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The Obesity Phenotype in Children with Asthma

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Abstract

Asthma and obesity have been increasing in prevalence internationally among children. Evidence points to an association between these chronic morbidities, suggesting the development of an ‘obese asthma’ phenotype in childhood. This review summarises the evidence that the proinflammatory environment created by excess adiposity may provide a mechanism leading to obese asthma in children and adolescents. Weight loss studies conducted in children without asthma have demonstrated a reduction in systemic inflammation. However, the impact of weight loss in the obese paediatric population with asthma has not been investigated. The paucity of information highlights the need for high quality randomised controlled trials of weight loss in this population that include assessment of systemic and airway inflammation, and clinical asthma outcomes. This will lead to refinements in management approaches for these patients.
1. The Link between Obesity & Asthma

Asthma has become increasingly prevalent worldwide over the past two decades in children and adults\(^1\). While this trend may have plateaued or slightly reversed in children, asthma remains the most common chronic condition impacting Australian children and adolescents, affecting 10% of children \(\leq 14\)yrs\(^2\). Childhood obesity rates have also been climbing globally over the past 20yrs with an estimated 22million children <5y overweight in 2007\(^3\) while approximately 17% and 6% of Australian youths aged 2-16yrs are overweight and obese respectively\(^4\).

Asthma and obesity have serious health consequences and significant financial costs. The burden of obesity on pulmonary function in children is highlighted by the increased frequency of bronchial hyper-responsiveness, increased number of prescribed medications and inhaled corticosteroid (ICS) use, and reduced peak expiratory flow rate in overweight / obese asthmatic children compared to non-overweight asthmatic children\(^5\).\(^6\). Excess body weight is also associated with an increase in the number of school days missed by asthmatic children and significantly reduced quality of life\(^6\).

Longitudinal studies have demonstrated a link between asthma and obesity in children and adolescents. Children who were overweight / obese at study enrolment\(^7\).\(^8\) or who gained excess weight during the study\(^7\).\(^9\), were found to be at increased risk of bronchial hyper-responsiveness, asthma symptoms and diagnosis. Gender differences in asthma risk have been noted with some studies only finding an increased risk for females\(^7\).\(^9\). These longitudinal studies demonstrate that excess adiposity preceded the development of asthma and respiratory symptoms in children and adolescents. However, recently published data from the Longitudinal Study of Australian Children has indicated asthma may also lead to the development of obesity. Children aged 4-5yrs suffering from wheeze or asthma, regardless of their baseline weight status, were more likely to become overweight / obese at age 6-7yrs compared to non-asthmatic children\(^10\).

2. The Obese Phenotype in Asthma
Epidemiological data obtained from adult populations suggests that ‘obese asthma’ exists as a distinct clinical phenotype, involving noneosinophilic inflammation. The association between asthma and obesity appears to be more prominent in nonatopic disease\textsuperscript{11} with no relationship shown between obesity and atopy or eosinophil counts\textsuperscript{12}, nor total or specific IgE levels\textsuperscript{13}. This supports the hypothesis that obesity promotes the development of a Th1-mediated nonatopic form of asthma. A recent cluster analysis has identified distinct asthma phenotypes in adults, that exhibit different clinical responses to treatment\textsuperscript{14}. A key cluster identified was obese, noneosinophilic asthma.

The pathogenesis of ‘obese asthma’ in children is unknown. However, characteristic of noneosinophilic asthma\textsuperscript{15}, obese asthmatic adults are resistant to inhaled steroid treatment\textsuperscript{16} and thus require alternative treatment approaches. Evidence suggests that obese asthmatic children may also be steroid resistant, as they more frequently use ICS\textsuperscript{6} and use an increased number of prescribed medications in comparison to non-obese asthmatic children\textsuperscript{5}. The relationship between obesity, inflammation and asthma in the paediatric population is considered in this review.

3. Obesity & Systemic Inflammation in Children

Adipose tissue communicates with other organs through endocrine capabilities\textsuperscript{17}, releasing important mediators produced by tissue-resident macrophages and adipocytes, including tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukins, leptin and adiponectin\textsuperscript{18}. Obesity creates a proinflammatory environment via an increase in adipocyte volume and number and production of inflammatory mediators\textsuperscript{17, 18}. The presence of excess adiposity therefore provides a consistent stimulus for chronic, low grade systemic inflammation.

