AN EPIDEMIOLOGICAL INVESTIGATION OF THE ROLE OF PHENOTYPE IN THE ASSOCIATION OF OBESITY AND ASTHMA

Sarah Louise Appleton

Faculty of Health Sciences

Discipline of Medicine at the Queen Elizabeth Hospital

University of Adelaide

South Australia

Australia

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For my Father, William Appleton

Table of Contents

Abstract

This thesis investigates the complexity in the relationship between obesity and asthma and asthma morbidity. Previous epidemiological studies exploring these relationships have been limited by sample bias and the use of restricted phenotypes of body mass index (BMI) and self-reported asthma, ignoring the problem of undiagnosed asthma, and more pathogenic central obesity phenotypes. Cardiovascular disease (CVD), a systemic manifestation of obesity may be augmented by asthma-related airway inflammation, yet studies inconsistently identifying an association with asthma have failed to assess the role of asthma phenotype or cardiotoxic effects of short acting beta-2 adrenergic agonists (SABA). Understanding the consequences of this complexity is fundamental to the development of appropriate policy and intervention.

The North West Adelaide Health Study, a representative biomedical population sample (n=4006) permitted an examination of the role of phenotype in the association of obesity [body mass index (BMI), waist circumference, waist to hip ratio] with asthma [atopy, significant bronchodilator reversibility (SBR)].

Optimising the identification of asthma in the absence of a gold standard test is important. The prevalence of undiagnosed asthma (SBR in absence of doctor diagnosis) was variable (1.6% to 4.5%) depending on the SBR criteria specified. The observed symptom burden and lung function impairments suggest that all criteria identified subjects with probable asthma. SBR criteria were associated with different socio-demographic factors and the 9% of the predicted criterion was least biased particularly in terms of age and sex.

Generalised (BMI) and central obesity were associated with asthma in females only. After consideration of atopic status, in males, central obesity and high BMI (likely to be distributed centrally) was associated with non-atopic asthma. In females central obesity was also associated with non-atopic asthma but a high BMI was associated with atopic asthma. This suggests different pathophysiological mechanisms for the relationship between obesity and atopic and non-atopic asthma.

In subjects with asthma, a significant burden of generalised and central obesity-related asthma morbidity (symptoms, beta-2 agonist use, lung function) occurred largely in males only, although quality of life impairments and increased primary care visits were not sex-specific. Only central obesity was associated with persistent airways obstruction in males.

Asthma was associated with CVD/stroke events, independent of traditional CVD risk factors in cross-sectional analyses. Asthma was not associated with diabetes or cardiovascular risk factors. No modifying effect of obesity was observed in these associations, suggesting that events may be related to aspects of asthma pathology, asthma phenotype or a direct cardiotoxic effect of SABA.

In females, incident CVD/stroke events were associated with asthma and as required SABA use, but the association was not modified by atopic status. In males, CVD/stroke events were associated with other respiratory morbidity. Few events occurred in men with asthma, but a significant interaction of asthma with atopic status was evident.

This work has contributed to emerging knowledge that improved phenotyping will advance our understanding of the relationship and mechanisms between obesity and asthma and has implications for asthma management. An unbiased SBR criterion will improve the identification of asthma in the absence of a gold standard test. The association of central obesity with non-atopic asthma indicates that asthma should be considered in such symptomatic individuals. Given the increased morbidity burden in obese subjects with asthma, healthy weight maintenance is an important component of asthma management. Management of macrovascular disease risk in women with asthma includes caution in the prescribing of SABA.

Declaration

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STATEMENT OF AUTHORSHIP

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The Journal of Allergy and Clinical Immunology 2005; 116:976-82.

Appleton, SL (Candidate)
Study conception and design, statistical analysis, interpretation of data, manuscript preparation, critical revision of the manuscript, corresponding author.

I hereby certify that the statement of contribution is accurate.

Adams, RJ
Supervised development of the work, data interpretation, critical revision of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Wilson, D
Supervised development of the work, critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Taylor, A
Management of the data, critical revision of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Ruffin, R
Critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

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Ruffin, R
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Appleton, SL (Candidate)
Study conception and design, statistical analysis, interpretation of data, manuscript preparation, critical revision of the manuscript, corresponding author.

I hereby certify that the statement of contribution is accurate.

Tucker, G
Assisted with statistical analysis, critical revision of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Wilson, D
Supervised development of the work, critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Ruffin, R
Critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

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Taylor, A
Management of the data, critical revision of the manuscript.

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Adams, RJ
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Interpretation of data, critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

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Adams, RJ
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Appleton, SL (Candidate)
Study conception and design, statistical analysis, interpretation of data, manuscript preparation, critical revision of the manuscript, corresponding author.

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Interpretation of data, critical revision of the manuscript. Conception and design of the North West Adelaide Health Study and funding acquisition.

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Adams, RJ
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Abbreviations

ACD	asthma control days
ACQ	Asthma Control Questionnaire
AF	attributable fraction
AHR	airway hyperresponsiveness
AQLQ	Asthma Quality of Life Questionnaire
ATM	adipose tissue macrophage
BMI	body mass index
CCHS	Canadian Community Health Survey
CCL5	regulated upon activation, normal t-cell expressed and secreted
CCR5	receptor for regulated upon activation, normal t-cell expressed and secreted
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
CT	computed tomography
CVD	cardiovascular disease
DEXA	dual emission x-ray absorptiometry
ECRHS	European Community Respiratory Health Study
ED	emergency department
ERV	expiratory reserve volume
F_{eNO}	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in one second
FP	fluticasone proprionate
FRC	functional residual capacity
FVC	forced vital capacity
GERD	gastro-oesophageal reflux disease
GINA	Global Initiative for Asthma
IC	inspiratory capacity
ICD	International Classification of Diseases
ICS	inhaled corticosteroid
IgE	Immunoglobulin E
IL	interleukin

LABA	long-acting beta-2 adrenergic agonist
M1	classically activated macrophages (pro-inflammatory)
M2	alternatively activated macrophages (anti-inflammatory)
MCP-1	monocyte chemoattractant protein-1
MRI	magnetic resonance imaging
$NF_{\kappa}B$	nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NWAHS	North West Adelaide Health Study
PC_{20}	provocative concentration causing a 20% fall in FEV_1
PEF	peak expiratory flow
RANTES	regulated upon activation, normal t-cell expressed and secreted
RV	residual volume
SABA	short-acting beta-2 adrenergic agonist
SF-36	Medical Outcomes Study Short Form 36
SBR	significant bronchodilator reversibility
TLC	total lung capacity
TNF-alpha	tumour necrosis factor-alpha
WC	waist circumference
WHR	waist to hip ratio
WSR	waist to stature ratio

Chapter 1. Introduction

Epidemiological studies in representative populations are used to measure the burden of disease and trends in diseases over time, and have identified the burden of obesity and asthma in Australia (Australian Bureau of Statistics 2006, Wilson 2006) and internationally (Ogden 2006, von Hertzen 2005). These studies identify associations and permit the characterisation of groups identified at risk by virtue of large sample sizes and the generation of robust estimates. Identification of target groups enables the development of targeted informed policy to deal with disease and disease risk at a population level. It is therefore critical to measure disease burden and associations accurately using valid measures.

Consistent with international epidemiological findings (Flegal 2002, Ogden 2006), the prevalence of obesity in Australia has increased to the point that around two thirds or more of the Australian population is overweight or obese (Cameron 2003, Australian Bureau of Statistics 2006). The medical consequences of obesity are incontrovertible and increasing BMI shows a strong relationship with mortality and morbid conditions including diabetes, cardiovascular disease, hypertension, dyslipidaemia, osteoarthritis, sleep apnoea, gall bladder disease, non-alcoholic steatohepatitis, infertility, and some cancers (Bray 2004, Caterson 2004, National Task Force on the Prevention and Treatment of Obesity 2000, Aronne 2002, Pi-Sunyer 2002, Rapp 2005). Obesity accounts for 4% of the total burden of disease in Australia (Mathers 1999). With the increase in obesity there has been a concomitant increase in asthma, although the prevalence of asthma may have stabilised (von Hertzen 2005, Lotvall 2009, Wilson 2006). Asthma is also a significant cause of disability and is the leading cause of disease burden in children (up to age 14) and is the 9th leading contributor to the burden of disease for all ages (Australian Centre for Asthma Monitoring 2005a).

There is a large body of international epidemiological data linking the simultaneous increase in asthma and obesity, suggesting that obesity is a risk factor for asthma (Ford 2005). The scale of the obesity problem raises important questions in terms of the nature of the relationship between them, the possibility of an increasing burden of asthma, and the implications for treatment, costs and policy. In Australia in 2000-01, health

expenditure on asthma amounted to $700 million of which 50% was attributable to pharmaceuticals (Australian Centre for Asthma Monitoring 2005b). As evident from a recent systematic review of 68 studies, asthma is associated with significant direct (hospitalisation, emergency service, doctor visits, drugs) and indirect costs (time lost from work, premature death) (Bahadori 2009). Hospitalisations and medications were the most important driver of direct costs, whereas work and school loss accounted for the greatest proportion of indirect costs. Importantly, increased costs of asthma were associated with poor asthma control. Asthma costs were additionally correlated with comorbidities, and age, which are also important correlates of obesity.

While cross-sectional epidemiological studies suggest an association between obesity and asthma that is sometimes specific to women, they preclude any conclusions being drawn in regard to the direction of the association. In contrast, a meta-analysis based upon longitudinal studies have demonstrated an association of increasing body mass index (BMI) with the development of asthma (incident asthma) in both women and men (Beuther 2007). The mechanisms that may explain this relationship have been reviewed and include effects of obesity on lung mechanics, systemic inflammation and energy regulating hormones, genetic factors, comorbidities, gender and early life exposures and nutrition (Weiss 2005, Beuther 2006, Shore 2008a, Litonjua 2008). There is however, a complexity inherent in the association between obesity (or body weight) and asthma and consequently, these findings need to be viewed with some caution. The complexity is largely related to the issue of the validity of measures of asthma and obesity used in epidemiological studies.

In the absence of a gold-standard test, identifying asthma in epidemiological studies from self-reported measures may be associated with limitations because of the heterogeneity in asthma expression (Anderson 2008) in terms of clinical, and physiological measures which may in turn contribute to the second problem of under-diagnosis of asthma in the community (Adams 2003). It is unclear how the consideration of alternative asthma phenotypes [atopic status, airway hyper-responsiveness (AHR) that are inconsistently expressed] modifies the association between self-reported asthma and obesity. Similarly, body mass index is a measure widely used in epidemiological studies because of the ease of measurement and the components (height and weight) may be self-reported. BMI is however a proxy

measures of total fat mass, given that it doesn't distinguish between lean and fat mass. These, and compartmentalised fat are accurately measurable by dual emission X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and computed tomography (CT), but these are expensive and impractical for epidemiological studies. This non-discrimination between lean and fat tissues has implications because one of the aetiological links between adiposity and asthma (Beuther 2006, Shore 2008a) is systemic inflammation and a relationship between the two should theoretically be driven by the absolute amount of adipose tissue or the amount in proportion to lean tissue mass. In addition, BMI does not describe fat distribution although it is highly correlated with measures of central adiposity. There is evidence that central adiposity is an independent predictor of health risk over BMI, (Aronne 2002) but measures of central obesity including waist circumference and waist to hip ratio may also have a stronger association with asthma through mass loading on the airways and the consequent mechanical factors that modify airway smooth muscle function (Beuther 2006, Shore 2008a).

The aim of this research was to obtain a better understanding of the relationship between asthma and obesity which may facilitate improved health outcomes and reduce avoidable morbidity through earlier diagnosis and improved management. This required a multidimensional examination of the role of phenotype in the relationship between obesity and asthma. A true causal association between obesity and asthma would be robust across populations and phenotypes, although the relative strength of the association may change when phenotypes of asthma and obesity are considered. This work also sought to determine the effect of obesity on asthma severity. Given the potential additive inflammatory effects of obesity and asthma, I assessed the independence of the relationship of asthma and obesity to the metabolic consequences of obesity- cardiovascular disease and diabetes. In order to do so, it was necessary to first optimise the identification of asthma in the study population which was the North West Adelaide Health Study by determining the relative performance of asthma management guideline reversibility criteria to identify asthma.

Findings from this project have the potential to improve health outcomes for people with respiratory disease by facilitating earlier diagnosis and improved management in the following ways.

1. Identification of optimal asthma spirometric criteria may reduce the burden of undiagnosed asthma.
2. Identification of body weight related risks (obesity/underweight) for poor respiratory outcomes permits an evidence based approach to informing asthma management guidelines on the importance of weight management.
3. Reducing the burden of undiagnosed respiratory disease and appropriate weight management for people with respiratory disease may result in reduced direct health system costs.

The implications of these for primary care intervention and screening include a focus on methods to allow reliable spirometry in general practice and a revision of existing management guidelines to also focus on weight management.

Chapter 2. Review of the Literature

Identifying obesity in populations

Body mass index (BMI) is the most commonly used measure to demonstrate the relationship between obesity and mortality and morbidity. Obesity is measured according to several criteria other than BMI, (defined as weight (kg) divided by height (m) squared, i.e.- kg/m^2), including waist circumference [WC (cm)], waist to hip ratio [WHR defined as waist circumference divided by hip circumference (cm)], and waist to stature ratio [WSR, defined as waist circumference divided height (m)]. These are commonly used measures in epidemiological studies but are proxy measures of total fat mass which can be determined by DEXA, MRI and CT.

