Chapter 1

LITERATURE REVIEW
1.1 – THE NATURE OF ASTHMA

Asthma is one of the most common chronic diseases worldwide. The prevalence and severity of asthma is continuing to increase in many countries in the developing and developed world both in adults and in children.

The National Asthma Council of Australia defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness (BHR) to a variety of stimuli (3). The diagnosis of asthma is usually based on history, examination and supportive diagnostic testing. Optimally the diagnosis of asthma would contain all of these components; airway inflammation, BHR and symptoms.

Despite knowledge of the risk factors that cause and exacerbate asthma, no modifications to lifestyle or allergen exposure have currently managed to make a significant impact on this increasing prevalence of asthma.
FIGURE 1.1.1 - INCREASING PREVALENCE OF ASTHMA IN CHILDREN AND ADOLESCENTS WORLDWIDE (5).

This graph shows the increasing prevalence of asthma in several countries worldwide and changes over time. The definitions of asthma used for prevalence vary widely with questionnaire data (4, 7-9, 11), symptoms and IgE levels (6), spirometry (10) and bronchial responsiveness used (2).

FIGURE 1.1.2 –INCREASING PREVALENCE OF ASTHMA IS ACROSS ALL AGE GROUPS IN THE USA (5).

This figure shows that the prevalence of asthma has increased in all age groups in the USA between 1985 and 1996.
This graph shows over the last 15 years that there has been an increase in the prevalence of asthma in adults in Australia, despite several different definitions of asthma. Current data suggests that the increase in prevalence may have reached a plateau over the last few years (13).

There are significant difficulties in the diagnosis of asthma for epidemiology studies. Questionnaire responses on symptoms are both subjective and are influenced by a wide variety of cultural, psychological and sociologic factors (14). Bronchial hyperresponsiveness is defined as an increase in the ease and degree of airway narrowing in response to bronchoconstrictor stimuli in vivo (15). Bronchial provocation tests provide an objective measure of airway abnormality, but used alone are neither sensitive nor specific for the diagnosis of asthma (16, 17). Although bronchial responsiveness may not be closely related to the severity of asthma, it appears to be related to recent respiratory symptoms both in population studies and in clinic populations (16-18). Airway obstruction itself is not a diagnostic feature of asthma and is present in chronic airflow limitation in emphysema (19). The variability of airflow limitation either spontaneously or in response to medication is what differentiates asthma from other conditions.
Difficulties also arise in the diagnosis of asthma in the obese. With symptoms that frequently co-exist in both conditions, diagnosis of true asthma has become an obstacle in the assessment of the association between these two common conditions.

1.2. DEFINITION OF OBESITY

Overweight and obesity in adults is commonly assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in metres (kg/m$^2$).

Overweight becomes the disease of obesity when excess fat has accumulated to the extent that it may adversely affect health. This point is most commonly defined by the body mass index (BMI). Although a BMI>25 can be associated with a reduced life expectancy and a risk of exacerbating many diseases, it is now usual to consider BMI of 30 as the cut-off point at which the accumulation of fat is a major health hazard.

TABLE 1.2.1: WHO GRADING FROM UNDERWEIGHT TO OBESITY (20)

<table>
<thead>
<tr>
<th>DEFINITION</th>
<th>BMI (kg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.0</td>
</tr>
<tr>
<td>Moderate obesity</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Severe obesity</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Very severe obesity</td>
<td>≥40.0</td>
</tr>
</tbody>
</table>

The majority of adults in the United States, Australia, and most of Western and Eastern Europe are overweight and more than 20% are obese (20). The recent National Health and Nutrition Examination Survey (NHANES) (21) from the US Centres for Disease Control and Prevention indicated that 64.5% of adults in the United States in 1999 were overweight and that 30.5% were obese.
Throughout the world in both developing and developed nations, a similar pattern is occurring (20). In Australia, there has been an increase in the proportion of overweight or obese women aged between 25 and 64 years from 27% in 1980 to 43% in 1995 and to 52.1% in 2000. Over the last 20 years the number of overweight or obese women has nearly doubled. The proportion of men in the same age group who are overweight or obese has increased from 48% in 1980 to 63% in 1995 and to 67.5% in 2000. In other words, over two thirds of adult Australian males in this age group are overweight or obese (22).

The increase in prevalence of obesity is even more disturbing. For females, there has been a 200% increase (from 7% in 1980 to 22% in 2000), while for males, there has been a 125% increase (from 8% to 19%). On average, men in 1995 weighed 3.6 kg more than their counterparts in 1980 and women 4.8 kg more.

**FIGURE 1.2.1: TRENDS IN THE AGE SPECIFIC PREVALENCE (%) OF OBESITY IN MALES IN AUSTRALIA: 1980-2000 (22)**

This figure shows the increasing prevalence of obesity across all age groups in Australian men between 1980 and 2000.
To date, there has not been the same level of agreement over the classification of overweight and obesity in children and adolescents as there has been in adults. Many countries have produced reference charts for growth based on weight for age and height for age. These measures are a collection of the child’s size (small or large) and provide no indication of relative fatness. Adult BMI increases very slowly with age, so age independent cut-off points can be used to grade fatness. In children, BMI changes substantially with age, rising steeply with infancy, falling during the pre school years and then rising again into adulthood. Variation also occurs in BMI with age in children. For this reason, child BMI needs to be assessed using age-related reference curves. Reference data from the US National Centre for Health Statistics (NCHS) (23) was used in this study.

The known health consequences of obesity are many and varied. There is an increased risk of premature death and controlling for smoking, there is a relationship between BMI and death (24).

**FIGURE 1.2.2 – THE RELATIVE RISK OF DEATH FROM ALL CAUSES AMONG US WHITE MEN ACCORDING TO BODY MASS INDEX (24).**
These graphs show the risk of death from all causes according to BMI among white US men and women who had never smoked and who had no history of disease. These subjects had no history of cancer, heart disease, stroke, respiratory disease (such as chronic bronchitis, emphysema or asthma) current illness (of any type), or weight loss of at least 10lb in the previous year. The reference category was made up of subjects with a body mass index of 23.5 to 24.9 kg/m² (24).

The non-fatal but debilitating health problems associated with obesity include respiratory difficulties, chronic musculo-skeletal problems, skin problems and infertility.

The more life threatening, chronic health problems associated with obesity fall into four main areas: (a) Cardiovascular problems including hypertension, stroke and chronic heart disease; (b) conditions associated with insulin resistance, namely type 2 diabetes mellitus; (c) certain types of cancers, mainly the hormonally related such as breast cancer in post menopausal women, endometrial cancer and large-bowel cancers; and (d) gallbladder disease (20).
### TABLE 1.2.2– RELATIVE RISK OF HEALTH PROBLEMS ASSOCIATED WITH OBESITY (20)

<table>
<thead>
<tr>
<th>Greatly increased (relative risk much greater than 3)</th>
<th>Moderately increased (relative risk 2-3)</th>
<th>Slightly increased (relative risk 1-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDDM</td>
<td>CHD</td>
<td>Cancer (breast cancer in postmenopausal women, endometrial cancer, colon cancer)</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>Hypertension</td>
<td>Reproductive hormone abnormalities</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Osteoarthritis (knees)</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Hyperuricaemia and gout</td>
<td>Impaired fertility</td>
</tr>
<tr>
<td><strong>Breathlessness</strong></td>
<td></td>
<td>Low back pain due to obesity</td>
</tr>
<tr>
<td><strong>Sleep apnoea</strong></td>
<td></td>
<td>Increased anaesthetic risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal defects associated with maternal obesity</td>
</tr>
</tbody>
</table>

This table shows the risks of disease associated with obesity. There is a greatly increased risk of respiratory symptoms such as breathlessness and the frequency of sleep apnoea is also greatly increased.

Known effects of obesity on pulmonary diseases include increased work of breathing, reduced lung volumes and obstructive sleep apnoea. Obesity hypoventilation and respiratory failure also contribute to the health care costs of obesity though currently these can be controlled with nasal continuous positive airway pressure (CPAP) (25) or bi-level positive airway pressure (BiPAP) (26).

Over the last 20 years, there has been a rapid increase in the prevalence of both asthma and obesity. Given the increases in both obesity and asthma, it is not surprising that questions have arisen.

Are these increases linked?
What is the nature of the association?
Does obesity cause asthma or does asthma cause obesity?
What are the implications for treatment given the current knowledge?
IS THE INCREASE IN ASTHMA LINKED TO THE INCREASE IN PREVALENCE OF OBESITY?

1.3 ASTHMA AND OBESITY IN ADULTS

1.3.1 Cross sectional studies in adults

Cross sectional studies discussed below have shown a diagnosis of asthma has been associated with obesity in both children and adults. Several of these studies noted the relationship was only present in women or in men. Similarly, increasing BMI has been associated with increasing symptoms of shortness of breath, and wheeze, bronchial hyperresponsiveness and atopy.

Young et al (27) performed a population based prevalence case control study of patients enrolled in TRICARE region 11, which encompasses Washington, Oregon and northern Idaho. TRICARE is a military health care system comparable to a traditional health maintenance organisation. The population includes active and retired service members of the US armed forces and their families residing in region 11. Questionnaires are mailed to patients enrolled in TRICARE after enrolment and then annually. Questionnaire data include demographic information; self reported height and weight, lifestyle information and history of medical problems. Asthma cases were defined as patients responding positively to the question, “Have you ever been told by a health professional that you have asthma?” other individuals were defined as controls. The questionnaire response rate was approximately 50%, and 45,743 questionnaires were returned.

A random sample of 1,000 asthmatics and 1,000 controls were generated. Asthmatic subjects were excluded if they were not using medications commonly indicated for asthma including inhaled or oral bronchodilators, or inhaled steroids. Those on oral steroids alone or on nasal steroids were excluded and those without BMI information were also excluded. Control cases were also reviewed and any subjects on medication commonly used for asthma were excluded, and those
without BMI information were also excluded. This left 386 asthmatic cases and 744 control cases.

After adjustment for age and gender, the risk of having asthma increased with increasing BMI with the greatest increase among individuals with a BMI between 40 and 60 (OR 2.8; 95%CI 2.3, 3.5 p for trend < 0.001). Asthmatic subjects were also more likely to be obese (BMI $\geq$30) compared with controls (29.5% vs 14.5%). In both analyses, there was no difference with adjustment for race.

In the final model for the overall group, increasing BMI, younger age, non-active duty, female gender, and a history of being diagnosed as having a stomach ulcer, depression, arthritis, or hypertension were significant independent predictors of asthma. With both asthma and obesity being reasons for rejection from military service, the subjects would have developed either or both since enlistment, which is more likely to show bias in the favour of linkage.

The BRFSS (Behavioural Risk Factor Surveillance System) (28) is a USA state based random digit-dialled telephone survey of non-institutionalized US adults aged 18 years of age or older. Information is collected about health behaviours associated with chronic diseases and other leading causes of death. In 2000, two questions about asthma were administered in all 50 states in the USA, Puerto Rico, and the District of Columbia. Survey participants were asked 1) have you ever been told by a doctor that you have asthma? And 2) do you still have asthma? A respondent was classified as having lifetime asthma if they answered yes to question 1 and current asthma if they answered yes to both questions. Other demographic information was also collected. In total 181,914 people responded to both questions about asthma. After exclusion of missing data for the independent variables, 160,537 observations were used.

Two percent of the population were underweight, 40.2% were in the normal weight range, 37.1% were overweight and 20.7% of the population were obese. This study showed an increase risk of lifetime asthma and current asthma in the
overweight and obese groups (Figure 1.3.1.1). This remained significant after adjustment for gender, age, race, Hispanic origin, socioeconomic status, smoking status, urban residence, physical activity and medical check up in the last 12 months. Interestingly being underweight was also a risk factor for both lifetime and current asthma.

FIGURE 1.3.1.1– ADJUSTED ODDS RATIOS FOR REPORTING CURRENT ASTHMA IN THE BRFSS (28).

This figure shows that there is an increase in the risk for current asthma with being overweight and obese. There is also an increase in the risk for the underweight group, with only 2% of the population were underweight.

Luder et al (29) analysed the data on 5524 subjects aged 18 years and older in the New York State BRFSS. After adjusting by age and gender and adjusting for ethnicity, education, health insurance, time since last physical examination, physical activity and smoking status, the results showed that the prevalence of asthma was 4.6% (95% CI 3.6-5.5%) among men and 8.1% (95% CI 7.1-9.1%) among women. In women, the prevalence of asthma was significantly increased in those with a BMI 25kg/m² or higher (BMI 25-27.5: OR=1.76, 95% CI: 1.06-2.94; BMI 27.5-29.9: OR=2.45, 95% CI: 1.41-4.25; BMI> 30.0 OR=2.67, 95% CI: 1.66-4.29) when compared to the reference category (BMI 22-24.9kg/m²). In men, the
prevalence of asthma was increased in the lowest weight category BMI<22kg/m² (OR=3.05, 95% CI: 1.37-6.78) and in the highest category (BMI>30.0 OR=2.92, 95% CI: 1.39-6.14) when compared to the reference category (BMI 22-24.9kg/m²).

In this study the differences between men and women in the association between asthma and BMI only differed in the underweight category. In women overweight and obesity were associated with asthma, while in men both extremes of weight are associated with a higher prevalence of asthma.

The 1970 British Cohort Study (BCS70) (30) is an ongoing follow up study of all individuals born between 5 and 11th April 1970 who are still living in Britain (excluding Northern Ireland). Data were collected from the cohort at birth, 5, 10, 16 and at 26 years of age. In total 8,960 individuals responded to the questionnaire at 26 years of age. At 26 years of age, the prevalence of asthma and wheeze increased with increasing adult BMI. The association between asthma and fatness was stronger in women, where overweight women (BMI 25.0-29.9kg/m²) had an increased risk of asthma with an OR of 1.51 (95%CI 1.11 to 2.06) and obese women (BMI>30kg/m²) had an OR of 1.84 (95%CI 1.19 to 2.84).

The NHANES III (The Third National Health and Nutrition Examination Survey) study was conducted between 1988 and 1994 by the National Centre for Health Statistics of the Centres for Disease Control and Prevention in the USA (31). Study participants were asked to complete a questionnaire and a comprehensive physical examination, which included spirometric measurement either in the household or at a specialty equipped mobile examination centre. From the larger data set of 40,000 Americans, Sin et al (32) examined data on 16,692 participants who were 17 years or older. These subjects were divided into 5 quintiles based on their body mass index (BMI) (1) BMI<22.1; (2) BMI>22.1-24.8; (3) BMI>24.8-27.3; (4) BMI>27.3-31.0; and (5) BMI>31.0. Outcome variables of interest were divided into 3 categories: (1) lung function, (2) self-reported asthma (including drug use) and (3) exercise performance. A positive answer to the question “has a doctor ever told you that you have asthma?” was used to define subjects with asthma. Participants who answered no to this question but were identified as using an
asthma medication (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) code 493) in any of the medication fields were also included.

This study shows an increase in prevalence of self-reported asthma and medication use for asthma with increasing BMI but lower prevalence of airway obstruction. Reductions in exercise and increasing symptoms of dyspnoea were also present in the obese (Table 1.3.1.1). Suggestions from this paper are that these subjects may not have true asthma, as no airway obstruction was present despite the increased use of asthma medication though no measures of bronchial responsiveness were performed. Obesity and being unfit may cause dyspnoea, rather than true asthma, and reductions in exercise may exacerbate the weight problem, thereby setting up a vicious circle of reductions in exercise and further weight gain.

**TABLE 1.3.1.1– ASSOCIATION BETWEEN BODY MASS INDEX AND SELF REPORTS OF ASTHMA AND EXERCISE LIMITATIONS (32)**

<table>
<thead>
<tr>
<th>Body Mass Index, kg/m²</th>
<th>Asthma</th>
<th>Bronchodilator use in the last month</th>
<th>Walked &gt;1 mile in last month</th>
<th>Dyspnoea walking up hill</th>
<th>Jogged or ran in the last month</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤22.1</td>
<td>0.90 (0.74-1.11)</td>
<td>0.84 (0.58-1.22)</td>
<td>1.01 (0.92-1.12)</td>
<td>0.97 (0.85-1.10)</td>
<td>1.13 (0.99-1.31)</td>
</tr>
<tr>
<td>&gt;22.1-24.8</td>
<td>1</td>
<td>1.08 (0.74-1.56)</td>
<td>0.96 (0.87-1.06)</td>
<td>1.27 (1.12-1.44)</td>
<td>0.95 (0.82-1.10)</td>
</tr>
<tr>
<td>&gt;24.8-27.3</td>
<td>1.21 (0.99-1.47)</td>
<td>1.30 (0.91-1.86)</td>
<td>0.96 (0.87-1.06)</td>
<td>1.76 (1.56-1.99)</td>
<td>0.74 (0.67-0.82)</td>
</tr>
<tr>
<td>&gt;27.3-31.0</td>
<td>1.50 (1.24-1.81)</td>
<td>1.94 (1.38-2.72)</td>
<td>0.74 (0.67-0.82)</td>
<td>2.66 (2.35-3.00)</td>
<td>0.45 (0.37-0.53)</td>
</tr>
<tr>
<td>&gt;31.0</td>
<td>1.50 (1.24-1.81)</td>
<td>1.94 (1.38-2.72)</td>
<td>0.74 (0.67-0.82)</td>
<td>2.66 (2.35-3.00)</td>
<td>0.45 (0.37-0.53)</td>
</tr>
</tbody>
</table>

*data are relative odds ratio (95% confidence interval) and have been adjusted for age, race, sex, smoking status, FEV₁ (% predicted) and FVC (%predicted).

This table shows that the risk of self reported asthma and bronchodilator use increased with increasing BMI. Those participants in the highest quintile for weight were most likely to report symptoms of dyspnoea with exercise and least likely to exercise.
TABLE 1.3.1.2– ASSOCIATION BETWEEN BODY MASS INDEX AND LUNG FUNCTION (32)

<table>
<thead>
<tr>
<th>Body Mass Index, kg/m^2</th>
<th>≤22.1</th>
<th>&gt;22.1-24.8</th>
<th>&gt;24.8-27.3</th>
<th>&gt;27.3-31.0</th>
<th>&gt;31.0</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of participants</td>
<td>3245</td>
<td>3387</td>
<td>3262</td>
<td>3419</td>
<td>3358</td>
<td></td>
</tr>
<tr>
<td>Airflow obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>(FEV₁/FVC&lt; lower limit</td>
<td>498 (14.8)</td>
<td>437 (12.8)</td>
<td>408 (12.6)</td>
<td>361 (10.7)</td>
<td>285 (8.7)</td>
<td></td>
</tr>
<tr>
<td>limit pred)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁≥80% predicted</td>
<td>209 (6.2)</td>
<td>219 (6.4)</td>
<td>208 (6.4)</td>
<td>160 (4.8)</td>
<td>109 (3.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>(mild obstruction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ 50%-&lt;80% pred</td>
<td>199 (5.9)</td>
<td>166 (4.9)</td>
<td>162 (5.0)</td>
<td>162 (4.8)</td>
<td>146 (4.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>(mod obstruction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ &lt;50% predicted</td>
<td>90 (2.7)</td>
<td>52 (1.5)</td>
<td>38 (1.2)</td>
<td>39 (1.2)</td>
<td>30 (0.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>(severe obstruction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are number (percentage) of subjects in each body mass index quintile.

This table summarises the relationship between BMI and lung function. The highest prevalence of airway obstruction was observed in quintile 1, and the lowest prevalence of airway obstruction in quintile 5. Obese subjects were less likely to have airflow obstruction than non-obese subjects despite the increased use of bronchodilators and self reported diagnosis of asthma.

These changes appear to be present in both rural and urban areas. Jang et al (33) recruited 707 older adults (aged 50-93 years) living in a high altitude (700m above sea level or higher) rural area in Korea. Trained field investigators interviewed each subject using a structured questionnaire. Questions included “wheezing in the last 12 months”, number of wheezing attacks in the last 12 months”, and “sleeping disturbing” and “exercise-limiting” wheezing in the last 4 weeks. Respiratory symptoms including wheezing and rhinitis were self-reported. Subjects were excluded if there was an acute or inflammatory disease, anti-allergy therapy or any respiratory infection in the previous 4 weeks. Spirometry and skin-prick testing were performed. Subjects were considered atopic if the erythema size to one or more allergens was equal or greater than that of histamine.

The prevalence of wheeze was higher in the group with BMI≥25 than in the group with BMI<25 (28.3% vs 12.6%, p<0.01). Atopy rates were higher in males than in females (40.3% vs 23.8%, p<0.01), and surprisingly higher in those who did not wheeze than those who did wheeze (30.4% vs 27.3%). Wheezing was associated
with a higher BMI (OR=1.1, 95%CI 1.03, 1.18) after adjusting for age, smoking status, FEV₁, gender, atopy and lipid profiles.

This study looks at a broad range of age of Korean adults and shows that symptoms of wheeze are associated with increased BMI in this group. No information on history of chronic airflow limitation or asthma was presented. Unusually, atopy rates were higher in those who did not wheeze.

Celedón et al (34) studied 7,109 adults (>18 years) from families of subjects with asthma in the province of Anhui, China. Asthma was defined either as a combination of physician-diagnosed asthma, bronchial responsiveness to methacholine at ≤25mg/ml and two or more respiratory symptoms (cough, wheezing, dyspnoea, or nocturnal cough/wheezing/dyspnoea) or asthma attacks (“asthma”); or as a combination of bronchial responsiveness to methacholine at ≤8mg/ml and two or more respiratory symptoms or asthma attacks (“symptomatic bronchial hyperresponsiveness” (BHR)). BMI was calculated for each subject and a skin test to 10 allergens with a positive and negative control.

After controlling for family history, age, skin-test reactivity to at least one aeroallergen, and cigarette smoking, there was a significant relationship between BMI and the risk of either asthma or symptomatic bronchial hyperresponsiveness in men and women. In the multivariable analysis, both underweight and overweight were associated with asthma in woman and underweight was associated with asthma in men. Among men, those with a BMI of 16 and 30kg/m² had 2.5 (95% CI 1.4 to 3.8) and 2.3 (95% CI 1.2 to 5.0) times higher odds of symptomatic BHR, respectively, than those whose BMI was 21kg/m². Among women, those with a BMI of 16 and 30kg/m² had 2.0 (95% CI 1.3 to 3.1) and 2.3 (95% CI 1.2 to 4.5) times higher odds of symptomatic bronchial hyperresponsiveness than those whose BMI was 21kg/m².
FIGURE 1.3.1.2  MULTIVARIABLE ANALYSIS OF THE RELATION BETWEEN BODY MASS INDEX AND ASTHMA AMONG ADULT MALE AND FEMALE STUDY SUBJECTS IN ANQING, CHINA (34).

This graph shows that both the underweight and obese men and women have an increased risk of asthma in rural China.

FIGURE 1.3.1.3  MULTIVARIABLE ANALYSIS OF THE RELATION BETWEEN BODY MASS INDEX AND BHR AMONG ADULT MALE AND FEMALE STUDY SUBJECTS IN ANQING, CHINA (34).

This figure shows that there is an increase in bronchial hyperresponsiveness in both the underweight and obese men and women in rural China.
The European Community Respiratory Health Survey (ECRHS) (35) is a large multi-centre cross sectional study of asthma and atopy in young men and women. There are 36 participating centres in 16 countries. These centres selected an area defined by pre-existing administrative boundaries with a population of at least 150,000. An up to date sampling frame was used to select randomly at least 1,500 men and 1,500 women aged 20-44 years. Subjects were sent the ECRHS screening questionnaire, a self-completed 9-item questionnaire asking about symptoms suggestive of asthma, the use of medication for asthma and the presence of hay fever or nasal allergies. In the second stage of the study a random sample of those who responded were invited to undergo further tests, including a more detailed interviewer led questionnaire with detailed information on respiratory symptoms, blood test for the measurement of specific IgE to D.pteronyssinus, cat, timothy grass, and Cladosporium, lung function by spirometry and bronchial challenge with methacholine. Height and weight were also measured.

Jarvis et al (36) examined data from 13,909 subjects from the ECRHS who had attended the clinic, provided blood samples for IgE and had height and weight measured. Both men and women who had a BMI≥30 were significantly more likely to report wheeze (men OR 1.49, 95%CI 1.16-1.92, women OR 1.72, 95%CI 1.34-2.20), wheeze with shortness of breath (men OR 1.85, 95%CI 1.41-2.42, women OR 2.03, 95%CI 1.59-2.58) and waking with shortness of breath (men OR 1.70, 95%CI 1.18-2.44, women OR 2.01, 95%CI 1.49-2.71). In women only who had a BMI≥30, there was an increase in the prevalence of an asthma attack in the previous 12 months (men OR 1.00, 95%CI 0.60 –1.66, women OR 1.81, 95%CI 1.27-2.60) and with physician diagnosed asthma after the age of 14 years (men OR 0.73, 95%CI 0.38-1.38, women OR 1.57, 95%CI 1.10-2.25). There were no significant increases in the use of asthma medications, or in nasal allergies.

There was no association between BMI and sensitisation to any of the 4 allergens tested. When stratified for atopic status, there was a trend for an increase in symptoms of wheeze and shortness of breath in the non-atopic group with a high BMI, though this difference did not reach statistical significance.
Chinn et al (37) then examined data from the same population and reported the results for 11,277 participants who had a methacholine challenge. They calculated the dose response slope as the measure of bronchial hyperresponsiveness (BHR), with a low slope indicating more severe BHR. Analyses were stratified by gender.

After adjusting for baseline lung function and atopy, bronchial hyperresponsiveness increased with increasing BMI in men (ECRHS slope changed by -0.027 for each unit increase in BMI, 95%CI -0.044 to -0.010, p=0.002), but the relationship in women was weak (-0.014, 95%CI -0.033 to 0.005, p=0.14).

The majority of these cross sectional studies show an excess of asthma among obese adults. The majority of these studies use self reported diagnosis of asthma whether diagnosed by a physician or not. Symptoms of wheeze and shortness of breath were also noted to be increased in the obese.

Body mass index was the principal anthropometric measure used across these studies. None looked at fat distribution or restriction in lung volume. In a few studies, where the studies examined differences by gender, the association was stronger in women. Information on BHR was conflicting, with one study showing an increase in BHR in men only (37), and another, increases in both genders (34). In another study which looked at spirometry only, despite the increase in diagnosed asthma and increased medication use, airway obstruction was not increased (32).
1.3.2 Prospective studies

In a prospective study of 85,911 women in the Nurses’ Health Study (38), participants answered a questionnaire about the following factors: age, race, current weight and height, weight at age 18, smoking status, physical activity, dietary intake, other risk factors and medical history. Participants were also asked if they had recently undergone a health screening examination and at the 2 year follow up examination, participants were also asked to measure the largest circumference around their hips and waist at the navel while standing.

All women who reported in the 1993 or 1995 follow up questionnaires that a physician had first diagnosed them as having asthma during the preceding 2 years received supplementary questionnaires on the symptoms, diagnosis, and therapy of asthma. Asthma was diagnosed if a physician had diagnosed a subject as having asthma and the subject was using a prescribed long-term preventive medication (such as inhaled corticosteroids, cromolyn sodium, nedocromil, or salmeterol) in the last year.

There were 1596 new cases of doctor-diagnosed asthma identified. Using a multivariable analysis, the relative risk of asthma was 2.7 (95%CI 2.3 to 3.1) for women with a BMI $\geq$30kg/m$^2$ compared with those in the reference group (BMI 20.0-22.4 kg/m$^2$) (figure 1.3.2.1). Increasing weight gain in these women also led to a higher risk of asthma (figure 1.3.2.2). Women who had gained 10 – 20kg since the age of 18 years had a relative risk of 1.4 (95% CI 1.2 to 1.7) of developing asthma compared with women whose weight remained stable, while those who had gained more than 25kg since the age of 18 had a much higher relative risk of developing asthma of 2.7 (95% CI 2.2 to 3.4).
This figure shows that with increasing BMI there was an increased risk of developing asthma, particularly with a BMI $\geq 30$ where the OR was 3.8 (2.9-5.0). Relative risks are adjusted for age, race, US region, smoking status, physical activity, energy intake, hysterectomy status, birth weight, and duration of breast feeding. This figure shows a marked increase in the risk of new onset of asthma in the group of nurses with a BMI $\geq 30$ kg/m$^2$. Asthma was defined as participant reported physician diagnosis of asthma on 2 separate questionnaires and use of an asthma medication since diagnosis and 1 month or less between symptom onset and physician diagnosis of asthma.
FIGURE 1.3.2.2 RELATIVE RISK OF ADULT ONSET ASTHMA DURING 4 YEAR FOLLOW UP ACCORDING TO CHANGE IN WEIGHT SINCE AGE 18 YEARS IN THE NURSES HEALTH STUDY (38).

This figure shows the strong association between weight gain and risk for the diagnosis of asthma.

When the data were further analysed, Camargo et al found that of the overall incidence of asthma in the cohort, 38% was accounted for by excessive body weight, defined as a BMI of 22.5 or higher. For women who were obese (BMI $\geq 30$), 62% of their increased risk could be accounted for by their excess weight. Alternatively, 26% of the overall incidence of asthma could be accounted for by weight gains of 2kg or more since age 18. Likewise, 60% of the risk among those gaining more than 25kg could be attributed to their weight gain after age 18.

Further analysis was also performed looking at new onset asthma of thin (BMI $\leq 18.5$) vs obese (BMI $\geq 30$) women. Compared with thin women with asthma, obese women were equally likely to report the use of an asthma medication in the past year (88% vs 90%, $p=0.50$) and the use of inhaled steroids (56% vs 59%, $p=0.49$). Thin women with asthma were also less likely than obese women with asthma to report at least 1 hospitalisation for asthma (5% vs 12%, $p=0.001$).
The Canadian National Population Health Survey (NPHS) (39, 40) followed a group of people over a 2-year period. The target population included household residents in all 10 provinces excluding Indian Reserves, Canadian Forces Bases, and some remote areas. In each household all members were asked to complete a short general questionnaire and one person was randomly selected for a more complete interview. The survey included questions related to the determinants of health, health-status and use of health services. The first cycle was performed in 1994-1995 and the second cycle in 1996-1997 using similar methodology including a longitudinal component. For the analysis, subjects were excluded if they were younger than 20 or older than 64 years, or who reported having asthma in the first cycle. In total 9,149 adults were included in the analysis. Asthma was diagnosed if the subject answered the question positively: “Do you have asthma diagnosed by a health professional?” Incident asthma cases were those who reported no asthma in the first cycle but reported having asthma in the second cycle.

