.50) to 1.26 (95%CI 0.90 to 1.75).

Table 1-1: Average FEV₁ and FEV₁ decline in relation to all-cause and CVD mortality according to sex and smoking status at baseline

<table>
<thead>
<tr>
<th></th>
<th>All causes of death</th>
<th>Cardiovascular death</th>
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<tbody>
<tr>
<td></td>
<td>Average FEV₁ (HR(95%CI))</td>
<td>Decline FEV₁ (HR(95%CI))</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.92 (0.56,1.52)</td>
<td>0.85 (0.63,1.14)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.37 (0.94,2.00)</td>
<td>1.06 (0.90,1.25)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.73 (1.16,2.59)</td>
<td>1.15 (1.00,1.32)</td>
</tr>
<tr>
<td>All</td>
<td>1.42 (1.08,1.87)</td>
<td>1.08 (0.98,1.20)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>1.46 (0.83,2.56)</td>
<td>1.24 (1.04,1.48)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3.09 (1.30,7.37)</td>
<td>1.29 (0.74,2.26)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.88 (0.74,4.82)</td>
<td>1.08 (0.78,1.51)</td>
</tr>
<tr>
<td>All</td>
<td>1.77 (1.09,2.86)</td>
<td>1.21 (1.04,1.41)</td>
</tr>
</tbody>
</table>

Extracted from Ryan et al.\(^{50}\)

FEV₁, forced expiratory volume in 1 second, HR(95%CI); hazard ratio(95% confidence intervals); CVD risk factors for a decrease of 1L in mean FEV₁ and an increase of 50ml in annual rate of decline of FEV₁ over 20 years. All adjusted for age, height, smoking and asthma.

Figure 1-7: Comparison of all-cause mortality risk by relative FEV₁ for lifelong non-smokers and heavy current smokers in the Renfrew and Paisley survey

From Hole et al.\(^{51}\)

Relative FEV₁: Fifths of Forced expiratory volume in one second.
Baseline category is that of a lifelong non-smoker with FEV₁ in top fifth. (1 = bottom, 5 = top)
Sex stratified relative hazard ratios are adjusted for diastolic blood pressure, serum cholesterol, body mass index, and social class
In 2005, Sin and Man completed a meta-analysis\textsuperscript{51} of 12 large prospective studies with over 15 years follow up and greater than 500 participants. Forest plots of the meta-analysis confirmed the negative association between baseline lung function (FEV\textsubscript{1}) and CVD mortality Figure 1-8a shows a significantly greater risk of CVD death in the bottom compared to the top quarter of FEV\textsubscript{1}. The results obtained for males and females were similar when the analysis was stratified by sex.

In seven studies, which adjusted for smoking status, the absolute risk of a CVD event was greater in smokers compared to non-smokers and in three studies limited to lifetime non-smokers (Figure 1-8b) the risk was slightly attenuated, but remained significant. This analysis confirmed that the observed associations were independent of smoking status although the absolute risk of a CVD event was greater in smokers.

Until recently, the studies of associations between lung function and mortality have been limited to middle aged or elderly participants. However, prospective data from a cohort of 9,544 Glasgow University graduates\textsuperscript{57} and 40 years of mortality data for the 1,503 youngest participants of the Midspan studies\textsuperscript{58} have demonstrated that lung function in young adulthood is also predictive of all cause and cardiovascular mortality. However, after multivariable adjustment for other predictive factors (BMI status, hypertension, bronchitis, smoking status, social economic status (non-manual labour), driving, height, blood pressure, alcohol, and cardiothoracic ratio) significant associations persisted for only FEV\textsubscript{1} and total mortality. This suggests that perhaps there may have been residual confounding in studies of older participants, who may have had undiagnosed CVD.
From Sin, Wu and Man. FEV$_1$, Forced expiratory volume in 1 second,

### 1.1.2 Morbidity

In the Malmo study of 5,452 healthy men (aged 28-61 at baseline) reduced FEV$_1$ and FVC volumes were associated with higher risks of fatal, but not non-fatal, outcomes up to 20 years later. The likelihood of a fatal outcome on the first day of the event in the lowest quarter of FEV$_1$ or FVC was double that of the highest quarter (p<0.05). In contrast the British Regional Heart Study, of 4,434 males (aged 40-59 years at baseline) also reported an increased risk in stroke with lower baseline FEV$_1$, but those most at risk were participants with pre-existing CVD disease or hypertension.

The 10 year follow up of the 14,000 middle aged participants of the USA’s Atherosclerosis Risk in Communities Study (ARIC) found that the incidence of CVD events was negatively associated with baseline FVC and the associations were stronger in women than men (Table 1-2). The associations were independent of smoking (Table 1-2, Model 2), but after adjustment for lipid levels and diabetes status the significance of the association was reduced in males (Table 1-2, Model 3). The twenty year follow up of 1,861 40 to 60 year olds from the NHANES I also identified significant trends in hospitalization for CVD episodes across quartiles of FEV$_1$ (p=0.049), but the trend lost significance (p=0.085) when the analysis was limited to non-smokers (n=1,168).
Table 1-2: The risk of a cardiovascular event in males and females according to FVC quartile.

<table>
<thead>
<tr>
<th>Quarter of FVC</th>
<th>Events (n)</th>
<th>Model 1‡</th>
<th>Model 2§</th>
<th>Model 3#</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
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<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lowest</td>
<td>142</td>
<td>2.19 (1.57,3.05)</td>
<td>1.67 (1.19,2.33)</td>
<td>1.36 (0.97,1.90)</td>
</tr>
<tr>
<td>2</td>
<td>149</td>
<td>2.15 (1.58,2.93)</td>
<td>1.83 (1.34,2.50)</td>
<td>1.53 (1.12,2.09)</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>1.60 (1.17,2.18)</td>
<td>1.47 (1.08,2.00)</td>
<td>1.36 (0.99,1.85)</td>
</tr>
<tr>
<td>Highest</td>
<td>69</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>130</td>
<td>6.88 (4.17,11.35)</td>
<td>5.61 (3.40,9.25)</td>
<td>3.54 (2.13,5.88)</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>3.24 (1.94,5.41)</td>
<td>2.85 (1.71,4.76)</td>
<td>2.19 (1.31,3.67)</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>2.69 (1.60,4.51)</td>
<td>2.52 (1.50,4.22)</td>
<td>2.21 (1.32,3.71)</td>
</tr>
<tr>
<td>Highest</td>
<td>20</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>


FVC, forced vital capacity; HR, Hazard Ratio (95% confidence intervals);
‡Model 1, adjusted for age, race, centre and height;
§Model 2, also adjusted for smoking status (whole cohort);
#Model 3, also adjusted for BMI, diabetes, hypertension, low density lipoprotein cholesterol and high density lipoprotein cholesterol.

The above studies provided evidence of an association between lung function volumes and CVD events and their outcomes. However they also suggest that some studies may be confounded by unmeasured CVD risk. In addition, none of them attempted to describe whether the association was attributable to deficits in lung function associated with restrictive or obstructive lung condition. Results from more recent analyses of the British Regional Heart Study, NHANES and ARIC data, which have considered FEV₁, FVC and FEV₁/FVC ratio, rather than just one measure of lung function have suggested that reduced FVC was as strongly associated with CVD disease and mortality as airway obstruction (indicated by reduced FEV₁ and FEV₁/FVC). Further, Burney et al concluded that in non-smokers, the association of lung function with CVD appears to be driven by FVC limitation (indicative of airway restriction, rather than obstruction) but they favoured a mechanism other than restrictive lung disease.
1.1.3 Lung function and cardiovascular risk factors in younger adults

There are few studies investigating the association of lung function and CVD outcomes in young adults as CVD events and mortality are low but there are a number of studies of lung function and CVD risk factors in young adult cohorts. One example, the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a bi-racial cohort study of around 5,000 of (18-30 year old) Americans established in 1985-6, found associations between baseline FEV$_1$ and FVC volumes of cohort participants were associated with higher levels of physical activity, higher high density lipoprotein (HDL) cholesterol, lower serum triglycerides and lower fasting insulin\textsuperscript{65} (Table 1-3).

Table 1-3: Correlation coefficients for CVD risk factors with FEV$_1$ data from the CARDIA study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Males n=1,125</th>
<th>Females n=1,223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>-0.09*</td>
<td>-0.15**</td>
</tr>
<tr>
<td>Subscapular skin folds</td>
<td>-0.11**</td>
<td>-0.1**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.06**</td>
<td>-0.03</td>
</tr>
<tr>
<td>High Density Lipoprotein (HDL)</td>
<td>0.07*</td>
<td>0.03*</td>
</tr>
<tr>
<td>Fitness (Treadmill duration)</td>
<td>0.08**</td>
<td>0.1**</td>
</tr>
<tr>
<td>BMI</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CARDIA, Coronary Artery Risk development in Young Adults study\textsuperscript{65}

Low-level elevations of systemic inflammatory mediators such as CRP and fibrinogen are also recognised as a predictor of CVD events and death in patients and healthy population samples.\textsuperscript{66-68}

Studies in young adults have found significant cross-sectional associations of lung function with C-reactive protein\textsuperscript{69,70} and fibrinogen, but longitudinal studies have provided conflicting results even within the same cohort.\textsuperscript{69-71} At the 10 year follow up of the CARDIA cohort, FVC (but not FEV$_1$) was predictable from levels of the inflammatory mediator fibrinogen measured 5, or 3 years, earlier (after adjustment for the 5 year FVC, age, race, sex, BMI, physical activity, oral contraceptive use and alcohol consumption, asthma status and baseline smoking status).\textsuperscript{72} The study in Chapter 6 investigates the association between CRP and lung function in the CDAH cohort.
1.1.4 Lung function and subclinical measures of arterial structure and function

**Intima medial thickness**

Cross-sectional studies of the association of FEV$_1$ with carotid intima-media thickness (cIMT) and reduced elasticity as determined by the ankle-brachial index (ABI), and presence of carotid plaques were investigated in the 14,000 strong ARIC cohort. Reduced FEV$_1$ was associated with reduced elasticity and increased cIMT (Figure 1-9) in the full cohort regardless of smoking status. However, in never smokers the association with cIMT was eliminated after adjustment for CVD risk factors. This suggests that lung function may not be causally associated with cIMT. FEV$_1$ may be an innocent bystander that is also reduced in participants with higher levels of CVD risk factors, including increased cIMT.

**Figure 1-9: Estimated mean FEV$_1$ according to measurement of the IMT. Atherosclerosis Risk in Communities Study 1987-89**

![Figure 1-9: Estimated mean FEV$_1$ according to measurement of the IMT. Atherosclerosis Risk in Communities Study 1987-89](image)

From Schroeder et al. IMT, carotid artery intima media thickness; FEV$_1$, Forced expiratory volume in 1 second; *Significant differences (p≤0.05) between FEV$_1$ & IMT reference group, (IMT<0.7 adjusted for age, race, study centre, height, height squared and sex). Full cohort also adjusted for smoking status and pack years.

More recently, a small Japanese study has compared the cIMT of middle-aged male smokers with airway obstruction with age-matched smokers without obstruction and non-smokers. Smokers with obstruction had significantly higher mean IMT (0.78mm) than never-smokers (0.73mm, p<0.01) and smokers without airway obstruction (0.78mm, p<0.005). In multivariable analysis per cent predicted FEV$_1$ was significantly negatively associated with IMT independently of BMI, smoking status, pack years, mean arterial blood pressure, heart rate, LDL, fasting glucose and CRP. This finding suggests that the smokers who had higher cIMT and airway obstruction may be a more genetically susceptible
group than those who did not have airways obstruction but this cannot be determined from this cross-sectional study.

Neither of these studies observed an association between lung function (FEV$_1$) and carotid plaques suggesting that associations between lung function and atherosclerosis might be indicative of an early stage in the disease process. In contrast, a 4 year follow up of 59-71 year old participants of a French cohort, with no history of CVD, found that the multivariate-adjusted odds ratio of carotid plaque occurrence in the bottom compared to the top fifth of baseline peak expiratory flow was 2.84 (95% CI, 1.45-5.71), (P =0.002). The odds ratio was very similar when the analysis was limited to non-smokers 2.80 (95% CI, 1.14-6.88). In addition in younger members of the same cohort (aged 29 to 56 years), average cIMT was observed to be higher in participants with bronchial hypersensitivity regardless of smoking status and asthma prevalence.

**Arterial stiffness**

The majority of studies which have investigated the association between arterial stiffness and lung function have been cross-sectional studies of COPD patients which have used PWV as the stiffness measure. Increased arterial stiffness observed in COPD patients and young adults with asthma and COPD suggest that these conditions may share a common pathway, but whether this is related to inflammatory mechanisms, changes to arterial structure, or perhaps secondary to hypoxic changes affecting musculature is not known.

In population based studies of males, PWV was found to be negatively associated with baseline FEV$_1$ and FVC after 4 years in a follow up of 174 volunteers (aged 30 to 70 years) and after 20 years in a middle-aged cohort. The associations in these studies were highly significant (P < 0.0001) and were largely unaffected by adjustment for smoking status, weight status, inflammatory mediators and metabolic factors.

Associations have also been reported in children as young as 7 years of age, whose arteries should be free of the effects of ageing. The observed associations were independent of maternal smoking and environmental smoke exposure. However the study may have residual confounding as although it was clear that some children had asthma, asthma status did not appear to be included in the analysis models.

To my knowledge, there is only one study reporting an association between lung function and cIMT in young adults. The Atherosclerosis Risk-factors in Male Youngsters (ARMY) study reported an association between low mid-expiratory flow rate (FEF$_{25-75}$) and high cIMT in 17-18 year old male smokers as an unexpected finding of their investigation of associations between CVD risk factors and
Exposure to both chronic and acute cigarette smoke is known to been associated with increased arterial stiffness\textsuperscript{87} and cIMT.\textsuperscript{88} However, the reversibility of the effects of cigarette smoke on cIMT and arterial stiffness is yet to be established. Van den Berkmortel \textit{et al.}\textsuperscript{89} found no change in cIMT or arterial elasticity two years after smoking cessation in an age sex matched sample of adults. Differences in outcomes may come from the different samples, methods of ascertaining smoke exposure or exposure to environmental tobacco smoke.

\subsection{1.1.5 Possible mechanisms and confounders}

Susceptibility to CVD and chronic lung disease may be pre-determined by genetic factors, but behavioural and environmental exposures throughout life are major contributors to the development, and the rate of progression of disease. Common early life exposures, such as retardation of uterine growth and low birth weight,\textsuperscript{90} affect lung growth and development, and genetic predisposition to disease processes have therefore been implicated as possible explanations for observed associations between lung function and CVD.

A large body of research has attributed increased risk of CVD to lifestyle factors such as smoking, poor diet, low physical activity and obesity (often a consequence of poor diet and low physical activity) to be major contributors to all chronic disease\textsuperscript{91} and premature death.\textsuperscript{92} These factors have also been associated with deficits in lung function\textsuperscript{93-95} and it is possible that they may likely be on a common pathway that leads to poor lung function and higher mortality.

The current focus of investigation appears to be the associations between lung function and insulin resistance and diabetes\textsuperscript{96} or the presence of a combination of risk factors defined as metabolic syndrome (abdominal obesity, elevated triglycerides, dyslipidaemia, elevated blood pressure, high blood glucose) as the risk of developing CVD in people with these conditions is substantially increased.\textsuperscript{97} Several studies have shown association of lung function with insulin resistance\textsuperscript{98-100} and metabolic syndromes,\textsuperscript{101,102} which are predictors of diabetes type two, a significant CVD risk factor for CVD.

Another focus of attention is on the inflammatory mediator proteins such as C-reactive protein (CRP) and fibrinogen which are also recognised as risk factors in CVD\textsuperscript{67} and have been identified in atheromatous plaques.\textsuperscript{103}

Several studies have shown that reduced lung function is associated with increased CRP, fibrinogen, and interleukins in subjects with existing lung disease such as COPD.\textsuperscript{104} Some authors favour the hypothesis that increased CVD is associated with an overspill of inflammatory activity from the lungs.
(in COPD patients)\textsuperscript{3,105} or other foci of low grade infection or inflammation. However, associations have also been observed in healthy middle-aged subjects.\textsuperscript{106} Studies investigating the association between lung function and changes in CRP levels over time however have conflicting results.\textsuperscript{69,107,108} The differences may be attributable to the means of measuring CRP as not all studies have used highly sensitive assays, but there are many biological factors and disease processes that can elevate levels of inflammatory mediators and need to be considered.\textsuperscript{109}

Elevated CRP is also associated with obesity,\textsuperscript{110} the metabolic syndrome\textsuperscript{111} and insulin resistance,\textsuperscript{112} which are all risk factors for CVD, and are also associated with reduced lung function.\textsuperscript{101} In one of the longitudinal studies elevated CRP levels were no longer associated with changes in lung function after changes in participant adiposity were considered.\textsuperscript{71}

The latest analysis of ARIC data, using a subset of 7,489 participants who had no respiratory symptoms at baseline,\textsuperscript{64} concluded that the association of lung function with mortality appears to be driven by FVC limitation through some process other than restrictive lung disease. Central adiposity is a potential culprit for such lung restriction, as excess adiposity centrally can restrict diaphragm movement and result in lung under-inflation (reducing FVC). Although adjustments were made for adiposity in this study, the measures used (waist hip ratio and BMI), may not be the best measures with which to assess the effects of adiposity on this association, particularly in females. Association between adiposity and lung function is the topic of Chapter 5 in this thesis.

As increased CVD risk and reduced lung function, elevated inflammatory mediators and insulin resistance are all associated with the lifestyle factors indicated above it is possible that the observed associations between lung function and CVD may be a result of confounding by these factors rather than a true association (Figure 1-10). It is possible that reduced lung function may be on the pathway to poor cardiovascular health, or may be an additional independent consequence of these exposures.
Figure 1-10: Modifiable CVD risk factors - possible confounders of the association between lung function and CVD

Smoking
Low physical activity
Poor quality diet
Obesity

Cardiovascular disease

Reduced lung function

?
1.2 Summary of the literature

- There is a clear association between reduced lung function and all-cause mortality regardless of smoking status. The associations appear stronger in females.

- There is an increased risk of CVD mortality in patients with obstructive lung disease.

- In some population samples it appears that restrictive effects on lung function may be associated with higher risk of CVD events.

- Subclinical measures of CVD (cIMT and arterial elasticity) are useful in determining the risk of future CVD events.

- Lung function is negatively associated with cIMT in older adults but the association is attenuated in smokers and eliminated in non-smokers after adjustment for other CVD risk factors.

- Reduced lung function and CVD have several risk factors in common: smoking, obesity, low levels of physical activity and cardiorespiratory fitness, poor nutrition and the presence of elevated inflammatory mediators.

- In general, the literature on the associations between lung function and CVD in young adults is limited. What is available, concentrates on the effects of smoking and asthma in small samples of participants not necessarily representative of the population from which they are drawn.
1.3 Aims

The aim of this thesis was to investigate associations between clinical measures of lung function with known CVD risk factors in a population based sample of young adults, aged 26-36 years, with no pre-existing cardiovascular morbidity.

The specific aims were:

- To understand the associations between three modifiable CVD risk factors (smoking, physical fitness and obesity) and young adult lung function.

- To investigate the cross-sectional association of lung function with inflammatory mediators, in particular C-reactive protein (CRP).

- To add to the knowledge of the relationship between lung function and CVD disease as determined by subclinical measures of arterial structure and function. In particular by investigating the contribution of the above modifiable CVD risk factors, CRP and other traditional risk factors, such as blood pressure and lipid levels, to the association.
1.4 Thesis outline

The main body of this thesis is presented in two parts.

Part one, examines associations between three well-established risk factors for CVD (smoking, obesity and physical fitness) and the lung function of young adults. These investigations helped to better understand the relationships between these factors and lung function, before considering their influence or contribution to any association between lung function and inflammatory mediators or subclinical measures of endothelial dysfunction.

Cross-sectional associations of smoking, physical fitness and obesity with adult lung function are examined using adult data collected for CDAH between 2004 and 2006.

Longitudinal effects of these risk factors on lung function are investigated using data from childhood collected by the ASHFS investigators, 20 years previously, when participants were between 7 and 15 years of age.

Part two, examines the cross-sectional associations between the inflammatory mediator C-reactive protein and lung function and investigates whether associations between CRP and lung function are independent of adiposity.

Finally, cross-sectional associations between lung function and measures of arterial structure and function are examined to determine whether lung function might potentially be an indicator of subclinical atherosclerosis.
Chapter 2: Methods
2.0 Preface

This chapter describes the data source and measures used in this thesis. Further detail is available in specific chapters. ASHFS study details are described only where relevant.

2.1 The study sample

The study sample for this investigation was a population-based sample of Australian men and women first measured in 1985 when they were children aged 7 to 15 years of age. The survey was called The Australian Schools Health and Fitness Survey (ASHFS).\textsuperscript{113} The follow up, 20 years later, was named the Childhood Determinants of Adult Health (CDAH) study.

2.1.1 ASHFS, the cohort and its characteristics

The aim of the baseline study was to obtain a cross-sectional snapshot of the physical fitness and health of Australian schoolchildren and collect information on their behaviours and attitudes in 1985. The data were intended to be used for future Australian comparisons and comparison with other countries. At that time, there was no intention of follow-up participants at a later date. The main aim of CDAH was to investigate how biological and lifestyle factors in childhood affect an individual’s risk of developing CVD as an adult.

A two-stage probability sampling method, routinely used to estimate academic performance, was used to select a random sample of primary, secondary, public and private schools in all Australian States and Territories. The sample plan was to include 500 children of each sex per chronological age from 7 to 15 years. Schools were selected in the first instance and of 121 schools approached 109 (90.1\%) agreed to participate. Although the target sample size required only 10 boys and girls of each age per school, parents of a random sample of 15 boys and 15 girls of each age were asked for their consent in order to allow for potential refusals, illness or data collection errors. In total 12,578 students were approached and 8,498 were included in the analysis. The original survey reported 8,484 participants\textsuperscript{113} but, when the data were reviewed in 2,000, an additional 14 participants were identified. The distribution of schools included in the baseline study is shown in Figure 2-1.
2.1.2 Tracing and follow up of ASHFS participants

To trace the original ASHFS participants, their name and date of birth were sent to the Australian National Death Index (NDI) and the Australian Electoral Commission (AEC). Of 120 potential matches from the NDI, 86 participants were identified as being deceased. The AEC provided addresses for 4183 participants, however only 40% proved current. Thus, the remaining 6,371 participants had to be traced by other means such as identifying participants and other family members in historical electoral rolls or telephone directories and through press coverage or other participants.

In total, 6,836 (80.4%) of the original ASHFS participants were traced and 5,170 (60.7%) agreed to participate in the follow-up. Those originally resident in the Northern Territory were the most difficult to trace. In addition, for one inner Sydney school where more than 50% of participants were born outside Australia and spoke a language other than English at home, only 49% of participants were traced compared to an overall average of 80.5%.

Compared to those not contactable, or unwilling to participate in the study, the 5,170 (60.7%) ASHFS participants who agreed to participate were older and more likely to be female, Australian born, native English speakers. An outline of the tracing process and the level of participation in CDAH are presented in Figure 2-2.
Figure 2-2: Flow diagram of tracing and recruitment of ASHFS participants and their participation in CDAH

8498 original ASHFS participants

Name and date of birth matched with AEC and NDI

Address info not available or not current. Participants sought using historical electoral rolls, telephone directory, internet searches, media and other participants N=6371

Address information available and current N=2041

Participants sent letter of invitation to participate N=6754

Participates consented to follow up and completed enrolment questionnaire N=5170

Completed study questionnaires only N=1146

Sent study questionnaires and invited to one of 34 clinic sites

Attended clinic, and completed study questionnaires N=2410

Completed study questionnaires & attended external path laboratory N=192

Unwilling or unable to attend clinic or complete questionnaires N=467

Lost to follow-up N=701

Lost to follow-up N=1658

817 No response

767 Refused

2001-2003

86 Deceased

AEC: Australian Electoral Commission. NDI: Australian National Death Index
2.1.3 CDAH participation

At enrolment (2001-2003) participants provided basic self-reported data on height, weight, smoking status and marital status by postal questionnaire or by telephone and consented to being contacted again in ‘a couple of years’ time’ for a health check and more detailed questionnaires.

Between 2004 and 2006, participants were invited to attend one of 34 ‘health check’ clinics across Australia (Figure 2-3) for physical measures and to complete more detailed questionnaires. Appendix 1 has a copy of the participant information leaflet sent to participants prior to clinic attendance. In an attempt to maximise attendance, clinics venues were selected in areas with the highest numbers of enrolled participants living within a 10km radius of the proposed site.

Figure 2-3: Geographical distribution of the 5170 enrolled CDAH participants and 34 CDAH clinic locations
CDAH clinics were held in the morning between 6:30am until around 1pm and a total of 2,410 participants (1,150 male) attended after an overnight fast (28.4% of the original ASHFS sample). Venues included church halls, school halls, sports halls and community centres.

A summary of the numbers of ASHFS participants who were traced, and the level of participation in CDAH by sex and state is presented in Table 2-1. Comparison of demographic features of enrolled participants who did and did not attend clinics showed that those attending clinics tended to be slightly older when they took part in the 1985 ASHFS study (11.1 years versus 10.9 years) and more highly educated (44% with degree or post-graduate qualifications versus 29% in the non-attenders). Marital status was similar in both groups. There were no significant difference in clinic attendance rates between those who completed the full complement of physical measures in the ASHFS study (when aged 9, 12 or 15 years) and those who completed only basic measures.

### Table 2-1: Tracing and participation in CDAH according to sex and state of origin in 1985

<table>
<thead>
<tr>
<th>State of residence in 1985</th>
<th>ACT</th>
<th>NSW</th>
<th>NT</th>
<th>QLD</th>
<th>SA</th>
<th>TAS</th>
<th>VIC</th>
<th>WA</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females (N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traced</td>
<td>70</td>
<td>1153</td>
<td>60</td>
<td>594</td>
<td>288</td>
<td>76</td>
<td>894</td>
<td>278</td>
<td>3413</td>
</tr>
<tr>
<td>(81%)</td>
<td>(80%)</td>
<td>(69%)</td>
<td>(80%)</td>
<td>(81%)</td>
<td>(94%)</td>
<td>(86%)</td>
<td>(80%)</td>
<td>(81%)</td>
<td></td>
</tr>
<tr>
<td>Enrolled</td>
<td>59</td>
<td>887</td>
<td>45</td>
<td>492</td>
<td>232</td>
<td>64</td>
<td>720</td>
<td>233</td>
<td>2732</td>
</tr>
<tr>
<td>(69%)</td>
<td>(62%)</td>
<td>(52%)</td>
<td>(66%)</td>
<td>(66%)</td>
<td>(79%)</td>
<td>(79%)</td>
<td>(69%)</td>
<td>(67%)</td>
<td>(80%)</td>
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<tr>
<td>Attended Clinic</td>
<td>33</td>
<td>356</td>
<td>24</td>
<td>230</td>
<td>111</td>
<td>30</td>
<td>361</td>
<td>115</td>
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</tr>
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<td>(38%)</td>
<td>(25%)</td>
<td>(28%)</td>
<td>(31%)</td>
<td>(31%)</td>
<td>(37%)</td>
<td>(37%)</td>
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<td>(33%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>Participated at any level</td>
<td>50</td>
<td>692</td>
<td>40</td>
<td>390</td>
<td>179</td>
<td>49</td>
<td>561</td>
<td>171</td>
<td>2132</td>
</tr>
<tr>
<td>(58%)</td>
<td>(48%)</td>
<td>(46%)</td>
<td>(52%)</td>
<td>(51%)</td>
<td>(61%)</td>
<td>(54%)</td>
<td>(54%)</td>
<td>(51%)</td>
<td></td>
</tr>
</tbody>
</table>

| **Males (N)**             |     |     |    |     |    |     |     |     |         |
| Traced                    | 73  | 1137| 67 | 589 | 288| 77  | 918 | 278 | 3427    |
| (82%)                     | (76%)| (76%)| (79%)| (81%)| (88%)| (85%)| (77%)| (80%)|         |
| Enrolled                  | 51  | 803 | 38 | 443 | 212| 50  | 648 | 192 | 2497    |
| (58%)                     | (53%)| (43%)| (59%)| (60%)| (56%)| (60%)| (60%)| (54%)| (58%)    |
| Attended Clinic           | 32  | 356 | 17 | 192 | 98 | 33  | 334 | 88  | 1150    |
| (36%)                     | (24%)| (19%)| (26%)| (28%)| (38%)| (31%)| (25%)| (27%)|         |
| Participated at any level| 41  | 590 | 26 | 352 | 155| 43  | 481 | 131 | 1819    |
| (47%)                     | (39%)| (30%)| (47%)| (44%)| (49%)| (44%)| (37%)| (42%)|         |

Traced participants were located at current address/telephone number or were deceased (n=86)
Enrolled participants completed a short demographics questionnaire (between 2001 and 2004)
Participation at any level includes clinic participants and participants who self-completed full study questionnaires (n= 435) or self-completed/telephone administered shortened questionnaires (n=909)

### 2.2 Data collection

An overview of the data collected in ASHFS and CDAH is presented in Figure 2-4 below. Details of measurement protocols in 1985 have been published elsewhere. Where possible, CDAH measures used the same devices and similar protocols to the original study. Participant measures at baseline
and follow up included CVD risk factor measures (e.g. body dimensions, blood pressure, blood lipids, smoking status and parental smoking status and physical activity measures), lung function and fitness.

**Figure 2-4: Overview of study measures at baseline and follow up**

A flow diagram illustrating the passage of participants through the CDAH clinics is shown below in Figure 2-5. This order was strictly maintained, in order to fulfil the requirements of the study measures, and to maximise the comfort and safety of participants. With the exception of the ultrasound technician and phlebotomist, the study recruited and trained technicians (mainly health science students or graduates) in each State. The project manager supervised data collection staff and performed continuous quality assurance evaluations at each clinic site.

On arrival at the clinic, participants completed an ‘Exclusion questionnaire’ that allowed clinic staff to identify any medical condition or previous injury that might preclude participants from completing any of the study measures. A copy of the exclusion questionnaire, used to determine the level of participation appropriate for each individual, is presented in Appendix 2.
2.2.1 The clinical measures

**Lung function**

At baseline, a vitalograph was used to measure lung function from the better of two recordings of the FEV₁ and FVC while the participant was seated with a nose clip in place.\(^{104}^{105}\)

At follow up, spirometry was performed in accordance with the ATS guidance documented in the paper by Miller et al. “General considerations on Spirometry.”\(^9\) Spirometry was performed in a standing position, using a MicroLab 3500 portable spirometer connected to a computer containing *Spida 5* software. The best combination of FVC and FEV₁, and FEF₂₅-₇₅ were recorded from a maximum of eight flow loops. A 3 litre syringe was used to calibrate the spirometer before each session of use (daily). Testing only proceeded if the calibration showed less than 5% difference between recorded test volumes.

The analysis presented in the following chapters include the best spirometry volumes from all participants with a valid flow volume loop, rather than the best of at least three, as recommended in the second paper in the series “Standardisation of spirometry.”\(^{10}\) However, in this paper, Miller et al indicate that the repeatability criteria are not recommendations to exclude participants from a study.
Prior to spirometry, participants were asked the details of any current lung condition, what medication, if any, they take for it and when they last took that medicine. Information on smoking status, any lung condition and how many cigarettes smoked per day was obtained by questionnaire. Responses to questions on the use of medications prior to spirometry and in the general study questionnaire were used as an indication of a diagnosis of current asthma (where relevant). Thirty-eight participants reported using asthma medication prior to their lung function test however the time of last use was not used in any of the analysis presented in the following chapters.

In addition to raw lung function volumes, the computer attached to the spirometer generated per cent predicted lung function for each participant. Two sets of prediction equations were trialled for use with the CDAH data. The first, provided by the spirometer computer software, was based on a sample of non-smoking North Americans (Knudson et al),\textsuperscript{114} the second was generated from a relatively small sample of non-smoking South Australian adults (n= 165 males and 249 females) aged 18-78 years of whom only 18% were between 25-34 years of age.\textsuperscript{115} Neither set of equations accurately predicted the lung function of our 26-36 year old Australian participants. As a result, the majority of the analyses in this thesis are based on adjustment of raw lung function volumes in accordance with the advice of Vollmer et al.\textsuperscript{116} However, in Chapter 5 (in response to peer review) prediction equations by Hankinson et al.,\textsuperscript{11} derived from NHANES data, were employed for the assessment of longitudinal trends in lung function between childhood and adulthood.

**Anthropometry**

In 1985 ASHFS participants wore sports kit for their assessment. At follow up in 2004-2006 participants wore light clothing. Participants' height, in bare feet, was measured using a Kawe height tape or rigid measuring tape at baseline and a Leicester height measure at follow up. They were weighed using daily-calibrated beam or medical spring scales at baseline and Heine scales at follow up. At follow up, pregnant women and one individual who attended clinic wearing a plaster cast were not weighed.

Height and weight were used to calculate body mass index (BMI), the most commonly used measure of adiposity in epidemiological studies, using the formula: $\text{BMI} = \frac{\text{weight, kg}}{(\text{height, m})^2}$. Adults were categorised as underweight, healthy weight, overweight or obese according to WHO criteria if their BMI was less than 18.5 kg/m\(^2\), between 18.5-24.9kg/m\(^2\), between 25.0-29.9kg/m\(^2\), or greater or equal to 30kg/m\(^2\) respectively. Participants were classified as overweight or obese in childhood according to the cut-points determined using pooled international data.\textsuperscript{109} Waist and hip circumferences were measured to the nearest 0.1cm with a constant tension tape at both time points.
Technicians, trained in accordance with the International Standards Anthropometric Assessment required by the International Society for the Advancement of Kinanthropometry (ISAK),\textsuperscript{117} used anatomical landmarks to locate and measure skin folds on the participants right side. Tricep, bicep, sub-scapular and sub-iliac skinfolds to the nearest 0.1mm were recorded after the callipers had been applied for 1-second using Holtain callipers (Holtain Ltd. UK) at baseline and Slim Guide callipers (SPRI products Inc. Illinois, USA) at follow up. Each site was measured three times and if there were differences between readings the average of the two closest readings was used as the location specific score. Due to the limited size of the callipers, skinfold measures above 40mm at follow-up were truncated and their true skinfold measures were predicted from BMI and waist circumference using Tobit regression. The sum of skin folds was then logarithmically transformed and used to estimate body density, using the equations of Durnin and Rahaman\textsuperscript{118} for 12 and 15 year old children and Brook for 9 year old children\textsuperscript{119} at baseline, and the equations of Durnin and Womersley\textsuperscript{120} for adults at follow-up. Calculations of body fat percentage were made using the equation specified by Siri: \( \% \text{Body Fat} = \frac{(495 / \text{Body Density}) - 450}{495} \).\textsuperscript{121} Fat free mass (or lean body mass (LBM)) was then estimated by subtracting fat mass from weight. (LBM= weight – ((fat x weight)/100). This methodology, although reported to have some inaccuracies at the individual level,\textsuperscript{122} has been found to be valid for estimating fat mass and lean mass in population samples of Australians of mainly Anglo-saxon origin.\textsuperscript{123}

**Muscular strength**

Several muscular strength measures were obtained at baseline and follow up. However, as there have been consistent reports of an association between handgrip strength and FVC, independent of age and height\textsuperscript{49,124,125} grip strength used as an indicator of participants’ muscular strength in this study.

At baseline and follow up, maximum grip strength was measured using a Smedley’s spring-type hand dynamometer: a pair of short parallel bars (adjusted for hand size) held between the flexed fingers and the palm with counter-pressure applied by the thumb (Figure 2.6). This hand dynamometer measures hand strength, against spring pressure, in a range from 0-100 kg in 0.5 kg divisions. After use the pointer remains at the maximum pressure until moved manually back to zero.
At follow up, the participant squeezed the bars as hard as possible and maintained maximal effort for two to three seconds. Three attempts were made for each hand with at least 1-minute rest between successive attempts on the same hand. The average of the three dominant and three non-dominant hand scores were used in the analysis.

**Cardio respiratory fitness**

At baseline and follow up, cardiovascular fitness (CRF) was estimated using a sub-maximal exercise test of physical work capacity (PWC) on a friction based bicycle ergometer (Monark Exercise AB, Sweden) pedalled at a cadence of 60 revolutions per minute. The protocol had three staged workloads of three minutes duration at baseline, and four minutes at follow up. The participant’s heart rate was monitored during the test, using a stethoscope in 1985, and a Polar heart rate monitor (Model M22, Polar Electro, Finland) at follow-up. Workloads were selected on an individual basis in order to induce steady-state heart rate responses within the ranges of 115-130, 130-145, and 145-160 beats per minute by the participant at the end of the first, second and third workloads respectively. At follow up there were occasions where a fourth workload stage was added if the target heart rate was not achieved.

The work capacity at a heart rate of 170 beats per minute (PWC$_{170}$) was then estimated by extrapolating the line of best fit from the heart rates recorded during each workload. At baseline only those aged 9, 12 or 15 years at examination had their PWC$_{170}$ measured. At CDAH clinics, pregnant women and those with a history of CVD were among those excluded from fitness testing (Appendix 2).
**Blood pressure**

At follow up participants’ sat quietly for at least 5 minutes with legs uncrossed before their blood pressure was measured on the right arm using an OMRON HEM907 digital automatic blood pressure monitor (Omron Corporation, Kyoto, Japan). Adult systolic and diastolic blood pressures were determined from the mean of three readings. Participants were given a one minute to rest between measurements.

**Blood measures**

A list of the blood markers measured was presented in the Venn diagram in Figure 2.4.

At follow up venous blood samples were collected from participants by an experienced MedVet phlebotomist after an 8 hour fast. MedVet is the commercial laboratory of the Institute of Medical and Veterinary Science (IMVS) located in Adelaide, South Australia and was the central processing laboratory for all CDAH blood samples. Blood samples were allowed to clot for 15 minutes. After centrifugation the serum was aliquot into fresh sample tubes and maintained at less than 4 degrees Centigrade until transfer to the central analysing laboratory. Temperature sensors included the insulated packaging indicated that the mean temperature during transportation was 2.6°C (range 0.7º to 3.6ºC).

Blood samples were obtained from 2,313 (96.0%) of CDAH clinic participants. Serum total cholesterol, triglyceride, and HDL cholesterol concentrations were determined enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). LDL cholesterol was calculated using the Friedewald formula: LDL cholesterol = total cholesterol - (triglycerides/2.2 + HDL cholesterol). Because of limited financial resources, assay of adult serum C reactive protein (CRP) was restricted to clinic attendees who had blood results available from 1985 (n=460) in the first instance. Samples not assayed at this time (n=1,800) were stored at -70 ºC until 2009 when additional funds for testing were obtained.

At both time points, serum C-reactive protein was determined using an automated analyser (Olympus AU5400) and a highly sensitive turbidimetric immunoassay kit (Olympus System CRP Latex reagent; Olympus Life and Material Science Europa GmbH, Ireland). There were no significant differences in the median values and distribution of CRP assayed in the fresh and frozen blood samples (p=0.46).
To examine measurement errors associated with processing, and analysis of blood samples, duplicate samples from the first participant scheduled for each clinic day were conducted by technicians blinded to the findings of the first run.

**Adult carotid artery ultrasound measures**

Ultrasound studies of participants’ left common carotid artery and left carotid bulb were performed according to a standard protocol using a portable Acuson Cypress ultrasound machine (Siemens Medical Solutions USA Inc., Mountainview, CA, USA) with a 7.0-MHz linear-array transducer by one trained technician who travelled to each of the 34 CDAH clinics (Figure 2-7).

Before being used in the field clinics a validation study, using a convenience sample of 23 healthy young adults, compared images of the brachial and carotid arteries generated using the Cypress ultrasound machine with those from a machine routinely used in clinical practice (Acuson Sequoia 512, Siemens Medical Solutions USA Inc., Mountainview, CA, USA). The results of the study indicated that there was a high level of agreement between the two machines. The mean difference observed for mean cIMT was -0.025mm (standard deviation 0.028mm) and the mean difference in brachial flow mediated dilatation was 0.27%.

*Figure 2-7 The Acuson Cypress portable ultrasound machine*
Several 3-5 second real-time images from the B-mode ultrasound of the carotid bulb and approximately 30 mm of the common carotid artery were made and stored in digital format for off-line analysis using Image Pro Plus version 5.02 (Media Cybernetics, Inc., Silver Spring, MD, USA). Each image was given a quality score (1, excellent (80%); 2, average (19%) and 3, unacceptable (1%) based on the presence of clear vessel boundaries. End systolic and end diastolic diameters were measured (twice) from the two best quality, end-diastolic, digital images. From these, the mean maximal and minimum diameters were calculated. Six measures of the carotid intima-medial thickness (cIMT) were then made from the distal wall of the common carotid at approximately 10 mm before the border of the carotid bulb (Figure 2-8).

Figure 2-8: The common carotid artery and the site of cIMT measurement, 10mm from the carotid bulb border

Arterial diameter and cIMT measurements were made by one of three readers. A sensitivity analysis of the inter-individual variation in measurement between readers was completed and significant differences in the mean cIMT were apparent. As allocation of images to reader had not been random, linear regression methods were used to correct for the minor differences in the measurements made by the three readers. Adjustments that equalised the means of each summary measure (mean IMT) at common values of age, BMI, waist circumference and, after stratification for sex, oral contraceptive use by women were used to calculate corrected values.
Three coefficients of local carotid arterial elasticity were determined using brachial blood pressure and the systolic and diastolic carotid artery diameter measured in good quality images (quality score 1 or 2). The three measures were: The distensibility coefficient (Cd), (KPa⁻¹), the relative change in vessel diameter associated with a given change of pressure is a measure of the artery’s ability to expand as a response to pulse pressure; the “Stiffness Index” (SI) a measure of arterial stiffness independent of blood pressure and the Young’s elastic modulus (YEM). The YEM is the pressure increase per cm² for a theoretically 100% stretch from resting length but it also takes the thickness of the arterial wall into consideration. YEM (KPa cm⁻¹) is calculated by dividing the arterial diameter by the Cd multiplied by the cIMT. A lower the Cd, results in a higher YEM and a higher YEM indicates higher arterial stiffness. The equations used to calculate these indices are presented in chapter 7.

