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

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A thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy, March 2010
For my Father, William Appleton
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Abstract

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

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

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

Generalised (BMI) and central obesity were associated with asthma in females only. After consideration of atopic status, in males, central obesity and high BMI (likely to be distributed centrally) was associated with non-atopic asthma. In females central obesity was also associated with non-atopic asthma but a high BMI was associated with atopic asthma. This suggests different pathophysiological mechanisms for the relationship between obesity and atopic and non-atopic asthma.
In subjects with asthma, a significant burden of generalised and central obesity-related asthma morbidity (symptoms, beta-2 agonist use, lung function) occurred largely in males only, although quality of life impairments and increased primary care visits were not sex-specific. Only central obesity was associated with persistent airways obstruction in males.

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

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

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

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Acknowledgements

This thesis would not have been possible without the commitment of the North West Adelaide Health Study Team. I am indebted to the Chief Investigators, the Population Research and Outcomes Study Unit of the South Australian Department of Health, the NWAHS clinic staff, and the study participants. The integrity and fervent dedication of this team has made the North West Adelaide Health Study and this remarkable data set possible.

I will be eternally grateful for the wisdom, encouragement, and humour of my supervisors, Associate Professor Robert Adams and Professor David Wilson.

I also wish to acknowledge the support of Professor Richard Ruffin, Dr Prue Cowled, fellow PhD student Ada Lam and departmental colleagues.

Finally, I wish to thank my family for their enduring support, love and encouragement in all things.
STATEMENT OF AUTHORSHIP

Spirometric Criteria for Asthma: Adding Further Evidence to the Debate.

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

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

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

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

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Ruffin, R
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Central Obesity is Associated With Nonatopic But Not Atopic Asthma in a Representative Population Sample.

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Asthma is Associated with Cardiovascular Disease in a Representative Population Sample.

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

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

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

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Cardiovascular Disease Risk Associated with Asthma and Respiratory Morbidity Might Be Mediated By Short-Acting $\beta_2$-Agonists.


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

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# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACD</td>
<td>asthma control days</td>
</tr>
<tr>
<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
</tr>
<tr>
<td>AF</td>
<td>attributable fraction</td>
</tr>
<tr>
<td>AHR</td>
<td>airway hyperresponsiveness</td>
</tr>
<tr>
<td>AQLQ</td>
<td>Asthma Quality of Life Questionnaire</td>
</tr>
<tr>
<td>ATM</td>
<td>adipose tissue macrophage</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CCHS</td>
<td>Canadian Community Health Survey</td>
</tr>
<tr>
<td>CCL5</td>
<td>regulated upon activation, normal t-cell expressed and secreted</td>
</tr>
<tr>
<td>CCR5</td>
<td>receptor for regulated upon activation, normal t-cell expressed and secreted</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual emission x-ray absorptiometry</td>
</tr>
<tr>
<td>ECRHS</td>
<td>European Community Respiratory Health Study</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>ERV</td>
<td>expiratory reserve volume</td>
</tr>
<tr>
<td>FeNO</td>
<td>fraction of exhaled nitric oxide</td>
</tr>
<tr>
<td>FEV₁</td>
<td>forced expiratory volume in one second</td>
</tr>
<tr>
<td>FP</td>
<td>fluticasone propionate</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>GERD</td>
<td>gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>IC</td>
<td>inspiratory capacity</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICS</td>
<td>inhaled corticosteroid</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>LABA</td>
<td>long-acting beta-2 adrenergic agonist</td>
</tr>
<tr>
<td>M1</td>
<td>classically activated macrophages (pro-inflammatory)</td>
</tr>
<tr>
<td>M2</td>
<td>alternatively activated macrophages (anti-inflammatory)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NFκB</td>
<td>nuclear factor kappa B</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NWAHS</td>
<td>North West Adelaide Health Study</td>
</tr>
<tr>
<td>PC_{20}</td>
<td>provocative concentration causing a 20% fall in FEV_{1}</td>
</tr>
<tr>
<td>PEF</td>
<td>peak expiratory flow</td>
</tr>
<tr>
<td>RANTES</td>
<td>regulated upon activation, normal t-cell expressed and secreted</td>
</tr>
<tr>
<td>RV</td>
<td>residual volume</td>
</tr>
<tr>
<td>SABA</td>
<td>short-acting beta-2 adrenergic agonist</td>
</tr>
<tr>
<td>SF-36</td>
<td>Medical Outcomes Study Short Form 36</td>
</tr>
<tr>
<td>SBR</td>
<td>significant bronchodilator reversibility</td>
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<tr>
<td>TLC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>tumour necrosis factor-alpha</td>
</tr>
<tr>
<td>WC</td>
<td>waist circumference</td>
</tr>
<tr>
<td>WHR</td>
<td>waist to hip ratio</td>
</tr>
<tr>
<td>WSR</td>
<td>waist to stature ratio</td>
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