

**CHANGE IN LUNG VOLUME IN ASTHMA  
WITH PARTICULAR REFERENCE TO OBESITY**

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## **DECLARATION**

Apart from the assistance which is acknowledged herein, this thesis represents the original work of the author.

This work has not been submitted for any other degree at this or any other institution.

Linda Michele Schachter

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## **DEDICATION**

To those who have supported, loved and put up with me while I  
have completed this thesis.

In particular to my husband James,

Without whom this would either have taken 4 years

or never would have been completed,

and

To Mum and Dad,

Who have led me to believe that anything is possible

and that I can achieve it all.

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In Chapter 2 and 3, I have used data that has been collected by other colleagues and fellow scholars at the Woolcock Institute, University of Sydney. I personally was involved with performing spirometry, lung volumes, histamine challenges, and skin prick testing in Belmont in 1997.

I personally formulated the research question, assisted with extracting the data and performed the analyses.

All data from the other chapters, was collected by myself with the technical assistance of Alyson Roberts, Hayley McClure, Kim Gooley, Steven Ng and I thank them for their assistance.

Ethics committee approval was obtained by the Human Ethics Committee of the University of Sydney for Chapters 2, 3 and 4, the Human Ethics Committee of Central Sydney Area Health Service, NSW for Chapter 5 and by the Human Ethics Committee of the Avenue Hospital, Victoria for Chapter 6.

The prevalence data from these studies have been published elsewhere (cited below). The relationship between asthma, symptoms, lung function and obesity from this data has not been reported elsewhere and has not been used in another thesis.

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## **PUBLICATIONS ARISING FROM THIS THESIS**

1. Schachter, L. M., C. M. Salome, J. K. Peat, and A. J. Woolcock. 2001. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax* 56(1):4-8.
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## **HYPOTHESES**

1. Obesity causes a reduction in lung volume and with this change in lung function predisposes obese subjects to an increase in diagnosis of asthma, bronchial hyperresponsiveness and symptoms of asthma including wheeze and shortness of breath.
2. This increase in asthma prevalence occurs in both obese adults and obese children.
3. Other factors that also cause a reduction in lung volume, such as lying supine will also increase bronchial hyperresponsiveness in both non-asthmatics and asthmatics.
4. Obesity primarily affects lung function through a direct mechanical effect on lung volumes. An alternative hypothesis exists that the effect of obesity on lung function is through associated conditions such as gastro oesophageal reflux or obstructive sleep apnoea, which are increased in the obese.
5. Obese subjects with reduced lung volume will have a change in position of the high dose methacholine curve and plateau in the absence of asthma diagnosis or symptoms.

## THESIS ABSTRACT

Over the last 20 years both asthma and obesity have increased in prevalence. What is the link? There are data to suggest that increasing obesity is a risk for the increase in prevalence of asthma. A number of mechanisms have been postulated including the effects of reduced lung volume on bronchial reactivity and mechanical changes with lower lung volumes. Other possibilities include other obesity-induced co-morbidities including gastro-oesophageal reflux.

The aim of this thesis was to evaluate the link between asthma and obesity in both adult and childhood populations and to undertake experimental studies to examine the effects of changes in lung volume on bronchial reactivity.

In chapter 1, the literature is reviewed. The current literature suggests that there is a link between diagnosis of asthma, new onset of asthma, symptoms of shortness of breath and wheeze.

In chapter 2, data on 1997 adults in 3 population studies were analysed and the association between body mass index (BMI) and symptoms of shortness of breath and wheeze, diagnosis of asthma, medication usage for asthma, lung function and bronchial responsiveness were studied. This study showed that obesity was a risk for recent asthma (OR 2.04; 95%CI 1.02-3.76,  $p=0.048$ ), symptoms of shortness of breath and wheeze (OR 2.6; 95%CI 1.46-4.70,  $p=0.001$ ), and medication usage for asthma (OR 2.53; 95%CI 1.36-4.70,  $p=0.003$ ).

There was a reduction in lung volume as measured by forced vital capacity (FVC), but there was no increase in bronchial hyperresponsiveness (BHR) (OR 0.87; 95% CI 0.35-2.21,  $p=0.78$ ). Thus although the symptoms of asthma are increased there were no increases in BHR, despite significantly reduced lung volumes. The increase the medication usage is unlikely to have normalised the BHR, as there were ongoing symptoms suggestive of asthma.

In chapter 3, data on 5993 children in 7 population studies were analysed and the association between BMI percentile and symptoms of cough, wheeze,

diagnosis of asthma, medication usage for asthma, atopy, lung function and bronchial responsiveness was studied.

After adjusting for atopy, sex, age, smoking and family history, BMI was a significant risk factor for wheeze ever (OR=1.06; 95%CI 1.01-1.10, p=0.008) and cough (OR=1.09; 95%CI 1.05-1.14, p=0.001) but not for recent asthma (OR=1.02; 95%CI 0.98-1.07 p=0.43), or bronchial hyperresponsiveness (OR=0.97; 95%CI 0.95-1.04 p=0.77). In girls, a higher BMI was significantly associated with higher prevalence of atopy ( $\chi^2$  trend 7.9, p=0.005), wheeze ever ( $\chi^2$  trend 10.4, p=0.001), and cough ( $\chi^2$  trend 12.3, p<0.001). These were not significant in boys.

