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

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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

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[*] Appleton S, Adams R, Wilson D, Taylor A, Ruffin R, on behalf of the North West Adelaide Cohort Health Study Team. Spirometric criteria for asthma: Adding further evidence to the debate. Journal of Allergy and Clinical Immunology 2005; 116:976-82.

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* Appleton S, Wilson D, Tucker G, Ruffin R, Taylor A, Adams R. Sex differences in asthma morbidity associated with obesity in a representative population sample. Journal of Allergy and Clinical Immunology 2008; 121:1285-7, e1.

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Abbreviations

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

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