**Leptin**

Leptin typically stimulates a Th1 cytokine response that leads to the production of additional pro-inflammatory cytokines\textsuperscript{18}. The amount of leptin secreted by adipose tissue is in direct proportion to the level of adiposity\textsuperscript{17}. Under normal conditions, leptin acts through the hypothalamus as an appetite suppressant and metabolic stimulant\textsuperscript{19}. Interestingly, cross-sectional studies comparing obese children with age-
and sex-matched non-obese children have consistently found significantly higher circulating leptin levels in obese children\textsuperscript{20-22} (See Table 1), suggesting leptin resistance occurs.

\textit{Adiponectin}

Adiponectin has anti-inflammatory effects, inhibiting nuclear factor-kappaB (NF-kB), interleukin-6 (IL-6) and TNF-\(\alpha\) production while up-regulating IL-10 and IL-1 receptor antagonist production\textsuperscript{18}. Cross-sectional studies have found that adiponectin levels are significantly lower in obese children compared to non-obese children\textsuperscript{22-24} and correlate negatively with adiposity indices\textsuperscript{22-25} (See Table 1). Lower adiponectin levels have also been associated with increased CRP levels in obese children and adolescents compared to non-obese equivalents\textsuperscript{26}.

\textit{C-Reactive Protein (CRP)}

CRP activates NF-kB signalling, complement & tissue factor, and the production of cytokines and chemokines which subsequently produce more CRP, creating a positive feedback loop\textsuperscript{27}. Studies have identified a positive relationship between BMI and CRP with significantly higher CRP levels consistently documented in obese children and adolescents compared to non-obese controls\textsuperscript{22,24,28-30} (See Table 1). Furthermore, CRP levels have been documented to increase with increasing adiposity and insulin resistance measures, with a regression model identifying waist circumference as an independent predictor of CRP levels\textsuperscript{26}.

\textit{Interleukin-6 (IL-6)}

IL-6 contributes to inflammation by raising CRP levels and suppressing adiponectin production\textsuperscript{17}. Multiple cross-sectional studies have identified significantly elevated levels of IL-6 in obese compared to non-obese children and adolescents\textsuperscript{20,28,31}, while only one study failed to identify a significant difference in IL-6 levels between these two groups\textsuperscript{22} (See Table 1). Interestingly, one paediatric study demonstrated that IL-6 levels are positively associated with adipocyte diameter but not with percentage fat or BMI\textsuperscript{32}.

\textit{Tumour Necrosis Factor-alpha (TNF-\(\alpha\))}

TNF-\(\alpha\) contributes to a proinflammatory environment by stimulating NF-kB signalling and increasing production of acute phase proteins and cytokines\textsuperscript{19,27}. Levels of TNF-\(\alpha\) have been found to be significantly higher in obese children and
adolescents compared to non-obese subjects\textsuperscript{20, 24, 30} (See Table 1). Chronically elevated TNF-\(\alpha\) levels impair the anorexigenic effects of leptin and insulin\textsuperscript{33}, suggesting increased TNF-\(\alpha\) levels may contribute to the apparent leptin resistance in the obese population. A positive correlation between adipocyte diameter and TNF-\(\alpha\) levels is documented, although BMI and fat mass have failed to correlate with TNF-\(\alpha\) levels\textsuperscript{32}.

4. Obesity, Inflammation & Asthma in Children

Asthma may present via the acquired immune system, with the key defining feature being the dominating presence of airway eosinophils\textsuperscript{34} or via the innate immune system, characterised by increased levels of airway neutrophils\textsuperscript{35}. Eosinophilic and neutrophilic asthma are activated by different stimuli and function via different pathways. Eosinophilic asthma is activated by allergens and the inflammatory pathway is primarily driven by IL-5\textsuperscript{35}. On the other hand, neutrophilic asthma is activated by viruses, bacteria, pollutants, and dietary components and involves an IL-8 driven inflammatory pathway\textsuperscript{35, 36}. Increased airway inflammation in children is associated with a poorer asthma prognosis as indicated by increased severity, nocturnal symptoms, wheezing and airflow obstruction\textsuperscript{34}. There is also evidence of systemic inflammation in children with asthma which may be exacerbated by the systemic inflammatory process caused by obesity\textsuperscript{37-39}.