Self-reported body weight and height were recorded at baseline and at follow-up. BMI was calculated and were grouped into four categories. BMI<20.0, BMI 20.0-24.9, BMI 25.0-29.9, and BMI≥30.0. Other information was collected on smoking history, educational status, history of allergy, age, immigrant status, household size, pets at home, alcohol intake and regular exercise.

Over a two-year period, the cumulative incidence of a new diagnosis of asthma was 1.6% for men and 2.9% for women. High baseline BMI was a strong predictor for women (OR 1.9, 95%CI 1.1, 3.4) but not for men (OR 1.1, 95%CI 0.3, 3.6). The average change in body weight over the 2-year period was only 0.7kg for both men and women.

The problem with this study is the small weight gain, and the short follow-up period. Weight gain of 1.4kg is unlikely to affect lung function and therefore unlikely to have any true impact on the incidence of asthma. If a weight gain of 1.4kg could affect the incidence of asthma or respiratory symptoms, then it is likely that the majority of the population would have asthma.
The 1970 British Cohort Study (BCS70) (30) is an ongoing follow up study of all individuals born between 5 and 11th April 1970 who are still living in Britain (excluding Northern Ireland). Data were collected from the cohort at birth, 5, 10, 16 and at 26 years of age. In total 8,960 individuals responded to the questionnaire at 26 years of age. The questionnaire asked whether the subject had suffered from asthma, wheezing with a cold or flu, hayfever, or eczema in the previous 12 months. Individuals who had suffered from asthma, wheeze or wheezy bronchitis in the previous 12 months at 10 years, according to information from the mother and from a medical examination were classified as having had “asthma/wheeze” at the age of 10. Birth weight was recorded by midwives from maternity records. At 10 years of age height, weight and head circumference were measured and at 26 years of age, subjects were asked to report their height and weight. BMI 25-29.9 was defined as overweight and BMI≥30 was defined as obese. Anthropometric measures were divided into quintiles.

The prevalence of asthma and wheeze at 26 years fell with increasing birth weight. This effect became stronger on controlling for gestational age (OR for asthma comparing <2kg with 3-3.5kg, 3.13 (95%CI 1.31 to 7.46)). The prevalence of asthma and wheeze increased with increasing adult BMI. The association between asthma and fatness was stronger in women, where overweight women (BMI 25.0-29.9kg/m²) had an increased risk of asthma with an OR of 1.51 (95%CI 1.11 to 2.06) and obese women (BMI≥30kg/m²) had an OR of 1.84 (95%CI 1.19 to 2.84). Similar associations between birth weight and adult BMI were present for wheeze (OR of 1.44, 95%CI 1.15 to 1.81) but not for hayfever (OR of 1.16, 95%CI 0.95 to 1.41) or eczema (OR of 1.09, 95%CI 0.85 to 1.39). There were no significant interactions between BMI and birth-weight.

BMI at 10 years was also not associated with asthma or wheeze at 26 years of age. There was no significant difference in mean BMI at 26 years between individuals with and without “asthma/wheeze” at 10-years (mean difference 0.15 (95% CI -0.17 to 0.47); p=0.36).
Beckett et al (41) tested whether asthma diagnosis is associated with weight gain and physical activity. They looked at 4,547 young American adults involved in the CARDIA (Coronary Artery Risk Development in Young Adults) study who were followed prospectively for 10 years. Follow up examinations were conducted at 2, 5, 7 and 10 years after baseline. At each examination, participants were asked whether they were taking medications for asthma or other breathing problems. They were also asked whether a doctor or nurse had ever told them that they had asthma, or whether they had a wheeze or other symptoms associated with asthma. Activity level at each examination was based on the Physical Activity History Score, which asks the frequency of participation in a range of specific heavy and moderate intensity activities in the last year.

Asthma was diagnosed if the subject had ever been told by a doctor or a nurse that they had asthma, or if the subject was taking a medication typically used to treat asthma. New onset of asthma was associated with highest and lowest baseline BMI and with an increase in body mass index. When stratified by gender, this association was only seen in females. Those subjects in the highest quintile of BMI change over the 10 years had an adjusted OR of 1.63 (1.17-2.29) for asthma incidence. Those who were in the highest quintile for BMI at baseline had an adjusted OR of 1.5 (1.05-2.16) and those who were in the highest BMI quintile at year 10 had an adjusted OR of 1.72 (1.25-2.38) for asthma incidence.

The asthma prevalence at baseline and 10-year asthma incidence was similar across the baseline physical activity quintiles. There was also no significant difference in asthma prevalence at baseline and incidence during 10-year follow-up across the 10-year change of physical activity quintiles. Subjects on average decreased physical activity and gained weight over time, but the decreased physical activity did not explain the association of weight gain with asthma.

In the Finnish twin study (42), a population of 10, 597 adult twins, initially free of asthma were followed for 9 years. The main outcome measure was questionnaire-based report of physician-diagnosed asthma. After adjusting for atopy and
respiratory symptoms, obesity at baseline increased the asthma risk in men (OR=3.00, 95% CI 1.64-5.50 for those with BMI>30 compared to those with normal weight BMI 20-24.9). There was also an association between weight and asthma in women though this was not significant. Those with a weight gain of >10kg also had a slightly increased risk of asthma. This was also not significant though may have been due to the small numbers in this group.

In the Finnish birth cohort born in 1966 (43), data was collected in pregnancy and at various ages. Adulthood doctor-diagnosed asthma with current symptoms and results of skin prick tests were obtained in 1997. The analysis was limited to 4719 subjects with complete information on asthma and atopy and anthropometric measures. Ponderal index at birth had a U shaped association with adult atopy, OR 1.30 (95% CI 1.11-1.52) for the lowest tertile and OR 1.33 (95% CI 1.13-1.55) for the highest tertile as compared to the middle tertile. The association was independent of obesity later in life. Those obese (BMI≥95th percentile) in adolescence (OR 2.09, 95% CI 1.23-3.57) and in adulthood (OR 1.99, 95% CI 1.14-3.47) had a higher occurrence of adult asthma than those with BMI<85th percentile.

Chronic inflammation associated with asthma causes an associated increase in bronchial hyperresponsiveness that leads to recurrent episodes of symptoms. Bronchial hyperresponsiveness is characteristic of asthmatic subjects and can be measured through a bronchial provocation challenge. Incremental doses of an irritant are given up to a fixed dose and FEV₁ measured at a time after the dose is given. A fall of greater than 20% in FEV₁ at or below this fixed dose of irritant is diagnostic of bronchial hyperresponsiveness. There are many different methods to perform this challenge and the variations include the type of provoking agent used, the method of delivery, and the lung function test used. Histamine and methacholine are thought to be the most useful substances for distinguishing normal from asthmatic subjects, and the technique of provocation appears to have only a small effect on the results (44).
The USA Veteran’s Administration normative aging study (45) looked at 2280 community dwelling men from the Greater Boston area who were 21-80 years of age at entry into the study which was from 1961 to 1969. Periodic examinations, consisting of a medical history and physical examination, together with spirometric tests were performed. Beginning in 1984, subjects have also been studied with a detailed respiratory symptoms and smoking questionnaire, methacholine challenge, allergy skin tests and serum IgE measurements.

Sixty-one men who had no BHR at methacholine challenge testing but who developed BHR about 4 years later were compared to 244 matched controls who also participated in the study. Initial BMI was found to have a non-linear relationship with the development of bronchial BHR in men. Compared with men with a BMI in the middle quintile, men with BMI in the lowest quintile (BMI 19.8-24.3 kg/m$^2$) and those with BMI in the highest quintile (BMI > 29.4 kg/m$^2$) were more likely to develop BHR (BMI 19.8-24.3 kg/m$^2$ OR = 7.0 (95% CI 1.8-27.7)) and BMI > 29.4 kg/m$^2$ OR = 10.0 (95% CI 2.6-37.9) respectively (Table 1.3.2.1).

<table>
<thead>
<tr>
<th>Quintiles of baseline BMI (kg/m$^2$)</th>
<th>No (%) of cases</th>
<th>univariate OR (95% CI)</th>
<th>Multivariable OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24.3</td>
<td>16 (26.2%)</td>
<td>7.0 (1.8 to 27.7)</td>
<td>7.5 (1.3 to 44.7)</td>
</tr>
<tr>
<td>&gt;24.3-25.9</td>
<td>11 (18%)</td>
<td>3.9 (1.0 to 15.0)</td>
<td>4.1 (0.7 to 25.0)</td>
</tr>
<tr>
<td>&gt;25.9-27.3</td>
<td>3 (5.9%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;27.3-29.4</td>
<td>11 (18.0%)</td>
<td>4.2 (1.0 to 16.9)</td>
<td>3.6 (0.7 to 18.5)</td>
</tr>
<tr>
<td>&gt;29.4</td>
<td>20 (32.8%)</td>
<td>10.0 (2.6 to 37.9)</td>
<td>7.5 (1.5 to 37.8)</td>
</tr>
</tbody>
</table>

*Model adjusted for age, smoking status (current, former and never smoked), packet years of smoking, log$_{10}$ IgE, and initial FEV$_1$.

This table shows that the relationship between BMI and incident BHR is non-linear with the lowest and highest quintiles having the greatest risk for BHR. This relationship was unchanged after controlling for smoking history and IgE levels and baseline FEV$_1$. 

TABLE 1.3.2.1 - CONDITIONAL LOGISTIC REGRESSION MODELS FOR THE ASSOCIATION BETWEEN INITIAL BMI AND INCIDENT BHR (45).
FIGURE 1.3.2.3 ASSOCIATION BETWEEN CHANGES IN BODY MASS INDEX (BMI) PER YEAR (IN QUINTILES) WITH DEVELOPMENT OF BRONCHIAL HYPERRESPONSIVENESS (45).

This figure shows that with weight gain, there was an increased risk of developing bronchial hyperresponsiveness and this increased with increasing weight. With weight loss, the risk of developing BHR fell.

These studies show that pre-existing obesity (Table 1.3.2.1) or weight gain (Figure 1.3.2.3) is a risk for asthma symptoms and for bronchial hyperresponsiveness. These results are inconsistent with some studies showing the increased risk is only present in women, while this study showed that obesity in men was associated with increased risk of developing bronchial hyperresponsiveness.
1.4 ASTHMA AND OBESITY IN CHILDREN

Cross sectional analyses have also shown an association between obesity and asthma in children.

Luder et al (46) looked at 209 black and Hispanic children aged between 2-18 years with asthma diagnosed by a pulmonologist but with no history of chronic oral corticosteroid use. These were compared to a general sample of 1017 black and Hispanic children aged 6-13 years enrolled in New York City schools.

Information was collected on demographics, height and weight measurements, PEFR, use of medication and number or emergency department (ED) visits and hospitalisations. A questionnaire was filled out by patients and parents. Asthma symptoms, the number of asthma medication prescribed and peak expiratory flow rate measurements were used to classify asthma severity and were related to BMI.

This study showed that black and Hispanic children with asthma were more overweight than the general population of black and Hispanic children. Of the asthmatic children, 39.7% had a BMI greater than or equal to 85th percentile (vs 32.9%), and 21.5% had a BMI in the 95th percentile (vs 15.3%) or greater. These asthmatic children were more likely to have a BMI≥85th percentile (OR 1.34, 95% CI 0.99, 1.82, p=0.06) and a BMI≥95th percentile (OR 1.51, 95% CI 1.05, 2.19, p=0.03). Having a BMI≥85th percentile was a risk factor for more severe asthma with > 30 school days missed per year (OR 2.18, 95% CI 1.09, 4.37, p=0.03), PEFR <60% predicted value (OR 6.34, 95% CI 1.83, 22.0, p=0.001), and ≥3 medications prescribed for asthma (OR 2.05, 95% CI 1.02, 4.13, p=0.05). There was no increase in the risk for ≥3 hospitalisations per year (OR 0.94, 95% CI 0.49, 1.82, p=0.85), ≥10 ED visits per year for asthma (OR 1.25, 95% CI 0.66, 2.38, p=0.50), or participation in play / sports (OR 0.85, 95% CI 0.49, 1.49, p=0.57).

Difficulties in the interpretation of this study include the broad range of ages of the children studied. More than 28% of the population of this study were in the age range 2-5 years. Lung function and asthma diagnosis are difficult in this age range.
From this study, it is impossible to determine whether the high BMI is the result of the asthma, the patient’s inactivity or medication or whether the overweight actually contributes to the development of asthma or severity of asthma. Only 12.4% of subjects were receiving inhaled steroids, though no comment is made about the percentage of subjects who received intermittent oral corticosteroids, only that there was no chronic oral corticosteroid use. In a group where 23.9% of the population required 3 or more hospital admissions in the previous year (40.2% had 1-2 admissions) and 72.2% had 3 or more presentations to the ED with asthma, the likelihood is that this group’s asthma is under treated. As a result, the increased work of breathing with being overweight or obese may have exacerbated the patient’s symptoms.

Brenner et al (47) performed a retrospective case control study of all patients 12-21 years with a diagnosis of asthma seen at a general paediatric outpatient clinic at a tertiary care paediatric facility from January 1996 to December 1997. This hospital serves south-eastern Virginia and north-eastern North Carolina Communities in the USA and cares for a predominantly insured African American population. Healthy controls were randomly selected by a computer program from a general paediatric outpatient clinic without asthma. Review of the medical records ensured that none of the controls had asthma. In addition to the asthma cases selected from the outpatient clinic, a group of asthmatic patients was selected from the pulmonary clinic from the same time period was studied to ensure a spectrum of disease severity for comparison.

Asthma severity was classified as mild or moderate to severe (48). Mild asthma was defined as those who used salbutamol, cromolyn, nedocromil, theophylline, or zafirlukast alone; had been to the emergency department less than two times for asthma and had never had been admitted to hospital for asthma during the 2-year study period. Moderate to severe asthma included those who used inhaled steroids or a combination of inhaled steroids and medications above, or had been to the emergency department 2 or more times for asthma, or had ever been admitted to the hospital for asthma during the 2-year study period. Obesity was defined as a
BMI $> 95^{th}$ percentile for age and gender and overweight was defined as a BMI between the 85$^{th}$ and 95$^{th}$ percentile for age and gender.

A total of 1,950 adolescent patients were treated in the general outpatient clinic of whom 265 (14%) were asthmatics.

### TABLE 1.4.1– COMPARISON OF PREVALENCE OF BEING OBESE OR OVERWEIGHT IN ASTHMATIC ADOLESCENTS AND NON-ASTHMATIC CONTROLS (47)

<table>
<thead>
<tr>
<th></th>
<th>All asthmatics (n=265)</th>
<th>Moderate and severe asthmatics (n=116)</th>
<th>Mild asthmatics (n=149)</th>
<th>Controls (n=482)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obese BMI $&gt; 95^{th}$ percentile</strong></td>
<td>52 (20%)</td>
<td>24 (21%)</td>
<td>28 (19%)</td>
<td>83 (17%)</td>
<td>1.17 (0.80-1.72)</td>
</tr>
<tr>
<td><strong>Overweight BMI 85$^{th}$ -95$^{th}$ percentile</strong></td>
<td>42 (16%)</td>
<td>18 (16%)</td>
<td>24 (16%)</td>
<td>73 (15%)</td>
<td>1.06 (0.70-1.60)</td>
</tr>
</tbody>
</table>

* All asthmatics vs control group

This table shows no significant increase in the prevalence of obesity or overweight between any of the groups.

This study in an adolescent population failed to show an association between asthma diagnosis or asthma severity and obesity (Table 1.4.1). This study looked at African-Americans. Potentially body fat distribution and the effects of obesity may differ between people of differing ethnic backgrounds. Gender differences were not analysed though previous studies suggest a stronger association between asthma and obesity in girls. In this study, the asthmatic population was 52% male and the control population 44% male and this difference may have confounded the results. The small number of subjects in this study may be causing a type 2 error, but Luder (46) studied only 209 asthmatic children and Gennuso (49) studied only 171 children and both of these studies showed an association.

The National Study of Health and Growth (50) collected data from 4-11 year old primary school children in England and Scotland from 1972 to 1994. Data were collected from 14 areas throughout Scotland, 22 areas throughout England and 20
English inner city areas. A parent, usually the mother, was asked to complete a questionnaire concerning the child’s asthma symptoms and socio-demographic information. Weight and height were also measured. Triceps and subscapular skinfold thickness were measured using the method described by Tanner et al (51). BMI and sum of triceps and subscapular skinfolds were converted to standard deviation scores and were used to assess levels of fatness. Asthma was defined as either at least one asthma attack in the previous year or a positive answer to the question “Does his or her chest ever sound wheezy or whistling?” Persistent wheeze information was also sought in the question “does he or she wheeze most days?” The questions on asthma and bronchitis were asked in all years from 1973 to 1994. The questions on wheeze were asked from 1973 to 1977 and from 1982 to 1994.

This analysis included 14,908 children. After adjusting for covariates age, birth weight, number of children, father’s social class, ethnicity, area and passive smoking, analyses were performed. BMI and asthma (OR 1.28, 95%CI 1.11 to 1.48), asthma attacks (OR 1.39, 95%CI 1.18 to 1.65) and persistent wheeze (OR 1.57, 95%CI 1.18 to 2.07) were positively associated. The sum of skinfolds was unrelated to asthma (OR 1.11, 95%CI 0.94 to 1.30), asthma attacks (OR 1.11, 95%CI 0.90 to 1.37) and persistent wheeze (OR 1.22, 95%CI 0.90 to 1.67). The association between asthma and BMI was stronger in girls (OR 1.56, 95%CI 1.14 to 2.14) than in boys (OR 1.14, 95%CI 0.88 to 1.47) in the inner city sample only, but was the same in the overall sample. This association was also present for asthma attacks and persistent wheeze in girls only in the inner city sample.

This study raises important questions about the concept of obesity and BMI. Why would the association be present for BMI and asthma and not for other measures of fatness such as skinfold thickness? Obese individuals differ not only according the degree of excess fat, which they store, but also in the regional distribution of fat within the body. It would be expected that an increase in subscapular skinfolds as measured in this study, indicating chest wall fat deposition, would have more of an effect on changes in respiratory function than BMI.
Skinfold thickness measurements are difficult to measure accurately, but this group reported that the variation of skinfold thickness measurement between field workers was small and the intra-class correlation for triceps skinfold was greater than 0.95 (52).

Chinn et al (53) used this data to examine the relationship between changes in BMI and prevalence of wheeze and diagnosed asthma over time. A single observation for each child was selected by restricting the data at each survey to cohorts reaching the age of 8 or 9 years from 1982 to 1994 to minimize the effects of puberty. Logistic regression was used to calculate trends in asthma, ever wheeze, persistent wheeze, and cough per year. Longitudinal data were also assessed in relation to BMI by linking data for children at cohort age 5 or 6 years with that collected 4 years later. Asthma at cohort age 9 or 10 was analysed by BMI group in children who were not reported to have asthma at the age of 5 or 6. Similar analyses were performed in relation to “ever wheeze”.

There was a significant increase in BMI in both boys and girls. Triceps skinfold thickness also increased significantly over time. There were also increasing trends for increase in asthma (OR 1.09, 95%CI 1.07 to 1.11), wheeze ever (OR 1.04, 95%CI 1.03 to 1.06), and persistent wheeze (OR 1.02, 95%CI 0.99 to 1.05), in both boys and girls. Adjusting for BMI or BMI group made no difference to the trends.
TABLE 1.4.2– UNADJUSTED TRENDS IN OUTCOME VARIABLES AND WITH ADJUSTMENT FOR AGE-SEX STANDARDISED BMI, FROM 1982-1994 IN 9,574 BOYS AGE 8 OR 9 YEARS (54).

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Relative risk per year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted trend</td>
</tr>
<tr>
<td>Attack of asthma in the last 12 months</td>
<td>1.08 (1.06-1.10)</td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>1.04 (1.02-1.05)</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>1.02 (0.99-1.04)</td>
</tr>
<tr>
<td>Attack of bronchitis in the last 12 months</td>
<td>0.95 (0.92-0.98)</td>
</tr>
<tr>
<td>Attack of asthma or bronchitis in the last 12 months</td>
<td>1.04 (1.02-1.06)</td>
</tr>
</tbody>
</table>

These tables show increasing trends in asthma and wheeze, but not in bronchitis in both boys and girls over time. Adjusting for BMI made no difference in these trends.

In 1982 there was a statistically significant variation in the odds ratio in boys (p=0.007) but no relation of asthma to BMI in girls. In 1994, there was a greater prevalence of asthma attacks in obese boys and girls than in children of normal weight and statistically significant trends with BMI SDS (boys OR 1.79, 95%CI 1.12 to 2.85, p value for trend with BMI 0.003) (girls OR 2.27, 95%CI 1.33 to 3.88, p value for trend with BMI SDS 0.011). No interaction was found between BMI SDS.
and year. Looking at children who were free of asthma attacks or wheeze at age 5 or 6 and had developed these symptoms by age 8 to 9 years, there was a clear trend of increasing incidence of both asthma (boys OR 4.74, 95%CI 2.23 to 10.09) (girls OR 4.09, 95%CI 1.40 to 11.93) and wheeze (boys OR 4.03, 95%CI 1.87 to 8.67) (girls OR 4.70, 95%CI 1.89 to 11.67) with increased BMI in both boys and girls.

This study shows inconsistencies in the association between boys and girls and also between 1982 and 1994. The study did show an increase in new symptoms of wheeze and diagnosed asthma with obesity over 4 years between the ages 5 or 6 and 8 or 9 years. This paper raises the possibility that the association between asthma and obesity may be new, and has only developed over the last 20 years, and suggests that alternative causes such as diet and lifestyle may be having the impact on asthma prevalence and not obesity itself.

The Third National Health and Nutrition Examination Survey (NHANES III) (55) explored the nutritional and health status of a stratified random sample of US population. Information was obtained on BMI, breast-feeding status, prevalence of asthma and hayfever, and atopic sensitisation as assessed by skin prick tests. Data analysis was restricted to children aged 4-17 years (n=7,505) in this analysis. Interviewers visited the subjects at home to gather demographic information and elicit a medical history. To assess the prevalence of asthma, subjects were asked whether a physician had ever told them they had asthma, whether they still had asthma, and whether a doctor had ever treated them for asthma. The number of episodes of wheeze in the past 12 months, the number of hospital and emergency room visits, the number of hours the subject watched television on the day before the examination, and the frequency of play or exercise per week were assessed. Exposure to cigarette smoking and breast-feeding status and the duration of breast feeding was also collected.
Height and weight were measured and BMI was calculated. BMI percentile scores (Z scores) were computed. Skin prick tests to a panel of aeroallergens were performed in 6-17 year old subjects.

Having been breast fed was found to be inversely related to BMI. After adjustment for potential confounding factors such as age, gender, ethnicity, household size, and exposure to passive smoke, a significant association between BMI and asthma was present.

**FIGURE 1.4.1. ASSOCIATION BETWEEN ASTHMA, WHEEZE AND ATOPY AND BMI QUARTILES IN CHILDREN AGED 4-17 YEARS (55).**

This figure shows that after adjustment for gender, ethnicity, age, household size, and passive smoke exposure, there is an increase in the risk for current asthma, treatment for asthma, and wheeze in the last 12 months in the highest quartile for weight. There was no association between atopy and BMI once corrected for the confounding factors.
Similar studies are appearing from all over the world. Bibi et al (56) in 1997 recruited 6,510 children from all 2nd grades (8 yr old) in the Ashkelon region in Israel. Of these 6,010 children completed the health questionnaire and performed spirometry. Weight and height were measured. Any child greater than the 95th percentile for BMI was defined as obese. All children (n=26) under the 5th percentile were excluded from the analysis.

Any child whose parents answered, “Yes” to the question, “Has your child been diagnosed “asthmatic” by a physician?” was defined as having asthma. Parents were similarly asked if a physician had ever diagnosed their children with allergy. All the asthmatic children were further investigated by spirometry before and after bronchodilators. Improvement in FEV₁>6% after bronchodilators was considered bronchial hyperresponsiveness.

Three hundred and two children (5.05%) were considered obese (males n=123, (40.7%) females n=179 (59.3%)). Israeli born children were more likely to be obese than immigrant children (5.3% vs 4.1%), though the difference was not significant (p=0.11). Socio-economic status was defined by crowding and parental education was not significantly different between the obese and non-obese groups (p=0.12 and p=0.14 respectively). Smoking by both parents was more common among the obese group than in the non-obese group (15.5% vs 10.9%, p=0.016).

Obese children were more symptomatic than non-obese children. Obese children reported more cough (16.2% vs 7.2%, p<0.001) and wheeze (20.5% vs 9.6%, p<0.001) than non-obese children respectively. Asthma and medication use was more common in obese children than non-obese children (asthma 11.9% vs 6.2%, p<0.001, medication use 15.9% vs 8.8%, p<0.001). There was no significant difference in the diagnosis of allergy.

There were significant differences between genders. More obese boys than girls complained about chest symptoms (cough 22% vs 11.7%, wheeze 26.8% vs 16.2% and shortness of breath 42.1% vs 26.3%), had more asthma (14.6% vs
10.1%), and used more medication (19.5% vs 13.4%), but there was no statistically significant difference in the diagnosis of allergy between obese boys and obese girls (24.2% vs 19.6).

Pulmonary function tests showed better FEV$_1$% predicted among the obese non-asthmatic subjects than the non-obese non-asthmatic subjects (94.2% vs 91.2%, p<0.005). FVC% predicted was also better in the obese non-asthmatic subjects than the non-obese non-asthmatic subjects (90.7% vs 87.4%), though it appears that this difference was not significant as no p value was given. There was no difference in obstruction as measured by FEV$_1$/FVC% between the obese and non-obese non-asthmatic groups (83.5% vs 84.0%). There were no differences between the obese and non-obese asthmatic groups in FEV$_1$% predicted (89.8% vs 89.7%), FVC% predicted (89.6% vs 88.4%), or FEV$_1$/FVC% (81.3% vs 81.2%). Post bronchodilator increase in FEV$_1$>6% was significantly greater among the non-obese asthmatic group than the obese asthmatic children (51.4% vs 27.8%, p<0.01).

No statistics were given if there was a significant difference in prevalence of symptoms, diagnosis of asthma or use of medication between obese boys and girls. With increasing symptoms in boys, it would also be interesting to know if there were lung function changes in the degree of restriction or obstruction between the genders. Surprisingly in this study, no data are presented on bronchodilator responsiveness in the obese non-asthmatic group despite using a liberal definition of bronchodilator responsiveness at an improvement in FEV$_1$ of 6%. If obesity were a risk for the development of asthma, it would be expected that a proportion of this group may be developing a degree of bronchial responsiveness. Is the paper no confidence intervals were presented, therefore the variability in these results is not known.

Several longitudinal studies have been undertaken in children. Castro-Rodriguez (57) looked at 1246 US children participating in a birth cohort enrolled between 1980 and 1984 in the longitudinal Tucson Children’s Respiratory Study. Parents
completed questionnaires when the children were age 6yr, 8yr, 11yr and 13yr. The questionnaires reported the child’s respiratory symptoms, start of puberty and exercise. “Infrequent wheezing” and “frequent wheezing” were defined as ≤3 and >3 wheezing episodes in the previous year. Children wheezing at 11 or 13 years of age were further classified as “persistent” if they wheezed at age 6 and “incident” if they did not. Weight and height were measured at year 6 and year 11. BMI percentile was calculated for each child. Children <85th percentile were considered “non-overweight”, ≥85th-95th percentile were “overweight” and ≥95th percentile were “obese”. Skin prick testing was performed at year 6 and year 11. PEFR recordings were performed at year 11 twice a day for 4 days and spirometry was performed before and after 2 inhalations of albuterol at year 11.

Females who became overweight or obese had a higher prevalence of infrequent (OR 3.5, 95% CI 1.3-9.9) and frequent wheeze (OR 3.1, 95% CI 0.7-13.6) at year 11 and of frequent wheeze at year 13 (OR 4.8, 95% CI 1.2-18.8) compared with females who did not become overweight or obese. Males who became overweight or obese had similar prevalence of infrequent (yr 11 - OR 0.9, 95% CI 0.3-2.5) and frequent wheezing (yr 13 - OR 0.7, 95% CI 0.1-6.2) at all surveys compared with males who did not become overweight or obese.

Increased peak flow variability (OR 3.1, 95% CI 1.0-9.6) and bronchodilator responsiveness defined as ≥15.2% change in predicted FEV₁ after albuterol (OR 5.7, 95% CI 1.6-20.1) was also demonstrated in girls only.

Among females, a trend was also observed for an association between change in BMI and the prevalence of at least one positive skin test to allergens at yr 6. A majority (54.2%) of females who became overweight or obese were skin test positive at year 6 compared with 35.9% of females who did not become overweight or obese, p=0.08. No such trend was observed among males (51.5% vs 48%, p=0.7). There was also no relation between changes in BMI status and skin prick testing at year 11 in either females or males.
Huang et al (58) recruited subjects from 7 junior high schools, one in Taipei city, 3 in towns and 3 from rural areas in Taiwan. All eighth grade students in randomly sampled classes filled in a questionnaire which was modified from the ISAAC core questionnaire (59). Wheezing and rhinitis were based on self-reported symptoms. All participants watched the ISAAC video in the previous year. Those who had both rhinitis and itchy/watery eyes were classified as having allergic rhinitis symptoms. Students who agreed to participate, with written informed consent form parents, received skin prick tests and methacholine provocation tests in the following days at school.