Measures of cIMT and carotid artery elasticity have previously been shown to be well correlated with traditional cardiovascular disease risk factors and are predictive of coronary artery disease and stroke.

2.2.2 Questionnaires

At baseline only participants 9 years of age and older completed study questionnaires, which requested information on physical activity, health knowledge, behaviours and attitudes to health.

At follow up, participants completed questionnaires at two stages. The first, at enrolment, requested basic demographic information, height, weight, and smoking habits. Then, in conjunction with the CDAH clinics, participants were sent a set of three questionnaires for self-completion at home. A general questionnaire requested information on demographics, medical history and family history, smoking status and history. It also included, the Short Form health (SF-12) general well-being questionnaire, the Henderson social support and a NEO five factor personality test. Females were also asked about their reproductive history. A physical activity questionnaire included the long version of the International Physical Activity Questionnaire (IPAQ) (that asks about work, leisure and total physical activity in the previous seven days in addition to time spend sedentary) and a historical summary of leisure time physical activities since 1985. At clinic participants also self-completed the CIDI mental health questionnaire, using a lap top computer. (A copy of the general questionnaire is attached at Appendix 3 for reference.)

The questionnaires were sent to participants along with the details of their clinic appointment and their participant information leaflet. Participants were asked to return completed questionnaires to the clinic. In some instances questionnaires were returned by post. Participants who did not return their questionnaires were contacted to do a shortened version of the questionnaire by telephone.
2.3 Statistical methods

Potential confounders and covariates for the analyses in this study were selected \textit{a priori} after literature review. Additional potential confounders were identified when assessing the characteristics of the sample using cross-tabulations, t-tests and correlations. To determine which of the identified variables were confounders or effect modifiers, bivariate associations between the independent variables (spirometry measures) and each factor were investigated before stepwise addition to regression models. With the exception of smoking status and current asthma, which were included in all regression equations, variables were only considered confounders if they resulted in a 10\% change in the regression coefficient for either males or females.

Interactions were tested where biologically plausible and where differences were observed by groups. Polynomial regression techniques have been used to investigate the possibility of nonlinear associations.

All statistical analyses were performed using STATA Versions 10 or 10.1 (STATA Corp, College Station, TX, USA), and statistical significance inferred at a 2-tailed P-value ≤0.05. More detailed statistical methods are provided in each chapter.
Part1: Modifiable cardiovascular risk factors and young adult lung function
Chapter 3: The effect of smoking on the lung function of young adults
3.0 Introduction

Tobacco smoke is an important modifiable risk factor for both CVD\textsuperscript{130-132} and chronic obstructive pulmonary disease (COPD)\textsuperscript{133} as well as many cancers and all-cause mortality.\textsuperscript{134,135} In vivo and in vitro studies have shown that cigarette smoke causes acute and chronic airway and systemic inflammation, and changes in endothelial function. Antioxidants such as vitamin A and C are reduced, increasing lipid peroxidation and inflammatory mediators such as CRP while fibrinogen and other plasminogen activators are reduced resulting in increased plasma viscosity. Nitric oxide levels are also decreased which increases the susceptibility of the endothelium to inflammatory processes.\textsuperscript{136}

Since 1964, the Surgeon General’s office of the United States (US) has published successive reports reviewing the evidence of the adverse effects of active and passive tobacco smoke exposure. In 2010, the Surgeon General’s report comprehensively reviewed the mechanisms by which cigarette smoke causes tissue damage in every organ system (Figure 3-1) and concluded that “There is no risk-free level of tobacco smoke and no safe tobacco product.”\textsuperscript{137}

Figure 3-1: Health outcomes causally linked to cigarette smoking or passive exposure to cigarette smoke

![Diagram of health outcomes](from 2010 Surgeon general’s report.\textsuperscript{137})
In response to many public health campaigns, the prevalence of smoking is declining in Australia and in most developed countries. The proportion of Australians who were daily smokers decreased from 24% to 17% between 1997-8 and 2007.\textsuperscript{2} The highest prevalence was in young adults (Figure 3-2). Adolescent females in particular, appear to be less receptive to public health messages than males.

\textbf{Figure 3-2: Prevalence of daily smoking in Australia in 2007}

Currently there are few contemporary data available on the effect of cigarette smoking on the lung function of young adults. The aims of this chapter are therefore i) to review the evidence on the known health effects of exposure to cigarette smoke in childhood and young adulthood and ii) to assess the effects of cigarette exposure on the lung function of young adult CDAH participants aged 26-36 years.
3.1 Literature review

This literature review was based on searches of Web of Science and PubMed electronic databases using combinations of the text words: ‘smoking, smoke, cigarette smoking’, ‘lung function’, ‘forced expiratory volume’, ‘vital capacity’, ‘population sample’ or ‘young adults’ in the title, keywords or abstract. As childhood exposure to tobacco smoke may also have long term effects on lung function, searches also included ‘children’, ‘passive’ and ‘parental’ as key text words. Studies restricted to participants with pre-existing lung diseases, or other co-morbidities, were excluded. References cited by the articles retrieved were also scanned, to identify any of relevance.

3.1.1 Exposure in utero and early childhood

In 1998-99, a systematic comprehensive review of the respiratory effects of passive cigarette exposure in children was published in a series of articles in Thorax.\textsuperscript{138,139} The review concluded that schoolchildren exposed to parental cigarette smoke had lower mid expiratory flow MEF and FEV\textsubscript{1} compared to those not exposed, suggesting early signs of airway obstruction. (Table 3-1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>% Difference (95%CI)</td>
</tr>
<tr>
<td>FVC</td>
<td>19</td>
<td>-0.2 (-1.9,0.1)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>21</td>
<td>-0.9 (-1.2,-0.7)</td>
</tr>
<tr>
<td>MEF</td>
<td>19</td>
<td>-4.8 (-5.4,-4.3)</td>
</tr>
</tbody>
</table>

FEV\textsubscript{1}, forced expiratory volume in 1 second; FVC, forced vital capacity; MEF, mid expiratory flow rate
Reproduced from Cook et al\textsuperscript{139}

Where comparisons were possible, maternal rather than paternal exposure had the most significant effect on childhood lung function, suggesting that the observed effect may be the result of in utero exposure. An Australian study included in the review also reported a dose response relationship between the respiratory function of neonates (1-7 days after birth) and exposure among mothers who smoked while pregnant\textsuperscript{140} but the differences observed shortly after birth were much reduced by 18 months of age. It is possible that such recovery may be similar to improvements observed in the lung function of ex-smokers after quitting.
More recently the multi-centred International Pollution and The Young Study (PATY) has investigated the differential effects of exposure to environmental tobacco smoke (ETS) in utero and in childhood on the lung volumes of 22,712 children, aged 6-12 years.\textsuperscript{141} The effects were of a similar magnitude to those estimated from Cook’s meta-analysis described previously.\textsuperscript{139} In utero exposure was associated with a significant reduction of 3-6% in MEF volumes in childhood; the Maximal Mid Expiratory Flow (MEF) was reduced by 4% and the odds of having MEF less than 75% predicted was increased by 40%. The effects of exposures to environmental tobacco smoke in the first two years of life were weaker than, but independent of, in utero exposure and resulted in reductions of 0.5% and 2% for FEF\textsubscript{25-75} and MEF\textsubscript{50} respectively. This study also reported that children exposed to tobacco smoke in utero and at the time of the study (aged 6-12 years) had 1% higher MEF\textsubscript{75} than those not exposed in childhood. Paradoxically, children not exposed in utero but subsequently exposed to environmental tobacco smoke in childhood had 1% lower peak expiratory flow volumes (PEF) than children never exposed. This suggests there may be a developmental adaptation in response to in utero tobacco exposure. A study following infants for the first 18 months after birth found that the reductions in flow attributed to maternal smoking reduced gradually from 17% to 5% during this time-period.

\textbf{3.1.2 The effect of passive childhood exposures on adult lung function}

Determining the effects of childhood exposure to parental smoking on lung function in adulthood is problematic as, in addition to the effects of passive exposure to parental cigarette smoke, children whose parents smoke are almost twice as likely to become smokers themselves.\textsuperscript{133,134}

The effect of parental smoking on adult lung function was studied in two large cohorts. In the multi-centred European Community Respiratory Health Survey (ECRHS)\textsuperscript{142} (n=7,678 men and 7,799 women), childhood exposure to parental cigarette smoke (paternal for males and maternal for females) was found to be associated with a greater likelihood of wheeze in adulthood. Maternal cigarette smoke was associated with significant reductions in FEV\textsubscript{1} and FER in current smoking males, the FEV\textsubscript{1} of current smoking females, and the FEV\textsubscript{1}/FVC ratio of both ex- and never smokers. Similarly, the Scottish MIDSPAN study of 884 male and 1,116 females (aged 30 to 59 years) observed that maternal smoking was positively associated with personal smoking and with reduced FEV\textsubscript{1} and FVC independently of adult smoking status. However, evidence of airway obstruction (reduced FEF\textsubscript{25-75} or FER) was apparent only in current smokers.\textsuperscript{143} Among ever-smokers who were also exposed to maternal smoking, of at least 10 cigarettes per day, the prevalence of obstructive airways disease was almost twice that of those not exposed (RR 1.7 (95% CI: 1.2 to 2.5)). The authors estimated that exposure to maternal smoking of 10 cigarettes per day was equivalent to ten years of personal...
Chapter 3: The effect of smoking on the lung function of young adults

smoking. These studies suggest that early life exposures do affect adult lung function but behaviours and exposures in later life are potentially more important for the development of obstructive lung disease.

In Australia a follow up of a cohort of 1,185 male and 1,224 female children of mothers, recruited during pregnancy in 1981, investigated the effects of maternal smoking on their lung function at age 21. Significant negative associations were found for male FEF$_{25-75}$ and FEV$_1$ but lost statistical significance after adjustment for asthma at age 14. Unfortunately as the authors appear to have used smoking status at age 14 (rather than 21) to classify participants’ smoking status it is possible that the observed effects on forced expiratory flow measures may be confounded by participants’ adult smoking status.

3.1.3 Cross sectional associations of smoking and lung function, in adolescents and young adults

A number of studies of adolescents and young adults have demonstrated a positive cross-sectional association of cigarette smoking with FVC and FEV$_1$. Among Dutch 13 year olds, Twisk et al. reported the partial correlation coefficients for smoking (No/Yes) were 0.22 (95%CI: 0.10 to 0.33) and 0.17 (95% CI: 0.02 to 0.20) for FVC and FEV$_1$, respectively. However the results from the Six Cities Study, presented below (Figure 3-3), indicate that although the absolute volumes of FVC were higher in smokers there is evidence of deficits in FEV$_1$, FEF$_{25-75}$ and FER.

One potential explanation for the higher FEV$_1$ and FVC volumes observed in adolescent and young adult smokers compared to non-smokers may be attributable to genetically determined factors such as lung size or the body’s response, and vulnerability, to the adverse effects of tobacco smoke. Studies of mono and di-zygotic twins suggest that around 60% of lung function may be genetically pre-determined. In discordant pairs of female twins (where one twin smoked and the other did not) the non-smoking twin had higher FEF$_{25-75}$ volumes than twins from a concordant pair of non-smoking twins.

Young adults who elect to smoke may be those with higher lung volumes. Persistent smokers are potentially a subset of smokers that are less susceptible to the adverse effects of tobacco smoke and experience fewer adverse symptoms to discourage them from continuing. This is described as the “healthy survivor” effect. Support for this self-selection and healthy survivor hypothesis has been provided by a five-year follow up of young persistent non-smokers and smokers, aged 13-23 years at baseline. The study found that although persistent male smokers, and never smokers who started smoking during the follow up period had higher baseline FEV$_1$, FVC, PEF and MEF$_{25-75}$ volumes than
persistent never-smokers, only their FVC was significantly higher at follow up. A similar trend was not seen in women. This may be because young women appear less likely to give up smoking in response to symptoms so there is less evidence of any healthy survivor effect. Such behaviour may also explain observations that for the same burden of smoking, women appear to have a greater prevalence of symptoms. Alternatively, it is also possible that young males, with poor lung function and/or respiratory symptoms, may be less likely to participate in research studies than females and may therefore be under-represented in these studies.

Figure 3-3: Dose dependent associations of direct cigarette smoke exposure and pulmonary function in 10-18 year old boys and girls

Adapted from Gold et al

The per cent differences and 95% confidence intervals for difference in the lung function parameters of 10-18 year old children according to smoking status compared to never smoking children of the same age and height.

Light smokers: ½ to 4 cigarettes per day, Medium: 5-14 cigarettes per day, Heavy: 15 or more cigarettes per day.

Volumes adjusted for age, height, residence, parental education, and maternal smoking status. FEV₁, forced expiratory volume in one second, FVC, Forced Vital Capacity, and FEF_{25-75} the forced expiratory flow between 25 and 75 per cent of the FVC.
3.1.4 The effect of active smoking on lung growth

The rate of lung growth peaks at around 12 years of age (95%CI: 8 to 17 years) in females and age 14 (95%CI: 10 to 16 years) in males, before gradually slowing as the adolescent growth spurt is completed. The annual growth in FEV\textsubscript{1} and FEF\textsubscript{25-75} for 5,158 male and 4,902 female adolescent smokers who participated in the US Six Cities\textsuperscript{145} follow up study is presented in Figure 3-4. Among females who smoked more than five cigarettes per day the rate of FEV\textsubscript{1}, and FEF\textsubscript{25-75} growth was consistently lower than never smokers and by the age of 18 their lung function already appeared to be in decline.

Figure 3-4: Mean rate of FEV\textsubscript{1} and FEF\textsubscript{25-75} growth according to age, sex and smoking status

From Gold et al\textsuperscript{145}

FVC, forced vital capacity, FEV\textsubscript{1} forced expiratory volume in the first second of the FVC and FEF\textsubscript{25-75} the forced expiratory flow between 25 and 75 percent of the FVC.

The number of children smoking at least 5 cigarettes per day at age 13, 14, 15, 16, 17 and 18 years of age were: 41, 120, 213, 311, 361 and 151, and 39, 109, 197, 254, 290 and 90 for boys and girls respectively.
Compared to never smokers, deficits in growth of FEV$_1$ detected in male smokers during early adolescence were no longer statistically significant at 17 and 18 years of age. A slower rate of growth of FVC was also seen in smokers who, at baseline, had higher FVC volumes than non-smokers (females, 25ml/year (95% CI: 10 to 39) ml; male’s 1 ml/year (95% CI: -13 to 15) ml).

Previously, a study of Bostonian adolescents had observed significant evidence of growth limitation of the FEV$_1$ and FEF$_{25-75}$ in smokers (after adjustment for age, height, somatic growth and maternal smoking). The prevalence of respiratory symptoms in smokers further reduced the rate of lung growth. Unfortunately, the attrition rate among 15 to 19 year old smokers increased with successive examinations, resulting in the prevalence of smoking in this age group declining from 37% to 10%, over the follow up period. This reduced the numbers available for comparison, and the power of the study to detect the effects of smoking.

### 3.1.5 Life-course studies of the effects of smoking on lung volumes

In 2009, lung function data from a 26 year follow up of 4,391 male and female participants of the Framingham offspring cohort (aged 13 to 71 years at baseline) were used to generate a plot of estimated FEV$_1$ over the life course, recreating the curves generated for men by Fletcher and Peto in 1977. The rate of lung function decline in those over 20 years of age was estimated using the first and last spirometry measure from any of the four follow-ups between 1971 and 1997 (27 years). Figure 3-5, shows the growth and decline of the FEV$_1$ of male and female never smokers from childhood (age 13) to old age as mean raw values and as a proportion of the mean value of the sample at age 25. For the cohort as a whole the rate of decline of FEV$_1$ either expressed as a volume or as a proportion of a baseline volume was similar for males and females (19.6ml/year (95% CI: 17.1 to 22.1) for males and 17.6ml/year (95% CI: 13.8 to 21.4) for females, p=0.266). As observed by others, the lung function of young adults appeared to plateau between the late teens and mid-twenties (17.4-25.9 years) for women and the mid-twenties to mid-forties (20-23 to up to 45 years) for males.

Some authors suggest that the observed plateau is the result of a combination of the variation in the rate of growth of individuals and the methodology used to analyse these data. The lungs of some individuals continue to grow slowly in their 20s and 30s while the volumes of others are already starting to decline. As analyses of trends generally consider the mean lung function of the sample the inter-individual variability in lung function over the life-course may be masked. Robbins et al re-analysed data from a 10 year follow up of a cohort of male metal workers (up to age 33) previously shown to have no significant slope. Using statistical techniques to identify individuals with an
increase or decline in lung volumes, 37% of participants had either an increase or decline in function during follow up. Smokers were less likely to have a positive slope.

**Figure 3-5: Lifetime Forced Expiratory Volume (FEV₁) of healthy never smokers: The Framingham offspring cohort. a) absolute volumes and b) as a proportion of FEV₁ at 25 years.**

When stratified by smoking status, continuous smoking did not affect the peak FEV₁ of females (Figure 3-6b) but, as observed by Gold et al, it reduced that achieved by males (Figure 3-6a). However, although the young smokers’ lung function appears to peak earlier than the non-smokers, it is possible that the volumes reached may not be the maximal volumes attained if these participants had realised their full potential. There were also significant differences in the rate of FEV₁ decline between smokers and healthy never smokers of both sexes. Compared to healthy never smokers, the mean FEV₁ decline in continuous smokers was 38.2ml/year (95% CI: 33.9 to 42.6) for males and 23.9ml/year (95% CI: 20.9 to 27.0) in females (p<0.05). Although the decline in per cent predicted FEV₁ was greater in males than females, when expressed as a proportion of the baseline volumes at age 25, the slopes for males and females were similar. After the age of 35 smokers are
most likely to have poorer lung function than non-smokers, there still appears to be some uncertainty in the literature as to whether smoking hastens the onset and/or increases the slope of age related declines in lung function. However, follow up of young adults into middle age has shown that participants who smoked in young adulthood have lower FEV\textsubscript{1}, FVC, FER and FEF\textsubscript{25-75} volumes than non-smokers and have almost twice the risk of developing chronic obstructive airways disease as never smokers (OR 1.89 (95% CI: 1.27 to 2.81; \(p<0.01\))).

Figure 3-6: The effect of continuous smoking over the lifetime on FEV\textsubscript{1}: The Framingham offspring cohort


Mean FEV\textsubscript{1} forced expiratory volume in one second.

NS- healthy never smokers CS continuous smokers: mean age of starting smoking was 17.5 (SD 3.6) and 18.8 (SD 4.2) for males and females respectively.
Differences in the rate of growth of lung volumes, higher mean FEV₁ and FVC and the more rapid decline in lung function, observed in young adult smokers, compared to never smokers, suggest that expected FEV₁ and FVC values generated from prediction equations using age and height data from populations of non/never smokers may potentially underestimate the effect of cigarette smoking in young adults unless some indication of their higher baseline lung function is also considered. This was illustrated by Tashkin et al.¹⁴⁹ in a cohort of never smoking adolescents and young adults aged 13-23. The per cent predicted FEV₁ of those who started smoking during the 5 year follow up was significantly higher than that of persistent never smokers but there were no significant differences between the percent predicted FEV₁ of the smokers and never smokers. If the latter result were presented in a cross-sectional study it would appear that smoking has little effect on LF.¹⁴⁹

3.1.6 Dose dependent effects of smoking

A major factor influencing the rate of decline in lung function associated with smoking is the level of exposure. The effect of increased daily consumption of cigarettes on the rate of FEV₁ decline in a cohort of 984 Australian men and women followed for 19 years¹⁵⁵ is shown in Figure 3-7. Age and smoking had significant effects on the rate of FEV₁ decline in men and women, and in males over 30 years of age there was also a dose dependent increase in the rate of age related decline according to the number of cigarettes smoked per day at follow-up.

Figure 3-7: The fall in FEV₁ for men and women combined by cigarettes smoked per day and compared to the age related decline of never smokers

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³FEV₁ forced expiratory volume in one second (adjusted for height³). NS never smokers
More recently, the Spanish arm of the European Cancer and Respiratory Health Study (ECRHS)\textsuperscript{156} found dose dependent deteriorations in the FEV\(_1\) and FER of young adults who smoked more than 10 cigarettes per day, independent of age, height, sex, geographical area, Immunoglobulin E and respiratory symptoms. Compared to participants not exposed to cigarette smoke, FEV\(_1\) was reduced by 83ml (\textit{p}=0.03) and 177ml (\textit{p}<0.01) and FEV\(_1\)/FVC by 1.2\% and 1.5\% (\textit{p}=0.02) in those smoking 10-20 cigarettes per day and more than 20 cigarettes per day respectively.

### 3.1.7 Cumulative dose effects

Despite the dose responses observed with daily exposure, current smoking status may not reflect the total exposure to cigarettes, particularly in young adults who may not have been smoking for long. In epidemiological studies, cumulative exposure is quantified as ‘Pack years’ (the number of packs of cigarettes smoked daily multiplied by the duration of exposure in years). The prevalence of poor lung function, in particular airway obstruction, increases with pack years independently of age.\textsuperscript{132,157} Estimates of the effects of each pack year of smoking on FEV\(_1\) vary, from 6ml/year for Caucasian males and females, in a cross-sectional analysis of eight large US studies,\textsuperscript{158} to 12ml/year in the Norwegian Nord-Trelag Health study.\textsuperscript{159} The results of these studies suggested that there were no differences in the effect on males and females. However the US Six Cities\textsuperscript{145} and the Tucson studies estimated FEV\(_1\) declines of 12-13ml/year for males and 7.5ml/year for females.\textsuperscript{160}

Participants with the greatest pack years are often those who started smoking in childhood and became persistent adult smokers\textsuperscript{132} These participants would be affected by the combined effects of lung growth limitation during adolescence, and an increased rate of decline in lung function associated with cigarette exposure in adulthood. The significance of cumulative exposure in a young cohort was investigated using an occupational cohort, of 391 young Canadians (aged 15-40 years in 1981-2).\textsuperscript{161} After eight years of follow up it was estimated that FEV\(_1\) decreased by 4.2ml per year for each 10 cigarettes smoked per day (\textit{p}=0.04). However, after adjustment for the number of cigarettes smoked prior to the study period, the observed effect dropped to 3ml/year, and was no longer statistically significant. This suggested that exposure to cigarettes prior to study entry was an important contributor to the decline in FEV\(_1\) during the study period.

In the literature, there are few studies of the effect of smoking on the lung function of young Australians. Excluding a recently published paper on the effects of maternal smoking on young adult lung function,\textsuperscript{162} most studies have dealt with the prevalence of asthma\textsuperscript{163} and respiratory symptoms or social issues associated with the prevalence of cigarette smoking in young adults. The last comprehensive study of the effects of smoking on the lung function of Australian adults was done in
the 1980s in Busselton\textsuperscript{155} but only 20\% of the study cohort were under the age of 40. We have no reason to assume that the effects of cigarette exposure on the lungs of the young adult Australian participants of CDAH are any different from those observed in Busselton or in other parts of the world. However, there have been considerable changes to the lifestyle of young Australians and reductions in the prevalence of adult smokers may have reduced exposure to passive smoking in the home. These factors, and differences in the composition of cigarettes and filters, may be relevant when estimating the effects of active smoking and lung function in young adults for international and intergenerational comparisons.
3.1.8 Summary of the literature

Based on the literature review, an overview of the effects of lifetime cigarette smoke exposure on lung function is illustrated in Figure 3-8, below.

Figure 3-8: Potential pathways of association between tobacco smoke exposure and adult lung function

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Behaviour</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal exposure</td>
<td>Parental smoker(s)</td>
<td>Reduced rate of lung growth and development in childhood</td>
</tr>
<tr>
<td></td>
<td>Childhood smoker</td>
<td>Lower maximally attained lung function</td>
</tr>
<tr>
<td></td>
<td>Adult smoker</td>
<td>Increased age-related lung function decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced lung function</td>
</tr>
</tbody>
</table>
3.2 Aims and research questions

Given the findings of the literature review, the aim of this chapter was to assess the effects of cigarette exposure on the lung function volumes of a population sample of young Australian adults by addressing the following research questions.

In this contemporary cohort of young Australian adults:

- How does current and cumulative exposure to tobacco smoke affect the lung function?
- Is exposure to tobacco smoke in childhood associated with lower lung function volumes?
- How does parental smoke exposure affect adult lung function?
- Are children with better lung function over-represented amongst adult daily smokers?
- Is starting to smoke in childhood associated with deficits in lung function independently of cumulative cigarette exposure?
Chapter 3: The effect of smoking on the lung function of young adults

3.3 Methods

3.3.1 Participants

Lung function measures were available for 2,247 of the 2,410 participants who attended CDAH clinics. After excluding those without information on smoking status (n=24), pregnant women (n=75), one individual with cystic fibrosis, and those without complete anthropometry measures (n=17), grip strength (n=186) or educational status at follow up (n=3), data from 1941 participants were available to investigate the effect of smoking on adult lung function.

3.3.2 Study measures

Lung function

Adult FEV₁, FVC and FEF₂₅₋₇₅ were measured in accordance with the ATS guidance, using a MicroLab 3500 portable spirometer as described in Chapter 2. The analysis presented in this chapter includes the best spirometry volumes from all participants with a valid flow volume loop. Participants were classified as current asthmatics if they reported having asthma, or taking an asthma medication on questioning prior to spirometry.

Tobacco smoke exposure

The baseline, ASHFS survey collected information about exposure to cigarette smoke in childhood from participants aged 9-15 years. The questions relating to cigarette smoke exposure are presented in Box 3-1. Participants were asked: Whether they smoked cigarettes; if they did, how long had they smoked; how many per day; whether their parents smoked and how many people, in total, smoked at home?

In adulthood information on tobacco use was obtained by questionnaire on two occasions. At enrolment (2001-2003) participants were asked whether they were currently, or ever, a regular smoker (defined as someone who had smoked at least 7 cigarettes cigars or pipes every week for at least 3 months). In the CDAH general questionnaire more detailed information was collected about smoking habits (Box 3-2).
Box 3-1: Questions on smoking exposure in the ASHFS questionnaire (1985). Children aged 9-15 years at baseline

1. Over your lifetime, have you smoked at least 100 cigarettes, or a similar amount of tobacco?
   - No --> SKIP TO SECTION 6 (Page 20)
   - Yes

2. How often do you smoke cigarettes, cigars, pipes or any other tobacco products?
   - Daily
   - At least once a week (but not daily) --> Skip to Question 7
   - Less often than weekly --> Skip to Question 7
   - Not at all --> Skip to Question 7

3. What do you currently smoke?
   (Please indicate types and enter how many you smoke)
   - Manufactured cigarettes
   - Hand-rolled cigarettes
   - Cigars
   - Pipes full of tobacco
   - [Columns for cigarettes per day, grams per week for any type of tobacco]
   * A one and three quarter ounce pouch of tobacco equals 90 grams

4. When you smoke manufactured cigarettes, which brand do you usually smoke?
   I do not smoke manufactured cigarettes.
   [Box for brand name if applicable]

5. Have there been any periods of time when you gave up daily smoking and then started smoking again?
   - No --> Skip to SECTION 6 (Page 20)
   - Yes

6. If yes, were any of these periods greater than 3 months duration?
   - No --> Skip to SECTION 6 (Page 20)
   - Yes

7. If yes, what is the total amount of time that you stopped smoking for?
   (Please add together all the periods of time when you stopped smoking)
   [Columns for years and months]
   [Note: New skip to SECTION 6 (Page 20)]

8. In the past have you ever been a daily smoker?
   - No --> Skip to SECTION 6 (Page 20)
   - Yes

9. When did you start smoking daily?
   [Columns for years of age and year]
   OR

10. When did you finally stop smoking daily?
    [Columns for years and month of stopping smoking]
Daily smokers were asked the most detailed questions. In addition, participants who were not daily smokers at follow up, but reported being daily smokers in the past (question 7), were asked to provide the same information on any past periods of daily smoking as requested in questions 4-6 for current smokers. This included when they started smoking, when they stopped and the type and quantity of tobacco smoked (questions 4-6). The general questionnaire, which included all the questions on smoking habit, is attached as Appendix 3.

The age or year that the participant reported starting smoking and the number of cigarettes smoked per day were used to calculate the cumulative exposure variable ‘Pack years’. Each pack year corresponded to 20 manufactured cigarettes each day for 1 year. Where participants smoked loose tobacco or a pipe we used the formula: (grams tobacco per day)/7) x years of smoking to convert loose tobacco to packs of 20 cigarette equivalents.

Information on the age or year that the participant started smoking was used to generate a binary variable indicating whether a daily smoking started before the age of 16 (i.e. whether they were a ‘childhood smoker’ (No=0 and Yes=1)).

**Covariates**

Detailed descriptions of study covariates are provided in Chapter 2. Briefly, those used in these analyses have been shown by others to be relevant in assessment of lung function volumes. Current asthma status (No/Yes) was classified as reported prior to spirometry and using medicine usage reported in the general questionnaire (Appendix 3). Educational attainment (from the general questionnaire) was used as an indicator of social status and was collapsed into three categories (school only, diploma/trade qualification or university educated). Clinic measurements included in the analysis were: participant’s height, average grip strength (the mean value of dominant and non-dominant hand) and body mass index (BMI) as previously described in Chapter 2.)
3.3.3 Statistical analysis

In order to assess the effects of smoke exposure on the lung function of men and women separately all analyses were stratified by sex a priori.

Mean values and standard deviations were calculated for key study variables and ANOVA methodology and chi squared tests were used to test for differences in variables across smoking categories.

For descriptive analysis FEV$_1$, FVC, FEF$_{25-75}$ volumes were standardised by dividing by height squared. Standardisation of FEV$_1$ and FVC by height squared has been recommended as an appropriate measure by Vollmer$^{115}$ and by Dockery$^{116,164}$ and has been used by others.$^{124}$ Age and height standardised childhood FEV$_1$ and FVC measures were also generated. Standardised adult FEV$_1$, FVC, FEF$_{25-75}$ and FER measures were then split into thirds using tertile cut-points.

Associations between smoking-status in adulthood (never, ex-smoker, occasional (non-daily) and daily smokers) and thirds of lung function were examined by cross-tabulations. Crude associations between adult lung function and exposure to parental cigarette smoke were investigated in never smokers using age and height adjusted thirds of adult lung function. In addition, age and height standardised childhood FEV$_1$ and FVC were used to determine whether participants who had higher lung function in childhood were over-represented among daily smokers.

To estimate dose dependent associations of cigarette smoking with lung function two new binary variables were generated to indicate if participants were ex-smokers or occasional smokers (No=0, and Yes=1). A daily dose variable indicated daily cigarettes or equivalents as zero, light, moderate or heavy daily exposure (0, 1-10, 11-20 and >20 cigarettes per day respectively). These cut-points for daily consumption were used by Urrutia et al$^{156}$ and would be equivalent to less than half a pack, up to a pack, and greater than one pack, of cigarettes per day. Never smokers were those who had all three smoking exposure categories set to zero.

In regression models absolute lung function parameters were used as continuous variables. In addition to cigarette exposure, final models included, adult height, age and asthma status, in addition to cigarette exposure. Additional adjustments were made for muscularity (grip strength), adiposity (BMI), and physical fitness. In these cross-sectional models, the resulting regression coefficients represent the difference in lung function in litres between smokers and the reference category, never smokers. ANOVA methodology was used to estimate mean FEV$_1$, FVC, FER and FEF$_{25-75}$ volumes after adjustment for covariates and potential confounders.
The effects of cumulative exposure (pack years) and the independent effect of starting to smoke before the age of 16 were also examined in separate regression models and with both measures in the same model. The latter investigations were restricted to daily smokers who at follow up provided information on the age, or year at which they had started smoking.

3.4 Results

3.4.1 Characteristics of adult participants

The characteristics of male and female participants included in the analysis are summarised in Table 3-2, according to smoking status at follow up.

After age and height adjustment, there were no significant differences between the lung function parameters of never smoking and daily smoking males or females. However, compared to never smokers, occasionally smoking males had a higher FEF\textsubscript{25-75} (p=0.02), were younger (p=0.02), had a significantly lower BMI (p=0.02) and prevalence of overweight (p=0.04) and obesity (p=0.04). Among males, ex-smokers had the greatest prevalence of overweight or obesity. Females who smoked daily were on average, heavier, (p=0.06) with a larger waist circumference, (p=0.03) and more likely to be overweight or obese than never smokers. While, female occasional smokers had greater grip strength (p=0.01) and fewer were overweight or obese than never smokers. However, these differences were not statistically significant.

A lower proportion of male current smokers (particularly occasional smokers) reported having asthma, or being prescribed an asthma medication (p=0.035). In contrast, for females there was no significant difference in the asthma prevalence across the smoking categories.

Compared to other participants, daily smokers were twice as likely to have reported having a school only education (males; 21.0\% vs. 42.5, p<0.001 and females 23.2\% vs. 46.7, p<0.001) (Figure 3-9).

The number of cigarettes (or equivalents) smoked per day was available for 299 (160 male and 139 female) daily smokers. Of whom, 60\% of males and 53\% of females were moderate smokers (who smoked 10 to 20 cigarettes per day) and 15.6\% of males and 9.4\% of females were ‘heavy smokers’ (who smoked more than 20 cigarettes per day).
Table 3-2: Characteristics of interest for 970 males and 971 female participants aged 26-36 years by smoking status

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>557, 175, 77, 161</td>
<td>535, 230, 67, 139</td>
</tr>
<tr>
<td>FEV₁, L, mean (SD)</td>
<td>4.36(0.4), 4.35(0.4), 4.43(0.3), 4.36(0.3)</td>
<td>3.26(0.2), 3.27(0.2), 3.26(0.2), 3.28(0.3)</td>
</tr>
<tr>
<td>FVC, L, mean (SD)</td>
<td>5.36(0.5), 5.36(0.5), 5.46(0.5), 5.38(0.4)</td>
<td>3.90(0.3), 3.92(0.3), 3.90(0.3), 3.92(0.3)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅, L, mean (SD)</td>
<td>4.01(0.3), 4.01(0.3), 4.08(0.2), 4.00(0.2)</td>
<td>3.23(0.2), 3.23(0.2), 3.24(0.2), 3.24(0.2)</td>
</tr>
<tr>
<td>FER, % (SD)</td>
<td>81.7(6.4), 81.2(6.4), 81.9(6.5), 80.8(6.3)</td>
<td>84.0(5.9), 83.2(6.1), 82.8(6.6), 83.9(6.1)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>31.6(2.5), 31.5(2.6), 30.8(2.8), 32.0(2.6)</td>
<td>31.3(2.7), 31.7(2.7), 30.9(2.4), 31.2(2.5)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>179.6(6.9), 179.4(6.9), 180.8(6.6), 179.8(6.3)</td>
<td>165.7(6.3), 166.1(6.1), 165.6(6.2), 166.1(6.8)</td>
</tr>
<tr>
<td>BMI kg/m², mean (SD)</td>
<td>26.6(4.4), 26.8(4.0), 25.4(1.0), 26.0(3.8)</td>
<td>24.8(5.2), 25.0(5.0), 24.6(4.7), 25.6(5.6)</td>
</tr>
<tr>
<td>Waist Circumference, cm, mean (SD)</td>
<td>89.3(11.0), 89.9(9.6), 87.4(9.0), 89.2(9.8)</td>
<td>77.4(11.0), 78.2(11.0), 76.4(10.7), 79.8(12.5)</td>
</tr>
<tr>
<td>Fitness, J/kg, mean (SD)</td>
<td>3.1(0.63), 3.1(0.61), 3.1(0.60), 2.9(0.67)</td>
<td>2.9(0.67), 2.9(0.61), 3.0(0.63), 2.9(0.64)</td>
</tr>
<tr>
<td>Grip strength, kg , mean (SD)</td>
<td>47.3(7.3), 49.2(7.3), 47.0(6.2), 48.3(8.0)</td>
<td>28.3(5.1), 29.0(4.7), 30.0(5.1), 29.2(4.7)</td>
</tr>
<tr>
<td>Overweight, n (%)</td>
<td>239(42.9%), 87(49.7%), 31(43.0%), 66(41.0%)</td>
<td>121(22.6%), 52(22.6%), 14(20.9%), 35(25.2%)</td>
</tr>
<tr>
<td>Obese, n (%)</td>
<td>97(17.4%), 32(18.3%), 6(7.8%), 27(16.8%)</td>
<td>76(14.2%), 32(13.9%), 6(9.0%), 24(17.3%)</td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>66(11.8%), 22(12.6%), 3(3.9%), 14(8.7%)</td>
<td>69(12.9%), 28(12.2%), 8(11.9%), 19(13.7%)</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow rate in the middle 50% of the FVC
†Age and height adjusted mean values
Fitness, Physical work capacity at 170 beats per minute standardised for lean body mass.
BMI: calculated from weight/height². Overweight, BMI>25kg.m⁻² & <30kg/m², Obese, BMI≥30kg/m⁻².
Chapter 3: The effect of smoking on the lung function of young adults

Figure 3-9: Highest level of education for male and female participants† according to smoking status reported at follow up (2004-2006)

![Education Distribution Diagram]

†Numbers on the bars represent the number of participants in each category

3.4.2 Cross-sectional associations between smoking and the lung function of CDAH participants.

Multivariable analysis

Multivariable regression models were used to examine the cross-sectional associations between smoking exposure and FEV$_1$, FVC, FER and FEF$_{25-75}$ after adjusting for other determinants of lung function. Final models included adult age, height, current asthma status, smoking status (coded as 0-4 as described above: never smoker, ex-smoker, occasional smoker or daily smoker). Although correlated with smoking status, educational attainment did not confound the association.

The cross-sectional associations of smoking status with FEV$_1$ and FVC are presented in Figure 3-10. The regression coefficients represent the estimated mean difference in lung function (ml) between the FEV$_1$ and FVC of never smokers and that of participants in the other smoking categories, including daily smokers categorised according to their daily cigarette consumption. These analyses were
stratified by sex a priori however, significant interactions between sex and current smoking were detected for FEV\textsubscript{1} (p=0.025) and FVC (p=0.008), and between sex and specific daily smoking categories (1-9 cigarettes and 10-20 cigarettes per day) for FVC (p= 0.015 and p=0.007 respectively).

The mean FEV\textsubscript{1} and FVC of male and female daily smokers was 129ml (95%CI: 42 to 216) ml and 228ml (95%CI: 122 to 334) ml and 129ml (95%CI 42 to 216) ml and 228ml (95%CI: 122 to 334) ml higher respectively than male and female never smokers. The positive association of daily smoking with FEV\textsubscript{1} and FVC were most apparent in participants who smoked less than 20 cigarettes per day. Being an ex-smoker was also associated with a higher FEV\textsubscript{1} and FVC for females and FVC for males, although the associations were weaker in females. Additional adjustment for lean body mass, BMI or fitness did not significantly affect the regression coefficients (data not shown).

No significant associations between smoke exposure and FEF\textsubscript{25-75} or FER were observed for either males or female but the results are presented in Supplementary Figure 3-14.

Addition of product terms to the sex-specific regression models indicated there were significant interactions of BMI with occasional smoking for FEV\textsubscript{1} (p=0.024) and FEF\textsubscript{25-75} (p=0.006) among males and with light smoking for the FVC of females. As BMI increased, the differences between the FEV\textsubscript{1} and FEF\textsubscript{25-75} of light smokers or occasional smokers and never smokers were reduced. An interaction was also detected between age and daily smoking for female FEF\textsubscript{25-75} (p=0.025).
Chapter 3: The effect of smoking on the lung function of young adults

Figure 3-10: Cross-sectional associations of different categories of smoking vs. never smoking on male and female FEV₁ and FVC.

Ex smoker   Occasional smoker  1-10 cigs/ day  11-20 cigs/ day  >20 cigs/day
Males
Females

FEV₁ forced expiratory volume in 1 second; FVC forced vital capacity;
Regression coefficient is the difference between the FEV₁ and FVC of never smokers and each smoking categories after adjustment for age, height and current asthma.
Participants in each smoking category: Males: 557 never smokers; 175 ex-smokers, 77 occasional smokers, and 161 daily smokers (39, 1-10, 96, 11-20 and 25, >20 cigarettes per day); Females 535 never smokers, 230 ex-smokers, 67 occasional smokers, and 139 daily smokers, (52, 1-10, 74, 11-20 and 13.>20 cigarettes per day).
3.4.3 The effects of cumulative smoke exposure in daily smokers

Cumulative cigarette exposure (pack years) was calculated for 145 male and 133 female daily smokers. The cumulative dose was 3 pack-years and 10 pack years for both male and female low, and moderate daily smokers respectively. However, male heavy smokers had significantly higher pack years than females (23 pack years for males vs. 21 pack years for females, p=0.001). Never smokers were assumed to have zero pack years.