The importance of obesity phenotype

Fat distribution may be an independent predictor of disease

BMI does not distinguish between lean and fat mass, and may misclassify individuals considered obese by WC (Booth 2000, Gill 2003), however WC and WHR can be considered imperfect proxy measures of abdominal fat. Fat distribution is an independent predictor of health risk (Aronne 2002). WC is associated with metabolic disorders (Janssen 2004, Wahrenberg 2005, Wei 2006), mobility disability (Guallar-Castillon 2007) and mortality (Bigaard 2004) independent of BMI or percentage fat (Wei 2006). For a given BMI, higher levels of visceral fat are associated with significantly higher insulin resistance and increased cardiovascular disease (Zavaroni 1989) and type 2 diabetes (Goodpaster 2005, Goodpaster 2003, Carey 1996, Zavaroni 1989) risks. In contrast, some studies have reported that abdominal adiposity is not an independent predictor of CHD (Rexrode 2001, Folsom 2000), diabetes (Folsom 2000, Wang 2005) or early carotid atherosclerosis (Takami 2001) after adjustment for BMI. Waist and hip circumferences measure different aspects of fat distribution- large hip and thigh circumferences have been shown to be associated with lower risks of diabetes

(Snijder 2003), and may be protective against cardiovascular disease (Seidell 2001) independent of BMI and WC.

Regional variation in adipokine production may have clinical relevance

Adipose tissue (AT) is an endocrine organ with important protein secretory function (Kershaw 2004). The increased secretion of fatty acids from visceral adipose tissue draining via the portal vein to the liver has important effects on the liver which may be related to metabolic abnormalities observed in obese individuals (Arner 1998). As reviewed by Arner there are anatomical regional differences in the levels of mRNA and protein of leptin, interleukin-6 (IL-6), angiotensinogen, and plasmin activator inhibitor-1 in subcutaneous compared to visceral fat (Arner 2001). In subcutaneous fat, leptin is increased, and IL-6 is reduced compared to visceral tissue but no differences in TNF-alpha have been consistently reported (Arner 2001). Inconsistent associations with visceral or subcutaneous abdominal fat have been reported for adiponectin (Park 2004, Farvid 2005) however, and the reduced levels of adiponectin in obese people (Arita 1999) has been proposed to lead to diabetes (Dietze-Schroeder 2005, Farvid 2005) and atherosclerosis via vascular immunopathological mechanisms (Lyon 2003, Ouchi 2003).

Is waist circumference more likely than BMI to measure clinically important subcutaneous or visceral fat?

Janssen *et al* studied the association of fat depots with anthropometric measures in 341 white men and women. For non-abdominal and abdominal subcutaneous fat, BMI explained an additional 23% of the variance in males but only 2% in females compared with WC alone (Janssen 2002). In relation to visceral fat, this study also identified that WC explained an additional 11% of the variance in visceral fat explained by BMI in men and an additional 16% in women. In contrast, BMI does not add significantly to the prediction of visceral fat by WC (Janssen 2002, Onat 2004, Stewart 2003, Chan 2003). Conflict in this literature exists however, and no greater predictive value of WC or BMI

for visceral (Oka 2009) or abdominal subcutaneous (Oka 2009, Chan 2003) fat has also been reported.

The association of obesity phenotypes with asthma

Based upon the preceding evidence, it is clear that it is important to consider obesity phenotype in the association with asthma. Measures of central/abdominal obesity such as waist circumference (WC) or waist hip ratio (WHR) are likely to have a stronger association with asthma than BMI, through 1) a greater association with visceral fat, 2) regional differences in secretion of adipocytokines 3) a greater modifying affect on airway smooth muscle function by mechanical factors (Shore 2005a).

Few population studies have examined the relationship between asthma and these alternate obesity phenotypes (Camargo 1999, Kronander 2004) or body composition (McLachlan 2007) and the findings are inconsistent. BMI, WC and WHR were significantly associated with incident asthma in the Nurses Health Study (n=85,900 females), however, asthma remained independently associated with BMI only, when WHR or WC were added as independent variables to the multivariable model. Kronander *et al* also described in a Swedish primary care population (n=4178, 20-50 yrs) a cross sectional association of obese levels of BMI and WC with asthma, and these associations generally held only in non-atopic subjects (overall and males and females) (Kronander 2004). Incident asthma cases were significantly associated with high BMI and WC, but the independence of these associations was not tested (Kronander 2004). In contrast, a Chilean study of 1232 young adults reported no associations of BMI or WC with diagnosed asthma and a positive association with asthma symptoms (wheeze, breathlessness following exercise) was reported for BMI only (Bustos 2005).

Studies have assessed asthma risk in relation to quantitated levels of fat. In a cross-sectional analysis of the Dunedin study (972 adult subjects aged 32 years) there was a significant association between the percentage of body fat and asthma in women but not in men, and in the absence of an association with airway inflammation (McLachlan 2007). A very recent study in 9810 adults free of asthma from the Aerobics Center

Longitudinal Study reported a decreased risk of incident asthma in overfat (body fat % exceeding 25% in males and 30% in females) but very cardiorespiratory fit individuals and the authors relate this effect to the deep inspiration hypothesis. (Ortega 2010) The absence of a bronchoprotective effect of deep inspiration in subjects with asthma has been observed (An 2007, Kapsali 2000). High levels of cardiorespiratory fitness, with an implied increased level and effectiveness of deep inspirations in obese subjects may therefore off-set an obesity-related inflammatory aetiology of asthma.

Identifying asthma in population studies in the absence of a gold standard

Asthma is complex and difficulties in defining asthma remain (Hargreave 2009). The definition of asthma by the Global Initiative for Asthma (GINA) includes inherent inconsistencies – i.e. "episodes are *usually* associated with widespread but *variable* airflow obstruction that is *often* reversible …."(Global Initiative for Asthma 2002).

Epidemiological studies usually identify asthma based on self-reported current doctor diagnosed asthma obtained by a "yes" response to the following questions: 1) "Have you ever been told by a doctor that you have asthma?" and 2) "Do you still have asthma?" This definition is widely used and has been shown to be a valid measure of asthma (Toren 1993). Furthermore, it is unlikely that participants self-reporting current asthma do not actually have the condition, however the converse is true, and the inherent problem with reliance upon self-reported diagnosed asthma is that not all asthma in populations is identified or diagnosed (Banerjee 1987, Parameswaran 1998, Enright 1999, McIvor 2001, Adams 2003, Backer 2009). In addition, under-diagnosis in adults is likely to be explained by under-perception of dyspnoea/symptoms and differential diagnoses including cardiac, neurological and drug related causes (Dow 1998). The diagnosis of asthma in adults may be difficult and confounded by co-morbidities and consequently, asthma is frequently under-diagnosed. A gold standard test would simplify the diagnosis of asthma and perhaps reduce the frequency of under-diagnosed asthma, however, no gold standard exists (Peat 2001). Under-diagnosis has implications for studies assessing associations of obesity (and other factors) with asthma. Associations with important explanatory factors may be diminished or even

negated depending on the proportion of subjects with asthma incorrectly assigned to the "no asthma" population.

The relationship between obesity and asthma phenotype

Heterogeneity in asthma expression is multidimensional, and includes variability in clinical, physiologic, molecular and pathologic parameters (Haldar 2008, Anderson 2008, Woodruff 2009). Moreover, Anderson has recently suggested that this substantial heterogeneity cannot be accounted for by the Th2-inflammation model (Anderson 2008). Given the limitations of self-reported asthma described previously, it is important to identify the relationship between obesity and other features or phenotypes of asthma. These include airway hyperresponsiveness (AHR), considered a hallmark of asthma although its sensitivity for asthma is not high (Grassi 2001, Marabini 2001), atopy, and measures of airway inflammation including sputum granulocyte counts and the fraction of exhaled nitric oxide (F_{eNO}).

The variation in the robustness of reported associations between asthma and obesity is clearly related not only to sample variability and bias, but also to the heterogeneity of asthma expressed in those samples.

There is heterogeneity of airway inflammation in persistent asthma and this heterogeneity may be responsible for the mis-match between airway inflammation and airway hyper-responsiveness and tissue remodelling (Anderson 2008). Distinct asthma phenotypes based upon sputum inflammatory granulocytes are evident. This classification scheme based upon the presence of eosinophils (>/< 1.9%) and neutrophils (>/< 61%) is as follows: (1) eosinophilic; (2) neutrophilic; (3) mixed (i.e., both neutrophils and eosinophils present); and (4) paucigranulocytic (few or no granulocytes in the sputum) (Douwes 2002). A review of studies identifies that only 50% of asthma is attributable to eosinophilic airway inflammation prompting these authors to suggest that "allergic mechanisms may not be the only and/or the most important underlying mechanism for asthma" (Douwes 2002). Studies suggest that neutrophilic asthma (eosinophils < 1.9%, neutrophils >61%) which has been shown to

be associated with innate immune activation (Douwes 2002, Simpson 2007) represents a more benign phenotype when the exacerbation frequency and severity are considered, and is characterised by diminished responsiveness to corticosteroids and less severe airway hyper-responsiveness (Haldar 2007). Limited data suggests that a neutrophilic asthma phenotype is non-atopic (Nadif 2009, Green 2002b, Drews 2009) and associated with obesity (Haldar 2008, Scott 2009). In contrast, eosinophilic asthma is characterised pathologically by thickening of the basement membrane zone and pharmacologically by corticosteroid responsiveness (Haldar 2007). That these subgroups represent different clinical phenotypes is indicated by studies personalising treatment based upon the type of airway inflammation (Jayaram 2006, Green 2002a).

The cellular heterogeneity in airway inflammation is supported by a recent study demonstrating that asthma can be divided into at least two distinct molecular phenotypes (Woodruff 2009). Gene expression analyses identified two distinct subgroups, ‘‘Th2-high’’ and ‘‘Th2-low’’ asthma based upon the expression level of IL-13 inducible genes. Th2-low was indistinguishable from control subjects, whereas Th2-high subjects demonstrated significantly increased expression of IL-5 and IL-13 in bronchial biopsies and increased levels of airway hyperresponsiveness, serum IgE, peripheral blood and BAL eosinophils, subepithelial fibrosis, and airway mucin gene expression compared to Th2-low. Inhaled corticosteroid (ICS) related lung function improvements were restricted to Th2-high asthma. Interestingly, Th2-low subjects showed a trend to less skin test reactivity than Th2-high subjects.

Relationship between body mass index and atopy

While asthma is strongly associated with atopy, the sensitivity and specificity of atopy for asthma is not high. Large epidemiological studies including the European Community Respiratory Health Study (ECRHS, subjects aged 20-44) and the National Health and Nutrition Examination Survey III (NHANES, subjects aged 6-59 years) have reported the attributable fraction (AF) of asthma caused by atopy. In the ECRHS, across 16 countries, the atopy prevalence (reactivity to at least one of seven allergens) ranged from 18-46%, the AF of asthma caused by atopy ranged from 4% to 61%, but overall,

the AF of asthma (wheezing and AHR) caused by atopy was 43% (Sunyer 2004). The prevalence of reactivity to at least one of ten allergens in NHANES III was 53%, and the AF of current diagnosed asthma caused by atopy was 56% (Arbes 2005). Given this, it is not surprising that epidemiological studies report no association between BMI and atopy despite finding associations of BMI with an asthma diagnosis and/or symptoms in those same studies (Bustos 2005, Hancox 2005, Schachter 2001, Jarvis 2002). In contrast, studies using non-standard cut-points of BMI show positive associations. In 4719 subjects from a Finnish birth cohort a significant cross-sectional association of the 85^{th} to 94^{th} percentile and $\geq 95^{th}$ percentile of BMI with atopy (to at least one of four allergens) and current doctor diagnosed asthma at age 31 was demonstrated (Xu 2002). Linneberg demonstrated a significant association of atopy (to >=1 of 10 allergens) and specific IgE with BMI 22.6-26.0, but not >26.0 compared with the lowest BMI group ($\leq$ 22.5) in The Copenhagen Allergy Study (Linneberg 2001).

The well described associations between obesity and asthma would suggest an effect of body fat on atopic disease. However, these findings in relation to atopy, suggest that the described associations between obesity and asthma may be modified by atopic status. The few studies examining the role of atopic status have generated inconsistent findings. Two studies have reported no modification by allergic status (Ronmark 2005, Schachter 2001) and another reports a stronger association in subjects who are non-atopic (Kronander 2004). Interestingly, Bråbäck *et al*, using a self-report of allergic rhinoconjuctivitis as a proxy marker of atopy, reported significant positive associations of obesity with asthma +/- allergic rhinoconjuctivitis, (but not with allergic rhinoconjuctivitis alone) in over one million male Swedish military conscripts (Bråbäck 2005). Although no formal tests for an interaction with atopic status were conducted, the odds ratios were larger in those with asthma without allergic rhinitis.

Relationship between body mass index and markers of airway inflammation

Sputum granulocytes

Given the now apparent and recently demonstrated complexity inherent in any discussion of asthma phenotype, there is little wonder that the nature of the airway inflammation associated with obesity has only been very recently reported (Scott 2009, Todd 2007). Granulocyte phenotyping in epidemiological studies has been problematic because of the invasiveness of sputum induction procedures required to acquire these markers, however Gibson suggests that the large sample sizes in epidemiological studies are likely to overcome any imprecision in phenotype classification derived from peripheral blood granulocytes (Gibson 2009). Nevertheless, in a study of the association of obesity with sputum cell counts in 727 adults presenting for evaluation of asthma, chronic cough and COPD, Todd *et al* reported no association of BMI as a continuous or categorical variable with measures of eosinophils, neutrophils, lymphocytes and macrophages (Todd 2007). The absence of association was observed in subjects with (n=163) and without asthma (n=564) even after adjusting for ICS use. Furthermore, in subjects with asthma, no associations were seen in both males and females. The increase in sputum eosinophils observed in subjects with asthma was equally likely to be present in the obese subjects compared with the normal weight subjects with asthma. In support of the proposal that mechanisms other than airway inflammation are involved in the relationship between asthma and obesity (Todd 2007), Sutherland *et al* demonstrated that in subjects with asthma, sputum eosinophilia >1% (87% vs 94%) or mixed cellularity (6.7 vs 6.3%) was equally prevalent in obese compared with normal weight subjects and a specific neutrophilic phenotype was absent although a non-significant increase in percent neutrophils with increasing BMI was observed (Sutherland 2008b). In contrast, Scott *et al* reported a significant correlation between BMI and % sputum neutrophils, but not eosinophils, in 103 subjects with asthma (Scott 2009).