A total of 1,459 students (completion rate 71.9%) had complete data. Spirometry and a methacholine challenge were performed. BHR was defined as a decline of 20% or more in FEV$_1$ from the post saline value with inhalation of methacholine at concentration of <10mg/ml. Height and weight of students were measured on the day of the test. Skin prick testing was also performed.

### TABLE 1.4.4: PREVALENCE OF ATOPY, ALLERGIC RHINITIS AND WHEEZING SYMPTOMS AND BRONCHIAL HYPERRESPONSIVENESS (BHR) ACCORDING TO QUINTILES IN GIRLS AND BOYS (58).

<table>
<thead>
<tr>
<th>BMI QUINTILES</th>
<th>Girls (n=692)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td></td>
<td>22.6</td>
<td>20.7</td>
<td>28.1</td>
<td>25.2</td>
<td>37.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Rhinitis symptoms</td>
<td></td>
<td>12.4</td>
<td>15.7</td>
<td>16.6</td>
<td>15.1</td>
<td>22.1</td>
<td>0.058</td>
</tr>
<tr>
<td>Ever wheezed</td>
<td></td>
<td>3.0</td>
<td>6.6</td>
<td>8.0</td>
<td>9.5</td>
<td>9.6</td>
<td>0.024</td>
</tr>
<tr>
<td>BHR</td>
<td></td>
<td>8.2</td>
<td>18.6</td>
<td>17.4</td>
<td>18.0</td>
<td>20.7</td>
<td>0.015</td>
</tr>
<tr>
<td>BHR in non-atopic</td>
<td></td>
<td>7.6</td>
<td>15.3</td>
<td>10.0</td>
<td>10.6</td>
<td>13.6</td>
<td>0.50</td>
</tr>
<tr>
<td>BHR in atopic</td>
<td></td>
<td>10.0</td>
<td>31.0</td>
<td>36.8</td>
<td>40.0</td>
<td>32.7</td>
<td>0.052</td>
</tr>
</tbody>
</table>
This table shows that there is an association between the highest quintile in BMI and atopy, wheeze and BHR in girls. This increase in BHR is present primarily in atopic and not in non-atopic girls. There is also a trend to an increase in symptoms of allergic rhinitis. Boys were more atopic than the girls, but none of the associations between BMI and atopy, rhinitis, wheeze or BHR are present in boys.

Further analyses were performed and living in the city and family history of asthma affected atopy risk in both sexes, whereas sibling number and parent education affected only boys. After controlling for these variables, girls with the highest BMI quintile had an increased risk of being atopic, compared to girls in the middle 3 quintiles (OR 1.77, 95%CI 1.15-2.73) and compared with boys (OR 0.90, 95%CI 0.60-1.34). The association between high BMI and rhinitis symptoms in girls was removed when adjusted for atopy.

Bronchial hyperresponsiveness to triggers such as histamine, methacholine and exercise is a frequent finding in children with asthma (17, 60). Exercise induced bronchospasm (EIB) has also been found significant proportions of non-asthmatic children with other atopic diseases, in relatives of atopic patients and in formerly “wheezy infants”. When symptomatic, exercise induced bronchospasm presents as cough, chest tightness, shortness of breath or easy fatigue and sometimes, as wheezing during or after exercise. Frequently overweight or obese adults or children may report similar symptoms.

Kaplan et al (61) recruited a cohort of prepubescent, non-asthmatic obese and non-obese children and looked at their bronchial response to exercise. Twenty
seven children were recruited – 14 non-obese and 13 obese children between 6-10 years of age. Obese subjects had a body weight >95th percentile for age and none of the subjects could have a history of asthma, wheezing, bronchitis, bronchodilator use, or any other cardiopulmonary disease.

The same investigator measured height and weight. Skinfold measurements were taken at the biceps, triceps, subscapular and supra-iliac sites using the method of Durnin and Womersley (62).

The exercise challenge was performed, with no warm up, and the treadmill was set at a grade of 10% and an initial speed of 2.0-3.5mph was chosen, based on the patient’s size and confidence on the apparatus. The speed was then increased to achieve a heart rate of at least 170 beats per minute (bpm) (approximately 85% of predicted maximal heart rate) as soon as possible. The exercise duration was 7 minutes. The results of the 2 best forced expiratory efforts before exercise were compared with results of seven single efforts collected every 3 minutes, starting at 2 minutes after exercise. Lung function test parameters analysed included FVC, FEV1, PEFR, and FEF 25%-75%. A positive result for EIB was defined as a fall in FEV1 or in PEFR of ≥15% or in FEF 25%-75% of ≥25% at any point within 20 minutes after exercise.

Ethnic distribution of the 27 subjects was 7 Anglo-Saxon (2 obese), 7 black (4 obese) and 13 Hispanic (7 obese). Five subjects had a history of allergic rhinitis or other allergies; 3 of these were obese (2 with EIB) and 2 were non-obese (1 with EIB). Eight subjects had a family history of asthma or other allergic diseases; 6 were obese (3 with EIB) and 2 were non-obese (1 with EIB).

Nine of thirteen obese and 6 of 14 control subjects met the criteria for EIB. While these proportions were not significantly different, a significant difference was obtained for a minimum fall of 15% (11 of 13 vs 6 of 14, p<0.05) for each of the 3 pulmonary function test parameters assessed.
FIGURE 1.4.2 – COMPARISON BETWEEN OBESE AND CONTROL SUBJECTS OF DEGREE OF PERCENTAGE FALL IN PULMONARY FUNCTION AFTER EXERCISE (61).

This figure shows that there was a significant fall in FEV₁% between the obese (10.4% +/- 7.3(SD)) and control group (4.1% +/- 7.4(SD)). There was also a significant fall in %FEF₂₅-₇₅% between the obese (24.4% +/- 11.2(SD)) and the control group (12.4% +/- 17.2(SD)). Although there was an increase in the fall in PEFR in the obese group, this was not significant due to the large variation in PEFR falls within the groups.

The time course pattern of bronchial reactivity was not different between the groups.

This study raises an important question. Does obesity predispose children to airway narrowing particularly of the small airways with exercise? Conversely do symptoms of EIB such as wheeze or shortness of breath with exertion stop these children from exercising or exercising at high intensity? This limitation may exacerbate or even cause weight gain.
This study has a difference in the number of atopic subjects in each group. Thirteen out of 27 subjects were atopic and 9 of these 13 subjects were in the obese group. Only 4 out of 13 obese subjects were non-atopic, whereas 10 out of 14 non-obese subjects were non-atopic. This predominance of atopic subjects in the obese groups makes it difficult to know if this increase in bronchoconstriction with exercise is due to the atopy causing a degree of BHR or whether it is the obesity affecting pulmonary function as none of the analyses were corrected for atopy. Differences in ethnicity are also present within the groups. With a small number in each cohort, the influence of ethnicity cannot be ascertained.

Another potential explanation in the causal pathway is that obesity itself increases the risk for atopy. There is increasing evidence in the literature that obesity is an inflammatory condition. Associations have been shown between tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6), IL-1β and C-reactive protein and the obese state (63-65). IL-6 and TNFα have been found to be expressed by adipocytes and to correlate with total fat mass (66, 67). Leptin is a satiety hormone expressed in adipocytes in proportion to their mass, and serum leptin concentrations are 4-6 times greater in severely obese humans in comparison to slim people (68), suggesting leptin resistance in obesity. In addition to its effects on the regulation of body weight, leptin is pro-inflammatory (69). Even after controlling for BMI, Guler et al (70) found that leptin levels were increased in asthmatic boys compared with non-asthmatic boys (3.09 (95% CI 1.99-7.51) vs 1.52 (95% CI 1.06-3.17) p=0.003) despite having a similar BMI. Atopic asthmatic subjects had significantly higher leptin levels than non-atopic asthmatic subjects (p=0.038) with a similar BMI. A significant, but weak correlation was observed between leptin levels and IgE in the boys (r=0.231, p=0.010). There was no relation between leptin levels and skin prick tests, pulmonary function tests, passive smoking, birth weight and duration of breast-feeding.

Shore et al (71) sensitized mice with ovalbumin to determine whether leptin can augment allergic responses in the lung. Saline or leptin were infused into the mice
as a continuous infusion. Two days later the mice were challenged with aerosols of either normal saline or ovalbumin once per day for 3 days. Measures of bronchial responsiveness, bronchoalveolar lavage were performed and blood was taken to measure IgE 24 or 48 hours after the last challenge. Leptin infusion increased serum leptin concentration, which were further increased after ovalbumin sensitization and challenge. Ovalbumin challenge increased bronchoalveolar lavage fluid cells and cytokines, serum IgE, lung cytokine mRNA expression and responses to inhaled, aerosolized methacholine. The changes in methacholine responsiveness and IgE were augmented in the leptin versus saline infused mice. These results indicated that serum leptin may further increase allergic reactions in the airways, suggesting that leptin may increase the response to other triggers.

Del Rio Navarro et al (72) performed a trial looking at 58 paediatric patients between 8-16 years old and divided them into 4 groups depending on their weight and clinical status. Group 1) 15 non-obese asthmatic subjects with body weight between 25-75th percentile and BMI between 15-20kg/m^2. Group 2) 15 obese asthmatic subjects with BMI>95th percentile and overweight greater than 120% of ideal body weight. Group. 3) 15 obese non-asthmatic subjects with body weight >95th percentile, BMI >25kg/m^2 and overweight greater than 120% of ideal body weight; group 4) 15 healthy non-asthmatic subjects with body weight between 25-75th percentile and BMI between 15-25kg/m^2. The non-asthmatic subjects had no family history of atopy and no history of any symptoms suggestive of asthma. There was no difference in age or height between the groups. There was also no difference in BMI between the non-obese asthmatic group (19.5 ± 3.5kg/m^2) and the non-obese non-asthmatic group (19.3 ± 3.5kg/m^2) or between the obese asthmatic group (30.5 ± 3.5kg/m^2) and the obese non-asthmatic group (30.5 ± 3.5kg/m^2).

All subjects exercised on a treadmill started at a speed of 1km/hr and a gradient of 0° increasing 1.5km/hr and 2.5% inclination each 30 seconds for 2 minutes until 6km/hr and 10° inclination was reached. When the patients achieved their sub maximal heart rate, they continued for 4 more minutes with the same workload.
The average time for the exercise challenge was 6-8 minutes. Spirometry was performed before the challenge and at 2, 5, 10, 15, 20, 25, 30 and 60 minutes after exercise. A positive test was defined when FEV$_1$ fell by >15% or FEF 25-75% fell by >25% from baseline value.

**FIGURE 1.4.3 - MEAN PERCENTAGE FEV$_1$% DURING EXERCISE IN ASTHMATIC AND ASTHMATIC AND IN OBESE AND NON-OBESE CHILDREN (72).**

This graph shows a significant fall in FEV$_1$% in all groups except the non-obese non-asthmatic group during exercise. The obese asthmatic group had the biggest fall in FEV$_1$. The non-obese asthmatic group and the obese non-asthmatic group had similar responses to exercise.

They further analysed each group separately and found that in the non-obese asthmatic group 12/15 subjects had EIB, in the obese asthmatic group 15/15 had EIB, in the obese non-asthmatic group 11/15 had EIB, though 0/13 had EIB in the non-obese non-asthmatic group.
This study showed that obese asthmatic subjects had an increased fall in FEV₁% from the non-obese asthmatic subjects during exercise. Obese non-asthmatic subjects had a similar fall in FEV₁% to non-obese asthmatic subjects with exercise.

There are several major problems with this study. It is hard to believe that none of the non-obese non-asthmatic group had exercise-induced bronchoconstriction. Statistics were performed showing a greater fall in 3 out of the 4 groups; but statistics were not given for differences between the groups. The authors also comment on increases in symptoms in the obese subjects, though their graphs conflict with the data presented in the article. None of the asthmatic subjects could have used corticosteroids in the last 2 months, which begs the question about the validity of the diagnosis of asthma, if only 12/15 had EIB. Other problems include the lack of baseline demographic information about the subjects. No other information was presented such as exposure to smoking in the household or family history of asthma. Lung function was also not corrected for percent predicted per subject, which may also affect the results.

Despite some major concerns, this is a very interesting study. Do subjects in obese asthmatic group hyperventilate more at the same level of exercise, resulting in a greater fall in lung function than in the non-obese asthmatic group? Furthermore, why do obese non-asthmatic subjects group with no family history of atopy have a fall in lung function with exercise? Does prevention of a deep breath cause changes in airway smooth muscle that causes bronchoconstriction in response to exercise without true airway inflammation, or do obese children have an increase in obesity regulating hormones such as leptin, which may also affect the lung and set off an inflammatory reaction, thereby causing a degree of bronchial hyperreactivity without a family history of atopy.
1.5 THE EFFECT OF ASTHMA ON WEIGHT

Cross sectional and case control studies cannot rule out the possibility that adults and children with asthma may exercise less and become overweight or obese, or that medication use for asthma may contribute to this weight gain.

During the 1950’s and 1960’s weight gain was one of the most frequently documented adverse side effects of oral corticosteroid treatment for patients with asthma (73). In the last 30 years new types of inhaled corticosteroids have been introduced which act locally and are more rapidly bio-transformed, but there is still a possibility that inhaled corticosteroid drugs have clinically relevant systemic side effects.

Corticosteroids, β2 agonists and theophylline have been the most common drugs for the treatment of asthma over the last 30 years. Since studies have shown weight reducing effects of β2 agonists (74) and theophylline (75), it is reasonable to assume that a positive association between self reported medication use for asthma and increasing body weight may be attributed to corticosteroids if other important risk or confounding factors could be controlled.

Hedberg et al (76) looked at the relationship between asthma medication and body weight in two combined randomised samples of the adult Swedish population 16-60 years of age. This age range was chosen to exclude subjects with chronic obstructive pulmonary disease (COPD).

In 1988 / 1989 13,295 people were interviewed and of these 11,690 people were also interviewed in 1996 / 1997. Information on self reported height and weight were obtained. Men and women with a BMI<30 were used as non-obese control groups, and those with a BMI≥30 were classified as obese. In tables where asthma medication was the dependent variable, subjects with BMI<18.5 were classified as underweight, 18.5-24.9 as normal and 25.0-29.9 as overweight. In the Living Condition Surveys 1988/1989 and 1996/1997, subjects were asked about self reported asthma and whether they had taken medication for asthma for at least 14
days during the last year. Subjects were also asked about their smoking history, degree of physical activity, education level, and regions where they lived.

TABLE 1.5.1 - PREVALENCE OF OBESITY IN THE ADULT MALE AND FEMALE POPULATION, 16-60 YEARS OF AGE AND MEDICATION USE FOR ASTHMA (76).

<table>
<thead>
<tr>
<th>Treatment status</th>
<th>Obese males</th>
<th>Odds ratio and 95% confidence intervals</th>
<th>$\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>(n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicated asthma</td>
<td>8.4</td>
<td>21/249</td>
<td>1.17 (0.52-2.68)</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-medicated asthma</td>
<td>7.3</td>
<td>11/151</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Obese females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>(n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicated asthma</td>
<td>11.7</td>
<td>44/377</td>
<td>2.16 (0.95-5.12)</td>
<td>3.9</td>
</tr>
<tr>
<td>Non-medicated asthma</td>
<td>5.8</td>
<td>8/139</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

This table shows that asthmatics taking medication were more likely to be obese than asthmatics not taking medication in both men and women, though this was only significant in women. After adjustment for other covariates including age, Swedish region, smoking history, physical activity and level of education, there was no significant increase in prevalence of obesity in subjects on asthma medication in men (OR 1.21, 95%CI 0.55-2.64) or women (OR 1.97, 95%CI 0.89-4.38) compared to men and women with non-medicated asthma.

Problems with this study include the lack of differentiation between types of asthma medication or between oral and inhaled administration of drugs. Those with inhaled $\beta_2$ agonists were grouped with those on oral corticosteroids, thereby making it difficult to truly assess the effects of asthma medication on weight.
TABLE 1.5.2– PREVALENCE, CRUDE ODDS RATIOS AND CHI SQUARE FOR TREND FOR MEN AND WOMEN ON SELF REPORTED ASTHMA MEDICATION USE IN RELATION TO BMI CATEGORIES IN 2 REPRESENTATIVE SAMPLES OF THE ADULT POPULATION 16-60 YEARS OF AGE (76).

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>Men on asthma medication*</th>
<th>Odds ratio and 95% confidence intervals</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>5.2 5/97</td>
<td>1.91 (0.68-4.98)</td>
<td>0.77</td>
<td>0.381</td>
</tr>
<tr>
<td>Acceptable weight</td>
<td>2.8 142/5143</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>2.7 81/2965</td>
<td>0.99 (0.74-1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>4.4 21/477</td>
<td>1.62 (0.99-2.64)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>Women on asthma medication*</th>
<th>Odds ratio and 95% confidence intervals</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>3.7 14/374</td>
<td>1.00 (0.56-1.78)</td>
<td>33.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Acceptable weight</td>
<td>3.7 225/6038</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>5.3 94/1763</td>
<td>1.46 (1.13-1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>9.9 44/446</td>
<td>2.83 (1.99-4.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Women and men with non-medicated asthma were excluded.

This table shows that there was an increase in proportion of men and women on asthma medication who were obese. This increase does not give an indication for the direction of causality only that asthma, asthma medication and obesity are linked.
1.6 THE EFFECT OF WEIGHT ON SEVERITY OF ASTHMA

Belamarich et al (77) studied the cohort of 1528 children recruited in the National Cooperative Inner-City Asthma Study (NCICAS). The study group consisted of 1528 children aged 4 to 9 years with asthma recruited from emergency departments and primary care clinics in 8 inner city areas in the USA. Participants were recruited during emergency department visits for asthma or other acute illnesses or injuries, or from primary care clinics during visits for routine care of asthma follow up care.

At recruitment, each study child was required to meet at least one of the following definitions of asthma: 1) having been told by a physician that the child has asthma, in combination with cough, wheezing, shortness of breath, or whistling or tightness in the chest lasting for >3 days within the past 12 months or 2) cough, wheezing, or shortness of breath that lasted > 6 weeks during the previous 12 months and 3 out of the following 5 conditions: a) cough wheezing, or shortness of breath present more than half the days and nights during the 6-week period, b) cough, wheezing, or shortness of breath aggravated by exercise or cold air, c) a parent or sibling with asthma, d) no history of antibiotic therapy for sinusitis, accompanying the cough, or e) cough, wheezing or shortness of breath that resulted in disturbance of the child’s sleep. Height and weight were also measured. Obesity was defined as a BMI >95th percentile using the NHANES II data (27). Non-obese children were defined as a BMI 5th percentile to BMI 95th percentile. Children with a BMI <5th percentile were considered to be underweight and were excluded from the analysis.

A structured interview was conducted with the child’s primary carer concerning the demographics of the household, ethnicity, access to medical care, and adherence to treatment and medication use in the 3 months before the baseline interview. Information on the home environment and exposure to tobacco smoke were also collected. Skin prick testing to indoor allergens was performed and urine was collected to assay for cotinine. The child’s psychological health was also measured.
using a modified version of the Child Behaviour Checklist (CBCL). At intervals of 3, 6, and 9 months from the baseline visit, measurements of health service use and asthma symptoms were obtained from the primary carer.

Information of health service use included: 1) hospitalisations for asthma, 2) unscheduled doctor or clinic visits for asthma (including ED visits), and 3) ED visits for asthma. Questions assessing asthma symptoms included the number of days the child wheezed, the number of nights the child was awakened by asthma, and the number of days the child’s play was slowed because of asthma symptoms in the previous 2 weeks. Medication usage was not assessed in the follow up period. Peak flow measurements were obtained using a mini-Wright peak flow meter. The recorded measurement was the highest of 3 maximal expiratory manoeuvres obtained during the baseline visit. For children recruited during an ED visit, measurements of baseline peak flow measurements were deferred for 4 weeks.

**TABLE 1.6.1– BASELINE DEMOGRAPHIC DATA ON ATOPY STATUS AND MEDICATION USE CHARACTERISED BY OBESITY (77).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese</th>
<th>Non-obese</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=249</td>
<td>N=1073</td>
<td></td>
</tr>
<tr>
<td>Number of positive skin reactions to indoor allergens</td>
<td>2.02±1.90</td>
<td>1.99±1.89</td>
<td>Not given</td>
</tr>
<tr>
<td>Oral steroid used in previous 3/12</td>
<td>75/246 (30%)</td>
<td>250/1042 (24%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Used ≥2 medications in previous 3/12</td>
<td>156/246 (63%)</td>
<td>570/1042 (55%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Results are presented ± standard deviation

This table shows that there was no difference in atopy status between the obese and non-obese subjects, but there was a significant increase in oral steroid use and medication usage in the 3 previous months.
TABLE 1.6.2 – PEAK FLOW, HEALTH SERVICE UTILISATION AND SYMPTOMS BY OBESITY (77)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese</th>
<th>Non-obese</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Predicted peak-flow baseline</td>
<td>85.54 (+19.19)</td>
<td>83.18 (+22.37)</td>
<td>0.15</td>
</tr>
<tr>
<td>Proportion hospitalised</td>
<td>0.12 (+0.33)</td>
<td>0.12 (+0.32)</td>
<td>0.81</td>
</tr>
<tr>
<td>Proportion with unscheduled visits</td>
<td>0.58 (+0.50)</td>
<td>0.51 (+0.50)</td>
<td>0.23</td>
</tr>
<tr>
<td>Proportion with ED visits</td>
<td>0.39 (+0.49)</td>
<td>0.31 (+0.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Days of wheezing /2 week period</td>
<td>3.97 (+3.22)</td>
<td>3.41 (+2.78)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nocturnal awakenings / 2 week period</td>
<td>1.68 (+2.14)</td>
<td>1.78 (+2.34)</td>
<td>0.64</td>
</tr>
<tr>
<td>Days of slowed activity / 2 week period</td>
<td>2.03 (+2.36)</td>
<td>1.95 (+2.27)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

This table shows no difference in the baseline PEFR between the obese and non-obese groups. There was also no difference in the proportion hospitalised with asthma, but there was a significant increase in the proportion of ED visits and days of wheezing. There was also no difference in nocturnal awakenings or slow activity.

This study shows no difference in lung function but increased wheezing, increased medication usage and increased ED visits. In the 3 months before the study, there was also an increase in prednisolone usage and more subjects had used 2 or more medications for their asthma.

With no baseline difference in lung function and increases in symptoms and medication usage, potentially asthma may not be the cause of wheeze. Increasing medication requirements for asthma, including oral corticosteroids, due to limited responses to bronchodilators and inhaled steroids, may be potentially increasing their obesity and symptoms. Thus, bronchoconstriction or airway inflammation may not be the cause of symptoms.

The childhood asthma management program (CAMP) (78) looked at 1,041 children with asthma. Inclusion criteria included age between 5-12 years, asthma for at
least 6 months, mild to moderate asthma severity and methacholine sensitivity. BMI was not associated with symptoms of asthma, nor was it associated with atopy. BMI was only associated with increased cough and wheeze with exercise. While BMI was positively associated with methacholine concentration that caused a 20% fall in forced expiratory volume in 1 second ($PC_{20}FEV_1$), this association did not persist after adjustment for $FEV_1$. Increasing BMI was associated with increasing $FEV_1$ and forced vital capacity (FVC) but decrements in the $FEV_1/FVC$ ratio.

Another study looked at all patients that were cared for at the Asthma Centre of Excellence in Brooklyn, New York, in the 12 month period from February 2000 through to February 2001 (79). All adults that had a diagnosis of asthma made by a pulmonologist were included into the study. The patient’s asthma was graded according to the NHLBI 1997 guidelines. These guidelines categorise asthma severity into four categories based on clinical symptoms, medication usage and pulmonary function results. Patients were labelled as either being mild intermittent, mild persistent, moderate persistent, or severe persistent asthmatics and mean BMI was calculated for each group.

One hundred and forty three adults aged 18-88 years were included. Of these 72% were obese. Females with asthma were significantly more overweight than males. Mean BMI for the 2 groups were 35.9kg/m$^2$ and 32.1kg/m$^2$ respectively ($p=0.01$). There was a significant relationship between worsening severity of asthma and increasing BMI ($r= 0.40$, $p<0.001$) (figure 1.6.1).
FIGURE 1.6.1- DIFFERENCES IN ASTHMA SEVERITY WITH BMI (79)

This figure shows the mean BMI of each of the asthma severity groups. There was an increase in BMI with increasing asthma severity. Due to the small number in each of the groups, there is a large overlap between the groups.

The problems with this study are that there is no objective assessment of the patients lung function, or of the diagnosis of asthma. This is a tertiary referral centre and being referred difficult patients with hard to treat asthma, it appears that despite optimal treatment, they have a large number of subjects requiring long-term oral corticosteroids at doses up to 60mg per day. Potential questions arise as to whether alternative diseases or other factors are contributing to the severity of asthma, or whether asthma alone is the diagnosis.
1.7 THE EFFECT OF INTENTIONAL WEIGHT LOSS ON ASTHMA

If obesity was a risk factor for asthma, then asthma severity and bronchial hyperresponsiveness may well improve and even potentially resolve with significant weight loss. There are several studies that have looked at the effect of weight loss on asthma symptoms, medication use and lung function.

Stenius-Aarniala (80) et al evaluated the effects of weight loss on asthma symptoms, lung function, courses of oral steroids and quality of life. This was a non-blinded trial where 38 patients were randomised either to an intensive dietary weight loss programme or to a control group. At the end of the weight reduction programme, the participants in the treatment group had lost a mean of 14.5% of their pre-treatment weight or 14.2kg and at 12 months, the mean weight reduction was 11.1kg (1.1-22.5kg) or 11.3% of their pre-treatment weight. In the control group, the changes in weight were small, with a mean weight loss of 0.3kg at the end of the programme and a mean gain of 2.3kg (2.2%) after one year. In the weight loss group, there was a 7.9% improvement in FEV$_1$% predicted (range 3.4% to 12.4%, p=0.001) and 7.9% improvement in FVC% predicted (range 4.4% to 11.4%, p=0.0001). Overall, there were also improvements in dyspnoea as measured by a visual analogue score. There was also a reduction in the use of rescue medication of 0.5 doses per day in the weight loss group and no change in the control group (p=0.002). Health status as measured by the St George’s respiratory questionnaire showed a significant improvement in symptoms (p=0.04) and impact scores (p=0.02).

In this study, there were parallel improvements in both FEV$_1$ and in FVC, which might occur in obese subjects without asthma also losing weight and may not be specific to obese asthmatics. No measures of bronchial responsiveness were performed, and it is unclear whether the improvements in lung function and respiratory health status are due to an improvement in asthma and bronchial reactivity or to improvements in lung volume and reduction in the work of
breathing. Alternatively, major changes in diet, such as a strict weight loss regime may also improve asthma.

Aaron et al (81) prospectively studied 58 obese women who presented to a weight loss clinic with a body mass index of >30kg/m$^2$ and were enrolled in an intensive 6 month weight loss program. Patients were commenced on 3 liquid meal replacement supplements per day, which delivered 300 kilocalories per meal for 6-12 weeks depending on baseline BMI. A restricted calorie diet, regular counselling and followed up of enrolled patients occurred on a weekly basis for at least 6 months. Patients were assessed with lung function including methacholine responsiveness, lung volumes and symptoms and disease specific quality of life questionnaire using the St George Respiratory Questionnaire (SGRQ) before the beginning the weight reduction program, at 3 and at 6 months after enrolling in the weight reduction program.

Twenty-four of the patients had a doctor diagnosis of asthma at enrolment and 21 of these patients were receiving mediation for asthma at enrolment. The mean BMI (± SD) of the patients was 43.1±8.8kg/m$^2$ and the mean body weight was 115±26kg. Fifty of the patients completed the study and lost an average of 20kg over the 6-month period or 17.4% of their pre-treatment weight.

For every 10% relative loss of weight, the FVC improved by 92ml (p=0.05) and the FEV$_1$ improved by 73ml (p=0.04), but bronchial reactivity did not significantly change with weight loss (p=0.23) (figure 1.7.2). Even those who lost >13% of their pre-treatment weight, despite improvements in FEV$_1$, FVC and TLC had no change in BHR (p=0.57). Patients who completed the 6-month weight loss program experienced improvements in respiratory health status, irrespective of weight loss.
This graph shows that weight loss at 6 months is correlated with improvements in both FEV$_1$ and FVC. There were no improvements in airway obstruction.

This figure shows no correlation between weight loss at 6 months and change in bronchial reactivity as measured by methacholine.
In a subgroup analysis of 24 patients who had a doctor diagnosis of asthma, no changes were shown in PC20 with weight loss. In these patients, for every 10% relative loss of weight the log$_2$ change in PC20 improved by only 0.19 (ie one fifth of a doubling dilution p=0.66).

Patients enrolled in the weight loss program experienced a significant improvement in their disease specific quality of life, as measured by the SGRQ. The largest changes were seen in the activity domain of the questionnaire, but all domains improved significantly. There was no correlation between weight loss and change in the SGRQ score over 6 months (r=-0.12, p=0.44). Patients in the lowest quartile of weight loss experienced similar 6 month improvements in symptoms (change in total SGRQ score -11.8+/− 13.1(SD)) compared to patients in the upper three quartiles who lost more weight (change in total SGRQ score -8.7+/− 10.5(SD), p=0.42).

The problem with this study is that there is no indication of the baseline levels of bronchial reactivity in either the asthmatic or non-asthmatic obese groups. If the group had non-reactive airways at the beginning of the study despite a degree of restriction, it would be unlikely for significant changes in bronchial reactivity to occur with weight loss. It would also be interesting to know the changes in asthma medication usage in the asthmatics with weight loss.