**Multivariable analysis**

Multivariable regression models adjusting for age, height and current asthma were then used to determine the independent effect of pack years on the lung volumes of daily smokers. The results are presented in Table 3-3. Significant negative associations were observed for male FEV$_1$ and FVC and although the coefficient for FEF$_{25-75}$ was of a similar magnitude it did not reach significance for males. In contrast for females, each pack year of smoking was associated with a deficit of 40ml in FEF$_{25-75}$ but no significant associations were observed with FEV$_1$ and FVC.

**Table 3-3: Associations between pack years of smoking and lung function by sex.**

<table>
<thead>
<tr>
<th></th>
<th>Males n=702</th>
<th>Females n=668</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B 95%CI</td>
<td>β 95%CI</td>
</tr>
<tr>
<td>FEV$_1$ (ml)</td>
<td>-19* (-36,-1)</td>
<td>-15 (-31,2)</td>
</tr>
<tr>
<td>FVC (ml)</td>
<td>-23* (-44,-2)</td>
<td>-11 (-32,9)</td>
</tr>
<tr>
<td>FEF$_{25-75}$ (ml)</td>
<td>-10 (-44,23)</td>
<td>-40* (-73,7)</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.2 (-0.2,0.2)</td>
<td>-0.1 (-0.4,0.2)</td>
</tr>
</tbody>
</table>

FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; FER, the ratio of FEV$_1$ to FVC; FEF$_{25-75}$ the rate of flow during the middle 50% of the FVC

β Regression coefficient associated with one pack year of smoking; 95%CI, 95% confidence intervals of the estimated association. Models were adjusted for age, height, asthma status and daily smoking status: never, 1-9, 10-20, >20

*p<0.05
Figure 3-11: The proportion of participants in each third of lung function according to when they started daily smoking.

FEV₁, Forced Expiratory volume in 1 second; FVC, Forced Vital Capacity; FER, the ratio of FEV₁ to FVC; FEF₂₅₋₇₅, forced expiratory flow in the mid 50% of the FVC.
3.4.4 The effect of childhood exposures on adult lung function

Forty-four per cent of our participant sample (451 males and 402 females) were at least 9 years old in 1985 and provided information on their childhood smoking experience and tobacco exposures at home. Of these, a greater proportion of participants who were smokers at follow up also reported being smokers in 1985 or having a parent or other smoker in their household. Compared to other participants, daily smokers were 1.7 times as likely to have had at least one parent that smoked.

**Childhood smoking**

At follow up 145 male and 133 female daily smokers provided details of the year or age at which they started smoking. Compared to males, a greater proportion of female, daily smokers reported starting smoking before the age of 16 (48.8% vs. 40.0%), (Figure 3-11). Those who smoked more than 20 cigarettes per day were also more likely to have started smoking in childhood, but this was statistically significant only for women (p=0.002).

**Multivariable analysis**

The cross-sectional relationship between childhood smoking status and adult lung function was investigated using multivariable regression, with childhood smoking as a binary variable. The results, presented in Table 3-4, indicate that significant deficits in the FEV₁ and FVC in males, and FEF₂₅₋₇₅ in females, are associated with regular smoking before age 16. The effects of childhood smoking on the latter (FVC for males and FEF₂₅₋₇₅ for females) were independent of pack years of exposure. Although there was no evidence of a sex/adolescent smoking interaction, there was a significant positive interaction between asthma and childhood smoking for male FEF₂₅₋₇₅ (p=0.017) and FER (p=0.004).

**Table 3-4: Cross-sectional analysis of starting smoking in childhood on the lung function volumes of male and female daily smokers.**

<table>
<thead>
<tr>
<th></th>
<th>MALES n=145</th>
<th>FEMALES n=133</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After adjustment for pack years</td>
<td>After adjustment for pack years</td>
</tr>
<tr>
<td>B</td>
<td>β 95% CI</td>
<td>B 95% CI</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>-196* (-363, -29)</td>
<td>-136 (-315, 43)</td>
</tr>
<tr>
<td>FVC (ml)</td>
<td>-278* (-479, -74)</td>
<td>-231 (-449, -13)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (ml)</td>
<td>-70 (-389, 249)</td>
<td>9 (-334, 353)</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.6 (-1.6, 2.7)</td>
<td>0.97 (-1.0, 3.4)</td>
</tr>
</tbody>
</table>

β, regression coefficient (95% confidence intervals) associated with starting to smoke before 16 years of age; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FER, the ratio of FEV₁ to FVC; FEF₂₅₋₇₅, forced expiratory flow in the mid 50% of the FVC. All models adjusted for age, height and current asthma. Significance * p<0.05, **p<0.01
Chapter 3: The effect of smoking on the lung function of young adults

Figure 3-12: Proportion of never smokers in each third of adult lung function according sex and exposure to parental smoking in childhood

FEV₁, forced Expiratory volume in 1 second, FVC, forced Vital Capacity; FEF₂₅-₇₅, forced expiratory flow in the mid 50% of the FVC; *Parental smoking reported when participants were aged between 9 and 15 years of age; Number of participants in each smoking category: None (Neither parent), 245 male, 246 female; Mother only 34 male, 35 female; Father only, 88 male, 74 female; both parents, 48 male, 47 female.
Effects of parental smoking on the lung function of young adult never smokers.

In order to eliminate confounding by adult smoking status, the effects of exposure to parental cigarette smoke (as reported in childhood) were examined in 451 male and 402 female never smokers. Thirds of age and height adjusted adult lung function were cross-tabulated using baseline data on whether one or more parent smoked (mother, father or both) (Figure 3-12). For females a higher proportion of those who had reported that their mother had smoked were in the top third of FEV₁ and FVC (42.8% and 45.7% respectively) while those whose father smoked were more likely to be in the bottom third of FEV₁ and FVC (52.7% and 46.0% respectively). In contrast, among males parental smoking appeared to have little effect on FEV₁, although a greater proportion of those exposed to maternal smoke were in the bottom third of FVC this effect was not seen if both parents smoked.

3.4.5 Childhood lung function and adult smoking status

In order to investigate whether participants with larger lung volumes were over-represented among smokers in adulthood, we tabulated the age and sex specific thirds of childhood height adjusted FEV₁ and FVC with adult smoking status of 657 participants (326 male and 331 female) who had childhood FEV₁ and FVC volumes available from baseline. The results are presented in Figure 3-13, according to smoking status, for men and women.

Compared to participants who had never smoked, a greater proportion of daily smoking males were in the top third of FEV₁ or FVC at baseline but there was no evidence of a similar trend in daily female smokers. The majority (86.9%) of women who reported smoking occasionally were in the bottom two thirds of FEV₁ or FVC.
Figure 3-13: Proportion of men in each third of childhood FVC and FEV₁ status by adult smoking status.

FEV₁ forced expiratory volume in the first second, FVC forced vital capacity.
3.5 Discussion

This investigation examined the association between cigarette smoking and lung function in a contemporary cohort of young Australian adults. The results of this study are generally in agreement with that reported in other population samples.¹⁶⁵

In the young adult male participants in this study, current smokers appeared to have better lung volumes than never smokers. However, adjustment for age, height and other potential confounders indicated that those with significantly better lung volumes were either occasional smokers or smokers of less than 20 cigarettes per day. Male smokers who smoked less than 20 cigarettes per day had significantly greater lung volumes, in particular FVC, than never smokers. Those who smoked less than 10 cigarettes per day also had greater FEV₁ but a negative association of FER with increased daily dose was not significant. Our estimates for the effect of each pack year were also in line with estimates from large longitudinal cohort studies.¹⁶¹

It is possible that persistent smokers are likely to be those who do not suffer any adverse symptoms. As reported in the literature review this “healthy smoker effect” has been observed by others, particularly in young males and does not appear to be apparent in females. In addition, as observed by Tashkin et al,¹⁴⁹ males with greater lung function volumes in childhood were also over-represented among daily smokers in this population sample (Figure 3-11).

In addition to having the highest lung function volumes, male occasional smokers also had the lowest mean BMI and waist circumference. This could potentially be related to other healthy lifestyle factors that might cluster with smoking only occasionally (e.g. being involved in team sports and smoking perhaps being limited to a few cigarettes in a social context rather than habitually). There have also been other reports that daily smoking is associated with a higher prevalence of central adiposity in young males, and among females of all ages.¹⁶⁶,¹⁶⁷ Addition of BMI to the regression equations did not alter the regression coefficients observed in the study analysis, however when interaction terms were included in the analysis it was apparent that the light smokers and occasional smokers of higher BMI were less likely than those of lower BMI to have higher FEV₁ and FVC volumes than never smokers.

Among daily smokers, not only was an increased daily dose associated with reduced lung volumes there was also an independent association of cumulative exposure (pack years) on the FEV₁ and FVC of males and the FEF₂₅-₇₅ of females. The estimates for the effect of each pack year in this cohort were in line with those from large longitudinal cohort studies.¹⁶¹
It was also interesting to note the sex differences in the effects of childhood smoking. Both childhood smoking and pack years of exposure had a significantly negative association with male FEV₁ and FVC (Table 3-3 and Table 3-4). The negative association of childhood smoking with FEV₁ was not independent of pack years whereas childhood smoking was associated with a reduced FVC independent of pack years. This result suggests that childhood smoking may be detrimental to the developing adolescent male lungs however it is also possible that other exposures that may also be associated with childhood smoking, such as poor diet and lower levels of physical activity may also contribute to this observation. Among females, pack years was not associated with FEV₁ or FVC however, there was significant evidence of early obstructive lung disease (reductions in FEF₂₅-₇₅) independently associated with pack years and childhood smoking. Several cohort studies have also observed that females who start smoking in childhood have a greater risk of developing COPD than males. Although no interaction was observed between sex and adolescent smoking, a positive interaction between adolescent smoking and asthma was observed for the FEV₁ and FER in males. This indicated that, among males with asthma, those who smoked had better lung function than those who did not smoke. No such interaction was apparent for females. This again, is indicative of the healthy smoker effects observed for males, but not females.

In the EPIC-Norfolk study, which included 1,416 female and 1,294 male (current) smokers, males who started smoking before the age of 16 were at increased odds of having bronchitis or emphysema (OR 1.29, 95% CI: 1.07 to 1.55). In females, the odds were slightly stronger (OR 1.54, 95%CI: 1.10 to 2.13) and independent of pack years. This study also observed that males who develop respiratory symptoms as a result of smoking are more likely to stop smoking than women, who often continue to smoke despite persistent symptoms of airway obstruction. These differences in behaviour between males and females may explain the apparent differences in the effect of childhood smoking on the lung function of males and females in this sample i.e. males who experience adverse symptoms of obstructive disease may have already discontinued smoking. It also suggests that any estimate of adverse effect that may be attributed to tobacco exposure on lung function is likely to be under-estimated for males.

The effects of exposure to parental smoking, reported when aged 9-15 years appeared to have minimal effect on adult lung volumes. This is consistent with literature which suggests that, although in utero exposure has a negative effect on childhood lung development, subsequent exposure in the first few years of life or in later childhood (when children may spend less time in the vicinity of smoking parents) has less of an effect. We have no information on in utero exposure for our participants. A number of studies have found effects in current smokers only, which suggests some potential enhancement of any adverse consequences of in utero exposure by personal smoking.
Study limitations

The main limitation of this study is that lung function data were available at only two time points, 20 years apart and there is no indication of when, or if our participants had reached maximal lung volumes. In addition, as CDAH was primarily a study of CVD we do not have detailed data on risk factors such as childhood asthma, family history of asthma or atopy, or details of severe respiratory infections before the age of five. Such factors have been shown to predict lower maximally attained lung volumes and increased risk of developing obstructive airway disease in later life independent of smoking status. A recent report from the CARDIA group has shown that even in apparently healthy young adults lower FEV$_1$ and FER values between age 18-40 years are predictive of poor lung function and COPD in later life independently of smoking status. Of 2,498 participants, 6.9% had an FER below the lower limit of normal at baseline and 52% also had evidence of airway obstruction at the 20 year follow up. The rate of decline in FEV$_1$ per year was also greater in those with baseline obstruction compared to those without (18ml/year vs. 14ml/year; p=0.005). Smoking status had little effect on those without pre-existing obstruction but increased the annual decline of those with pre-existing obstruction from 12 to 19ml/year (p=0.01). Such an observation suggests that lung function in early adulthood, or even in early childhood, may identify individuals at risk.

It is possible that some of the observed deficits in FEF$_{25-75}$ observed for females may contain residual confounding attributable to asthma status rather than smoke exposure. As no adjustment was made for those who self-administered a bronchodilator at, or immediately prior to, the CDAH clinic, it is likely that there may be some underestimation of asthma effects. Spirometry measures pre and post administration of a bronchodilator may have helped differentiate the effects of asthma and cigarette smoke in the study sample.

In addition to smoking tobacco many young Australians also smoke cannabis. The potential effects of cannabis exposure were not considered in this study at all. However, a recent review of the evidence suggested that smoking cannabis may be associated with large airway inflammation and increased airway resistance, symptoms of bronchitis and lung hyperinflation but that there is little evidence for any association with obstructive lung conditions.

Familial traits are also important determinants of lung volumes and how the body deals with tobacco smoke. Although around 90% of presentations with obstructive lung disease are associated with cigarette smoke, some individuals appear to be immune to its effects while others appear more susceptible to the development of disease. However, as the scope of this thesis does not include genetic factors, this has not been discussed in detail.
3.6 Conclusion

In general, young adults who smoke have greater lung volumes than never smokers but this appears to be a reflection of their lung function prior to taking up smoking. Amongst young adult daily smokers dose dependent deficits in lung function are apparent for those who smoke more than 20 cigarettes per day and those who started smoking in childhood. It is therefore important to discourage growing adolescents from smoking to reduce the likelihood of them becoming habitual smokers in adulthood.
3.7 Chapter Summary

What is known about this subject?

- Passive smoking in the home has a detrimental effect on the lung function of children.
- The children of smoking parents are more likely to become smokers themselves.
- Young, particularly male, smokers may have larger FVC values than never smokers.
- There is some evidence those with higher lung function values self-selection to start smoking and the negative effect of smoking may be underestimated because of the higher baseline values of these individuals.

What is the contribution of this investigation?

Amongst young adult daily smokers dose dependent deficits in lung function are apparent for those who smoke more than 20 cigarettes per day and those who started smoking in childhood.

Our results in this contemporary cohort of young Australians reflect the literature:

- Young adults who smoke appear to have greater lung volumes than never smokers but this appears to be a reflection of their lung function prior to taking up smoking.
- Childhood smoking is associated with signs of obstructive lung disease in young adulthood.

What is the message from this work?

- It is important to establish the cumulative dose, and age of starting to smoke, when assessing the effect of cigarette smoke on lung function.
- Cross-sectional studies may underestimate the effects of smoking on the lung function of young adults.
3.8 Supplementary tables/figures

Supplementary Figure 3-14: Cross-sectional associations of smoking vs never smoking on male and female FEF<sub>25-75</sub> and FER

**Males**

<table>
<thead>
<tr>
<th>Category</th>
<th>FEF&lt;sub&gt;25-75&lt;/sub&gt; Regression Coefficient (ml)</th>
<th>FER Regression Coefficient (%)</th>
</tr>
</thead>
<tbody>
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<td>Ex_smoker</td>
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<td>-500</td>
</tr>
<tr>
<td>Occasional</td>
<td>-3</td>
<td>-400</td>
</tr>
<tr>
<td>1-10 cigs/ day</td>
<td>-2</td>
<td>-300</td>
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<td>-100</td>
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<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Females**

<table>
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<tr>
<th>Category</th>
<th>FEF&lt;sub&gt;25-75&lt;/sub&gt; Regression Coefficient (ml)</th>
<th>FER Regression Coefficient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex_smoker</td>
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<td>-400</td>
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<tr>
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<td>-300</td>
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<td>-100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

FEF<sub>25-75</sub> forced expiratory flow in the mid 50% of the FVC, FER the ratio of FEV<sub>1</sub>/FVC,
Regression coefficient is the difference between the FEF<sub>25-75</sub> and FER of never smokers and each smoking categories after adjustment for age, height and current asthma.
Participants in each smoking category: Males: 557 never smokers; 175 ex-smokers; 77 occasional smokers and 161 daily smokers (39, 1-10, 96, 11-20 and 25, >20 cigarettes per day). Females 535 never smokers; 230 ex-smokers; 67 occasional smokers and 139 daily smokers, (52, 1-10, 74, 11-20 ad 13,>20 cigarettes per day)
Chapter 4: The effect of physical fitness on the lung function of young adults
4.0 Preface

This chapter introduces physical fitness and reviews the evidence for its association with lung function.

In the second half of the chapter, data from the CDAH study is used to determine whether there are any independent associations between fitness and lung function in young adults.

4.1 Introduction

Physical fitness is the capacity to perform physical activity. It describes the performance of athletes but also relates to the health of the body in general including: cardiovascular and respiratory function, body composition, strength, endurance, lower back flexibility and co-ordination. Two of the main contributors are cardiorespiratory (or cardiovascular) fitness (CRF) and muscular fitness. CRF is the capacity of the cardiovascular and respiratory systems to carry out prolonged strenuous exercise. Muscular fitness is the ability to work against resistance and includes strength, muscle endurance and explosive strength (power).

Tests of cardiorespiratory fitness either measure, or predict, maximal oxygen uptake (maximal aerobic power, VO$_2$ max). This is the gold standard measure of cardiorespiratory endurance and reflects the maximal capacity of the body to deliver and utilise oxygen during exercise. It is measured using a graded exercise test that involves walking, or running, on a treadmill or cycling on an exercise bicycle (a bicycle ergometer). The test may be maximal (continued until the participant is completely exhausted) but in population samples submaximal tests are more common in order to minimize subject burden, equipment needs, and the risks associated with maximal exertion. Submaximal tests use equations to estimate maximal consumption. For example, the physical work capacity (PWC) test predicts VO$_2$ max from a subject’s estimated workload at a heart rate of 170 beats per minute, which is derived by extrapolating the line of best fit through the measured steady state heart rate values achieved at 3 or 4 increasing workloads. Derived PWC$_{170}$ values are then standardised for body size by dividing by body weight or lean mass.

The determinants of fitness and the health outcomes associated with fitness were summarised in a review by Ortega. Age and genetics determine a significant proportion (approximately 25%) of the fitness of any individual however, the remainder is attributable to behaviour and environmental factors. Fitness can be improved by increased physical activity.
Higher levels of CRF are associated with a better cardiovascular (CVD) risk profile and lower levels of adiposity in children and adults. A number of studies have demonstrated that although fitness tracks from childhood to adulthood, after reaching a peak in early adulthood, both CRF and muscular fitness decline with age. Adults who were physically fit as children are less likely to suffer from obesity and insulin resistance than those who were unfit in childhood. Persistent CRF is also associated with a reduction of CVD events and all-cause mortality independently of BMI. A meta-analysis of 38 studies (with 317,908 person-years of follow-up) demonstrated a 60% reduction in CVD risk above the 20th percentile of physical fitness (Figure 4-1).

Figure 4-1: Relative risk of CVD according to relative fitness level (percentiles of the distribution)

Breathing is dependent on muscular activity. Inhalation is a consequence of downward movement of the diaphragm and contraction of the intercostal muscles, which increases the thoracic cavity and generates a negative pressure gradient between the environment and the alveoli of the lungs and results in air entering the airways. During exercise, in assessment of pulmonary function by spirometer and in physically compromised individuals, accessory muscles of the neck and chest may be recruited and increased muscle strength is likely to increase spirometric volumes.

Respiratory muscle strength is measured by maximal inspiratory pressure (MIP). It is plausible that respiratory muscle strength is, in general, correlated with the more global measures of body strength. One of the most common measures of strength used in epidemiological studies is grip strength. Grip strength is easily measured, and unlike measures of explosive strength (such as standing long jump or a vertical jump), the measurement process has minimal risks associated with
it. There have been consistent reports of a significant positive association between handgrip strength and lung function independent of age and sex. The Honolulu heart study\textsuperscript{190} identified a positive correlation (r=0.15) between handgrip strength and FEV\textsubscript{1} after adjusting for age and height while the Framingham cohort found significant correlations (r=0.2-0.4) between handgrip strength and FVC.\textsuperscript{49} Studies, mainly in the elderly or in patients with debilitating conditions, have also shown that grip strength is correlated with respiratory muscle strength.\textsuperscript{191-193}

In older adults, reduced respiratory muscle strength (measured as reduced maximal inspiratory pressure) is an independent risk factor for myocardial infarction and fatal CVD outcomes.\textsuperscript{191,194} As reduced lung function is also associated with obesity and increased CVD risk and mortality,\textsuperscript{46,63,195,196} it is therefore possible that reduced lung function may be an indicator of the association between physical fitness and cardiovascular health (Figure 4-2). However, it is also possible that poor lung function is a determinant of poor CRF, as those with poor lung function may be less likely to participate in strenuous high intensity physical activity that would improve their fitness.

There is very little information in the literature about the effects of CRF on the spirometry measures of population samples of young adults. This chapter reviews existing evidence regarding the association between fitness and lung function and then investigates associations between the fitness and lung function of CDAH’s young adult participants.

\textbf{Figure 4-2: Determinants of physical fitness and its associations with lung function and CVD}
4.2 Literature review

Relevant literature articles were identified using searches of the Web of Science and PubMed electronic databases and combinations of the text words: ‘young adults’, ‘children’, ‘Fitness’, ‘cardiorespiratory fitness’, ‘VO₂ max’, ‘lung function’, ‘forced expiratory volume’ and ‘vital capacity’ in the title and or abstract. References cited by the articles retrieved were also scanned to identify any of relevance. Studies of participants with specific morbidity or lung impairment were excluded.

Most studies of physical fitness and lung function have been of athletes or intervention studies in order to determine the effects of increased fitness (usually secondary to increased physical activity) on the lung volumes, and growth, of school children.

4.2.1 Athletes and intervention studies

Studies of young athletes and intervention studies using physical training to improve childhood fitness have generally shown that those with higher cardiorespiratory fitness have, or develop, higher lung function which could not be attributed to growth alone (height or body size). Physical activity regimens that increase fitness are also associated with increased muscle (lean mass). Lean mass (LBM), and muscle strength, have previously been shown to have positive associations with lung function and improve the prediction of lung volumes.

Biersteker et al. compared the lung function of young male and female athletes with young adults of intermediate fitness and ‘sedentary’ medical students. They observed that although physical activity or training improved cardiovascular fitness and vital capacity, differences in FVC between active and inactive/untrained participants were eliminated after adjustment for increased muscle mass. Elite swimmers are amongst the most commonly studied athletes as their lung function volumes and diffusion capacities are routinely greater than predicted. Armour et al. suggested that larger chest size and an increased number of alveoli may be a more important determinant of larger lung volumes than fitness or muscle strength in these subjects. The results of a cross-sectional study comparing the lung function of elite male swimmers with runners, and a control group of sedentary participants found that swimmers had higher vital capacity, inspirational capacity, FEV₁ and pulmonary diffusing capacity than land based adults. However, differences in the lung volumes between levels of competitive swimmers were eliminated after adjustment for years of training, or lean mass.

These results suggest that the additional lung capacity observed in elite swimmers may be a result of their intensive training regimen, strengthening and conditioning respiratory muscles to contract faster and at shorter lengths. A study of the efficacy of flow resistant devices, designed to develop
inspiratory musculature, Mickleborough et al\textsuperscript{203} found no differences in the lung function of those using the devices and elite swimmers taking part in a competitive swimming program. They concluded that flow resistant devices would not provide any additional benefits to elite swimmers in training.

4.2.2 Population based studies

The majority of population based studies that have investigated associations between CRF and lung function have focused on the effect of physical activity on CRF and lung function and have had participants from a very wide age range. A Northern Irish study of 1,600 16-70 year olds and a Scandinavian study of 42 to 60 year olds (n=936) reported significant univariate associations between VO\textsubscript{2} max and FEV\textsubscript{1} and FVC.\textsuperscript{204,205} However, after adjustment for confounders including age, BMI, alcohol intake, smoking and blood pressure the associations were no longer significant. Interestingly, in the Scandinavian study, stratification by age (either 42-48 years or 54-60 years) revealed a significant association of FEV\textsubscript{1} with fitness in the older age group only, while the duration of physical activity (previously a significant predictor) became insignificant.

In the USA’s population-based Aerobics Center Longitudinal Study of 24,536 adults (aged 25-55 years), higher levels of physical activity were associated with better CRF and lung function. In addition, of 5,707 who participated in the 5 year follow up, males who had remained physically active, or who became active, had higher CRF than participants who were sedentary. Men who were persistently active also had FEV\textsubscript{1} and FVC values that were 50ml and 70ml higher respectively than non-active participants.\textsuperscript{95} In longitudinal analyses, changes in treadmill time were also significantly associated with FVC.\textsuperscript{206} After stratification by quintile cut-points, those most likely to ‘gain’ were those whose baseline FEV\textsubscript{1} was in the lowest fifth while the greatest rate of decline appeared to be in those with highest baseline FEV\textsubscript{1} who were not persistently active. In the Finnish Seven Countries Study\textsuperscript{207} which followed 450 middle aged participants for at least 10 years, Pelkonen et al.\textsuperscript{207} also observed that the annual decline in pulmonary function of those in the highest third of physical activity was 10% lower than those in the lowest third.

In one of the few studies to investigate associations between fitness and lung function in a population sample, the CARDIA study, significant associations were observed between the baseline maximal treadmill fitness test and height adjusted FEV\textsubscript{1} (FEV\textsubscript{1}/Height\textsuperscript{2}) of 18-30 year old Americans.\textsuperscript{208} A further assessment of the fitness in this cohort, using a submaximal test of work capacity at 130 beats per minute found similar associations independent of smoking status and race, but the associations were not significant after adjustment for skinfolds (rather than BMI).\textsuperscript{208,209} This suggests that body composition rather than body mass is a potential confounder of the association between fitness and lung function.
4.2.3 Childhood fitness and adult lung function

There is little information available, from population samples, on the effect of childhood fitness on lung function in adulthood. A ten year follow up of 30 young female swimmers (age 12-16 at baseline),\textsuperscript{210} when the majority were no longer training, found that although their fitness (VO\textsubscript{2} max) was reduced, their vital capacity (adjusted for ‘body size’) was not significantly different from baseline. The Amsterdam Growth and Health Longitudinal Study\textsuperscript{144} also found no significant associations between CRF and FEV\textsubscript{1} or FVC but significant associations were observed between lung function and strength, speed and flexibility measurements.\textsuperscript{144} As there were only 167 participants in the latter study it is possible that the study did not have enough power to detect any significant trends with CRF and, as the data came from children of only two selective schools in Amsterdam,\textsuperscript{211} the results may not be a representative of the general young adult population.
4.2.4 Summary of the literature

- There are few population based studies of young adults.

- The literature suggests that there is an association between cardiorespiratory fitness and lung function but that it is weak. The association may be determined by genetic traits where those with greater cardiovascular capacity also have larger lungs.

- Physical activity is an antecedent of fitness. Increased cardiorespiratory fitness is also associated with increased lean mass and muscle strength and lower levels of adiposity which all have positive effects on lung function.

- Evidence from studies of athletes indicate that when physical activity levels are reduced there appears to be a corresponding reduction in cardiorespiratory fitness but lung function is maintained. Consequently, the association between the two outcomes is lost.

- Longitudinal studies with a variety of follow up times (3 to 25 years) suggest that maintenance of physical fitness throughout life helps to attenuate the decline in lung function associated with age.

- As cardio-respiratory fitness is available for CDAH participants who were aged nine, 12 or 15 in 1985 there is an opportunity to add to the literature on this topic.
4.3 Aims and research questions

The aim of this chapter was to assess effect of cardiovascular fitness on lung function volumes and to address the following research questions:

- Are higher levels of adult cardiovascular fitness associated with better lung function in this cohort of young Australian adults?
- If there is a positive association with fitness, is it independent of muscle mass (lean body mass), muscle strength (grip strength) and body composition?
- Is physical fitness in childhood associated with better adult lung function?
- Is maintenance of a higher level of fitness between childhood and adulthood associated with better adult lung function?
4.4 Methods

4.4.1 Participants

Of the 2,410 ASHFS participants who attended CDAH clinics between 2004-2006, 840 males and 879 females had measures of CRF and lung function and complete data on anthropometry, grip strength and information on smoking and asthma status available for cross-sectional analysis of associations between adult fitness and lung function (Figure 4-3).

Data from 553 participants, who also had fitness data available from childhood, were used to investigate the longitudinal effects of childhood fitness, and fitness maintenance, on adult lung function.

Figure 4-3: Selection of participants for analysis of associations between fitness and lung function
Chapter 4: The effect of physical fitness on the lung function of young adults

4.4.2 Study measures

All study measures used in this analysis have been described previously in Chapter 2, but in summary:

**Lung function**

Adult FEV$_1$, FVC and FEF$_{25-75}$ was measured in accordance with the ATS guidance, using a MicroLab 3500 portable spirometer and the analysis presented includes the best spirometry volumes from all participants with a valid flow volume loop.

**Cardiovascular fitness**

At baseline and follow up, participants completed at least 3 x 3 minutes on a bicycle ergometer at increasing workloads. From heart rate recordings the maximal work capacity at 170 beats per minute was determined and standardised by dividing by the participant’s lean mass (kg). In 1985 fitness was measured only on participants aged 9, 12 or 15 years of age.

**Other covariates**

At follow up, adult grip strength was one of three measures of isometric strength. A dynamometer, adjusted for hand size, was used to measure grip strength. Each hand was measured three times, with a break of at least one minute between tests and the average of the dominant and non-dominant hand strength was used in the analysis.

Current smoking status (Yes/No) was determined from self-administered questionnaires. Current asthma status was determined from data collected prior to spirometry and from the medications section of the participant’s questionnaire.

4.4.3 Statistical methods

Summary statistics for the main variables of interest and potential confounders were compared using t-tests and chi-square tests to evaluate differences between men and women and those included and excluded from the analysis. The characteristics of those included in the analysis were similar to those described for those attending clinics and those who did not, as presented in Chapter 2.

Univariate analyses of fitness and lung function with other potential covariates were used to determine variables of interest. The cross-sectional relationship between fitness and lung function, partial correlation coefficients was explored using continuous lung function and fitness measures sequentially adjusted for age, height, smoking, asthma, lean mass (muscle mass), grip strength (muscle strength) and adiposity (BMI).
In addition to using fitness as a continuous measure, a binomial fitness variable was generated as follows: Lean mass adjusted adult CRF measures (PWC170lbm) were split into thirds at tertile cut points. Participants were classified as ‘fit’ if their PWC170lbm was in the top two thirds of PWC170lbm; those in the lowest third were ‘unfit’.

To test the “Fit and Fat” hypothesis, a category variable indicative of healthy weight (BMI<25kg/m²) overweight (BMI≥25 m² and <30kg/m²) or obese(>30kg/m²) was also included in the model. Estimates of mean FEV₁, FVC, FEF₂₅-₇₅ and the FER for each third of fitness (and for each fitness and fatness category) were generated using ANOVA regression.

To assess the effect of childhood fitness on adult lung function age and sex-standardised childhood and adult fitness scores (z-scores), with a mean of zero and a standard deviation (SD) of one, were generated. Standardised childhood fitness scores were also divided into thirds of fitness and participants were classified into 4 categories (‘Trajectories of fitness’) according to their relative fitness at baseline and follow up (Table 4-1). ANOVA was used to estimate mean lung function volumes according to fitness trajectory.

Table 4-1: Generating fitness trajectories from age adjusted childhood and adult fitness.

<table>
<thead>
<tr>
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<th>Adult Fitness</th>
<th>Trajectory</th>
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<td>Bottom third</td>
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</tr>
<tr>
<td>Middle third</td>
<td>Bottom third</td>
<td>Becoming unfit</td>
</tr>
<tr>
<td>Top third</td>
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<td>Persistently fit</td>
</tr>
<tr>
<td>Top third</td>
<td>Middle or top third</td>
<td>Persistently fit</td>
</tr>
</tbody>
</table>

*Tertile cut-points were used to determine relative high, moderate and low levels of fitness of children and adults

The independent effect of childhood fitness on adult lung function was determined using linear regression standardised childhood fitness (z-score) and the relative change in fitness between childhood and adulthood. The change in fitness variable was generated as the difference between the childhood z-score and the equivalent adult z-score generated from the ranked lean mass standardised adult fitness measure.
4.5 Results

4.5.1 Participant characteristics

Fitness, physical activity and lung function measures were available for 840 men and 879 women. A summary of participant characteristics of interest is presented in tables Table 4-2 and Table 4-3 for the whole sample and according to thirds of PWC170lbm in for males and females respectively.

Overall males were taller with greater lung volumes, fitness, lean body mass and grip strength than females. In both males and females there were significant negative trends in BMI across fitness thirds total activity and leisure activity across fitness thirds. Among males, age and height adjusted FEV$_1$, FVC and FEF$_{25-75}$ also increased with increasing fitness, in contrast the FEV$_1$, FVC and FEF$_{25-75}$ decreased as fitness increased. The proportion of participants with tertiary education was significantly higher in the top compared to the bottom third of fitness (p<0.001) while a lower prevalence of asthma in the top compared to the bottom third of fitness was significant only for females (p<0.001).

A substantial proportion (25%) of fit male, and female (20%), participants were smokers. There were significant differences between the mean FEV$_1$ and FVC volumes of fit and unfit female non-smokers (p=0.025 and 0.001 respectively) and between the FEV$_1$, FEF$_{25-75}$ and FER of fit and unfit male non-smokers (p=0.02, 0.006 and 0.026 respectively). Compared to fit participants, unfit participants were twice as likely to be overweight or obese (males 11.4% vs. 22.5% Chi squared, p<0.001 and females 9.6% vs. 22.9% p<0.001).

There were no significant differences between the mean baseline fitness of participants with childhood fitness data who contributed to this analysis and those who did not.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>Bottom third</th>
<th>Middle third</th>
<th>Top third</th>
<th>TRENDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>840</td>
<td>280</td>
<td>280</td>
<td>280</td>
<td>p</td>
</tr>
<tr>
<td>PWC170lbm (W/kg), mean (SD)</td>
<td>3.1</td>
<td>(0.64)</td>
<td>2.4</td>
<td>(0.3)</td>
<td>3.0</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>31.6</td>
<td>(2.6)</td>
<td>31.4</td>
<td>(2.6)</td>
<td>31.7</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>179.9</td>
<td>(6.7)</td>
<td>179.5</td>
<td>(6.8)</td>
<td>179.4</td>
</tr>
<tr>
<td>† FEV1, L, mean (SD)</td>
<td>4.344</td>
<td>(0.35)</td>
<td>4.607</td>
<td>(0.35)</td>
<td>4.603</td>
</tr>
<tr>
<td>† FVC, L, mean (SD)</td>
<td>5.350</td>
<td>(0.47)</td>
<td>5.361</td>
<td>(0.47)</td>
<td>5.330</td>
</tr>
<tr>
<td>† FEF25-75, L mean (SD)</td>
<td>4.006</td>
<td>(1.25)</td>
<td>4.022</td>
<td>(0.26)</td>
<td>4.006</td>
</tr>
<tr>
<td>FER (%), mean (SD)</td>
<td>81.5</td>
<td>(6.6)</td>
<td>81.5</td>
<td>(6.6)</td>
<td>81.8</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.4</td>
<td>(4.2)</td>
<td>27.1</td>
<td>(5.0)</td>
<td>26.5</td>
</tr>
<tr>
<td>Lean body mass, kg, mean (SD)</td>
<td>64.1</td>
<td>(7.8)</td>
<td>64.3</td>
<td>(8.5)</td>
<td>64.0</td>
</tr>
<tr>
<td>Grip strength, kg, mean (SD)</td>
<td>47.7</td>
<td>(7.3)</td>
<td>47.5</td>
<td>(7.5)</td>
<td>47.9</td>
</tr>
<tr>
<td>Total PA, minutes (SD)</td>
<td>791</td>
<td>(546)</td>
<td>735</td>
<td>(511)</td>
<td>783</td>
</tr>
<tr>
<td>Leisure time PA, minutes(SD)</td>
<td>171</td>
<td>(21.6)</td>
<td>111</td>
<td>(141)</td>
<td>162</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>199</td>
<td>(23.7)</td>
<td>56</td>
<td>(20)</td>
<td>71</td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>95</td>
<td>(11.7)</td>
<td>37</td>
<td>13.2</td>
<td>28</td>
</tr>
</tbody>
</table>

| Education level:                    |                    |              |              |           |        |
| School only, n (%)                  | 343                | (41.0)       | 67           | (23.9)    | 75     | (26.8) | 52     | (18.8)    | 0.51 |
| Diploma/skilled, n (%)              | 300                | (35.8)       | 114          | (40.7)    | 98     | (35)   | 88     | (31.8)    | <0.01 |
| University, n (%)                   | 194                | (23.2)       | 99           | (35.4)    | 107    | (38.2) | 137    | (49.5)    | <0.01 |

†Age and height adjusted: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25-75, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV1 to FVC; Fitness, cardiorespiratory fitness, Physical work capacity at 170 beats per minute, standardised for lean mass; PA, Self-reported physical activity using the International Physical Activity Questionnaire (IPAQ). Test for trend: nptrend test for continuous variables, Mantel-Haenszel Chi-Square for categorical.
Table 4-3: Summary characteristics of female participants overall and according to thirds of fitness at follow up

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>Bottom third</th>
<th>Middle third</th>
<th>Top third</th>
<th>TEND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>879</td>
<td>293</td>
<td>293</td>
<td>293</td>
<td>p</td>
</tr>
<tr>
<td>PWC170lbm (W/kg), mean (SD)</td>
<td>2.925</td>
<td>(0.64)</td>
<td>2.3</td>
<td>0.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>31.4</td>
<td>(2.7)</td>
<td>31.3</td>
<td>(2.6)</td>
<td>31.3</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>165.9</td>
<td>(6.3)</td>
<td>166.1</td>
<td>(6.7)</td>
<td>166.1</td>
</tr>
<tr>
<td>FEV1, L, mean (SD)</td>
<td>3.265</td>
<td>(0.44)</td>
<td>3.277</td>
<td>(0.34)</td>
<td>3.274</td>
</tr>
<tr>
<td>FVC, L, mean (SD)</td>
<td>3.914</td>
<td>(0.55)</td>
<td>3.930</td>
<td>(0.23)</td>
<td>3.927</td>
</tr>
<tr>
<td>FEF25-75, L, mean (SD)</td>
<td>3.227</td>
<td>(0.78)</td>
<td>3.239</td>
<td>(0.21)</td>
<td>3.235</td>
</tr>
<tr>
<td>FEV1/FVC, %, mean (SD)</td>
<td>84.0</td>
<td>(5.9)</td>
<td>84.0</td>
<td>(5.9)</td>
<td>83.6</td>
</tr>
<tr>
<td>FPR, %, mean (SD)</td>
<td>24.9</td>
<td>(5.1)</td>
<td>26.3</td>
<td>(6.5)</td>
<td>24.7</td>
</tr>
<tr>
<td>Lean body mass, kg, mean (SD)</td>
<td>44.8</td>
<td>(6.4)</td>
<td>46.3</td>
<td>(7.9)</td>
<td>44.7</td>
</tr>
<tr>
<td>Grip strength, kg, mean (SD)</td>
<td>28.7</td>
<td>(5.0)</td>
<td>28.6</td>
<td>(4.9)</td>
<td>29.0</td>
</tr>
<tr>
<td>Total PA, minutes (SD)</td>
<td>745</td>
<td>(484)</td>
<td>736</td>
<td>(482)</td>
<td>736</td>
</tr>
<tr>
<td>Leisure time PA, minutes (SD)</td>
<td>160</td>
<td>(180)</td>
<td>104</td>
<td>(130)</td>
<td>145</td>
</tr>
<tr>
<td>Current smokers, n (%</td>
<td>177</td>
<td>(20.1)</td>
<td>58</td>
<td>(19.8)</td>
<td>61</td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>110</td>
<td>(12.4)</td>
<td>44</td>
<td>(15)</td>
<td>39</td>
</tr>
<tr>
<td>Education level:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School only, n (%)</td>
<td>433</td>
<td>(49.2)</td>
<td>91</td>
<td>(31.1)</td>
<td>82</td>
</tr>
<tr>
<td>Diploma/skilled, n (%)</td>
<td>214</td>
<td>(24.4)</td>
<td>87</td>
<td>(29.7)</td>
<td>67</td>
</tr>
<tr>
<td>University, n (%)</td>
<td>232</td>
<td>(26.4)</td>
<td>115</td>
<td>(39.3)</td>
<td>144</td>
</tr>
</tbody>
</table>

†Age and height adjusted: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25-75, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV1 to FVC; PWC170, physical work capacity at 170 beats per minute, standardised for lean mass. PA, self-reported physical activity using the International Physical Activity Questionnaire (IPAQ) which included work and leisure time PA as well as total. Test for trend: np trend test for continuous variables, Mantel-Haenszel Chi-Square for categorical variables.
4.5.2 Adult fitness and lung function: Cross-sectional associations

Scatterplots showing the associations of lean mass standardised cardiovascular fitness with age and height adjusted FEV₁ and FVC are illustrated in Figure 4-4 suggest a weak positive associated of cardiovascular fitness with FEV₁ and FVC, for both males and females.

