Journal of Inflammation Research

Dovepress
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REVIEW

Inflammatory Dysregulation, Asthma, and Obesity in Children: What is the Relationship?

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Abstract: Pediatric obesity is one of the foremost global chronic medical conditions. It affects almost every organ system via mechanisms that tend to be organ-specific. Obesity-related asthma is one such pediatric comorbidity that is rising in incidence such that obesity is now considered the foremost modifiable risk factor for asthma. Immune dysregulation of both innate and adaptive responses is one of the best understood pathobiologic mechanisms underlying obesity-related asthma. From the perspective of innate immune dysregulation, there are higher proportions of pro-inflammatory M1 macrophages in systemic circulation and in the airway in pediatric studies; the underlying mechanisms are only studied among adults wherein airway M1 macrophages impaired efferocytosis and induced neutrophil recruitment in the airway. From the perspective of adaptive immune responses, there are higher proportion of T helper 1 cells that are associated with lower lung function supporting the non-allergic phenotype of pediatric obesity-related asthma. There is also substantial new literature from bulk and single cell transcriptomic T cell analyses that have identified novel pathways and distinct differentiation of Th cells in obese children as compared to healthy-weight children with asthma. CDC42 pathway is one such pathway that is upregulated in Th cells from obese children with asthma and is associated with Th cell chemotaxis and adhesion to airway smooth muscle (ASM), activating pathways that promote ASM contractility and proliferation. There is also increased recognition of the role of neutrophils, as compared to eosinophils, in pediatric obesity-related asthma but the mechanistic pathways that are functional relevance in disease phenotype have not yet been investigated. Finally, obesity-mediated metabolic abnormalities, including insulin resistance and dyslipidemia, have been epidemiologically linked with pediatric asthma but their underlying mechanisms are not known. In summary, there have been several strides in understanding the immune pathobiology of pediatric obesity-related asthma which have firmly established it as a distinct asthma phenotype, which have highlighted the need for further scientific investigation of mechanisms that underlie the contribution of immunometabolism.

Keywords: obesity, asthma, children, immune responses

Introduction

Obesity is now one of the most common chronic pediatric medical conditions worldwide that adversely affects almost all organ systems.[1,2] From the perspective of the respiratory system, pediatric obesity is not only a risk factor for asthma but is also a disease modifier that augments severity and morbidity. Although there is no consensus definition of obesity-related asthma, incident asthma in children as a consequence of obesity is a poorly controlled asthma phenotype that is resistant to conventional management, including steroids, and thereby diverges from classical atopic asthma with activation of alternate inflammatory pathways.[3–7] It has lifelong consequences wherein adults with childhood onset of obesity-related asthma persist with poor disease control and high burden.[8,9] On the other hand, asthma that is complicated by onset of obesity retains its atopic phenotype but is associated with attenuated medication responsiveness.[10] For these reasons, the rising co-occurrence of pediatric obesity and asthma has resulted in a significant public health challenge, such that obesity is now identified as the one modifiable risk factor for incident asthma,[11] emphasizing the importance of understanding the underlying pathobiology for effective prevention and management.

https://doi.org/10.2147/JIR.S546304
Received: 21 October 2025
Accepted: 16 February 2026
Published: 24 February 2026

Obesity adversely affects organ systems, including the respiratory system, via different mechanisms that include truncal adiposity, systemic immune dysregulation, and metabolic abnormalities, including insulin resistance and dyslipidemia.[12] Among these, substantial inroads have been made on the role of the immune system, which tends to be organ-specific.[13–20] These include dysregulation of innate responses that are non-specific defense mechanisms that are activated early following exposure to various environmental antigens, and of adaptive immune responses that are specialized responses, programmed by the innate responses, and responsible for immunologic memory.[21]

What is unique about the respiratory system, as compared to the cardiovascular or endocrine systems, is its interaction with the external environment which requires innate immune programming to address noxious environmental exposures. Thus, the respiratory system is baseline enriched for the presence of airway and alveolar macrophages, dendritic cells, and innate lymphoid cells that orchestrate physiologic and pathologic innate immune responses, to induce recruitment of T cells, B cells, mast cells, and granulocytes (eosinophils and neutrophils) to orchestrate physiologic and pathologic adaptive immune responses. In this review, we discuss seminal studies over the past decade that have informed our understanding of innate and adaptive immune dysregulation in pediatric obesity-related asthma and emphasize scientific developments over the past five years. While we emphasize studies on immune dysregulation in pediatric obesity-related asthma, we include specific adult studies that provide mechanistic insights into immune dysregulation patterns reported in pediatric obesity-related asthma. The studies included in this narrative review were identified on literature search on PubMed and Google Scholar for studies in English language on immune underpinnings of obesity-related asthma in children between 1/1/2010 and 6/30/2025, focusing on several cell types that are part of innate and adaptive immune responses.