Fraction of exhaled nitric oxide (F_{eNO})

The relationship between BMI and F_{eNO}, a marker for predominantly eosinophilic airway inflammation and useful for the diagnosis of atopic but not non-atopic asthma (Henriksen 2000, Pendharkar 2008) has been examined in only one population study by McLachlan *et al*, where in 972 adult subjects aged 32 years, no significant correlation of F_{eNO} and percentage body fat was observed in either males or females and this persisted after adjustment for ICS use (McLachlan 2007). Several studies have assessed the relationship between BMI and F_{eNO} in selected samples of people with mild to

severe persistent asthma (van Veen 2008, Sutherland 2009a, Komakula 2007, Kazaks 2005, Barros 2006, Sutherland 2008b) and with sample sizes ranging from 39 (Sutherland 2008b) to 1256 subjects derived form ten Asthma Clinical Research Network clinical trials (Sutherland 2009a). Despite the large variation in sample sizes, these studies consistently report an inverse association of F_{eNO} with BMI, with the exception of one of the smaller studies (Kazaks 2005). Importantly, the significant inverse relationship reported by Barros *et al* in 297 subjects, persisted after adjustment for ICS use (Barros 2006). Furthermore, although F_{eNO} was significantly higher in subjects with asthma compared to those without, this association was not modified by obesity status (Sutherland 2008b).

In contrast, variable results have been seen in studies with small samples of subjects without asthma. Small positive associations of 1.5 ppb/kg/m^2 have been demonstrated by some (Kazaks 2005, De Winter-De Groot 2005) but not in another study that also reported no association between F_{eNO} and leptin or adiponectin (Komakula 2007).

Relationship between body mass index and airway hyperresponsiveness

Obese mice exhibit innate airway hyperresponsiveness regardless of whether the obesity is genetically or diet-induced (Shore 2008a). However, despite an increasing number of studies assessing the relationship between obesity and airway hyperresponsiveness in humans, the evidence remains inconsistent. This inconsistency is most likely related to differences in populations including variability in the sensitivity of AHR for asthma (Grassi 2001) and the definition of AHR including the use of symptomatic AHR.

Chinn *et al* reported an association of increasing AHR with increasing BMI in 11,277 20-44 yr old subjects from the ECRHS (Chinn 2002). A U-shaped association between BMI and incident AHR in men has been described in the Normative Ageing Study (Litonjua 2002). These findings were not reproduced in a Chilean sample utilising the ECRHS questionnaire (n=1132) where BMI was inversely associated with AHR overall and in females, and no association with diagnosed asthma was observed (Bustos 2005).

Negative findings have been reported by three epidemiological studies (Hancox 2005, Schachter 2001, King 2005). The two larger studies (Hancox 2005, Schachter 2001) reported no significant associations of BMI with airway responsiveness in populations where associations of high BMI with asthma and wheeze were present. In support of this, weight loss in obese subjects with asthma has been associated with improved lung function measures independent of changes in airway hyperresponsiveness, suggesting an effect of mass loading on the airways (Stenius-Aarniala 2000, Aaron 2004).

A relationship of BMI with symptomatic AHR has been reported by three studies, two of which evaluated 1141 (Sood 2005) and 861 adults (Sharma 2008) for respiratory symptoms and a Chinese study of 7,109 adults from families of subjects with asthma (Celedon 2001). Class I-III obesity was associated with AHR (Sharma 2008) however, Sood *et al* demonstrated that in females only, overweight and class I (BMI 30-34.9), but not class II and III (BMI 35-40 or 40+ respectively) were significantly associated with symptomatic AHR (Sood 2005). In the Chinese study, where the 95th percentile of BMI was 25.2 in males and 25.9 in females, a U-shaped relationship was observed in both genders.

Sood *et al*, demonstrated a weakly significant interaction (p=0.08) between asthma status and body mass index on the degree of airway responsiveness (Sood 2006b). This study in 1725 subjects evaluated for respiratory symptoms reported that BMI was a significant predictor of AHR, overall, and in subjects without asthma (n=1021), but not in subjects with asthma (n=704). This lack of association in subjects with asthma is supported by another small study (n=88) (Lessard 2008).

In small samples of subjects without asthma, AHR was significantly associated with obesity (Torchio 2009), but no difference in the maximal response to methacholine between obese and non obese subjects has been observed (Salome 2008). These data identify the importance of assessing obesity in relation to AHR in large samples of subjects without asthma in order to determine whether obesity alone is sufficient to alter airway responsiveness. As proposed by Salome *et al*, obesity may cause asthma not by increasing AHR, but by inducing symptoms in people with asymptomatic AHR due to

increased elastic loads as indicated by greater negative reactance after challenge (Salome 2008).

Effects of obesity on lung function

There is a general consensus in the literature that accumulation of fat around the thorax and abdomen affects lung mechanics (Parameswaran 2006, Weiss 2005, Shore 2008a, Tantisira 2001). As summarised by Parameswaran *et al*, obesity is also associated with decreased chest wall compliance, increased airway resistance and work of breathing, respiratory muscle dysfunction, ventilation perfusion inequality and alterations in gas exchange (Parameswaran 2006). The dyspnea observed in obese subjects maybe due to the increased work of breathing, deconditioning, diastolic dysfunction or mild pulmonary hypertension (Parameswaran 2006). Observed abnormalities include reductions in expiratory reserve volume (ERV) due to reductions in functional residual capacity (FRC), generally in the absence of effects on vital capacity or total lung capacity except in extreme obesity. Obesity may lead to dyspnea being diagnosed as asthma. The low FRC associated with obesity increases the sensation of dyspnea and may also enhance airway responsiveness by unloading of the airway smooth muscle to enhance shortening when activated by normal parasympathetic tone or bronchoconstricting agonists (Shore 2008a). Obese subjects also breathe at lower tidal volumes which leads to airway narrowing through reduced airway smooth muscle strain (Shore 2008a) and referred to as the latch hypothesis (Tantisira 2001, Weiss 2005). Shore proposes that additional mechanical factors may increase the likelihood for airway narrowing and AHR; Small airway closure in obese subjects may lead to reductions in partial pressure for oxygen in alveoli causing hypoxic pulmonary vasoconstriction, leading to higher pulmonary artery pressures and fluid cuffing around the airways which uncouples the airways from the parenchyma (Shore 2008a).

Most studies examining the effects of adiposity on lung function measures have used small and selected samples. Evidence form large samples including the Normative Aging Study (Lazarus 1997), the Coronary Artery Risk Development in Young Adults Study (Thyagarajan 2008), the Baltimore Longitudinal study of Aging (Harik-Khan

2001), The Survey of the Fitness of Australians (Lazarus 1998a), random population samples (Ochs-Balcom 2006, Bottai 2002), and a large general practice sample of older men free of cardiovascular disease and cancer (Wannamethee 2005), demonstrate that increased adiposity [BMI, waist circumference, waist-hip ratio, fat mass, and %body fat] has deleterious effects on FEV_1 and FVC. In contrast, the effects on the ratio of FEV_1 to FVC have been variously reported. FEV_1/FVC been shown to be positively associated with BMI and fat free mass (Lazarus 1997, Wannamethee 2005), to be unaffected by obesity (Schachter 2001, Jones 2006) and negatively associated with % body fat in females but not males (McLachlan 2007).

Lazarus *et al* identified the limitations of using BMI to determine the effects of adiposity when they reported opposing effects of fat mass and fat free mass on FVC (Lazarus 1998a). In contrast to the effects seen with obesity measures, fat free mass has been shown to be positively associated with lung function measures in other studies (Santana 2001, Wannamethee 2005, Sutherland 2008c).

Longitudinal studies have also identified important associations between adiposity and lung function. Weight gain (Chinn 2005, Chen 1993, Thyagarajan 2008) or becoming obese (Pistelli 2008) was associated with declines in FVC and FEV_1, whereas becoming non-obese has been associated with improved airflow limitation and FEV_1 and FVC measures (Pistelli 2008, De Lorenzo 2001). Interestingly, some studies have shown greater effects of adiposity on lung function in men than women (Harik-Khan 2001). The estimates of loss of FEV_1 per kg of weight gained ranged from 11-23 ml in men and 4-9 ml in women (Chinn 2005, Chen 1993, Wise 1998). These differences may represent in part mechanical effects related to differences in fat distribution, with fat generally distributed centrally in males whereas females may have central and/or peripheral distribution (Lemieux 1993, Stevens 2010). However, over time these losses are likely to have clinical significance and depending on the weight gain per year may approach tobacco related lung function losses (Xu 1994, Anthonisen 2002, James 2005).

Despite consistent effects of various obesity phenotypes on lung function, there is significant heterogeneity in the associations of obesity with asthma phenotypes which may be related to sample size and/or representativeness of the samples. Nevertheless it

will be important that future studies identify obesity related lung function impairments that promote airway narrowing concurrently with airway inflammation.

Is there a role for detection bias?

Studies reporting no significant associations of BMI with airway responsiveness in populations where associations of high BMI with asthma and wheeze were present suggest a role for detection bias in the association of asthma with obesity (Hancox 2005, Schachter 2001). Another study (Sin 2002) suggests that asthma might be overdiagnosed in the obese population, given that obese participants were at a lower risk for objectively measured airflow obstruction. In contrast a recent study has shown that over-diagnosis of asthma is just as likely in normal weight (29%) people as in the obese (32%) (Aaron 2008). Similarly, in a Chinese population, both extremes of the BMI distribution were associated with symptomatic AHR in men and women and both extremes of BMI were associated with asthma in women, and underweight was associated with asthma in men, (Celedon 2001) arguing against detection bias.

A pathological basis to the modification of asthma severity by obesity

Obesity may cause and exacerbate asthma symptoms via mechanical factors, but there are also pathophysiological reasons as to why this may be the case. Adipose tissue (AT) generates a chronic low-grade systemic inflammation, potentially induced by AT hypoxia (Trayhurn 2008) and contains cell types other than adipocytes including T lymphocytes, macrophages (ATMs), pre-adipocytes, fibroblasts, and endothelial cells. AT secretes a number of proinflammatory molecules including tumour necrosis factor (TNF)-alpha, interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1, also known as CC chemokine ligand-2) (Fantuzzi 2005, Lyon 2003). These adipokines have been implicated as active participants in the development of insulin resistance and the increased risk of cardiovascular disease associated with obesity (Spranger 2003, Cottam 2004, Lyon 2003, Rajala 2003, St-Pierre 2005).

A cardinal feature of obesity-induced inflammation that may contribute to asthma morbidity is the recruitment of immune cells, including T-lymphocytes (Kintscher 2008, Wu 2007) and bone marrow–derived macrophages (Weisberg 2003, Xu 2003) to AT.

T-lymphocyte infiltration into AT (Kintscher 2008, Wu 2007) may precede macrophage infiltration, (Kintscher 2008) through up-regulation of Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES)/also named CCL5 and its receptor (CCR5) on adipocytes and stromal/vascular cells of obese mice and humans. Increased RANTES expression in obesity may have importance for asthma severity because it is chemotactic for and activates eosinophils, and along with eotaxin and MCP-1 has been implicated in the allergic inflammation that occurs in asthma (Jia 1996, Luster 1998, Zietkowski 2008). Blockade of CCR5 leads to inhibition of airway inflammation (Chvatchko 2003, Suzaki 2008) and AHR in mouse models of asthma (Suzaki 2008).

ATMs are a fundamental component of adipose tissue even in lean states, and macrophages exist in different activation states with distinct properties (Martinez 2008). The precise pathophysiological and molecular mechanisms responsible for ATM recruitment remain unclear. AT expansion is associated with necrotic (rather than apoptotic) adipocyte death (Cinti 2005) and AT remodelling and the majority of ATMs expressing increased TNF-alpha and IL-6 form crown like structures surrounding dead adipocytes (West 2009, Cinti 2005, Strissel 2007). Macrophage specific genes are up-regulated in AT in obesity (Xu 2003) and gene expression analysis has shown that ATM are the primary sources of TNF-alpha and other pro-inflammatory molecules in adipose tissue (Weisberg 2003, Fain 2004). The number of ATMs correlate positively with BMI (Ortega Martinez de Victoria 2009, Weisberg 2003) and adipocyte size (Weisberg 2003) and weight loss reduces ATM content (Cancello 2005, Bruun 2006). Medical and surgical interventions to induce weight loss have also been associated with improved asthma outcomes (Eneli 2008, Haselkorn 2009) possibly through an associated reduction in ATMs. ATM accumulation also plays a major role in adipose tissue angiogenesis (Bourlier 2008, Pang 2008) and therefore AT expansion. The importance of ATM accumulation is shown by mouse model studies where insulin resistance develops subsequent to the infiltration of macrophages to adipose tissue (Kamei 2006, Kanda 2006, Nomiyama 2007).

In lean mice, “resident ATMs” uniformly express markers of an anti-inflammatory M2a alternative activation producing immunosuppressive factors, such as IL-10, IL-1RA, whereas obesity leads to specific migration of circulatory pro-inflammatory classically activated monocytes (M1) to ATM clusters (Lumeng 2008). Studies in mouse models of obesity and humans do not conclusively confer and the validity of the M1/M2a model in human ATMs has not been established. Two studies in humans have failed to identify ATM subtypes with a strict M1 or M2 bias. In one of these studies, ATMs showed a mixed expression of pro-and anti-inflammatory factors but with AT increase the ATMs expressed an M2 remodeling phenotype (Bourlier 2008). Similarly, Zeyda *et al* demonstrated that human ATMs were M2 like by surface marker expression but were also able to be induced into excessive pro-inflammatory mediator production (Zeyda 2007).