Figure 4-4: Scatterplots of cardiorespiratory fitness with age and height adjusted adult FEV₁ and FVC

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity, FEF₂₅-₇₅, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV₁ to FVC. Fitness, physical work capacity at 170 beats per minute adjusted for lean body mass. (Watts, \( \text{kg}^{-1} \))

The association between standardised fitness and lung function was further investigated using partial correlation coefficients adjusted for age and height smoking and asthma status. Significant positive associations of fitness with FEV₁ and FVC for women and FVC for males (rho 0.09, 0.10 and 0.08 respectively (p<0.05)) were independent of grip strength, but after adjustment for BMI the association lost strength (rho 0.05), and significance, in males but not females. There were no significant correlations between fitness and FEF₂₅-₇₅ or FER in either males or females.
4.5.3 Lung function according to relative fitness level

ANOVA estimates of the mean FEV₁ and FVC for participants in each third of fitness after adjustment for age, height, current smoking, asthma (Model 1) grip strength (Model 2) and BMI (Model 3), presented in Table 4-4, reflect the above correlations. FEV₁ and FVC were positively associated with fitness. Between the top and bottom thirds of fitness there were significant differences in FVC for males, and FEV₁ and FVC for females independent of strength. The trends in female FVC and FEV₁ also remained significant after adjustment for BMI. There were no significant trends observed with FEF₂₅₋₇₅ or the FER for males or females (data not shown).

Table 4-4: Estimated mean FEV₁ and FVC according to thirds of fitness level by sex.

<table>
<thead>
<tr>
<th>MALES n=840</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness third</td>
<td>FEV₁</td>
<td>FVC</td>
</tr>
<tr>
<td></td>
<td>Model1</td>
<td>Model2</td>
</tr>
<tr>
<td></td>
<td>Mean             95%CI</td>
<td>Mean            95%CI</td>
</tr>
<tr>
<td>P trend</td>
<td>0.23            0.17</td>
<td>0.96</td>
</tr>
<tr>
<td>P trend</td>
<td>0.051 0.043</td>
<td>0.104</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEMALES n=879</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness third</td>
<td>FEV₁</td>
<td>FVC</td>
</tr>
<tr>
<td></td>
<td>Model1</td>
<td>Model2</td>
</tr>
<tr>
<td></td>
<td>Mean             95%CI</td>
<td>Mean            95%CI</td>
</tr>
<tr>
<td>P trend</td>
<td>0.024 0.028</td>
<td>0.051</td>
</tr>
<tr>
<td>P trend</td>
<td>0.004 0.004</td>
<td>0.010</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Fitness measured by work capacity at a heart rate of 170 beats per minute (standardised by lean body mass)
All models adjusted for age, height, asthma and smoking status (Yes/No)
Model 2: additionally adjusted for grip strength
Model 3: additionally adjusted for grip strength and BMI
Significance, P trend from linear regression.
Chapter 4 The effect of physical fitness on the lung function of young adults

Figure 4-5: Estimated mean FEV₁ and FVC measures by sex, according to fitness, and weight status.

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity adjusted for age, height and grip strength.

Fitness categories: 239 Healthy weight, 246 overweight and 68 obese males and 389 healthy weight, 137 overweight and 58 obese females were ‘fit’ (in the top two thirds of lean body mass standardised fitness (PWC170lbm)); 96 healthy weight, 116 overweight and 65 obese males and 159 healthy weight, 66 overweight and 68 obese females were ‘unfit’.
4.5.4 Fitness and fatness

Estimates of mean lung function volumes for participants categorised according to fitness and weight status were estimated using ANOVA regression are presented in Figure 4-5.

Obese participants had significantly lower FEV₁ and FVC than non-obese participants regardless of their fitness level. No significant interactions between weight status and fitness status when interaction terms (fitness category x weight status) were included in the regression models and excluding participants who reported having asthma at follow up did not change the outcome of the analyses (Supplementary Figure 4.7).

4.5.5 Childhood fitness and adult lung function: Longitudinal associations

Cardiorespiratory fitness data from baseline (1985) and follow up approximately 20 years later were available for 277 males and 276 females. Although the majority of participants (60% of males and 57% of females) changed, rather than maintained, their relative CRF status (Figure 4-6), there was a significant correlation between childhood and adult CRF in both males and females. When stratified according to age at baseline, the correlation was strongest for the youngest females (Table 4-5).

Figure 4-6: The proportion of male and female participants from each third of childhood fitness in each third of adult fitness for males and females.

Fitness measured by Work Capacity at a heart rate Fitness measured by Work Capacity at a heart rate of 170 beats per minute (standardised by lean body mass) (PWC170lbm, Watts per kg lean body mass)
Table 4-5: Spearman correlation between ranked fitness variables in childhood and adulthood by sex and age at baseline.

<table>
<thead>
<tr>
<th>Baseline age</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>rho</td>
<td>n</td>
<td>rho</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>91</td>
<td>0.261*</td>
<td>95</td>
<td>0.357**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>92</td>
<td>0.253*</td>
<td>97</td>
<td>0.237*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>94</td>
<td>0.265*</td>
<td>84</td>
<td>0.265*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>277</td>
<td>0.273**</td>
<td>276</td>
<td>0.284**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fitness= Watts per kg of lean body mass (PWC170lbm) *p<0.05; **p=<0.005

4.5.6 Fitness tracking and lung function

Around 40% of participants who had high CRF at baseline were also the top third of FEV₁, FVC, FEF₂₅₋₇₅ and FER (compared to 15%, 20%, 20% and 37%, respectively, for those with persistently low CRF).

ANOVA estimates of FEV₁, FVC and FEF₂₅₋₇₅, according to relative CRF in childhood and adulthood are presented in Table 4-6 (adjusted for age, height, smoking status and current asthma). Male participants who had low childhood fitness, but who improved their relative fitness between baseline and follow up, appeared to have higher lung volumes than those who were persistently unfit. However, the differences were not statistically significant. Among females, the mean FEV₁, FVC and FEF₂₅₋₇₅ of those who were fit at baseline, and at follow-up, were significantly higher than those with persistently low fitness. These differences were independent of BMI. Females whose relative fitness had increased since 1985, also had higher FEV₁ and FEF₂₅₋₇₅ volumes than those with persistently low fitness, only the association with FEF₂₅₋₇₅ persisted after adjustment for BMI. The results of the analysis, after additional adjustment for BMI, are presented in Supplementary tables/figures.

Supplementary Table 4-8.

A sensitivity analysis excluding participants with current asthma at follow up did not change the outcome of the analyses. The results are presented in Supplementary Figure 4-8.
## Table 4-6: Adjusted estimates for mean FEV₁ FVC, FEF₂₅-₇₅ and FER according to childhood and adult fitness.

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
<th>FEF₂₅-₇₅</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALES n=277</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistently unfit</td>
<td>41</td>
<td>4.339</td>
<td>(4.192 4.486)</td>
<td>5.332</td>
</tr>
<tr>
<td>Becoming unfit</td>
<td>51</td>
<td>4.337</td>
<td>(4.244 4.506)</td>
<td>5.389</td>
</tr>
<tr>
<td>Becoming fit</td>
<td>50</td>
<td>4.444</td>
<td>(4.311 4.577)</td>
<td>5.477</td>
</tr>
<tr>
<td>Persistently fit</td>
<td>135</td>
<td>4.370</td>
<td>(4.288 4.450)</td>
<td>5.350</td>
</tr>
<tr>
<td><strong>FEMALES n=276</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistently unfit</td>
<td>46</td>
<td>3.186</td>
<td>(3.083 3.288)</td>
<td>3.847</td>
</tr>
<tr>
<td>Becoming unfit</td>
<td>46</td>
<td>3.249</td>
<td>(3.147 3.352)</td>
<td>3.945</td>
</tr>
<tr>
<td>Becoming fit</td>
<td>45</td>
<td>3.293*</td>
<td>(3.190 3.398)</td>
<td>3.943</td>
</tr>
<tr>
<td>Persistently fit</td>
<td>139</td>
<td>3.273*</td>
<td>(3.214 3.332)</td>
<td>3.945*</td>
</tr>
</tbody>
</table>

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅-₇₅, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV₁ to FVC.

All analysis adjusted for age, height, current asthma, smoking status, and grip strength.

Persistently higher fitness refers to those whose fitness was in the top two thirds of fitness at both time points. Persistently poor fitness refers to those whose fitness was in the bottom third of fitness at both time points. Significance: * p<0.05
4.5.7 Childhood fitness and adult lung function

Multivariable regression models were used to determine the effect of childhood fitness on adult lung function, independently of adult fitness, by adjusting for the change in fitness between childhood and adulthood. The change in fitness was calculated as the difference between the childhood and adult standardised relative fitness scores (z scores). In addition to fitness, the final models included age, height, asthma and smoking status and grip strength.

In this sample, no significant associations between childhood fitness and lung function were observed (before or after adjustment for change in fitness) for either males or females (Table 4-7, Models 1 and 2 respectively). The only significant fitness association observed was 73 ml increase in FEV₁ with a one unit (standard deviation) increase in female fitness between childhood and adulthood (Table 4-7, Model 3). This association was independent of BMI (Model 4).
Table 4-7: The effect of childhood fitness on adult lung function before and after adjusting for change in fitness between childhood and adulthood.

<table>
<thead>
<tr>
<th>MALES</th>
<th>Fitness</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95%CI</td>
<td>β</td>
<td>95%CI</td>
<td>β</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (ml)</td>
<td>Child</td>
<td>55 (-45,154)</td>
<td>39 (-59,138)</td>
<td>37 (-81,159)</td>
<td>34 (-87,157)</td>
</tr>
<tr>
<td>Δ</td>
<td></td>
<td>3 (-101,94)</td>
<td>-6 (-105,93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (ml)</td>
<td>Child</td>
<td>28 (-94,149)</td>
<td>7 (-115,126)</td>
<td>18 (-128,164)</td>
<td>7 (-139,155)</td>
</tr>
<tr>
<td>Δ</td>
<td></td>
<td>12 (-105,131)</td>
<td>27 (-119,120)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt; (ml)</td>
<td>Child</td>
<td>179 (-20,377)</td>
<td>162 (-35,359)</td>
<td>106 (-138,366)</td>
<td>106 (-138,352)</td>
</tr>
<tr>
<td>Δ</td>
<td></td>
<td>-82 (-280,143)</td>
<td>69 (-283,144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FER (%)</td>
<td>Child</td>
<td>0.7 (-0.5,1.9)</td>
<td>0.7 (-0.5,1.9)</td>
<td>0.6 (-0.9,2.1)</td>
<td>0.7 (-0.8,2.2)</td>
</tr>
<tr>
<td>Δ</td>
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<tr>
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<td>23 (-49,95)</td>
<td>-6 (-77,66)</td>
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<td>Δ</td>
<td></td>
<td>73* (9,137)</td>
<td>71* (5,138)</td>
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<td>FVC (ml)</td>
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<td>0.7 (-0.5,1.9)</td>
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</tbody>
</table>

FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF<sub>25-75</sub>, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV<sub>1</sub> to FVC; Fitness in Childhood Age and sex specific standardised z-score, Δ Difference in z-score between childhood and adulthood

β, regression coefficient (95% confidence intervals) per 1 standard deviation increase in fitness.

All models adjusted for adult age, height, current asthma and current smoking status.

Model 2, additionally adjusted for lean body mass and grip
Model 3, Model 2, additionally adjusted for change in fitness (Δ) between childhood (1985) and adulthood (2004-6)
Model 4, Model 3 additionally adjusted for adult BMI

Significance: * p<0.05
4.6 Discussion

The review of the literature on physical fitness and lung function suggested that CRF is positively associated with lung function volumes. The observed association may be attributable to genetic predisposition. However, higher levels of CRF achieved through vigorous activity, are also associated with increased physical strength and lower levels of adiposity which are also associated with improved lung function.

In this sample of young adults, statistically significant positive associations of adult CRF (measured by PWC at 170 beats per minute) were observed with male FVC and female FEV₁ and FVC. However, for males the trend lost significance after adjustment for BMI. While among females statistically significant associations of fitness with FEV₁ and FVC were independent of BMI. As no statistical interaction was detected between sex and fitness, the differences observed may be attributable to the different distribution of adipose tissue in males and females.

These findings are in contrast to the results of a previous cross-sectional analysis of the association between childhood fitness and lung function in the ASHFS participants which showed a significant association of CRF with FEV₁ and FVC for males only. However, the regression model in the baseline study included only weight, height and age so there is the possibility that there may have been residual confounding. An eight factor summary of physical fitness generated using ASHFS cardiorespiratory endurance (CRF and a 1.6km run), explosive strength, static strength, flexibility, blood pressure, lung function, body girth and skinfolds data, also demonstrated that lung function was positively correlated with girth (r=0.47), static strength (r=0.69) and weakly with cardiovascular endurance (-0.027) and did not make a major contribution to the summary fitness model.

In addition to improving physical fitness, higher levels of physical activity are also associated with lower levels of body fat and better conditioned musculature. The independent effects of fitness and adiposity were examined in a study of the effect of a physical training regimen on a sample of middle aged participants with a family history of type-2 diabetes. The 12 month follow up of the study found negative associations of obesity with lung function that were not attenuated by physical activity or fitness (as measured by VO₂ max). In addition, a randomised trial comparing the effects of weight loss or physical training, on the lung function of healthy, middle-aged-to-elderly male volunteers found that, although the VO₂ max of participants who completed an aerobic exercise programme increased by 14%, their lung function volumes were unchanged. In contrast, participants who completed the weight loss programme had a mean body fat reduction of 21%, which was associated with a 3% increase in FVC.
In the longitudinal analysis of fitness trajectories between childhood and adulthood, females with persistently low fitness had significantly lower FEV$_1$, FVC and FEF$_{25-75}$ compared to those who were persistently fit. However, the regression analysis presented in Table 4-7 suggests that childhood fitness is not a significant contributor to young adult lung function. These results suggest that adult fitness, not childhood fitness, is a determinant of adult lung function but that the association is confounded by adiposity. The stratified analysis presented in Figure 4-5, according to fitness and weight status, indicates that obesity has a stronger association with FEV$_1$ and FVC than cardiorespiratory fitness. As physical fitness is negatively associated with adiposity, positive associations between physical fitness and lung function may be reduced in participants with higher levels of adiposity and conversely any association between fitness and lung function may be attributable to participants being leaner rather than fitness itself.

Although childhood fitness appears to have little direct effect on adult lung function, childhood and adult fitness are highly correlated. This suggests that it is important to encourage children to participate in activities and develop a lifestyle that involves physical activity in order to maximise their cardiorespiratory potential and prevent obesity.

**Strengths and limitations**

Unfortunately, we do not know the asthma status of participants at baseline. Childhood asthma has negative effects on lung growth and participants with childhood asthma may also have limited participation in physical activity (and consequently their capacity to improve their CRF). However, participants who had childhood asthma but do not have asthma as an adult, are likely to have had mild symptoms in childhood. The study analysis may also have underestimated the effect of asthma on lung function as no correction was made for medication use prior to spirometry. However, sensitivity analysis, of the key regression analysis, restricted to those who did not report having asthma at follow up did not significantly affect our results (Supplementary Figure 4-7 and Supplementary Figure 4-8).

The relatively low number of CDAH participants who had fitness measures from childhood and adulthood may have limited the power of the analysis to detect significant effects associated with tracking of fitness and lung function. However, the results suggest that adult fitness is more relevant to adult lung function than childhood fitness. This finding is consistent with the longitudinal findings of Eriksson et al who followed elite female swimmers for 30 years and who found that although their fitness had decreased since childhood, their lung volumes had not.
Although submaximal tests of cardiorespiratory fitness are not the gold standard method of assessing VO₂ max, they are well correlated with maximal fitness tests.¹⁷⁶

Few studies have looked at the independent effects of cardiorespiratory fitness on adult lung function, of those that have, most have been in relation to rehabilitation programs increasing the physical fitness and lung function of patients with asthma, obstructive pulmonary disease or other debilitating conditions. This study, in a population-based sample of mainly healthy young adults, is therefore a useful addition to the literature.

### 4.7 Conclusion

The fit and fat hypothesis observed for cardiovascular and all-cause mortality does not appear to hold true for lung function. Adiposity appears to be more important than physical fitness in the determination of lung function.

Other than significant tracking of fitness from childhood to adulthood, childhood fitness levels were not associated with adult lung function. Higher levels of adult cardiorespiratory fitness appear to be associated with better lung function in young adults (particularly females) but the effects were confounded by adiposity.
4.8 Chapter Summary

What is known about this subject?

- Positive effects of physical fitness on lung function may be attributable to increased muscle and muscle strength secondary to vigorous physical activity.
- Poor physical fitness is also associated with increased adiposity - which is also associated with reduced lung function.

What is the contribution of this investigation?

- In this cohort of young adults, higher fitness had significant positive associations with FEV$_1$ and FVC in women and FVC in men.
- Childhood fitness was not associated with adult lung function. After accounting for adult fitness childhood fitness is not a significant predictor of adult FEV$_1$ or FVC
- Maintaining high fitness was associated with better lung function in females
- These associations were independent of lean mass and grip strength but were confounded by adiposity.

What is the message from this work?

- Adiposity appears to be more important than physical fitness in the determination of lung function.
- Maintenance of cardiorespiratory and muscular fitness, and minimising obesity, may help maintain good lung volumes.
## Supplementary Table 4-8: Adjusted estimates for mean FEV₁, FVC, FEF₂₅-₇₅ and FER according to childhood and adult fitness

<table>
<thead>
<tr>
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<th>MALES n=277</th>
<th>FEMALES n=276</th>
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<tr>
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</tr>
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<tr>
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<tr>
<td><strong>FEMALES</strong></td>
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<td>FEV₁</td>
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</tr>
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</tr>
<tr>
<td>Persistently fit</td>
<td>139</td>
<td>3.272</td>
</tr>
</tbody>
</table>

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅-₇₅, forced expiratory flow rate at 25-75% of the FVC; FER, ratio of FEV₁ to FVC

Persistently higher fitness refers to those whose fitness was in the top two thirds of fitness at both time points. Persistently poor fitness refers to those whose fitness was in the bottom third of fitness at both time points.

†All analyses adjusted for age, height, current smoking, current asthma, grip strength and BMI

*Significantly different from persistently unfit (p<0.05)
Supplementary Figure 4-7: Adjusted estimates for mean FEV\textsubscript{1} and FVC, according adult fitness and weight status after exclusion of participants with asthma.

FEV\textsubscript{1}: forced expiratory volume in one second; FVC: forced vital capacity adjusted for age, height and grip strength.

Fit participants, in top two thirds of fitness (218 healthy weight, 215 overweight and 62 obese males; 351 healthy weight, 117 overweight and 50 obese females).

Unfit participants, in the bottom third of fitness (83 healthy weight, 101 overweight and 57 obese males and 141 healthy weight, 117 overweight and 50 obese females).

Healthy weight, BMI<25kg/m\textsuperscript{2}; Overweight, BMI ≥25kg/m\textsuperscript{2} and < 30kg/m\textsuperscript{2}; Obese, BMI ≥ 30kg/m\textsuperscript{2}.
Supplementary Figure 4-8: Adjusted estimates for mean adult FEV$_1$, FVC and FEF$_{25-75}$ according fitness trajectories after exclusion of participants with asthma.

<table>
<thead>
<tr>
<th></th>
<th>Persistently unfit</th>
<th>Becoming unfit</th>
<th>Becoming fit</th>
<th>Persistently fit</th>
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<tbody>
<tr>
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<td>5</td>
<td>5.5</td>
<td>5.5</td>
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</tr>
<tr>
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<td>4</td>
<td>4</td>
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</tr>
<tr>
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<td>4.5</td>
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FEV$_1$, Forced expiratory volume in 1 second; FVC, forced vital capacity; FEF$_{25-75}$, forced expiratory flow rate at 25-75% of the FVC. Persistently fit: those in the top two thirds of fitness at both time points. Persistently unfit fitness was in the bottom third of fitness at both time points.

N=35, 46, 42 and 122 males and 39, 36, 39 and 125 females were persistently unfit, becoming unfit, becoming fit and persistently fit respectively.

All analysis adjusted for age, height, smoking status, and grip strength. Significance, *p<0.05
The following chapter has been removed for copyright or proprietary reasons

Chapter 5: The effect of obesity on the lung function of young adults (p. 119 – 138)

Published in

*Obesity* 2011; 19(10):2069-75.

*Longitudinal Associations of Adiposity With Adult Lung Function in the Childhood Determinants of Adult Health (CDAH) Study (pages 2069–2075)*

Beverley A. Curry, C. Leigh Blizzard, Michael D. Schmidt, E. Haydn Walters, Terence Dwyer and Alison J. Venn

http://dx.doi.org/ 10.1038/oby.2011.47

Abstract

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Chapter 5: The effect of obesity on the lung function of young adults (p. 119 – 138)

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Chapter 5: The effect of obesity on the lung function of young adults

Published in

*Obesity* 2011; 19(10):2069-75.
5.0 Preface

This study investigates the longitudinal effect of childhood BMI on adult lung function (LF) in response to a published paper that had reported that increased adiposity in childhood (as measured by BMI) was associated with better LF in adulthood.

Prior to this study an investigation of the relative effects of different measures of body composition BMI, fat mass, waist circumference, waist hip ratio and on LF was undertaken.

Spirometry and adiposity were measured as described in Chapter 2. Separate analysis using regression analysis using z-scores of each. The results (presented in Supplementary Table 5-4) indicated that BMI was not significantly associated with lung function. However addition of lean mass to the regression models allowed the real negative effect of the fat component of BMI to be evaluated.

Give the negative effect of adiposity on LF I felt it was important to differentiate between the effects of the lean mass and fat mass components of BMI. Since publication of this article, Fogarty et al have also reported that lean mass is a confounder of the effect of BMI on lung function.

5.1 Introduction

It is well recognized that obesity impairs pulmonary function and accelerates age-related decline. The mechanisms proposed include the mechanical effects of excess central adiposity reducing chest wall compliance and increasing the workload of respiratory muscles, and abdominal adiposity impeding diaphragmatic descent and so reducing lung volume. Under-inflation results in some small peripheral airways failing to expand, basal lung unit atelectasis and reduction in the area of respiratory membrane available for gaseous exchange.

In cross-sectional and longitudinal studies of adults’ lung function, negative associations have been observed with a variety of adiposity measures including increased weight, waist-hip ratio, waist circumference and skin-fold or x-ray absorptiometry derived measures such as fat percent and fat mass. In contrast, lean body mass (LBM), which predominantly reflects muscle mass, and muscle strength have positive associations with lung function and inclusion of LBM to regression models has been shown to improve the prediction of lung volumes.

The most common indicator used to define obesity or overweight is BMI. However, as BMI does not distinguish between the opposing effects of fat mass and lean mass and gives no information on fat distribution, evidence of the effect of BMI on lung function has been conflicting, possibly
reflecting differences in body composition in the populations under study. In young males, a higher than average BMI may be due to musculature\textsuperscript{223} while in the elderly the proportion of skeletal muscle is generally low.\textsuperscript{212}

Few studies have examined the effects of adiposity on the development of lung function from childhood to early adulthood. Most have focused on birth-weight, BMI and growth in the first few years of life (when most alveolar development occurs) and have, in general, shown positive associations with adult lung function.\textsuperscript{213-216} A study of 400 Danish male army recruits also reported that BMI at 7 years was positively associated with adult lung function 19-40 years later, independent of age, height, current BMI, smoking and education.\textsuperscript{217}
5.2 Aim

The aim of this paper was to extend current knowledge by investigating the effect of childhood and adult BMI on adult lung function in 654 males and females, aged 27 to 36 years, who participated in the Childhood Determinants of Adult Health Study (CDAH) and who might be expected to be in a plateau phase of lung growth. Our analysis considered the effects of BMI independent of the effects of LBM and grip strength which are known to be positively associated with lung function.

The study hypotheses were:

1. That BMI is not the best measure to use to evaluate the effect of adiposity on the lung function of young adults.

2. That childhood adiposity is not associated with better lung function in adulthood

5.3 Methods

5.3.1 Participants

The Childhood Determinants of Adult Health study (CDAH) is a prospective cohort study investigating the associations between childhood characteristics and adult cardio-metabolic disease. The CDAH study was approved by the Southern Tasmania Health and Medical Research Ethics Committee.

Between 2001 and 2005, 6,840 (80.5%) of the original 8498 participants of the 1985 Australian Schools Health and Fitness Survey (ASHFS) were traced and invited to take part in the CDAH follow-up study. The ASHFS sampling and data collection methods have been described elsewhere. Of those traced, 86 (1.3%) were deceased and 5,170 (76.5%) provided informed consent and completed enrolment questionnaires. Between 2004 and 2006, 2410 enrollees (47%) attended one of 34 clinics for physical measures and blood sampling and completed study questionnaires.

In the original study of 7-15 year old children only 9, 12 and 15 year olds were selected for complete anthropometry, including skin fold measurements (n=2,752). Of these 760 (27.6%) attended follow up clinics in 2004-2006 and had acceptable spirometry recordings. After exclusion of pregnant women (n=31), those missing grip strength (n=68) and those missing information on smoking status (n=7), data from 654 participants remained for analysis.
5.3.2 Clinical measures

**Anthropometry**

Participants’ heights and weights were measured to the nearest 0.1cm and 0.1kg respectively. BMI was calculated using the standard formula BMI=weight (kg)/height squared (m2) and classified as normal, overweight or obese according to age and sex-specific cut-points in childhood\(^{109}\) and standard international thresholds in adulthood (BMI < 25kg/m\(^2\), BMI ≥25kg/m\(^2\) and < 30kg/m\(^2\), and ≥30kg/m\(^2\) respectively).\(^{222}\)

Technicians, trained in accordance with the International Standards Anthropometric Assessment, used anatomical landmarks to locate and measure Skin folds. Triceps, bicep, sub-scapular and sub-iliac skin folds were measured to the nearest 0.1mm, using Holtain callipers (Holtain Ltd. UK) at baseline and Slim Guide callipers (SPRI products Inc. Illinois, USA) at follow up.\(^{117}\) LBM was calculated using weight (kg) and estimates of per cent body fat derived from the sum of skin folds according to published equations for adults and children\(^{111-113}\) (LBM= weight – ((fat%*weight)/100).

**Lung function**

Adult FVC, FEV\(_1\), and FEF\(_{25-75}\) were measured, with the participants in a standing position, using a MicroLab 3500 portable electronic spirometer (Micro Medical Ltd. UK) and Spida 5 software (Micro Direct Inc. Lewiston, ME USA). Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society standards.\(^9\) A three-litre syringe was used to calibrate the spirometer before each clinic. The analysis however, included the best test from all participants with acceptable volume–time and flow volume curves.

Prior to spirometry, participants were asked if they had any current lung condition and if so, the name and time of the last dose of any medication they had taken for the condition. Current asthmatics were defined as those who reported having asthma, or who reported taking asthma medications. In childhood, lung function was measured using a vitalograph with the participant seated with a nose clip in place as previously described.\(^{113,212}\) Per cent predicted values in childhood and adulthood were generated using equations from Hankinson et al.\(^{11}\)

**Muscular strength**

Maximal grip strength was measured using a Smedley’s spring-type hand dynamometer (Stoelting Co. Illinois, USA). Three attempts were made, with each hand with at least a one-minute rest between successive attempts, on the same hand. The analysis used an average of the dominant and non-dominant hand scores.
5.3.3 Other measures

Current smoking status (yes or no) and highest level of education completed (school only; trade, technical training or diploma; and university) at follow up were obtained from a self-administered questionnaire.

5.3.4 Statistical analysis

Analyses were stratified by sex a priori. For all variables of interest, mean values and standard deviations (SD) were calculated. Student’s t-test for continuous variables, and the Chi-squared test for categorical variables, were used to investigate differences in relevant study factors between those included in the follow up analysis and those not. Pearson correlation coefficients were used to assess the relationship between physical characteristics and lung function measures.

Correlation analyses and multivariable regression models were used to estimate cross-sectional associations at ages 27-36 years between BMI and each of the following outcomes: FEV₁, FVC, FER and FEF₂₅₋₇₅. Absolute lung function measures were used as the dependent variable in accordance with the suggestions of Vollmer et al.

The final model included adult height, age, current asthma status, current smoking status and educational attainment. The effects of grip strength and LBM on the associations are illustrated in sequential models.

The effect of BMI in childhood (9, 12 and 15 years) on lung function in adulthood (27-36 years) was examined using linear regression. In these longitudinal analyses sex specific, age adjusted, standardized BMI measures (z-scores) were used to facilitate comparisons across ages and at two time points. The z-scores, computed for baseline and follow-up, were the standardized residuals of regressing BMI on age, separately for males and females (generating a z-score with a mean of zero and a standard deviation (SD) of unity) Final models included adjustment for baseline height in addition to the covariates used in the cross-sectional models. The analyses were repeated to investigate the contribution of childhood and adult LBM to the overall effect of childhood BMI.

Product terms were included in the regression models to assess statistical interactions between BMI and study covariates. Change-in-coefficient methods were used to assess confounding, with covariates being retained in the regression model if their inclusion changed the coefficient of the BMI by 10% or more for either sex. The scaling of covariates was carefully checked but there was no evidence of non-linearity in the associations with adult lung function measures. Stata 10.1 (Stata Corporation, College Station, Texas, USA) was used to perform all statistical analyses.
In additional analyses for Figure 5-1, we stratified childhood weight status by adult obesity. Because of the very low prevalence of obesity at baseline (1%), childhood obese and overweight categories were combined. Six exposure categories were generated depending on whether or not participants were of healthy weight in childhood and whether they were of healthy weight, overweight or obese at follow-up. Analysis of variance methods were used to compare mean lung function volumes across categories for males and females separately.

5.4 Results

5.4.1 Characteristics of participants

Descriptive statistics for the 326 men and 328 women included in this analysis are presented in Table 5-1. The baseline mean age, height, age-adjusted BMI and skin fold thickness, and age and height-adjusted FEV$_1$ and FVC of those included in the analysis were not significantly different from those lost to follow-up or excluded. Fewer of those included in the analysis reported being childhood smokers, (10.8% vs. 16.7% males P=0.01 and 11.9% vs. 15.4% females, P=0.1) or having at least one parent who was a smoker (42.4% vs. 51.6% males, P=0.004 and 40.9% vs. 51.0% females, P=0.002). In addition, a greater proportion were of healthy weight in childhood 91.4% vs. 87.8% of males (P=0.07) and 91.8% vs. 86.4% of females (P=0.01).

Mean FEV$_1$, FVC and strength measures were significantly greater for males than females at both time points. Mean per cent predicted FEV$_1$ and FVC for adult males were greater than 100% possibly reflecting the different source population (North American) used to derive the prediction equations.$^{11}$ Similar proportions of men and women (<9%) were overweight or obese as children but more men, than women, were overweight or obese at follow up. The proportion of participants who had childhood asthma was unknown but at follow up the prevalence of asthma increased according to weight status (9.8%, 11.6%, 12.5% and 10.7%, 14.7% and 22.9% for healthy weight, overweight and obese men and women respectively).

Compared to the general population of Australian adults aged 25-34 years$^{226,227}$ the proportions of participants who were overweight or obese (49.9% vs. 49.5%, P=0.8) or reported current asthma (12% vs. 11%, P=0.3) were similar but the proportion of males who were current smokers was significantly less (27% vs. 33%, P=0.03).
Table 5-1: Characteristics Childhood Determinants of Adult Health Study participants at baseline (1985) and follow-up (2004-2006)

<table>
<thead>
<tr>
<th></th>
<th>Men (n=326)</th>
<th>Women (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr., mean (SD)</strong></td>
<td>11.9 (2.4)</td>
<td>31.9 (2.5)</td>
</tr>
<tr>
<td><strong>Height, cm, mean (SD)</strong></td>
<td>153.0 (15.5)</td>
<td>180.0 (6.5)</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>44.5 (14.2)</td>
<td>85.9 (14.2)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (SD)</strong></td>
<td>18.5 (2.75)</td>
<td>26.5 (3.92)</td>
</tr>
<tr>
<td><strong>Sum of 4 skinfolds, mm, mean (SD)</strong></td>
<td>30.7 (16.0)</td>
<td>65.3 (25.0)</td>
</tr>
<tr>
<td><strong>Lean Mass, mean (SD)</strong></td>
<td>36.4 (11.3)</td>
<td>64.5 (7.8)</td>
</tr>
<tr>
<td><strong>Fat per cent, mean (SD)</strong></td>
<td>17.8 (5.0)</td>
<td>24.3 (5.8)</td>
</tr>
<tr>
<td><strong>FEV₁, L, mean (SD)</strong></td>
<td>2.62 (0.96)</td>
<td>4.37 (0.58)</td>
</tr>
<tr>
<td><strong>FVC, L, mean (SD)</strong></td>
<td>2.97 (1.05)</td>
<td>5.37 (0.71)</td>
</tr>
<tr>
<td><strong>Predicted FEV₁, (%)</strong></td>
<td>94.4 (14.8)</td>
<td>117.2 (12.9)</td>
</tr>
<tr>
<td><strong>Predicted FVC, (%)</strong></td>
<td>92.1 (12.6)</td>
<td>115.7 (12.5)</td>
</tr>
<tr>
<td><strong>Grip strength, kg, mean (SD)</strong></td>
<td>25.5 (10.4)</td>
<td>47.7 (7.4)</td>
</tr>
<tr>
<td><strong>Overweight, n (%)</strong></td>
<td>23 (7.1)</td>
<td>147 (45.1)</td>
</tr>
<tr>
<td><strong>Obese, n (%)</strong></td>
<td>5 (1.5)</td>
<td>56 (17.2)</td>
</tr>
<tr>
<td><strong>Current smokers, n (%)</strong></td>
<td>34 (10.8)</td>
<td>89 (27.3)</td>
</tr>
<tr>
<td><strong>Current asthma, n (%)</strong></td>
<td>n/a</td>
<td>36 (11.0)</td>
</tr>
</tbody>
</table>

**Education level:**
- **School only, n (%)** | 84 (25.8) | 90 (27.4) |
- **Diploma/skilled, n (%)** | 123 (37.3) | 88 (26.8) |
- **University, n (%)** | 119 (25.8) | 150 (45.7) |

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF₂₅-₇₅%, forced expiratory flow in the middle 50% of FVC; % Predicted FEV₁, FVC and FEF₂₅-₇₅% were generated using equations from Hankinson et al.¹¹;

Sum of 4 skin folds: (biceps, triceps, sub scapular and iliac); n, number of participants; n/a, not available

¹Childhood data collected in 1985 Australian Schools Health and Fitness Survey, participants 9, 12 and 15 years of age.

²Childhood FEV₁ and FVC data available for 320 males, 326 females;

³Fat per cent was calculated using sum of 4 skin folds according to published equations for adults and children.¹¹¹-¹¹³.

⁴Overweight in childhood as per Cole et al.¹⁰⁹. Overweight in adulthood BMI ≥25kg/m² and <30 kg/m², Obese in adulthood BMI ≥30 kg/m²;

⁵Current smokers in childhood were those who, in 1985, reported they were smokers and had smoked more than 10 cigs ever. Childhood smoking data were available for 316 males and 320 females.
5.4.2 Cross-sectional associations in adults

In cross-sectional linear regression analyses, FEV₁ and FVC were negatively associated with adult BMI independent of height, age, grip strength, lean body mass, current smoking, current asthma and education (Table 5-2). Although the regression coefficients were greater for FVC than for FEV₁ and generally greater for men than for women, when compared to the mean FEV₁ and FVC, the effects were similar (1.2-1.5%). In men, there was a statistically significant positive association of BMI with FEF_{25-75} until adjusted for grip strength or LBM. There were no significant associations with FER in men or women.

Table 5-2: Cross-sectional associations of BMI with lung function in 326 men and 328 women aged 27-36.

<table>
<thead>
<tr>
<th>Regression coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
</tr>
<tr>
<td>0.008 (0.000, 0.021)</td>
</tr>
<tr>
<td>0.006 (0.010, 0.022)</td>
</tr>
<tr>
<td>0.05 (0.102, 0.21)</td>
</tr>
<tr>
<td>0.025* (0.000, 0.052)</td>
</tr>
<tr>
<td><strong>BMIb</strong></td>
</tr>
<tr>
<td>0.001 (0.013, 0.014)</td>
</tr>
<tr>
<td>-0.003 (0.019, 0.013)</td>
</tr>
<tr>
<td>0.05 (0.102, 0.23)</td>
</tr>
<tr>
<td>0.021 (0.000, 0.049)</td>
</tr>
<tr>
<td><strong>BMIc</strong></td>
</tr>
<tr>
<td>-0.051** (-0.077, -0.025)</td>
</tr>
<tr>
<td>-0.066** (-0.097, -0.035)</td>
</tr>
<tr>
<td>0.03 (0.31, 0.38)</td>
</tr>
<tr>
<td>-0.035 (0.000, 0.020)</td>
</tr>
<tr>
<td>WOMEN</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
</tr>
<tr>
<td>0.000 (0.007, 0.007)</td>
</tr>
<tr>
<td>-0.002 (0.011, 0.007)</td>
</tr>
<tr>
<td>0.05 (0.07, 0.17)</td>
</tr>
<tr>
<td>0.010 (0.006, 0.025)</td>
</tr>
<tr>
<td><strong>BMIb</strong></td>
</tr>
<tr>
<td>-0.004 (0.011, 0.004)</td>
</tr>
<tr>
<td>-0.007 (0.016, 0.001)</td>
</tr>
<tr>
<td>0.06 (0.06, 0.19)</td>
</tr>
<tr>
<td>0.007 (0.000, 0.020)</td>
</tr>
<tr>
<td><strong>BMIc</strong></td>
</tr>
<tr>
<td>-0.041** (-0.061, -0.021)</td>
</tr>
<tr>
<td>-0.059** (-0.083, -0.036)</td>
</tr>
<tr>
<td>0.22 (0.14, 0.58)</td>
</tr>
<tr>
<td>-0.014 (0.058, 0.031)</td>
</tr>
</tbody>
</table>

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF_{25-75}, forced expiratory flow in the middle 50% of FVC.

The regression coefficients represent the difference in litres of FEV₁, FVC and FEF_{25-75} or the FER (%), associated with a unit increase in BMI.

*All models adjusted for age, height, current smoking, current asthma, education level.

*BMI adjusted for average grip strength

*BMI adjusted for grip strength and lean body mass.

*P < 0.05; **P < 0.005
Table 5-3: Estimated association of childhood BMI (z-score) with young adult lung function.

<table>
<thead>
<tr>
<th></th>
<th>MALES (n=326)</th>
<th>FEMALES (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>Child BMI z-score(^c)</td>
<td>Child BMI z-score(^c) adjusted for adult BMI z score</td>
</tr>
<tr>
<td><strong>FEV(_1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child BMI z-score</td>
<td>0.054 (0.002, 0.111)</td>
<td>0.080(^*) (0.012, 0.161)</td>
</tr>
<tr>
<td>Adult BMI z-score</td>
<td>-0.046 (-0.112, 0.021)</td>
<td>-0.217(^{**}) (-0.326, -0.107)</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood BMI z-score</td>
<td>0.082(^{**}) (0.014, 0.149)</td>
<td>0.130(^{**}) (0.049, 0.211)</td>
</tr>
<tr>
<td>Adult BMI z-score</td>
<td>-0.085 (-0.006, -0.165)</td>
<td>-0.245(^{**}) (-0.375, -0.116)</td>
</tr>
<tr>
<td><strong>FEV(_1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child BMI z-score</td>
<td>0.038 (-0.002, 0.078)</td>
<td>0.070(^{**}) (0.022, 0.117)</td>
</tr>
<tr>
<td>Adult BMI z-score</td>
<td>-0.054 (-0.100, -0.009)</td>
<td>-0.113(^{**}) (-0.206, -0.020)</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood BMI z-score</td>
<td>0.040 (-0.007, 0.088)</td>
<td>0.093(^{**}) (0.037, 0.150)</td>
</tr>
<tr>
<td>Adult BMI z-score</td>
<td>-0.091 (-0.143, -0.037)</td>
<td>-0.146(^{**}) (-0.256, -0.037)</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV\(_1\), forced expiratory volume in 1 second; LBM, lean body mass

\(^{a}\)Regression coefficient (95% CI); The regression coefficients represent the difference in litres of FEV\(_1\), FVC associated with a unit increase in the BMI z-score (1 SD).

\(^{b}\)Childhood BMI z-score, age and sex standardized measure (with a mean of zero and a SD of unity) generated using residuals of regressing BMI on age, separately for males and females.

\(^{c}\)All models adjusted for baseline height, adult height, age, grip strength, smoking status (no or yes), asthma status and educational level

\(* P<0.05;\quad ** P<0.005\)
5.4.3 Longitudinal associations from childhood to adulthood

The estimated effects of a one SD increase in childhood BMI on adult FEV$_1$ and FVC are shown in Model 1, Table 5-3. For FEV$_1$ and FVC the associations suggested that for every SD increase in age-standardised childhood BMI (2.9kg/m$^2$) there was an increase of 54ml and 38ml of FEV$_1$ and 82ml and 40ml of FVC in men and women respectively. The association was significant for FVC in men only. After adjusting for adult BMI (Model 2), a one SD increase in childhood BMI had a significantly positive effect on the FEV$_1$ and FVC of both males and females. However, adjustment for childhood and adult LBM eliminated any positive effect of childhood BMI on FEV$_1$ or FVC (Model 3) and strengthened the negative effect of adult BMI (Model 4). Associations of childhood BMI with FER and FEF$_{25-75}$ did not reach statistical significance in any model (Supplementary Table 5-5).

5.4.4 Stratified analysis

The results stratified by BMI status in childhood and adulthood are illustrated in Figure 5-1. Notably, no male and only four female participants were overweight or obese as children and of healthy weight in adulthood.

Irrespective of childhood weight status, obese adult males had significantly lower FEV$_1$ and FVC volumes than those of healthy weight at both time points, with deficits of 440ml (10.1%) and 549ml (12.5%) in FEV$_1$ and 627ml (11.6%) and 694ml (12.9%) in FVC for those of healthy and unhealthy childhood weight respectively.