The chronic inflammatory process created by excess adiposity has been implicated in the pathophysiology of numerous conditions\textsuperscript{18} and it may also be an underlying factor in asthma pathogenesis, with the hypothesis that the increase in obesity-associated systemic inflammatory mediators exacerbates pulmonary inflammation, a direct component of asthma pathophysiology (See Figure 1).

\textit{Leptin}

Leptin may contribute to asthma pathogenesis via vascular endothelial growth factor (VEGF)-induced airway remodelling and angiogenesis, as VEGF release from human airway smooth muscle (ASM) cells is enhanced following leptin stimulation\textsuperscript{40}. In allergic mouse models, exogenous leptin enhanced airway hyperresponsiveness (AHR) after ovalbumin challenge\textsuperscript{41} and augmented the airway inflammatory response
to ozone, with increases in BAL levels of IL-6, eotaxin, MIP-2, KC, sTNFR1 and sTNFR2. In a murine pneumococcal pneumonia model, exogenous leptin increased BAL neutrophil count, IL-6 and LTB4 levels and macrophage phagocytosis. Cross-sectional studies have found significantly higher leptin levels in healthy weight asthmatic children versus healthy controls, with increased leptin levels identified as a predictive factor in asthma onset (See Table 1). Multiple regression analysis indicated that both asthma and BMI predicted leptin levels in children. Another study evaluated the association between leptin, asthma and BMI across 3 age groups and found no association between leptin and asthma in aged 3-18yrs and 9-24yrs but found higher leptin levels in obese asthmatic adults compared to non-obese asthmatic adults. In a 12yr follow-up study in children, leptin levels were significantly higher in overweight children with asthma compared to overweight non-asthmatic children. Interestingly, there was no difference in leptin levels between the non-overweight children with and without asthma. The potential for leptin to contribute to obese asthma exists and further investigation is warranted.

**Adiponectin**

Adiponectin inhibition of vascular smooth muscle proliferation has been demonstrated. If this function is exerted in the airways, ASM mass may increase in the presence of reduced adiponectin levels, contributing to asthma. However, in vitro studies to date have not been able to establish this link. A cohort study found no association between adiponectin and asthma during childhood, adolescence or adulthood. In addition, cross-sectional analysis of non-atopic asthma, atopic asthma, and controls found no difference in adiponectin levels between the groups of children. However, adiponectin correlated positively with FEF25-75%. Levels of adiponectin are yet to be compared in the obese and non-obese paediatric population with and without asthma.

**C-Reactive Protein (CRP)**

CRP was shown to be elevated in asthmatic children during periods of exacerbation, with CRP levels negatively correlating with FEV1. Although there was no association between BMI and CRP levels, all subjects were non-obese so the data set does not elucidate the CRP levels in the obese. Interestingly, the largest CRP reduction following resolution of exacerbation was measured in those in the lowest
BMI percentile suggesting the leanest children have low levels of background CRP. A recent study in obese and non-obese children, with and without asthma, failed to find a significant difference in CRP levels between the groups\textsuperscript{37} (See Table 1). However, this study was limited by its sample size. Further investigation is needed.

**Interleukin-6 (IL-6)**
IL-6 is involved in the acute-phase and late-phase asthma response\textsuperscript{7,27} and correlates with asthma disease activity\textsuperscript{47}. Cell studies obtained from children with and without asthma have found a significantly increased release of IL-6 from the epithelial cells of children with asthma\textsuperscript{48}. Increased levels associated with obesity therefore have the potential to contribute to increased pulmonary inflammation and asthma symptoms. A study in female adults discovered IL-6 was significantly higher in obese asthmatics compared to non-obese asthmatics and healthy controls\textsuperscript{47}. This is yet to be confirmed in the paediatric population.