Although there are data supporting the notion that ATM-related inflammation contributes to the pathogenesis of obesity induced complications including insulin resistance, the links to asthma pathogenesis are less clear. Apart from its role in the generation of obesity related insulin resistance, (Cawthorn 2008, Ryden 2007) the pro-inflammatory cytokine TNF-alpha is also found in increased concentrations in asthmatic airways and is involved in the initiation of allergic asthmatic airway inflammation and the generation of airway hyper-responsiveness (Lampinen 2004, Babu 2004, Howarth 2005). TNF-alpha has been shown to be increased in severe corticosteroid dependent asthma (Howarth 2005). Furthermore, meta-analysis shows an association of TNF-alpha-308 gene promoter polymorphisms with asthma susceptibility with a dose response effect evident (Gao 2006) and the polymorphisms modify the association of obesity with asthma, particularly in non-atopic subjects (Castro-Giner 2009). It is possible that the association of obesity and asthma may be partly mediated through TNF-alpha, and RANTES and as such, an increase in severity of asthma may occur with increasing obesity. In addition, a relationship between obesity and asthma may be mediated by the obesity induced disruption of the AT secreted energy regulating hormones (adiponectin, leptin, and resistin) and evidence supporting this in mouse models has been reviewed (Shore 2007).

Adiponectin, which is reduced in obesity (Arita 1999), inhibits vascular smooth muscle proliferation (Ouchi 2003), augments skeletal muscle fatty acid oxidation (Yamauchi

2001) and protects against atherosclerosis (Kubota 2002, Yamauchi 2003). Adiponectin has anti-inflammatory properties (Fantuzzi 2008) and has been shown to reduce macrophage (Yokota 2000) and vascular TNF-alpha production (Yamauchi 2003) and increase Il-10 production (Kumada 2004). In relation to asthma, anti-inflammatory properties of adiponectin are also visible and exogenous adiponectin attenuated airway hyper-responsiveness and airway inflammation in a mouse model of asthma (Shore 2006). In this study antigen challenge resulted in the reduction of protective adiponectin levels.

Leptin is a satiety hormone that is found in markedly increased concentrations in obesity and regulates weight control in a central manner, via its cognate receptor in the hypothalamus (Friedman 1998). Leptin is considered to be pro-inflammatory as it has been demonstrated to modulate monocyte-macrophage function and the activation and proliferation of human T lymphocytes and induce the expression of monocyte cytokines IL-6 and TNF-alpha (Friedman 1998). However, as suggested by Shore (Shore 2007), leptin doesn't mediate the relationship between asthma and obesity, but that systemic manifestations of continued airway inflammation in asthmatic subjects lead to increased leptin release from adipocytes, consistent with findings from a mouse model of asthma where allergen challenge increased serum leptin, and leptin treatment augmented allergen induced AHR through a mechanism that did not involve amplification of Th2 mechanisms (Shore 2005b).

In humans, the evidence to date that these adipokines mediate the relationship between obesity and asthma is not overwhelming. These findings are contrary to those obtained in mouse models of asthma (Shore 2007) and may possibly reflect the inconsistencies observed in alternatively or classically activated ATM phenotypes in mouse models and humans. In NHANES III, leptin was higher in female subjects with current asthma than those without and although BMI was associated with asthma in females, this association remained unchanged after adjustment for leptin levels, suggesting that leptin is not mediating the relationship (Sood 2006a). Other epidemiological studies have also reported no independent associations of leptin and adiponectin with asthma (Sood 2008, Jartti 2009, Sutherland 2009b).

Evidence for an effect of obesity on asthma morbidity

While in-vivo and in-vitro evidence suggests that obesity may worsen asthma severity, the existing evidence to date on the effect of obesity on clinically important measures of asthma morbidity in humans is derived from almost entirely convenience samples and is inconsistent. At the time this research was conceived, no evidence from representative asthma samples was available, and since then, only two studies in addition to the work presented in Chapter 4 have been published and these did not assess morbidity in relation to measures of central adiposity (Taylor 2008, Accordini 2008). Other studies have sampled from Health Maintenance Organisations (Vortmann 2007, Mosen 2008), hospital asthma clinics (Lavoie 2006, The ENFUMOSA Study Group 2003, Wenzel 2007, Lessard 2008, van Veen 2008, Saint-Pierre 2006, Varraso 2005, Akerman 2004, Tavasoli 2005, Pelegrino 2007), hospital emergency departments (Thomson 2003, Rodrigo 2007), and asthma therapy randomised control trial populations (Dixon 2006, Stempel 2009, Peters-Golden 2006, Boulet 2007, Sutherland 2009a). Within these various study settings, studies have specifically sampled people with severe asthma (Vortmann 2007, van Veen 2008, Wenzel 2007, Thomson 2003, Rodrigo 2007).

Interpretation of the evidence across these studies is made difficult by inconsistencies in the use of asthma morbidity measures and also high selection bias operating in most samples. Hospital-based asthma clinics and emergency departments sample subjects with uncontrolled/severe asthma, while subjects with asthma recruited to randomised control trials are required to meet strict trial inclusion criteria and consequently unstable subjects, smokers and those with co-morbidities are generally excluded.

Evidence from representative asthma samples

Taylor *et al* (Taylor 2008) assessed the relationship between obesity, (calculated from self-reported measures of height and weight), and asthma morbidity in 3095 adults (≥18 years) with physician diagnosed asthma recruited to the four state sample of the Centres for Disease Control sponsored National Asthma Survey (n=5741, including children) in the USA (response 49%). Subjects reporting symptoms or asthma medication use within the previous 5 years, but not in the last 12 months but were classified as being in

remission and retained in the sample. The methodology used in this study may have underestimated the effects observed given the inclusion of subjects with remitting asthma and the use of self-reported measures of height and weight. Studies have reported both random and systematic errors in the use of self-reported height and weight, the predictors of which are gender specific (Stommel 2009, Villanueva 2001) and lead to underestimation of obesity through underreporting of weight and over-reporting of height (Stommel 2009, Nyholm 2007, Gorber 2007, Taylor 2006, Niedhammer 2000). The misclassification of BMI due to the use of self-reported measures has been reported to negate the positive association of obesity with asthma evident in men with measured height and weight (Santillan 2003). It is possible that self-reported measures may also affect the association of obesity with measures of asthma morbidity or severity. None of the following associations showed effect modification by gender.

Asthma severity

Obesity was significantly associated with persistent asthma (mild to severe GINA class II-IV) and severe persistent asthma (GINA IV) (OR 1.42, 1.05- 1.90), and inversely associated with asthma remission (0.56, 0.38- 0.82).

Symptoms and activity limitation

Obesity was significantly associated with continuous symptoms (1.66, 1.09- 2.54), and missing ≥ 3 work days (1.35, 1.01- 1.81).

Medication use

Obesity was significantly associated with the use of any short-acting beta-2 agonist [SABA (1.36, 1.06- 1.75)]; ICS (1.34, 1.01- 1.79) but not oral corticosteroid (OCS). Obesity was significantly associated with any controller medication according to GINA guidelines (1.37, 1.01-1.85).

Health services

A borderline association of obesity with ≥ 1 emergency department (ED) visit in the previous 12 months was demonstrated, but not with one or more urgent visit to primary care providers or hospital admissions.

No dose-response effect of BMI was seen in this large sample, with the exception of one outcome; overweight was also inversely associated with asthma remission (Taylor 2008).

The socioeconomic burden of asthma associated with obesity was identified in 1152 subjects with doctor confirmed asthma plus at least one symptom, asthma attack or asthma medication use in previous year in the ECRHS-II (1999-2002) (Accordini 2008). Economic burden in the previous 12 months was defined by the number of lost leisure and working days, and hospital services (ED visits and number nights admitted) which are also measures of asthma control. Burden was categorised into None; light (per month, ≤ 12 lost working days and/or ≤ 3 days with limited leisure activities but no hospital services); and heavy burden (per month, > 12 lost working days and/or > 3 days with limited leisure activities and/or ≥ one hospital services). In this study, obesity was independently associated with both light (2.2, 1.2-4.0) and heavy burden (2.8, 1.5-5.1) in the fully adjusted model.

Evidence from Health Maintenance Organisation populations

Vortmann and Eisner prospectively followed 843 adults with severe asthma for up to 4.3 yrs, (median 1.7, 53% interview completion rate) where participants were identified and interviewed after hospitalisation for asthma in Californian Kaiser Permanente (KP) hospitals, using the primary or secondary International Classification of Diseases (ICD)-9 discharge diagnosis code. ICD-9 codes were used to exclude other respiratory diseases and doctor diagnosed asthma was confirmed at interview (Vortmann 2007). Mosen *et al* generated a random sample of 1600 adults (aged 35+ years) from 9420 KP members (Colorado and Oregon) with persistent asthma, identified by at least one asthma related medical encounter and a 6 month supply of asthma medication dispensed in the previous 2 years. A questionnaire was completed by 85% (n=1317) leaving 1113 study subject after exclusion of 204 subjects who denied having asthma (Mosen 2008).

Asthma control

Poor asthma control, (identified by the presence two or more of four control problems on the Asthma Therapy Assessment Questionnaire) was significantly associated with obesity (Mosen 2008).

Asthma specific quality of life

The mean asthma specific quality of life score (Marks Asthma Quality of Life Questionnaire, AQLQ) and generic physical health status scores (SF-12) were significantly worse in obese subjects compared to normal weight subjects (Vortmann 2007) and consistent with this, a significantly higher number of restricted activity days in the previous month were also observed in obese subjects. The worsening of the AQLQ score and increase in restricted activity days were strongly mediated by Center for Epidemiologic Studies Depression (CES-D) scale scores and perceived asthma control scores (Vortmann 2007). Similarly, obesity was associated with poor asthma-specific quality of life, overall and in the domains of symptoms, emotions, activity and environment, as measured by a Juniper mini-Asthma Quality of Life Questionnaire score of < 3.9 (Mosen 2008).

Asthma severity and symptoms

Vortmann and Eisner, reported that obesity was associated with a significant risk for daily/near daily asthma symptoms, but demonstrated no clear association of obesity with the severity of asthma scores derived from a 13 item instrument assessing systemic CS use, asthma therapies, a history of asthma hospitalisations and intubations, and symptom frequency (Vortmann 2007).

Health service utilisation

Obesity was associated with an increased risk of asthma-related hospitalizations (Mosen 2008) in contrast to findings reporting no clear association of obesity with ED visits or hospitalisations (Vortmann 2007).

Evidence from hospital asthma clinics

The number of participants in these studies ranged from 88 (Lessard 2008) to 800 (Wenzel 2007), and few sample sizes exceeded 300 (Lavoie 2006, Saint-Pierre 2006, Varraso 2005). Females were prevalent in most samples (50-84%) and most samples were non-smokers with few exceptions (Lavoie 2006, Saint-Pierre 2006, Pelegrino 2007). Five studies analysed the association of severity with obesity with obesity as the outcome (Pelegrino 2007, Akerman 2004, Tavasoli 2005, The ENFUMOSA Study Group 2003, Wenzel 2007).

Asthma control

Using the asthma control questionnaire, obesity (BMI $\geq$ 30) was associated with significantly worse asthma control which was not modified by sex (Lavoie 2006). Similar findings were reported when obesity was classified by BMI, and WC but not WHR (Lessard 2008). When asthma control was defined in a longitudinal study according to Canadian guidelines as acceptable or unacceptable, Markov modelling demonstrated that subjects with a BMI $\geq$ 25 were less likely to transition form an unacceptable to an acceptable level of control, although the effects of smoking were not controlled for (Saint-Pierre 2006).

Asthma Quality of Life

Obesity was associated with significant reductions in Juniper AQLQ total scores as well as in dimensions of activity limitation and environmental triggers and males experienced sharper declines in these scores than females (Lavoie 2006).

Asthma severity

BMI was not related to GINA classified asthma severity (Lavoie 2006), however, the clinical severity score, ranging from 0-7 (based on frequency of asthma attacks, presence of persistent symptoms between attacks and hospitalisations in the past year) was positively related to BMI in women only and young age at menarche strengthened this association (Varraso 2005).

Data from two studies of non-smoking subjects with asthma (Akerman 2004, Tavasoli 2005) reported significantly increased odds ratios of obesity associated with mild,

moderate and severe persistent asthma compared with the mild intermittent group (as classified by 1997 NHLBI and 2004 GINA guidelines) which is in contrast to no relationship reported between asthma severity and BMI (Pelegrino 2007). Studies specifically investigating the severe asthma phenotype report conflicting findings. In the Severe Asthma Research Program (Wenzel 2007) no differences in obesity rates were reported between moderate and severe subjects with asthma, whereas female subjects with severe asthma had a significantly higher unadjusted BMI those controlled on low dose ICS (The ENFUMOSA Study Group 2003).

Lung function and airway inflammation

Lessard *et al* reported that airway responsiveness to methacholine and mean percentage of predicted FEV_1, FVC, and FEV_1/FVC ratios and were not significantly different between those with a BMI < 25 and a BMI > 30 (Lessard 2008). Both BMI groups reported similar levels of wheezing, chest tightness, dyspnea and phlegm production when FEV_1 had fallen 20% during the methacholine challenge suggesting that the poor control demonstrated in the obese group in this study was not due to symptom over-perception. Total lung capacity (TLC), residual volume (RV), ERV were significantly inversely associated with BMI, WHR and WC, and inspiratory capacity (IC) showed a significant positive association with BMI and WC (Lessard 2008). In subjects with difficult to treat asthma [treated with at least 1600mcg/day ICS or equivalent and long acting beta-2 agonist (LABA)], obese subjects had a significantly higher FEV_1% predicted, but not FEV_1/FVC compared with non-obese patients (BMI <30) and FRC/TLC % predicted was significantly inversely associated with BMI (van Veen 2008).

Lessard *et al* induced sputum samples in only 51 of 88 study participants and demonstrated that sputum eosinophil, neutrophil, macrophage and lymphocyte counts were not significantly different, between those with a BMI <25 and a BM> 30, but sputum eosinophils showed a significant inverse correlation with WC and the correlation with BMI was of borderline significance. Systemic inflammatory markers including serum C-reactive protein, positively correlated with all obesity measures and fibrinogen correlated with BMI and WC only (Lessard 2008). Similarly, BMI was inversely related with sputum eosinophils and F_{eNO} (van Veen 2008).