For women, the FEV$_1$ and FVC of obese adults who were of healthy weight in childhood were not significantly different from those who were of healthy weight at both time-points. Obese women who were also overweight or obese in childhood had significant deficits of 259ml (7.9%) and 455ml (11.5%) in FEV$_1$ and FVC respectively. The effect of adiposity on female lung function was also modified by an interaction (p=0.03) between weight status and age. The negative effects of persistently higher levels of adiposity increased with age. Compared to women of healthy weight at both time-points, the estimated deficit in FEV$_1$ and FVC of obese women who were of unhealthy weight in childhood was 253ml (95%CI: 7ml to 499ml) and 437ml (95% CI: 149ml to 725ml) respectively at age 32 and 515ml (95%CI: 199ml to 830ml) and 769ml (95%CI: 399ml to 1.14L) respectively at age 35.

The differential effects of obesity on FEV$_1$ and FVC observed in women resulted in non-significant increases in FER (data not shown). This effect was not observed in men. Repetition of the analysis excluding 80 participants with current asthma did not affect the results.
Figure 5-1: Estimated FVC and FEV₁, of 654 young adults according to weight status in childhood and adulthood.

**Males**

- Healthy weight adult (n=123)
- Overweight adult (n=137)
- Obese adult (n=38)

**Females**

- Healthy weight adult (n=201)
- Overweight adult (n=69)
- Obese adult (n=31)

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; (Estimated means and 95% confidence intervals).

Childhood data collected in 1985 Australian Schools Health and Fitness Survey, participants 9, 12 and 15 years of age. Childhood healthy and overweight/or obese classified according to international standard age and sex specific cut-points. Adult data collected 2004-2006 when participants were age 27-36 years. Healthy weight adult BMI≤25kg/m²; Overweight adult BMI ≥25kg/m² and <30kg/m²; Obese adult BMI ≥30kg/m².

All analyses adjusted for baseline height and lean body mass; adult height, age, grip strength, lean body mass, current smoking asthma status and educational attainment.

*Indicates beta coefficient for effect of weight change statistically different from those of healthy weight in childhood and adulthood P<0.05.
5.5 Discussion

In this population-based sample of young adults, FEV$_1$ and FVC were strongly and inversely associated with current adiposity, and adiposity persisting since childhood, as measured by BMI adjusted for LBM. Cross-sectional analysis of baseline data from this cohort had previously been used to demonstrate negative associations of adiposity with childhood FEV$_1$ and FVC$^{228}$. Initial longitudinal analyses, using BMI measures obtained when the subjects were aged 9, 12 or 15 years suggested a positive association between childhood BMI and adult lung function. This finding is consistent with the results of a previous study of Danish male army recruits$^{217}$ in which BMI at 7 years was positively associated with FEV$_1$ and FVC 19-40 years later after adjustment for adult overweight (BMI ≥ 25kg/m$^2$). However, in the current study adjustment for LBM largely eliminated the positive effect of childhood BMI, suggesting that the positive association between childhood BMI and adult lung function is explained by lean mass rather than fat mass. Our finding that both cross-sectional and longitudinal effects of adiposity were greater on FVC than FEV$_1$ and the lack of any significant effects on the FER are consistent with other publications indicating a restrictive effect of adiposity on lung function, rather than an obstructive defect.$^{94,125,217,229}$

The results of Model 2 and Model 4 show that the estimated effect of childhood adiposity is dependent on adult adiposity. After adjustment for LBM, the effect of childhood BMI was modest compared with the effects of adult BMI irrespective of whether participants had high BMI z-scores only at follow up or at both time-points. Using this model, we predict lower lung volumes in those maintaining higher BMI and those with the largest increases in BMI z-score between childhood and adulthood.

Our findings demonstrate that the effect of childhood BMI on adult lung function should not be viewed in isolation from change in BMI over time.

Although the regression coefficients for the effect of adult adiposity suggest a greater effect on the lung function of males than females, when compared to the mean values of FEV$_1$ and FVC the reduction in volumes were similar. (Cross-sectional analysis: 1-1.5% per unit lean adjusted BMI and longitudinal analysis: 3-5% per standard deviation adult BMI after adjustment for lean mass and childhood adiposity).
Strengths and limitations

This study of a relatively large, population-based cohort of young Australian adults is one of the few studies to have investigated the relationship between childhood adiposity and adult lung function using longitudinal data. Its limitations need to be borne in mind, however. First, we had longitudinal data from only two time points with no data on when participants attained their peak lung function or what their peak volumes were. So although our results suggest that adiposity in young adulthood has an important detrimental influence on lung function, that reverses any beneficial effect of childhood lean mass, we could not examine the effect of adiposity on lung development or the pattern of increasing BMI during the transition to adulthood.

Neither childhood smoking nor parental smoking were significant confounders or effect modifiers in our analyses (data not shown) but we did not have information on other potential determinants of adult lung function such as exposure to environmental pollution, childhood asthma, prematurity and maternal smoking during pregnancy. As reported elsewhere we observed a positive association between adiposity and asthma prevalence. However, in these analyses, asthma had little effect on the association between adiposity and FEV₁ or FVC and exclusion of participants who reported asthma at follow up did not affect our conclusions.

There was a large shift in the proportion of overweight and obese individuals between baseline and follow up in this sample. In childhood, 92% of participants were of healthy weight compared with 51% (38% men and 62% women) at follow up. Consequently, a male child of average, healthy weight with no change in z-score between childhood and adulthood would be an overweight adult. For this reason we also presented simple stratified analyses according to international cut-points of healthy weight, overweight and obesity in childhood and adulthood.

For males, the results (Figure 5-1) were consistent with those of our statistical modelling (Table 3) but for females, the effects of persistently higher levels of adiposity between childhood and adulthood were more detrimental to adult lung function.

The low prevalence of childhood obesity in this sample may also have limited our power to estimate the true effect of obesity persisting from childhood to adulthood. However, Bua et al found no difference in the estimates of the effect of childhood BMI on adult lung function between those identified as juvenile obese (n=179) and non-obese (n=188) males. We are not aware of any published literature of note on this issue in women.

There has been some concern about the accuracy of the equations used to convert skin folds to fat mass and enable calculation of LBM. However, because the proposed method of correction is to
add sex-specific constants to the equations\textsuperscript{122} it is unlikely that the observed associations would be affected. Further, any inaccuracy might be expected to attenuate findings towards the null and cannot explain the main outcomes of this study.

### 5.6 Conclusion

To summarise our findings, in this sample of generally healthy young Australian men and women first assessed 20 years earlier, BMI in childhood had a positive effect on FEV\textsubscript{1} and FVC in adulthood but this effect was attributable to LBM. When adjusted for LBM, greater childhood BMI (adiposity) had little effect on adult lung function unless high adiposity persisted into adulthood.

We have shown that it is necessary to track adiposity throughout the life course to understand its effect on adult lung function. Obese children and healthy weight children who become obese adults can expect to have poorer FEV\textsubscript{1} and FVC than those of healthy weight at each life stage. These results highlight the importance of encouraging healthy weight maintenance throughout life.
5.7 Chapter Summary

What is known about this subject?

- Obesity, particularly morbid obesity has negative effects on lung function
- Childhood BMI has been reported to be positively associated with adult lung function

What is the contribution of this investigation?

- There was a strong deleterious effect of adult adiposity on lung function irrespective of childhood BMI
- Any apparent beneficial effect of childhood BMI on adult lung function was eliminated after adjustment for childhood lean mass.
- Obese children who become obese adults can expect to have poorer lung function than those who maintain healthy weight but large deficits in lung function are also likely for healthy weight children who become obese adults.

What is the message from this work?

- Young adults should be encouraged to maintain a healthy weight throughout their lifetime.
## 5.8 Supplementary tables/figures

### Supplementary Table 5-4: Cross-sectional association of adult adiposity measures with lung function parameters.

<table>
<thead>
<tr>
<th></th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.026</td>
<td>-0.006</td>
</tr>
<tr>
<td></td>
<td>(-0.029, 0.081)</td>
<td>(-0.061, 0.049)</td>
</tr>
<tr>
<td>SSF4</td>
<td>-0.068*</td>
<td>-0.076†</td>
</tr>
<tr>
<td></td>
<td>(-0.122, -0.013)</td>
<td>(-0.129, -0.024)</td>
</tr>
<tr>
<td>Waist</td>
<td>0.014</td>
<td>-0.014</td>
</tr>
<tr>
<td></td>
<td>(-0.042, 0.070)</td>
<td>(-0.069, 0.042)</td>
</tr>
<tr>
<td>Waist/Hip</td>
<td>0.032</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>(-0.025, 0.089)</td>
<td>(-0.052, 0.062)</td>
</tr>
<tr>
<td>Fat mass</td>
<td>-0.084</td>
<td>-0.053†</td>
</tr>
<tr>
<td></td>
<td>(-0.087, 0.018)</td>
<td>(-0.104, -0.002)</td>
</tr>
<tr>
<td>Fat per cent</td>
<td>-0.065*</td>
<td>-0.073†</td>
</tr>
<tr>
<td></td>
<td>(-0.117, -0.013)</td>
<td>(-0.123, -0.022)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.007</td>
<td>-0.013</td>
</tr>
<tr>
<td></td>
<td>(-0.030, 0.045)</td>
<td>(-0.050, 0.025)</td>
</tr>
<tr>
<td>SSF4</td>
<td>-0.038*</td>
<td>-0.046*</td>
</tr>
<tr>
<td></td>
<td>(-0.076, -0.001)</td>
<td>(-0.083, -0.009)</td>
</tr>
<tr>
<td>Waist</td>
<td>-0.003</td>
<td>-0.017</td>
</tr>
<tr>
<td></td>
<td>(-0.042, 0.036)</td>
<td>(-0.055, 0.022)</td>
</tr>
<tr>
<td>Waist/Hip</td>
<td>-0.010</td>
<td>-0.009</td>
</tr>
<tr>
<td></td>
<td>(-0.042, 0.041)</td>
<td>(-0.049, 0.032)</td>
</tr>
<tr>
<td>Fat mass</td>
<td>-0.018</td>
<td>-0.033</td>
</tr>
<tr>
<td></td>
<td>(-0.057, 0.022)</td>
<td>(-0.072, 0.006)</td>
</tr>
<tr>
<td>Fat per cent</td>
<td>-0.039*</td>
<td>-0.047†</td>
</tr>
<tr>
<td></td>
<td>(-0.078, -0.001)</td>
<td>(-0.085, -0.009)</td>
</tr>
</tbody>
</table>

β, Standardised regression coefficients, indicating the difference in FEV<sub>1</sub> or FVC (ml) for each standard deviation of adiposity.

BMI; SSF4 (Sum of 4 skinfolds); waist, waist height ratio; waist hip ratio; fat mass; fat per cent and fat mass index.

All models adjusted for age, height, current asthma and current smoking. Model 2 also adjusted for grip strength, Model 3 for lean body mass. Significance: **p≤0.05, ***p≤0.001

Measurement of waist, height, hip and skinfolds and the equations used to calculate fat per cent and fat mass are presented in Chapter 2, Section 2.5.2
Supplementary Table 5-5: Association of childhood BMI (z-score) with adult FER and FEF25-75

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for child and adult LBM</td>
<td>Adjusted for child and adult LBM</td>
<td>Adjusted for child and adult LBM</td>
<td>Adjusted for child and adult LBM</td>
</tr>
<tr>
<td><strong>MALES n=326</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FER</td>
<td>Child BMI z-score</td>
<td>-0.252 (0.985, 0.482)</td>
<td>-0.504 (-1.390, 0.366)</td>
<td>0.359 (-0.079, 1.508)</td>
</tr>
<tr>
<td></td>
<td>Adult BMI z-score</td>
<td>0.445 (-0.422, 1.283)</td>
<td></td>
<td>0.390 (-1.833, 1.052)</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>Childhood BMI z-score</td>
<td>0.028 (-0.089, 0.146)</td>
<td>-0.020 (-0.161, 0.122)</td>
<td>0.018 (-0.165, 0.202)</td>
</tr>
<tr>
<td></td>
<td>Adult BMI z-score</td>
<td>0.084 (-0.054, 0.223)</td>
<td></td>
<td>-0.210 (-0.439, 0.020)</td>
</tr>
<tr>
<td><strong>FEMALES n=328</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FER</td>
<td>Childhood BMI z-score</td>
<td>0.060 (-0.654, 0.775)</td>
<td>-0.249 (-1.106, 0.608)</td>
<td>-0.022 (-1.359, 1.315)</td>
</tr>
<tr>
<td></td>
<td>Adult BMI z-score</td>
<td>0.548 (-0.281, 1.336)</td>
<td></td>
<td>0.321 (-1.363, 2.005)</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>Childhood BMI z-score</td>
<td>0.058 (-0.030, 0.143)</td>
<td>0.038 (-0.066, 0.142)</td>
<td>-0.037 (-0.200, 0.124)</td>
</tr>
<tr>
<td></td>
<td>Adult BMI z-score</td>
<td>0.032 (-0.067, 0.130)</td>
<td></td>
<td>-0.011 (-0.215, 0.193)</td>
</tr>
</tbody>
</table>

FER, Ratio (%) of Forced expiratory volume in 1 second to forced vital capacity; FEF25-75, forced expiratory flow in the middle 50% of FVC; LBM, Lean body mass

*Regression coefficient (95% CI); The regression coefficients represent the difference in litres of FEV1, FVC associated with a unit increase in the BMI z-score (1 SD).

bChildhood BMI z-score, age and sex standardized measure (with a mean of zero and a SD of unity) generated using residuals of regressing BMI on age, separately for males and females.

cAll models adjusted for baseline height, adult height, age, grip strength, smoking status (no or yes), asthma status and education level; *p < 0.05; **P <0.005
PART 2: Lung function, inflammation and vascular health
Chapter 6: Systemic inflammation and young adult lung function
Chapter 6: Systemic inflammation and young adult lung function

6.0 Preface

Given the results of the previous chapter, this study examines the possibility that associations between CRP and lung function remain confounded by adiposity when BMI is the measure of adiposity used for adjustment.

6.1 Introduction

Systemic inflammation, characterised by elevated levels of C reactive protein (CRP) or fibrinogen, has been associated with increased cardiovascular disease risk (CVD) and reduced spirometric lung function in patients with chronic obstructive pulmonary disease and in population samples. Although the causal pathway is uncertain, systemic inflammation has been proposed as the potential mechanism for the observed association between poor lung function and CVD.

Increased adiposity has been associated with higher levels of CRP in cross-sectional and longitudinal studies of adults. Increased adiposity in childhood has also been associated with higher CRP levels in adulthood. As obesity is associated with reduced lung function it is possible that the association of CRP and lung function is a consequence of confounding by adiposity.

In studies of young adults to date, the association between lung function and CRP has been reported to be independent of adiposity, when defined as body mass index (BMI). BMI is the most commonly used measure of relative adiposity. It is highly correlated with body fat and has been shown to be as effective as other adiposity measures at predicting cardiovascular risk. However, its association with lung function is not consistent across populations or between males and females.

The most likely explanation for these inconsistent results is that the effect of BMI on lung function is dependent on the relative proportions of fat mass (FM) and lean mass (or fat free mass, FFM) which have opposite effects on lung function. Even after accounting for differences attributable to participant ethnicity, age and sex, a wide range of body fat measures may still be associated with any given BMI. In patients with mild to moderate COPD, poorer outcomes have been associated with higher levels of CRP only when accompanied by higher relative FM as a result of increased adiposity or as a consequence of sarcopenia in those with normal BMI. In young men increased body mass may also be due to greater lean (muscular) mass rather than adiposity. It is therefore important to determine the relative contributions of FM and FFM to the associations between CRP and lung function.
6.2 Aim

The aim of this study was to disentangle the association between CRP and lung function in a population sample of young adults using estimates of fat mass and fat free mass derived from skin-fold measures, as well as BMI and waist circumference.

The hypothesis being that:

In otherwise healthy individuals, negative associations observed between lung function and C-reactive protein may be confounded by adiposity.
6.3 Methods

6.3.1 Participants

The Childhood Determinants of Adult Health study (CDAH) is a prospective cohort study investigating the associations between childhood characteristics and adult cardio-metabolic disease. Between 2001 and 2005, 6840 (80.5%) of the original 8498 participants of the population-based 1985 Australian Schools Health and Fitness Survey (ASHFS) were traced. Of those traced, 86 (1.3%) were deceased. The remainder were invited to take part in the CDAH follow-up study and 5,170 (76.5%) completed enrolment questionnaires and provided informed consent for follow up at later date. Between 2004 and 2006, 2,410 participants completed study questionnaires and attended for follow up clinical measures at one of 34 clinic sites around Australia. Valid lung function and CRP levels were available for 2,155 participants. Exclusion of participants without cardiorespiratory fitness data (n=170), those missing information on medicine use and smoking status (n=95), pregnant women (n=69), participants with incomplete anthropometric measurements (n=15), participants with a previous diagnosis of angina, myocardial infarction or stroke (n=6), and one individual with cystic fibrosis, left 1,983 participants (912 males and 887 females) with data suitable for analysis.

6.3.2 Clinical measures

Spirometry

Lung function parameters, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and their ratio (FER) were measured, with the participants in a standing position, using a MicroLab 3500 portable electronic spirometer (Micro Medical Ltd. UK) and Spida 5 software (Micro Direct Inc. Lewiston, ME USA), in accordance with American Thoracic Society/European Respiratory Society guidelines. Prior to spirometry, participants were asked the details of any current lung condition and, if so, the name and time of the last dose of any medication they had taken for the condition. Current asthmatics were defined as those who reported having asthma, or who reported taking asthma medications.

Blood samples

Venous blood samples were collected from participants after an overnight fast of at least 8 hours. Blood samples were allowed to clot for 15 minutes. They were then centrifuged before aliquots of serum were distributed between fresh sample tubes. Samples were maintained at less than 4ºC until the end of the clinic and during overnight transfer to the central analysing laboratory. Serum CRP was determined using an automated analyser (Olympus AU5400) and a highly sensitive turbidimetric immunoassay kit (Olympus System CRP Latex reagent, Olympus Life and Material Science Europa
GmbH, Ireland) by MedVet, the commercial laboratory of the Institute of Medical and Veterinary Science (IMVS), Adelaide, South Australia.

In the first instance the study protocol restricted assay of CRP levels to 460 (23.4%) of participants who had blood results available from 1985. Samples not assayed at this time were stored at -70 ºC until 2009 when additional funds for testing were obtained. There were no significant differences in the median values and distribution of CRP assayed in the fresh and frozen blood samples (p=0.46).

**Anthropometry**

Participants’ heights and weights were measured to the nearest 0.1cm and 0.1kg respectively. BMI was calculated using the standard formula BMI=weight (kg)/height squared (m²). Skin folds (triceps, biceps, sub-scapular and iliac crest) were measured to the nearest 0.5mm using Slim Guide callipers (SPRI products Inc. Illinois, USA). Skin fold measures greater than 40mm were truncated at 40mm and skin fold values in these instances were imputed from BMI and waist circumference using Tobit regression. The sum of four skinfolds was used to predict body density and calculate FM (kg) according to published equations for adults. The balance of body weight not attributable to FM was considered to be fat free mass (FFM).

**Cardio-respiratory Fitness**

Cardiorespiratory fitness, expressed as watts per kg (Wkg⁻¹) of lean body mass, was determined using a friction-braked bicycle ergometer (Monark Exercise AB, Sweden) as described previously.

**6.3.3 Questionnaires**

Information of participant’s smoking status, classified as current smoker, ex-smoker or never smoker (if they had smoked less than 100 cigarettes in their lifetime); alcohol consumption; highest level of education completed (school only, trade, technical training or diploma and university); history of cardiovascular disease and medication use; and the date of any recent overt pyrexial illness were obtained from self-completed questionnaires.

**6.3.4 Statistical analysis**

Analyses were stratified by sex a priori. Mean values and standard deviations (SD) were calculated for all variables of interest. As the distribution of CRP was highly left skewed the K-sample medians test and the Kolmogorov test for equality of distribution medians were used to compare CRP levels. Student’s t-tests, Chi-squared tests, Spearman correlation and partial correlation were used to test for differences and estimate associations between CRP and spirometric lung function and other covariates.
Associations of CRP with FEV\textsubscript{1}, FVC and FER were investigated using multivariable regression. Final models included adjustment for age, height, smoking status, asthma status and cardiorespiratory fitness and parity for females. Male fitness, anti-inflammatory medication use, oral contraceptive use and alcohol consumption were not significant contributors to the model. Separate models adjusted for FM and lean body mass or alternatively BMI were used to investigate the effects of different measures of adiposity on the observed associations. Additional adjustment for waist circumference was used to determine the contribution of central adiposity. We did not adjust for percentage body fat.\textsuperscript{240}

In order to assess the association of CRP with lung function at different levels of adiposity, sex-specific z-scores, with a mean of zero and a standard deviation (SD) of unity, were generated for each adiposity measure.

Where necessary, the lung function outcome variables were transformed (e.g. by taking the natural logarithms) prior to regression analysis to reduce skewness and heteroskedasticity of the residuals. The possibility of non-linear associations was tested using fractional polynomial regression. Product terms were included in the regression models to assess statistical interaction between CRP and other covariates. All statistical analyses were carried out using Stata software, version 10.1, (Stata Corp, Texas).

Sensitivity analyses were performed by restricting the analyses to participants who had CRP levels less than 10mg/l and in never smokers who did not report current asthma.
6.4 Results

6.4.1 Participant characteristics

The characteristics of the study sample are presented in Table 6-1. Males had higher FEV₁ and FVC than females, with similar FER, but a lower median CRP and lower prevalence of CRP levels greater than 3mg/l (15.0% vs. 25.1%) mg/l. In addition, 6.7% of females and 4.0% of males had CRP levels greater than 10mg/l. Although females had higher mean levels of body fat, a greater proportion of males were overweight or obese and consumed more than 140mg alcohol per week. A similar proportion of males and females reported current asthma but a greater proportion of females reported using anti-inflammatory medications. The median CRP level among the 305 (34%) females using oral contraceptives was 3.0mg/l (IQR: 1.7 to 6.0) mg/l, but otherwise the CRP levels of females were similar to that observed for males (1.0mg/l, IQR; 0.5 to 2.8) mg/l.

Table 6-1: Characteristics of study participants, Childhood Determinants of Adult Health Study, 2004-2006.

<table>
<thead>
<tr>
<th></th>
<th>Males (n=912)</th>
<th>Females (n=887)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>31.1 (2.6)</td>
<td>30.9 (2.7)</td>
</tr>
<tr>
<td>CRP, mg/l, median, (IQR)a</td>
<td>1.1 (0.5,2.4)</td>
<td>1.7 (0.6,4.1)</td>
</tr>
<tr>
<td>FEV₁, Litres , mean (SD)</td>
<td>4.386 (0.6)</td>
<td>3.278 (0.4)</td>
</tr>
<tr>
<td>FVC, Litres , mean (SD)</td>
<td>5.407 (0.8)</td>
<td>3.938 (0.5)</td>
</tr>
<tr>
<td>FER, % (SD)</td>
<td>81.4 (6.4)</td>
<td>83.5 (5.9)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.3 (4.0)</td>
<td>24.5 (4.5)</td>
</tr>
<tr>
<td>Fat free mass*, kg, mean (SD)</td>
<td>64.0 (7.8)</td>
<td>44.4 (5.8)</td>
</tr>
<tr>
<td>Fat mass*, kg, mean (SD)</td>
<td>21.0 (8.3)</td>
<td>23.2 (8.4)</td>
</tr>
<tr>
<td>Percentage body fat, %, mean (SD)</td>
<td>24.0 (6.0)</td>
<td>33.4 (5.8)</td>
</tr>
<tr>
<td>Waist circumference, cm, mean (SD)</td>
<td>89.1 (10.2)</td>
<td>77.7 (10.9)</td>
</tr>
<tr>
<td>Overweight, n (%)</td>
<td>393 (44.9)</td>
<td>185 (22.2)</td>
</tr>
<tr>
<td>Obese, n (%)</td>
<td>132 (15.1)</td>
<td>104 (12.51)</td>
</tr>
<tr>
<td>Cardio-respiratory fitness, watts/kg, mean,(SD)</td>
<td>3.1 (0.6)</td>
<td>2.9 (0.6)</td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>103 (11.5)</td>
<td>106 (12.0)</td>
</tr>
<tr>
<td>Ex-smokers‡, n (%)</td>
<td>158 (17.3)</td>
<td>214 (24.1)</td>
</tr>
<tr>
<td>Current smokers‡, n (%)</td>
<td>221 (24.2)</td>
<td>185 (20.9)</td>
</tr>
<tr>
<td>Alcohol consumption &gt;140mg/week, n (%)</td>
<td>113/901 (12.5)</td>
<td>47/875 (5.4)</td>
</tr>
<tr>
<td>Anti-inflammatory medication§, n (%)</td>
<td>17(1.9)</td>
<td>38(4.3)</td>
</tr>
</tbody>
</table>

CRP, C - reactive protein; IQR: interquartile range, (25th and 75th percentiles).
FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FER, the ratio of FEV₁ to FVC.
BMI, body mass index. Overweight, BMI ≥25kg/m²-30kg/m², Obese, BMI ≥30kg/m²
†Cardio-respiratory fitness, the estimated physical work capacity at 170 beats per minute (PWC170)
‡Smokers were defined as those who had smoked at least 100 cigarettes in their lifetime.
§Anti-inflammatory medications include Aspirin
6.4.2 Partial correlations

Associations between CRP, lung function and adiposity measures were examined using age- and height-adjusted partial correlation coefficients (Table 6-2). CRP was negatively associated with both FEV₁ and FVC, but only weakly associated with FER. BMI and FM both had positive associations of a similar magnitude with CRP but only FM was significantly associated with FEV₁ and FVC and more strongly among males than females. The associations were stronger for males than females. Among females, asthma, cardiorespiratory fitness and having had at least one live birth were also significantly associated with both CRP and lung function.

Table 6-2: Partial correlation coefficients of adiposity measures with CRP and lung function indices

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males n=912</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1</td>
<td>-0.14**</td>
<td>-0.14**</td>
<td>-0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.34**</td>
<td>-0.02</td>
<td>-0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.37**</td>
<td>-0.17**</td>
<td>-0.19**</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.37**</td>
<td>-0.06**</td>
<td>-0.09*</td>
<td>0.04</td>
</tr>
<tr>
<td>Females n=887</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>1</td>
<td>-0.12**</td>
<td>-0.16**</td>
<td>0.07*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.44**</td>
<td>0.03</td>
<td>0.004</td>
<td>0.06</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.46**</td>
<td>-0.04</td>
<td>-0.07*</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.43**</td>
<td>-0.015</td>
<td>0.04</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

Partial correlation coefficients adjusted for age and height.
CRP: C-reactive protein. As CRP levels were left skewed the natural logarithm was used in this analysis. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FER, the ratio of FEV₁ to FVC; *p<0.05 **p<0.001
Table 6-3: Differences in FEV₁ and FVC associated with a 1mg/l increase in CRP before and after adjustment for measures of body composition.

<table>
<thead>
<tr>
<th></th>
<th>Model 1†</th>
<th></th>
<th></th>
<th>Model 2†</th>
<th></th>
<th></th>
<th>Model 3†</th>
<th></th>
<th></th>
<th>Model 4†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>(95% CI)</td>
<td>R²</td>
<td>Regression coefficient</td>
<td>95% CI</td>
<td>R²</td>
<td>Regression coefficient</td>
<td>95% CI</td>
<td>R²</td>
<td>Regression coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>MALES</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>-6*</td>
<td>(-11,-1)</td>
<td>34.9</td>
<td>-6*</td>
<td>(-11,-1)</td>
<td>34.9</td>
<td>-6*</td>
<td>(-11,-1)</td>
<td>38.2</td>
<td>-5*</td>
<td>(-10,-0.3)</td>
</tr>
<tr>
<td>FVC (ml)</td>
<td>-8*</td>
<td>(-13,-2)</td>
<td>38.8</td>
<td>-7*</td>
<td>(-13,-2)</td>
<td>38.7</td>
<td>-7*</td>
<td>(-12,-0.8)</td>
<td>42.3</td>
<td>-6*</td>
<td>(-11,2)</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.01</td>
<td>(-0.06,0.05)</td>
<td>0.01</td>
<td>-0.01</td>
<td>(-0.07,0.05)</td>
<td>5.7</td>
<td>-0.01</td>
<td>(-0.07,0.05)</td>
<td>5.6</td>
<td>0.01</td>
<td>(-0.07,0.05)</td>
</tr>
<tr>
<td>FEMALES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>-4*</td>
<td>(-9,-0.1)</td>
<td>33.6</td>
<td>-6*</td>
<td>(-10,-1.6)</td>
<td>34.1</td>
<td>-5*</td>
<td>(-10,-1)</td>
<td>38.5</td>
<td>-5*</td>
<td>(-9,-1)</td>
</tr>
<tr>
<td>FVC (ml)</td>
<td>-9*</td>
<td>(-14,-4)</td>
<td>37.1</td>
<td>-11*</td>
<td>(-16,-5)</td>
<td>37.4</td>
<td>-10*</td>
<td>(-15,-5)</td>
<td>41.5</td>
<td>-9*</td>
<td>(-15,-4)</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.09*</td>
<td>(0.02,0.15)</td>
<td>5.9</td>
<td>0.08*</td>
<td>(0.01,0.15)</td>
<td>5.8</td>
<td>0.08*</td>
<td>(0.02,0.15)</td>
<td>5.7</td>
<td>0.08*</td>
<td>(0.02,0.15)</td>
</tr>
</tbody>
</table>

Values are regression coefficients (95% confidence intervals) as ml of FEV₁ (forced expiratory volume in 1st second) and FVC (forced vital capacity), or per cent of FER (The ratio of FEV1 to FVC). CRP, C-reactive protein, SD, standard deviation
†All models adjusted for: age, height, smoking-status, asthma and cardio-respiratory fitness and parity (No/Yes) in females
Model 2: adjusted for BMI z-score
Model 3: adjusted for fat mass z-score and fat free mass z-score
Model 4 adjusted for fat mass z-score and fat free mass z-score and waist (cm)
*P<0.05
6.4.3 Multivariable analysis

The regression coefficients in Table 6-3 indicate the estimated cross-sectional associations of a 1mg increase in CRP with lung function (Model 1). A 1mg increase in CRP was associated with a weak, but significant negative differences in FEV₁ and FVC for males and females (5-6ml and 8-10ml respectively). Adjustment for BMI (Model 2), or FM and FFM (Model 3) and further adjustment for waist circumference (Model 4) had little or no effect on the estimated associations between CRP and FEV₁ or FVC. In females, a significant association was also observed between CRP and FER.

6.4.4 Assessment of interaction

For males, the associations of CRP with FEV₁ and FVC were significantly modified by adiposity after inclusion of product terms in Model 2 (interaction by BMI for FVC, p=0.046) or Model 3 (interaction by FM for FEV₁, p=0.025 and FVC, p=0.006). The estimated differences in FEV₁ and FVC associated with a 1mg increase in CRP at different levels of FFM adjusted FM or BMI are presented in Figure 6-1. For male participants, a 1mg increase in CRP is associated with a significant reduction in FEV₁ or FVC only among participants with higher BMI (Figure 6.1a). The same pattern was observed for FFM adjusted FM (Figure 6.1c). In models that also included waist circumference, the slope of the interactions of BMI for FVC and FM for FEV₁ and FVC were no longer statistically significant (p=0.31, p=0.13 p=0.054 respectively) however, significant negative associations persisted for those with at least average FM (Figure 6-1d).

Among females, the slopes of interaction were not statistically significant for either BMI or FM interaction terms. However, as observed for males, significant negative associations were only apparent for those with at least average FM (Figure 6-2). In contrast, increased BMI appeared to be associated with an increasingly positive association of CRP with FVC (Figure 6-3a). This observation reflected the correlation coefficient presented in Table 6-2, where female BMI appeared to have a positive association with both CRP and lung function (although the associations with lung function did not reach significance). The slope was the same in models that included waist circumference (Figure 6-3b) but was eliminated after FFM was added to the model (Figure 6-3c).

6.4.5 Sensitivity analysis

Restricting the sample to participants with CRP levels less than 10mg/l strengthened the regression coefficients, but the modification of the CRP association by adiposity, observed in the full sample, persisted for males and females (Supplementary Figure 6-4).
Figure 6-1: Differences in FEV₁ and FVC of males associated with a 1mg/l increase in CRP at different levels of fat mass or BMI with and without adjustment for waist circumference.

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity;
All models adjusted for age, height, smoking and asthma.
Modes c and d also adjusted for fat free mass
Models b and d also adjusted for waist circumference (cm)
Mean fat mass 21.2kg, (1 SD =8.4kg); Mean BMI 26.3kg/m², (1 SD =4 kg/m²)
Figure 6-2: Differences in FEV$_1$ and FVC of females, associated with a 1mg/l increase in CRP at different levels of fat mass

<table>
<thead>
<tr>
<th>a) No adjustment for waist circumference</th>
<th>b) Also adjusted for waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph a) No adjustment for waist circumference" /></td>
<td><img src="image" alt="Graph b) Also adjusted for waist circumference" /></td>
</tr>
</tbody>
</table>

FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity;
All models adjusted for age, height, smoking status, asthma, lean mass, parity (Yes/No) and cardiorespiratory fitness.
Mean fat mass= 23.4kg, SD, 8.4kg.

Figure 6-3: Differences in FVC of females, associated with a 1mg/l increase CRP at different levels of BMI

<table>
<thead>
<tr>
<th>a) No waist adjustment</th>
<th>b) Adjusted for waist</th>
<th>c) Adjusted for waist and FFM</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph a) No waist adjustment" /></td>
<td><img src="image" alt="Graph b) Adjusted for waist" /></td>
<td><img src="image" alt="Graph c) Adjusted for waist and FFM" /></td>
</tr>
</tbody>
</table>

All models adjusted for age, height, smoking and asthma, parity (Yes/No) and cardiorespiratory fitness.
b) Additionally adjusted for waist circumference;
c) Additionally adjusted for fat free mass and waist circumference
Mean BMI= 24.5 kg, SD, 4.5kg.
6.5 Discussion

This study is one of only five which have examined the association between CRP and lung function in a population sample of young adults, and the first to investigate in detail the effects of adiposity on this association using a measure other than BMI. It is also the first study to provide data on the distribution of CRP in young Australian adults, with the exception of data on Aborigines.

As observed by others, the initial analysis of the association of a 1mg/l increase in CRP with FEV₁ and FVC indicated negative associations that were weak, but independent of the adiposity. The association was apparent regardless of whether the measure of adiposity used was BMI or FFM adjusted FM (Table 6-3) and additional adjustment for waist circumference had little effect on the associations observed. However, after further investigation, statistically significant modification of the associations of CRP with FEV₁ and FVC among males by BMI and fat mass.

While the slopes of the interactions were not statistical significance for female FEV₁ and FVC, increasing adiposity enhanced the negative associations of CRP with female FVC (Figure 6-2a). Significant negative associations of CRP with female FVC were apparent only in those with at least average fat mass the results were similar in models that included adjustment for central adiposity (Figure 6-2b).

Among males, the modifying effect of adiposity in participants of greater than average FM also persisted in models also adjusted for waist circumference (Figure 6-1b) but the effects of greater BMI were no longer significant (Figure 6-1d). This indicated that in males, some of the association may be accounted for by central adiposity, potentially thorough mechanical effects, but overall body fat may be more relevant to the association. It also suggests that in studies of young adults there may be residual confounding when BMI is the only measure used to adjust for adiposity, as BMI does not allow quantification of the different effects of lean mass and fat mass components of body composition.

The differences in the slopes and extent of the interaction between males and females may be attributable to the differences in distribution of adipose tissue between the sexes association of CRP with FEV₁ and FVC. Of note is the apparent increase in lung function associated with increasing BMI in females. As the association was eliminated after adjustment for lean mass this suggests that in females, lean mass is a greater determinant of lung function than overall body mass.

The results of this study are supported by the findings of a Korean study of COPD-free adults which found that, compared to participants with CRP levels below 0.9mg/l, participants with CRP levels
above 0.9mg/l had a greater prevalence of restrictive lung disease only if their proportion of body fat was also in the top 25% (25.5% and 31% respectively for males and females). Percentage body fat was not presented in the current analysis because others have argued that this may lead to over adjustment. 240

Adipose tissue is now recognized as having a major role in a number of metabolic processes including lipid metabolism, blood pressure control and activation of the inflammatory response. 243 It has previously been shown to be an independent predictor of CRP levels in both adulthood235,244 and childhood. 236 Historical analysis of data from the Odense schoolchild study reported that baseline BMI (at age 14) was the main determinant of a significant negative association between CRP levels at baseline and FVC at age 20. 71 Follow up of this cohort at age 29 found that in males higher CRP levels at age 20 (and changes in CRP between age 20 and 29) were predictive of a greater decline in FEV\textsubscript{1} and FVC. 69 However, although baseline BMI was also associated with follow up CRP levels, as well as the changes in CRP and FEV\textsubscript{1} between baseline and follow up, the potential confounding effect of a significant increase in BMI over the 9 years of follow up was not investigated.

Recent analysis of data from the 20 year follow up of the CARDIA cohort has also reported that CRP and fibrinogen levels at year 7 were associated with higher rates of FVC decline and lower FVC 13 years later. 232 However, at year 7 and year 20, higher CRP and fibrinogen levels were also associated with increased adiposity, and although the investigators adjusted for BMI and change in waist circumference over the period of follow up they did not report any investigation of any potential interaction between adiposity and inflammation. Similarly in the Whitehall study, baseline BMI and waist to hip ratio measures were used to adjust for adiposity but there was no indication of, or adjustment for, any change in adiposity in the study sample during the follow up period.

Although unable to attribute causality, the results of this study suggest that the observed association between CRP and reduced lung function may be confounded by adiposity. Consequently, CRP could potentially be an innocent bystander, or maybe just a marker for more significant adipokine activity not measured here. This is a plausible hypothesis, as adipocytes (and macrophages in adipose tissue) produce an array of adipokines, including Interleukin 6 (IL-6) which is one of three Interleukins that promote the synthesis of C-reactive protein by the liver. As adiposity increases, adipocytes grow larger and the adipose tissue is infiltrated by a greater number of interleukin producing macrophages. 245

Perhaps IL-6 may be a more appropriate molecule, particularly as it regulates the synthesis of CRP. IL-6 has also been associated with reduced lung function in both COPD patients 104,246 and recently in population samples. 230,231 Participants of the Whitehall study who were free from self-reported
respiratory problems at baseline, had small but significant reductions in FEV₁ (3.0 ml and 7.3 ml) and FVC (4.7 ml and 12.6 ml) associated with a 10% increase in CRP and IL-6 (approximately 0.16 mg/l and 0.13 pg/l, respectively) when measured 12 years later. Interleukin and several other biomarkers (e.g. leptin, homocysteine and apolipoprotein) were considered by the CDAH investigators as potential study measures. However, as funding was limited it was not possible to measure them all.

Interest in the association between inflammatory mediators and lung function has increased in the last few years because inflammation has been proposed as a potential link between reduced lung function and increased cardiovascular disease risk. The mechanism for such an association is far from clear. Some researchers have suggested that CRP, generated in response to tissue damage secondary to chronic irritation, infection or inflammation in the lungs, or elsewhere may overflow into the circulation and result in inflammation of the vascular endothelium. Alternatively, it is possible that reduced lung function and elevated inflammation mediators (of which CRP is only one) are concurrent but independent consequences of excess adiposity. In addition to being associated with increased CVD increased adiposity is associated with higher insulin resistance and metabolic syndrome scores which are being increasingly reported to be associated with deficits in lung function but are also indicative of higher CVD risk.

In support of this hypothesis, a recently published study of 282 non-smoking, sedentary, middle-aged Canadian males concluded that obesity related changes in lung function did not appear to be associated with CRP, leptin or tumour necrosis factor. However as the study was cross-sectional, and data on inflammatory mediators was only available for small subgroups of participants its capacity to show any associations may have been limited.

**Strengths and potential weaknesses**

CDAH was primarily a study of CVD, although data on participant asthma status, smoking status and medication usage were collected no standard data on respiratory symptoms or airway hyper-responsiveness, which have also been reported to be associated with elevated inflammatory mediators, were available.

It is also possible that there may be some selection bias due to the large loss to follow up from the original, population based representative baseline sample. However, although differences with respect to age and BMI at baseline were observed, there were no significant differences in baseline age and height adjusted lung function between participants and non-participants. Moreover, the characteristics of participants in adulthood were comparable with estimates of the prevalence of
BMI, current smoking and self-reported asthma in the current Australian population of a similar age (24-34 years).\textsuperscript{19} It is unlikely that the differences in the samples would have affected the observed cross-sectional associations observed here. However, as the current study is cross-sectional it is not possible to imply causality from these results.

Despite the loss to follow up, this study has a number of strengths. It is still a study of a large population-based sample of young, relatively healthy people, both males and females. CRP was determined using a high sensitivity assay and a wide range of covariates were available for assessment. As discussed in previous chapters, the method of ascertaining FM and FFM was not the gold standard measure (Dual Energy X-ray Absorptiometry), however the 15 technicians that measured skinfolds were trained in accordance with the International Society for the Advancement of Kinanthropometry and the equations used to calculated fat mass from skinfolds have been validated for use in an Australian population sample.\textsuperscript{123,250}

\section*{6.6 Conclusion}

In this sample of young adults, the cross-sectional association of CRP with lung function was weak overall but was stronger in those in the higher ranges of adiposity. The main driver of this apparent relationship between CRP and lung function seems to be the association of obesity with both.
6.7 Supplementary tables/figures

Supplementary Figure 6-4: Differences in male and female FEV₁ and FVC associated with a 1mg/l increase CRP on FEV₁ and FVC at different levels of BMI and fat mass for participants with CRP less than 10mg/l.

a) Males

b) Females

c) Males

d) Females

FEV₁, forced expiratory Volume in 1 second; FVC, forced vital capacity
All models adjusted for age, height, smoking and asthma. Females also adjusted for parity (Yes/No) and cardio-respiratory fitness.