**Tumour Necrosis Factor-alpha (TNF-\(\alpha\))**
TNF-\(\alpha\) receptors are located on ASM cells and human in vivo studies have demonstrated airway hyper-responsiveness to TNF-\(\alpha\) stimulation\textsuperscript{19}. TNF-\(\alpha\) levels are reported to be 5.6 times higher in the alveolar macrophages of infants with wheeze compared to infants without wheeze\textsuperscript{49}. A study conducted in children and adults found elevated levels of TNF-\(\alpha\) and TNF receptor -1 and -2 in participants with bronchial hyper-reactivity when compared to those without hyper-reactivity\textsuperscript{50}. In addition, these TNF markers negatively correlated with FEV\textsubscript{1}\textsuperscript{50}. Significantly elevated TNF-\(\alpha\) levels were recently documented in obese adults with asthma when compared to obese adults without asthma and non-obese adults with and without asthma\textsuperscript{47}. Although a 12yr paediatric follow-up study conducted in overweight and healthy weight children with or without asthma found no difference in TNF-\(\alpha\) levels between the four groups, this study was limited by the small sample of asthmatic children and the disproportionate sample size across the four groups\textsuperscript{45}. More insight is needed into the role of TNF-\(\alpha\) in paediatric obese asthma.

5. **Weight Loss in Obese Children & Adolescents**
Interventions to address paediatric obesity to date have used varying protocols. However, key features include dietary modification, increasing the ratio of physical activity to sedentary behaviour, and parental support for behaviour change. In a small proportion of severely obese adolescents, bariatric surgery has become a consideration. Although no RCT has been conducted using bariatric surgery in severely obese adolescents, available evidence suggests this approach may result in a weak to moderate reduction in BMI.

Table 2 presents a summary of lifestyle induced weight loss interventions in otherwise healthy children and adolescents and the effect upon inflammatory markers. Both long term and short term studies have achieved a significant alteration in the systemic inflammatory profile of obese participants following weight loss or a change in body composition.

Although a one year dietary intervention significantly reduced energy intake in all participants, a reduction in BMI was only achieved in 43% of the obese group. Weight loss was accompanied by a 15% increase in adiponectin and 19% reduction in leptin. Similarly, substantial weight loss following a combined diet, activity and behavioural intervention produced a significant decrease in CRP levels but no effect upon TNF-α levels while a 1yr RCT found no reduction in CRP following a reduction in BMI Z-score in overweight and obese children. In a small 3mth randomised study a favourable change in body composition but not BMI was detected in the intervention group, which was associated with significant reductions of 30% and 25% in CRP and IL-6. The same intervention period also achieved a 34% increase in adiponectin levels following positive body composition changes in obese adolescents.

In contrast to these long term interventions, a diet and exercise combination in obese children has effectively reduced CRP levels after 6wks following weight and percentage body fat reduction. Furthermore, significant reductions in BMI, fat mass, IL-6 and leptin concentrations was achieved after only 3wks following a diet and physical activity intervention. Unfortunately, the majority of studies to date have inadequately detailed the dietary intervention and the subsequent impact on dietary intake; failed to employ power calculations to determine sample size; not included
adequate follow-up of participants; and used varying weight / adiposity indices and criteria used to classify obesity\textsuperscript{51}. Although limited by design, overall these studies do suggest that relative body fat loss in obese children and adolescents is associated with a reduction in systemic inflammation.

6. Weight Loss in Asthma

Few weight loss intervention studies have been conducted in persons with asthma. Of those conducted, study participants have been adults and most weight loss has been surgically-induced\textsuperscript{56}. To date there have been no intervention studies designed to investigate the impact of weight loss in children / adolescents with asthma.

Only one adequately designed RCT, conducted in adults, met the criteria for a Cochrane review on dietary induced weight loss interventions in the population with asthma\textsuperscript{57}. The ineligible studies did not impose a weight loss intervention, were non-randomised or uncontrolled. The RCT that was included randomised obese asthmatic adults to a control group or a 14wk weight reduction program that involved an 8wk very low calorie diet (VLCD)\textsuperscript{58}. Compared to the control group, there was a significant improvement in FEV\textsubscript{1}, FVC, and reported dyspnea and rescue medication use in the intervention group following a mean 14.5\% weight loss\textsuperscript{58}. Use of a VLCD in an 8wk non-randomised uncontrolled study in asthmatic adults produced a significant improvement in FEV\textsubscript{1}, FVC, morning and evening peak expiratory flow and dyspnoea score following a mean weight loss of 13.5kg\textsuperscript{59}. A more recent uncontrolled study used an alternate day calorie restriction and ad libitum diet in 9 obese asthmatic adults for 8wks and reported a significant improvement in post-salbutamol FEV\textsubscript{1} following an mean 8\% weight loss\textsuperscript{60}. Another non-randomised uncontrolled 6mth intervention conducted in 58 obese females used a calorie restricted diet, including a 6wk or 12wk period of liquid meal replacements, depending on the level of obesity\textsuperscript{61}. Greater weight loss was associated with significantly greater improvements in lung function (FEV\textsubscript{1}, FVC, TLC)\textsuperscript{61}.