Co-morbid conditions

Obese patients had significantly increased risks for gastro-oesophageal reflux disease and sleep apnoea (van Veen 2008). This, taken together with the bronchial and systemic inflammatory characteristics and the specific pattern of lung function impairments suggest other factors than airway inflammation alone explain the relationship between obesity and asthma severity.

Evidence from emergency department settings

The relationship between obesity and acute asthma has been assessed in two studies; a retrospective analysis of 572 people aged 18-54 years, attending 26 North American emergency departments over a two week period as part of the Multicentre Airway Research Collaboration (Thomson 2003), and a second prospective study of 426 people age 18-50 years attending a Uruguayan tertiary care hospital (Rodrigo 2007).

In the North American study, 44% of subjects were obese, and females were over-represented (77%) (Thomson 2003). BMI groups were similar in terms of acute or chronic asthma severity measures with few gender specific exceptions: In males, obese subjects were significantly more likely to report use of ICS in the previous four weeks, but less likely to be admitted to hospital. In females, obese subjects were significantly more likely than their normal BMI counterparts to report a duration of symptoms prior to attendance in excess of 24 hours. Peak expiratory flow (PEF) % predicted at presentation and response to acute treatment were similar across BMI groups and the risk of hospital admission in obese subjects was not significantly increased compared to normal weight subjects.

Rodrigo *et al* reported that 38% of subjects were at least overweight (BMI> 25.0) and females were over-represented (73%) (Rodrigo 2007). Compared with those with a BMI <24.9, subjects with a BMI ≥ 25.0 demonstrated a longer duration of ED treatment and increased admission rate but not worse PEF recovery. Of those subjects admitted, those with a BMI> 25.0 had higher wheezing scores despite similar FEV_1 and PEF % predicted. Compared with normal weight subjects, overweight/obese males and females

demonstrated significantly higher PEF % predicted despite severe self-rated dyspnea, and higher rates of ICS and theophylline use in the previous 7 days.

Evidence from randomised control trial (RCT) settings

Five studies conducted post-hoc analyses of subjects with asthma recruited to RCTs, where current smoking was an exclusion criterion for all studies. These generally large studies have permitted an evaluation of the effect of obesity on treatment response and include:

1) 3,073 moderately severe asthmatic adults enrolled in 4 RCTs comparing treatment with montelukast (n= 1,439), beclomethasone (n=894) and placebo (n= 740) (Peters-Golden 2006).

2) 1256 subjects with mild-moderate persistent asthma derived from ten Asthma Clinical Research Network clinical trials of 8-48 weeks in duration (Sutherland 2009a).

3) 473 African American subjects aged ≥12 years of age who were symptomatic on 100mcg fluticasone proprionate (FP) and stepped up to 4-week open-label FP 250 mcg BID (Stempel 2009).

4) 1242 moderately persistent uncontrolled asthmatic patients (according to GINA) not currently using ICS who were enrolled in five clinical trials comparing 12 weeks treatment with FP and FP + salmeterol (Boulet 2007).

5) 488 subjects with mild to moderate persistent asthma sub-optimally controlled on their current therapy enrolled in a RCT of low dose theophylline add on therapy (Dixon 2006).

In two studies obesity was sub-classified as class I: 30.0-34.9, II:35.0-39.9, III: ≥ 40.0 (Stempel 2009, Boulet 2007).

Asthma control

These studies generally suggest a reduction in asthma control associated with obesity. Using the Juniper Asthma Control Questionnaire (ACQ), obese subjects reported significantly worse control compared to those of normal weight (Dixon 2006) which is in contrast to no significant changes in the Mini ACQ scores per unit increase in BMI (Sutherland 2009a). Control was also defined as the number of asthma control days (ACD, a day with ≤2 puffs beta-2 agonist, no night time awakenings, and no asthma

attacks requiring primary care or ED visit, hospitalisation or oral steroid use) as a percentage of total days on treatment (Peters-Golden 2006). In this study in placebo treated subjects, overweight/obese subjects (pooled because of similar rates of ACD) demonstrated a significantly lower % ACD (25%) than normal BMI subjects (34%) with no effect modification by sex and this amounted to an extra month per year of asthma control for the normal weight subjects (Peters-Golden 2006). Boulet *et al* defined achievement of asthma control as having ≥2 of the following: Symptoms no more than 2 days with score of >1; no more than 2 days rescue SABA/week, ≥ 80% predicted morning PEF every day; and never any night time wakening, emergency visits, or exacerbations (Boulet 2007). For both treatments, compared with severely obese (class III), all other BMI groups including obesity class I and II, were significantly more likely to achieve asthma control at 12 weeks with odds ratios in the order of 2-3. However there was a significant interaction of atopic status and BMI, and in non-atopic subjects, no difference was observed in achieving control across BMI categories. In atopic subjects, only the underweight group and class II obese subjects had significant increased likelihood of achieving asthma control, compared with obesity class III. Sex specific analyses were not possible due to the small number of men.

Asthma specific quality of life

Obese subjects have demonstrated significant but clinically modest differences in AQLQ (0.29 lower) scores compared with normal weight subjects (Sutherland 2009a).

Lung function, airway inflammation and symptoms

Consistent with their findings of the relationship between outcomes and BMI as a continuous variable, Sutherland reported that compared with normal weight subjects, obese subjects demonstrated small significant differences in % predicted FEV_1 (2% reduction), provocative concentration of methacholine producing a 20% decline in FEV_1 (PC_{20} methacholine, 0.25 mg/ml increase), F_{eNO} (2.5 ppb lower), and daily rescue albuterol use (increase in 0.19 puffs), regarded as being of limited clinical importance (Sutherland 2009a). This study suggested clinically meaningful worsening of impairment did not occur with increasing BMI (Sutherland 2009a). Similarly, reductions in baseline FEV_1 (-0.47%) and FVC (-0.40%) and significantly higher rescue medication in obese subjects have been reported per unit increase of BMI by Dixon *et al* despite no observed differences between obese and normal weight subjects in levels of

airflow obstruction, bronchodilator responsiveness or bother from dyspnea, cough or wheeze (Dixon 2006). Stempel *et al* demonstrated that the baseline morning and evening PEF showed inverse J-curve distribution across BMI categories (Obesity was sub-classified as class I: 30.0-34.9, II:35.0-39.9, III: ≥ 40.0), in the absence of differences in screening symptom scores and rescue albuterol use (Stempel 2009).

Asthma exacerbations

The study by Stempel *et al* suggests an increased asthma exacerbation rate (39%) in subjects with class III obesity, compared with 16-21% in the lower BMI categories (Stempel 2009).

Co-morbid conditions

The burden of gastro-oesophageal reflux disease (GERD) was significantly higher in obese subjects compared with normal weight subjects (Dixon 2006).

Response to treatment

Peters-Golden *et al* demonstrated that in terms of % ACD, with increasing BMI (continuous and categorical), the response to ICS decreased, while the response to monteleukast remained stable (Peters-Golden 2006). The placebo response for all end points including change in FEV_1, and the % of nights awake were generally lower with increasing BMI category but not significantly so (Peters-Golden 2006). After 4 weeks of FP treatment, Stempel *et al* (Stempel 2009) reported no variation by BMI in the improvement in FEV_1, symptom scores and night time awakenings, however, change in PEF was lowest for the lowest and highest BMI categories.

Similarly, a differential response of overweight/obese subjects to treatment was reported by Sutherland *et al* in only few outcomes (Sutherland 2009a); Overweight/obese subjects in the ICS treatment arms demonstrated a smaller mean reduction in F_{eNO} than normal BMI subjects of borderline significance (3.6 vs 6.5 ppb, p=0.06). Overweight/obese subjects in the ICS + LABA treatment arms showed significantly smaller improvements in absolute FEV_1 (80ml) and FEV_1/FVC (1.7%). However, no other differences in lung function, and inflammatory and clinical, outcomes (including asthma exacerbations) were observed across BMI categories in

either the ICS or ICS + LABA treatment arms. No differential response to treatment across BMI categories were observed with montelukast. In placebo treated subjects, no differences were observed in any study outcomes between lean and overweight/obese subjects over the treatment period (Sutherland 2009a).

Although the evidence of reduced responsiveness to ICS is not strong, it is important to consider that no recent history of smoking (6-12 months) was an inclusion criteria for these RCTs. Corticosteroid insensitivity has been described in people with asthma who smoke (Lazarus 2007, Tomlinson 2005, Chalmers 2002). Considering that smoking rates are similar across BMI categories in a representative asthma sample, (Taylor 2008) it is therefore possible that a greater reduction in clinical efficacy of ICS may occur in community based obese smokers with asthma. Furthermore, an *in-vitro* study investigated molecular mechanisms by which glucocorticosteroid insensitivity may occur (Sutherland 2008a). In this study, the ability of glucocorticosteroids to inhibit pro-inflammatory gene expression by negatively regulating signal pathways was reduced in peripheral blood mononuclear cells and bronchoalveolar lavage cells from overweight/obese subjects compared to lean subjects with asthma (Sutherland 2008a).

Is there a common pathway linking obesity with asthma and cardiovascular disease?

The obesity related inflammatory milieu is an established causal factor in the development of insulin resistance, diabetes and cardiovascular disease (Lyon 2003, Fantuzzi 2005). Based upon the epidemiological evidence that obesity is a risk factor for asthma it is possible that asthma and cardiovascular disease share a developmental pathway that includes insulin resistance (Thuesen 2009, Husemoen 2008). Systemic inflammation may also occur in asthma. In epidemiological studies, elevated C-reactive protein (CRP) is associated with current asthma (Arif 2007) and non-atopic asthma, but not atopic asthma (Olafsdottir 2005, Butland 2008). However, after adjustment for confounders including obesity, as CRP is under transcriptional control by IL-6 (Pepys 2003), these associations did not consistently persist (Butland 2008, Jartti 2009).

Sutherland *et al* suggest that systemic and airway inflammation operate independently of each another (Sutherland 2008b). In this study that was underpowered to detect interactions, the increase in sputum supernatant levels of IL-5, and TNF-alpha observed in obese subjects were higher (but not statistically significant) in those with asthma compared to those without, whereas the relative increases in CRP were similar.

Questions which need addressing include whether airway inflammation and possibly systemic inflammation that occurs in asthma is related to CVD and diabetes and furthermore, whether this relationship is strengthened by considering the contribution of obesity related inflammation. Although ventilatory function has shown to be associated with insulin resistance in men (Lazarus 1998b, Lazarus 1998c) there is little and conflicting evidence of the relationship of asthma to diabetes. (Ford 2004, Rana 2004) Cross-sectional (Dogra 2007) and longitudinal epidemiological studies (Iribarren 2004, Onufrak 2007, Onufrak 2008, Schanen 2005) have inconsistently identified an association of asthma with coronary heart disease and stroke. Few studies have considered the role asthma phenotype. The studies by Onufrak in the Atherosclerosis Risk in Communities Study have demonstrated an association with adult onset asthma which may reflect non-atopic asthma. In a very large sample of 74,342 subjects in Canadian Community Health Survey, Dogra *et al* demonstrated that in male subjects with asthma, non-atopic subjects were significantly more likely to report CVD events than atopic subjects. Interestingly, in relation to asthma phenotype, airway hyperresponsiveness has been shown to be associated with increased carotid intima-media thickness in men. (Zureik 2004) A direct relationship of asthma with CVD may however be related to cardiotoxic effects of beta-2 adrenergic agonists (Salpeter 2004). Systemic anaphylaxis, which although rare, may also lead to cardiac manifestations including arrhythmias, and infarctions (Triggiani 2008).

Summary of the review of the literature

The review of the literature has identified a number of problems which serve to limit our understanding of the relationship between weight and asthma and the conclusions we draw that can substantially inform asthma policy and management guidelines. An understanding of the relationship between obesity and asthma is limited by the inadequate consideration of the nuances and complexity of asthma and obesity phenotypes. The value of an examination of the role of phenotype is that it may identify target groups for prevention or intervention in order to reduce the burden of morbidity in people with asthma.

The lack of a gold standard test for asthma is likely to be contributing to under-diagnosis of asthma in epidemiological studies and this undiagnosed phenotype is as important to assess in relation to obesity as other measures such as lung function, AHR, and measures of inflammation including fraction of exhaled nitric oxide and granulocytes. With the exception of the observed effects on lung function, there is significant heterogeneity in the described associations of obesity with these asthma phenotypes and sample size and/or representativeness of the samples have been inadequate in a number of these studies. There is a very limited understanding of the association of obesity phenotypes with self-reported asthma or specific asthma phenotypes. Irrespective of a possible causative association between obesity and asthma, there remains little information available on the effect of obesity phenotypes on morbidity in representative asthma populations. At the time this PhD work was conceived, all available evidence was derived from a few selected samples of subjects with severe asthma. These small studies taken together with additional evidence since that time in mostly severe asthma, suggest a deleterious effect on asthma control.

The few studies addressing the contribution of asthma related inflammation to obesity related outcomes including diabetes and cardiovascular disease report an inconsistent increased risk of macrovascular events associated with asthma. These studies have failed to consider the role of asthma phenotype or considered a relationship mediated by cardiotoxic beta-2 adrenergic agonists.

Chapter 3. Methods

Sample population

The North West Adelaide Health Cohort Study (NWAHS) is a representative biomedical population study of people aged eighteen years or older living in the north western suburbs of Adelaide, South Australia (regional population 0.6 million) and the methods have been previously described (Grant 2006, Grant 2008). The aims of the study were to provide estimates of chronic conditions and associated risk factors and quality of life for the northern and western regions of Adelaide.