*Mean female fat mass: 23.2kg, SD 9.0kg, mean BMI, 24.9, SD 5.0
*Mean male fat mass: 21.0kg, SD 8.4kg, mean BMI, 26.3, SD 4.1
Chapter 7: Lung function and measures of arterial structure and function in young adults


7.0 Introduction

Several large population-based cohort studies, mostly of middle-aged or older adult males, have shown that reduced lung function is associated with increased mortality and risk of cardiovascular disease (CVD).\(^5\) This association is most apparent in those with restrictive\(^2\) or obstructive pulmonary disease\(^2\) but is also observed in population samples and in lifelong non-smokers without respiratory disease.\(^5\) Potential mechanisms for the association include genetic susceptibility, or common risk factors such as smoking and obesity or mediators of systemic inflammation, such as C-reactive protein (CRP), which are often elevated in patients with COPD.\(^3\)

Although CVD is predominantly a disease of older adults, necropsy studies of young adult casualties of war in Korea and Vietnam\(^2\) and childhood victims of trauma\(^2\) have demonstrated that manifestations of atherosclerosis begins in childhood.

In the last 20 years advances in techniques such as high sensitive ultrasound and magnetic resonance imaging have allowed non-invasive, early assessment of vascular health in asymptomatic individuals. Early changes in arterial properties indicative of atherosclerosis, such as carotid intima media thickness (cIMT) and measures of arterial stiffness, have been shown to be associated with traditional CVD factors across a wide age range\(^3\) and to predict future cardiovascular events in older adults and those below 50 years of age.\(^4\) The U.S National Institute of Health has recently recommended increased use of measures such as cIMT to assess CVD risk in otherwise asymptomatic patients.\(^2\)

There are however few studies of lung function and these atherosclerotic measures.\(^3\)

The first study to report a negative association between FEV\(_1\) and cIMT and carotid plaque development came from the British Regional Heart Study.\(^2\) However, Ebrahim \textit{et al} made no adjustment for smoking status. Statistically significant, cross-sectional negative associations between FEV\(_1\) with cIMT were also observed in the Atherosclerosis Risk in Communities (ARIC) study, but the associations were not independent of smoking and other known CVD risk factors.\(^3\)

The majority of studies which have investigated associations between lung function and atherosclerosis have been cross-sectional and have tended to focus on patients with COPD,\(^8\) asthma\(^7\) or cigarette exposure.\(^7\) The evidence from these studies suggests that poor lung function, related to COPD or asthma are associated with increased cIMT and arterial stiffness. Population based cohort studies of males have also shown that FEV\(_1\) and FVC in middle age were
negatively associated with arterial stiffness up to 20 years later,\textsuperscript{83,84} but there is still some debate as to the contribution of chronic smoking to arterial stiffness.\textsuperscript{87}

Few studies have investigated the association between vascular health and lung function as a continuous variable. In a recent publication, the Multi-Ethnic Study of Atherosclerosis investigated associations between lung function and subclinical atherosclerosis in the carotid arteries, the peripheral circulation and the coronary circulation. In their population-based sample of 3,542 participants 45-60 years of age\textsuperscript{265} they found that airway obstruction was associated with increased cIMT, but not with the peripheral arterial stiffness (measured by ankle brachial index) or coronary calcification. Peripheral artery stiffness was however associated with emphysema, suggesting that different mechanisms of association.

To date there are no studies on lung function and atherosclerosis in population samples of young adults. The Atherosclerosis Risk Factors in Male Youngsters (ARMY) study of army recruits observed a significant negative association between MEF and the cIMT of 17-18 year old male participants. However as the lung function measure was not their main measure of interest, the association was assumed to be due to poor physical fitness or exposure cigarette smoke.
7.1 Aim

The aims of this chapter were:

- To investigate the relationships between lung function and ultrasound measures of carotid artery structure (intima-media thickness (cIMT)) and function (distensibility, stiffness index and Young’s elastic modulus (YEM)) in a population based sample of young adult males and females.

- To assess any effect modification by adiposity, cardiorespiratory fitness, CRP or other traditional CVD risk factors on these associations.
7.2 Methods

The Childhood Determinants of Adult Health (CDAH) study is a prospective cohort study investigating the associations between childhood characteristics and adult cardio-metabolic disease.\textsuperscript{172} It was approved by the Southern Tasmanian Health and Medical Research Ethics Committee.

CDAH is a follow up of the 1985 Australian Schools Health and Fitness Survey (ASHFS) which was a cross-sectional survey of a representative sample of 8498 Australian children aged 7-15 years. The ASHFS sampling and data collection methods have been described elsewhere.\textsuperscript{113}

The current cross-sectional analysis uses a subsample of data from 2,410 participants (28\% of the original ASHFS sample) who attended one of 34 clinics across Australia for physical measures and blood sampling, and completed study questionnaires, between 2004 and 2006.

Of those who attended clinics, 1,916 non pregnant participants had both spirometry and ultrasound measures. After exclusion of participants without complete data on covariates, 797 male and 742 female participant records remained for analysis.

7.2.1 Clinic measures

Carotid artery ultrasound

Ultrasound studies of each participant’s left common carotid artery and left carotid bulb were performed by one trained technician according to standardised protocols used in the Cardiovascular Risk in Young Finns Study.\textsuperscript{32,266} A portable Acuson Cypress ultrasound machine (Siemens Medical Solutions USA Inc., Mountainview, CA, USA)\textsuperscript{127} with a 7.0-MHz linear-array transducer was used to generate several 3-5 second real-time images from the B-mode ultrasound from the carotid bulb and approximately 30 mm of the common carotid artery. Images were stored in digital format for off-line analysis, using the analysis program Image Pro Plus version 5.02 (Media Cybernetics, Inc., Silver Spring, MD, USA).

Carotid IMT

The two best quality end-diastolic frames were selected from the five second images by one of three readers. Six measures of the cIMT were then made from the far wall of the common carotid approximately 10 mm proximal to the border of the carotid bulb and a mean cIMT was calculated. To correct for minor differences in the measurements made by the three readers, linear regression methods were used to calculate adjustments that equalised the means of each summary measures
(mean IMT) at common values of age, BMI, waist circumference and, after stratification for sex, oral contraceptive use by women.

**Carotid Elasticity**

End systolic and end diastolic diameters of the carotid artery were measured (twice) from the two best quality end-diastolic frames. Brachial blood pressure was also measured during the ultrasound study with an automated sphygmomanometer (Omron HEM 907, Omron Matsusaka Co Ltd). These ultrasound and blood pressure measures were used to calculate three indicators of carotid artery elasticity (carotid distensibility (Cd), stiffness index (SI) and Young’s elastic modulus (YEM) according to the formulae below (Box 7-1), where $D_s$ and $D_d$ are the end-systolic and end-diastolic diameters and $P_s$ and $P_d$ are the brachial systolic and diastolic blood pressures respectively.

**Box 7-1: Equations used to calculate carotid artery elasticity.**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid distensibility (Cd)</td>
<td>$Cd = \frac{[D_s-D_d]}{D_d} - (P_s-P_d) \times 1000$</td>
</tr>
<tr>
<td>Stiffness index (SI)</td>
<td>$SI = \ln\left(\frac{P_s-P_d}{[D_s-D_d]/D_d}\right)$</td>
</tr>
<tr>
<td>Young’s elastic modulus (YEM)</td>
<td>$YEM = \frac{[P_s-P_d] \times D_d}{[D_s-D_d]/cIMT}$</td>
</tr>
</tbody>
</table>

Carotid distensibility (Cd) is a measure of an artery’s ability to expand in response to pulse pressure (the pressure change between peak systolic and diastolic blood pressure). It is the percentage change in diameter for each 10mmHg increase in blood pressure. It increases with artery size and decreases secondary to loss of arterial wall elasticity.

The arterial stiffness index (SI) is ratio of the difference in systolic and diastolic pressure and the change in arterial diameter. The SI increases as arterial stiffness increases. It is independent of blood pressure and artery size.

The Young’s Elastic Modulus (YEM) is the stiffness of the artery per cm of wall thickness. As the thickness of the cIMT affects arterial elasticity, this measure provides an estimate of arterial stiffness independent of cIMT and artery size. A higher YEM is associated with increased arterial stiffness.
Chapter 7 Lung function and arterial structure and function in young adults

**Spirometry**

Lung function parameters were recorded in a standing position using a MicroLab 3500 portable electronic spirometer (Micro Medical Ltd. UK) and Spida 5 software (Micro Direct Inc. Lewiston, ME USA) in accordance with American Thoracic Society/European Respiratory Society guidelines as described in Chapter 2. The analyses presented here include data from all participants who had at least one valid flow-loop volume.

Prior to spirometry, participants were asked the details of any current lung condition and the name and time of the last dose of any medication they had taken for the condition. Current asthmatics were defined as those who reported having asthma, or who reported taking asthma medication.

**Anthropometry**

As described in Chapter 2, participants’ heights and weights were measured to the nearest 0.1cm and 0.1kg respectively. Body mass index (BMI) was calculated using the formula BMI = weight (kg)/height squared (m²). Skin folds (triceps, biceps, sub-scapular and sub-iliac) were measured to the nearest 0.1mm. Fat mass and fat free mass (or lean body mass (LBM)) were estimated using weight (kg) and estimates of per cent body fat derived from the sum of skin folds according to published equations for adults (LBM = weight – (per cent body fat x weight)/100).

**Blood lipids and CRP**

Blood samples were collected from participants after an overnight fast of at least 8 hours. Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) concentrations were determined enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan) and serum CRP using a highly sensitive turbidimetric immunoassay kit (Olympus System CRP Latex reagent) (Olympus Life and Material Science Europa GmbH, Ireland). The ratio of total cholesterol to HDL-C (TCh/HDLr) was calculated. Low density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula.

**Blood pressure and fitness**

Blood pressure was measured from the right arm using an OMRON HEM907 digital automatic blood pressure monitor (Omron Corporation, Kyoto, Japan) by the ultrasound technician. Cardiorespiratory fitness, expressed as watts per kg (W/kg) of lean body mass was determined using a friction-braked bicycle ergometer (Monark Exercise AB, Sweden) as described previously. Maximal grip strength was measured using a Smedley’s spring-type hand dynamometer (Stoelting
Co. Illinois, USA). Three attempts were made on both left and right hands with at least a one-minute rest between successive attempts on the same hand. The analysis used an average of the dominant and non-dominant hand scores.

**Other covariates**

Participants’ smoking status (never or ever smokers, depending on whether they had smoked at least 100 cigarettes in their lifetime); alcohol consumption; the highest level of education completed; medication use and female parity were obtained from self-administered questionnaires. Cumulative exposure (pack-years) was calculated for participants who had ever been daily smokers and had daily consumption and years of smoking available.

### 7.2.2 Statistical analysis

Analyses were stratified by sex a priori. Mean values and standard deviations (SD) were calculated for all variables of interest. Student’s t-tests for continuous variables and the Chi-squared test for categorical variables were used to investigate differences in relevant baseline study factors between those included and excluded from the analysis. Age- and height-adjusted Pearson correlation coefficients were used to identify significant relationships between variables of interest and the dependent (cIMT, and elasticity measures Cd, SI and YEM) and independent (FEV$_1$, FVC and FEF$_{25-75}$ and FER) variables, and the outcome measures of mean cIMT, and elasticity measures Cd, SI and YEM. The primary vascular health measures were cIMT and YEM.

The magnitude of any cross-sectional associations between the continuous variables FEV$_1$, FVC, FEF$_{25-75}$ and FER and each outcome were also assessed using linear regression. The final models included adult height, age, current asthma status, asthma medication (yes/no), ever smoking (yes/no) and parity (yes/no) for females. The effects of adiposity, fitness and CRP on the associations were then assessed in 3 successive models. A further model included other cardiovascular risk factors from Table 7-1 which significantly contributed to the model of interest. Note that the models may differ according to the dependent variable and by sex.

Regression analyses were repeated after stratification by smoking status and a subsample of daily smokers with pack years of exposure available.
7.3 Results

7.3.1 Participant characteristics

Descriptive statistics for the 797 males and 742 females included in this analysis are presented in Table 7-1. Compared to the ASHFS participants not included in the analysis, male participants were slightly older \( (p=0.003) \) and female age-adjusted BMI was lower but there were no differences in the age and sex adjusted fitness or height-adjusted \( FEV_1 \) and FVC.

At follow up female participants had lower mean lung function indices, cIMT, SI and YEM than males but higher Cd than males. Mean female CRP and HDL-C levels were higher than male levels but (with the exception of percentage body fat) body composition measures, fitness, blood pressure, total cholesterol, LDL-c and triglycerides levels were all lower than males’. A slightly higher proportion of females than males reported having asthma and ever smoking. 19 Forty eight per cent of females \( (n=360) \) reported having had at least one live birth and 44\% \( (n=322) \) currently used oral contraceptives.

7.3.2 Correlations between lung function, vascular measures and potential confounders

Associations between dependent and independent variables and key covariates were first assessed using partial correlation. No significant associations between lung function and any of the vascular measures were detected in the sample as a whole (not shown). However, in analysis stratified according to smoking status there were statistically significant correlations of \( FEF_{25-75} \) \( (\rho=-0.16, \ p=0.006) \) and FER \( (\rho=-0.16, \ p=0.005) \) with cIMT for male, and FVC \( (\rho=-0.11, \ p=0.04) \) and FER \( (\rho=-0.13, \ p=0.02) \) with YEM for female ever-smokers. The results of age and height adjusted partial correlation analyses used to develop regression models are presented in Supplementary Table 7-6.
Table 7-1: Summary statistics for 797 male and 742 female CDAH study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males n=797</th>
<th>Females n=742</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averaged cIMT, μm, mean (SD)</td>
<td>574 (91)</td>
<td>547 (70)</td>
</tr>
<tr>
<td>Maximal cIMT, μm, mean (SD)</td>
<td>619 (100)</td>
<td>581 (80)</td>
</tr>
<tr>
<td>SI, mean (SD)</td>
<td>5.8 (2.25)</td>
<td>5.3 (2.38)</td>
</tr>
<tr>
<td>Cd, % per 10mmHg, mean (SD)</td>
<td>2.0 (0.64)</td>
<td>2.4 (0.79)</td>
</tr>
<tr>
<td>YEM, mmHg per mm, mean (SD)</td>
<td>323 (138)</td>
<td>251 (113)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>31.1 (2.6)</td>
<td>30.9 (2.6)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>179.7 (6.9)</td>
<td>165.9 (6.4)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>85.4 (14.4)</td>
<td>68.3 (14.8)</td>
</tr>
<tr>
<td>FEV1, L, mean (SD)</td>
<td>4.381 (0.63)</td>
<td>3.270 (0.45)</td>
</tr>
<tr>
<td>FVC, L, mean (SD)</td>
<td>5.399 (0.78)</td>
<td>3.931 (0.55)</td>
</tr>
<tr>
<td>FER, %, mean (SD)</td>
<td>4.024 (6.3)</td>
<td>3.207 (5.9)</td>
</tr>
<tr>
<td>FEF25-75, L, mean (SD)</td>
<td>81.4 (1.0)</td>
<td>83.4 (0.76)</td>
</tr>
<tr>
<td>BMI, kg/m2, mean (SD)</td>
<td>26.4 (4.1)</td>
<td>24.8 (5.0)</td>
</tr>
<tr>
<td>Fat mass, kg, mean (SD)</td>
<td>21.3 (8.3)</td>
<td>23.6 (9.0)</td>
</tr>
<tr>
<td>Lean mass, kg, mean (SD)</td>
<td>64.1 (7.8)</td>
<td>44.6 (6.3)</td>
</tr>
<tr>
<td>Cardiorespiratory Fitness, Watts/kg, mean(SD)</td>
<td>3.10 (0.6)</td>
<td>2.93 (0.64)</td>
</tr>
<tr>
<td>Grip strength, kg, mean(SD)</td>
<td>47.9 (7.2)</td>
<td>29.0 (5.0)</td>
</tr>
<tr>
<td>Systolic BP, mmHg, mean (SD)</td>
<td>126 (10.7)</td>
<td>112 (10.0)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg, mean (SD)</td>
<td>75.0 (8.9)</td>
<td>70.3 (8.4)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg, mean (SD)</td>
<td>51 (8.5)</td>
<td>41 (6.9)</td>
</tr>
<tr>
<td>Total cholesterol, mg/l, mean (SD)</td>
<td>4.95 (1.0)</td>
<td>4.78 (0.85)</td>
</tr>
<tr>
<td>HDL-C, mg/l, mean (SD)</td>
<td>1.29 (0.27)</td>
<td>1.54 (0.32)</td>
</tr>
<tr>
<td>LDL-C, mg/l, mean (SD)</td>
<td>3.09 (0.84)</td>
<td>2.81 (0.75)</td>
</tr>
<tr>
<td>Total cholesterol: HDL-C ratio, %, mean (SD)</td>
<td>395 (1.00)</td>
<td>321 (0.80)</td>
</tr>
<tr>
<td>Triglycerides, mg/l, median (IQR)</td>
<td>1.28 (0.7,1.5)</td>
<td>0.92 (0.6,1.1)</td>
</tr>
<tr>
<td>Insulin, mg/l, median (IQR)</td>
<td>7.48 (4.4,9.07)</td>
<td>6.76 (4.4,8.3)</td>
</tr>
<tr>
<td>C-Reactive protein, mg/l, median (IQR)</td>
<td>2.51 (0.5,2.3)</td>
<td>3.45 (0.6,3.8)</td>
</tr>
<tr>
<td>Alcohol, g/wk., median (IQR)</td>
<td>45 (18,87)</td>
<td>26 (8.64)</td>
</tr>
<tr>
<td>Current Asthma, n, %</td>
<td>88 (11.0)</td>
<td>95 (12.8)</td>
</tr>
<tr>
<td>Ever smokers, n, %</td>
<td>325 (40.4)</td>
<td>332 (44.4)</td>
</tr>
</tbody>
</table>

CDAH Childhood Determinants of adult health. cIMT, carotid intima-media thickness; SI, arterial stiffness index; DC, carotid artery compliance; YEM, young’s elastic modulus; FEV1 forced expiratory volume in the first second; FVC, forced vital capacity; FEF25-75 the flow rate in the middle 50% of the FVC. Cardiorespiratory fitness the estimated work capacity at a heart rate of 170 beats per minute standardised for lean body mass(kg); Grip strength is the mean value of dominant and non-dominant hands; BP, blood pressure in mmHg ; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein. LDL–C was available for only 797 male participants. As the distribution of triglycerides, C-reactive protein, alcohol consumption and were skewed, median values and interquartile ranges (IQR) are presented for these variables. As per WHO guidelines,260 participants were classified as ever-smokers if they reported smoking at least 100 cigarettes in their lifetime.
7.3.3 Multivariable models

**Lung function and cIMT**

The results of the stepwise regression of FEV$_1$, FVC, FEF$_{25-75}$ and FER with cIMT are presented in sequential models in Table 7-2 and Table 7-3 for all males and females respectively, before and after stratification by smoking status.

After adjustment for age, height, ever-smoking, lean mass, fat mass, systolic blood pressure and serum insulin, no statistically significant associations were observed between lung function and cIMT for males in the full sample. Although a borderline association was observed between FEF$_{25-75}$ and cIMT in the full sample ($p=0.06$). After stratification, negative associations of FEF$_{25-75}$ and FER with cIMT were apparent in ever smokers (Table 7-2), $p=0.008$ and $p=0.02$ respectively.

For females, an association of borderline significance was observed, between FEV$_1$ and cIMT, after adjustment for systolic blood pressure and total to HDL-c cholesterol ratio (TChHDLr ($\beta=-0.14$mm (95% CI, -0.029, 0.001) mm ($p=0.06$). However, after stratification, significant negative associations were observed for FEV$_1$ and FVC with mean cIMT in never-smokers (Table 7-3). No significant association was observed between FER and cIMT.

**Lung function and arterial elasticity**

The associations of FEV$_1$, FVC, FEF$_{25-75}$ and FER with Cd, SI and YEM were assessed in separate models. For males, no significant associations with observed with either YEM (Table 7-4) or Cd (Supplementary Table 7-7). A borderline significant positive association between FEV$_1$ and SI was eliminated after stratification by smoking status (Supplementary Table 7-7).

Among females a negative association was observed between FER and YEM for ever-smokers ($\beta=-0.007$ (95% CI -0.013, -0.0002), $p=0.04$), but this was not significant after adjustment for CRP (Table 7-5). A significant positive association observed between FVC and SI ($\beta = 0.062$ (95% CI, 0.004, 0.119, $p=0.02$) was independent of other CVD risk factors but also lost significance after stratification by smoking status (Supplementary Table 7-7).

There were no statistically significant associations between FER and arterial elasticity. Results are not tabulated as all beta coefficients were less than 0.001%.

When the main analyses were repeated, excluding participants who had reported a diagnosis of asthma at clinic, the association of FEV$_1$ and FVC with cIMT, in females, became statistically significant ($\beta=-0.020$ (95% CI -0.042, -0.000), $p=0.04$ and $\beta=-0.022$ (95% CI -0.040, -0.004), $p=0.016$.
respectively after adjustment for age, height, parity, fat mass, fat free mass, fitness and CRP), but associations with stiffness and elasticity measures were eliminated.

### 7.3.4 Adjustment for pack years of smoking

Cumulative smoke exposure (pack-years) was available for a subsample of daily smoking participants (199 males and 227 females). After additional adjustment for pack-years of smoking, the associations of FEF25-75 and FER with cIMT among males, and between FER and YEM among females, were no longer statistically significant. (In the regression models of FER and YEM, for females, each pack year of smoking was associated with approximately 3μm increase in cIMT (p=0.002)).
Table 7-2: Associations of lung function parameters with carotid intima-media thickness (cIMT) for young adult males, according to smoking status

<table>
<thead>
<tr>
<th></th>
<th>Model 1‡</th>
<th>Model 2‡</th>
<th>Model 3‡</th>
<th>Model 4‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.005</td>
<td>-0.017</td>
<td>0.008</td>
<td>-0.010</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.000</td>
<td>-0.010</td>
<td>0.011</td>
<td>-0.003</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>-0.004</td>
<td>-0.010</td>
<td>0.003</td>
<td>-0.006</td>
</tr>
<tr>
<td>FER (%)</td>
<td>-0.001</td>
<td>-0.002</td>
<td>0.000</td>
<td>-0.001</td>
</tr>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.003</td>
<td>-0.019</td>
<td>0.013</td>
<td>-0.008</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>-0.003</td>
<td>-0.016</td>
<td>0.011</td>
<td>-0.006</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>0.001</td>
<td>-0.008</td>
<td>0.009</td>
<td>-0.001</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.000</td>
<td>-0.001</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>Ever smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.011</td>
<td>-0.032</td>
<td>0.010</td>
<td>-0.016</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.005</td>
<td>-0.012</td>
<td>0.021</td>
<td>0.001</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>-0.014*</td>
<td>-0.024</td>
<td>-0.003</td>
<td>-0.015*</td>
</tr>
<tr>
<td>FER (%)</td>
<td>-0.002*</td>
<td>-0.004</td>
<td>0.000</td>
<td>-0.002*</td>
</tr>
</tbody>
</table>

β values are regression coefficients, mm(95% confidence intervals) per unit increase in the independent variable. Significance, P #<0.1, P *<0.05.

‡ FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅-₇₅, forced expiratory volume in the middle 50% of the FVC; FER, the ratio of FEV₁/FVC.

† All models adjusted for age, height, ever smoking, current asthma, asthma medication (and parity (yes/no) for females); Model 2 also adjusted for fat mass, lean mass and female cardiopulmonary fitness, Model 3, Model 2 adjusted for C-reactive protein. Model 4 Adjusted for CRP and systolic blood pressure and insulin.

Never smokers n=474, Ever smokers n=323. Ever smokers: had smoked at least 100 cigarettes in their lifetime.
Table 7-3: Associations of lung function parameters† with carotid intima-media thickness (cIMT) for young adult females, according to smoking status

<table>
<thead>
<tr>
<th></th>
<th>Model 1‡</th>
<th>Model 2‡</th>
<th>Model 3‡</th>
<th>Model 4‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.011</td>
<td>-0.025</td>
<td>0.003</td>
<td>-0.014</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>-0.007</td>
<td>-0.019</td>
<td>0.005</td>
<td>-0.009</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>-0.003</td>
<td>-0.010</td>
<td>0.005</td>
<td>-0.003</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.000</td>
<td>-0.001</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Never smokers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.018‡</td>
<td>-0.036</td>
<td>0.001</td>
<td>-0.018‡</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>-0.016*</td>
<td>-0.032</td>
<td>-0.001</td>
<td>-0.018*</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>-0.002</td>
<td>-0.012</td>
<td>0.008</td>
<td>-0.002</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.000</td>
<td>-0.001</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Ever smokers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-0.002</td>
<td>-0.024</td>
<td>0.020</td>
<td>-0.006</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.004</td>
<td>-0.013</td>
<td>0.022</td>
<td>0.002</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>-0.002</td>
<td>-0.013</td>
<td>0.008</td>
<td>-0.004</td>
</tr>
<tr>
<td>FER (%)</td>
<td>-0.001</td>
<td>-0.002</td>
<td>0.001</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

β values are regression coefficients, mm (95% confidence intervals) per unit increase in the independent variable. Significance, P †<0.1, *<0.05
† FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory volume in the middle 50% of the FVC; FER the ratio of FEV₁/FVC.
‡ All models adjusted for age, height, ever smoking, current asthma, asthma medication (and parity (yes/no) for females). Model 2 also adjusted for fat mass, lean mass and female cardiorespiratory fitness, Model 3. Model 2 adjusted for c-reactive protein. Model 4 Adjusted for CRP and systolic blood pressure.
Never smokers n=410 Ever smokers n=332. Ever smokers: had smoked at least 100 cigarettes in their lifetime
Table 7-4: Associations of lung function parameters† with Young Elastic Modulus (YEM) for young adult males, according to smoking status

<table>
<thead>
<tr>
<th></th>
<th>Model 1‡</th>
<th></th>
<th>Model 2‡</th>
<th></th>
<th>Model 3‡</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.036</td>
<td>-0.014, 0.087</td>
<td>0.028</td>
<td>-0.024, 0.079</td>
<td>0.033</td>
<td>-0.019, 0.084</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.029</td>
<td>-0.012, 0.071</td>
<td>0.026</td>
<td>-0.016, 0.068</td>
<td>0.030</td>
<td>-0.012, 0.072</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>0.009</td>
<td>-0.017, 0.035</td>
<td>0.003</td>
<td>-0.024, 0.029</td>
<td>0.004</td>
<td>-0.022, 0.030</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.036</td>
<td>-0.014, 0.087</td>
<td>0.028</td>
<td>-0.024, 0.079</td>
<td>0.033</td>
<td>-0.019, 0.084</td>
</tr>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.031</td>
<td>-0.032, 0.095</td>
<td>0.029</td>
<td>-0.037, 0.094</td>
<td>0.036</td>
<td>-0.029, 0.101</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.021</td>
<td>-0.034, 0.076</td>
<td>0.022</td>
<td>-0.034, 0.078</td>
<td>0.030</td>
<td>-0.025, 0.085</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>0.013</td>
<td>-0.020, 0.047</td>
<td>0.008</td>
<td>-0.026, 0.042</td>
<td>0.010</td>
<td>-0.024, 0.043</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.0001</td>
<td>-0.005, 0.005</td>
<td>-0.001</td>
<td>-0.006, 0.005</td>
<td>-0.001</td>
<td>-0.006, 0.005</td>
</tr>
<tr>
<td>Ever smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.036</td>
<td>-0.048, 0.120</td>
<td>0.015</td>
<td>-0.070, 0.101</td>
<td>0.017</td>
<td>-0.069, 0.104</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.038</td>
<td>-0.026, 0.103</td>
<td>0.021</td>
<td>-0.046, 0.088</td>
<td>0.022</td>
<td>-0.045, 0.089</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L)</td>
<td>0.000</td>
<td>-0.043, 0.043</td>
<td>-0.005</td>
<td>-0.047, 0.037</td>
<td>0.039</td>
<td>0.039</td>
</tr>
<tr>
<td>FER (%)</td>
<td>-0.001</td>
<td>-0.008, 0.006</td>
<td>-0.001</td>
<td>-0.007, 0.006</td>
<td>0.000</td>
<td>-0.007, 0.006</td>
</tr>
</tbody>
</table>

β values are regression coefficients, mm (95% confidence intervals) per unit increase in the independent variable.

dIMT, Carotid Intima-media thickness (mm)

† FEV₁ forced expiratory volume in 1 second; FVC Forced Vital Capacity; FEF₂₅-₇₅, Forced expiratory Volume in the middle 50% of the FVC; FER the ratio of FEV₁/FVC.

All models adjusted for age, height, ever smoking, current asthma

Model 2 Also adjusted for fat mass, lean mass

Model 3 Model 2, adjusted for C-reactive protein.

Never smokers n=474, Ever smokers n=323. Ever smokers: had smoked at least 100 cigarettes in their lifetime

Significance, P **<0.1, P *<0.05
Table 7-5: Associations of lung function parameters† with Young Elastic Modulus (YEM) for young adult females according to smoking status

<table>
<thead>
<tr>
<th></th>
<th>Model 1‡</th>
<th></th>
<th>Model 2‡</th>
<th></th>
<th>Model 3‡</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.021</td>
<td>-0.048</td>
<td>0.089</td>
<td>0.027</td>
<td>-0.045</td>
<td>0.099</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.038</td>
<td>-0.018</td>
<td>0.095</td>
<td>0.051*</td>
<td>-0.009</td>
<td>0.110</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>-0.001</td>
<td>-0.036</td>
<td>0.034</td>
<td>-0.005</td>
<td>-0.040</td>
<td>0.029</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.036</td>
<td>-0.014</td>
<td>0.087</td>
<td>0.028</td>
<td>-0.024</td>
<td>0.079</td>
</tr>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.001</td>
<td>-0.088</td>
<td>0.089</td>
<td>0.023</td>
<td>-0.070</td>
<td>0.116</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>-0.006</td>
<td>-0.031</td>
<td>0.069</td>
<td>0.017</td>
<td>-0.063</td>
<td>0.096</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>0.011</td>
<td>-0.036</td>
<td>0.058</td>
<td>0.009</td>
<td>-0.038</td>
<td>0.055</td>
</tr>
<tr>
<td>FER (%)</td>
<td>0.002</td>
<td>-0.004</td>
<td>0.008</td>
<td>0.001</td>
<td>-0.005</td>
<td>0.007</td>
</tr>
<tr>
<td>Ever smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.039</td>
<td>-0.071</td>
<td>0.149</td>
<td>0.024</td>
<td>-0.090</td>
<td>0.138</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.086*</td>
<td>0.000</td>
<td>0.173</td>
<td>0.081*</td>
<td>-0.010</td>
<td>0.171</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (L)</td>
<td>-0.019</td>
<td>-0.071</td>
<td>0.033</td>
<td>-0.023</td>
<td>-0.075</td>
<td>0.029</td>
</tr>
<tr>
<td>FER (%)</td>
<td>-0.007*</td>
<td>-0.013</td>
<td>0.000</td>
<td>-0.007</td>
<td>-0.013</td>
<td>0.000</td>
</tr>
</tbody>
</table>

β values are regression coefficients, mm(95% confidence intervals) per unit increase in the independent variable.

Table 7-5: Associations of lung function parameters† with Young Elastic Modulus (YEM) for young adult females according to smoking status

All models adjusted for age, height, ever smoking, current asthma (and parity (yes/no) for females).
Model 2 Also adjusted for fat mass, lean mass and female cardiorespiratory fitness,
Model 3 Model 2, adjusted for C-reactive protein.

Never smokers n=410 Ever smokers n=332. Ever smokers: had smoked at least 100 cigarettes in their lifetime
Significance, P #<0.1, P *<0.05
7.4 Discussion

In this study of young adults, the associations between lung function and subclinical measures of vascular health, smoking and asthma confounded associations of lung function with measures of arterial stiffness, and cIMT in males, While a restrictive pattern of lung function (reduced FEV₁ and FVC) was associated with higher cIMT in never smoking females.

Although reduced FER and FEF₂₅-₇₅ (indicators of airway obstruction) were associated with a poor vascular profile (indicated by increased cIMT and YEM) in smokers, these associations were eliminated after adjustment for cumulative smoke exposure. This suggests that the observed obstruction, and loss of elasticity, were associated with cigarette smoke rather than a consequence of poor lung function per se. As Iwamoto et al⁷⁴ reported an association of FEV₁ with cIMT only in middle aged smokers who already had signs of airflow limitation, it is possible that at this stage of their lives CDAH participants were too young, and their lung volumes too well preserved, for any association to be observed.

The apparent negative associations of FEV₁ and the positive association of FVC with SI, in the non-stratified regression models for males (suggesting that increased LF is associated with increased arterial stiffness) appear to be perplexing in the first instance. However, given that these associations are eliminated after stratification by smoking status this may be a consequence of the higher mean FEV₁ and FVC values in ever smokers compared to never smokers.

In female never-smokers, reductions in both FEV₁ and FVC, were significantly associated with cIMT (p=0.044 and p=0.018 respectively). This finding is similar to that observed in the ARIC study.⁷³ Although ARIC participants were older, and had cIMT measures considerably greater than CDAH participants’, a negative association between both mean FEV₁ and FVC (but not FER) and cIMT category was observed to be stronger among never smoking females. This finding warrants further investigation. The 15 year follow up of the ARIC cohort found that participants with a restrictive pattern of lung function impairment also had an increased risk of a cardiovascular events.⁶³ However, in contrast to our observations, their associations were weakened when adjusted for other CVD risk factors. It is possible that the observed associations may also be confounded by residual adiposity. Alternatively it is possible that the association of FEV₁ and FVC with cIMT in these young females may be an indicator of some other exposure, or physiological process, which affects both lung function and the vascular endothelium. For example, impaired foetal growth has been associated with higher cIMT in children²⁷⁰ and females have been reported to be more susceptible to these effects than...
males. \textsuperscript{271} There is also evidence that passive smoking in childhood is associated with higher cIMT and arterial stiffness in never smoking adults.\textsuperscript{85,272,273}

Sex differences in the aetiology of atherosclerosis development have been suggested by Kerkhof et al who used structural equation modelling to explore the pathways leading to atherosclerosis (determined by cIMT) in 322 young adults aged 18-24 years.\textsuperscript{274} For males, the pathway appeared to be a direct effect of LDL-c and Apo lipoprotein b on cIMT, but for females their results suggested a more indirect effect secondary to increased plasma acetylation of proteins involved in lipid metabolism. They also suggested that perhaps the smaller size of LDL particles in females, or the hypo-lipidaemic properties of oestrogen, may be important mediators of the pathway. Whatever the mechanism, the longitudinal evidence from the ARIC cohort suggests that, in the absence of overt restrictive respiratory condition, individuals who appear to have restricted lung volumes might be targeted and encouraged to improve their CVD risk factor profile in order to reduce their risk of a future CVD event.

\textit{Strengths and limitations}

This study has several possible limitations. Selection bias due to differential loss to follow up may have been present. However, although differences with respect to age and BMI at baseline between participants and non-participants there were no significant differences in baseline lung function. Moreover, the characteristics of participants in adulthood were comparable with estimates of the prevalence of overweight, obesity, current smoking and self-reported asthma, in the current Australian population of a similar age (24-34 years).\textsuperscript{19} It is unlikely that the differences in the samples would have affected the observed cross-sectional associations.

As CDAH was primarily a study of CVD, we have no standard data on respiratory symptoms or airway hyper-responsiveness that may have affected lung function, but data on participant asthma status, smoking status and medication use was collected. Also current recommendations for studies of respiratory function indicate that lung function spirometry should be measured pre and post bronchodilator treatment to improve validity and repeatability of measures. Because CDAH clinics were conducted in a variety of community venues and not in medical establishments more detailed lung function testing was not feasible.

Reading of ultrasound images was not an automated process. Image resolution, reader expertise and inter-reader variability are potentially limiting factors. In this study there were differences in the mean measures obtained by different readers, who were allocated digital images based on research priorities rather than at random. This was addressed and corrected measurements were generated
using linear regression techniques prior to this analysis. Semi-automated methods of measuring cIMT are now available and may have prevented such variation in future studies.

In order to calculate arterial elasticity measures brachial arterial pressure measured supine, at the same time as the ultrasound study, were used as a surrogate for aortic or carotid pulse pressure. As central arteries are usually more elastic than peripheral arteries in young subjects, using brachial artery pressure may have resulted in overestimation of carotid artery stiffness. Ideally, blood pressure measured directly from the artery under study (the carotid) should ideally be used however, such invasive procedures this would not be appropriate in field studies.

In a clinical setting, the ‘gold standard’ measure of arterial stiffness is pulse wave velocity (PWV). Although PWV and carotid artery stiffness measures provide similar clinical information on arterial stiffness in normal subjects, PWV studies do not measure artery diameter or wall thickness. In contrast, ultrasound measures not only allow visualisation of the site of interest, but also allow measurement of the cIMT and calculation of the YEM, which is an indicator of arterial wall elasticity independent of geometry.

A recent review of techniques for measuring arterial stiffness has suggest that the main difference between ultrasound-determined elasticity and PWV is the potential for operator bias. As CDAH had only one ultrasound technician taking measurements, systematic operator bias is unlikely. We did however have significant differences in the measures obtained by different readers who were allocated digital images based on research priorities, rather than at random. We addressed this and generated corrected measurements using linear regression techniques prior to this analysis.

As this is a cross-sectional study, it is not possible to attribute causality or temporality to the association of lung function with cIMT in young females. Our models explained less than 5 per cent of the variation in participant cIMT and arterial elasticity.

This study does however have some major strengths. No other study, which has investigated the association between lung function and arterial structure and function in young adults, has been of this magnitude. Even after exclusion of ever-smokers, our analysis is based on a large sample of young men and women apparently free of CVD. The cIMT measures, and the correlations of traditional cardiovascular risk factors with cIMT and arterial stiffness observed for CDAH study participants, were comparable to those of other studies of young adults. We have also been able to consider and take into account a comprehensive list of potentially confounding factors including smoking, adiposity, cardiorespiratory fitness, muscular strength and other known CVD risk factors.
7.5 Conclusion

In these young adults, airway obstruction (reduced FEV₁, FEF<sub>25-75</sub> or FER) was associated with a poor vascular profile (increased cIMT and YEM) in male smokers, but the associations were eliminated after adjustment for pack years of exposure.

No associations were found between the lung function of never smoking males and subclinical measures of atherosclerosis. However, among never-smoking females deficits in FEV₁ and FVC, but not FER were associated with increased cIMT independent of adiposity. More detailed analysis of cardiac vascular measures and related respiratory physiology and environmental smoke exposure in young females is now indicated.
### 7.6 Supplementary tables/figures

**Supplementary Table 7-6: Age and height adjusted partial correlation coefficients of metabolic CVD risk factors and other covariates with lung function, and arterial structure and function**

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FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FEF₂₅₋₇₅, rate of flow in the middle 50% of the FVC; FER, the ratio of FEV₁ to FVC; cIMT, carotid intima-media thickness; SI, arterial stiffness index; Cd, carotid artery compliance; YEM, young’s elastic modulus; BP, blood pressure; TChHDLr, the ratio of total cholesterol to high density cholesterol, CRP, C-reactive protein

$^\text{a}$ Fasting measures

$^\text{§}$ Fitness, Work capacity at 170 beats per minute standardised by lean mass

Significance, *p<0.05 **p <0.001
Age and height adjusted partial correlation coefficients showed asthma, adiposity and CRP were positively associated with cIMT and SI, and negatively associated with YEM and lung function for both males and females. Grip strength was significantly associated with the FEV$_1$, FVC and FEF$_{25-75}$ of both males and females but only with arterial elasticity measures in females.

Ever smoking was positively associated with FEV$_1$ and FVC and negatively with FER for both males and females. For females ever smoking was also associated with cIMT. Having at least one live birth was positively associated with FVC and cIMT, and negatively with FER. Blood pressure, triglycerides, TChDLr and insulin were positively associated with cIMT and YEM and negatively with Cd in both males and females. Triglyceride, insulin and TChDLr were negatively associated with FEV$_1$ and FVC. The associations were similar in strength to those observed by other studies of young adults.

Supplementary Table 7-7: Associations of lung function parameters with carotid distensibility (Cd) and stiffness index (SI), for males and females, aged 27-36 years.

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$^a$β values are regression coefficients (95% confidence intervals) per 1 L increase in FEV$_1$ or FVC and FEF$_{25-75}$

FEV$_1$, forced expiratory volume in one second; FVC Forced Vital Capacity; FEF$_{25-75}$, Forced expiratory Volume in the middle 50% of the FVC; Cd, distensibility coefficient; SI, stiffness Index.