With increasing BMI in children, there was no reduction in lung volume, no increase in airway obstruction and no increase in bronchial responsiveness.

In chapter 4, the hypothesis that obesity per se is associated with bronchial responsiveness was tested. Six obese women without asthma were compared to 6 non-obese women without asthma with high dose methacholine challenges to assess the bronchial responsiveness.

There was no increase in bronchial responsiveness, and no difference in the position or shape of the high dose methacholine curve despite the fact that these women had reduced lung volumes associated with their obesity.

In chapter 5, the hypothesis whether reduced lung volume per se would cause a change in greater mechanical effect, ie more marked airway narrowing in both non-asthmatic and asthmatic subjects was tested. Lung volumes and methacholine challenges were undertaken in the supine and erect position on different days. As expected in normal subjects there was a small reduction in lung volume on lying down, 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 suggests changes in bronchial reactivity can occur without any relationship to lung volume change.

These negative results suggest that lung volume changes that may occur in obesity are unlikely contributors to the apparent increase in asthma symptoms.

In chapter 6, the hypothesis that the supposed increase in asthma symptoms in the obese were due to the effects of gastro-oesophageal reflux were assessed in 147 obese subjects graded for gastro-oesophageal reflux severity using manometry and gastroscopy. This study showed that subjects with increased 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 parenchymal disease.

The overall results are that there is an increase of diagnosis of asthma, increase in symptoms of asthma and medication usage for the treatment of asthma in the obese. Objectively despite reductions in lung volume, there is no increase in bronchial responsiveness in this group suggesting that these symptoms are not related to true asthma, 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 parenchymal disease.

This suggests that the increase in symptoms of wheeze and shortness of breath in the obese should not be attributed to asthma in the absence of variable airflow limitation that is reversible spontaneously or with treatment, or with an increase in the existing bronchial hyperresponsiveness (BHR) to a variety of stimuli.

## ABBREVIATIONS

ANOVA - Analysis of variance  
ASM – Airway smooth muscle  
ATS - American Thoracic Society  
BHR - Bronchial hyperresponsiveness  
BiPAP - Bi-level positive airway pressure  
BMI - Body mass index  
Bpm - Beats per minute  
BR - Bronchial responsiveness  
CI - Confidence interval  
CO – Carbon monoxide  
CPAP – Continuous positive airways pressure  
 $D_{CO}$  – Diffusing capacity  
 $D_{LCO}$  – Single breath diffusing capacity  
 $D_{LCO}/V_A$  - Single breath diffusing capacity corrected for alveolar volume  
DRC – Dose response curve  
DRR - Dose response ratio  
 $EC_{50}$  – The MCh concentration at 50% of the maximum fall in  $FEV_1$   
ED - Emergency department  
EDS – Excessive daytime somnolence  
EELV - End expiratory lung volume  
EIB - Exercise induced bronchospasm  
ESS – Epworth sleepiness scale  
 $FEF_{25-75\%}$  - Forced expiratory flow  
 $FEV_1$  - Forced expiratory volume in 1 second  
FRC - Functional residual capacity  
FVC - Forced vital capacity  
GER - Gastro oesophageal reflux  
GERD - Gastro oesophageal reflux disease  
IC - Inspiratory capacity  
ILD – Interstitial lung disease  
IPF – Idiopathic pulmonary fibrosis  
IUATLD - International Union against Tuberculosis and lung disease questionnaire

KCO - Single breath diffusing capacity corrected for alveolar volume  
Kg - kilogram  
L – Litres  
LAGB (Lap-Band®) - Laparoscopic adjustable gastric banding  
LV – Lung volume  
M - Metre  
MCh – Methacholine  
MEFV – Maximal expiratory flow volume  
MR – Maximal response  
NHANES – National Health and Nutrition Examination Survey  
NS - Not significant  
NSW - New South Wales  
OR - Odds ratio  
PD<sub>20</sub>FEV<sub>1</sub> - Dose of histamine that caused a 20% fall in FEV<sub>1</sub>  
PEEP – Positive end expiratory pressure  
PEFR - Peak expiratory flow rates  
PEFV – Partial expiratory flow volume  
PFT - Pulmonary function test  
P<sub>L</sub> - Pulmonary elastic recoil pressure  
Raw – Airways resistance  
R<sub>L</sub> - Pulmonary resistance  
SD - Standard deviation  
SEM – Standard error of mean  
SGRQ - St George Respiratory Questionnaire  
SOBOE – Shortness of breath on exertion  
TLC - Total lung capacity  
US - United States of America  
V20c – Flows measured from the MEFV curve at a volume equivalent to 80%  
of the baseline vital capacity below TLC  
V20p - Flows measured from the PEFV curve at a volume equivalent to 80%  
of the baseline vital capacity below TLC  
V<sub>50</sub> – Flow rate at 50% of the vital capacity  
VQ – Ventilation perfusion  
VS - Versus  
WHO - World Health Organisation