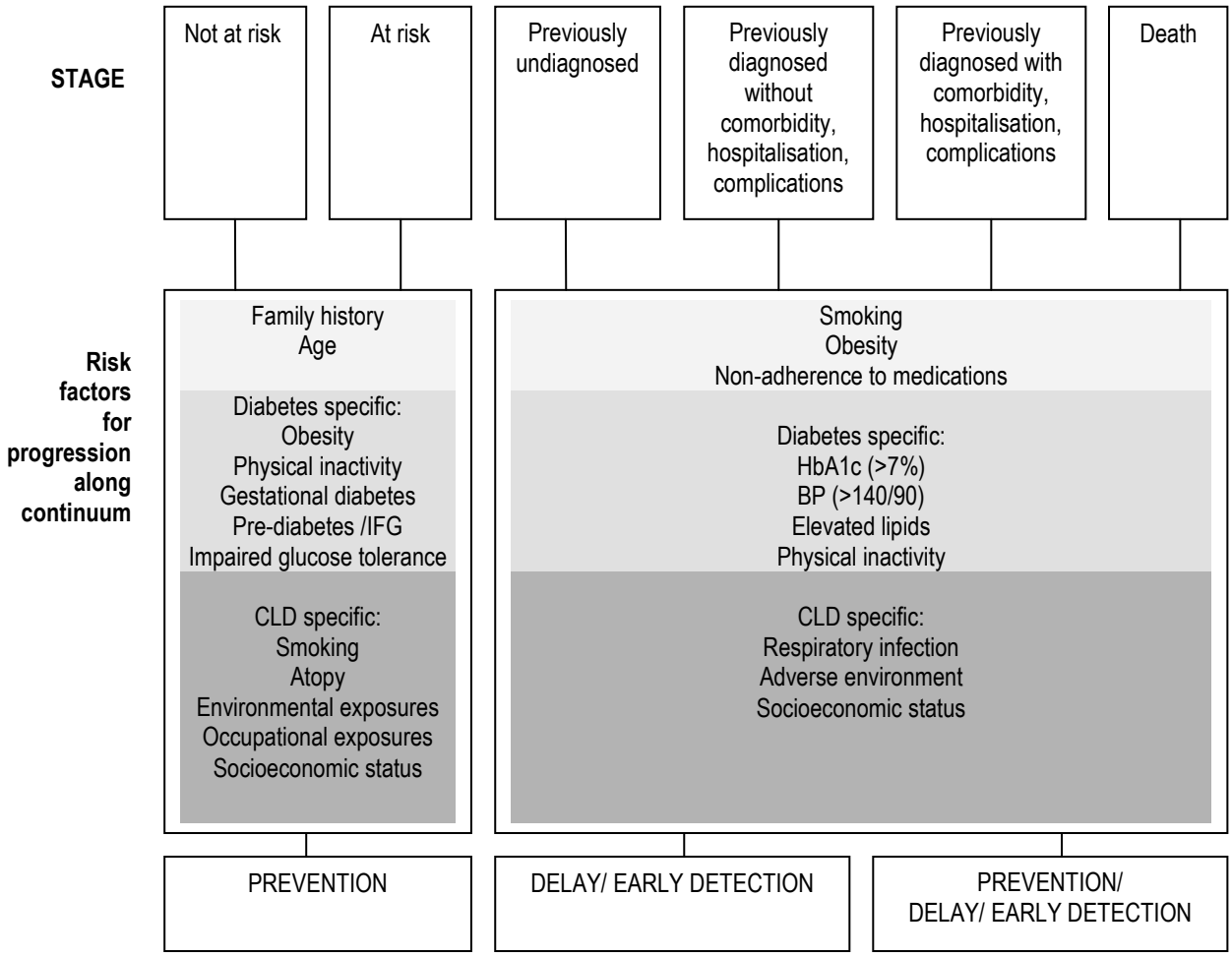
Specifically the study aimed to segment a large representative population sample according to stage of disease, as shown in Figure 1. The concept of the disease continuum acknowledges people with chronic conditions are not a homogenous group. This permits the identification of each segment's characteristics and change over time and targeted interventions aimed at these groups. Theoretically this will lead to better health outcomes and more efficient use of resources.

Study method

Households selected at random from the electronic *White Pages* telephone directory were eligible for inclusion in the study. In each household the person aged 18 years or older who was last to have a birthday was asked to participate in the telephone interview and recruited to a clinical assessment. There was no replacement for refusal, or for non-response after up to ten call-backs.

Telephone interviews by trained health interviewers investigated self-reported health status (including asthma), smoking status and demographic variables. A questionnaire was then sent to each participant for self-completion, comprising items on risk factor prevalence, including smoking, alcohol consumption, recreational physical activity levels, health-related quality of life using the Medical Outcomes Study Short Form-36 (SF-36) questionnaire (Ware 1993) and more detailed demographic information.

Figure 1. Chronic Disease continuum



Information on self-reported health conditions including asthma, emphysema, diabetes, stroke, myocardial infarction and angina was also collected. Current confirmed asthma (CA) was assessed by a positive response to all three following questions: 1) “Have you ever had asthma?”, 2) “Was your asthma confirmed by a doctor?”, and 3) “Do you still have asthma?” Spirometry was conducted in two hospital-based clinics (Microlab 3300 spirometer, Micro Medical LTD, Kent, UK) according to American Thoracic Society criteria. (American Thoracic Society 1987). Each subject performed at least three acceptable and reproducible FVC manoeuvres. Significant bronchodilator reversibility (SBR) was defined as the increase in forced expiratory volume in one second (FEV_1) following inhalation of 400mcg salbutamol, of at least 9% of predicted FEV_1, (Dales 1988, Calverley 2003) or 12% of the baseline FEV_1 (providing the increase exceeded 200ml). Airway obstruction was defined as a post-bronchodilator FEV_1 to forced vital capacity ratio less than 0.70. Skin prick testing was conducted to the following allergens: rye grass, cat dander, house dust mite, *Alternaria*, feather, cockroach. Lengths and widths of wheals were measured after 15 minutes. The skin test was considered valid if the positive control (histamine) wheal was greater than 2 mm in diameter. An allergen specific skin test response was considered positive if the mean of the length and width of wheal was at least 3mm greater than the negative control response. Atopy was defined as having at least one positive reaction to this panel of allergens.

Medical assessment of participants included measurements of blood pressure, lipids, fasting plasma glucose, Haemoglobin A1c, height (measured to the nearest 0.5 cm using a stadiometer), weight (measured to the nearest 0.1 kg in light clothing and without shoes using standard digital scales), waist circumference (measured at minimal inspiration to the nearest 0.1cm with an inelastic tape, midway between the last rib and iliac crest), and hip (measured at the level of the maximum posterior extension of the buttocks).

Body mass index, waist circumference (WC) in centimetres and waist to hip ratio (WHR) were categorised according to the following gender specific international criteria:

Table 1. Obesity Measures Defined

	Body Mass Index (kg/m^2) (World Health Organization 1997)	*Waist Circumference (cm)* (World Health Organization 1997)	*Waist to hip ratio* (National Heart Lung and Blood Institute 1998)
Normal/ Not at risk	18.5-24.9	M: ≤ 94 F: ≤ 80	M: ≤ 0.9 F: ≤ 0.8
Overweight/ Risk category 1	25.0-29.9	M: 95-101 F: 80-87	M: 0.91-0.99 F:0.81-0.84
Obese/ Risk category 2*	≥ 30.0	M: ≥102 F: ≥88	M:≥1.0 F: ≥ 0.85

* obesity is further sub-classified as class I: BMI 30.0-34.9; class II: BMI 35.0-39.9; class III: BMI ≥ 40.0

Chapter 4

Spirometric criteria for asthma: Adding further evidence to the debate

Sarah L. Appleton, Robert J. Adams, David H. Wilson, Anne W. Taylor [a], Richard E. Ruffin, on behalf of the North West Adelaide Cohort Health Study Team.

The Health Observatory, Discipline of Medicine, University of Adelaide, and the [a]Population Research and Outcomes Study Unit, South Australian Department of Health, Adelaide, South Australia.

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The lack of a gold standard test for asthma contributes to difficulties in diagnosing asthma and therefore to the problem of under-diagnosis of asthma. Although guidelines recommend the demonstration of a significant post-bronchodilator response in FEV_1 or peak expiratory flow (Global Initiative for Asthma 2008), the recommended criteria are variable including 12% to 15% of baseline FEV_1, 9% of the predicted value and an absolute volume of 400ml. It is unknown if these criteria perform equally in terms of the numbers of people identified and the characteristics of those people.

This paper was chosen as *Editor's Choice* article and made significant contributions to the literature by identifying for the first time that the prevalence of undiagnosed asthma (defined as significant bronchodilator reversibility in the absence of doctor diagnosed asthma) was variable (1.6% to 4.5%) depending on the criteria specified. Asthma could therefore be misclassified depending on the reversibility criterion used. All reversibility criteria identified subjects with highly probable asthma given the demonstrated symptom burden and lung function impairments. Secondly, the reversibility criteria were associated with different socio-demographic factors and the 9% of predicted criterion was least biased particularly in terms of age and sex. This had also not been previously demonstrated but has implications for 1) reducing the avoidable burden of undiagnosed asthma in populations by improved identification and 2) improving the robustness of asthma risk estimates associated with obesity and other important explanatory factors.

Appleton, S., Adams, R., Wilson, D., Taylor, A. & Ruffin, R. (2005) Spirometric criteria for asthma: Adding further evidence to the debate.
The Journal of Allergy and Clinical Immunology, v. 116(5), pp. 976-982

Chapter 5

Central obesity is associated with nonatopic but not atopic asthma in a representative population sample

Sarah L. Appleton, Robert J. Adams, David H. Wilson, Anne W. Taylor [a], Richard E. Ruffin, on behalf of the North West Adelaide Health Study Team.

The Health Observatory, Discipline of Medicine, University of Adelaide, and the [a]Population Research and Outcomes Study Unit, South Australian Department of Health, Adelaide, South Australia

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Having optimised the identification of undiagnosed asthma in the previous chapter this work attempted to determine the robustness of the association of obesity with asthma when phenotypes were considered. At the time that this work was conceived, the relationship of asthma to alternative obesity phenotypes including waist circumference and waist to hip ratio had been reported in few non-representative samples with conflicting results (Camargo 1999, Bustos 2005, Kronander 2004). Similarly, few studies had investigated the relationship of obesity with asthma phenotype but these inconsistently reported no modifying effect of atopy (Ronmark 2005, Schachter 2001, Kronander 2004).

This paper made a significant contribution to the literature by identifying an association of central measures of obesity with asthma in a representative population sample. In this study, generalised (BMI) and central obesity were associated with all asthma in females only. However, when atopic status was considered, central obesity measures were consistently associated with non-atopic asthma only, in both males and females. In males, a high BMI which is likely to be distributed centrally (Lemieux 1993, Stevens 2010) was also associated with non-atopic asthma. In females, generalised obesity which is likely to reflect a central and/or a peripheral distribution (Lemieux 1993, Stevens 2010) was associated only with atopic asthma.

This suggests a different pathophysiological background for the relationship between obesity and atopic and non-atopic asthma. According to our findings, (central) obesity may lead to non-atopic asthma along a pathway possibly involving innate mechanisms (Wood 2009a) and recent evidence suggests that obesity may lead to atopic asthma via a pathway including insulin resistance (Thuesen 2009, Husemoen 2008). Central fat distribution may represent a different inflammatory profile to peripheral fat and this may also have an effect on the asthma phenotype exhibited. Alternatively, the association of central adiposity and non-atopic asthma may also reflect an effect on airway mechanics. Further work in this area using more detailed asthma phenotyping is clearly required.

From a clinical point of view, these findings suggest that asthma should be considered in non-atopic, older, centrally obese, symptomatic individuals.

Appleton, S., Adams, R., Wilson, D., Taylor, A. & Ruffin, R. (2006) Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *The Journal of Allergy and Clinical Immunology, v. 118(6), pp. 1284-1291*

Chapter 6

Sex differences in asthma morbidity associated with obesity in a representative population sample

Sarah L. Appleton, David H. Wilson, Graeme Tucker [a], Richard E. Ruffin, Anne W. Taylor [b], Robert J. Adams.

The Health Observatory, Discipline of Medicine, University of Adelaide, [a]Epidemiology Branch, South Australian Department of Health, and the [b]Population Research and Outcomes Study Unit, South Australian Department of Health, Adelaide, South Australia.

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The North West Adelaide Health Study was funded by The University of Adelaide and the South Australian Department of Health

Regardless of the existence of a causal association of obesity and asthma, it is important to establish if obesity adds to the burden of asthma morbidity. When this PhD work was conceived there was no evidence of the effects of obesity on asthma morbidity in representative samples of asthma. Only limited evidence was available that was derived largely from severe asthma samples in emergency department and asthma outpatient clinic settings (Lavoie 2006, Thomson 2003, Varraso 2005). Additional findings since this time have been reported from settings where selection bias is also likely to operate including randomised controlled trials, and managed care organisations and severe asthma samples. Other than the present findings, the only evidence derived from a randomly selected population sample showed that in 3095 adults from the National Asthma Survey in the United States, obesity (derived from self-reported height and weight) was associated with several measures of asthma severity including continuous symptoms, days lost from work, and use of short acting beta-2 agonists and inhaled corticosteroids (Taylor 2008). Another limitation of the studies to date is that other than a small study in 88 subjects recruited from an asthma clinic (Lessard 2008), all studies to date have confined their assessment of the effect of obesity on morbidity to a limited obesity phenotype, i.e. BMI.

Although our asthma sample was significantly smaller than the National Asthma Survey sample, (Taylor 2008) a strength of the NWAHS is the availability of unbiased measured levels of height, weight (and waist circumference) compared with self-reported measures and their associated random and systematic errors, (Stommel 2009, Gorber 2007) the predictors of which are gender specific (Villanueva 2001). The following paper shows that the burden of obesity-related asthma morbidity occurred largely in males and not females although the reduction in quality of life and increased primary care visits were not sex-specific. Deleterious effects were observed with both measures of generalised and central obesity, however, only central obesity was associated with persistent airways obstruction in males. Although the direction of the association cannot be identified, our findings suggest that healthy weight maintenance is an important component of asthma management in order to reduce avoidable morbidity. This is supported by a recent review reporting improvement in asthma outcomes following weight loss (Eneli 2008).