Dixon et al (82) evaluated symptom scores from 32 obese asthmatic subjects before and after obesity surgery after a laparoscopic adjustable gastric banding (LAGB) (Lap-Band®). The prevalence of doctor diagnosed asthma initially was 24.6% of the population, which is significantly higher than the general prevalence in the Australian community of 12 to 13% (83). Thirty-two patients who were followed up had mean weight loss of 36.1kg (preoperative weight 125.2kg and follow up weight of 89.3kg) and mean BMI decreased from 45.7kg/m$^2$ preoperatively to 32.9kg/m$^2$ at follow up. The study looked at self reported severity of asthma, its impact on day to day living and medication use for asthma. All self reported severity of asthma improved and medication used to treat asthma was
significantly reduced. Twenty were using much less, 6 were using less and 6 were using the same amount of medication. None was using more medication. Before surgery, 14 patients took daily medication for asthma with β2 agonists and at least one preventer, and two patients were taking continuous oral corticosteroids. Seven patients were admitted to the hospital on one or more occasions for severe asthma in the year prior to surgery. None required hospitalisation for asthma during the follow up period after surgery and 6 were taking daily medication for asthma, with none on continuous oral corticosteroids. Overall, 24 patients rated their asthma much improved, 6 were improved and 2 were unchanged. Eleven (34%) of the respondents had complete resolution of all asthma symptoms and felt that it no longer affected their day to day living in any way.

This study showed marked improvements in asthma severity after significant weight loss with bariatric surgery. Lap-Band® surgery is also good anti-reflux surgery and in conjunction with marked improvements in sleep apnoea due to weight loss, may have contributed to the improvements in asthma severity. Marked changes in energy intake due to markedly reduced stomach capacity occur with changes in dietary composition after the surgery. It is unknown which of these factors may have contributed to the improvement in asthma status. It is also unknown how rigorously the diagnosis of asthma was made initially and no lung function was performed. With no verification of the diagnosis of asthma and the appropriateness of the medication being used, changes in symptoms of shortness of breath and wheeze associated with obesity itself may have underscored the changes in diagnosis, medication use and symptoms of asthma.
POTENTIAL MECHANISMS OF THE RELATIONSHIP BETWEEN ASTHMA AND OBESITY

1.8 EFFECT OF CHANGE IN LUNG VOLUME AND POSTURE ON BRONCHIAL RESPONSIVENESS IN ASTHMATICS AND NON-ASTHMATICS

Ding et al (84) studied 9 non-asthmatic male subjects and looked at the effects of changing the end expiratory lung volume on the magnitude of methacholine induced bronchoconstriction. Subjects were chosen from the laboratory staff and ranged in age between 29 to 55 years of age.

A methacholine (MCh) challenge was performed and dose response curves were measured. MCh was used in doubling concentrations using pulmonary resistance ($R_L$) as the response. MCh was nebulised and the duration of the dose given was 2 minutes and the dosage interval was 5 minutes. Measurements of $R_L$ were made for 30 seconds at functional residual capacity (FRC), 1 minute after the dose of MCh. For these measurements, the subjects breathed tidally but at a rate of 30 breaths per minute. The subjects then breathed to a new end expiratory lung volume and measurements of $R_L$ were made again for at least 30 seconds. In 5 subjects, the new target end expiratory lung volume (EELV) was FRC -0.5L and in 2 subjects FRC+0.5L. Measurements were made in a body plethysmograph and an oesophageal balloon in situ. $R_L$ was calculated as the average value obtained over 10 consecutive breaths. Two subjects could not complete the protocol which left 7 subjects.

There was a marked difference between the dose response curves to MCh for $R_L$ measured at FRC and at lower EELV. In the initial dose response curves, 4/5 subjects reached a maximum $R_L$ well below the highest MCh concentration of 256mg/ml. The dose response curve to MCh for $R_L$ measured at FRC–0.5L was displaced upward, and these differences were most marked at the higher concentrations of MCh. Only 1/5 subjects reached a plateau of $R_L$ at FRC–0.5L.
The dose response curves to MCh for the 2 subjects who responded were measured at FRC and FRC+0.5L. The maximal response of both subjects was much less at FRC+0.5L. After a change in EELV the value of $R_L$ changed rapidly, and although there was a variation between the subjects, $R_L$ had changed in all subjects within 5 breaths.

The problem with this study is the small number of subjects included in the study. Changes in $R_L$ were also not corrected for airway size. As the lung volume fell by half a litre, airway size would also have fallen.

Because a change in body posture from sitting to supine is associated with a reduction in lung volume, Shardonofsky et al (85) hypothesised that bronchial responsiveness to inhaled methacholine should be affected by body posture. Ten laboratory staff (non-smokers) were recruited, aged 24 to 42 years. Nine had no history of respiratory disease and 1 had a history of mild asthma but was stable and required no treatment at the time of the study.

Bronchial responsiveness was assessed in both sitting and supine postures on separate days. Subjects inhaled aerosols of saline and methacholine in progressively doubling concentrations (0.125 to 256 mg/ml). Aerosols were inhaled for 2 minutes of tidal breathing through the open mouth via a face mask, always in the sitting posture. BR was assessed in both sitting and supine postures in random order on separate days and at the same time of day, by measuring partial and complete forced expiratory flow-volume curves (PEFV and MEFV, respectively) obtained 30 seconds after the cessation of aerosolization. After several tidal breaths, subjects were asked to perform a forced expiration from the inspiratory end tidal volume to residual volume (RV), and then a full inspiration to total lung capacity (TLC) followed by a forced expiration to RV, and finally a full inspiration to TLC. Flows were measured from both the PEFV and MEFV curves at a volume equivalent to 80% of the baseline vital capacity below TLC and were termed V20p and V20c respectively.
As indices of BR, the authors used the concentration of MCh at which the FEV\textsubscript{1} fell by 10% relative to post saline FEV\textsubscript{1}, the concentration of MCh at which V\textsubscript{20p} fell by 20% relative to post saline V\textsubscript{20p} and the maximal percentage fall in FEV\textsubscript{1} relative to the post saline value. Lung volumes were measured in the upright position by using a body plethysmograph. In 9 subjects, an oesophageal balloon was inserted and volume pressure relationship of the lung was also studied.

There were no significant differences in FVC, FEV\textsubscript{1} and V\textsubscript{20p} with change from the upright to supine posture. Lung volumes were not measured in the supine posture. TLC was assumed to be unchanged in the supine posture and change in FRC was calculated by subtracting the values of the inspiratory capacity (IC) from those of TLC in the upright position. $\Delta$FRC from sitting to supine was calculated to be -0.85±0.09L (SEM). The MCh at which the FEV\textsubscript{1} and V\textsubscript{20p} fell by 20% relative to the post saline values and MCh concentration at 50% of the maximal fall in FEV\textsubscript{1} were also calculated (EC\textsubscript{50}).

In the supine posture most of the subjects had an increase in BR to MCh relative to that in the sitting posture with a significant increase in maximal response (MR) (mean maximal fall in FEV\textsubscript{1} 16.3% sitting and 29.9% supine, p<0.009) and decrease in PC\textsubscript{10} values (mean change in PC\textsubscript{10} 16.3mg/ml sitting and 3.0mg/ml supine, p<0.02). The MCh concentration at 50% of the maximum fall in FEV\textsubscript{1} (EC\textsubscript{50} 1.1mg/ml sitting and 1.1mg/ml supine) was similar in both body positions implying that the position of the methacholine concentration response curves did not change. Using V\textsubscript{20p} as an alternative index of BR, showed increased responses in 4/10 subjects in the supine position, but there was no significant difference in the group as a whole (V\textsubscript{20p} 2.0mg/ml sitting and 0.6mg/ml supine, p=0.26).

An inverse relationship was found between $\Delta$MR and pulmonary elastic recoil pressure ($P_L$) at 90% TLC ($r=0.73; p<0.05$). $\Delta$MR was not correlated with the $\Delta P_L$ or with $\Delta$FRC. The mean baseline V\textsubscript{20c}/V\textsubscript{20p} ratio was 1.06 for sitting and 1.04 for the supine posture. During MCh challenge they increased to 5.86 for
sitting and 17.04 for supine posture. $\Delta$MR was independent of $V20c/V20p$ in either posture.

This paper shows an increased maximal response to an airway challenge with change in posture from sitting to the supine posture. The increased maximal response was also inversely related to pulmonary elastic recoil. No change in the position of the methacholine curve was present.

Major faults with this paper include the lack of information about the length of time that the subject was in the supine posture before the challenge. No information was presented as to whether the subjects were supine for 1 minute or 30 minutes before the challenge. All of the lung function testing was also performed in the sitting posture even in the supine challenge. The subjects did not stay supine for more than 1 minute in the intervals between aerosol inhalations, implying that the time on the nebulisers was also spent in the upright position, thereby limiting the effect of the supine posture on lung function. In fact with only one minute spent supine, it is surprising that there was any effect on lung function. Several breaths were also performed during each dose and deep inspiration may have had an effect on overcoming airway obstruction. Corrections were also not made for airway size, which may have explained the changes seen.

1.9 GASTRO-OESOPHAGEAL REFLUX AND POTENTIAL EFFECTS ON LUNG FUNCTION.

Asthma is a disease in which multiple triggers cause or exacerbate an inflammatory response thereby increasing symptoms and or inflammation. Gastro-oesophageal reflux (GER) is potentially one of these triggers.

GER is a condition where gastric contents flow in a retrograde direction across the gastro-oesophageal junction into the oesophagus causing symptoms or inflammation.

The results of studies investigating the prevalence of GER disease among asthmatics vary greatly. Studies using 24-hour pH monitoring report GER
prevalence ranging from 32% to 82% (86, 87). Kiljander et al (88) recruited all adult patients examined because of asthma in 4 teaching hospitals in Finland in 1990. In total 2,225 patients attended the outpatient clinics or were treated on the wards of the study hospitals during that year. A random sample of 158 asthmatics was formed by arranging the patients in ascending order according to date of birth and social security number and selecting every 14th patient for the sample. Patients were excluded if their asthma diagnosis was not made according to the American Thoracic Society (ATS) criteria (89). Sixty per cent (90 subjects) agreed to participate. A 24-hour oesophageal pH monitor was performed on all patients participating in the study. All subjects also filled out a questionnaire including questions about their pulmonary and gastric symptoms. Patients were considered to be free of GER symptoms if they reported heartburn less than weekly.

Pulmonary function tests including flow volume loops were performed during the same visit when the pH monitoring was completed. All subjects that had a FEV₁>45% predicted also had a methacholine challenge performed. During the challenge, MCh was nebulised in 5 cumulative doses up to 2,600mcg and spirometry was repeated after each dose. The challenge was stopped when FEV₁ fell >20% compared to baseline, or the maximum dose of methacholine had been administered. A patient was considered to have BHR if his or her FEV₁ decreased ≥20% during the challenge. All study interventions occurred during the years 1992-1993. Gastro-oesophageal reflux disease (GERD) was defined as abnormally high acid exposure time in the distal oesophageal during the 24-hour oesophageal pH monitoring.

Of the 90 subjects who agreed to participate, 75 had a FEV₁>45% predicted and were challenged with MCh. BHR was found in 52 of these subjects (69%). Abnormal acid reflux into the distal oesophagus was documented in 32 of the subjects (36%). Eight of these patients (25%) were free from typical GERD symptoms. As to demographic data, the patients with abnormal acidic reflux did not differ from those without (n=58). Due to the small numbers, symptomatic (24) and
non-symptomatic subjects (8) with GERD were not compared. Forty-seven of the patients (52%) presented with typical GERD symptoms. Twenty-four of these patients (51%) had GERD on pH monitoring.

No significant correlation between FEV\textsubscript{1} and pH parameters in the distal oesophagus was present. Neither was there a significant association between FEV\textsubscript{1} and pH parameters in the proximal oesophagus, except a weak association between FEV\textsubscript{1} and the number of reflux episodes \((r=0.29, p<0.05)\), and the time during which the pH<4 in the upright position \((r=0.27, p<0.05)\).

This study showed that 36% of a random sample of adult asthmatic patients had GERD. Not all of these patients had typical GER symptoms such as heartburn or regurgitation. Interestingly, the presence of typical GER symptoms in an asthmatic patient did not guarantee the presence of significant GER.

Concerns about this study include the fact that only 69% of the asthmatic group had a positive methacholine challenge, which may lead to concerns about the diagnosis of asthma, though 70% of the group were taking inhaled corticosteroids, and 6% were using oral corticosteroids which may normalise BHR if present (90). Methacholine challenges were performed and although the percentage of asthmatics with a positive challenge were given, it would have been interesting to know whether there was any correlation with BHR and degree of GERD present.

Reflux of gastric contents may affect asthma and lung function through a variety of mechanisms. Possibilities include vagal oesophageal bronchial reflex causing bronchoconstriction, heightened bronchial reactivity, or micro-aspiration of oesophageal contents into the upper airway. Oesophageal acid may also increase minute ventilation and respiratory rate without bronchoconstriction.

Wright et al (91) studied 136 subjects and found significant reductions in airflow and oxygen saturation after oesophageal acid infusion. Atropine pre-treatment abolished these findings, providing more evidence for an acid induced vagally mediated oesophageal bronchial reflex.
Field (92) performed a review of all studies using the 1966 to 1997 MEDLINE database looking at the effects of spontaneous reflux and acid perfusion (AP) in adult asthmatics. Eighteen studies of GER and acid perfusion in asthmatic adults were identified.

**TABLE 1.9.1 – EFFECTS OF ACID PERFUSION (AP) ON PULMONARY FUNCTION (92)**

<table>
<thead>
<tr>
<th></th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>FEF&lt;sub&gt;25-75%&lt;/sub&gt;</th>
<th>PEFR</th>
<th>V&lt;sub&gt;50&lt;/sub&gt;</th>
<th>V&lt;sub&gt;25&lt;/sub&gt;</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic GER</td>
<td>6/126</td>
<td>6/75</td>
<td>52/69</td>
<td>13/41</td>
<td>21/20</td>
<td>69/42</td>
</tr>
<tr>
<td>No symptomatic GER</td>
<td>0/48</td>
<td>0/26</td>
<td>0/28</td>
<td>7/24</td>
<td>0/11</td>
<td>0/52</td>
</tr>
<tr>
<td>All asthmatics</td>
<td>6/174</td>
<td>6/101</td>
<td>52/97</td>
<td>20/65</td>
<td>21/31</td>
<td>69/94</td>
</tr>
<tr>
<td>Percent unaffected by AP</td>
<td>97%</td>
<td>94%</td>
<td>65%</td>
<td>77%</td>
<td>60%</td>
<td>58%</td>
</tr>
</tbody>
</table>

This table gives a summary of 18 studies that were reviewed by Field (92). The numbers in each section show the number of asthmatics in the studies who did show changes in pulmonary function / those who did not show changes in pulmonary function during acid perfusion. The last line of the table shows the percent of the total population who were unaffected by acid perfusion.

Table 1.9.1 gives a summary of the 18 studies. These reports which contain data on 312 asthmatics, found that the FEV<sub>1</sub> and mid-expiratory rates did not change during acid perfusion and GER in the studies containing 97% and 94% of the asthmatics, respectively. Flow volume loop indices, including the flow rate at 50% of the vital capacity (V<sub>50</sub>), flow at 25% of the vital capacity, and the peak expiratory flow rate, did not change during AP or GER in the studies with 77%, 60% and 64% of the asthmatics respectively. Small changes in the resistance were reported in the studies containing 42% of the asthmatics. Among asthmatics without symptomatic GER, no changes in spirometry, resistance, and flow volume indexes were found, except for a 10% decline in V<sub>50</sub> in one study with 7 subjects.

Clearly, the data presented in this review does not support the hypothesis that GER-induced bronchospasm accounts for the pulmonary function worsening in
asthmatics with GER. Yet asthmatics with GER frequently experience reflux associated respiratory symptoms including shortness of breath.

These acid perfusion studies may not have shown an effect on lung function, but asthmatics have different sensitivities to a variety of triggers, such as allergens, exercise and cold air. It would be reasonable to expect that some asthmatics might respond to GER whereas others might not, or the effects of GER may be delayed. Asthmatic medication was continued in some of the studies, which may have blunted the potential changes in lung function due to GER. Alternatively rather than having a direct effect on lung function, GER may increase the sensitivity to other triggers.

None of these studies has looked at whether there is an effect of GER on carbon monoxide diffusing capacity. Aspiration of acid or bulk fluid into the airways and potentially thence into the lung parenchyma or alveolar tissue could cause chronic inflammation. Chronic inflammation in the lung parenchyma may progress to pulmonary fibrosis with airway obstruction and gas exchange impairment.

Animal studies have shown that continuous aspiration of acid into lungs causes pulmonary inflammation and pulmonary fibrosis (93). Fifteen young hybrid rabbits of either sex were used. Eight rabbits had milk aspiration and remaining 7 had saline aspiration as a control group. The rabbits were sedated, paralysed, intubated and ventilated, and an oesophageal balloon was inserted. Rabbits without any initial response to MCh were excluded from the study. MCh challenge was performed at 4 points, 1) initial, before tracheal instillations; 2) middle, after two weekly instillations; 3) final, after five weekly instillations; and 4) recovery, after a 3-week recovery period from the time of the last instillation. After each MCh challenge, and before the saline or milk instillations, a bronchial wash was performed. Following the MCh challenges, supine rabbits were given instillations through a suction catheter positioned through and 1cm beyond the tip to the endotracheal tube. Sterile physiological saline or sterile cow’s milk was then instilled at a volume of 0.25mL/kg over 5 seconds. Airway physiology
measurements included transpulmonary pressure, airflow, tidal volume, central airways resistance, and dynamic lung compliance.

There was no significant difference in bronchial reactivity between the rabbits at the initial and middle observation points, but the milk group had significantly increased bronchial reactivity at the final and recovery points. Differential counts of bronchial lavage specimens showed increased polymorphonuclear leukocyte percentages at the middle and final observation points between the milk and saline groups. Differences were also noted in pulmonary alveolar macrophage percentages at the final point and eosinophils at recovery. There was no difference in the lipid laden macrophage numbers.

This study shows that there is a significant difference in bronchial reactivity after four consecutive weekly instillations of milk as opposed to saline in a group of rabbits. The difference continues after a 3 week recovery period. This occurred without any significant change in baseline airway resistance. Bronchial washings showed increases in neutrophils and activated alveolar macrophages after the further week in the milk group. There were also a significantly higher percentage of eosinophils in the milk group after recovery.

This study interestingly shows that regular milk aspiration causes airway inflammation and increases in bronchial reactivity in a group of rabbits with a degree of bronchial reactivity at baseline. Eight weeks is apparently a long time in the life of a rabbit, so could repeated aspiration into human lungs in a predisposed subject cause a similar response? The problems with this study, is the small number of rabbits studied, and the rabbits had to have a degree of bronchial reactivity initially or else they were excluded. We also have no knowledge of the applicability of the results of this study to human lungs or to whether aspiration of gastric contents in humans is similar to instilling milk into animal lungs.

Tobin et al (94) looked at the question of how GER may affect lung function by a completely alternative method. He recruited 17 consecutive patients with newly
diagnosed idiopathic pulmonary fibrosis (IPF) and 8 patients with interstitial lung disease (ILD) other than IPF at the University of Washington Medical Centre. All patients underwent dual channel ambulatory oesophageal pH monitoring. All patients had an extensive evaluation, including a medical history including a careful history of pulmonary and gastro-oesophageal reflux symptoms, medications, ethanol intake and smoking history, chest x-ray, pulmonary function tests including diffusing capacity of carbon monoxide corrected for haemoglobin and surgical lung biopsy. Height and weight were also recorded.

Eight of 17 subjects with IPF and 3 of 8 with ILD were receiving oral corticosteroids at the time of the study and 2 of 17 patients with IPF and 1 of 8 with ILD were receiving inhaled β2 agonists at the time of the study. No subjects were on theophylline at the time of the study. No patients referred specifically for GER symptoms were included in the study.

Sixteen of 17 (94%) patients with IPF had abnormal acid exposure in the distal and/or proximal oesophagus. Eleven patients with IPF had abnormal distal and proximal acid exposure, 4 had abnormal distal acid exposure and only 1 had abnormal proximal acid exposure times. In the 8 patients with ILD, 3 had abnormal distal and proximal values and one had abnormal proximal exposure only (p=0.02). When the supine position only was investigated, there were more acid exposure times in the patients with IPF than the patients with ILD. Comparing the mean percentage of acid exposure times between the IPF and ILD groups in the distal oesophagus, there were significant differences for total (13.6 vs 3.34, p=0.006), upright (12.4 vs 5.1, p=0.04) and supine reflux (14.7 vs 0.88, p=0.02). In the proximal oesophagus, there was a significant difference between the IPF and the ILD group in the mean percent acid exposure time in the supine position only (7.5 vs 0.24, p=0.04). Results were unchanged after controlling for potential confounders (gender, age, lung function, $D_{LCO}$, BMI, oral corticosteroid or β2-agonist use). There was no association between lung function (as measured by $D_{LCO}$) and acid exposure times in this study (p>0.4 for all acid exposure times).
Twelve of the 16 patients (75%) with IPF and the entire ILD group with abnormal reflux did not have the typical GER symptoms of heartburn or regurgitation. The most prominent symptom in both groups was cough.

This study shows that patients with IPF have a high prevalence of abnormal oesophageal acid exposure without typical GER symptoms. GER tends to occur at night and often extends into the proximal oesophagus. Potentially GER may be an aetiological factor or exacerbating in patients with IPF.

Potentially patients with lung disease may be at an increased risk for GER because of increased pressure gradient across the diaphragm, changes in pulmonary mechanics or medication effects.

Anvari et al (95) looked at 69 consecutive patients with severe GERD booked for laparoscopic fundoplication. All patients had been on long term (greater than 1 year) anti-reflux (Omeprazole 20-80mg) medication. Preoperatively all subjects underwent full pulmonary function testing, 24-hour pH recording, oesophageal manometry, endoscopy and a full symptom assessment. The pulmonary function testing was repeated at 1 month postoperatively and again at a minimum of 6 months later. In addition, the 24-hr pH study, oesophageal manometry and symptoms scores were repeated 6 months or more following the surgery. Twenty five of the 69 patients were referred for intractable respiratory symptoms related to GERD.
TABLE 1.9.2 PREOPERATIVE PULMONARY FUNCTION TESTING (95).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean ± SD % predicted</th>
<th>Number &lt;70% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>69</td>
<td>103.22 ± 14.03</td>
<td>1</td>
</tr>
<tr>
<td>FEV₁</td>
<td>69</td>
<td>100.20 ± 13.39</td>
<td>0</td>
</tr>
<tr>
<td>TLC</td>
<td>68</td>
<td>101.24 ± 14.17</td>
<td>2</td>
</tr>
<tr>
<td>D_{LCO}</td>
<td>68</td>
<td>74.84 ± 11.91</td>
<td>25</td>
</tr>
<tr>
<td>D_{LCO}/VA</td>
<td>68</td>
<td>79.03 ± 14.76</td>
<td>16</td>
</tr>
</tbody>
</table>

This table shows that preoperatively in the group there was no airway obstruction or reduced lung volumes. There was a reduction in diffusing capacity and diffusing capacity corrected for lung volume. 36.7% of subjects had a $D_{LCO}$ less than 70% predicted and 23.5% of subjects had a $D_{LCO}$/VA less than 70% predicted.

Significant improvements were present in all measures of GER 6 months postoperatively with reduction in 24-hr pH score, increase in lower oesophageal sphincter tone and improvement in symptom scores for heartburn and cough. Of the 49 patients with preoperative cough, 36 reported improvement or total abolition of their cough, 4 patients reported no change, and 2 patients reported worsening of their cough.

Thirty-two patients completed pulmonary function tests at 1 month and 40 had tests at 6 months or later. There was no significant difference between preoperative pulmonary function and measurements at 1 month and greater than 6 months.
FIGURE 1.9.1 CHANGES IN DIFFUSING CAPACITY POST-OPERATIVELY IN ALL SUBJECTS (95).

This figure shows no difference in $D_{CO}$ or $K_{CO}$ at 1 or 6 months post-operatively. The 13% fall in $D_{CO}$ on the second post-operative day, once corrected for lung volume shows a 6% increase in $K_{CO}$ which indicates that the fall in diffusing capacity was due to the reduction in lung volume.

FIGURE 1.9.2 CHANGES IN DIFFUSING CAPACITY 6 MONTHS POST-OPERATIVELY IN SUBJECTS WITH AN ABNORMAL $D_{CO}$ (95).

This figure shows that of the sixteen patients with a reduced diffusing capacity pre-operatively, there was an improvement in $D_{CO}$ and $K_{CO}$ at 6 months post-operatively.
This study does not give any information about preoperative lung disease or smoking history. Statistics and numerical data were not presented about the post-operative lung function changes only that they were significant, though when looking at the figure, the confidence intervals overlap markedly with the pre-operative results.

This study shows that potentially GER may affect lung function and exacerbate lung disease in pre-disposed subjects.
1.10 SUMMARY OF LITERATURE

Multiple studies, including several reviews (96, 97), provide evidence that the increases in obesity and asthma are linked. This association is present in both adults and in children, in various ethnic groups, in both urban and rural communities and in different parts of the world.

In most of the studies, asthma was defined as physician-diagnosed asthma, presence of asthma symptoms such as shortness of breath and wheeze, use of asthma medication, or emergency department visits related to asthma. Concerns include whether these symptoms in the obese are measuring asthma-like symptoms rather than true asthma. Diagnosing asthma is not always an easy task. The National Asthma Council of Australia defines asthma as a chronic inflammatory disorder of the airways in which causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning in susceptible individuals. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness (BHR) to a variety of stimuli (3). The diagnosis of asthma is usually based on history, examination and supportive diagnostic testing. Optimally, the diagnosis of asthma would contain all of these components; airway inflammation, BHR and symptoms. How well or consistently physicians diagnose asthma is unknown.

Large epidemiological studies also have difficulty with the “gold standard” definition of asthma. Optimally the definition includes symptoms, along with the demonstration of airflow obstruction that is at least partially reversible or BHR. The exclusion of alternative diagnoses is also important.

Testing of bronchial responsiveness itself has difficulties, as a significant number of people thought to have asthma do not have BHR and a considerable proportion
of people with BHR are asymptomatic. This overlap is particularly striking in population-based studies.

Once the definition of asthma in these studies includes the presence of BHR, the association between obesity and asthma is far less consistent with studies showing a range of results from a small increase in risk in men only (37), or in both genders (34).

In children and adolescents, studies have shown an increased risk of BHR induced by an exercise challenge in obesity regardless of asthma status (61, 72), but other studies have shown no BHR with methacholine (98) or hypertonic saline challenge (99).

**TEMPORALITY OF ASSOCIATION**

If obesity is a cause of asthma, it must precede the development of the disease, rather than the reverse. It has been suggested that asthma might lead to physical inactivity and subsequent weight gain and obesity. However, several prospective studies have now found a positive association between weight gain and development of new asthma, thereby providing support for the thought that obesity in fact precedes the development of asthma.

Alternatively, we should consider whether asthma medication could increase the risk of obesity. Although obese asthmatics have increased use of medication compared with non-obese asthmatics, it is unlikely that this is the case. Small amounts of weight loss have been shown with β2 agonists and theophylline and no studies have shown significant weight gains with inhaled corticosteroids. Although oral corticosteroids have significant side effects including weight gain, with the advent of newer inhaled corticosteroids, oral corticosteroid use for asthma is reducing in frequency.
DOSE RESPONSE

The presence of a dose response gradient (ie more of a dose leads to more of an effect) supports the idea of causality. A modest dose response relationship has in fact has been described in various studies whereby the risk of asthma increases with increasing weight gain (38). Several studies have also shown an increase in asthma risk in the underweight.

MECHANICAL ASSOCIATIONS

Obesity itself has a mechanical effect on airway calibre, reducing the ability of deep inspiration to dilate the airways or lack of tidal stretch causing latching of airway smooth muscle. These mechanical changes may affect bronchial responsiveness.

The most consistent alteration in lung function found in obesity is a reduction in functional residual capacity (FRC) due to the effect of the abdominal contents on the position of the diaphragm (100). Obesity has also been associated with decrements in tidal volume, which fails to increase during time of dynamic stress such as exercise (101). In severe obesity, the majority of tidal breaths are taken around closing volume (102). Decreases in FRC and low tidal volumes infer small cycling rates, resulting in the conversion of airway smooth muscle from rapidly cycling actin-myosin cross bridges to slowly cycling latch bridges (103). The attainment of the latch state has been hypothesised to be the reason that obstruction persists in asthmatic airways (103). The latch state has also been postulated to result in increased bronchial responsiveness (103).
The latch hypothesis. Obesity leads to decrements in functional residual capacity (FRC) and tidal volumes (VT), resulting in dynamic decreases in smooth muscle stretch. The resultant latching of the smooth muscle leads to enhanced airways reactivity and irreversibility of obstruction. These effects may be enhanced by breathing around the closing volume, which is characteristic of severe obesity.

Furthermore, these effects may be enhanced by breathing around closing volume (104). The latch state may therefore explain the observations that decrements in FRC, as occur in obesity have been tightly correlated with increased airways resistance and responsiveness to methacholine (84).

In addition to its effects on FRC, tidal volume, and closing volumes, obesity has been associated with decrements in forced expiratory flow in the mid portion of FVC (FEF_{25-75}) (105). FEF_{25-75} improves significantly with weight loss (106). The FEF_{25-75}/FVC ratio has also been independently associated with methacholine responsiveness of the airways (107).

In children, the mechanical load of obesity might affect lung growth, leading to reduced pulmonary function, a known risk factor for asthma. The observation that weight loss results in improved pulmonary function but unaltered airway responsiveness is consistent with a role for obesity in airway remodelling, which is not often reversible.