‡All models adjusted for age, height, ever smoking and current asthma

Model 2, also adjusted for fat mass, lean mass and cardiorespiratory fitness,

Model 3, Model 2 also adjusted for C-reactive protein

Significance, *p<0.05, $^b$p<0.1
Chapter 8: Summary, future directions and conclusions
8.0 Cardiovascular disease and lung function

Two of the main causes of morbidity and death in developed (and also increasingly in developing countries) are CVD and COPD. CVD is the most common cause of death amongst those with COPD but higher rates of cardiovascular events and all-cause mortality have also been observed among participants of population based studies who have reduced spirometry measures, but no evidence of respiratory disease. Some authors have recommended that lung function should be used in conjunction with the Framingham CVD risk score to predict an individual’s risk of a CVD event.

CVD includes a number of conditions of the heart and vascular system. The majority (>80%) of these conditions (coronary heart disease, stroke and peripheral artery disease) are caused by ischemia secondary to the development and progression of atherosclerotic changes in the endothelium and arterial walls. The pathogenesis of atherosclerosis is complex; risk factors include non-modifiable factors such as age, sex, family history and ethnicity, but modifiable factors such as obesity, smoking, physical inactivity, hypertension, hyper-cholesterolaemia and low fruit and vegetable consumption are also important and, although the atherosclerotic process has been shown to start in childhood, for the majority of the population, the symptoms of CVD are not apparent until at least middle age.

Some of the determinants of CVD indicated above are also associated with poor lung function. It is therefore possible that the association between poor lung function and CVD is confounded by such common determinants such as smoking, obesity, sedentary behaviour, poor diet or by a common disease process e.g. systemic inflammation, characterised by elevated CRP which is prevalent in patients with lung function deficits and has also been associated with acute CVD events. It is also evident that some individuals are more predisposed to developing these conditions than others because of their genetic make-up which may render them less able to deal with adverse exposures or metabolites. In recent years the genetics of inflammatory mediators has received some attention by those investigating lung function CVD associations.

Early studies of the association between lung function and CVD were based on CVD events in the middle aged and elderly but it is now possible to detect early atherosclerotic changes in arterial structure and function in young, asymptomatic, subjects long before the onset of any clinical disease. Measures of early atherosclerotic changes in young adults have been shown to be associated with future CVD. If lung function is associated with early arterial changes, simple spirometry measures, obtained in the doctors’ surgeries, could provide a readily available means of identifying those at risk of progressive CVD.
This thesis has:

- Investigated the longitudinal and cross-sectional associations between three modifiable CVD risk factors (smoking, physical fitness and adiposity) and young adult lung function;
- Examined the cross-sectional associations between CRP and lung function and determined whether the association was independent of adiposity measures other than BMI;
- Determined whether there was an association between young adult lung function and ultrasound measures of vascular structure and function.

### 8.1 Lung function and modifiable cardiovascular risk factors

#### 8.1.1 Cigarette smoke and young adult lung function.

In the first instance the cross-sectional association between smoking adult lung function was assessed. Smoking is generally accepted as having a negative effect on lung function and a dose dependent negative effect of smoking was apparent amongst smokers, more so in females than males. However, the mean lung volumes of participants who smoked less than 20 cigarettes per day were greater than those of non-smokers. This has been observed by others.\(^{149}\) Young smokers who continue to smoke appear to have higher baseline lung function than those who never smoke or who become ex-smokers. Those who experience symptoms (and potentially lower volumes) may have discontinued smoking and those who continue to smoke are those who remain asymptomatic resulting in a ‘healthy smoker effect’. This apparent selection effect was not observed in participants who were overweight or obese.

Secondly, the effect of starting to smoke in childhood and cumulative (pack years of) cigarette smoke exposure were investigated amongst daily smokers. Significant negative associations of cumulative exposure were observed for the FEV\(_1\) and FVC of males, but not females. The effects of starting to smoke before the age of 16 were also different for males and females. Childhood smoking appeared to be associated with airway restriction in males (negative associations with FEV\(_1\) and FVC) and airway obstruction in females (reduced FEV\(_1\) and FEF\(_{25-75}\)) independent of cumulative exposure. It is possible that females may be affected by cigarette smoke in a different way but it may also be a consequence of the effect of smoking on the rate of lung growth. Female lung growth is at its peak during early adolescence and is generally complete by the late teenage years while males do not reach peak lung function until between 26-36 years of age at which time female lung function may have already started to decline.\(^{16}\)
In contrast to the effects of childhood smoking, exposure to parental smoking did not appear to have a detrimental effect on the lung function of adult never smoking females, but was associated with signs of airway obstruction (lower FEF\textsubscript{25-75} and FER) among males. However the major contribution of parental smoking in this cohort appeared to be through the higher uptake of smoking by participants who were exposed to smoking at home.

In the final investigation in this chapter we also found that male participants who had greater lung volumes in childhood were over-represented amongst daily smoking participants. There was no such trend for females, notably females who smoked occasionally were more likely to have had lower spirometric volumes in childhood. This could possibly suggest that the extent of their smoking habit may be limited by respiratory symptoms.

These findings suggest that, smoking status and daily, or cumulative cigarette exposure, should be considered when assessing associations between lung function and CVD.

### 8.1.2 Is cardiorespiratory fitness an important determinant of young adult lung function?

In the first instance cross-sectional associations between cardiorespiratory fitness and lung function were investigated. In the sample as a whole there were no cross-sectional associations between adult male cardiorespiratory fitness and lung function, but among females significant positive associations between cardiorespiratory fitness and lung function were seen, independently of BMI. When participants were categorised as “fit” or “unfit”, compared to fit participants unfit males had significantly lower FEV\textsubscript{1}, FEF\textsubscript{25-75} and FER and unfit females had lower FEV\textsubscript{1} and FER. However further analysis according to fitness and weight category demonstrated that regardless of fitness level, obese participants had lower spirometric volumes than those of fit healthy weight participants.

Second, the effect of persistent fitness in childhood and adulthood was assessed. Participants who were in the top two thirds of fitness in childhood, and as an adult, had higher FEV\textsubscript{1} and FVC volumes than those in the bottom third of fitness at both time points. However, after adjustment for adult adiposity the positive effects of fitness were no longer apparent for males.

Finally, assessment of the effect of childhood fitness, independent of the change in fitness between childhood and adulthood, found no significant association between childhood fitness and adult lung function in either males or females.

These results indicate that in young adult males the positive association of cardiorespiratory fitness with lung function is not independent of adiposity. In addition, where there does appear to be an
independent association in females, childhood fitness does not have an effect on adult lung function independent of adult fitness.

These findings suggest that physical fitness may be a confounding variable for the association between CVD and lung function for females, but not males. However, the effect of fitness is confounded by adiposity.

### 8.1.3 How does adiposity affect young adult lung function?

In chapter five, the associations between lung function and adiposity were investigated. Preliminary investigations prior to this analysis observed that BMI was not associated with young adult lung function in either males or females. BMI reflects both lean mass and fat mass components and significant negative associations between BMI and lung function were only observed after adjustment for fat free (lean) mass. This finding indicates that in investigations of the association between lung function and CVD risk in young adults, BMI is not the best measure to use to adjust for adiposity, as any association of the fat mass component of BMI with lung function is confounded by lean mass. This is an important observation that has been supported by a recent study by Fogarty et al\(^{216}\) and is pertinent to future studies of lung function in young adults.

The effect of childhood adiposity on adult lung function was assessed using BMI adjusted for lean mass, the negative associations of adult adiposity with lung function were found to be far stronger than the effect of childhood adiposity. Childhood adiposity had a negative effect on adult lung function only if higher levels of adiposity persisted into adulthood. There were no significant differences in the lung function of obese males who had been healthy weight or unhealthy (overweight or obese) as children. This finding was in contrast to other studies which had not adjusted for the positive effects of lean mass on lung function and had concluded that childhood BMI had a positive effect on adult lung function\(^{217}\).

Few studies have investigated the differential effects of fitness and fatness on the lung function of population based samples of participants. Improving fitness through an exercise regimen often results in an accompanying loss of weight and improved muscle strength so it is difficult to determine which is most important. The few studies that have investigated the differential effects of fitness (or more often physical activity) and fatness on lung function, support the conclusion that adiposity is a stronger determinant of lung function than fitness.\(^{214,282}\) Weight loss rather than improved fitness has been shown to improve lung function.\(^{283,284}\)
8.2 Is the association between inflammatory mediators and lung function confounded by obesity?

Based on the previously observed negative associations of adiposity with lung function and the reports of others indicating that increased adiposity was associated with levels of inflammation, Chapter 6 investigated the cross-sectional association between the most common and metabolically stable inflammatory mediator, CRP, and adult lung function before and after adjustment for adiposity.

The results of this study indicated that CRP appeared to have very little effect on the lung function of participants of ‘healthy weight’. A 1mg increase in CRP was weakly associated with lung function but the association was statistically significant only in those with at least average fat mass or BMI, which in the case of CDAH participants is actually overweight for males (26.3kg/m²) and the high end of healthy weight for females (BMI 24.5kg/m²). In males, the slope of the interaction was reduced slightly by adjustment for central adiposity in models but the effect of higher levels of overall adiposity were still observed in models which included fat mass rather than BMI.

Repetition of the analyses restricting the dataset to participants with CRP levels of less than 10mg/l appeared to strengthen the association between CRP and lung function, but again significant associations were observed only for those who were at least of average adiposity. This finding suggests that adiposity may be a confounder of the association between CRP and lung function.

This conclusion is supported by evidence that obese patients with moderate to severe COPD have three times the likelihood to have elevated CRP than patients of normal weight. Elevated inflammatory mediators, of which CRP is only one, have been shown to be a consequence of adipokine activity in healthy adults and COPD patients who may have an imbalance of lean and fat mass, because of obesity, fatty infiltration of muscle (myosteatosis) or loss of muscle mass associated with chronic disease (sarcopenia). Studies of genetic variants of CRP have also found no association with lung function.

Most studies of the association between CRP and lung function have been cross-sectional, and those that have included a longitudinal analysis have had conflicting results. In these studies the potential confounding effect of body composition and change in body composition has often not been considered in the analysis, or if it was, the body composition measure used was BMI, which has been identified in Chapter 5 as an inadequate measure for assessing the effects of adiposity on the lung function of young adults.
As increased adiposity is also associated with cardiovascular disease, it is possible that lung function might be an innocent bystander in the hypothesis that systemic inflammation might be the link between poor lung function and increased CVD and mortality.

### 8.3 Is young adult lung function associated with measures of arterial structure and function?

This is the first large study of mainly healthy, young adult males and females, which has investigated the associations of lung function (rather than smoking or asthma) with ultrasound measures of arterial wall thickness (cIMT) and elasticity.

First, the associations between lung function measures and ultrasound measures were assessed and estimates of the arterial parameters were determined for participants according to smoking and asthma status. The findings reflected what has been reported in the literature; smoking was positively associated with cIMT in males and females but was significant only for females (p=0.006), while asthma was associated with greater arterial stiffness and thicker cIMT in males.

As indicated in the discussion of Chapter 7, the effects of chronic cigarette smoke exposure on arterial elasticity is still a matter for debate. For that reason the main analysis was stratified according to ever or never-smoking status.

In male smokers FEV$_1$ and FEF$_{25-75}$ (indicators of airway obstruction) were associated with increased cIMT but this association was eliminated after accounting for cumulative cigarette exposure. For females the finding of most interest was an association between the FEV$_1$ and FVC of never smoking females with mean cIMT, which was independent of other CVD risk factors (adiposity, systolic blood pressure, and CRP and blood lipids). As there was no association of FER with cIMT this was suggestive of a restrictive deficit in lung function.

This association has previously been reported by the ARIC study; data from the 15 year follow up of the ARIC cohort found that participants who had a restrictive lung function impairment had an increased risk of a cardiovascular events (although the association was almost eliminated after adjusting for CVD risk factors). This result would suggest that in the absence of overt respiratory disease (or even in the presence of disease), individuals who appear to have restricted lung volumes might be especially encouraged to improve their CVD risk factor profile in order to reduce their risk of a CVD event.
After stratification, no associations between lung function and arterial elasticity measures were detected for ever-smoking males or females. This indicates that smoking and asthma are confounders of observed associations of lung function with cIMT in males and measures of arterial stiffness in both males and females. Both smoking and asthma have previously been shown to be associated with increased cIMT\textsuperscript{76} and arterial stiffness.\textsuperscript{87}

As age is the biggest determinant of cIMT and arterial elasticity, the lack of evidence for an independent association between lung function and arterial stiffness in this cohort may be a consequence of their youthfulness (aged 26-36). As presented in Chapter 1, young males are still likely to be at their peak lung function at this time.

### 8.4 Possible limitations of this study

The baseline data used in CDAH were collected from a population-based representative sample of Australian children between the ages of 7-15 years in 1985. When the original study was done, no follow up was intended, so a minimal amount of identifying information was collected from participants. The data used to trace participants, to invite them to participate in the follow-up, was limited to the participant’s name and the school they attended when they participated in the study (in 1985) and their date of birth. In addition, only 2,410 (38%) of the 5,170 original participants who were traced and agreed to participate in the follow up attended a clinic for follow up of physical measures. A major factor that may have contributed to this attendance rate was the limited access to CDAH clinics which were restricted to 34 clinics around Australia for only a few days per clinic. Although geographical software was used to identify potential clinic sites in areas with the highest density of participants, some regional areas of Australia had to miss out. Consequently there was a large loss to follow up between baseline data collection in 1985 and 2004-6 that could potentially, have resulted in some selection bias. Comparison of the baseline characteristics of participants who attended clinics and those who did not showed that those attending clinics were older and had lower age and sex specific BMI scores. They were also more likely to have been childhood smokers or have parents that smoked. Similar differences with respect to age and body mass and childhood smoke exposure were observed between clinic attendees and the remainder of the ASHFS participants. Despite this, the proportions of participants who were overweight or obese or reported asthma were all comparable with estimates of the prevalence of these factors in the current Australian population of a similar age. In addition there was a wide range of values of the study measures and other covariates of interest so it is unlikely that the lower than expected response rate has biased the study findings.
As is the case with many respiratory cohort studies which have looked at associations between lung function and cardiovascular risk factors 287 CDAH was primarily a study of the determinants of CVD. While lung function measures and information on respiratory illness and medications were collected, the study could have benefited from additional information on childhood respiratory conditions and details of respiratory symptoms at follow up to provide a clearer picture of the respiratory health of CDAH participants.

The estimates of fat mass and lean mass used in the analysis of several of the preceding chapters were derived from skinfolds and the equations of Durnin & Rahmen. 118 Although this methodology may not be the gold standard for determining the body composition of individuals it would have been costly (if not impossible) to transport a DEXA machine around 34 field study sites. In contrast it is relatively simple to measure participant skinfolds (after appropriate training), the equipment used is portable, and the equations used have been validated for use in samples of Caucasian Australians 115 and are used extensively by other groups worldwide. Intra-observer variation was kept to a minimum by ensuring that technicians were trained according to the International Society for the Advancement of Kinanthropometry (ISAK). 117 The number of technicians making such measurements was also minimised. Of 2,281 sets of measurements made, 75% were made by four technicians (99% by nine).

The technicians administering the spirometry tests at the clinic sites were following ATC guidelines however, the analysis presented in this thesis has used lung function data from all participants with a valid spirometry trace. However the external validity of the results may be questioned by others despite the ATS guidelines indicating that the guidelines on reproducibility (having a minimum of three valid flow loops) are not intended to exclude participants from studies. 10

Although current asthma was included in the regression models of this study, no allowance or standardisation of inhaler usage prior to spirometry was performed. This may have resulted in an under-adjustment and residual confounding for asthma in the analysis. In addition, a complete smoking history for all participants, rather than only current daily smokers and those who had been daily smokers in the past, may have increased the power to detect the dose dependent effects of smoking. Pre and post bronchodilator spirometry measures would also have helped with differentiation of the effects of asthma and cigarette smoke on the airways however as CDAH clinics were conducted in church halls and other community venues and not in medical establishments where any adverse events attributable to bronchial challenge could be managed.

In order to better understand the associations of lung functions with the other variables of interest in this study I tested associations with all four spirometry measures available (FEV₁, FVC, and FEF₂₅-₇₅)
Chapter 8: Summary, future directions and conclusions

and FER) but I have not made any attempt to adjust for multiple comparisons in these analyses as none of the associations tested were truly joint hypotheses. According to Rothman288 “A policy of not making comparisons is preferable because it will lead to fewer errors of interpretation when the data under evaluation are not random numbers, but actual observations.” I have therefore presented the data, and the accompanying significance tests, and will allow the reader to make comparisons if they wish.

Ethnicity has been identified as one of the determinants of both lung function and cardiovascular disease. However, whether ethnic associations with CVD and lung disease are attributable to common genetic traits or may be explained by exposure to common risk factors such as body composition, diet, behaviours or environmental exposures is difficult to determine and has not been addressed here. The CDAH study sample is mainly (95%) Caucasian, and ethnicity was not found to be a confounder of any analyses. However, this proportion would be considerably different if a representative sample of Australian children was selected in 2011. Therefore while the findings of this study might be generalisable to young adults of Caucasian origin, they might not apply to other ethnic groups.

Despite 40 years of investigation, the nature of the association between poor lung function and cardiovascular disease and all-cause mortality is still unclear. I believe that increased adiposity may be the link between reduced lung function and increased CVD and mortality and that, in the absence of other signs or symptoms, levels of inflammatory mediators and body composition (lean and fat mass measures) may better quantifying the risk of CVD in participants with reduced spirometry. However, although some longitudinal data have been presented, the majority of the analyses in this thesis are cross-sectional associations and therefore no assumptions can be made about the temporal relationships of the observations. It is quite possible that poor lung function may result in a lack of participation in physical activities, which in turn may lead to increased obesity, increased inflammatory mediators and ultimately CVD.
8.5 Conclusion

The major contributor to reduced lung function in these young adults was adiposity, which was stronger than the effects of fitness or cigarette exposure. The association of FEV₁ and FVC with cIMT in never smoking females requires further investigation. The associations between reduced lung function in males and cIMT appear to be attributable to smoking. The messages from this study are therefore familiar ones:

‘In order to have optimal lung function and arterial structure and function for your age, and to reduce your risk of cardiovascular disease in the future, maintain a healthy body weight and don’t smoke.’

8.6 Future directions

This thesis has contributed to the body of knowledge on the relationship between lung function and CVD. It has provided clear evidence that, in the absence of overt pulmonary disease, maintaining a healthy weight is an important determinant of optimal lung function. It has also demonstrated that BMI is not a helpful measure to use to estimate the effect of adiposity on the lung function of young adults.

Chapter 8 indicates that even in young women with no history of CVD, there appears to be an association of restricted lung function with increased cIMT (a significant predictor of stroke and coronary heart disease in later life).

Further follow up of the CDAH cohort, when participants are no longer at their peak lung function and have a greater prevalence of CVD risk factors and reduced vascular function, may help shed further light on the association between lung function and CVD and potentially identify some causal associations.

Future areas of investigation would ideally include:

- A review of the associations of lung function with traditional cardiovascular risk factors, insulin resistance and metabolic syndrome including adjustments for lean and fat mass rather than BMI and/or waist circumference.

- Longitudinal studies to establish the temporal relationship between lung function and CVD, when the age (and smoking related) decline in lung function begins and atherosclerosis becomes more apparent. Would adjustment for age, changes in body composition and smoke exposure eliminate any associations observed?
In older adults the addition of lung function to the Framingham risk score has already been shown to add to the prediction of mortality and CVD disease in those with a moderate Framingham risk score. It would therefore be of investigation of the utility of lung function in enhancing the Pathobiological Determinants of Atherosclerosis progression in Youth score currently used to predict CVD progression in young adults.

An investigation of whether lung function enhances the healthy lifestyle score recently validated as a predictor of CVD risk in CDAH participants. The use of a spirometer in the doctor’s surgery and the lifestyle score may provide an effective, non-invasive indicator of a patient’s risk of CVD.

Further investigation of the association of restricted airways with cIMT in never-smoking females. Are there any genetic or other physiological explanations for the association of lung function with cIMT in never-smoking females? What the clinical significance of this finding in these young women and whether there is uncontrolled confounding from e.g. unmeasured visceral adiposity, other CVD risk factors, inflammatory mediators or childhood exposures not considered in this study.

An investigation of the longitudinal relationship between CRP (or other adipokines such as interleukin and adiponectin) with lung function also accounting for changes in adiposity over the same time period is required to further disentangle the association between systemic inflammation and lung function.

In the second follow up of CDAH 2010-11 participants were asked specifically about respiratory symptoms. An investigation of any associations of subclinical measures of cIMT or arterial elasticity with respiratory symptoms in these young adults may be of interest. If an association is found it may be the result of genetic susceptibility. Identifying those most at risk of developing COPD and CVD and encouraging preventative strategies could be of great benefit to the individuals concerned and the wider community.
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Appendices
Appendix 1: CDAH participant information for clinic visit
Are the tests safe?
The tests and measurements we conduct have been selected because they are safe. All CDAH staff are trained in the correct conduct of these tests. While you will be supervised carefully while undergoing the tests, we will also ask you to fill the forms even if you are experiencing discomfort or finding it difficult to complete the test. You are free to withdraw from a particular test at any time.

What about discomfort?
As in any similar health check, there may be some slight discomfort resulting from the collection of the blood sample. For those participants who are asked to have the extended ultrasound scan, measurement of the arm artery may involve a small amount of discomfort as a blood pressure cuff is tightened around the lower arm. However, this discomfort lasts for only a few minutes.

Do I have to complete all of the tests?
To obtain the most complete picture of your current health status, it would be preferable if you could complete all tests. However, if there are any of our tests that you are unable or prefer not to complete, we would still value your participation in all other areas.

Please let staff at the clinic know if you have concerns about any of the tests, or are pregnant at the time of attending the clinic, or have any health problems.

What if I have to travel some distance to the clinic?
Reimbursement of expenses incurred in traveling to the clinic will be offered to those participants who are far-away students, who hold a Medicare card or who have travelled greater than 50km each way to attend the clinic. If you fall into one of these categories and wish to claim reimbursement, you may obtain a claim form from the registration desk when you attend your appointment.

Can I bring my children with me?
You are encouraged to make provision for childcare before attending the clinic as we are unable to offer any childcare facilities at the clinic, and cannot take any responsibility for children who are in attendance. However, we understand that sometimes there is no alternative available to you and we will do our best to provide some toys for short-term entertainment.

What happens next?
Before leaving the clinic, all participants will be issued with a pediometer, which is a small instrument that measures the amount of steps taken by the wearer. We will ask you to wear this instrument to your workplace during working hours for seven days and to write down the number of steps that the pediometer records each day, and then return it to us in a pre-paid post packet that will be provided.

Why do you ask so many questions?
Many of the risk factors for cardiovascular disease and diabetes are thought to be related to lifestyle issues, and cannot be assessed through physical testing. We are therefore interested in asking questions about your family history and experiences during childhood, past and current physical activity levels and current dietary patterns. When you attend the clinic we will also ask you to complete computer-administered questions relating to emotional well-being, and your smoking and drug status.

Why do you want to know my Medicare number?
The CDAH study needs reliable methods of finding out who develops cardiovascular disease and diabetes. One way of doing this is to access data from Medicare and the Pharmaceutical Benefits Schedule (PBS). We are seeking your permission to access Medicare and PBS data about future treatments used by you in relation to cardiovascular disease and diabetes, or any other medical intervention, and your Medicare number. By doing this we can provide a more accurate record of your treatment history.

Please be assured that Health Insurance Commission will not release any details of any other type of medical service you have received - ONLY those relating specifically to cardiovascular disease and diabetes.

The Health Insurance Commission will only release data to us with your signed consent. You can withdraw the consent at any time.

Do I get any of my results?
All participants will receive a summary of selected results sent to them following attendance at the clinic. These include blood glucose and cholesterol levels, body mass index, blood pressure, lung function and bone density.

What will happen to the information collected about me?
Any information collected from you before or during the clinic is confidential and will only be handled by staff involved in the CDAH study. All cover sheets on questionnaires and clinic record forms that have your name on them will be removed and shredded before the data is entered into the CDAH database. Data relating to participants will be transferred to a specially designed secure database stored at the Menzies Research Institute in Tasmania. All information will be stored with 16 characters only - identifying information such as names will be kept separately from other data.

Can I find out my results from 1985?
Yes! When you attend the clinic, we will provide you with a summary of some of your individual results from when you took part in 1985.

THANK YOU for agreeing to take part in this important study. We look forward to meeting you at your clinic visit!

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WHAT TO EXPECT AT YOUR APPOINTMENT

Appendices
BEFORE YOUR APPOINTMENT

Some questionnaires to complete

These questionnaires are designed to obtain information on factors which may be related to cardiovascular disease and diabetes; In some instances we use standard questionnaires that are commonly used in health research.

We understand that the questionnaires are quite time consuming and that is why we have sent them to you so that you can do them at your leisure, prior to your appointment. They form a very important part of this research.

Please bring your completed questionnaires to the health check clinic with you.

If you have any questions when filling out the questionnaires, the clinic staff will be happy to answer these at your visit. Alternatively, you can call our toll-free number on 1800 654 124 for assistance.

Please do not have any food or drink (apart from water) for 12 hours before your appointment.

This is necessary so that we can accurately measure your blood glucose and cholesterol levels. Even tea and coffee must be avoided during this time. However, if you take any regular medications it is important that you take these as usual.

If possible, please wear loose, comfortable clothing to the clinic. This will make it easier to perform some of the tests. It is also necessary to wear or bring some gym shoes with you.

AT YOUR APPOINTMENT

It will take approximately 2.5 - 3 hours to complete all the testing at the clinic. If you have chosen to attend the clinic during work time, the clinic staff can provide you with a certificate stating your attendance at the clinic.

Blood Test

A small sample of your blood (approximately 30ml) will be taken from your arm by staff members experienced in this procedure. It will be sent to a medical laboratory to determine the amounts of some blood components that may predict risk of heart disease and diabetes in the long term. These components include glucose, cholesterol, triglycerides, C-reactive protein, serum insulin and, in females, the hormones oestrogen and sex hormone binding globulin. A small sample of your blood will be stored for DNA analysis. We will also store some extra blood samples for future analysis of other components that are thought to have associations with cardiovascular disease and diabetes.

Ultrasound Test of Blood Vessels

A small portable ultrasound machine will be used to visualise the carotid artery in your neck. This is a painless, safe and non-invasive procedure. Some people (selected randomly) will also be asked to have an extended procedure which will view the artery in the arm and the thickness of the heart wall.

Body Composition Measurement

You will be directed into a private area where you will have your height, weight, waist and hips measured by a technician. We will also take a measurement of body fat by using callipers to measure skinfold thickness on the arm, abdomen, hip and upper back.

Male participants will also have a quick assessment made of their pattern of hair loss (if any), by comparing their hair-line to standard pictures on a card. This is because some patterns of baldness in males have been linked to heart disease and diabetes risk.

Blood Pressure Measurement

Your blood pressure will be measured using an automatic blood pressure machine.

Breakfast

Some procedures in the clinic require you to be fasting. However, when you have completed these, we will serve you a light breakfast before asking you to do the fitness tests.

Ultrasound Test of Bone Density

Another small, portable ultrasound machine enables us to make an assessment of your bone density by placing your heel in the machine. This is a quick and painless procedure.

Computerised Questionnaires

In addition to heart disease and diabetes, we are also interested in other health issues of importance to young adults. These include issues such as anxiety, depression, and alcohol and drug use. These have also been linked to higher risks of heart disease. To ensure your privacy we will ask you to complete a questionnaire on a special laptop computer at the clinic. Only your ID number will be entered with your answers and you will not be required to show your answers to clinic staff.

Lung Function Test

The health of your lungs will be measured with a simple breathing test, which you are asked to blow into a machine.

Fitness Tests

A common fitness test will be performed using a stationary exercise bike. You will be encouraged to cycle for a total of 12 minutes while your heart rate is monitored. The standing long jump is a good measure of muscular power. You will be asked to jump as far as you can on an exercise mat from a standing start (after being given some practice time first). Some instruments called 'dynamometers' will be used to measure the strength of different muscles. A technician will guide you to push or pull against these instruments.
Appendix 2: CDAH Exclusion questionnaire
Fitness Testing - Automatic Exclusion Questionnaire

All Fitness Tests
1. Do you have severe neck or back pain?  □  Yes  □  No  □  Exclude from all fitness tests
2. Resting systolic blood pressure ≥180 mmHg? *(From Data Record Form)  □  Yes  □  No  □  Exclude from all fitness tests
3. Resting heart rate ≥100 bpm? *(From Ultrasound Resting Pulse Rate)  □  Yes  □  No  □  Exclude from all fitness tests

SLJ & PWC170
4. Have you ever had a knee or hip replacement?  □  Yes  □  No  □  Exclude from SLJ & PWC170, skip to Q.10

SLJ
5. Are you pregnant?  □  Yes  □  No  □  Exclude from SLJ, go to Q.7
6. Do you have any current OR past injury that could be made worse by performing a standing long jump? (Probe: Do you think you can do the long jump test without aggravating a current or previous injury?)  □  Yes  □  No  □  Exclude from SLJ, go to Q.7

PWC170
7. Are you more than 3 months pregnant?  □  Yes  □  No  □  Exclude from PWC170, skip to Q.10
8. Do you have any current OR past injury that could be made worse by cycling? (Probe: Do you think you can do the bicycle ergometer fitness test without aggravating a current or previous injury?)  □  Yes  □  No  □  Exclude from PWC170, skip to Q.10
9. Weight ≥ 160 kg? *(From Data Record Form)  □  Yes  □  No  □  Exclude from PWC170, go to Q.10

Dynamometry
10. Do you have any current OR past injury that could be made worse by performing a maximum contraction of the leg, back, shoulder, or hand muscles? (Probe: Do you think you can contract these muscles without aggravating a current or previous injury?)  □  Yes  □  No  □  Exclude from dynamometer testing

EXCLUDED TESTS:  □ SLJ  □ PWC170  □ Dynamometry

If ALL 3 boxes are ticked, do not continue - subject is excluded from all fitness tests
If < 3 boxes are ticked, continue to modPARQ over page
Appendix 1

List of reasons for exclusions based on hospitalisation from ACSM Guidelines, 5th Ed (p. 42).

Note: Probe questions are designed to provoke discussion between technician and participant.

1. Ischaemic heart disease (angina or heart attack).
2. Irregular heart beat (abnormally rapid or abnormally slow heart beat).
3. Aneurysm (aneurysm in heart or arteries).
4. Systemic or pulmonary blood clot (clot in veins or lungs).
5. Heart failure (symptoms: severe breathing problems, swelling of legs).
6. Active or suspected myocarditis or pericarditis (inflammation of heart muscle or lining of the heart).
7. Heart valve dysfunction (narrowed heart valve or leaky heart valve).
8. Acute or chronic infections (e.g. bacterial infections, pneumonia, glandular fever, hepatitis).
10. Uncontrolled metabolic disease (diabetes, abnormal thyroid function).
11. Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise.
Modified Physical Activity Readiness Questionnaire (modPARO)

1. Have you been hospitalized in the last 3 months? If so, was it for any of the following conditions? (See Appendix i)  
   - Yes  
   - No

2. Do you avoid exercise because of any medical reason?  
   - Yes  
   - No

3. Has a doctor ever said that you have a heart condition and that you should only do physical exercise recommended by a doctor?  
   - Yes  
   - No

4. Have you had chest pain that a doctor has told you was due to a heart condition?  
   - Yes  
   - No

5. Do you lose your balance because of dizziness or lose consciousness on a regular basis?  
   - Yes  
   - No

6. Do you have a bone or joint problem that could be made worse by physical activity? (Probe: Do you think you can do the fitness tests without injuring yourself?)  
   - Yes  
   - No

7. Are you currently taking any prescription medications for your blood pressure?  
   - Yes  
   - No

8. Are you currently taking any prescription medications for a heart condition?  
   - Yes  
   - No

9. Do you have any immediate (parents or siblings) family history of sudden death or heart attack under the age of 50 years?  
   - Yes  
   - No

10. Do you know of any reason why you should not do physical activity?  
    - Yes  
    - No

11. Are there any other conditions that might prevent you from doing these tests?  
    - Yes  
    - No

If **YES** to any of the above questions exclude from all exercise testing

If **NO** to all questions perform any tests not excluded previously.
Appendix 3: CDAH General Questionnaire
SECTION A: This section asks you some questions about yourself. You may feel you have already answered these questions in our enrolment questionnaire, however your circumstances may have changed since you completed our enrolment questionnaire.

1. Today's date
   __________________________ / __________________________ / __________________________

2. What sex are you?
   ○ Male  ○ Female

3. What is your date of birth?
   __________________________ / __________________________ / __________________________

4. What is your current marital status?
   ○ Single
   ○ Married
   ○ De facto
   ○ Separated/Divorced
   ○ Widowed
   ○ Other __________________________
     (please specify)

5. What is the highest level of education you have completed? (Select only one answer)
   ○ Primary School
   ○ Year 7, 8 or 9 or equivalent
   ○ Year 10 or equivalent
   ○ Year 11 or equivalent
   ○ Year 12 or equivalent
   ○ Trade/apprenticeship (e.g. hairdresser, chef)
   ○ Certificate/diploma (e.g. child care, technician)
   ○ University Degree
   ○ Higher University Degree (e.g. Grad Dip, Masters, PhD)
   ○ Other __________________________
     (please specify)
6. What is your main source of income? (Select only one answer)

- Wages or salary
- Own business or share in partnership
- A government pension or cash benefit
- Superannuation
- Investment/Interest
- Other income (please specify)

7. What is your main occupation NOW? (Select only one answer)

- Manager or administrator (e.g. magistrate, farm manager, general manager, director of nursing, school principal)
- Professional (e.g. scientist, doctor, registered nurse, allied health professional, teacher, artist)
- Associate professional (e.g. technician, manager, youth worker, police officer)
- Tradesperson or related worker (e.g. hairdresser, gardener, florist)
- Advanced clerical or service worker (e.g. secretary, personal assistant, flight attendant, law clerk)
- Intermediate clerical, sales or service worker (e.g. typist, word processing/data entry operator, receptionist, child care worker, nursing assistant, hospitality worker)
- Intermediate production or transport worker (e.g. sewing machinist, machine operator, bus driver)
- Elementary clerical, sales or service worker (e.g. filing/mail clerk, parking inspector, sales assistant, telemarketer, housekeeper)
- Labourer or related worker (e.g. cleaner, factory worker, general farm hand, kitchen hand)

- No paid job
8. Which of the following describes your current employment status? You can pick more than one.

- Working full-time
- Working part-time
- Not working (but not retired)
- Home duties
- Full-time student
- Part-time student
- Retired
- Permanently unable to work / Ill
- Other

   (please specify)

SECTION B: This section is about your health and your medical history

1. Have you ever been told that you have high blood pressure?

- No  --> Skip to Question 2
- Yes

   IF 'YES'

1a) When were you first told this?  [ ] [ ] [ ] (Year)

1b) Was this during pregnancy?

- Yes  -  No  -  Not applicable

1c) Are you currently taking medication prescribed by a doctor to lower your blood pressure?

- Yes  -  No

1d) Has a doctor in the past year recommended you change your way of life, in order to lower your blood pressure?

- Yes  -  No
2. Have you ever been told that you have angina?
   ○ No → Skip to Question 3
   ○ Yes

   **IF 'YES'**

   2a) When were you first told this? _______ (Year)

   2b) Are you currently on tablets or other treatment for angina?
   ○ Yes  ○ No

3. Have you ever been told that you have had a heart attack (includes 'coronary', 'coronary occlusion', 'coronary thrombosis', 'myocardial infarction')?
   ○ No → Skip to Question 4
   ○ Yes

   **IF 'YES'**

   3a) When were you first told this? _______ (Year)

4. Have you ever been told that you have had a stroke?
   ○ No → Skip to Question 5
   ○ Yes

   **IF 'YES'**

   4a) When were you first told this? _______ (Year)
5. Have you ever been told that you have high cholesterol?
   ○ No  --> Skip to Question 6
   ○ Yes

   **IF 'YES'**
   5a) When were you first told this?  [ ] [ ] [ ] [ ] (Year)

   5b) Are you currently taking medication prescribed by a doctor to lower your blood cholesterol?
       ○ Yes  ○ No

   5c) Has a doctor in the past year recommended that you change your way of life, in order to lower your blood cholesterol?
       ○ Yes  ○ No

6. Have you ever been told that you have high triglycerides?
   ○ No  --> Skip to Question 7
   ○ Yes

   **IF 'YES'**
   6a) When were you first told this?  [ ] [ ] [ ] [ ] (Year)

7. Are you currently taking aspirin-containing medication to prevent or treat heart disease or stroke?
   ○ No
   ○ Yes
8 Has a doctor or nurse ever told you that you have diabetes?

- No  --> Skip to Question 9
- Yes

**IF \text{’YES’}**

8a) In what year were you first told that you had diabetes? \underline{\text{[Year]}}

8b) Were you told that you had:

- \text{(select one)}
  - Type 1 diabetes  
    (previously known as "insulin-dependant diabetes")
  - Type 2 diabetes  
    (previously known as "non insulin-dependant diabetes")
  - Don't know which type

8c) What advice and/or treatment have you had for diabetes? (\text{select all that apply})

- Diet advice
- Tablets
- Insulin injections
- Diet advice and tablets
- Diet advice and insulin injections
9. Are you currently taking any medication prescribed by a doctor?

○ No → Skip to Question 9b
○ Yes

9a) In the table below please provide the name (or type of medication) and what it was prescribed for. Please continue at the bottom of page 28 if you need more space.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prescribed for</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

9b) Are you currently using any of the following hormonal medications?
(If you are female using hormonal contraceptives please do not include them in the "Other" category. We ask about contraception in Section D)

○ I do not use any hormone medications
○ Hormone replacement therapy
○ Testosterone treatment (e.g., Androderm)
○ Anabolic steroids
○ Other (please specify) 

10. Have you had any illness causing a high temperature during the last two weeks?

○ No → Skip to SECTION C (Page 8)
○ Yes

IF 'YES':

10a) What was the duration of the fever? ☐ ☐ days

10b) Was your temperature measured?

○ No

○ Yes, but temperature not known

○ Yes, my temperature was ☐ ☐ °C

10c) How many days ago did the fever stop? ☐ ☐ Days ago
SECTION C: The following questions ask for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. In general would you say your health is:

   • Excellent   • Very Good   • Good   • Fair   • Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

   2a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.

      YES, limited a lot  YES, limited a little  NO, not limited at all

      o                      o                      o

   2b) Climbing several flights of stairs.

      o                      o                      o

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

   3a) Accomplished less than you would like

      All of the time  Most of the time  Some of the time  A little of the time  None of the time

      o                      o                      o                      o                      o

   3b) Were limited in the kind of work or other activities.

      o                      o                      o                      o                      o

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)

   4a) Accomplished less than you would like

      All of the time  Most of the time  Some of the time  A little of the time  None of the time

      o                      o                      o                      o                      o

   4b) Did work or other activities less carefully than usual

      o                      o                      o                      o                      o

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(QOLSA SF-12c Standard, English (Australia), 7/03)
5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

<table>
<thead>
<tr>
<th>How much of the time during the past 4 weeks:</th>
<th>All of the time</th>
<th>Much of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a) Have you felt calm and peaceful?</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>6b) Did you have a lot of energy?</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>6c) Have you felt downhearted and depressed?</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>
SECTION D: This section is for WOMEN ONLY.
If you are MALE please skip to SECTION E (page 15). The answers to the following questions will help us investigate the influence of hormones on the cardiovascular system.

1. Are you currently using any of the following hormonal contraceptives, even if you are using them for reasons other than contraception?
   - Oral contraceptive pill
   - Minipill (progesterone only pill)
   - Weekly contraceptive patch
   - Progestagen (e.g., Implanon)
   - Progestagen injection (e.g., Depo Provera)
   - Progestin injection (e.g., Noristerat)
   - Progestin releasing intrauterine device (e.g., Mirena, Copper T380A)
   - Progestin releasing implant (e.g., Norplant)
   - Other (please specify) _________________________________

2. How old were you when you had your first menstrual period?
   - Years ____________  Months ____________

3. Have you had a hysterectomy; that is, an operation to remove your uterus?
   - No --> Skip to Question 4
   - Yes

   IF YES
   3a) What age were you when you had the hysterectomy? ____________ Years

   3b) Were your ovaries removed as well?
   - Yes, both ovaries removed
   - Yes, only one ovary removed
   - No
   - Don't know

   SKIP TO Question 5
4. The menstrual cycle is the time from the first day of one period to the first day of the next.

<table>
<thead>
<tr>
<th>Bleeding days</th>
<th>Non-bleeding days</th>
<th>Bleeding days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Menstrual cycle

4a) How long is your usual menstrual cycle? In other words, how many days are there from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT?

[ ] [ ] Days

4b) What is the longest menstrual cycle you have had in the last 12 months? Again count from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT.

[ ] [ ] Days

4c) What is the shortest menstrual cycle you have had in the last 12 months? Again count from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT.

[ ] [ ] Days

5. Thinking about the most recent time when you were having periods and were NOT using hormonal contraceptives (e.g., the pill) and were not pregnant or breastfeeding:

5a) Would you describe your periods as:
   - Very regular
   - Fairly regular
   - Irregular
   - Very irregular

5b) How old were you at this time?

That is, at the most recent time when you were having periods and were NOT using hormonal contraceptives (e.g., the pill) and were not pregnant or breastfeeding.