Appleton, S., Wilson, D., Tucker, G., Ruffin, R., Taylor, A. & Adams, R. (2008) Sex differences in asthma morbidity associated with obesity in a representative population sample. *The Journal of Allergy and Clinical Immunology, v. 121(5), pp. 1285-1287.e1*

Chapter 7

Asthma is associated with cardiovascular disease in a representative population sample

Sarah L. Appleton, Richard E. Ruffin, David H. Wilson, Anne W. Taylor [a], Robert J. Adams.

The Health Observatory, Discipline of Medicine, University of Adelaide, and the [a]Population Research and Outcomes Study Unit, South Australian Department of Health, Adelaide, South Australia.

Obesity Research and Clinical Practice 2008; 2:91-9

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Asthma and cardiovascular disease may share a developmental pathway that includes obesity and insulin resistance (Thuesen 2009). Systemic manifestations of obesity including diabetes and CVD may be augmented by asthma-related airway and systemic inflammation. Although ventilatory function has shown to be associated with insulin resistance in men (Lazarus 1998b, Lazarus 1998c) there is little and conflicting evidence of the relationship of asthma to diabetes. (Ford 2004, Rana 2004) Cross-sectional (Dogra 2007) and longitudinal epidemiological studies (Iribarren 2004, Onufrak 2007, Onufrak 2008, Schanen 2005) have inconsistently identified an association of asthma with coronary heart disease and stroke.

This study identified a positive cross-sectional association of asthma with CVD/stroke events, but no association with diabetes or cardiovascular risk factors (including lipids, hypertension or the metabolic syndrome) was observed. No modifying effect of obesity was observed in these associations which has not been formally tested and reported before, nor were traditional CVD risk factors independently associated with CVD/stroke events. Together, this suggests that events may be related to some aspect of asthma pathology and that the relationship of macrovascular events to atopy and the cardiotoxic effects of beta-2 agonists warrants examination.

Appleton, S., Ruffin, R., Wilson, D., Taylor, A. & Adams, R. (2008) Asthma is associated with cardiovascular disease in a representative population sample.
Obesity Research and Clinical Practice, v. 2(2), pp. 91-99

Chapter 8

Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short-acting β_2-agonists.

Sarah L. Appleton, Richard E. Ruffin, David H. Wilson, Anne W, Taylor [a], Robert J. Adams.

The Health Observatory, Discipline of Medicine, University of Adelaide, and the [a]Population Research and Outcomes Study Unit, South Australian Department of Health, Adelaide, South Australia

The Journal of Allergy and Clinical Immunology 2009; 123:124-30, e1

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Findings from Chapter 7 suggested an association between asthma and CVD/stroke events that did not involve systemic inflammation and traditional cardiovascular risk factors. To determine the direction of the association it was necessary to conduct a longitudinal analysis of the data. This research addressed important gaps in the literature as studies investigating the risk of macrovascular events associated with asthma have generally failed to consider the role of asthma phenotype or considered a more direct cardiotoxic effect of short acting beta-2 adrenergic agonists.

Recent studies have attempted to address the heterogeneity of asthma subtypes by considering age of asthma onset (Onufrak 2008, Onufrak 2007). These studies showed that females, but not males, with adult-onset asthma (onset after age 21 suggestive of non-atopic asthma) demonstrated increased carotid artery intima-media thickness (Onufrak 2007) and increased risks of incident CHD and stroke (Onufrak 2008) independent of CVD risk factors, which persisted in never smokers.

The work presented in this thesis progressed these important findings by 1) assessing CVD risk in relation to atopic status in asthma, 2) considering the relationship of asthma medication use, specifically beta-2 agonist use with CVD/stroke events and 3) by considering all asthma as determined by self-reported physician diagnosis and also significant bronchodilator responsiveness in the absence of a physician diagnosis. This study identified for the first time that in females, the significant increased risk of incident CVD/stroke events associated with asthma was not modified by atopic status. Events were also associated with as required SABA use in females which has not previously been reported in a representative sample free of existing CVD/stroke. In contrast, in males, incident events were associated with respiratory symptoms. Although few events occurred in men with asthma, a significant interaction of asthma with atopic status was evident and this may explain the absence of the association of asthma and CVD/stroke events described previously in males.

Although further work is required to confirm these findings, caution in the prescribing of SABA in older females with asthma is warranted. Asthma management should incorporate management of macrovascular disease risk.

Appleton, S., Ruffin, R., Wilson, D., Taylor, A. & Adams, R. (2009) Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short acting β2-agonists.
The Journal of Allergy and Clinical Immunology, v. 123(1), pp. 124-130.e1

Chapter 9. Discussion

Contribution and impact

The North West Adelaide Health Study, a large biomedically assessed representative and weighted population sample, has permitted an important examination of the roles of obesity and asthma phenotypes in further study of the association of the two disorders. Central obesity measures and atopic status have been largely neglected in previous studies. The work presented in this thesis identifies an equally important role of central obesity and the intriguing notion that the pathological basis for the association between obesity and asthma may be related to non-allergic mechanisms. These findings taken together with recent evidence of the heterogeneity of asthma expression indicate that our present approach to understanding the association based on simple measures of self-reported asthma is likely to be inadequate. Lack of adequate phenotyping of subjects with asthma is a major limitation to advances in understanding the relationship between obesity and asthma. As stated by Gibson, in a discussion of the characterisation of the clinical phenotype *"I have long puzzled over how scientists can define a person's genotype to the level of a single nucleotide yet accept a phenotype characterisation in the same individual that is as (im)precise as the answer to the question ''Do you wheeze?''* (Gibson 2009). Future studies will be unlikely to identify putative mechanisms of the association without improved phenotyping of both asthma and obesity.

Chapter 4 confirms findings in a smaller initial NWAHS sample (Adams 2003) that undiagnosed asthma was common in our large population sample, however, the present work revealed that this was variable (1.6% to 4.5%) depending on the criteria used to classify a significant FEV_1 bronchodilator response. All reversibility criteria identified subjects with significantly worse or comparable % predicted pre-bronchodilator FEV_1 to those with diagnosed asthma and significantly higher symptom levels than those without asthma (no doctor diagnosed asthma or reversibility). Post-bronchodilator % predicted FEV_1, were improved but remained significantly lower than subjects with no asthma. As hypothesised, the bronchodilator reversibility criteria were associated with

different socio-demographic factors and the criterion based upon post-bronchodilator change expressed as percentage of the predicted FEV_1 was least biased particularly in terms of age and sex. This had not been previously demonstrated and led to the selection of this paper as an "Editors' Choice" article. Based upon these findings, where possible and practical (given the widespread acceptance and promotion of the 12% of baseline FEV_1 reversibility criterion in asthma management guidelines), the 9% predicted FEV_1 criterion was used to identify undiagnosed asthma in subsequent analyses. If our findings can be extrapolated to other populations, under-diagnosis has implications for studies assessing associations of obesity with asthma where up to 25% of people with asthma, may be included in the no asthma category thereby diminishing or negating the associations. If factors related to under-diagnosis are differentially expressed in populations then this may partly account for reported inconsistencies observed in the obesity-asthma association.

As shown in Chapter 5, obesity was not significantly associated with atopy alone, but a robust association of all obesity phenotypes with current asthma was observed in females only. Furthermore, when atopic status was considered, a robust association across obesity phenotypes was observed with non-atopic asthma only in males. Associations with a non-atopic asthma phenotype were less robust in females where only central obesity measures were associated with non-atopic asthma, and an association of BMI $\geq$ 35.0 with atopic asthma was observed. Given that F_{eNO} is a marker for predominantly eosinophilic airway inflammation and useful for the diagnosis of atopic but not non-atopic asthma, this may explain the generally negative associations between BMI and F_{eNO} (Sutherland 2009a, Komakula 2007, Barros 2006, Sutherland 2008b). These findings indicate that further studies are clearly required to investigate a non-allergic pathophysiological mechanism relating obesity and asthma. The finding that central obesity measures were consistently associated with non-atopic asthma suggests that central fat distribution may represent a different inflammatory profile to peripheral fat. Compared with subcutaneous abdominal fat, visceral fat is more strongly associated with the metabolic syndrome (Fox 2007) and therefore the "pathogenicity" of fat depots may also have an effect on the phenotype exhibited in people with asthma. Alternatively, the association of central adiposity with non-atopic asthma may reflect an effect on airway mechanics, i.e. centrally obesity results in increased work of breathing that is manifested as dyspnea. Further work in this area using more detailed asthma

phenotyping is clearly required. From a clinical point of view, these findings suggest that asthma should be considered in non-atopic, older, centrally obese, symptomatic individuals who may be perceived as having a low clinical probability of having asthma.

Compared with normal weight phenotypes, no obesity phenotypes were inversely associated with either of two bronchodilator phenotypes assessed (representing undiagnosed asthma), indicating an absence of detection bias operating in obese subjects. In contrast, our findings raise the notion of detection operating in the thinnest subjects- the likelihood of undiagnosed asthma assessed by two reversibility criteria, was significantly increased in underweight females with a BMI < 18.5. The reasons for this are speculative and it is possible that bronchodilator reversibility does not reflect a level of symptoms that are regarded as bothersome enough or perceptible, and may particularly in older women, (who are more likely to be identified by the 12% of baseline reversibility criterion), be considered to be a consequence of ageing. This finding is consistent with reported U-shaped associations of asthma with BMI (Celedon 2001). Whether this phenomena reflects sarcopenia in addition to low levels of fat, and therefore unable to be captured by central measures of obesity merits further investigation.

Subsequent to the publication of these findings in Chapter 5, other studies have added important evidence in relation to the roles of alternative obesity phenotypes and atopy phenotype in the relationship between obesity and asthma in adults. Recent epidemiological studies also report an association of asthma with obesity classified using BMI and WC. Similar to our findings, and published at the time our paper was submitted, Chen *et al* reported that in the Canadian Humboldt study (2057 adults, response rate 71%), BMI 25-29.9 and 30+, and WC ≥ 100cm (for males and females) were significantly associated with recent asthma (told by a doctor you have asthma in past 12 months) in females but not males (Chen 2005).

Similarly, in the California Teachers Study (CTS) cohort of women, current asthma was associated with overweight and all obesity classes, in addition to the 2^{nd} to 4^{th} quartiles of waist circumference and waist to stature ratio compared to the lowest quartile (Von Behren 2009). The extreme size of this cohort (n=88,304) may have overcome sample

bias generated from an initial study response rate of 40% in 1995 (n=133,479) and the exclusion of 41,000 subjects who did not complete a questionnaire containing asthma measures.

Chen *et al* also suggest that obesity is likely to have a greater effect on non-allergic asthma, given their findings in the Canadian Community Health Survey (CCHS), an interview survey of 86,144 (aged 20-64) subjects with a high (85%) response rate. (Chen 2006). In the CCHS, allergic status was assesses by self-report (do you have food/other allergies diagnosed by a health professional) and in females, the odds ratio for current doctor diagnosed asthma per unit change of BMI was significantly greater in non-allergic (OR=1.07, 95% CI: 1.06-1.09) compared with their allergic females (OR=1.04, 95%: 1.03-1.05). In males, the significant association of BMI with asthma was not modified by allergic status (Chen 2006). A recent report based upon the smaller Canadian Humboldt study population discussed above (Chen 2009) shows an association of generalised obesity (BMI $\geq$ 30 kg/m2) with non-atopic asthma only. A lack of association of WC > 100cm with asthma in this study is likely to be related to the use of 1) non-sex specific WC cut points and 2) subjects with a WC < 100cm as the reference group which contains subjects with increased asthma risks, particularly in women where increased risks are evident at levels of > 88cm. This study highlights the inherent problems in dichotomising a continuous variable where the asthma risk is likely to increase linearly across the distribution of WC and caution should be taken in the interpretation of these findings.

In another large cohort study of 5114 German adults (Loerbroks 2008) aged 40-65 at baseline (51% response rate), BMI 25.0-29.9 was significantly associated with asthma and BMI $\geq$ 30 showed a marginal association (OR=1.37, 95% CI 0.95-1.99), and the p value for the interaction for obesity and gender approached significance (p=0.08). These associations remained unchanged in subjects with and without hay fever, however, this study suggests that effect modification by hay fever depends on gender given that in sex-specific analyses the significant association with obesity remained in females without hay fever only. The complexity of the associations in these studies may relate to the use of proxy measures of skin prick test measures of allergy, but a role for allergic status in the relationship, as prominent as a role for gender, appears to be emerging.

A recent paper has contributed additional insights to the relationship between obesity phenotype, atopy and asthma by considering the contribution of insulin resistance to asthma (Husemoen 2008). This study was based on a random sample of Danish adults (n=6784, 52.5% response rate) of whom 3609 underwent assessment of specific IgE to 19 aeroallergens. Obesity measures (BMI, WC and WHR) were significantly associated with both atopy and ever asthma, but only the associations with ever asthma persisted after additional adjustment for insulin resistance, (with the exception of atopy and WHR). Similarly, insulin resistance was also a significant predictor of atopy and ever asthma, but only the associations with atopy persisted after adjustment for BMI. When atopic status of asthma was considered, although obesity measures were associated with atopic and non-atopic asthma, after adjustment for insulin resistance, only the associations with non-atopic (ever) asthma persisted. These findings suggest that obesity is related to atopy and atopic asthma, (but not non-atopic asthma) through mechanisms that are also involved in the development of insulin resistance, and perhaps include adipokines such as TNF-alpha. As such, the pathophysiological background for the association between asthma and obesity are likely to differ between atopic and non-atopic asthma. In support of this, insulin resistance and diabetes were associated with atopic asthma only (Husemoen 2008) and gestational diabetes increased the risk of early childhood atopic manifestations, including atopic dermatitis and allergen sensitization (Rajesh 2009).