Gastro-oesophageal reflux is commonly associated with asthma. The estimated prevalence of GER in asthmatics ranges above 80% in adults (86) and up to 60%
in children (108, 109). Possible mechanisms for GER related asthma symptoms include acid induced bronchoconstriction, either by direct micro aspiration or by a vagally mediated reflex. Medical or surgical treatment of GER results in an improvement in asthma symptoms in about 70% of patients. Obesity has been frequently cited as an independent risk factor for GER and GER symptoms. Mechanically this effect may be mediated via increased abdominal pressures, which increase the gastro oesophageal pressure gradient. Both medical and surgical weight loss regimens have been associated with improvements in GER symptoms. These findings have lead to the speculation that GER might mediate the relationship between asthma and obesity.

INCREASED SYMPTOMS

Some of the studies showed an increase in asthma in obesity without changes in lung function consistent with obstruction or BHR. This suggests that obesity itself may cause increases in shortness of breath and wheeze in the absence of true asthma. Symptoms may due to increased work of breathing associated with obesity itself, reduction in lung volume, deconditioning or changes in perception of symptoms with obesity. Alternatively, diseases with increased frequency in obesity, such as gastro oesophageal reflux and obstructive sleep apnoea may also present with shortness of breath, wheeze and waking at night with symptoms. The lack of specificity of the questions about symptoms such as shortness of breath or wheeze may also lead to increased reporting of symptoms when asthma is not present.

INCREASED ATOPY / INFLAMMATION IN OBESITY

There is increasing evidence in the literature that obesity is an inflammatory condition, with a chronic, low grade systemic inflammation characterised by increased circulating leukocytes and increased serum concentrations of cytokines, cytokine receptors, chemokines and acute-phase proteins. The origin of this inflammation appears to be at least in part the adipose tissue itself. Importantly, systemic inflammatory markers correlate with the presence of diseases common to
obesity, including type II diabetes and atherosclerosis. Obesity increases serum TNF-α, while TNF receptors are expressed on airway smooth muscle, and exogenous TNF-α has been shown to increase in vitro contractility of mouse airways to a variety of contractile agonists (110). Leptin is a satiety hormone expressed in adipocytes in proportion to their mass, and serum leptin concentrations are 4-6 times greater in severely obese humans in comparison to slim people (68), suggesting leptin resistance in obesity. In addition to its effects on the regulation of body weight, leptin is pro-inflammatory (69) which might have a pro-inflammatory effect on the airway. Coupled with the increased serum leptin observed in obesity, the pro-inflammatory effects of leptin suggest that this hormone might be relevant to asthma. Interestingly, even after controlling for BMI, increased leptin levels are present in the serum of asthmatic boys compared to non-asthmatic children.

Adiponectin may also have a role in the association between asthma and obesity. Adiponectin is the most abundant gene product of adipose tissue. Plasma adiponectin levels are decreased in obesity and increase after weight loss (111, 112). Although the primary effects of adiponectin are on metabolism, adiponectin also has anti-inflammatory properties, which inhibits proliferation and migration of cultured vascular smooth muscle cells induced by mitogens (113). It is not known whether adiponectin has similar effects on airway smooth muscle.

Several studies are now showing increases in the prevalence of atopy in the obese, which may suggest that the pathway of causation may be obesity → atopy → asthma.

ENVIRONMENTAL FACTORS

Obesity might also be associated with environmental factors such as sedentary lifestyle, leading to increased exposure to indoor allergens, different dietary nutrient intake that might affect respiratory status, and developmental factors leading to different fetal programming of the airway.
WEIGHT CHANGE STUDIES

Several prospective studies conducted among adults, have examined the effect of weight gain on the future risk of incident asthma. In the Nurses’ Health Study (38) and the Coronary Artery Risk Development in Young Adults study increases in self-reported weight strongly predicted asthma incidence. However, in the National Population Health Survey (40) and Finnish Twin Cohort study (42), increases in weight were associated with a non-significant increase in asthma incidence. Short follow up periods and small weight gains may reduce the ability to show an effect.

If excess weight does cause asthma, then weight loss could be expected to improve the clinical status of patients with asthma. The results from bariatric surgery are impressive with significant weight loss, and improvements in asthma control, medication usage and symptoms (82). Physician diagnosed asthma was used to define the patient group and neither lung function nor bronchial hyperresponsiveness was studied. Changes in dietary composition and energy intake occur post operatively and significant improvements in gastro-oesophageal reflux are present post surgery (114). Other studies have examined the effects of weight loss achieved through diet modification such as very low calorie diets (80). These studies have shown improvements in lung function such as $\text{FEV}_1$ and $\text{FVC}$, dyspnoea, use of rescue medication and number of exacerbations and health status, but no changes in bronchial hyperresponsiveness were present (81).
CONCLUSIONS:

1) Obesity and asthma are increasing in all age groups.

2) The increases in obesity and asthma appear to be linked.

3) Obese patients have increased incidence of breathlessness, wheeze and doctor diagnosed asthma.

4) Very few studies have confirmed the diagnosis of asthma with bronchial hyperresponsiveness. In the studies that have data including bronchial responsiveness, the results are conflicting.

5) Weight loss improves symptoms of shortness of breath, wheeze and reduces medication usage for asthma and reduces number of emergency department presentations for asthma but has not effect on bronchial hyperresponsiveness.

6) Increases in atopy are also present in obesity.

7) The underweight have increases in asthma that also need to be investigated.
Chapter 2

RELATIONSHIP BETWEEN OBESITY, ASTHMA SYMPTOMS, LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS IN ADULTS
2.1 BACKGROUND

In the past two decades there has been a significant increase in the prevalence of both asthma (115) and obesity (20) worldwide. Previous cross sectional studies have shown an association between obesity and both wheezing and diagnosed asthma (30, 58, 116). The nature of this relationship has not been established and, furthermore, if the association is causal, the direction of causation remains unknown.

There are several mechanisms by which obesity could cause either respiratory symptoms or more fundamental changes in the airways leading to asthma. In obese people symptoms of breathlessness and wheeze may be due to increased work of breathing (117). Alternatively, obesity may have a direct effect on the mechanical behaviour of the respiratory system by altering lung volume, airway calibre, or respiratory muscle strength (118, 119). In obesity, functional residual capacity (FRC) is reduced by approximately 500ml (120). Changes in lung volume of this magnitude induced by voluntarily breathing below FRC and changes in posture have been shown to increase bronchial responsiveness in normal subjects (84, 85, 89).

On the other hand, factors associated with asthma could lead to an increase in obesity. Inactivity or inability to exercise in asthmatics or people with atopy could cause weight gain (57, 58). Medication required for treatment of severe asthma such as oral steroids may cause weight gain, which may cause asthmatics to become obese or worsen pre-existing obesity.

The aim of this analysis was to determine if obesity, as measured by body mass index (BMI) is associated firstly with an increase in the prevalence of wheeze, shortness of breath, diagnosed asthma or medication use for asthma and secondly with a reduction in lung function or an increase in the prevalence of atopy or bronchial responsiveness to histamine.
2.2 STUDY METHODS

2.2.1 SAMPLES AND SELECTION CRITERIA

Three large epidemiological studies were conducted in 3 rural regions of NSW, Australia (Belmont, Lismore and Wagga Wagga) between 1991–1997. These studies were performed through the Woolcock institute.

Subjects were recruited in Belmont in 1982 where all children in school grades 3 and 4 at 8 of the 10 primary schools were asked to participate. The 2 schools omitted had less than 30 children in the appropriate grades. At the initial study, the consent rate was 88% and 718 children were studied. Each second year thereafter until 1992, and then again in 1997, an attempt was made to contact and study each subject. Data included in this study are from 1992 where 407, 18-19 year olds were studied and 1997 where 87 subjects that had not been studied in 1992 were included. Adults from Lismore and Wagga Wagga were recruited by asking parents or adult carers of study participants of the childhood study (chapter 3) if they were willing to participate.

The response rate for Belmont was 57%, for Lismore was 66% and for Wagga Wagga was 62%. All non-responders were telephoned and asked about their medication use for asthma. The rates of medication use between responders and non-responders were not significantly different in any region although they suggest that current asthmatics were slightly less likely to attend so that the prevalence rates reported may be an underestimate of the true disease rate. No information was available on the BMI of the non-responders. This low response rate would influence the prevalence of asthma in the population studied, but should not bias the relationship between the 2 variables BMI and bronchial responsiveness.

The same two senior researchers were present at all studies and trained and supervised all other staff involved. A large random group of adults aged 17-73 years was studied. Less than 5% of the sample was non-Caucasian and their data
were excluded from the analysis. Subjects were included in the current analyses if data available included height, weight, age and a measure of bronchial responsiveness. Diagnosis of asthma ever, history of wheeze, smoking history, family history of asthma was obtained by a self-administered questionnaire, which all subjects completed. The questionnaire was a modified version of the International Union against Tuberculosis (IUATLD) questionnaire (121), which has been previously validated (122).

All of the raw data (questionnaires, lung function tests and allergy testing) were taken from these 3 studies and no new interventions were made. The methodology for collecting all of the questionnaire data, lung function and allergy testing were identical in all 3 studies.

2.2.2 DEFINITIONS

Recent wheeze was defined as a positive reply to questions concerning the presence of wheeze in the last 12 months. Recent asthma was defined as recent wheeze plus a doctor diagnosis of asthma ever.

2.2.3 LUNG FUNCTION AND HISTAMINE INHALATION CHALLENGE

Lung function was recorded before and after a saline inhalation using a Mijnhardt VRS dry rolling-seal spirometer (Mijnhardt BV, Bunnik, The Netherlands) connected to a IBM compatible laptop computer running Scientific and Medical (S&M) data acquisition software. The equipment was routinely calibrated daily. Forced expiratory manoeuvres were repeated until two measurements of forced expiratory volume in one second (FEV₁) within 100 ml of each other were obtained. The largest FEV₁ was used in the analysis. Subjects who had taken a β agonist < 6 hours before the test were asked to make another appointment and to withhold treatment with this medication before testing. Values for FEV₁ and FVC are reported as percent of predicted values (123).
Bronchial responsiveness (BR) was measured by histamine inhalation test using the rapid method (124). The dose of histamine that caused a 20% fall in FEV$_1$ ($PD_{20}$FEV$_1$) was calculated, but the majority of subjects in population studies do not achieve a 20% fall in FEV$_1$ during a bronchial challenge. To overcome this problem, O’Connor et al (125) suggested the use of the dose response ratio (DRR) which is calculated by the percentage change in final FEV$_1$ from baseline divided by the total dose of histamine administered, as it can be calculated for all subjects, and can be used to compare lung function changes during bronchial challenge in epidemiological studies and relates well to symptom history (126). Because many subjects had an FEV$_1$ that remained stable or improved slightly during the challenge and this had a zero or negative DRR value, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion. Subjects with a fall in FEV$_1$ of 20% or more at $\leq$3.9 µmol of histamine were defined as having bronchial hyperresponsiveness (BHR), which is equivalent to a DRR of $>$ 8.1. To compare those with and without BHR, we used DRR as the measure of BR in this study.

2.2.4 BODY MASS INDEX

Height and weight were measured without shoes. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m$^2$). According to the WHO classification (20), a BMI<18.5 is underweight, BMI 18.5 - 24.9 is normal, BMI 25.0 - 29.9 is overweight. A BMI $\geq$ 30 is classified as obese and this group was further divided into moderate obesity (BMI 30.0 - 34.9), severe obesity (BMI 35.0 - 39.9) and very severe obesity (BMI $\geq$ 40.0). In the sample only 12 subjects had a BMI $\geq$ 40 and their lung function, symptoms and bronchial responsiveness were not significantly different from the group with severe obesity (BMI 35.0-39.9). Therefore data from subjects with very severe obesity (BMI$\geq$40) and severe obesity (BMI 35-39.9) were combined for analysis.
2.2.5 ATOPY

Skin prick test reactions on the forearm to eight common allergens were measured. The allergens tested with *Dermatophagoides farinae* and *D. pteronyssinus*, house dust, cat dander, cockroach, rye grass, plantain and *Alternaria tenuis* (Hollister-Stier). Histamine and glycerol were used as positive and negative controls. Wheal size was recorded as the long axis and its perpendicular: mean wheal size was used in analyses. A wheal of 4mm or greater was regarded as positive for the study (127). Subjects were considered atopic if they had a positive reaction to any of the tested allergens.

2.2.6 STATISTICAL METHODS

Data were analysed using the statistical package SPSS (SPSS Inc, IL, USA). Geometric mean values are reported for DRR values, which were converted to base 10 logarithms before analysis. For all analyses, p values < 0.05 were regarded as significant. Prevalence rates and mean values are reported with 95% confidence intervals. The chi-square ($\chi^2$) statistic was used to determine the significance of differences in prevalence across all 5 BMI groups and between different BMI groups in comparison to the normal group (BMI 18.5-24.9). Further analyses were performed to allow the large range of the normal group in narrowing the BMI range to BMI 20-22kg/m$^2$. Logistic regression was used to compute odds ratio for current asthma, wheeze and BHR in the presence of obesity and adjusted for family history of asthma, age, gender, atopy status and smoking history. Pearson’s correlation coefficient was used to assess correlation between BMI and bronchial responsiveness. Linear regression was performed to assess the correlation between BMI and DRR corrected for airway calibre as measured by FEV$_1$/FVC% (128).

A one way ANOVA was used to analyse means of grouped data. Duncan’s range test using the pooled variance was also performed to correct for multiple comparisons when comparing specific groups. This was performed to avoid
multiple pair-wise comparisons. Trend tests were not performed, as the data did not suggest that there was a dose response trend. Multiple comparisons were not performed in order to reduce the Type 1 error rate.
2.3 RESULTS

Data were analysed from 1971 Caucasian adults. The BMI distribution in the sample (Table 2.3.1) was similar to the distribution in the general population in Australia (129).

**TABLE 2.3.1 - ANTHROPOMETRIC AND QUESTIONNAIRE DATA FOR SUBJECTS CLASSIFIED ACCORDING TO BMI**

<table>
<thead>
<tr>
<th></th>
<th>underweight BMI &lt; 18.5</th>
<th>normal BMI 18.5-24.9</th>
<th>overweight BMI 25.0-29.9</th>
<th>moderate obesity BMI 30.0-34.9</th>
<th>severe obesity BMI≥35.0</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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<td>1127</td>
<td>592</td>
<td>141</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17.3%</td>
<td>37.9%</td>
<td>60.1%</td>
<td>48.9%</td>
<td>30.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>26.7 (24.4,29.0)</td>
<td>32.3 (31.7,32.9)</td>
<td>35.9 (35.2,36.6)</td>
<td>36.5 (35.1,37.9)</td>
<td>34.6 (32.6,36.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Atopic *</td>
<td>52.8 (39.4,66.2)</td>
<td>42.1 (39.2,45.0)</td>
<td>45.3 (41.3,49.3)</td>
<td>47.2 (39.0,54.4)</td>
<td>41.4 (38.7,54.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>% Family history of asthma</td>
<td>25.0 (13.2,36.8)</td>
<td>21.8 (19.4,24.2)</td>
<td>24.2 (20.7,27.7)</td>
<td>19.9 (13.3,26.5)</td>
<td>28.8 (17.2,40.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>% Wheeze in last 12 months</td>
<td>33.3 (20.5,46.1)</td>
<td>20.4 (18.0,22.8)</td>
<td>19.8 (16.6,23.0)</td>
<td>25.9 (18.7,33.1)</td>
<td>37.9 (25.5,50.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>% SOBOE in last 12 months</td>
<td>40.0 (20.8,59.2)</td>
<td>17.7 (15.0,20.4)</td>
<td>21.2 (17.6,24.8)</td>
<td>29.2 (21.1,37.3)</td>
<td>49.0 (35.3,62.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Recent asthma</td>
<td>17.0 (6.8,27.2)</td>
<td>12.3 (10.4,14.2)</td>
<td>10.4 (7.9,12.9)</td>
<td>14.6 (8.8,20.4)</td>
<td>21.7 (11.2,32.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>% Used medication in last 12 months</td>
<td>11.4 (2.8,20.0)</td>
<td>14.3 (12.3,16.3)</td>
<td>13.4 (10.7,16.1)</td>
<td>15.5 (9.5,21.5)</td>
<td>35.3 (23.1,47.5)</td>
<td>0.028</td>
</tr>
<tr>
<td>% Current smoker</td>
<td>25 (13.2,36.8)</td>
<td>15.4 (13.3,17.5)</td>
<td>17.4 (14.3,20.5)</td>
<td>18.4 (12.0,24.8)</td>
<td>10.2 (2.5,17.9)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values are means and 95% CI or prevalence and 95% CI.

This table shows in severe obesity, an increase in prevalence of wheeze, shortness of breath and medication use with no increase in atopy or family history of asthma.
The prevalence of symptoms and medication use differed significantly between groups classified by BMI (table 2.3.1). Further analysis showed that, compared to normal weight subjects, subjects with severe obesity had significantly higher prevalence of wheeze ($X^2=16.65$ $P<0.01$) (figure 2.3.1), shortness of breath on exertion ($X^2=39.40$ $P<0.001$) and medication use for asthma in the last 12 months ($X^2=12.33$ $P<0.05$) (figure 2.3.2). There was no difference between the groups in the prevalence of atopy ($X^2=4.42$, $p=0.27$) (figure 2.3.3).

**FIGURE 2.3.1 – THE PREVALENCE OF SYMPTOMS OF WHEEZE ACCORDING TO BMI GROUP AND GENDER**

This figure shows increases in both men and women in the prevalence of wheeze in the last 12 months with obesity. There was no significant difference between the genders. Note there is an increase in wheeze in both the underweight men and women.
FIGURE 2.3.2 – PREVALENCE OF MEDICATION USAGE FOR ASTHMA ACCORDING TO BMI GROUP AND GENDER

This graph shows that there was an increase in medication use for asthma in the obese group. Despite a higher prevalence of symptoms of shortness of breath and wheeze, the underweight did not have higher use of medication for asthma.

FIGURE 2.3.3 – PREVALENCE OF ATOPY ACCORDING TO BMI GROUP AND GENDER

This figure shows that there was no increase in prevalence of atopy in either the obese men or women. The trend was for an increase in atopy in the underweight men only, though there were only 9 in this group.
Separate analyses showed that there were no significant differences between atopic and non-atopic subjects (table 2.3.2) or between men and women in the strength of the associations between BMI and recent asthma, wheeze in the last 12 months, medication use or BHR (table 2.3.3). There did appear to be a trend in the increase in symptoms in non-atopic subjects but this was not significant, and potentially due to the small numbers in the severe obesity group (table 2.3.2).

**TABLE 2.3.2 – ADJUSTED ODDS RATIO FOR SYMPTOMS AND BHR IN BOTH ATOPIC AND NON-ATOPIC SUBJECTS IN COMPARISON TO THE NORMAL WEIGHT GROUP.**

<table>
<thead>
<tr>
<th></th>
<th>Underweight BMI &lt; 18.5</th>
<th>Overweight BMI 25–29.9</th>
<th>Moderate obesity BMI 30–34.9</th>
<th>Severe obesity BMI ≥ 35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wheeze in last 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>1.75</td>
<td>0.97</td>
<td>1.24</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>(0.80, 3.82)</td>
<td>(0.68, 1.38)</td>
<td>(0.70, 2.20)</td>
<td>(0.73, 4.02)</td>
</tr>
<tr>
<td>Non-atopics</td>
<td>0.57</td>
<td>1.31</td>
<td>2.37</td>
<td>5.10</td>
</tr>
<tr>
<td></td>
<td>(0.16, 2.05)</td>
<td>(0.86, 2.00)</td>
<td>(1.23, 4.56)</td>
<td>(2.27, 11.45)</td>
</tr>
<tr>
<td><strong>SOBOE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>2.34</td>
<td>1.18</td>
<td>1.89</td>
<td>2.96</td>
</tr>
<tr>
<td></td>
<td>(0.71, 7.76)</td>
<td>(0.76, 1.84)</td>
<td>(0.98, 3.64)</td>
<td>(1.15, 7.62)</td>
</tr>
<tr>
<td>Non-atopics</td>
<td>2.99</td>
<td>1.92</td>
<td>2.87</td>
<td>8.83</td>
</tr>
<tr>
<td></td>
<td>(0.86, 10.31)</td>
<td>(1.23, 2.97)</td>
<td>(1.51, 5.49)</td>
<td>(3.79, 20.58)</td>
</tr>
<tr>
<td><strong>Recent asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>1.42</td>
<td>0.99</td>
<td>1.21</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>(0.59, 3.45)</td>
<td>(0.65, 1.51)</td>
<td>(0.62, 2.35)</td>
<td>(0.54, 3.79)</td>
</tr>
<tr>
<td>Non-atopics</td>
<td>0.38</td>
<td>0.90</td>
<td>2.21</td>
<td>4.08</td>
</tr>
<tr>
<td></td>
<td>(0.05, 3.02)</td>
<td>(0.47, 1.72)</td>
<td>(0.92, 5.33)</td>
<td>(1.52, 10.98)</td>
</tr>
<tr>
<td><strong>Medication usage in last 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>0.93</td>
<td>0.87</td>
<td>0.87</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>(0.37, 2.32)</td>
<td>(0.59, 1.27)</td>
<td>(0.47, 1.64)</td>
<td>(0.75, 4.16)</td>
</tr>
<tr>
<td>Non-atopics</td>
<td>0.85</td>
<td>1.15</td>
<td>1.80</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>(0.23, 3.06)</td>
<td>(0.72, 1.85)</td>
<td>(0.87, 3.75)</td>
<td>(1.40, 7.81)</td>
</tr>
<tr>
<td><strong>BHR (DRR &gt; 8.1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>2.08</td>
<td>0.72</td>
<td>1.08</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>(0.91, 4.73)</td>
<td>(0.46, 1.12)</td>
<td>(0.56, 2.08)</td>
<td>(0.36, 2.81)</td>
</tr>
<tr>
<td>Non-atopics</td>
<td>1.62</td>
<td>1.03</td>
<td>0.51</td>
<td>* no subjects in this group</td>
</tr>
<tr>
<td></td>
<td>(0.34, 3.70)</td>
<td>(0.44, 2.40)</td>
<td>(0.05, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

*All results are shown with adjusted OR (95% confidence intervals)

This table shows the difference in OR between atopic and non-atopic subjects. In comparison to the atopic group, the non-atopic group had a much higher risk of symptoms of wheeze, shortness of breath on exertion, recent asthma, and medication use with obesity, but there was no increase in bronchial responsiveness with increasing weight in either the atopic or non-atopic groups.
**TABLE 2.3.3 – ADJUSTED ODDS RATIO FOR SYMPTOMS AND BHR IN BOTH MEN AND WOMEN IN COMPARISON TO THE NORMAL WEIGHT GROUP.**

<table>
<thead>
<tr>
<th></th>
<th>Underweight BMI &lt; 18.5</th>
<th>Overweight BMI 25–29.9</th>
<th>Moderate obesity BMI 30–34.9</th>
<th>Severe obesity BMI &gt; 35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wheeze in last 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.47 (0.36, 5.98)</td>
<td>1.15 (0.78, 1.70)</td>
<td>1.18 (0.61, 2.29)</td>
<td>3.60 (1.18, 10.96)</td>
</tr>
<tr>
<td>Women</td>
<td>1.08 (0.53, 2.24)</td>
<td>0.95 (0.65, 1.40)</td>
<td>1.74 (0.99, 3.06)</td>
<td>2.75 (1.37, 5.51)</td>
</tr>
<tr>
<td><strong>SOBOE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0 (0.95, 2.64)</td>
<td>1.59 (1.17, 5.33)</td>
<td>2.50 (1.23, 3.95)</td>
<td>11.08 (2.97, 41.40)</td>
</tr>
<tr>
<td>Women</td>
<td>2.97 (1.22, 6.99)</td>
<td>1.43 (0.97, 2.11)</td>
<td>2.21 (1.23, 3.95)</td>
<td>4.12 (2.05, 8.31)</td>
</tr>
<tr>
<td><strong>Recent asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.44 (0.05, 3.84)</td>
<td>1.14 (0.70, 1.88)</td>
<td>1.79 (0.84, 3.82)</td>
<td>2.76 (0.78, 9.80)</td>
</tr>
<tr>
<td>Women</td>
<td>1.07 (0.45, 2.50)</td>
<td>0.76 (0.46, 1.26)</td>
<td>1.05 (0.50, 2.25)</td>
<td>2.06 (0.92, 4.61)</td>
</tr>
<tr>
<td><strong>Medication usage in last 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.62 (0.07, 5.27)</td>
<td>0.91 (0.57, 1.41)</td>
<td>1.14 (0.56, 2.33)</td>
<td>1.85 (0.50, 6.83)</td>
</tr>
<tr>
<td>Women</td>
<td>0.80 (0.35, 1.80)</td>
<td>0.98 (0.66, 1.45)</td>
<td>1.09 (0.58, 2.06)</td>
<td>2.84 (1.41, 5.68)</td>
</tr>
<tr>
<td><strong>BHR (DRR &gt; 8.1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.77 (0.61, 12.54)</td>
<td>0.76 (0.43, 1.34)</td>
<td>0.94 (0.38, 2.32)</td>
<td>0.56 (0.07, 4.80)</td>
</tr>
<tr>
<td>Women</td>
<td>1.61 (0.70, 3.71)</td>
<td>0.76 (0.44, 1.32)</td>
<td>0.96 (0.41, 2.24)</td>
<td>0.92 (0.30, 2.73)</td>
</tr>
</tbody>
</table>

All results are shown with adjusted OR (95% confidence intervals)

This table shows that there was no difference between men and women in the strength of the association between obesity and asthma. Severe obesity was a risk for wheeze, shortness of breath on exertion, and medication use for asthma in the last 12 months in both men and women. Obesity was not a risk for bronchial hyperresponsiveness in either men or women.
There were significant differences between groups in lung function parameters including \( \text{FEV}_1 \), FVC, PEFR, \( \text{FEF}_{25-75\%} \) and DRR, although the groups mean values remained within the predicted normal range (Table 2.3.4). Post hoc comparison showed that \( \text{FEV}_1 \) was significantly reduced in the underweight and severe obesity group (figure 2.3.4) and FVC was reduced in the underweight, moderate and severe obesity groups \((p<0.001)\). There was no significant difference in \( \text{FEV}_1 / \text{FVC}\% \) between the groups (figure 2.3.5). In the underweight group there was a significant increase in symptoms of shortness of breath and wheeze (table 2.3.1). In this group post hoc comparison showed a reduction in flow rates, measured by PEFR and \( \text{FEF}_{25-75\%} \) and a higher prevalence of BHR (Table 2.3.3). In the group with severe obesity flow rates and bronchial responsiveness were not different from the normal group.

After adjusting for atopy, sex, age, smoking history and family history, severe obesity was a significant risk factor for recent asthma, defined as recent wheeze plus a previous diagnosis of asthma \((\text{OR 2.04; 95\%CI 1.02-3.76, \( p=0.048 \)})\). Increases in risk of wheeze in the last 12 months \((\text{OR 2.6; 95\%CI 1.46-4.70, \( p=0.001 \)})\) and medication use in the last 12 months \((\text{OR 2.53; 95\%CI 1.36-4.70, \( p=0.003 \)})\) were also present in severe obesity but not for BHR \((\text{OR 0.87; 95\% CI 0.35-2.21, \( p=0.78 \)})\). Furthermore, obesity was a significant risk for wheeze without BHR \((\text{OR 4.01, 95\%CI 2.17-7.4 \( p<0.001 \)})\) but not for wheeze in the presence of BHR \((\text{OR 0.72; 95\% CI 0.10-5.05, \( p=0.72 \)})\). There was no significant correlation between BMI as a continuous variable and bronchial responsiveness in men \((r=-0.041, p=0.07)\) or women \((r=-0.042, p=0.16)\). Further analyses were performed looking at interactions between smoking and gender and there was no significant difference.
### TABLE 2.3.4 - LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS AS CLASSIFIED BY BMI.

<table>
<thead>
<tr>
<th></th>
<th>underweight BMI &lt; 18.5</th>
<th>normal BMI 18.5-24.9</th>
<th>overweight BMI 25.0-29.9</th>
<th>moderate obesity BMI 30.0-34.9</th>
<th>severe obesity BMI≥35.0</th>
<th>( P ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( FEV_1 ) % Predicted</td>
<td>95.0 * (91.9,98.1)</td>
<td>102.0 (101.3,102.7)</td>
<td>100.5 (99.5,101.5)</td>
<td>99.2 (97.3,101.1)</td>
<td>98.1 * (95.2,101.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( FVC ) % Predicted</td>
<td>94.2 * (91.5,96.9)</td>
<td>99.4 (98.7,101.1)</td>
<td>97.4 (96.4,98.4)</td>
<td>95 * (93.1,96.9)</td>
<td>93.6 * (90.7,96.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( FEV_1/FVC ) %</td>
<td>86.4 (84.3,88.5)</td>
<td>86.3 (85.9,86.7)</td>
<td>85.8 (85.4,86.2)</td>
<td>86.9 (85.9,87.9)</td>
<td>87.6 (86.1,89.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>( PEFR ) % Predicted</td>
<td>89.9 * (85.7,94.1)</td>
<td>102.2 (101.1,103.3)</td>
<td>105.5 (104.1,106.9)</td>
<td>106.2 (103.2,109.2)</td>
<td>106.2 (101.8,110.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( FEF_{25-75} ) % Predicted</td>
<td>85.8 * (79.7,91.9)</td>
<td>97.1 (95.7,98.5)</td>
<td>98.5 (96.5,100.5)</td>
<td>101.4 (97.4,105.4)</td>
<td>101.2 (94.3,108.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>( DRR ) (Measure of BR)</td>
<td>6.32* (4.88,8.18)</td>
<td>4.71 (4.52,4.92)</td>
<td>4.42 (4.23,4.62)</td>
<td>4.72 (4.28,5.21)</td>
<td>4.66 (4.08,5.33)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

All values are means ± 95% CI

*Significant difference is present compared to the normal group (BMI 18.5-24.9).