[ ] Years

5c) During this time, approximately how many periods did you have in the space of 12 months?
   - More than 13
   - 11-13
   - 6-10
   - 1-5
   - None
6. Have you ever seen a doctor because of irregular periods?
   ○ No  ---» Skip to Question 7
   ○ Yes

   **IF YES**
   6a) How old were you when you first saw your doctor about irregular periods?
      
      [ ] Years

   6b) Have you ever taken prescribed hormone medications for irregular periods?
      ○ Yes  ○ No

   6c) Has a doctor ever told you that you have polycystic ovaries or polycystic ovary syndrome?
      ○ Yes  ○ No

7. Have you ever seen a doctor because of concern about the amount of hair on your face?
   ○ No  ---» Skip to Question 8
   ○ Yes

   **IF YES**
   7a) Were you prescribed any treatment for this?
      ○ No

      ○ Yes  [ ] (please specify)

8. Has a doctor ever told you that you have acne?
   ○ No  ---» Skip to Question 9
   ○ Yes

   **IF YES**
   8a) Were you prescribed any treatment for this?
      ○ No

      ○ Yes  [ ] (please specify)
9. Have you ever tried to become pregnant for 12 months or more without succeeding?
   ○ Yes  ○ No

10. Have you ever seen a doctor because you were having trouble becoming pregnant?
    ○ No  → Skip to Question 11
    ○ Yes

   **IF YES**

   10a) Did you have any of the following fertility investigations?

    ○ Test of blood or urine hormone levels
    ○ Laparoscopy (incision in your stomach to look at your reproductive organs)
    ○ Your partner's semen analysed

   10b) Did a doctor ever tell you that you or your partner had:

    ○ An ovulatory problem?
    ○ A tubal problem?
    ○ Any other female fertility problem?
      - Please specify
    ○ Semen abnormalities?
    ○ An unexplained fertility problem?

11. Have you ever been pregnant?
    ○ No  → Skip to SECTION E (Page 15)
    ○ Yes

12. How many times have you been pregnant?  ■■ times
13. How many live births have you had?  

13a) When were these babies born?

<table>
<thead>
<tr>
<th>Baby</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>First baby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second baby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third baby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourth baby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fifth baby</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you have had more than 5 live births please continue at the end of this section.

14. When you were pregnant were you ever tested for diabetes?  
That is, did you have a blood or urine sugar test? This may have involved drinking a very sugary drink.

○ Yes  ○ No

15. Were you ever told that you had gestational diabetes or pregnancy related diabetes?

○ Yes  ○ No
SECTION E: This section is about your family's medical history

The following questions are about your BIOLOGICAL parents and siblings. Because heart disease in women under 50 is uncommon, some questions are only asked about your male relatives. Please do not include adoptive or step-parents or siblings here.

1. Was your biological mother diagnosed with diabetes when she was under the age of 50?
   - Yes
   - No
   - Don't Know

2. Is your biological mother alive now?
   - Yes
   - No
   - Don’t Know

   If NO:
   2a) How old was she when she died? [ ] [ ] Years

   2b) Was the cause of her death diabetes?
   - Yes
   - No
   - Don't Know

3. Was your biological father diagnosed with diabetes when he was under the age of 50?
   - Yes
   - No
   - Don’t Know

4. Was your biological father diagnosed with heart disease when he was under the age of 50?
   - Yes
   - No
   - Don’t Know

5. Is your biological father alive now?
   - Yes
   - No
   - Don’t Know

   If NO:
   5a) How old was he when he died? [ ] [ ] Years

   5b) Was the cause of his death:
   - Heart disease?
     - Yes
     - No
     - Don't Know
   - Diabetes?
     - Yes
     - No
     - Don't Know
6. Do you have any **BIOLOGICAL** brothers?

- [ ] Yes
- [ ] No → Skip to question 7
- [ ] Don’t Know → Skip to question 7

**IF YES**

6a) Have any of your biological brothers been diagnosed with the following illnesses **when under the age of 50**?

- Heart disease
  - [ ] Yes
  - [ ] No
  - [ ] Don’t Know

- Diabetes
  - [ ] Yes
  - [ ] No
  - [ ] Don’t Know

6b) If ‘YES’ to either of the above, please complete details below (space has been allowed for you to complete details for up to 3 brothers if necessary):

### HEART DISEASE

<table>
<thead>
<tr>
<th>Age at diagnosis (if known)</th>
<th>Did this result in his death?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>2</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>3</td>
<td>[ ] Yes [ ] No</td>
</tr>
</tbody>
</table>

### DIABETES

<table>
<thead>
<tr>
<th>Age at diagnosis (if known)</th>
<th>Did this result in his death?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>2</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>3</td>
<td>[ ] Yes [ ] No</td>
</tr>
</tbody>
</table>
Appendices

7. Do you have any **BIOLOGICAL** sisters
   
   ○ Yes
   ○ No -> Skip to SECTION F
   ○ Don’t know -> Skip to SECTION F

**IF YES**
7a) Have any of your biological sisters been diagnosed with diabetes when **under the age of 50**?
   
   ○ Yes  ○ No  ○ Don’t Know

7b) If ‘YES’, please complete details below (space has been allowed for you to complete details for up to 3 sisters if necessary):

<table>
<thead>
<tr>
<th>Age at diagnosis (if known)</th>
<th>Did this result in her death?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>○ Yes ○ No</td>
</tr>
<tr>
<td>2</td>
<td>○ Yes ○ No</td>
</tr>
<tr>
<td>3</td>
<td>○ Yes ○ No</td>
</tr>
</tbody>
</table>

**SECTION F:** This section is about smoking tobacco

1. Over your lifetime, have you smoked at least 100 cigarettes, or a similar amount of tobacco?
   
   ○ No -> SKIP TO SECTION G (Page 20)
   ○ Yes

2. How often do you now smoke cigarettes, cigars, pipes or any other tobacco products?
   
   ○ Daily
   ○ At least once a week (but not daily) -> Skip to Question 7
   ○ Less often than weekly -> Skip to Question 7
   ○ Not at all -> Skip to Question 7
3. When did you **start** smoking daily?  
   Years of Age  OR  Year

4. What do you currently smoke?  
   (Please indicate types and enter how many you smoke)

   4a) O Manufactured cigarettes  Cigarettes per day
   4b) O Hand-rolled cigarettes  Grams per week*  
   4c) O Cigars  Cigars per week  
   4d) O Pipes full of tobacco  Grams per week*  

   * A one and three quarter ounce pouch of tobacco equals 50 grams

5. When you smoke manufactured cigarettes, which brand do you usually smoke?  
   I do not smoke manufactured cigarettes O
   
   The brand I usually smoke is  
   (Please give as much detail as possible, eg Marlboro Lights)

6. Have there been any periods of time when you gave up daily smoking and then started smoking again?  
   No O  --> Skip to SECTION G (Page 20)  
   Yes O

   **IF YES**
   6a) Were any of these periods greater than 3 months duration?  
   No O  --> Skip to SECTION G (Page 20)  
   Yes O

   **IF YES 6b)** What is the total amount of time that you stopped smoking for?  
   (Please add together all the periods of time when you stopped smoking)  
   Years  Months  
   Now skip to SECTION G (Page 20)
7. In the past have you ever been a daily smoker?
   - No ○ ---> Skip to SECTION G (Page 20)
   - Yes ○

8. When did you start smoking daily?

9. When did you finally stop smoking daily?

10. When you smoked daily, how much did you usually smoke?
    (Please indicate types and enter the number smoked)

<table>
<thead>
<tr>
<th>10a)</th>
<th></th>
<th>Cigarettes per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Manufactured cigarettes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10b)</th>
<th></th>
<th>Grams per week*</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Hand-rolled cigarettes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10c)</th>
<th></th>
<th>Cigars per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Cigars</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10d)</th>
<th></th>
<th>Grams per week*</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Pipes full of tobacco</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A one and three quarter ounce pouch of tobacco equals 50 grams

11. When you smoked manufactured cigarettes, which brand did you usually smoke?

I did not smoke manufactured cigarettes ○

The brand I usually smoked was ____________________________
   (Please give as much detail as possible, e.g. Marlboro Lights)

12. Prior to the time when you finally stopped daily smoking, were there any periods of time when you gave up daily smoking and then started smoking again?
   - No ○ ---> Skip to SECTION G (Page 20)
   - Yes ○

   **IF YES**

   12a) Were any of these periods greater than 3 months duration?
   - No ○ ---> Skip to SECTION G (Page 20)
   - Yes ○

   **IF YES 12b)** What is the total amount of time that you stopped smoking for?
   (Please add together all the periods of time when you stopped smoking)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>Months</td>
</tr>
</tbody>
</table>
SECTION G: These questions are about your life when you were growing up until the age of 12. They are mostly about your parents or other adults who you lived with and who were responsible for you.

1. This question is about only the people who lived in the same house as you and were like parents to you for most of the time until you turned 12.

1a) Did you live in the same house as your father or another male who was like a father to you?

○ No --> Skip to question 1c

○ Yes

IF YES

1b) What is the highest level of education completed by your father (or other male who lived with you and was like a father to you)

○ No schooling

○ Primary School only

○ Year 7, 8 or 9 or equivalent

○ Year 10 or equivalent

○ Year 11 or equivalent

○ Year 12 or equivalent

○ Trade/apprenticeship (e.g. hairdresser, chef)

○ Certificate/diploma (e.g. child care, technician)

○ University Degree

○ Higher University Degree (e.g. Grad Dip, Masters, PhD)

○ Other (please specify) ___________________________
1c) Did you live in the same house as your mother or another female who lived with you and was like a mother to you?

- No ---> Skip to question 2
- Yes

IF YES
1d) What is the highest level of education completed by your mother (or other female who lived with you and was like a mother to you)

- No schooling
- Primary School only
- Year 7, 8 or 9 or equivalent
- Year 10 or equivalent
- Year 11 or equivalent
- Year 12 or equivalent
- Trade/apprenticeship (e.g. hairdresser, chef)
- Certificate/diploma (e.g. child care, technician)
- University Degree
- Higher University Degree (e.g. Grad Dip, Masters, PHD)
- Other (please specify)
2. What was the MAIN occupation of your father (or other male who lived with you and was like a father to you), and your mother (or other female who lived with you and was like a mother to you) until you turned 12? Please only select one answer for your father and one answer for your mother.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Father</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manager or administrator (e.g. magistrate, farm manager, general manager, director of nursing, school principal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional (e.g. scientist, doctor, registered nurse, allied health professional, teacher, artist)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate professional (e.g. technician, manager, youth worker, police officer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tradesperson or related worker (e.g. hairdresser, gardener, florist)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced clerical or service worker (e.g. secretary, personal assistant, flight attendant, law clerk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate clerical, sales or service worker (e.g. typist, word processing/data entry operator, receptionist, child care worker, nursing assistant, hospitality worker)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate production or transport worker (e.g. sewing machinist, machine operator, bus driver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary clerical, sales or service worker (e.g. filing/mail clerk, parking inspector, sales assistant, telemarketer, housekeeper)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labourer or related worker (e.g. cleaner, factory worker, general farm hand, kitchenhand)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No paid job</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Thinking about until you were 12, how many rooms were there in the home where you lived the longest?
Please include buildings on the property that were regularly used for living, such as bungalows. If your house had open plan areas, consider each area as a separate room (i.e. an open plan kitchen, dining and living area would count as three rooms). Do not include separate toilets.

Rooms in house
4. Thinking about most of the years until you were 12, did your parents or the people who brought you up own the house you mostly lived in, or did they rent it?

- They owned or were paying off the house
- They rented the house
- Unsure

5. Thinking about the years until you were 12, how many times did you move house?
   If you did not move house, please write "0"

   Times

6. All together, how many brothers and sisters did you have in your family until you were 12? Include adopted, step and half brothers and sisters. Please also include any brothers or sisters that may have died, but not those who died before you were born.

   I did not have any brothers or sisters
   - Older brothers
   - Older sisters
   - Younger brothers
   - Younger sisters
   - Twin brother to you
   - Twin sister to you

7. About how much did you weigh when you were born?

- 3 pounds or less (less than 1360g)
- More than 3 pounds and up to 5 pounds (1361-2270 grams)
- More than 5 pounds and up to 8 pounds (2271-3630 grams)
- More than 8 pounds (more than 3630 grams)
- Don't know
## SECTION H: The following statements have been used by many people to describe how much support they get from other people.

*We would like to know whether you share any of these feelings and how strongly you feel about them, by filling in the circle according to whether you strongly agree, agree, disagree or strongly disagree with each one. If you are undecided, select the column with this heading.*

<table>
<thead>
<tr>
<th></th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Undecided</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. People do not come and visit me as often as I would like.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<td>○</td>
</tr>
<tr>
<td>2. I find it easy to make friends.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<td>○</td>
</tr>
<tr>
<td>3. I often need help from other people but can’t get it.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>4. I’m afraid of being left alone.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>5. I seem to have a lot of friends.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>6. I don’t have anyone that I can confide in.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>7. The person who means most to me takes an interest in my affairs.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>8. There is someone who needs me as much as I need them.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>9. I don’t have a very close friend.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>10. The person who means most to me does spend time with me.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>11. I have no-one to lean on in times of trouble.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>12. I have someone to share good news with.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>13. There is someone who can always cheer me up.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>14. I often feel very lonely.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>15. I feel there is something missing from my life.</td>
<td>○</td>
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</tbody>
</table>
SECTION I: This section contains 60 statements. Read each statement carefully. For each statement fill in the circle with the response that best represents your opinion. Make sure your answer is in the correct box.

*Fill in Strongly Disagree if you strongly disagree or the statement is definitely false.*
*Fill in Disagree if you disagree or the statement is mostly false.*
*Fill in Neutral if you are neutral about the statement, you cannot decide, or the statement is about equally true and false.*
*Fill in Agree if you agree or the statement is mostly true.*
*Fill in Strongly Agree if you strongly agree or the statement is definitely true.*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am not a worrier.</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>2. I like to have a lot of people around me.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>3. I do not like to waste my time.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>4. I try to be courteous to everyone I meet.</td>
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<td>○</td>
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<tr>
<td>5. I keep my belongings clean and neat.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>6. I often feel inferior to others.</td>
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<tr>
<td>7. I laugh easily.</td>
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<tr>
<td>8. Once I find the right way to do something, I stick to it.</td>
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<td>○</td>
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<tr>
<td>9. I often get into arguments with my family and co-workers.</td>
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<td>○</td>
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<tr>
<td>10. I am pretty good about pacing myself so as to get things done on time.</td>
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<td>○</td>
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</tr>
<tr>
<td>11. When I am under a great deal of stress, sometimes I feel like I am going to pieces.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>12. I do not consider myself especially &quot;light-hearted&quot;.</td>
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<td>○</td>
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</tr>
<tr>
<td>13. I am intrigued by the patterns I find in art and nature.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>14. Some people think I am selfish and egotistical.</td>
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<td>○</td>
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</tr>
<tr>
<td>15. I am not a very methodical person.</td>
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<td>○</td>
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</tr>
<tr>
<td>16. I rarely feel lonely or blue.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Statement</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>17. I really enjoy talking to people.</td>
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<td>○</td>
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</tr>
<tr>
<td>18. I believe letting students hear controversial speakers can only confuse and mislead them.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>19. I would rather cooperate with others than compete with them.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>20. I try to perform all the tasks assigned to me conscientiously.</td>
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<td>○</td>
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<tr>
<td>21. I often feel tense and jittery.</td>
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<td>○</td>
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</tr>
<tr>
<td>22. I like to be where the action is.</td>
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<td>○</td>
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</tr>
<tr>
<td>23. Poetry has little or no effect on me.</td>
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<td>○</td>
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<tr>
<td>24. I tend to be cynical and sceptical of others’ intentions.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>25. I have a clear set of goals and work toward them in an orderly fashion.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>26. Sometimes I feel completely worthless.</td>
<td>○</td>
<td>○</td>
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<tr>
<td>27. I usually prefer to do things alone.</td>
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<td>○</td>
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<tr>
<td>28. I often try new and foreign foods.</td>
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<td>○</td>
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</tr>
<tr>
<td>29. I believe that most people will take advantage of you if you let them.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>30. I waste a lot of time before settling down to work.</td>
<td>○</td>
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<tr>
<td>31. I rarely feel fearful or anxious.</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>32. I often feel as if I am bursting with energy.</td>
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<td>○</td>
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<td>○</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Undecided</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
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</tr>
<tr>
<td>33. I seldom notice the moods or feelings that different environments produce.</td>
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</tr>
<tr>
<td>34. Most people I know like me.</td>
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<tr>
<td>35. I work hard to accomplish my goals.</td>
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<tr>
<td>36. I often get angry at the way people treat me.</td>
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<tr>
<td>37. I am a cheerful, high-spirited person.</td>
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<tr>
<td>38. I believe we should look to our religious authorities for decisions on moral issues.</td>
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<tr>
<td>39. Some people think of me as cold and calculating.</td>
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<tr>
<td>40. When I make a commitment, I can always be counted on to follow through.</td>
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<tr>
<td>41. Too often, when things go wrong, I get discouraged and feel like giving up.</td>
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</tr>
<tr>
<td>42. I am not a cheerful optimist.</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>43. Sometimes when I am reading poetry or looking at a work of art, I feel a chill or wave of excitement.</td>
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<tr>
<td>44. I am hard-headed and tough-minded in my attitudes.</td>
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<tr>
<td>45. Sometimes I am not as dependable or reliable as I should be.</td>
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<tr>
<td>46. I am seldom sad or depressed.</td>
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<tr>
<td>47. My life is fast-paced.</td>
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</tr>
<tr>
<td>48. I have little interest in speculating on the nature of the universe or the human condition.</td>
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</tr>
<tr>
<td>49. I generally try to be thoughtful and considerate.</td>
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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Undecided</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. I am a productive person who always gets the job done.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>51. I often feel helpless and want someone else to solve my problems.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>52. I am a very active person.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
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</tr>
<tr>
<td>53. I have a lot of intellectual curiosity.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>54. If I do not like people, I let them know it.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>55. I never seem to be able to get organised.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>56. At times I have been so ashamed I just wanted to hide.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>57. I would rather go my own way than be a leader of others.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>58. I often enjoy playing with theories or abstract ideas.</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>59. If necessary, I am willing to manipulate people to get what I want.</td>
<td>o</td>
<td>o</td>
<td>o</td>
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</tr>
<tr>
<td>60. I strive for excellence in everything I do.</td>
<td>o</td>
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</tr>
</tbody>
</table>
Appendix 4: Published papers
Longitudinal Associations of Adiposity With Adult Lung Function in the Childhood Determinants of Adult Health (CDAH) Study

Beverley A. Curry1, C. Leigh Blizzard1, Michael D. Schmidt1,2, E. Haydn Walters3, Terence Dwyer3 and Alison J. Venn1

Childhood BMI has been reported to be positively associated with adult lung function. The aim of this study was to investigate the effect of childhood BMI on young adult lung function independently of the effects of lean body mass (LBM). Clinical and questionnaire data were collected from 654 young Australian adults (aged 27–36 years), first studied when age 9, 12, or 15 years. Adult lung function was measured by forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, and the forced expiratory flow in the middle 50% of FVC (FEF25-75). BMI and LBM were derived from anthropometric measures at baseline (1985) and at follow-up (2004–2006). Multivariable models were used to investigate the effect of age and sex standardized BMI in childhood on adult lung function, before and after adjustment for LBM. Adult adiposity had a strong deleterious effect on lung function irrespective of childhood BMI, and adjustment for childhood LBM eliminated any apparent beneficial effect of childhood BMI on adult FEV1 or FVC. This suggests that the beneficial effect of increased BMI in childhood on adult FEV1 and FVC observed in previous longitudinal studies is likely to be attributable to greater childhood LBM not adiposity. Obese children who become obese adults can expect to have poorer lung function than those who maintain healthy weight but large deficits in lung function are also likely for healthy weight children who become obese adults. This highlights the importance of lifetime healthy weight maintenance.

INTRODUCTION

It is well recognized that obesity impairs pulmonary function (1) and accelerates age-related decline (2). The mechanisms proposed include the mechanical effects of excess central adiposity reducing chest wall compliance and increasing the workload of respiratory muscles, and abdominal adiposity impeding diaphragmatic descent and so reducing lung volume. Under-inflation results in some small peripheral airways failing to expand, basal lung unit collapse, and reduction in the area of respiratory membrane available for gaseous exchange.

In cross-sectional and longitudinal studies of adult lung function, negative associations have been observed with a variety of adiposity measures including increased weight (3–5), waist-hip ratio (1–4), waist circumference (1, 6) and skinfold or X-ray absorptiometry-derived measures such as fat percent and fat mass (7, 8). In contrast, lean body mass (LBM), which predominantly reflects muscle mass, and muscle strength have positive associations with lung function (7, 8) and inclusion of LBM to regression models has been shown to improve the prediction of lung volumes (9, 10).

The most common indicator used to define obesity or overweight is BMI (11). However, as BMI does not distinguish between the opposing effects of fat mass and lean mass and gives no information on fat distribution, evidence of the effect of BMI on lung function has been conflicting, possibly reflecting differences in body composition in the populations under study. In young males, a higher than average BMI may be due to musculosity (12) whereas in the elderly the proportion of skeletal muscle is generally low (13).

Few studies have examined the effects of adiposity on the development of lung function from childhood to early adulthood. Most have focused on birth-weight, BMI, and growth in the first few years of life (when most alveolar development occurs) and have, in general, shown positive associations with adult lung function (14–17). A study of 400 Danish male army recruits also reported that BMI at 7 years was positively associated with adult lung function 19–40 years later, independent of age, height, current BMI, smoking, and education (18).

The aim of this article was to extend current knowledge by investigating the effect of childhood and adult BMI on adult...
lung function in 654 males and females, aged 27–36 years, who participated in the Childhood Determinants of Adult Health (CDAH) Study and who would be expected to be in a plateau phase of lung growth (19,20). Our analysis considered the effects of BMI independent of the effects of LBM and grip strength, which are known to be positively associated with lung function (7).

**METHODS AND PROCEDURES**

**Participants**

The CDAH study is a prospective cohort study investigating the association between childhood characteristics and adult cardiometabolic disease (21). The CDAH study was approved by the Southern German Health and Medical Research Ethics Committee.

Between 2001 and 2003, 6,840 (40.5%) of the original 8,498 participants of the 1985 Australian Schools Health and Fitness Surveys (ASHS) were traced and invited to take part in the CDAH follow-up study. The ASHS sampling and data collection methods have been described elsewhere (22). Of these traced, 86 (1.3%) were deceased and 8,178 (99.6%) provided informed written consent questionnaires. Between 2004 and 2006, 1,410 enrollees (47%) attended one of 34 clinics for physical measures and blood sampling and completed study questionnaires.

Intheprospective study of 7–15-year-old children only, 9, 12, and 15-year-olds were selected for complete anthropometry, including skinfold measurements (n = 1,732). Of these, 741 (21.6%) attended follow-up clinics in 2004–2006 and had acceptable body mass recordings. After exclusion of pregnant women (n = 31), those missing grip strength (n = 68) and those missing information on smoking status (n = 7), data from 654 participants remained for analysis.

**Clinica measures**

**Anthropometry.** Participants’ heights and weights were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated using the standard formula BMI = weight (kg)/height squared (m²) and classified as normal, overweight, or obese according to age- and sex-specific cutoffs in childhood (23) and standard international thresholds for childhood overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²). The references are 24 and 25 kg/m², respectively (21).

Technicians trained in accordance with the international standards of anthropometric assessment, used anatomical landmarks to locate and measure skinfolds. Triceps, biceps, subscapular, and supraclavicular skinfolds were measured to the nearest 0.1 mm, using Holtain calipers (Holtain, Pantalim, Cilfrew, UK), and 1R (Rohrer, Age, and Slim Goode calipers (SPP Products, Belmar, NJ) at follow-up (24). LM = calculated using weight (kg) and estimates of percent body fat derived from the sum of skinfolds according to published equations for adults and children (25–27). BMI = weight (kg)/height² (m²).

**Lung function.** Adult lung function parameters forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory flow in the middle 50% of FVC (FEF25–75) were measured, with the participants in a standing position, using a Microlab 3500 portable electronic spirometer (Micro Medical Hampshire, UK) and Iden 5 software (Micro Direct, Lewton, ME), in accordance with the American Thoracic Society/European Respiratory Society standards (28). A 3-L syringe was used to calibrate the spirometer before each clin.

Before spirometry, participants were asked if they had any current lung condition and so, the name and time of the last dose of any medication they had taken for the condition. Current asthma was defined as those who reported having asthma, or who reported taking asthma medications. In childhood, lung function was measured using a spirometer with the participant seated with a nose clip in place as previously described (29,30). Recent predicted values in childhood and adulthood were generated using equations from Hankinson et al. (30).

**Muscular strength.** Maximal grip strength was measured using a Smedley’s spring-type hand dynamometer (Smedley, Wood Dale, IL). Three attempts were made, with each hand with a total 1-min rest between successive attempts, on the same hand. The analysis used an average of the dominant and non-dominant hands.

**Other measures**

Current smoking status (yes or no) and highest level of education completed (school only, trade, technical or diploma, and university) at follow-up were obtained from a self-administered questionnaire.

**Analysis**

Analyses were stratified by sex and age. Mean values and s.d. were calculated for all variables of interest. Student’s t-test for continuous variables and the χ²-test for categorical variables were used to investigate the differences in relevant study factors between those included in the follow-up analysis and those not. Pearson correlation coefficients were used to assess the relationship between physical characteristics and lung function measures.

Correlation analyses and multivariable regression models were used to estimate the cross-sectional associations at ages 27–36 years between BMI and each of the following outcomes: FEV1, FVC, FEV1/FVC ratio, and FEF25–75. Absolute lung function measures were used as the dependent variable in accordance with the suggestions of Ollent et al. (31).

The final model included adult height, age, current asthma status, current smoking status, and educational attainment. The effects of grip strength and LBM on the associations are illustrated in sequential models.

The effect of BMI in childhood (6, 12, and 5 years) on lung function in adulthood (27–36 years) was examined using linear regression. In these analyses, sex-specific, age-adjusted, and standardized BMI measures (z-scores) were used to facilitate comparisons across ages and at two time points. The z-scores, computed for baseline and follow-up, were the standardized residuals of regression BMI on age, separately for males and females (generated a z-score with a mean of zero and s.d. of unity). Final models included adjustment for baseline height in addition to the covariates used in the cross-sectional models. The analyses were repeated to investigate the contribution of childhood and adult BMI to the overall effect of childhood BMI.

Product terms were included in the regression models to assess statistical interaction between BMI and study covariates. Change-in-coefficient methods were used to assess confounding with covariates being retained in the regression model if their inclusion changed the coefficient of the BMI by 10% or more for each sex. The scaling of covariates was carefully checked but there was no evidence of non-linearity in the associations with adult lung function measures. StataCorp (Stata, College Station, TX) was used to perform all statistical analyses.

In additional analyses for Figure 1, we stratified childhood weight status by adult obesity. Because of the very low prevalence of obesity at baseline (1%), childhood obesity and overweight categories were combined. Six exposure categories were generated depending on whether or not participants were of healthy weight in adulthood and whether they were of healthy weight, overweight, or obese at follow-up. Analysis of variance methods were used to compare mean lung function values across categories for males and females separately.

**RESULTS**

**Characteristics of participants**

Descriptive statistics for the 316 men and 328 women included in this analysis are presented in Table 1. The baseline mean age, height, age-adjusted BMI, and skinfold thickness, and age and height-adjusted FEV1 and FVC of those included in the analysis were not significantly different from those lost to follow-up or excluded. Fewer of these included in the analysis
Appendices

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Figure 1: Estimated forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) of 694 young adults according to weight status in childhood and adulthood. (Estimated means and 95% confidence intervals.) Childhood data collected in 1985 Australian Schools Health and Fitness Survey, participants 9, 12, and 15 years of age. Childhood healthy and overweight/obese classified according to international standard age and sex-specific cutpoints (25). Adult data collected 2004–2006 when participants were aged 27–36 years. Healthy weight/adult BMI <25 kg/m^2; overweight/adult BMI 25–30 kg/m^2; obese adult BMI ≥30 kg/m^2. All analyses adjusted for baseline height and lean body mass, adult height, age, grip strength, lean body mass, current smoking status, asthma status, and educational attainment. *Indicates coefficient for effect of weight change statistically different from those of healthy weight in childhood and adulthood P < 0.06.

reported being childhood smokers (10.8% vs. 16.7% males P = 0.01 and 11.8% vs. 15.8% females, P = 0.1) or having at least one parent who was a smoker (42.4% vs. 51.6% males, F = 0.004 and 40.9% vs. 51.0% females, F = 0.022). In addition, a greater proportion were of healthy weight in childhood 91.4% vs. 87.8% of males (P = 0.07) and 91.8% vs. 86.4% of females (P = 0.04).

Mean FEV1, FVC, and strength measures were significantly greater for males than females at both time-points. Mean percent predicted FEV1, and FVC for adult males were >100% possibly reflecting the different source population (North American) used to derive the prediction equations (30). Similar proportions of men and women (<9%) were overweight or obese as children but more men, than women, were overweight or obese at follow-up. The proportion of participants who had childhood asthma was unknown but at follow-up, the prevalence of asthma increased according to weight status (5.8%, 11.6%, 12.5% and 16.7%, 14.7% and 22.9% for healthy weight, overweight, and obese men and women, respectively).

Compared to the general population of Australian adults aged 25–34 years (32,33), the proportions of participants who were overweight or obese (49.9% vs. 49.2%, P = 0.8) or reported current asthma (12% vs. 11%, P = 0.3) were similar but the proportion of males who were current smokers was significantly less (27% vs. 33%, P = 0.03).

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Cross-sectional associations in adults
In cross-sectional linear regression analyses, adult BMI was negatively associated with FEV1 and FVC, independent of height, age, grip strength, ILM, current smoking, current asha and, education (Table 2). Although the regression coefficients were greater for FVC than for FEV1, and generally greater for men than for women, when compared to the mean FEV1 and FVC, the effects were similar (1.2–1.5%). In men, there was a statistically significant positive association of BMI with FEV1,5 only adjusted for grip strength or ILM. There were no significant associations with FEV1/FVC in men or women.

Longitudinal associations from childhood to adulthood
The estimated effects of a 1 s.d. increase in childhood BMI on adult FEV1 and FVC are shown in model 1 (Table 3). Per FEV1 and FVC, the associations suggested that for every s.d. increase in age-standardized childhood BMI (2.9 kg/m²) there was an increase of 54 and 38 mL of FEV1 and 92 and 40 mL of FVC in men and women, respectively. This association is significant for FVC in men only. After adjusting for adult BMI (model 2), a 1 s.d. increase in childhood BMI had a significantly positive effect on the FEV1 and FVC of both males and females. However, adjustment for childhood and adult ILM eliminated any positive effect of childhood BMI on FEV1 or FVC (model 3). Associations of childhood BMI with FEV1/FVC and FEF25–75 did not reach statistical significance in any model (see Supplementary Table 51 online).

Stratified analysis
The results stratified by BMI status in childhood and adulthood are illustrated in Figure 1. Notably no male and only four female participants were overweight or obese as children and of healthy weight in adulthood.
Table 2: Cross-sectional associations of BMI with lung function in 326 men and 329 women aged 27-36

<table>
<thead>
<tr>
<th></th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>FVC</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio (%)</th>
<th>FEF&lt;sub&gt;25-75&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.026</td>
<td>0.006</td>
<td>(-0.006, 0.022)</td>
<td>(-0.010, 0.022) (0.00)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.001</td>
<td>-0.03</td>
<td>(-0.013, 0.014)</td>
<td>(-0.018, 0.013) (0.00)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-0.05**</td>
<td>-0.07</td>
<td>(-0.071, -0.032)</td>
<td>(-0.067, -0.033) (0.00)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.004</td>
<td>-0.002</td>
<td>(-0.007, 0.007)</td>
<td>(-0.011, 0.007) (0.00)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.004</td>
<td>-0.002</td>
<td>(-0.011, 0.004)</td>
<td>(-0.018, 0.001) (0.00)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-0.04**</td>
<td>-0.06</td>
<td>(-0.061, -0.031)</td>
<td>(-0.063, -0.038) (0.00)</td>
</tr>
</tbody>
</table>

All models adjusted for age, height, current smoking, current asthma, and education level. The regression coefficients represent the difference in liters of FEV<sub>1</sub>, FVC and FEF<sub>25-75</sub>, or the FEV<sub>1</sub>/FVC (%) associated with a one-unit increase in BMI. CI = confidence interval; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEF<sub>25-75</sub>, forced expiratory flow in the middle 65% of FVC. BMI adjusted for age, grip strength; BMI adjusted for grip strength and lean body mass. \(P < 0.05 \); \(P < 0.006\).

Table 3: Estimated association of childhood BMI (z-score) with young adult lung function

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child BMI z-score</strong></td>
<td>Adjusted for adult</td>
<td>Adjusted</td>
<td>Adjusted for adult</td>
<td>Adjusted for adult</td>
</tr>
<tr>
<td><strong>Child BMI z-score</strong></td>
<td>adjusted for adult</td>
<td>BMI score</td>
<td>adjusted for adult</td>
<td>BMI score</td>
</tr>
<tr>
<td><strong>Men (n = 326)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, Child BMI z-score</td>
<td>0.064</td>
<td>(-0.032, 0.161)</td>
<td>0.080</td>
<td>(-0.013, 0.161)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, Adult BMI z-score</td>
<td>-0.046</td>
<td>(-0.113, 0.021)</td>
<td>-0.067</td>
<td>(-0.113, 0.021)</td>
</tr>
<tr>
<td>FVC, Child BMI z-score</td>
<td>0.052**</td>
<td>(0.014, 0.148)</td>
<td>0.130*</td>
<td>(0.049, 0.211)</td>
</tr>
<tr>
<td>FVC, Adult BMI z-score</td>
<td>-0.095**</td>
<td>(-0.200, -0.190)</td>
<td>-0.068**</td>
<td>(-0.200, -0.190)</td>
</tr>
<tr>
<td><strong>Women (n = 329)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, Child BMI z-score</td>
<td>0.038</td>
<td>(-0.002, 0.076)</td>
<td>0.072*</td>
<td>(0.022, 0.117)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, Adult BMI z-score</td>
<td>-0.054**</td>
<td>(-0.103, -0.006)</td>
<td>-0.113**</td>
<td>(-0.162, -0.064)</td>
</tr>
<tr>
<td>FVC, Child BMI z-score</td>
<td>0.040</td>
<td>(-0.007, 0.086)</td>
<td>0.093*</td>
<td>(0.037, 0.150)</td>
</tr>
<tr>
<td>FVC, Adult BMI z-score</td>
<td>-0.019**</td>
<td>(-0.143, -0.037)</td>
<td>-0.146*</td>
<td>(-0.255, -0.037)</td>
</tr>
</tbody>
</table>

Regression coefficient 65% CI; the regression coefficients represent the difference in liters of FEV<sub>1</sub>, FVC associated with a unit increase in the BMI z-score (1.64). Child BMI z-score, age- and sex-standardized median with a mean of zero and a s.d. of unity (generating using residuals of regressing BMI on age, sex, and height to generate northwestern BMI using residuals of regressing BMI on age, sex, and height to generate northwestern BMI). CI = confidence interval; FVC, forced Vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; BMI, body mass index. All models adjusted for baseline age, height, sex, grip strength, smoking status (no or yes), asthma status, and educational level. \(P < 0.05 \); \(P < 0.006\).

Irrespective of childhood weight status, obese adults had significantly lower FEV<sub>1</sub> and FVC volumes than those of healthy weight at both time-points, with deficits of 440 ml (10.1%) and 549 ml (12.5%) in FEV<sub>1</sub> and 627 ml (11.6%) and 694 ml (12.9%) in FVC for those of healthy and unhealthy childhood weight, respectively. For women, the FEV<sub>1</sub> and FVC of obese adults who were of healthy weight in childhood were not significantly different from those who were of healthy weight at both time-points. Obese women who were also overweight or obese in childhood had significant deficits of 259 ml (7.9%) and 455 ml (11.5%) in FEV<sub>1</sub> and FVC, respectively. The effect of adiposity on female lung function was also modified by an interaction \(P = 0.03\) between weight status and age. The negative effects of persistently higher levels of adiposity increased with age. Compared to women of healthy weight at both time-points, the estimated deficit in FEV<sub>1</sub> and FVC of obese women who were of unhealthy weight in childhood was 253 ml (95% confidence interval: 7 ml, 499 ml and 437 ml (95% confidence interval: 149 ml, 725 ml), respectively at age 32 and 515 ml (95% confidence interval: 199 ml, 810 ml) and 769 ml (95% confidence interval: 399 ml, 1,141 ml), respectively at age 55.

The difference effects of obesity on FEV<sub>1</sub> and FVC observed in women resulted in nonsignificant increases in FEV<sub>1</sub>/FVC (data not shown). This effect was not observed in men. Repetition of the analysis excluding 90 participants with current asthma did not affect the results.
DISCUSSION
In this population-based sample of young adults, FEV<sub>1</sub> and FVC were strongly and inversely associated with current adiposity, and adiposity persisting since childhood, as measured by BMI adjusted for LBM. Cross-sectional analysis of baseline data from this cohort had previously been used to demonstrate negative associations of adiposity with childhood FEV<sub>1</sub> and FVC (34).

Initial longitudinal analysis, using BMI measures obtained when the subjects were aged 5, 12, or 15 years suggested a positive association between childhood BMI and adult lung function. This finding is consistent with the results of a previous study of Israeli male army recruits (18) in which BMI at 7 years was positively associated with FEV<sub>1</sub> and FVC: 19-40 years later, adjustment for adult overweight (BMI ≥25kg/m<sup>2</sup>). However, in the present study adjustment for LBM largely eliminated the positive effect of childhood BMI, suggesting that the positive association between childhood BMI and adult lung function is explained by lean mass rather than fat mass. Our finding that both cross-sectional and longitudinal effects of adiposity were greater on FVC than FEV<sub>1</sub>, and the lack of any significant effects on the FEV<sub>1</sub>/FVC ratio are consistent with other publications indicating a restrictive effect of adiposity on lung function, rather than an obstructive defect (14,7,13).

The results of model 2 and model 4 show that the estimated effect of childhood adiposity is independent of adult adiposity. After adjustment for LBM, the effect of childhood BMI was modest compared with the effects of adult BMI irrespective of whether participants had high BMI z-scores only at follow-up or at both time points. Using this model, we predict lower lung volumes in those maintaining higher BMI and those with the largest increases in BMI z-score between childhood and adulthood.

Our findings demonstrate that the effect of childhood BMI on adult lung function should not be viewed in isolation from change in BMI over time.

Although the regression coefficients for the effect of adult adiposity suggest a greater effect on the lung function of males than females, when compared to the mean values of FEV<sub>1</sub> and FVC the reduction in volumes were similar. (Cross-sectional analysis: 1-1.5% per unit lean-adjusted BMI and longitudinal analysis: 3-5% per s.d. adult BMI after adjustment for lean mass and childhood adiposity)

Strengths and limitations
This study of a relatively large, population-based cohort of young Australian adults is one of the few studies to have investigated the relationship between childhood adiposity and adult lung function using longitudinal data. Its limitations need to be borne in mind, however. First, we had longitudinal data from only two time points with no data on when participants attained their peak lung function or what their peak volumes were. Therefore, although our results suggest that adiposity in young adulthood has an important detrimental influence on lung function, that reverses any beneficial effect of childhood lean mass, we could not examine the effect of adiposity on lung development or the pattern of increasing BMI during the transition to adulthood.

Neither childhood smoking nor parental smoking were significant confounders or effect modifiers in our analyses (data not shown), but we did not have information on other potential determinants of adult lung function such as exposure to environmental pollution, childhood asthma, prematurity, and maternal smoking during pregnancy. As reported elsewhere we observed a positive association between adiposity and asthma (35). However, in these analyses, asthma had little effect on the association between adiposity and FEV<sub>1</sub> or FVC, or exclusion of participants who reported asthma at follow-up did not affect our conclusions.

There was a large shift in the proportion of overweight and obese individuals between baseline and follow-up in this sample. In childhood, 92% of participants were of healthy weight compared with 51% (38% men and 62% women) at follow-up. Consequently, a male child of average healthy weight with no change in z-score between childhood and adulthood would be an overweight adult. For this reason, we also presented simple stratified analyses according to international cutpoints of healthy weight, overweight, and obesity in childhood and adulthood.

For males, the results (Figure 1) were consistent with those of our statistical modeling (Table 3) but for females, the effects of persistently higher levels of adiposity by childhood and adulthood were more detrimental to adult lung function.

The low prevalence of childhood obesity in this sample may also have limited our power to estimate the true effect of obesity persisting from childhood to adulthood. However, Buja et al. (18) found no difference in the estimates of the effect of childhood BMI on adult lung function between those identified as juvenile obese (n = 179) and nonobese (n = 188) males. We are not aware of any published literature of note on this issue in women.

There has been some concern about the accuracy of the equations used to convert skinfolds to fat mass and enable calculation of LBM (25,56). However, because the proposed method of correction is to add sex-specific constants to the equations (38) it is unlikely that the observed associations would be affected. Furthermore, any inaccuracy might be expected to attenuate findings toward the null and cannot explain the main outcomes of this study.

To summarize our findings, in this sample of generally healthy young Australian men and women first assessed 20 years earlier, BMI in childhood had a positive effect on FEV<sub>1</sub> and FVC in adulthood but this effect was attributable to LBM. When adjusted for LBM, greater childhood BMI (adiposity) had little effect on adult lung function unless high adiposity persisted into adulthood.

We have shown that it is necessary to track adiposity throughout the life course to understand its effect on adult lung function. Obese children and healthy weight children who become obese adults can expect to have poorer FEV<sub>1</sub> and FVC than those of healthy weight at each life stage. These results highlight the importance of encouraging healthy weight maintenance throughout life.
SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

ACKNOWLEDGMENTS
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DISCLOSURE
The authors declared no conflict of interest.

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