Despite the limitations of small sample sizes, low power, predominant use of subjective reporting on asthma presence and status, and an inability of the study
design to adequately control for potential confounders, previous studies have identified an improvement in some aspect of asthma following weight reduction in adults \(^{56}\) (See Figure 2). This is yet to be investigated in children and adolescents.

### 7. Conclusion

Obese asthma has emerged as a distinct clinical asthma phenotype in adults that may require a different treatment approach. Paediatric obese asthma may also emerge as a distinct phenotype, requiring a specialised treatment plan. As the number of children and adolescents with obese asthma increases, improvement in their management has the potential to greatly impact on population health. Although associations demonstrating a link between asthma and obesity in children and adolescents have been documented, there have been no weight loss intervention studies specifically conducted in children and adolescents with asthma, nor has the potential inflammatory link between the two chronic conditions been adequately explored. The few studies conducted in adults cannot be extrapolated to the paediatric population as the pathogenesis of asthma in children and adolescents follows a different pattern to that which occurs in adults. In order to optimise treatment strategies for obese children and adolescents with asthma, it is necessary to understand the nature of the existing airway inflammation. If a causal association between asthma and obesity in children and adolescents exists, then weight loss should reverse the negative impact of obesity on asthma status. High quality randomised controlled weight loss trials conducted in obese children and adolescents which assess airway inflammation and clinical asthma measures as primary outcomes are needed, in order to design optimal management approaches for these patients.

### 8. Acknowledgements

This work was supported by a Hunter Medical Research Institute project grant sponsored by the Gastronomic Society Lunch.
9. References