This table shows that both \( FEV_1 \) and \( FVC \) were reduced in the obese group. There was no increase in bronchial obstruction as measured by \( FEV_1/FVC \%) and no reduced flow rates as measured by \( PEFR \) or \( FEF_{25-75} \%). There was also no increase in BR in the obese group. In the underweight group, both \( FEV_1 \) and \( FVC \) were reduced. They also had reduced flow rates and increased BR.
FIGURE 2.3.4 – FEV$_1$% PREDICTED BY BMI GROUP AND GENDER.

This figure shows a reduction in FEV$_1$% predicted in both the obese and the underweight groups in both men and women.

FIGURE 2.3.5 – FEV$_1$/FVC% PREDICTED BY BMI GROUP AND GENDER.

This figure shows no increase in airway obstruction as measured by FEV$_1$/FVC% between any of the groups or between men or women.
FIGURE 2.3.6 – PEFR% PREDICTED BY BMI GROUP AND GENDER.

This figure shows no decrease in flow rates as measured by PEFR% predicted in the obese group. In the underweight group flow rates were significantly lower.

FIGURE 2.3.7– BRONCHIAL RESPONSIVENESS MEASURED BY DOSE RESPONSE RATIO ACCORDING TO BMI GROUP AND GENDER.

This graph shows no difference in bronchial responsiveness in the obese group in either men or women. The only group with an increase in bronchial responsiveness is the underweight group.
This graph shows no increase in airway responsiveness with increasing BMI. A trend was present for a reduction in DRR with increasing BMI. (Subjects with a fall in FEV\textsubscript{1} of 20% or more at $\leq 3.9$ µmol of histamine were defined as having bronchial hyperresponsiveness (BHR), which is equivalent to a DRR of $> 8.1$, which is marked on the graph).

Potentially inclusion of subjects with a BMI 18.5-19.9 kg/m\textsuperscript{2} may have been problematic, and other investigators have shown increased risk of doctor diagnosed asthma with a BMI of 23-24 kg/m\textsuperscript{2}. Further analyses were performed to allow for this, in narrowing the BMI range of the normal group to BMI 20-22 kg/m\textsuperscript{2}. This tightened the association between severe obesity and recent asthma (OR 2.73; 95%CI 1.27-5.86, p=0.01), wheeze in the last 12 months (OR 3.53; 95%CI 1.83-6.79, p<0.001) and medication use in the last 12 months (OR 3.28; 95%CI 1.64-6.53, p=0.001). The risk for BHR in severe obesity, though increased slightly (OR 1.21; 95%CI 0.41-3.57, p=0.73) was not significantly different from the previous analysis using a normal range BMI of 18.5-24.9 kg/m\textsuperscript{2}. Further analyses were performed in the assessment of risk of BHR in the obese in correcting for airway calibre (128) with no difference found (OR 1.12; 95%CI 0.39-3.23, p=0.83).
2.4 DISCUSSION

This study shows that severe obesity, defined as a body mass index of greater than 35, was associated with a higher prevalence of wheeze, diagnosed asthma and medication use. Despite the fact that FEV\textsubscript{1} and FVC were significantly reduced in severely obese subjects, these subjects did not have evidence of airflow obstruction or reduced flow rates, nor was there any increase in bronchial responsiveness to histamine.

In this study, data was used from a large number of randomly selected Caucasian adults in three rural towns in NSW. The distribution of BMI in these samples was representative of the general population in Australia (129). The methods and the IUATLD questionnaire were similar to those used in other large epidemiology studies and are well validated (122).

Obesity could increase the risk of asthma if the functional consequences of changes to the respiratory system were sufficient to modify airway behaviour and increase bronchial responsiveness in susceptible individuals. Reductions in lung volume induced by voluntarily breathing below functional residual capacity (FRC) (84) and changes in posture (85) have been shown to increase bronchial responsiveness in normal subjects. Response to methacholine is altered when the FRC is reduced by approximately 500ml, a level of reduction that is commonly found in obese or severely obese subjects. Changes in compliance or elastic recoil, due to low lung volume, could decrease the tidal fluctuations of airway smooth muscle and enhance contractility (130), and thus shift the dose response curve or increase the level of the maximal response. No evidence was found of any reduction in flow rates or any increase in bronchial responsiveness in obese subjects.

Alternatively the anatomical changes could cause increased symptoms of wheeze and shortness of breath without altering airway behaviour. It has been reported that obese subjects are more likely to report asthma like symptoms, without an
increase in bronchial hyperresponsiveness or prevalence of atopy (131). Breathlessness and wheeze might be attributable to other causes in obese subjects, such as increased work of breathing or deconditioning (117).

Severe obesity may cause changes in the upper airway (132) and wheeze may result from extra-thoracic obstruction due to fat deposition. Obstructive sleep apnoea is also increased in severe obesity (133) and the combination of asthma like symptoms plus waking at night with shortness of breath or choking may be misinterpreted as asthma. Finally, the high level of reported wheeze in the obese group may be related to the lack of specificity in questions regarding the presence of wheeze (122).

Although the prevalence of wheeze and shortness of breath was increased in the severely obese group, there was no airway narrowing on spirometric testing, no reduction in flow rates and no increase in bronchial responsiveness. While the increased rate of diagnosis of asthma in this group probably reflects the increase in prevalence of symptoms, there is little objective evidence to support the diagnosis. If the definition of asthma includes airway inflammation then it is unlikely that this group genuinely have asthma, since there is no evidence that obesity is associated with increased airway inflammation. It is also unlikely that the asthmatic group selectively became obese, either as a result of increased medication use or reduced activity levels, since the prevalence of atopy was not increased in the obese group.

Medication use, particularly inhaled corticosteroids, may have affected the outcome of the study if the severely obese group were receiving sufficient treatment to normalise bronchial responsiveness (134). Although detailed information is not available on the type or dose of medication taken, this seems an unlikely explanation. Despite the fact that a greater proportion of severely obese subjects had taken anti asthma medication, as a group, they continued to have symptoms, suggesting that the medication was inadequate or inappropriate to control their symptoms.
If symptoms in this group are due to causes unrelated to asthma, then asthma medication would be unlikely to affect their symptoms. The high level of medication use in the severely obese subjects probably reflects a high level of presentation for medical intervention. Symptoms alone do not appear to be a good guide for asthma treatment in this group.

The underweight group appeared to have more respiratory problems. Their increased prevalence of symptoms was associated with poorer lung function, indicated by a reduction both in FVC and in flow rates and an increase in bronchial responsiveness. There are several possible causes for this. The high levels of bronchial responsiveness and low levels of medication use suggest that they may have under-treated asthma. Reduction in respiratory muscle strength and function may also be a potential cause. The causes for these abnormalities are unknown and deserve further investigation.

This study has significant clinical implications. This study found that obese people with symptoms of dyspnoea and wheeze are frequently diagnosed with asthma even though there is no evidence of bronchial obstruction, reduced flow rates or bronchial hyperresponsiveness. It is likely that the prevalence of asthma in this group is similar to that in the rest of the population. It is important that obese patients are fully assessed with measurement of lung function, reversibility or bronchial responsiveness if they present for health care with symptoms consistent with asthma. If treatment for asthma is commenced, clinical and adverse effects should be closely monitored as treatment with either oral or high dose inhaled steroids may cause further weight gain and maybe an inappropriate mode of treatment for this group.
Chapter 3

RELATIONSHIP BETWEEN ASTHMA, ATOPY AND OBESITY IN CHILDREN
3.1 INTRODUCTION

In children, cross sectional studies of large random population samples have shown that excess body weight is associated with a higher rate of both symptoms and diagnosed asthma (49, 58, 61).

In Taiwanese teenagers, obesity was associated with an increase in bronchial hyperresponsiveness, atopy and atopic symptoms in girls but not boys (58). This suggests that the association between asthma and excess body weight may differ between adults and children as gender differences and differences in atopy in children did not appear as prevalent in adults.

It is possible that obesity could cause atopy or inflammation or potentially some common factor may predispose to both obesity and atopy. The results from previous studies tend to be confusing with one study showing that obesity was associated with an increase in atopy in girls, but not in boys (58) and another study showed no association with atopy, allergic symptoms or IgE levels in more than 15,000 young adults (36). Xu et al (135) showed that increased BMI was associated with an increased risk of atopy in Finnish adults, though no analysis on gender differences were performed.

In this study, an analysis of cross sectional data in a large population of Caucasian Australian children was performed. The aim was firstly to determine if increased body weight, as measured by body mass index, is associated with a higher prevalence of asthma or atopy or with an increase in airway obstruction or bronchial responsiveness to histamine in children. Secondly, whether the association between body weight, atopy and symptoms of asthma was different between girls and boys.
3.2 METHODS

3.2.1 POPULATIONS

Data from 7 large epidemiological studies of children aged 7-12 years conducted in 7 regions of NSW, Australia between 1991–1993 were pooled. Six regions were selected because their documented admission rates for childhood asthma covered the entire range for the State of New South Wales and their different geographic and climatic conditions suggested that the local dominant allergens would be different. The climate of the regions varied from arid through temperate to semitropical. A seventh region, western Sydney, was also included.

Data were collected in the winters of 1991-93, except for coastal Sydney, which were collected in spring 1992. In each region all primary schools were included in the sampling frame, and were chosen at random. In Wagga Wagga, a random two in three selection of schools was made. One school in Lismore and two schools in Belmont were omitted for logistic reasons as the schools were too small. Children in years 3, 4, and 5 (age 8-11 yrs) at each selected school were invited to participate. Only children whose parents had given informed consent were studied. Children who had height, weight, age and bronchial responsiveness (BR) measured were included in this analysis. Less than 5% of children were non-Caucasian and their data were excluded from the analysis.

Information relating to symptoms, family history and diagnoses were collected by a parent-completed questionnaire (121). Recent wheeze was defined as the presence of wheeze in the last 12 months. Recent asthma was defined as recent wheeze plus a doctor diagnosis of asthma ever.

3.2.2 ATOPY

Skin prick test reactions on the forearm to eight common allergens were measured. The allergens tested with Dermatophagoides farinae and D. pteronyssinus, house dust, cat dander, cockroach, rye grass, plantain and
Alternaria tenuis (Hollister-Stier). Histamine and glycerol were used as positive and negative controls. In western Sydney, plantain was replaced by Bermuda grass. Wheal size was recorded as the long axis and its perpendicular: mean wheal size was used in analyses. A wheal of 3mm or greater was regarded as positive for the study (127). Subjects were considered atopic if they had a positive reaction to any of the tested allergens.

3.2.3 LUNG FUNCTION

Lung function was recorded before and after saline inhalation using Mijnhardt VRS dry rolling-seal spirometers (Mijnhardt BV, Bunnik, The Netherlands) and Scientific and Medical (S&M) data acquisition software. Forced expiratory manoeuvres were repeated until two measurements of forced expiratory volume in one second (FEV₁) within 100 ml were obtained. The largest FEV₁ was used in analyses. Children were tested after withholding β agonist for at least 6 hours. %Predicted FEV₁, FVC and PEFR were calculated (136).

Bronchial responsiveness (BR) was measured by the rapid histamine inhalation test (124). The dose of histamine that caused a 20% fall in FEV₁ (PD20FEV₁) was calculated. However, the majority of subjects in population studies do not achieve a 20% fall in FEV₁ during a bronchial challenge. To overcome this problem, O’Connor et al (125) suggested the use of the dose response ratio (DRR) which is calculated by the percentage change in final FEV₁ from baseline divided by the total dose of histamine administered, as it can be calculated for all subjects, and can be used to compare lung function changes during bronchial challenge in epidemiological studies and relates well to symptom history (126). Because many children had an FEV₁ that remained stable or improved slightly during the bronchial challenge, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion. Participants with a fall in FEV₁ of 20% or more at ≤3.9 µmol of histamine were defined as having bronchial hyperresponsiveness (BHR), which is equivalent to a DRR of > 8.1.
3.2.4 BODY MASS INDEX

Height and weight were measured without shoes. BMI was calculated by dividing weight (kg) by the square of height (m) \( (\text{kg/m}^2) \). There is no standard for weight distribution in children so BMI percentiles per sex per age were used as a measure of standardized weight \((137, 138)\). NHANES I was used as the reference population for the BMI percentiles \((139)\) as there are no reference data available for Australian children. No studies have compared distribution of overweight and obese Australian children in this age group with those in the USA. This is unlikely to have invalidated the study outcomes, since the trend for the increase in obesity in children in Australia is closely following the USA trend \((140)\). Although BMI may not be the best measure of obesity in children, it is widely used and information was not available from this study on which to base an alternative definition.

Results are presented as BMI percentiles corrected for age and sex. BMI percentile scores \((Z\) scores\) divided into quintiles were used to assess the relationship between standardized weight, symptoms and lung function. Analyses were also performed with BMI as a continuous variable and BMI divided into overweight \((\text{BMI } 85^{\text{th}} - 95^{\text{th}} \text{ percentile})\) and obese \((\text{BMI }>95^{\text{th}} \text{ percentile})\).

3.2.5 STATISTICS

Data were analysed using the statistical package SPSS \((\text{SPSS Inc, IL, USA})\). Geometric mean values are reported for DRR values, which were converted to base 10 logarithms before analysis. For all analyses, P values < 0.05 were regarded as significant. Pearson’s chi square \((X^2)\) statistic and chi square trend were used to determine the significance of differences in prevalence between different BMI groups.

Logistic regression was used to compute odds ratio for outcomes in the presence of higher BMI and adjusted for family history of asthma, age, gender, atopy status and exposure to cigarette smoke. Partial correlation and logistic regression was
used to assess correlation between BMI and bronchial responsiveness adjusting for airway size using FVC% predicted and FEV\textsubscript{1}/FVC% (128).

Linear regression was used to assess the relation between lung function and BMI percentile. One-way ANOVA was used to analyse means of grouped data with Duncan’s post hoc test to limit the number of multiple comparisons.

Tests for homogeneity were performed between the 7 studies (Meta-view in Review Manager (RevMan), Version 4.2, Update Software) and used in the analysis for the prevalence of wheeze, cough and BHR.

The relationship between obesity and asthma would be affected by the range of BMI in the total sample and not by between centre differences in BMI. Therefore, because differences in BMI between the centres would not have affected the relationship between obesity and asthma in these studies, no further tests for homogeneity were performed.
3.3 RESULTS

Complete data were available for 5993 children. The response rates were Belmont 82.7%, Lismore 76.8%, Sydney 76.8%, Western Sydney 75.9%, Moree 74.2%, Wagga Wagga 82.7%, and Broken Hill 80%. The proportion of participants in each group, classified according to quintiles of BMI percentile is shown in Table 3.1. Tests for homogeneity were performed between the 7 regions and there were no significant differences in the prevalence of wheeze ($\chi^2=8.42$, $p=0.21$), cough ($\chi^2=2.99$, $p=0.81$) or BHR ($\chi^2=4.33$, $p=0.63$).

In separate analyses of data from girls and boys (table 3.3.2), a higher BMI was significantly associated with higher prevalence of atopy, wheeze in the last 12 months, wheeze ever, cough, and the use of medication for asthma in girls, but not in boys. There was no significant association between BMI and the prevalence of diagnosed asthma or recent asthma in either boys or girls.
This table shows that boys had a higher prevalence of atopy than girls overall, but a higher BMI was associated with a higher prevalence of atopy in girls only. There was no significant association with BMI and family history of asthma for either girls or boys. Exposure to cigarette smoke had a highly significant association with a higher BMI in both girls and boys. Those with a higher BMI also tended to be taller.
**TABLE 3.3.2 - SYMPTOMS ACCORDING TO BMI QUINTILE**

<table>
<thead>
<tr>
<th></th>
<th>BMI quintile 1</th>
<th>BMI quintile 2</th>
<th>BMI quintile 3</th>
<th>BMI quintile 4</th>
<th>BMI quintile 5</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wheeze in last 12 months</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>26.9 (23.3, 30.5)</td>
<td>23.6 (20.3, 26.9)</td>
<td>25.7 (22.3, 29.1)</td>
<td>25.5 (22.0, 29.0)</td>
<td>28.7 (25.0, 32.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Girls</td>
<td>19.2 (16.0, 22.4)</td>
<td>22.9 (19.5, 26.3)</td>
<td>22.2 (18.8, 25.6)</td>
<td>22.6 (19.3, 26.0)</td>
<td>25.1 (21.7, 28.5)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Wheeze ever</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>40.5 (36.5, 44.5)</td>
<td>41.0 (37.2, 44.8)</td>
<td>40.3 (36.4, 44.2)</td>
<td>45.6 (41.7, 49.6)</td>
<td>43.6 (39.5, 47.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Girls</td>
<td>29.9 (26.2, 33.6)</td>
<td>33.7 (29.9, 37.5)</td>
<td>33.6 (29.7, 37.5)</td>
<td>34.2 (30.4, 38.0)</td>
<td>39.4 (35.6, 43.2)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Cough in last 12 months</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>20.3 (17.0, 23.6)</td>
<td>21.3 (18.1, 24.5)</td>
<td>19.4 (16.3, 22.5)</td>
<td>23.9 (20.5, 27.3)</td>
<td>24.4 (20.9, 28.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Girls</td>
<td>19.3 (16.1, 22.5)</td>
<td>17.4 (14.4, 20.5)</td>
<td>22.7 (19.3, 26.1)</td>
<td>23.7 (20.3, 27.1)</td>
<td>26.5 (23.0, 30.0)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Asthma ever diagnosed</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>32.6 (28.8, 36.4)</td>
<td>34.1 (30.4, 37.8)</td>
<td>33.8 (30.1, 37.5)</td>
<td>35.6 (31.8, 39.4)</td>
<td>34.9 (31.0, 38.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Girls</td>
<td>25.5 (22.0, 29.0)</td>
<td>23.6 (20.2, 27.0)</td>
<td>26.7 (23.1, 30.3)</td>
<td>27.3 (23.7, 30.9)</td>
<td>28.9 (25.4, 32.5)</td>
<td>0.065</td>
</tr>
<tr>
<td><strong>Recent asthma</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>20.2 (16.9, 23.5)</td>
<td>17.6 (14.6, 20.6)</td>
<td>19.2 (16.1, 22.3)</td>
<td>18.8 (15.7, 21.9)</td>
<td>21.1 (17.7, 24.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Girls</td>
<td>13.6 (10.8, 16.4)</td>
<td>14.1 (11.3, 16.9)</td>
<td>15.1 (12.2, 18.0)</td>
<td>15.1 (12.2, 18.0)</td>
<td>16.5 (13.6, 19.4)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Medication use in last 12 months</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>27.2 (23.6, 30.8)</td>
<td>25.8 (22.4, 29.2)</td>
<td>26.4 (22.9, 29.9)</td>
<td>27.0 (23.5, 30.5)</td>
<td>31.9 (28.1, 35.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Girls</td>
<td>19.2 (16.0, 22.4)</td>
<td>22.1 (18.8, 25.4)</td>
<td>21.0 (17.7, 24.4)</td>
<td>24.6 (21.2, 28.1)</td>
<td>25.2 (21.8, 28.6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Results are reported as prevalence and 95% confidence intervals

Further analyses were performed and BMI was divided into normal group BMI 5th-85th percentile, overweight 85th-95th percentile, and obese>95th percentile (table 3.3.3).
3.3.3). After adjusting for atopy, family history of asthma and exposure to cigarette smoke, a higher BMI was associated with a higher prevalence of wheeze ever, cough, and medication use for asthma (table 3.3.3). However, there was no significant association between a higher BMI and the prevalence of diagnosed asthma, recent asthma or BHR (table 3.3.3).

### TABLE 3.3.3 – ADJUSTED OR FOR SYMPTOMS AND BHR IN OVERWEIGHT AND OBESE CHILDREN IN COMPARISON TO NORMAL WEIGHT GROUP (BMI PERCENTILE 5TH-85TH).

<table>
<thead>
<tr>
<th></th>
<th>BMI percentile 85th-95th</th>
<th>p value</th>
<th>BMI percentile 95th-100</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze in last 12 months</td>
<td>1.12 (0.85, 1.46)</td>
<td>0.42</td>
<td>1.34 (0.98, 1.83)</td>
<td>0.07</td>
</tr>
<tr>
<td>Wheeze ever</td>
<td>1.23 (0.97, 1.55)</td>
<td>0.08</td>
<td>1.26 (1.01, 1.56)</td>
<td>0.04</td>
</tr>
<tr>
<td>Recent asthma</td>
<td>1.15 (0.85, 1.56)</td>
<td>0.37</td>
<td>0.95 (0.67, 1.35)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diagnosed asthma</td>
<td>1.10 (0.86, 1.42)</td>
<td>0.45</td>
<td>0.87 (0.65, 1.17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Cough in the last 12 months</td>
<td>1.26 (0.97, 1.63)</td>
<td>0.09</td>
<td>1.40 (1.05, 1.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dry cough</td>
<td>1.16 (0.91, 1.47)</td>
<td>0.24</td>
<td>1.36 (1.05, 1.77)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medication usage for asthma ever</td>
<td>1.35 (1.01, 1.72)</td>
<td>0.02</td>
<td>0.90 (0.68, 1.20)</td>
<td>0.47</td>
</tr>
<tr>
<td>Medication usage for asthma in last 12 months</td>
<td>1.09 (0.84, 1.48)</td>
<td>0.57</td>
<td>1.06 (0.73, 1.54)</td>
<td>0.75</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>0.84 (0.62, 1.14)</td>
<td>0.27</td>
<td>0.85 (0.61, 1.20)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

OR were calculated correcting for gender, atopy status, family history of asthma, and family smoking history. Results are reported as adjusted odds ratios and 95% confidence intervals.

This table shows that after correcting for gender, atopy, family history of asthma and family smoking history, there was an increase in risk for wheeze and cough in obese children. There was no increase in the risk for asthma diagnosis, medication use for asthma or for BHR. There was also no significant difference between the overweight and obese groups in regard to risk for symptoms, diagnosis of asthma or BHR.
Table 3.3.4 shows spirometric function and bronchial responsiveness for girls and boys in each of the BMI quintiles. For all spirometric variables, mean values were within the predicted normal range for all of the BMI groups. In both girls and boys, there were significant differences between BMI quintiles in FEV₁% predicted and FVC% predicted. Post hoc comparison showed that FEV₁% predicted and FVC% predicted were significantly reduced in the lowest quintile compared to the rest of the population measured. There were no differences in FEV₁/FVC ratio, suggesting that low BMI was not associated with an increase in airway obstruction in girls or boys. This observation was supported in boys by the finding that there was also no difference between BMI quintiles in flow rates as measured by PEF % predicted or FEF₂₅₋₇₅% predicted.

In girls there was a significant difference in PEFR% predicted and FEF₂₅₋₇₅% predicted between the lowest BMI quintile in comparison to the highest quintile. There was no significant association between BMI and either the prevalence of BHR or the severity of bronchial responsiveness, measured by DRR (figure 3.3.1), in either boys or girls. This remained true after adjusting DRR for airway size using FVC% predicted and FEV₁/FVC% (128), (standardised coefficient Beta=-0.002, p=0.89).
This graph shows a slight increase only in bronchial responsiveness with increasing BMI percentile in boys (R=0.004, p=0.82). (Subjects with a fall in FEV₁ of 20% or more at ≤3.9 µmol of histamine were defined as having bronchial hyperresponsiveness (BHR), which is equivalent to a DRR of > 8.1, which is marked on the graph).
This graph shows no increase in bronchial responsiveness with increasing BMI percentile in girls. A slight reduction in DRR was present with increasing BMI ($R=-0.007$, $p=0.69$).

All analyses looking at symptoms and lung function were repeated using BMI as a continuous variable, or with children categorised as normal (BMI <85\textsuperscript{th} percentile), overweight (BMI 85\textsuperscript{th} – 95\textsuperscript{th} percentile) or obese (BMI >95\textsuperscript{th} percentile). The results of these analyses were not different from the original analyses (data not shown).
TABLE 3.3.4 - LUNG FUNCTION ACCORDING TO BMI QUINTILE

<table>
<thead>
<tr>
<th>BMI quintile</th>
<th>BMI quintile 2</th>
<th>BMI quintile 3</th>
<th>BMI quintile 4</th>
<th>BMI quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P value for trend</strong></td>
<td></td>
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**FEV₁ % predicted**

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
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<th></th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>(101.0, 102.8)</td>
<td>(103.4, 105.2)</td>
<td>(104.4, 106.3)</td>
<td>(105.2, 107.0)</td>
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<tr>
<td><strong>Boys</strong></td>
<td>101.9</td>
<td>104.3</td>
<td>105.6</td>
<td>105.4</td>
<td>106.1</td>
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<tr>
<td><strong>Girls</strong></td>
<td>106.7</td>
<td>109.3</td>
<td>109.5</td>
<td>110.4</td>
<td>111.0</td>
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</table>

**FVC % predicted**

<table>
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<tr>
<td></td>
<td>(97.7, 99.4)</td>
<td>(100.9, 102.7)</td>
<td>(102.1, 104.2)</td>
<td>(103.2, 105.1)</td>
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<tr>
<td><strong>Boys</strong></td>
<td>98.5</td>
<td>101.8</td>
<td>103.1</td>
<td>103.3</td>
<td>104.2</td>
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<tr>
<td><strong>Girls</strong></td>
<td>102.0</td>
<td>104.7</td>
<td>105.5</td>
<td>107.2</td>
<td>107.4</td>
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</table>

**FEV₁/FVC%**

<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>(90.2, 91.1)</td>
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<td><strong>Boys</strong></td>
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<td>89.7</td>
<td>89.8</td>
<td>89.2</td>
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<tr>
<td><strong>Girls</strong></td>
<td>92.8</td>
<td>92.3</td>
<td>92.1</td>
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</table>

**PEFR% predicted**

<table>
<thead>
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<tr>
<td></td>
<td>(86.7, 89.3)</td>
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<td>88.7</td>
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<td>88.7</td>
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<tr>
<td><strong>Girls</strong></td>
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<td>93.3</td>
<td>93.2</td>
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**FEF₂₅₋₇₅ % PRED**

<table>
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<tr>
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<td>(93.1, 96.3)</td>
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<td><strong>Boys</strong></td>
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<td>94.2</td>
<td>94.7</td>
<td>93.5</td>
<td>94.6</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>98.2</td>
<td>99.4</td>
<td>100.6</td>
<td>99.7</td>
<td>103.2</td>
</tr>
</tbody>
</table>

**DRR (DRR=%fall in FEV₁/dose of histamine) + 3**

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(5.51, 6.37)</td>
<td>(5.84, 6.84)</td>
<td>(5.41, 6.23)</td>
<td>(5.35, 6.06)</td>
<td>(5.35, 6.09)</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>5.92</td>
<td>6.32</td>
<td>5.80</td>
<td>5.70</td>
<td>5.71</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>4.81</td>
<td>4.96</td>
<td>4.93</td>
<td>4.95</td>
<td>4.86</td>
</tr>
</tbody>
</table>

**BHR (DRR > 8.1)**

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(19.4, 26.0)</td>
<td>(20.1, 26.9)</td>
<td>(18.6, 25.4)</td>
<td>(18.9, 25.3)</td>
<td>(17.9, 24.5)</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>22.7</td>
<td>23.5</td>
<td>22.0</td>
<td>22.1</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>16.3</td>
<td>15.1</td>
<td>15.2</td>
<td>16.6</td>
<td>14.8</td>
</tr>
</tbody>
</table>

* Results are reported as mean and 95% confidence intervals
** Results are reported as prevalence and 95% confidence intervals

This table shows no obstruction or restriction and no decrease in flow rates in either obese boys or girls. There was also no increase in the degree or prevalence of bronchial responsiveness in obese boys or girls.
3.4 DISCUSSION

This study confirms the findings of previous studies that show that a higher BMI is associated with a higher prevalence of symptoms of wheeze and cough in children. This association was stronger in girls than in boys, was independent of atopic status and there was no association between higher BMI and the presence of either bronchial obstruction or BHR. Neither diagnosed asthma nor the combination of diagnosed asthma and recent symptoms were associated with higher body weight.

These findings suggest that a higher BMI in children is associated with a higher prevalence of symptoms that are often attributed to asthma, but not with a higher prevalence of asthma. Although a higher BMI in children was not associated with a higher prevalence of diagnosis of asthma, it was associated with a higher prevalence of atopy in girls but not in boys.

The distribution of BMI in these samples is similar to the general population in Australia (140). The methods and the questionnaire were similar to those used in other large epidemiological studies.

BMI percentiles were calculated from USA data, as this information is not available currently for Australia. This is unlikely to have invalidated the study outcomes, since the trend for the increase in obesity in children in Australia is closely following the USA trend (140). Although BMI may not be the best measure of obesity in children, it is widely used and information was not available from this study on which to base an alternative definition (137).

The association between a higher BMI and symptoms of wheeze and cough in children has been observed in previous studies (49, 50, 53). Wheeze and cough are non-specific symptoms, which may be attributed to a number of different causes, including asthma. To confirm a diagnosis of asthma in a children presenting with a history of wheeze or cough, it would usually be necessary to find evidence of variable airway obstruction. In this population, the increased
prevalence of wheeze and cough associated with increased BMI was not associated with any higher prevalence of airway obstruction, or BHR. This suggests that the excess symptoms among overweight children may be due to causes other than asthma. Increased BMI is associated with an increase in the occurrence both of gastro-oesophageal reflux (141) and of sleep apnoea (142), and both of these conditions may be a cause of symptoms of wheeze or cough without changes in lung function or bronchial responsiveness.

Alternatively, increased BMI may be associated with a number of changes to the mechanical function of the lungs and airways that could lead to symptoms of wheeze and cough. Other studies have shown that a higher BMI is associated with a higher rate of wheeze with exercise (61). In this study, we did not collect information that allowed us to differentiate between wheeze at rest and wheeze with exertion and thus cannot determine the extent to which the excess of wheezing in the overweight subjects was due to wheeze during exercise. Exertional wheeze in overweight subjects may be due to an increase in the work of breathing, with upper airway collapse or changes in lung mechanics increasing the load on the upper airway. Other studies have shown an increase in airway resistance in the obese (143), and wheeze may be due to changes in airway calibre, collapsibility, or inability to overcome airway hysteresis.