Another recent study also supports the hypothesis that insulin resistance is involved in the aetiology of asthma (Thuesen 2009). This Danish study of 6784 randomly recruited adults (response rate 53%) reported that at follow-up (n=4516), obesity (BMI, WC, WHR) and insulin resistance (but not diabetes) were significantly associated with incident wheeze and asthma-like symptoms (yes to at least one of: In the last 12 months have you experienced wheezing while breathing, been woken by an attack of shortness of breath, had an attack of shortness of breath when at rest?). The associations of the obesity measures WC and WHR were attenuated, and became non-significant for BMI $\geq$ 30.0, when insulin resistance was added to the models. In contrast, the associations of insulin resistance and incident wheeze and asthma like symptoms were independent of obesity by any measure and interestingly, these associations persisted in normal weight subjects (BMI 18.5-24.9).

Evidence from mouse models adds contradictory evidence however. Shore *et al* suggests that hyperglycaemia is unlikely to account for the pulmonary phenotype observed in obese mice as metformin treatment did not attenuate innate AHR and inflammatory responses to ozone despite decreases in fasting blood glucose (Shore 2008b).

These findings suggest that progressing our understanding of the asthma-obesity relationship in future studies requires consideration of not only asthma phenotype but also an obesity phenotype that includes a measure of insulin sensitivity.

As one of only few studies to assess asthma morbidity in relation to obesity in unselected representative asthma population samples (Taylor 2008, Accordini 2008), Chapter 6 shows that either high BMI or WC were associated with significantly more respiratory symptoms, medication use, primary care visits and significant reductions in lung function and quality of life in men. These findings that WC was significantly associated with asthma morbidity had not been previously shown. In contrast to findings of Taylor *et al* (Taylor 2008) who used self-reported height and weight measures, we observed that sex significantly modified the associations of obesity with asthma morbidity. Given that predictors of systematic errors in self-reported height and weight are gender specific (Stommel 2009, Villanueva 2001) and lead to underestimation of obesity through underreporting of weight and over-reporting of height (Stommel 2009, Nyholm 2007, Gorber 2007, Taylor 2006, Niedhammer 2000), it is possible that self-reported measures affect the association of obesity with measures of asthma morbidity or severity. Indeed, misclassification of BMI due to the use of self-reported measures has been reported to negate the positive association of obesity with asthma evident in men with measured height and weight (Santillan 2003).

In females, the burden of morbidity was experienced by overweight subjects, although similar to the findings in males, significant reductions in quality of life and increased primary care visits were also associated with obesity in females. Subsequent to the publication of this work, two primary care studies have reported upon the effect of obesity on asthma control (Stanford 2009, Diez 2008). These studies are likely to have

the least issues with selection bias after the studies in population samples. The Asthma Control Characteristics and Prevalence Survey Study (ACCESS) recruited 2238 subjects with asthma (93% response rate) through 35 primary care practises across the United States and assessed control with the asthma control test, a 5 item test (score 0-20) assessing symptoms, activity limitation, rescue medication use, and self-rated overall asthma control during the previous month (Stanford 2009). A Spanish study (Diez 2008) of 6518 subjects with persistent asthma (95.5% response rate) also assessed asthma control using the Asthma Control Questionnaire where mild, moderate and severe asthma was present in 41%, 51% and 7% of subjects respectively. Despite differences in asthma control measures, both studies reported that poor asthma control was independently associated with body mass index, in addition to severity, sex, race, smoking, level of education, habitual activity, years since diagnosis of asthma, number of exacerbations and admissions to hospital during the last year.

Despite the variation in outcome measures and study settings, the emerging picture is for a consistent deleterious effect of obesity on asthma control (in nine of ten studies measured largely with the Asthma Control Questionnaire and Asthma Control Test), and quality of life, although only four studies including the present have assessed this important outcome. An effect of obesity on asthma severity (in five of eight studies classified largely by guideline criteria including GINA) is less consistently reported and although assessed in few studies, there is also a relatively consistent worsening of components of asthma control including symptom levels (in five of seven studies), increased ICS (in all three studies where assessed) and short-acting beta-2 agonist use (four of five studies) and days lost from usual activities (two studies). There are inconsistent effects on hospital emergency department visits, asthma admissions and primary care visits, and lung function. That obesity was associated with gastro-esophageal reflux disease in the two studies assessing co-morbidities (van Veen 2008, Dixon 2006) adds to the conflicting arguments around the associations of reflux symptoms and asthma and their independence of BMI (Hancox 2006, Gunnbjornsdottir 2004).

Although an effect modification by sex was infrequently tested in these asthma samples, this was also inconsistently observed. In the published studies to date, the effect of obesity phenotype has been rarely addressed other than in the present study and in an

asthma clinic setting (Lessard 2008) and is clearly an important area for additional research. Similarly, obesity may affect morbidity in asthma in a phenotype dependent manner and other than the studies reviewed in this thesis that sampled severe asthma, it is presently unknown if obesity worsens asthma control to a greater extent in atopic subjects or in those subjects displaying eosinophilic or neutrophilic asthma. The present study was unable to assess morbidity in relation to atopic status due to sample size constraints. An issue of critical importance is the need for prospective studies to evaluate the effect of body weight and fat distribution on treatment responses in well phenotyped subjects with asthma given the limited findings of reduced responsiveness to ICS in obese subjects (Peters-Golden 2006) and the diminished responsiveness to corticosteroids that is observed in neutrophilic asthma (Haldar 2007).

Based upon the epidemiological evidence that obesity is a risk factor for asthma it is possible that asthma and cardiovascular disease share a developmental pathway that includes insulin resistance (Thuesen 2009, Husemoen 2008). The findings presented in this thesis (Chapter 7) support the hypothesis that cross-sectionally, asthma is associated with cardiovascular disease and stroke events, but not diabetes, or cardiovascular disease risk factors, and importantly that this association was not modified by obesity. This argues against the involvement of systemic inflammation or pathways involving traditional cardiovascular disease risk factors contributing to events.

Because the direction of the association between asthma and CVD/stroke events was unclear, this work was followed in Chapter 8 by an analysis of the risks of incident cardiovascular/stroke events associated with asthma and the effects of atopic status on the association. Given that the only Australian data on cardiovascular disease risks associated with asthma date from 1987 and relate specifically to ischaemic heart disease deaths identified in nearly 10,000 adults discharged from Western Australian hospitals with a diagnosis of asthma between 1976 and 1980 (Musk 1987), the importance of this works lies in the representativeness of the NWAHS sample. Asthma was significantly associated with incident CVD/stroke events in females after adjustment for confounders. In males however, daily cough and sputum and a lung function impairment that was not COPD were predictors of CVD/stroke events. This work made

a significant contribution to the literature by our consideration of asthma phenotype (atopy) and the effects of beta-2 agonist use in subjects free of events at baseline. Previous studies have either not assessed (Iribarren 2004, Schanen 2005) or not reported (Onufrak 2008) the effects of medication use. Similarly, late-onset asthma has been used as a proxy measure of non-atopic asthma in two studies (Onufrak 2007, Onufrak 2008), and the other utilised self-reported allergy (Dogra 2007).

The findings reported in Chapter 8, support an argument against the involvement of systemic inflammation in females and perhaps a rather more simple aetiology involving cardiotoxicity of short-acting beta-2 agonists. This work raised other interesting findings worthy of further study, particularly the role of atopic status in the association of asthma with events in men. Phenotype may have implications for macrovascular outcomes and these relate to possible reduced responsiveness to ICS in obese subjects (Peters-Golden 2006) and the diminished responsiveness to corticosteroids is observed in neutrophilic asthma (Haldar 2007). Therefore, obese subjects with asthma, and subjects with neutrophilic asthma may be less likely to experience the ICS related reductions in MI suggested by some (Suissa 2003, Camargo 2008) but not all studies (Zhang 2009).

Another aetiology linking asthma to CVD may involve depression as an intermediate factor. Epidemiologial studies show that allergy (Patten 2007, Patten 2009, Timonen 2003) and asthma (Adams 2004, Strine 2008) are associated with depression. Allergy and asthma related cytokines including interleukin-1 Beta, TNF-alpha and IL-6 provoke neuroendocrine and neurotransmitter changes suggesting that the brain reacts to immune activation as a stressor (Anisman 2009). Activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system by these cytokines have been reported (Hurwitz 2001, Anisman 2009, Loftis 2010). Meta-analyses and epidemiological studies (Davidson 2009) suggest that depression and depressive symptoms are an independent risk factor for MI and cardiovascular mortality (Lett 2004, Nicholson 2006, Van der Kooy 2007). Although the mechanisms underpinning the association are poorly understood (Nabi 2008), HPA axis and autonomic nervous system dysregulation may also link depression to CVD, among other mechanisms including inflammation, behavioural risk factors, and increased platelet reactivity (Lett 2004). Few studies have investigated whether inflammation accounts for some of the

excess CVD risk conferred by depression in healthy populations, but those that have reported that inflammation (including CRP and interleukin-6) explains very little of the association between depression (Davidson 2009) or psychological distress (Nabi 2008) and incident CHD. This supports the hypothesis that CVD events in subjects with asthma may be related to SABA cardiotoxicity.

Future directions for research

The work presented in this thesis indicates that further studies are required to investigate both allergic and non-allergic pathophysiological mechanism relating obesity and asthma. Given that only 50% of asthma cases are attributable to eosinophilic inflammation (Douwes 2002), the heterogeneity of asthma phenotype expressed is likely to be an important factor in the inconsistencies that are observed across studies of the association of obesity and asthma. Non-allergic asthma triggers include air pollution and ozone, bacterial endotoxins (lipopolysaccharides) and viruses which activate innate immune mechanisms resulting in neutrophilic airway inflammation (Simpson 2008). Emerging evidence suggests that obesity, as a consequence of a western diet low in anti-oxidants and high in saturated fats, may represent a non-allergic trigger leading to neutrophilic asthma (Wood 2009a). As reviewed by Wood *et al*, a low antioxidant intake impairs the scavenging of reactive oxygen species, thereby promoting a nuclear factor kappa B (NFκB)-mediated innate immune response, resulting in oxidative damage. Similarly, saturated fats directly activate toll-like receptor 4 leading to an NFκB-driven innate response and a corresponding inflammatory cascade including TNF-alpha, IL-6, CRP and reactive oxygen species. These mediators may contribute additionally to airway and systemic inflammation driven by adipocytokines (Wood 2009a, Wood 2009b, Simpson 2008). Given that there is evidence, albeit limited, to suggest that a neutrophilic asthma phenotype is non-atopic (Nadif 2009, Green 2002b, Drews 2009) innate immune mechanisms may partially account for the associations of central obesity and non-atopic asthma presented in this thesis. In support of this, small studies have also reported an association of neutrophilic asthma phenotype with obesity (Haldar 2008, Scott 2009).

Establishing the relationship between obesity and specific asthma phenotypes is therefore the most pressing area for further research and this may be achieved by assessing peripheral blood granulocytes (Nadif 2009) in both epidemiological studies and case-control studies. This may explain the underlying association of obesity and non-atopic asthma identified in the present work. The next phase of the North West Adelaide Health Study will provide white cell counts to enable further testing of this hypothesis. Improved obesity phenotyping which includes measures of insulin

sensitivity and adipocytokines may also provide important insights into a pathological mechanism for the association.

Prospective studies are required to evaluate the effect of body weight and fat distribution on morbidity and treatment responses in relation to specific patterns of granulocyte inflammation. This may lead to an improved understanding of factors associated with poor asthma control, and ultimately to improved outcomes through targeted therapeutic strategies. Additionally, assessment of the relationship of obesity with other factors including perception, denial and coping behaviours could provide knowledge to support interventions in subjects with asthma.

Prospective studies in subjects free of existing CVD are required to elucidate the pathway by which asthma exposes older women to excess macrovascular risk. This includes establishing the risks associated with short acting beta-2 agonists and a potential protective effect of long acting beta-2 agonist/ICS therapy. Further investigation of macrovascular risk in relation to asthma phenotype (including severity, atopy and granulocytic inflammation), and asthma-related depressive symptoms, in large population samples is required.

Conclusions

This work has identified that a lack of adequate phenotyping of subjects with asthma is a major limitation to advances in understanding the relationship between obesity and asthma obtained in epidemiological studies.

A significant proportion of asthma is unable to be identified by self-reported measures and the prevalence of undiagnosed asthma identified by FEV_1 bronchodilator reversibility was variable. The finding of an association of central obesity with non-atopic asthma indicates the necessity to consider these important obesity and asthma phenotypes. For the first time, an association of central obesity, (in addition to a generalised obesity phenotype) with significant asthma morbidity has been described in a representative asthma sample. Finally, asthma was associated with macrovascular disease in cross-sectional and longitudinal analyses. Incident CVD/stroke events were associated with asthma and short-acting beta-2 agonist use in females and with respiratory morbidity in men independent of the level of BMI. This provides evidence for a more direct effect of medication use on CVD events rather than a hypothesised effect of airway or systemic inflammation. These studies have significantly added to the knowledge in the field.

Large representative biomedical population samples are critical to investigate the inherent complexity in the association of obesity and asthma and to address the possibility of interactions between factors. The North West Adelaide Health Study is a large study but even so was underpowered to investigate some of the questions raised. The difficulties in collecting adequate information to further explore obesity-asthma associations at the level that appears necessary will not be easily overcome as this will involve invasive techniques (including airway hyperresponsiveness testing and sputum induction, and allergy testing) and high costs (for assay of peripheral blood granulocytes, cytokines, adipocytokines, insulin and DXA/MRI determined fat mass). Furthermore, this necessitates a study design that permits both adequate cell sizes and careful sample selection. Such well designed studies would however, provide population estimates on the basis of which public health policy and strategy decisions can be informed.

The perfect epidemiological study to address all of these phenotypic characteristics is unlikely to be feasible but the evidence that obesity is a risk factor for asthma is generally compelling. Given this, hypothesis driven mechanistic studies are also a possible approach to determining a causal pathway between the two.

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