## Table 1: Cross-sectional studies in children and adolescents that have measured markers of inflammation

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Study Design</th>
<th>Population</th>
<th>Groups</th>
<th>Obesity definition</th>
<th>n</th>
<th>Inflammatory Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Cross-sectional 21</td>
<td>7-10y</td>
<td>O vs NO</td>
<td>BMI SDS &gt;3 (Turkish reference population)</td>
<td>0=60, NO=60</td>
<td>↑ leptin in O vs NO.</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional 26</td>
<td>mean 9.8y</td>
<td>AA vs NAA vs HC</td>
<td>age and sex specific BMI percentiles based on international data that correspond to adult BMI values of 25 and 30kg/m2 (Cole et al, 2000)</td>
<td>AA=149; NAA=37; HC=54 (of which HW=158; OW=43; O=39)</td>
<td>Leptin was not significantly different between AA, NAA and HC. Leptin differed significantly between HW, OW and O groups (values by weight status not provided). Leptin positively correlated with BMI percentile.</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional + pharmacological intervention 29</td>
<td>HWA: mean 6.4y; HW controls: mean 7y</td>
<td>HWA vs HW controls</td>
<td>HWA: mean BMI 16.7kg/m2; HW: mean BMI 16.9kg/m2</td>
<td>HWA=23; HW=20</td>
<td>↑ leptin in HWA vs HW controls</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional 30</td>
<td>mean 5.9y</td>
<td>HWA vs HW controls</td>
<td>BMI used. No groupings.</td>
<td>HWA=102 (65M:37F); HW controls=33 (19M:14F)</td>
<td>↑ leptin in HWA vs HW controls in males</td>
</tr>
<tr>
<td></td>
<td>Case-control 22</td>
<td>6-9y</td>
<td>O vs NO</td>
<td>&gt;90th BMI percentile for reference population</td>
<td>O=51; NO=51</td>
<td>↑ leptin in O vs NO. Leptin an independent predictor of BMI in O.</td>
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<tr>
<td></td>
<td>Case-control 20</td>
<td>7-10y</td>
<td>O vs NO</td>
<td>120% mean BW for Turkish reference population and when BMI for age &gt;99th%</td>
<td>O=63; NO=63</td>
<td>↑ leptin in O vs NO. Leptin correlated with BMI in obese.</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Case-control 22</td>
<td>6-9y</td>
<td>O vs NO</td>
<td>&gt;90th BMI percentile for reference population</td>
<td>O=51; NO=51</td>
<td>↓ adiponectin in O vs NO. Adiponectin correlated negatively with BMI.</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional 28</td>
<td>mean 9.8y</td>
<td>AA vs NAA vs HC</td>
<td>age and sex specific BMI percentiles based on international data that correspond to adult BMI values of 25 and 30kg/m2 (Cole et al, 2000)</td>
<td>AA=149; NAA=37; HC=54 (of which HW=158; OW=43; O=39)</td>
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<td></td>
<td>Case-control 24</td>
<td>8-15y</td>
<td>O vs NO</td>
<td>≥95th percentile &amp; &lt;85th percentile (reference population not specified)</td>
<td>O=73; NO=30</td>
<td>↓ adiponectin in O vs NO. Adiponectin negatively correlated with BMI</td>
</tr>
<tr>
<td>Study Type</td>
<td>Age Range</td>
<td>Comparison</td>
<td>BMI Criteria</td>
<td>adiponectin levels in O vs HW. BMI, BF% &amp; trunk fat mass negatively correlated with adiponectin levels. LM% positively associated with adiponectin.</td>
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<tr>
<td>Cross-sectional 21</td>
<td>14-18y</td>
<td>HW vs O</td>
<td>BMI &gt;30</td>
<td>HW=6; O=15</td>
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<tr>
<td>Cross-sectional 20</td>
<td>2.3-19y</td>
<td>O vs NO</td>
<td>BMI percentiles (NCHS 2000 reference values). Obese: &gt;95th percentile</td>
<td>O=131; NO=114</td>
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<tr>
<td>Cross-sectional 62</td>
<td>8-16y</td>
<td>representative sample of US children (NHANES III)</td>
<td>&gt;85th BMI percentile or sum of 3 skinfolds for reference population (NHANES III)</td>
<td>n=3512</td>
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<tr>
<td>Cross-sectional 37</td>
<td>10-16y</td>
<td>O vs NO vs NOA vs OA</td>
<td>CDC BMI percentiles. Obese: &gt;95th percentile; Healthy weight: &lt;85th percentile</td>
<td>OA=33; NOA=19; O=37; NO=20</td>
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<tr>
<td>Cross-sectional 28</td>
<td>15-16y</td>
<td>HW vs O</td>
<td>BMI&gt;30</td>
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<tr>
<td>Cross-sectional 30</td>
<td>Mean age 11y</td>
<td>O vs NO</td>
<td>≥97th BMI percentile based on population-specific data</td>
<td>NO=14; O=31</td>
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<td>Cross-sectional 30</td>
<td>15-16y</td>
<td>HW vs O</td>
<td>BMI&gt;30</td>
<td>HW=6; O=15</td>
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<tr>
<td>Cross-sectional 31</td>
<td>10-13y</td>
<td>HW vs O</td>
<td>BMI&gt;85th percentile for age and sex (NHANES I data)</td>
<td>O=49; HW=69</td>
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<tr>
<td>Case-control 20</td>
<td>7-10y</td>
<td>O vs NO</td>
<td>120% mean BW for Turkish school children national data and when BMI &gt;95th percentile in study population growth curve</td>
<td>O=63; NO=63</td>
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</tbody>
</table>

**CRP**

- **O** vs NO:
  - ↑ hsCRP in O vs NO. Relationship between hsCRP and BMI.
  - OW more likely to have ↑ CRP (OR 3.17 girls and 3.74 boys based on BMI or 5.11 boys and 2.89 girls based on skinfolds)

**IL-6**

- **O** vs NO:
  - ↑ IL-6 in O vs NO.