Changes in compliance or elastic recoil, due to low lung volume, could decrease the tidal fluctuations of airway smooth muscle and enhance contractility (130), and thus shift the dose response curve to methacholine or increase the level of the maximal response (84). There was no evidence of lower flow rates or higher BHR in the highest quintile. Although it has been shown previously that FVC is reduced in obese adults (144), there was not a significant reduction in FVC in children in the highest BMI quintile. Lung volumes were not measured and therefore it is unclear whether the effects of obesity on lung volume are not as prevalent in children as in adults or are less prominent if a higher body weight is present before puberty. Fat distribution was also not assessed in this study. Further studies are required to look at lung volumes in obese children and changes with puberty.
Although inhaled corticosteroid medication can normalise lung function and bronchial responsiveness (90), it is unlikely that the use of such medication could account for the absence of any association between a higher BMI and increased airway obstruction or BHR, since there was only a slight trend to a higher rate of medication use with higher weight. Furthermore it is unlikely that symptoms would persist during inhaled corticosteroid medication treatment if BHR or airway obstruction had been normalised.

A previous study found that increased BMI is associated with a higher prevalence of atopy and symptoms of wheeze in girls, but not in boys, which this study confirms (58). The cause for this is unknown and may relate to differences in hormonal levels, inflammatory markers, or body fat distribution. A correlation between BMI and BHR was found in Taiwanese girls (58), whereas another large study showed this association in men only (37). This study does not confirm this, since it was shown that BMI was not correlated with bronchial responsiveness, measured by DRR, nor was higher BMI associated with increased prevalence of BHR in either boys or girls.

This study has significant clinical implications. Previous studies have shown higher rates of in diagnosed asthma in obese children (46, 49, 50, 58, 61, 145). Without evidence of airway obstruction, or bronchial responsiveness, it is unlikely that these children truly have asthma. It is important to elucidate the true aetiology of symptoms in overweight children. Increasing symptoms with higher weight may be due to being unfit, worsening asthma, gastro-oesophageal reflux or to sleep disordered breathing. The treatment options for these aetiologies vary markedly. Some may require inhaled or even oral corticosteroids, which if used indiscriminately may exacerbate the weight problem. Others may be more likely to benefit from a weight loss program, H2 blockers or even nasal continuous positive airway pressure.

It is unlikely that a higher BMI is a risk factor for asthma or bronchial hyperresponsiveness in children, and it is likely that the prevalence of asthma in
obese children is the same as in the rest of the population. Obesity and asthma are both significant health problems and must be addressed both in children and adults to optimise lung function and quality of life.
Chapter 4

COMPARISON OF HIGH DOSE METHACHOLINE CHALLENGES BETWEEN OBESE AND NON-OBESE WOMEN
4.1 INTRODUCTION

Dose response curves for inhaled bronchoconstricting agents can be used to measure airway sensitivity as well as to determine the maximal airway narrowing produced. It is thought that the shape and the position of the high dose methacholine or histamine curve and presence or absence of a plateau can differentiate asthmatics and non-asthmatics (146).

Preventing the effect of deep inspiration has also been shown to alter the response of non-asthmatic subjects to an antagonist by causing heterogeneous narrowing of airway calibre that is thought may predispose these subjects to an increase in bronchial responsiveness (147, 148).

The hypothesis that chronic limitation of deep inspiration with reduction in lung volume by severe obesity (144, 149) would cause an increase in bronchial responsiveness or a change in the shape or position of the maximal curve to methacholine may explain the increase in asthma prevalence in obesity.

Dynamic and static lung volumes and high dose methacholine challenges were performed on a group of 6 obese non-asthmatic women and compared this with a group of matched non-obese non-asthmatic women to assess if there was a change in either the shape of the curve or the position of the plateau. Skin prick testing was also performed to assess atopy status.
4.2 METHODS

4.2.1 SUBJECTS

Six women with severe obesity were recruited from the endocrinology unit of Royal Prince Alfred Hospital. Normal subjects were recruited from among the staff and students of the Institute of Respiratory Medicine, the University of Sydney. All subjects were non-asthmatic. All participants had no previous respiratory disease and no history of symptoms consistent with asthma.

This was a pilot study to determine the size of the effect that we should be looking for.

4.2.2 BODY MASS INDEX (BMI)

Height and weight were measured without shoes. BMI was calculated by dividing weight (kg) by the square of height (m) (kg/m$^2$). All subjects recruited for the study in the obese group had a BMI $> 35$kg/m$^2$ and all recruited for the non-obese group had a BMI $< 27$kg/m$^2$.

4.2.3 LUNG FUNCTION

A Sensormedics Vmax spirometer (Sensormedics Inc, Yorba Linda CA, USA) was used to obtain FEV$_1$ and FVC at baseline and one minute after inhalation of normal saline or methacholine. At baseline, lung function measurements were repeated to obtain two measurements with FEV$_1$ and FVC repeatable to within 100ml or 5%, whichever was the smaller.

However, during the challenge, only one measurement was made after each dose, in order to maintain strict control over the volume history and allow reliable measurements of the effects of deep inspiration. FEV$_1$ and FVC are expressed as a percentage of predicted values (150).
4.2.4 METHACHOLINE CHALLENGE

Methacholine challenge tests were carried out using the method of Chai et al (151). Methacholine chloride was administered in doubling, cumulative doses ranging from 0.15 to 199 µmol, with a Devilbiss No 646 nebuliser attached to oxygen at 138kPa. Endpoints of the challenge were when FEV₁ fell by more than 20% from baseline, or when there was less than 5% variability between post methacholine FEV₁ on three successive doses of methacholine, or the maximum dose of methacholine was reached.

The dose response ratio (DRR) (percentage change in first FEV₁ of the plateau from baseline divided by the cumulative dose of methacholine to achieve the first dose of the plateau) was calculated. Because many participants had an FEV₁ that remained stable or improved slightly during the challenge and this had a zero or negative DRR value, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion.

4.2.5 LUNG VOLUMES

A Morgan dry rolling seal spirometer with kymograph, CO₂ absorber and fan was connected to a Morgan md2-FRC helium analyser (P.K. Morgan Ltd, Kent, England) to measure lung volumes by the closed-circuit helium dilution technique. Measurements recorded were functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC). Hyperinflation was quantified as the RV/TLC ratio. These measurements were compared with predicted values using the equations of Crapo et al (152).

4.2.6 SKIN PRICK TESTING

Skin prick test reactions on the forearm to eight common allergens were measured. The allergens tested with Dermatophagoides farinae and D. pteronyssinus, house dust, cat dander, cockroach, rye grass, timothy grass and Alternaria tenuis (Hollister-Stier). Histamine and glycerol were used as positive and
negative controls. Wheal size was recorded as the long axis and its perpendicular: mean wheal size was used in analyses. A wheal of 4mm or greater was regarded as positive for the study. Subjects were considered atopic if they had a positive reaction to any of the tested allergens.

4.2.7 STATISTICS

Data were analysed using the statistical package SPSS (SPSS Inc, IL, USA). Geometric mean values are reported for DRR values, which were converted to base 10 logarithms before analysis. For all analyses, p values < 0.05 were regarded as significant.

An unpaired Student’s t-test was performed to assess significant differences between the groups. Partial correlation coefficient was used to assess correlation between BMI, lung volumes and height and position of the plateau adjusting for atopy status.

4.2.8 POWER CALCULATIONS

This study was a pilot study to determine the size of the effect that we should be looking for.

The sample size for future studies was calculated to be 20 in each group, to give the study power of 80% with alpha =0.05 to detect a difference of one doubling dose difference in overall DRR or in the position or shape of the plateau.
4.3 RESULTS

Six obese and six non-obese women were studied. Subject demographics are in table 4.1.

<table>
<thead>
<tr>
<th>TABLE 4.3.1 - SUBJECT DEMOGRAPHICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>AGE (yrs)</td>
</tr>
<tr>
<td>(95% CI)</td>
</tr>
<tr>
<td>NON-OBESE</td>
</tr>
<tr>
<td>49.4</td>
</tr>
<tr>
<td>(44.7, 54.1)</td>
</tr>
<tr>
<td>OBESE</td>
</tr>
<tr>
<td>54.4</td>
</tr>
<tr>
<td>(52.1, 56.7)</td>
</tr>
<tr>
<td>P VALUE</td>
</tr>
<tr>
<td>0.09</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
</tr>
<tr>
<td>(95% CI)</td>
</tr>
<tr>
<td>NON-OBESE</td>
</tr>
<tr>
<td>23.6</td>
</tr>
<tr>
<td>(22.2, 24.9)</td>
</tr>
<tr>
<td>OBESE</td>
</tr>
<tr>
<td>39.5</td>
</tr>
<tr>
<td>(37.0, 41.9)</td>
</tr>
<tr>
<td>Number Atopic</td>
</tr>
<tr>
<td>3/6</td>
</tr>
<tr>
<td>4/6</td>
</tr>
<tr>
<td>P VALUE</td>
</tr>
<tr>
<td>0.60</td>
</tr>
</tbody>
</table>

An Unpaired t test was performed to assess significant differences between the groups.

This table shows that the obese group were slightly older than the non-obese group. There was no significant difference in the number of atopic subjects between the groups.

There were significant differences between groups in lung function parameters including FEV$_1$ and FVC, although the groups mean values remained within the predicted normal range (Table 4.3.2). Despite these differences, there was no increase in the degree of airway obstruction as measured by FEV$_1$/FVC% between the groups (p=0.69).
### TABLE 4.3.2 - LUNG FUNCTION RESULTS

<table>
<thead>
<tr>
<th></th>
<th>NON-OBESE</th>
<th>OBESE</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1} % predicted</td>
<td>107.9 (92.2, 123.6)</td>
<td>90.1 (79.3, 100.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>115.6 (104.1, 127.2)</td>
<td>95.0 (85.7, 104.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>FEV\textsubscript{1} / FVC%</td>
<td>79.3 (73.5, 85.0)</td>
<td>80.3 (77.3, 83.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>113.0 (107.8, 118.2)</td>
<td>93.6 (77.9, 109.3)</td>
<td>0.04*</td>
</tr>
<tr>
<td>TLC (litres)</td>
<td>5.70 (4.85, 6.54)</td>
<td>4.53 (3.5, 5.56)</td>
<td>0.047*</td>
</tr>
<tr>
<td>FRC % predicted</td>
<td>101.1 (81.7, 120.4)</td>
<td>74.9 (52.5, 97.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>DRR</td>
<td>3.8 (2.9, 4.9)</td>
<td>3.4 (3.1, 3.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>HEIGHT OF PLATEAU</td>
<td>12.9 (9.7, 16.0)</td>
<td>18.7 (9.4, 27.9)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*All results are means (95% confidence intervals)*

An Unpaired t test was performed to assess significant differences between the groups.

This table shows that there was a significant reduction in lung volume in the obese group as measured by FVC, TLC and TLC % predicted. Despite reductions in lung volume in the obese group, there was no increase in airway obstruction or bronchial responsiveness.

There was a significant difference in lung volumes between the groups despite the small number of subjects sampled. There was a 770ml difference in mean FRC
and 1170ml difference in mean TLC, which are similar to reductions in lung volumes due to obesity shown in other studies (120, 153).

High dose methacholine challenges were performed on all subjects. A plateau was reached in all subjects in both the obese and non-obese groups. The position of the slope of the curve (figure 4.3.1), and the position of the height of the plateau (figure 4.3.2) were not significantly different between the obese and non-obese group (table 4.3.1).

**FIGURE 4.3.1 - SHAPE OF THE HIGH DOSE METHACHOLINE CURVE VS DOSE USED IN OBESE AND NON-OBESE SUBJECTS.**

This graph shows that there was no significant difference in the height of the plateau or the shape of the high dose methacholine curve between the obese or non-obese group. There does appear to be a trend towards an increase in response in obese subjects, but this was not significant.
This graph shows that despite differences in TLC %predicted, there were no changes in bronchial responsiveness as measured by DRR.
4.4 DISCUSSION

This study found that despite reduced lung volumes associated with severe obesity, there was no change in the position or shape of the high dose methacholine curve. FEV$_1$ and FVC were also both significantly reduced in severely obese subjects, however these subjects did not have evidence of airflow obstruction, nor was there any change in the degree of bronchial responsiveness to methacholine.

In this study, data from 6 obese women and 6 non-obese controls were analysed. Women were studied as it is thought that there is an increase in asthma with obesity in women and it was more likely that changes would be present in obese women.

The technique only performed one breath per dose, which would limit the effect of deep inspiration or lung volume changes and would optimise the changes on the high dose methacholine plateau. Despite the technique being unchanged in both groups, there was no difference in the slope or the plateau.

Potentially the small number of subjects may mask any real small differences between these groups. Further studies are required in larger groups to assess if a difference does exist.

Lung volume is a major determinant of airway smooth muscle (ASM) function and lung function (154). Nagase et al (155) showed that elevated lung volume using positive end-expiratory pressure (PEEP), caused a 12% reduction in the response of airway resistance (Raw) to inhaled histamine for every cmH2O of PEEP increase. Using a rat model where small volume oscillations were used to nearly instantaneously measure airway responses to injected methacholine, Bates et al (156) showed that an increase in lung volume (2-6cmH2O of PEEP) halved the rate of rise in Raw. These findings suggest that ASM contractility is profoundly influenced by increases in lung volume. Ding et al (84) showed that 500ml
reduction in lung volume could cause bronchial hyperresponsiveness in non-asthmatic subjects. Skloot et al (157) demonstrated that when there was inhibition of deep breaths, normal subjects became hyperresponsive to inhaled methacholine. These findings suggest that failure to periodically inflate the lung to high volumes allows some bronchoprotective mechanism to be lost (157, 158). This bronchoprotective effect may be much more potent than bronchodilation cause by a deep breath in controls (159). In asthmatics and even in patients with rhinitis, the bronchoprotective effect of a deep breath is lost regardless of the degree of asthma (159, 160). These studies suggest changes in lung volumes are important in regulating bronchial reactivity, and presumably, this regulation results from the stretch (or lack of stretch) or ASM that occurs following lung volume alteration. These factors may be important in recovery from bronchospasm and in normal subjects may even prevent the development of BHR.

McClean et al (161) showed how the chronic loss of volume affects airway smooth muscle, by reducing lung volume in sheep by having sheep wear a leather corset for 4 weeks. Three groups were studied: neonates, adolescents and adults. While the FRC was reduced by approximately 25%, no significant changes in tidal volume or number of sighs were observed, nor were there changes in blood gases. Tracheal ASM contractility was unchanged, but in adolescent and adult cheep, bronchial ASM contractility was increased. There were no apparent differences in the amount of ASM, suggesting that hypertrophy had not occurred. Neither myosin light chain kinase content nor phosphorylation of ASM were changed. It was unclear what the cause of increased bronchial contractibility was. The authors demonstrated remodelling of the bronchial ASM to a hyperresponsive phenotype due to chronic length restriction, which further suggests that lung volume is an important determinant of ASM function and phenotype.

Information was not available about tidal breathing and deep inspiration in our study group though the TLC and FRC was reduced an amount similar to that which has been shown previously in the obese (120).
However, in this study, despite significant lung volume changes, there were no differences in the curve or the plateau of the high dose methacholine challenge between the obese and non-obese non-asthmatic subjects. More significant lung volume changes may be necessary in non-asthmatics to increase the degree of hysteresis.

Information was not available about the duration of obesity. Sudden changes in airway calibre such as chest strapping or lying down may have a bigger impact on bronchial responsiveness or changes may need to be long term, implying changes may be required over several years or during maximal lung growth to cause these changes.

Significantly despite significant lung volume changes, there may be no changes to deep inspiration in the obese, or to sighing during sleep, which may overcome airway hysteresis and prevent a predisposition to an increase in bronchial responsiveness to methacholine. Other mechanisms may be present to increase symptoms of wheeze in the obese.

In summary, despite significant lung volume changes there was no change in the position or shape of the high dose methacholine curve suggesting that low lung volumes in obesity have no effect on degree of bronchial responsiveness or on airway smooth muscle shortening.
Chapter 5

THE RELATIONSHIP BETWEEN CHANGES IN LUNG VOLUMES AND BRONCHIAL RESPONSIVENESS IN NORMAL SUBJECTS AND SUBJECTS WITH ASTHMA.
5.1 INTRODUCTION

Ding et al (84) has previously shown that bronchial responsiveness (BR) increases by voluntarily breathing below functional residual capacity (FRC) and Shardonofsky et al (85) has shown similar changes with lying down. These changes may be due to a decrease in lung volume (LV), particularly in FRC.

Reductions in lung volume are thought to increase BR due to changes in compliance or elastic recoil, decreasing the tidal fluctuations of airway smooth muscle and enhancing contractility (130, 161), and therefore shift the dose response curve (DRC) or increase the level of the maximal response (146).

It is likely that the effect of a change in lung volume on changes in bronchial responsiveness are different in asthmatics and non-asthmatics and the differences between these 2 groups may provide further information as to the changes that predispose to worsening of asthma with obesity.

The aim of this study was to investigate

a) The change in shape and position of the methacholine curve with a change in position from upright to supine,

b) The correlation with these changes and changes in lung volume in asthmatic and non-asthmatic subjects
5.2 METHODS

5.2.1 SUBJECTS

Eighteen non-asthmatic subjects and 14 subjects with previous doctor diagnosis of asthma of any severity on any anti-asthma medication with a history of episodic wheeze or chest tightness were recruited. The healthy subjects had no history of respiratory disease and no regular past or current treatment for respiratory disease. Current cigarette smokers and subjects with recent upper respiratory tract infection were excluded from the study.

5.2.2 LUNG FUNCTION

A Sensormedics Vmax spirometer (Sensormedics Inc, Yorba Linda CA, USA) was used to obtain $\text{FEV}_1$, FVC and partial and maximal flow volume curves at baseline and one minute after inhalation of normal saline or methacholine. At baseline, lung function measurements were repeated to obtain two measurements with $\text{FEV}_1$ and FVC repeatable to within 100ml or 5%, which ever was the smaller.

5.2.3 LUNG VOLUMES

Lung volumes were measured before challenge in both the upright and supine postures. Lung volumes were tested after the subjects were lying supine for 30 minutes. A Morgan dry rolling seal spirometer with kymograph, CO$_2$ absorber and fan was connected to a Morgan $md2$-$FRC$ helium analyser (P.K. Morgan Ltd, Kent, England) to measure lung volumes by the closed-circuit helium dilution technique. Measurements were made of functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC). Lung hyperinflation was quantified by the RV/TLC ratio. Lung volume measurements were compared with predicted values using the equations of Crapo et al (152).
5.2.4 METHACHOLINE CHALLENGE

Methacholine challenge tests were carried out using the method of Chai et al in both the upright and supine positions (151). Methacholine chloride was administered in doubling, cumulative doses ranging from 0.1 to 10 µmol in the asthmatic subjects and 0.1 to 200 µmol in the non-asthmatic subjects, with a Devilbiss No 646 nebuliser attached to oxygen at 138kPa. The partial and maximal flow volume curves were measured 60 seconds after each inhalation and the next dose given immediately. Each subject had one blow at that time to try to control for volume history. The challenge was stopped when FEV$_1$ fell by more than 20% from baseline or the maximum dose of methacholine was reached.

The dose response ratio (DRR) (percentage change in first FEV$_1$ of the plateau from baseline divided by the cumulative dose of methacholine to achieve the first dose of the plateau) was calculated. Because many participants had an FEV$_1$ that remained stable or improved slightly during the challenge and this had a zero or negative DRR value, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion.

Doubling dose difference implies a shift in PD20 from 0.1 to 0.2 micromoles is regarded as equal in magnitude as a shift from 1 to 2 µmol. It is calculated as the difference between log values ie (log PD$_{10}$20a - log PD$_{10}$20b) divided by 0.3. The 0.3 is the log of 2, and converts the difference to "doubling" units.

5.2.5 SKIN PRICK TESTING

Skin prick test reactions on the forearm to eight common allergens were measured. The allergens tested with Dermatophagoides farinae and D. pteronyssinus, house dust, cat dander, cockroach, rye grass, timothy grass and Alternaria tenuis (Hollister-Stier). Histamine and glycerol were used as positive and negative controls. Wheal size was recorded as the long axis and its perpendicular: mean wheal size was used in analyses. A wheal of 4mm or greater was regarded
as positive for the study. Subjects were considered atopic if they had a positive reaction to any of the tested allergens.

5.2.6 STATISTICS

Data were analysed using the statistical package SPSS (SPSS Inc, IL, USA). Geometric mean values are reported for DRR values, which were converted to \( \log_{10} \) before analysis. For all analyses, p values < 0.05 were regarded as significant.

The response threshold, measured as the dose causing a 5% fall in FEV\(_1\) (PD\(_5\)FEV\(_1\)) was used to characterise the position of the curve. This value was determined by linear interpolation of the dose response curve. In subjects with a 20% fall in FEV\(_1\) the PD\(_{20}\)FEV\(_1\) was also determined by linear interpolation of the dose response curve. Values for PD\(_5\)FEV\(_1\) and PD\(_{20}\)FEV\(_1\) were log\(_{10}\) transformed prior to analysis and their summary statistics are reported as geometric means and 95% confidence intervals. The % fall in FEV\(_1\) at the maximum dose common to both the upright and supine challenges was recorded as a measure of the maximum response for comparison purposes.

A paired Student’s t-test was performed to assess significant differences between the upright and supine positions. An Unpaired Student’s t-test was performed to assess differences between the groups of asthmatic and non-asthmatic subjects.

Pearson correlation coefficient and multiple linear regression were used to assess the significance of association between lung volumes and change in lung volumes with change in bronchial responsiveness, allowing for posture and airway calibre.

5.2.7 POWER CALCULATIONS

The sample size was calculated to be 20 in each group, to give the study power of 80% with alpha =0.05 to detect a difference of one doubling dose difference in DRR.
5.3 RESULTS

Information was available for 14 asthmatics and 18 non-asthmatic subjects. A broad range of asthma severity was recruited (DRR mean 14.6, range 3.8-110.5). No medication was altered for the challenges. There was no difference in age, or height in the subjects, however there was a trend for an increase in the prevalence of atopy in the asthmatic group (table 5.3.1).

| TABLE 5.3.1 – SUBJECT DEMOGRAPHICS AND BASELINE LUNG FUNCTION IN ASTHMATICS AND NON-ASTHMATIC SUBJECTS. |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Gender (no m/f)                                 | Non-asthmatics  | Asthmatics      | P value         |
| Age (years)                                     | 8/10            | 8/6             |                 |
| Mean (95% CI)                                    | 34.3 (30.7, 38.0) | 33.7 (26.1, 41.3) | 0.88            |
| Height (cm)                                     | 170.6 (165.5, 175.8) | 170.9 (166.1, 175.7) | 0.95            |
| Mean (95% CI)                                    |                 |                 |                 |
| No atopic (% of no)                             | 7 (39%)         | 10 (71%)        | 0.07            |
| FEV\textsubscript{1} % predicted                | 103.3 (97.4, 109.1) | 92.4 (86.2, 98.7) | 0.02            |
| Mean (95% CI)                                    |                 |                 |                 |
| FVC % predicted                                 | 109.8 (102.5, 117.2) | 102.9 (96.7, 109.1) | 0.19            |
| Mean (95% CI)                                    |                 |                 |                 |
| FEV\textsubscript{1}/FVC%                        | 80.8 (77.5, 84.1) | 76.0 (71.2, 80.9) | 0.11            |
| Mean (95% CI)                                    |                 |                 |                 |
| TLC % predicted                                 | 103.1 (95.2, 110.9) | 102.3 (95.9, 108.8) | 0.87            |
| Mean (95% CI)                                    |                 |                 |                 |
| FRC %predicted                                  | 104.6 (93.6, 115.6) | 95.0 (83.2, 106.8) | 0.25            |
| Mean (95% CI)                                    |                 |                 |                 |
| RV/TLC                                          | 0.31 (0.26, 0.37) | 0.26 (0.22, 0.29) | 0.14            |
| Mean (95% CI)                                    |                 |                 |                 |
| DRR                                             | 4.42 (3.61, 5.42) | 14.60 (8.71, 24.49) <0.001 |

All results are in the upright position
P values are for Unpaired t-tests

This table shows that there was an increase in atopic subjects in the asthmatic group. The asthmatic group had a lower FEV\textsubscript{1} and an increase in airway responsiveness, though no difference in lung volumes.
Baseline lung function showed differences between asthmatics and non-asthmatics with no significant difference in FEV$_1$/FVC although it was slightly lower in asthmatics (table 5.3.1). However there was no difference in FVC or any lung volume measurement or degree of hyperinflation as measured by RV/TLC between the asthmatic and non-asthmatic subjects while upright (table 5.3.1).

In the non-asthmatic group, baseline lung function was within normal limits. On lying down, FRC fell by 663ml +/- 189.6 ml (figure 5.3.1), though there were no changes in RV or TLC. Both FEV$_1$ and FVC fell (table 5.3.2), but there was no increase in airway obstruction as measured by FEV$_1$/FVC %. There was a significant increase in bronchial responsiveness on lying down (figure 5.3.2).

**FIGURE 5.3.1: CHANGE IN FRC (ML) WITH CHANGE IN POSITION FROM UPRIGHT TO SUPINE IN BOTH NON-ASTHMATIC AND ASTHMATIC SUBJECTS**

This figure shows a significant fall in FRC of 663ml ± 189.6 in non-asthmatic group and 524.3ml ± 171.6 in asthmatic subjects in changing from upright to supine position.
TABLE 5.3.2 – LUNG FUNCTION CHANGES BETWEEN UPRIGHT AND SUPINE POSITIONS IN NON-ASTHMATICS AND ASTHMATICS

<table>
<thead>
<tr>
<th></th>
<th>Non-Asthmatics</th>
<th>Asthmatics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ (litres)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>3.64 (3.29, 3.98)</td>
<td>3.17 (2.80, 3.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FVC (litres)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>4.56 (4.02, 5.10)</td>
<td>4.15 (3.64, 4.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FEV₁/FVC%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>80.8 (77.5, 84.1)</td>
<td>77.0 (74.5, 79.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>TLC (litres)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>6.11 (5.48, 6.74)</td>
<td>6.08 (5.37, 6.80)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>FRC (litres)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>3.25 (2.87, 3.62)</td>
<td>2.58 (2.21, 2.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>RV (litres)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>1.86 (1.58, 2.14)</td>
<td>1.79 (1.54, 2.03)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>RV/TLC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>0.31 (0.26, 0.37)</td>
<td>0.30 (0.27, 0.32)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>DRR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (95% CI)</td>
<td>4.42 (3.61, 5.42)</td>
<td>7.17 (4.96, 10.36)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P values given are for paired t tests.

This table shows that in both non-asthmatic and asthmatic groups, there was a decrease in FEV₁, FVC and an increase in airway obstruction and BR with changing from upright to supine positions. However in the asthmatic group only there was a significant increase in RV and RV/TLC with lying down.
This figure shows that in the majority of non-asthmatics bronchial responsiveness increased with lying down, and there were only 2 subjects with no change in BR with change in position. In the asthmatic group, there was a variable change in bronchial responsiveness with 5/14 subjects having little or no change, and no significant increase in BR with change in position.

In the non-asthmatic group baseline %predicted FRC was correlated with bronchial responsiveness while upright ($r=-0.498$, $p=0.042$), and changes in lung volume as measured by % change in FRC was correlated with change in BR as measured by $\triangle \log$ DRR or doubling dose difference in BR (figure 5.3.3) ($r= -0.39$). Analysis was also performed, which corrected for airway size, which showed that this association between lung volumes and bronchial responsiveness persisted.
There was a significant association between changes in lung volume as measured by fall in FRC %predicted and changes in bronchial responsiveness in non-asthmatics. No association was seen in asthmatics.

Baseline lung function in the asthmatic group showed that although FEV₁ and FVC were within normal limits, mild obstruction was present (table 5.3.1). Lung volumes were all within normal limits with no increase in gas trapping, as measured by RV/TLC (table 5.3.1). There was an increase in baseline bronchial responsiveness (table 5.3.1).

In the asthmatic group, on lying down, there was a slight but not significant reduction in TLC, though there was an increase in airway obstruction and VC (table 5.3.2). FRC and FRC % predicted fell significantly (p<0.001) and there was a significant increase in RV and RV % predicted (p=0.008). There was also an
increase in bronchial responsiveness with there being a 0.79 doubling dose increase.

In the asthmatic group, upright FRC % predicted was not correlated with baseline bronchial responsiveness ($r = -0.26$, $p=0.37$). Linear regression was performed and changes in position and changes in lung volume were not independently associated with changes in bronchial responsiveness.

The mean maximum dose of methacholine common to the non-asthmatic subjects was 9.38 (95%CI 4.14, 14.61) µmol and 2.64 (95%CI 0.81, 4.48) µmol in asthmatic subjects. At that dose the mean maximum fall in FEV₁ was significantly higher in the supine position in both the non-asthmatic (4.53±2.5% vs 14.5±4.1%, $p=0.002$) and asthmatic groups (12.2±4.2% vs 19.4±5.7%, $p=0.01$). In the non-asthmatic group, while upright 15 out of 18 subjects had a plateau at a mean 9.6±2.3% fall in FEV₁. On the dose response curves in the supine position, a plateau was present on the curves from only 9 out of 18 subjects implying changes in the maximum amount of airway smooth muscle contraction. In these remaining subjects, that had a plateau in both positions, the mean fall in FEV₁ while supine was 10.1±2.6%. There was no significant difference between the heights of the plateaus ($p=0.83$).

