Paediatric Obesity, Inflammation & Asthma

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BNutrDiet(Hons)

A thesis submitted for the degree of Doctor of Philosophy

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Statement of Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary institution and, to my knowledge and belief, contains no material previously published or written by another person, except where due reference has been given in text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository, subject to the provisions of the Copyright Act 1968.

Acknowledgement of Authorship

I hereby certify that the work embodied in this thesis contains published papers/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/scholarly work.

............................................................
Megan E Jensen
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PEER-REVIEWED ABSTRACTS


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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
</tr>
<tr>
<td>AHR</td>
<td>Airway hyperresponsiveness</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APARQ</td>
<td>Adolescent Physical Activity Questionnaire</td>
</tr>
<tr>
<td>ASAQ</td>
<td>Adolescent Sedentary Activity Questionnaire</td>
</tr>
<tr>
<td>BAL</td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>BHR</td>
<td>Bronchial hyperresponsiveness</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CAMP</td>
<td>Childhood Asthma Management Program</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>eNO</td>
<td>Exhaled nitric oxide</td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FCI-II</td>
<td>Food Cravings Index-II</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis model assessment of insulin resistance</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroid</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>MCP</td>
<td>Monocyte chemotactic protein</td>
</tr>
<tr>
<td>MEF</td>
<td>Maximum expiratory flow</td>
</tr>
<tr>
<td>METS</td>
<td>Metabolic Equivalent</td>
</tr>
<tr>
<td>MUFA</td>
<td>Monounsaturated fatty acid</td>
</tr>
<tr>
<td>NF-kB</td>
<td>Nuclear factor-kappa B</td>
</tr>
<tr>
<td>PAI</td>
<td>Plasminogen activator inhibitor</td>
</tr>
<tr>
<td>PAQLQ</td>
<td>Pediatric Asthma Quality of Life Questionnaire</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PD_{15}</td>
<td>Provocation dose required to induce a drop in FEV1 of 15%</td>
</tr>
<tr>
<td>PDSS</td>
<td>Pediatric Daytime Sleepiness Scale</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDS</td>
<td>Standard deviation score</td>
</tr>
<tr>
<td>Th</td>
<td>T-helper</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor-alpha</td>
</tr>
<tr>
<td>TST</td>
<td>Total sleep time</td>
</tr>
<tr>
<td>TTA</td>
<td>Total time awake</td>
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Synopsis

Obesity and asthma are the most common conditions affecting the paediatric population worldwide, with obesity being more prevalent in the population with asthma. Obesity in children with asthma is associated with increased asthma symptoms, increased number and severity of exacerbations, and increased use of medications, including inhaled corticosteroids. With the advent of obese asthma, occurring in parallel with Westernisation, the role of obesity and associated metabolic and lifestyle factors in the development and/or pathogenesis of asthma, and in asthma management, have been called into question. Although obese asthma has been described in the adult population as a distinct clinical phenotype, characterized by neutrophilic airway inflammation, reduced static lung function and corticosteroid resistance, there has been minimal research on obese asthma in the paediatric population.

The current thesis aims to characterise the inflammatory, physiological and clinical aspects of obese asthma in children; to understand the prevalence of risk factors for weight gain in children with asthma; and to investigate the feasibility and efficacy of dietary intervention to induce weight loss and improve asthma outcomes in paediatric obese asthma.

Chapter III presents the airway and systemic inflammatory profile, dynamic and static lung function, and clinical asthma outcomes in obese and non-obese children, with and without asthma. In this cross-sectional study, we found a poorer quality of life and reduced static lung function (expiratory reserve volume (ERV)) in obese asthmatic children. Sputum %eosinophils and the prevalence of eosinophilic asthma was lower in obese females compared to obese males, indicating that the female
gender may be associated with a different pattern of airway inflammation in obese asthma. This is important to asthma management and requires further investigation. However, the overall airway and systemic inflammatory profile did not differ between obese and non-obese asthmatic children.

In Chapter IV, the associations between lung function and body composition in children, with and without asthma, were explored. Body weight, fat mass and lean mass were inversely associated with static lung function (functional residual capacity (FRC) and ERV), suggesting that obesity, regardless of composition, is associated with reduced static lung function. Conversely, lean mass was positively associated with improvements in dynamic lung function. This study indicates that it is important to consider body composition as fat and lean mass, which both increase with obesity, may have differential effects on lung function. Chapter III and IV demonstrate that obesity is associated with lung deficits that are not detectable through routine spirometry. This suggests that in clinical practice static lung function needs to be routinely measured in obese asthmatic children.

In Chapter V, the presence of key modifiable risk factors for weight gain were compared in a cross-sectional study of non-obese children, with and without asthma, including sleep architecture, appetite and dietary intake, and physical and sedentary behaviour. Sleep latency was extended, and triglyceride levels were higher, in children with controlled asthma compared to non-asthmatic children. This study did not detect differences in plasma appetite hormone concentrations, food cravings, dietary intake or physical activity levels. However, in this group of asthmatic and non-asthmatic children, daytime sleepiness and reduced sleep duration were associated with adverse changes in plasma lipids, dietary patterns and sedentary
behaviour, which can potentially lead to positive energy balance and warrants further investigation.

In Chapter VI, the feasibility and efficacy of a ten week dietary intervention to induce acute weight loss in a group of obese children with asthma was demonstrated in a pilot randomised controlled trial. Dietary intervention induced statistically significant acute weight loss in asthmatic children, with improvements in asthma control and static lung function. This indicates that dietetic consultation is beneficial and should be integrated as part of the management of the obese child with asthma.

The research conducted as part of this thesis has contributed to the understanding of paediatric obese asthma; investigated the prevalence of key lifestyle risk factors for obesity in asthmatic and non-asthmatic children; and provided pilot data to support the efficacy of dietary-induced weight loss to improve asthma outcomes in obese asthmatic children.