**TNFα**

- **O** vs NO:
  - ↑ TNFα in O vs NO. TNFα correlated with SDS-BMI.
<table>
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<th>O group ↑ TNF-α vs NO group</th>
</tr>
</thead>
</table>

HW Healthy Weight; O Obese; OA Obese Asthmatics; HWA Healthy Weight Asthmatics; OW Overweight; OWA Overweight Asthmatics; NO Non-Obese; NOA Non-Obese Asthmatics; LM lean mass; BF body fat; AA Atopic Asthma; NAA Non-Atopic Asthma; HC Healthy Controls
Table 2: Weight loss studies in children and adolescents that have measured markers of inflammation

<table>
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<tr>
<th>Inflammatory Marker</th>
<th>Study Design</th>
<th>Population</th>
<th>Obesity definition</th>
<th>Intervention</th>
<th>Length</th>
<th>n</th>
<th>Weight change</th>
<th>Inflammatory Difference</th>
</tr>
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<tbody>
<tr>
<td>Leptin</td>
<td>Uncontrolled longitudinal</td>
<td>10-13y</td>
<td>BMI percentile &gt;85th for age and sex (NHANES I data)</td>
<td>restricted energy intake (3.8-5MJ) + PA</td>
<td>3wks</td>
<td>49 (31F:18M)</td>
<td>↓ BMI, BF &amp; %BF</td>
<td>↓ leptin</td>
</tr>
<tr>
<td>Leptin</td>
<td>Uncontrolled longitudinal (subgroups based on LOW)</td>
<td>8-13y</td>
<td>≥97th BMI percentile based on German population</td>
<td>Diet (HC, LF)</td>
<td>1yr</td>
<td>37</td>
<td></td>
<td>Group 1: n=16 obese LOW ≥0.5 BMI-SDS; Group 2: n=21 obese LOW &lt;0.5BMI-SDS</td>
</tr>
<tr>
<td>Leptin</td>
<td>RCT</td>
<td>14-18y</td>
<td>BMI &gt;30</td>
<td>PA-behavioral-diet intervention based on 'Shapedown'</td>
<td>3mths</td>
<td>Control=7; Intervention =8</td>
<td>Intervention group: no change in BW / BMI (↓ BF% ↑ LM%). Control group gained BW.</td>
<td>Intervention: ↑ 34% adiponectin. Control: no change</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Uncontrolled longitudinal</td>
<td>Mean age 10.2y</td>
<td>≥97th BMI percentile based on population-specific data</td>
<td>Based on 'Obeldicks' program (HC, LF diet, PA, behaviour)</td>
<td>1yr</td>
<td>42 (24F:18M)</td>
<td></td>
<td>Group I: n=16 obese with LOW ≥0.5 BMI-SDS; Group 2: n=26 obese with LOW &lt;0.5 BMI-SDS. However, no significant difference in BMI-SDS or BF% between Group I &amp; II.</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Uncontrolled longitudinal</td>
<td>8-13y</td>
<td>≥97th BMI percentile based on German population</td>
<td>Diet (HC, LF)</td>
<td>1yr</td>
<td>37</td>
<td></td>
<td>Group 1: n=16 obese with LOW ≥0.5 BMI-SDS; Group 2: n=21 obese children with LOW &lt;0.5BMI-SDS</td>
</tr>
<tr>
<td>CRP</td>
<td>RCT</td>
<td>15-16y</td>
<td>BMI &gt;30</td>
<td>PA-behavioral-diet intervention based on 'Shapedown'</td>
<td>3mths</td>
<td>Control=7; Intervention =8</td>
<td>Intervention group maintained BW (↑FFM%, ↓BF%). Control group gained BW</td>
<td>Intervention group: ↓ CRP. Control group: no change.</td>
</tr>
<tr>
<td>CRP</td>
<td>RCT</td>
<td>14-18y</td>
<td>BMI &gt;30</td>
<td>PA-behavioral-diet intervention based on 'Shapedown'</td>
<td>3mths</td>
<td>Control=7; Intervention =8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>Randomised uncontrolled</td>
<td>12-18y</td>
<td>Obesity: BMI percentile ≥95th (CDC)</td>
<td>Diet + PA</td>
<td>6wks</td>
<td>35 (19M:16F)</td>
<td>↓ BMI, BMI-SDS, BF%, WC &amp; BW</td>
<td>↓ CRP</td>
</tr>
<tr>
<td>Study Type</td>
<td>Age Range</td>
<td>BMI Percentile Criteria</td>
<td>Intervention Details</td>
<td>Duration</td>
<td>Change in BMI z-score</td>
<td>Change in hsCRP</td>
<td>Additional Observations</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
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<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled longitudinal 30</td>
<td>11y</td>
<td>≥97th BMI percentile based on population-specific data</td>
<td>Diet based on 'Obeldicks' program (HC, LF diet, PA, behaviour)</td>
<td>1yr</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT 54</td>
<td>5.5-9.99y</td>
<td>Overweight and obese: defined according to the International Obesity Task Force cut-off points</td>
<td>3 treatment groups: Diet OR PA OR Diet + PA</td>
<td>1yr</td>
<td>Diet=42; PA=63; Diet+PA=60</td>
<td></td>
<td>All groups had a reduction in BMI z-score. However, greater reductions were seen in Diet group and Diet + PA group.</td>
<td></td>
</tr>
<tr>
<td>RCT 28</td>
<td>15-16y</td>
<td>BMI &gt;30</td>
<td>PA-behavioral-diet intervention based on 'Shapedown'</td>
<td>3mths</td>
<td>Control=7; Intervention=8</td>
<td></td>
<td>Intervention group maintained BW (↑LM%, ↓BF%). Control group gained BW</td>
<td></td>
</tr>
<tr>
<td>RCT 23</td>
<td>14-18y</td>
<td>BMI &gt;30</td>
<td>PA-behavioral-diet intervention based on 'Shapedown'</td>
<td>3mths</td>
<td>Control=7; Intervention=8</td>
<td></td>
<td>Intervention group: ↓ IL-6. Control group: no change.</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled longitudinal 31</td>
<td>10-13y</td>
<td>BMI percentile &gt;85th for age and sex (NHANES I data)</td>
<td>Energy intake restriction to 3.8-5MJ + PA</td>
<td>3wks</td>
<td>49 (31F:18M)</td>
<td></td>
<td>↓ BMI, BF &amp; %BF</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>Mean age 11y</td>
<td>≥97th BMI percentile based on population-specific data</td>
<td>Diet based on 'Obeldicks' program (HC, LF diet, PA, behaviour)</td>
<td>1yr</td>
<td>31</td>
<td></td>
<td>Group 1 &amp; Group 2: no change.</td>
<td></td>
</tr>
</tbody>
</table>