The threshold for the response to methacholine was measured as the dose that caused a 5% fall in FEV₁ (PD₅₀FEV₁). In the non-asthmatic subjects, PD₅₀FEV₁ was significantly lower in the supine position. The geometric mean PD₅₀FEV₁ decreased by 1.61 doubling doses (95%CI 0.40, 2.81) from 4.93 to 1.63 µmol ($p=0.019$) (figure 5.3.4). In the asthmatic subjects, PD₅₀FEV₁ at the upright challenge was 0.46 (0.24, 0.88) µmol, which was highly significantly different from the non-asthmatics 4.93 (2.63, 9.26) µmol, ($p<0.001$), however in the asthmatic subjects, there was not a significant change with lying down ($p=0.33$).
This figure shows that in the majority of the non-asthmatic group there was a significant increase in bronchial responsiveness, however the in the asthmatic group there was a heterogeneous response.
5.4 DISCUSSION

This principal finding of this study is that measures of bronchial responsiveness were correlated with changes in lung volumes in non-asthmatic subjects only. This effect was not due to changes in airway dynamics or the effect of recumbency on lung function. Despite similar falls in lung volumes and an increase in airway obstruction with lying down in the asthmatic subjects, an association between changes in lung volumes and increases in bronchial responsiveness was not present in the asthmatic subjects.

Subjects were recruited from a university population and there was a broad range of initial bronchial responsiveness. Despite this there was no significant difference between the groups in baseline airway obstruction as measured by FEV$_1$/FVC% or RV/TLC. It was thought that a broad range of asthma severity would increase the likelihood of an association if it were present. The age range of the asthmatic and non-asthmatic subjects were similar and as expected there was an increase in atopy in the asthmatic subjects.

Reduction in lung volume in the non-asthmatic subjects appeared to shift the methacholine curve as measured by PD$_5$ and changed the position of the methacholine plateau in 9 out of 18 subjects, therefore implying the subjects become more sensitive to irritants. Potentially this increase in bronchial responsiveness on reducing lung volumes may predispose certain at risk subjects to long term airway changes that may be consistent with asthma.

The changes in lung volumes in the subjects were similar to those in other studies looking at changes in lung volumes with chest strapping (84) or with changes in posture (85) and therefore it would have expected similar effects on bronchial responsiveness. Shardonofsky et al (85) found that lying supine decreased FRC by 850ml, and increased the maximal response from 16% to 30 % fall in FEV$_1$. However in this study the procedure was stopped if there was a greater than 20% fall in FEV$_1$ and therefore subjects who did not have a plateau may simply have not
reached maximal smooth airway muscle bronchoconstriction. However there was also an increased sensitivity as measured by PD$_5$ in non-asthmatic subjects only. This may have been due to the challenge protocol which required only a single breath after the methacholine dose to minimise the bronchodilator effect of deep inspiration.

In non-asthmatic subjects, reductions in lung volumes may predispose certain at risk subjects to increases in bronchial responsiveness, and therefore to long term asthma and in this group, treating the reduction in lung volume, whether it be caused by obesity or chest wall restriction, becomes a priority.

Subjects were lying down for 30 minutes before the lung volumes and methacholine challenges were performed, which may not be long enough for the maximal effect of recumbency to take place.

The relationship between effects of recumbency and decrease in functional residual capacity need to be further investigated.
Chapter 6

ASSOCIATION BETWEEN SEVERITY OF GASTRO-OESOPHAGEAL REFLUX, ASTHMA, AND LUNG FUNCTION IN OBESITY
6.1 INTRODUCTION

Gastro-oesophageal reflux (GER) is known to be associated with many forms of respiratory disease, including asthma, pulmonary fibrosis, cystic fibrosis, scleroderma, (94, 162-165) and obstructive sleep apnoea syndrome (166). It may be causative or exacerbate pre-existing lung disease.

Potential mechanisms for GER affecting lung function are aspiration of acid or bulk fluid into the airways and potentially thence into the lung parenchyma causing chronic inflammation. Chronic inflammation in the lung parenchyma may progress to pulmonary fibrosis with airway obstruction and gas exchange impairment. In the airways reflux of acid may also cause bronchial constriction. Any pre-existing lung disease may be exacerbated by GER or potentially GER may be a causative factor in the development of chronic lung disease. Animal studies have shown that continuous aspiration of milk into animal lungs causes pulmonary inflammation and pulmonary fibrosis (93).

Other important explanations for a positive association between lung disease and GER may include lung disease itself exacerbating GER, particularly in those where chronic cough is a major symptom (167-169). Some systemic diseases, such as scleroderma or connective tissue diseases may also affect both the respiratory and gastrointestinal systems therefore suggesting that lung disease and GER coexist rather than one or the other being causative (163).

It would therefore be expected that control of GER might improve lung function or reduce deterioration in chronic lung conditions. Studies have shown an improvement in asthma symptoms and lung function associated with medical or surgical treatment for severe GER (162, 170-172). In children with cystic fibrosis with symptomatic GER, changing from postural drainage with positive expiratory pressure (PEP) chest physiotherapy to upright PEP physiotherapy, improved GER symptoms and reduced amount of GER, improved lung function over 6 months,
decreased the deterioration in lung function, and reduced hospital admissions over 18 months (162).

Both lung disease and GER have a high prevalence worldwide (173, 174). These conditions are frequently coexistent. Although it is known that massive GER may cause pulmonary fibrosis, or exacerbate asthma and cystic fibrosis, it is not known whether moderate to severe GER may cause or exacerbate milder forms of lung disease, or cause lung function changes in the absence of overt symptomatic lung disease.

No previous studies have compared the severity of GER with prevalence of asthma and changes in lung function that have included measurements of carbon monoxide diffusion. The aim of this study was to explore further the relationship between severity of GER, diagnosis of asthma and lung dysfunction using measures of static and dynamic lung volumes and carbon monoxide diffusing capacity in a group of obese adults.
6.2 METHODS

6.2.1 SAMPLES AND SELECTION CRITERIA

Data on 147 consecutive patients who presented for weight loss surgery were assessed retrospectively. Patients are considered for obesity surgery if they present with a BMI greater than 35kg/m² or BMI>30kg/m² and suffering from significant medical, physical, or psychosocial disabilities.

Preoperatively a full medical history and examination was performed. Information on GER included history, previous investigations, and medication usage. Patients completed a questionnaire of respiratory disease and symptoms, which was a modified form of the International Union against Tuberculosis (IUALTD) (121) which has been validated (122). No patient had significant lung disease other than asthma. No patient had significant cardiac disease and a full cardiac history and examination was performed. Routine preoperative laboratory tests were performed. These included Hb, fasting insulin, plasma glucose, and liver function tests.

6.2.2 LUNG FUNCTION

Lung function was assessed preoperatively on all patients using a Sensormedics Vmax © 22 system (Sensormedics Inc, Yorba Linda CA, USA). A respiratory scientist blinded to the presence or severity of GER performed these measures. Spirometry was measured using a calibrated mass flow sensor with the flow signal digitally integrated to calculate volume. Values for FEV₁ and FVC are reported as percent of predicted values (123).

Single breath diffusing capacity (D_{LCO}) was measured using a rapid carbon monoxide (CO) and methane (CH₄) analyser, which was calibrated prior to each measurement. Values for D_{LCO} and diffusing capacity corrected for lung volume (D_{LCO}/VA) were obtained, and are reported as percentage of predicted values (175).
Lung volumes were measured using the inert gas (nitrogen washout) technique. All instrumentation met and tests were performed following American Thoracic Society (ATS) standards. Lung volumes were obtained and are reported as a percentage of predicted values (176).

### 6.2.3 DEFINITIONS

A physician, who was blinded to lung function, graded GER according to severity prospectively. Grade 3 subjects had a history of severe GER diagnosed on pH monitoring and/or gastroscopy. All patients with grade 3 GER were on daily proton pump inhibitors, with ongoing symptoms. Grade 2 subjects reported symptoms consistent with GER and were often on regular anti-reflux therapy, but without investigation or only mild or moderate GER on gastroscopy or pH monitoring. Grade 1 had no symptoms and no medication was used at all for treatment of GER. If there was any doubt about the severity, or if the subjects were inadequately investigated, they were placed into grade 2.

Asthma was defined as a previous diagnosis of asthma ever by a doctor and answering positively to the question “have you wheezed in the last 12 months?”. Excessive daytime somnolence (EDS) was defined as an Epworth Sleepiness Scale (ESS) (177, 178) > 10.

Smoking history was divided into those who had never smoked (0 pack-years), mild history of smoking (>0 - 10 pack-years), a moderate history of smoking (>10 – 20 pack-years), and a heavy smoking history (>20 pack-years).
6.2.4 BODY MASS INDEX

Weight and height were measured without shoes. Body mass index (BMI) (kg/m$^2$) was calculated. All subjects were obese (BMI range 31.7-70 kg/m$^2$). Anthropometric measurements included waist, hip and neck circumference.

6.2.5 STATISTICAL METHODS

Data was analysed using the statistical package SPSS (SPSS Inc, IL, USA). Prevalence rates and mean values are reported with 95% confidence intervals (CI). One-way ANOVA with Duncan’s range test was used to analyse means of grouped data based on the category of pre-operative gastro-oesophageal reflux grading. This was performed to avoid multiple pair-wise comparisons. Student’s t-test was used to compare mean values of those in grades 1 and 3 where indicated. Kruskall Wallis analysis was used when the data distribution was skewed for example pack years previously smoked. $\chi^2$ statistics was used to determine the significance of differences in prevalence. Linear regression analysis was used to control for age, gender, BMI, smoking history, and haemoglobin (Hb).
6.3 RESULTS

Data from 147 consecutive obese patients (BMI range 31.7 – 70 kg/m²) were analysed retrospectively. Patient demographics are in table 6.3.1. The patients with grade 3 GER were significantly older (p=0.006).

**TABLE 6.3.1 – RELATIONSHIP BETWEEN PATIENT DEMOGRAPHICS AND GER SEVERITY.**

<table>
<thead>
<tr>
<th></th>
<th>NO REFLUX GER 1</th>
<th>INTERMEDIATE REFLUX GER 2</th>
<th>SEVERE REFLUX GER 3</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>66</td>
<td>60</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gender % Male #</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Age*</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>40.3(^A) (37.9, 42.8)</td>
<td>41.0(^A) (38.7, 43.3)</td>
<td>47.8(^B) (44.0, 51.6)</td>
<td></td>
</tr>
<tr>
<td>BMI*</td>
<td></td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>46.9 (45.0, 48.8)</td>
<td>45.4 (43.5, 47.3)</td>
<td>45.5 (43.0, 47.9)</td>
<td></td>
</tr>
<tr>
<td>Doctor diagnosed asthma #</td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>36.4%</td>
<td>46.7%</td>
<td>42.9%</td>
<td></td>
</tr>
<tr>
<td>Current smokers #</td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>9.2%</td>
<td>21.3%</td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Snoring #</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>39.4%</td>
<td>53.3%</td>
<td>47.6%</td>
<td></td>
</tr>
<tr>
<td>Witnessed apnoeas #</td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>22.7%</td>
<td>25.0%</td>
<td>28.6%</td>
<td></td>
</tr>
<tr>
<td>Mean ESS*</td>
<td></td>
<td></td>
<td></td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>6.5 (5.2, 7.8)</td>
<td>8.1 (6.7, 9.5)</td>
<td>9.5 (7.2, 11.8)</td>
<td></td>
</tr>
<tr>
<td>Waist Hip Ratio*</td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>WHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.91 (0.89, 0.93)</td>
<td>0.88 (0.85, 0.92)</td>
<td>0.89 (0.86, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (Hb)</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>138.7 (135.9, 141.4)</td>
<td>134.7 (131.4, 138.0)</td>
<td>133.5 (128.5, 138.5)</td>
<td></td>
</tr>
</tbody>
</table>

All values are means (95% CI) or % proportion
*Differences between groups were assessed using ANOVA using Duncan’s range test. Values marked A & B were significantly different.
# Analysed using chi squared statistic
The group with grade 3 GER (n=21) did not have an increased prevalence of current smoking (table 6.3.1), although there was a difference between groups in pack-years previously smoked (data not shown, p<0.001). There was also an increase in current smoking in the mild grade 2 GER group only and not between grade 1 GER and grade 3 GER (table 6.3.1). There was also a trend to a reduced Hb in the group with grade 3 GER (p=0.09), which may have been secondary to chronic slow blood loss due to oesophagitis. Smoking history, current smoking status, and Hb were allowed for in all further analyses.

Table 6.3.2 shows the results of lung function testing. There were no differences in FEV₁, FVC % predicted, FEV₁/FVC% (figure 6.3.1), or lung volumes between subjects with grade 1 GER and those with grade 3 GER. Flow rates were also analysed and there was no difference in FEF50 % predicted. There was a significant reduction in DLCO (figure 6.3.2), DLCO/VA and DLCO % predicted in those with grade 3 GER (n=21) when compared with subjects with grade 1 GER (n=66). GER category explained significant variance in DLCO, DLCO/VA, and DLCO% predicted when modelled with age, gender, BMI, smoking history, and haemoglobin.

When smoking history was divided into 4 groups depending on pack-years previously smoked, there was no difference in DLCO (p=0.61), DLCO/VA (p=0.89), and DLCO % predicted (p=0.17) between these groups (data not shown). There was also no correlation between pack-years smoked as a continuous variable and DLCO (r=0.20, p=0.38), DLCO/VA (r= 0.08, p=0.73), or DLCO % predicted (r= -0.14, p=0.54) (figure 6.3.3).
### TABLE 6.3.2 – RELATIONSHIP BETWEEN LUNG FUNCTION AND SEVERITY OF GASTRO-oesophageal REFLUX.

<table>
<thead>
<tr>
<th></th>
<th>NO REFLUX GER 1</th>
<th>INTERMEDIATE REFLUX GER 2</th>
<th>SEVERE REFLUX GER 3</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ %predicted</strong></td>
<td>87.0&lt;sup&gt;A&lt;/sup&gt; (83.4, 90.6)</td>
<td>93.6&lt;sup&gt;B&lt;/sup&gt; (90.0, 97.1)</td>
<td>88.0 (81.1, 94.8)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>FVC %predicted</strong></td>
<td>91.7 (87.9, 95.6)</td>
<td>97.7 (94.4, 101.1)</td>
<td>94.7 (88.3, 101.1)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>FEF&lt;sub&gt;50&lt;/sub&gt; %predicted</strong></td>
<td>82.8 (76.6, 88.9)</td>
<td>87.1 (79.4, 94.7)</td>
<td>76.8 (64.7, 89.0)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>FRC %predicted</strong></td>
<td>67.9 (61.1, 74.7)</td>
<td>68.6 (62.9, 74.2)</td>
<td>68.1 (59.6, 76.7)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>RV / TLC</strong></td>
<td>0.21 (0.18, 0.25)</td>
<td>0.23 (0.20, 0.26)</td>
<td>0.26 (0.22, 0.29)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>D&lt;sub&gt;LCO&lt;/sub&gt; mL/min/mmHg</strong></td>
<td>26.3&lt;sup&gt;A&lt;/sup&gt; (24.4, 28.2)</td>
<td>24.6&lt;sup&gt;B&lt;/sup&gt; (22.9, 26.2)</td>
<td>21.1&lt;sup&gt;B&lt;/sup&gt; (18.9, 23.2)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>D&lt;sub&gt;LCO&lt;/sub&gt;/VA</strong></td>
<td>5.32&lt;sup&gt;A&lt;/sup&gt; (5.12, 5.51)</td>
<td>5.04&lt;sup&gt;B&lt;/sup&gt; (4.81, 5.27)</td>
<td>4.61&lt;sup&gt;B&lt;/sup&gt; (4.30, 4.93)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>D&lt;sub&gt;LCO&lt;/sub&gt; % predicted</strong></td>
<td>102.5&lt;sup&gt;A&lt;/sup&gt; (97.2, 107.8)</td>
<td>93.9&lt;sup&gt;B&lt;/sup&gt; (89.3, 98.5)</td>
<td>88.9&lt;sup&gt;B&lt;/sup&gt; (80.7, 97.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

All values are means (95% CI)

Values marked A & B were significantly different. Differences between groups were assessed using ANOVA with Duncan’s range test.

This table shows despite no changes in flow rates or lung volumes, there was a decrease in carbon monoxide transfer in the group with severe GER in comparison with the group with no GER.
FIGURE 6.3.1 – RELATIONSHIP BETWEEN FEV\textsubscript{1}/FVC% AND SEVERITY OF GASTRO-OESOPHAGEAL REFLUX.

This graph shows that there was no difference in the degree of airway obstruction between the groups with differing severity of gastro-oesophageal reflux.

FIGURE 6.3.2 RELATIONSHIP BETWEEN CARBON MONOXIDE DIFFUSING CAPACITY AND SEVERITY OF GASTRO-OESOPHAGEAL REFLUX.

This graph shows a significant reduction in carbon monoxide diffusing capacity in the group with severe gastro-oesophageal reflux.
This figure shows no association between smoking history measured as packet-years smoked and carbon monoxide gas transfer ($D_{LCO}$ % predicted) in subjects with severe GER (Grade 3 GER) ($r=-0.14$, $p=0.54$).

In Grade 2 GER, subjects reported symptoms consistent with GER and were often on regular anti-reflux therapy, but without investigation or only mild or moderate GER on gastroscopy or pH monitoring. If there was any doubt about the severity of GER, or if the subjects were inadequately investigated, they were placed into Grade 2. This group represents a mixed severity of GER and therefore the significance of results in this group is unclear.

Results are shown as percent predicted. With many of the prediction equations, the normal values are not inclusive of severe obesity. However there was no difference in BMI ($p=0.48$), waist hip ratio ($p=0.38$) (table 6.3.1), or neck circumference ($p=0.8$) across the 3 groups of severity of GER.

To determine if these differences in diffusing capacity could be due to differences in sleep disordered breathing, usual factors associated with sleep apnoea were assessed. There was no difference in male gender, BMI, body habitus, including
waist hip ratio (table 6.3.1), neck circumference, or prevalence of hypertension (p=0.29). There were also no differences in self-reported snoring, or witnessed apnoeas (table 6.3.1). There was however an increase in daytime somnolence in the group with grade 3 GER when compared with grade 1 GER as measured by the mean ESS (t-test, p=0.03).

Liver disease may also influence diffusing capacity by increasing the hepatic pulmonary shunt (179). Obese subjects have an increase in the prevalence of steatohepatitis (180, 181) associated with insulin resistance. There was no significant difference in aminotransferase levels AST (p=0.32) or ALT (p=0.78), diabetes (p=0.93), or insulin resistance (67) (p=0.68) across the groups of GER (data not shown).
6.4 DISCUSSION

The principal finding of this study is that severe gastro-oesophageal reflux defined by pH monitoring and/or gastroscopy is associated with a reduction in diffusing capacity for carbon monoxide. This effect was not due to differences in obesity, weight distribution, spirometric function, lung volumes or smoking history. Furthermore, there did not appear to be any other relevant medical history to account for these gas exchange abnormalities.

The current series is the largest to date assessing GER, prevalence of asthma and lung function including diffusing capacity. No previous studies have compared a control group with a group with severe GER for changes in lung function including diffusing capacity. Only one previous study has shown an improvement in diffusing capacity at 1 and 6 months after laparoscopic Nissen fundoplication surgery for severe GER in a group of 16 out of 69 subjects with diffusing capacity abnormalities pre-operatively (95).

The patient demographics in this study are not representative of the general population. These patients are obese and the majority of patients are female, with a lower prevalence of current smoking than the general population, and all were presenting for obesity surgery. The changes in lung function may be influenced by the co-morbidity of obesity however the degree of obesity and weight distribution was not different across the groups and an independent association between GER and diffusing capacity reduction persists after controlling for BMI.

An assessment as to whether GER may account for the increase in diagnosed asthma in the obese was performed. There was no difference in prevalence of the diagnosis of asthma across the severity of GER, and no differences in the degree of airway obstruction as measured by FEV₁ or FEF₅₀. doctor diagnosed asthma was used as most of the epidemiology studies used this definition for asthma and we thought if GER alone was contributing to the linkage, then changes of prevalence would appear across the groups.
The group with severe GER reported an increase in mean Epworth Sleepiness Score, though these results were still within the normal range. Sleep disordered breathing is associated with obesity and in one study an increase in $D_{LCO}$ (182). The patients did not have polysomnographic studies, however all usual factors associated with sleep disordered breathing were assessed, and there was no difference in male gender, degree of obesity or body composition as measured by neck circumference, waist hip ratio, or hypertension, and no difference in prevalence of snoring or self-reported witnessed apnoeas. It is likely that an increase in somnolence is due to GER causing an increase in number of arousals (166) rather than to a difference in prevalence of sleep disordered breathing.

Potential mechanisms for the reduction in diffusing capacity include micro-aspiration into the tracheo-bronchial tree causing airway inflammation with subsequent ventilation perfusion (V/Q) maldistribution. Previous studies have shown micro-aspiration in asthma (109), scleroderma (164) and cystic fibrosis (183). Acidification or irritation of the airways could cause an increase in airway inflammation and may exacerbate pre-existing lung disease (184). Both mechanisms may also be operative. Although RV/TLC was not increased, we did not have other measures of airway function, which may be relevant to V/Q maldistribution. The abnormal gas transfer remained even when correcting for lung volume ($D_{LCO}/VA$) suggesting a true interstitial gas transfer defect rather than a reduction in surface area.

In this study, diffusing capacity impairment in subjects with severe GER in the absence of spirometric abnormality, suggests that this study may be looking at the earliest measurable dysfunction in a progressive pathway in the evolution of progressive pulmonary fibrosis. A case can then be put forward for sorting severity of subjects with severe GER with lung function tests including diffusion capacity and if these are deteriorating, in the absence of another cause, then more aggressive treatment of their GER may be warranted to prevent lung damage.
Smoking is associated with lung function impairment and through relaxant effects of smoking on lower oesophageal sphincter tone, also with GER. The possibility of smoking confounding the association between GER and lung function impairment needs to be addressed. We obtained an extensive history on previous packet-years smoked and current smoking status. Subjects with severe GER had a greater smoking history, as previously found in other studies (185, 186). The differences in diffusing capacity between GER groups however remained significant after a multivariate linear regression was performed adjusting for smoking history, packets of cigarettes smoked and current smoking status. In the group with severe GER, there was also no correlation between the number of cigarettes ever smoked and changes in diffusing capacity. This lack of correlation excludes direct tobacco damage as an explanation for the low D_LCO. No significant difference in the prevalence of current smokers between the GER groups, suggests that cessation of smoking may not affect severity of GER once established.

The cross sectional nature of this study does not allow issues of temporality in the relationships between reflux and impairment in gas diffusion to be addressed. Nevertheless, if GER can exacerbate or cause lung disease, either treatment of GER may be inadequate with ongoing acid or bulk fluid aspiration with or without ongoing symptoms, or the reduction in diffusion is due to chronic damage unimproved with regular treatment.

Other potential associations include the possibility that lung disease may exacerbate GER. However, in this study, none of the patients had lung disease other than asthma and the prevalence of doctor-diagnosed asthma or airway obstruction did not differ between groups.

Other factors that may cause a reduced diffusing capacity may also confound these results, however none of these patients had significant cardiac, pulmonary vascular or connective tissue disease on history or examination by two physicians and anaemia, renal, and hepatic disease were assessed in the routine
preoperative laboratory tests. It seems unlikely that in this group of otherwise well obese subjects presenting for obesity surgery, significant other morbidity is present.

These findings are significant in that GER and lung diseases are both very common and frequently coexist. If GER can exacerbate or cause lung disease, it needs to be considered in all patients complaining of respiratory symptoms, particularly those with pre-existing lung conditions. In patients with chronic lung disease, treatment of GER may be an important aspect of overall management.

Could severe GER explain the increase in asthma-like symptoms in the obese? Despite differences between the groups based on severity of GER, there was no difference in the prevalence of doctor-diagnosed asthma and airway obstruction did not differ between the groups. It is therefore unlikely to explain the worldwide increase in prevalence of asthma in the obese.

Because of the retrospective nature of this study, there are limitations on drawing firm conclusions. Further studies are ongoing to see if there is an improvement in gas exchange with more aggressive treatment of GER in these patients.
7.1 DISCUSSION

The overall results of this thesis show that there is an increase in the diagnosis of asthma, increase in symptoms of wheeze and shortness of breath and medication usage for the treatment of asthma in both obese adults and children. Despite reductions in lung volume, there is no increase in bronchial reactivity in this group suggesting that these symptoms are not related to true asthma, as there is no airway inflammation or obstruction, but to alternative co-morbidities associated with obesity such as gastro-oesophageal reflux. Notably gastro-oesophageal reflux was not associated with increased asthma prevalence or airway obstruction. However it was associated with reduced gas transfer suggesting abnormalities in lung parenchyma.

In Chapter 2 in which the relationship between obesity, asthma symptoms, lung function and bronchial responsiveness in adults was studied, increases in diagnosed asthma, increased symptoms of shortness of breath and wheeze, and increased medication usage for asthma in the obese were found. However there were no changes in lung function suggestive of obstruction or increased bronchial responsiveness in the obese group. There were no differences between men and women or between atopic and non-atopic subjects in these symptoms, prevalence of the diagnosis of asthma, or lung function changes.

Paradoxically the underweight group seem to have more problems with increased atopy, increased symptoms and diagnosed asthma with increased bronchial responsiveness but with no increased medication usage for asthma, suggesting under treated asthma.

The limitations of this study are that no co-morbidities of obesity such as gastro-oesophageal reflux or obstructive sleep apnoea were examined. Body fat distribution was also not taken into account. Potentially different distributions of fat may have variable effects on lung function.
This is a cross sectional study and it would be important to carry out follow up studies to examine those who developed bronchial hyperresponsiveness and look at risk factors, and changes in lung volumes.

In chapter 3 in which the relationship between asthma, atopy and obesity in children was studied, it was found that a higher body mass index in children was a significant risk factor for wheeze ever and cough but not for diagnosed asthma or bronchial hyperresponsiveness. In girls only, a higher body mass index was significantly associated with higher prevalence of atopy, wheeze ever and cough.

With increasing body mass index in children in either girls or boys, there was no reduction in lung volume, no increase in airway obstruction and no increase in bronchial responsiveness.

This study has several potential limitations. BMI percentiles were calculated from USA data, as this information is not available currently for Australia. This is unlikely to have invalidated the study outcomes, since the trend for the increase in obesity in children in Australia is closely following the USA trend.

Although BMI may not be the best measure of obesity in children, it is widely used and information was not available from this study on which to base an alternative definition. Several definitions of obesity such as BMI quintiles, BMI>95th percentile and BMI as a continuous variable were used to try to overcome the problems with diagnosis of obesity in children, and the results did not alter the findings. Skin fold thickness testing was not performed. Body fat distribution may play a variable role in the effects of obesity on lung function.

No information was obtained on pubertal status so it is not known whether the onset of puberty in a proportion of the group might have accentuated or reduced the differences between the genders. No symptoms of gastro-oesophageal reflux or obstructive sleep apnoea were sought and therefore no allowances can be made for these confounding factors.
In chapter 4 a comparison of high dose methacholine challenges between obese and non-obese women was performed. It was found that despite changes in lung volumes with obesity there was no increase in bronchial reactivity, and no difference in the position or shape of the high dose methacholine curve.

Potentially the small number of subjects may mask any real small differences between these groups. Further studies are required in larger groups to assess if a difference does exist.

The length of time that a person is obese may also have an effect on lung function changes, or whether the person is obese over puberty may also have an effect at this time of maximum lung growth. It would also be important to perform this study before and after weight loss.

In chapter 5 in which the relationship between changes in lung volumes and bronchial responsiveness in normal subjects and subjects with asthma was studied. It was shown that in normal subjects there was a small reduction in lung volume on lying down and this was associated with an increase in the measure of bronchial reactivity DRR. In contrast, in asthmatics, there was no acute fall in lung volume and there were variable changes in the index of reactivity suggesting non-homogeneity in the lung function abnormality.

This study did not have a third group of obese non-asthmatic subjects to see if there were further changes with change in posture which may further predispose obese subjects to lung function changes.

In chapter 6 in which the association of severe gastro-oesophageal reflux, asthma and lung function was studied, shows that an obese group of subjects with severe gastro-oesophageal reflux did not have subjective increases in asthma prevalence, obstructive sleep apnoea, or snoring however they had a clear worsening of gas transfer as measured by carbon monoxide transfer suggesting a greater level of lung parenchymal disease.
The limitations of this study include the lack of objective information about the diagnoses of asthma. The study reported doctor diagnosis of asthma, which may not be very reliable in the obese. Follow up studies after surgery in these patients would be important looking at changes in carbon monoxide diffusing capacity.
7.2 FUTURE DIRECTIONS FOR RESEARCH

The results of this thesis have implications for future research on the linkage between obesity and airway function:

1) Examination of differences in contractile properties of bronchial smooth muscle from obese and non-obese subjects.

2) Performing high dose methacholine challenges in a larger group of non-atopic obese subjects and normal subjects to examine if changes in shape or position of the dose response curve to methacholine are present.

3) Studying obese asthmatics with methacholine challenges, pH monitoring and polysomnographic studies and changes immediately before and following bariatric surgery before weight loss has commenced and then post significant weight loss to assess improvements in co-morbidities such as gastro-oesophageal reflux.

4) Examination of body fat distribution and changes in lung volumes in both adults and children.

5) The perception of symptoms at similar workloads may be different in obese subjects compared with non-obese subjects at similar levels of airflow obstruction.

6) Investigation of the increase in prevalence of asthma in the underweight and potential causes of this.
7.3 CONCLUSION

In summary, this thesis suggests that obesity is not a risk for asthma, if asthma includes airway inflammation, symptoms and bronchial hyperresponsiveness.

The increase in symptoms of wheeze and shortness of breath in the obese should not be attributed to asthma in the absence either of variable airflow limitation that is reversible spontaneously or with treatment, or with an increase in bronchial responsiveness to a variety of stimuli.

If treatment for asthma is commenced, clinical and adverse effects should be closely monitored as treatment with oral corticosteroids may cause further weight gain and may be an inappropriate mode of treatment for this group.

Symptoms of wheeze, cough and shortness of breath may be aggravated or caused by obesity and weight reduction should be a key therapeutic goal in the management of the obese asthmatic.
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