Exploring the Link Between Obesity and Asthma

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STATEMENT OF ORIGINALITY

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I hereby certify that the work embodied in this thesis contains published papers and scholarly work of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications.

…….

Hayley A Scott

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Abstract List

1. **Scott HA**, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, Wood LG. Clinical Asthma Outcomes Are Improved After Body Fat Reduction In Overweight And Obese Asthmatics. *Am J Respir Crit Care Med*. 183: A2661; 2011. *(Denver, USA; May 2011 – poster presentation)*.

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Abbreviations

ACQ	Asthma Control Questionnaire
AHR	Airway hyperresponsiveness
AI	Adequate Intake
AIHW	Australian Institute of Health and Welfare
ALA	α-linolenic acid
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AQLQ	Asthma Quality of Life Questionnaire
BALF	Bronchoalveolar lavage fluid
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BP	Blood pressure
CRP	C-reactive protein
CT	Computed tomography
DAA	Dietitians Association of Australia
DALY	Disability-adjusted life year
DHA	Docosahexaenoic acid
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
ECP	Eosinophil cationic protein
EER	Estimated Energy Requirements
eNO	Exhaled nitric oxide
EPA	Eicosapentaenoic acid
FA	Fatty acid
ERV	Expiratory reserve volume
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FSANZ	Food Standards Australia New Zealand
FVC	Forced vital capacity
GINA	Global Inititative for Asthma

HDL	High density lipoprotein
HMW	High molecular weight
HPLC	High performance liquid chromatography
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile range
kJ	Kilojoule
LA	Linoleic acid
LDL	Low density lipoprotein
LED	Low Energy Diet
LMW	Low molecular weight
LPS	Lipopolysaccharide
MBP	Major basic protein
MCP	Monocyte chemotactic protein
METS	Metabolic Equivalent Tasks
MMP-9	Matrix metalloproteinase-9
MMW	Medium molecular weight
MRI	Magnetic resonance imaging
MUFA	Monounsaturated fatty acid
NF-κB	Nuclear factor-kappa B
PD15	Provocation dose required to induce a drop in FEV_1 of 15%
PUFA	Polyunsaturated fatty acid
PWV	Pulse wave velocity
QoL	Quality of life
RBC	Red blood cell
RDI	Recommended Dietary Intake
RED	Reduced Energy Diet
RV	Residual volume
SD	Standard deviation
SFA	Saturated fatty acid
T2DM	Type 2 diabetes mellitus

TFEQ-R18	Three-Factor Eating Questionnaire Revised 18-Item
TLC	Total lung capacity
TLR	Toll-like receptor
TNF-α	Tumour necrosis factor-alpha
VAT	Visceral adipose tissue
VLED	Very Low Energy Diet
WAT	White adipose tissue

Synopsis

Obesity and asthma are associated conditions, with asthma incidence almost doubled in obese compared with healthy weight individuals. Obese asthmatics experience more severe asthma symptoms, poorer lung function and a reduced quality of life compared with asthmatics of a healthy weight. Furthermore, they do not respond well to inhaled corticosteroid medications; the mainstay of asthma pharmacotherapy. The mechanisms responsible for this association are not understood. A number of hypotheses have been proposed including inflammation, gastro-oesophageal reflux and mechanical factors.

Asthma is an inflammatory condition of the airways, in which both eosinophilic and noneosinophilic patterns of inflammation have been described. Noneosinophilic asthma is characterised by an increase in airway neutrophils, airway hyperresponsiveness and activation of the innate immune response.

Obesity is also an inflammatory condition, as the presence of excess adipose tissue leads to chronic low-grade inflammation. A high dietary fat intake is often associated with obesity and may also contribute to inflammation in obesity, as saturated fatty acids stimulate innate immune pathways. It is plausible that this activation of the innate immune response extends to the airways of susceptible individuals, leading to increased levels of airway neutrophils. Neutrophils are of importance in asthma because elevated levels in the airways are associated with the most severe forms of asthma and negatively correlate with airflow obstruction.

In Chapter 3 of this thesis, we examined the association between obesity and airway inflammation in subjects with asthma. There was a significant association between body mass index and airway neutrophils in females with asthma. In asthmatic males, saturated fatty acids were associated with increased neutrophilic airway inflammation. These observations suggest that both obesity and saturated fat may independently activate innate immune responses, leading to a more neutrophilic pattern of airway inflammation, with distinct differences between males and females.

In Chapter 4, the relationship between body composition, lung function and inflammation is investigated. Previous research has shown that increased adiposity within the android and thoracic regions is associated with respiratory function impairment. This thesis suggests that these influences are sexually dimorphic in nature. Android and upper body adiposity were negatively associated with lung function in females, whilst android lean mass was an important positive predictor of lung function in males.

In Chapters 5 and 6, the effect of dietary restriction and/or increased physical activity on weight loss and asthma outcomes is explored. This pilot study found that both caloric restriction and increased physical activity are not only feasible and efficacious weight loss strategies in asthma, but also lead to improved quality of life and asthma control. Importantly, a decrease in neutrophilic airway inflammation correlated with adipose tissue reduction in females, and dietary fat in males, supporting our observations in Chapter 3, that these factors contribute to the obese-asthma phenotype.

Also in Chapter 6, we describe a relationship between increased physical activity and reduced airway eosinophilia. Obese adults are 50% less likely to participate in sufficient physical activity compared to those within the healthy weight range. Therefore, it is plausible that physical inactivity is a driver of the obese-asthma phenotype. This thesis indicates that increased exercise is associated with reduced eosinophilic airway inflammation in overweight and obese individuals with asthma.

The aetiology of obesity is multifactorial, often involving an elevated dietary fat intake, low level of exercise and ultimately an excess of adipose tissue. This thesis suggests that these aetiologies are also independently involved in the development of the obese-asthma phenotype. This phenotype involves both innate and adaptive immune responses, and mechanical effects of excess adipose tissue. Importantly these inflammatory pathways are reversible, which suggests that the obese-asthma phenotype is also reversible. The data presented in this thesis suggests several mechanisms by which dietary intake and physical activity modulate the expression of obese-asthma. Further work is this area will enable management strategies to be developed for this large and increasingly prevalent asthma phenotype.