HC: High carbohydrate; LF: Low fat; PA: Physical activity; BMI-SDS: Body mass index Standard deviation score; LOW: loss of weight; CDC: Centre for Disease Control; BF: body fat; LM: lean mass; FFM: fat free mass; WC: waist circumference; BW: body weight; PA: physical activity; hsCRP: high sensitivity C-reactive protein.
11. Figure Legends

**Figure 1.**
Excess adiposity increases systemic inflammation, subsequently augmenting airway inflationation and contributing to asthma pathogenesis. AHR airway hyper-responsiveness; ASM airway smooth muscle.

**Figure 2.**
Improvements in asthma measures following weight loss in adults with asthma. ASM airway smooth muscle.
12. Figures

Figure 1

OBESITY
Increased adipose tissue

↑ circulating leptin, TNF-α, & IL-6
↓ circulating adiponectin

↑ Airway neutrophils

Airway Inflammation

ASM contraction

AHR

Airway obstruction

ASTHMA
Figure 2

↓ Kilojoule intake

Weight loss

↓ Inflammation (systemic & airway)
↓ ASM contraction
Improved chest wall mechanics

Improved Lung Function
↓ FEV₁, ↑ FVC
↓ PEFR, ↑ TLC

Improved Symptoms
↓ Rescue medication use
↓ Dyspnea score

Weight loss

↓ Inflammation (systemic & airway)
↓ ASM contraction
Improved chest wall mechanics

Improved Lung Function
↓ FEV₁, ↑ FVC
↓ PEFR, ↑ TLC

Improved Symptoms
↓ Rescue medication use
↓ Dyspnea score