Obesity Induced Dysregulation of Innate Immunity and Its Association with Obesity-Related Asthma

Pulmonary Macrophages

Despite the abundance of macrophages in the respiratory tract, their role in obesity-related asthma has been investigated to a limited extent. Pulmonary macrophages, comprised of airway and interstitial macrophages, are essential for innate immune responses in the respiratory tract and serve various roles such as removing cellular debris from the respiratory tract, regulating defense mechanisms against pathogens, using cell surface pattern recognition receptors to differentiate between self and foreign stimuli, and recruit cells involved in adaptive immune responses. Airway macrophages are traditionally characterized as M1 or M2 macrophages, of which the former are pro-inflammatory and protect the respiratory tract from intracellular pathogens,[22] while the latter are alternatively activated and produce anti-inflammatory and pro-allergic cytokines (IL-4 and IL-13) that play an important role in efferocytosis and extracellular pathogens.[23]

Macrophages play a seminal role in initiation of immune dysregulation in obesity. There is greater recruitment of M1 macrophages to the adipose tissue (AT) in response to tissue hypoxia due to delay in regional neo-angiogenesis in the setting of rapid AT proliferation.[24–26] Local release of TNFα, IL-8, and IL-6 by M1 macrophages induces recruitment of pro-inflammatory CD4+T and CD8+ T cells which sets the stage for AT inflammation which then induces low grade systemic inflammation.[27] Higher proportion of AT macrophages were found among children with obesity-related asthma[28] and their activation has been reported among adults with obesity-related asthma.[29]

Mechanisms Linking Macrophages with Obesity-Related Asthma

Focusing on airway macrophages, studies on mice made obese on high fat diet (HFD) reported higher proportion of airway macrophages in bronchoalveolar lavage fluid (BAL) that were primarily of M1 phenotype and secreted IL-1β and TNF-α (Figure 1);[30] their depletion was associated with decreased airway hyper-responsiveness (AHR).[31] Leptin, an adipokine produced by AT with pro-inflammatory effects, has been associated with M1 polarization when it synergistically couples with lipopolysaccharide (LPS) and interferon gamma (IFN-γ) to activate the leptin receptor.[32] One of the mechanisms by which HFD induces macrophage activation is through its effects on saturated fatty acids, as confirmed by in-vitro stimulation of human monocytes and macrophages with palmitic acid in adults.[30,33] Additional pathways that induce M1 polarization in airways of murine obese asthma models include JAK2/STAT3 pathway that is attenuated by

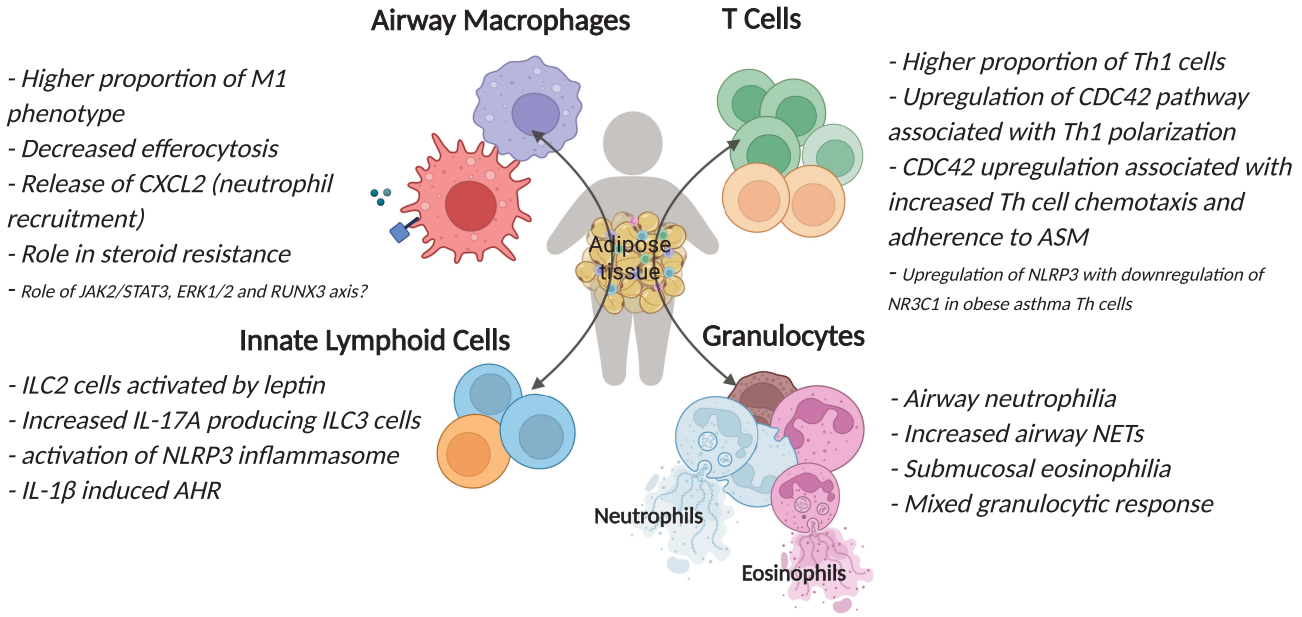

Figure 1 Summary of the mechanisms that underlie the association of innate and adaptive immune cells with obesity-related asthma. Figure created with BioRender.com.

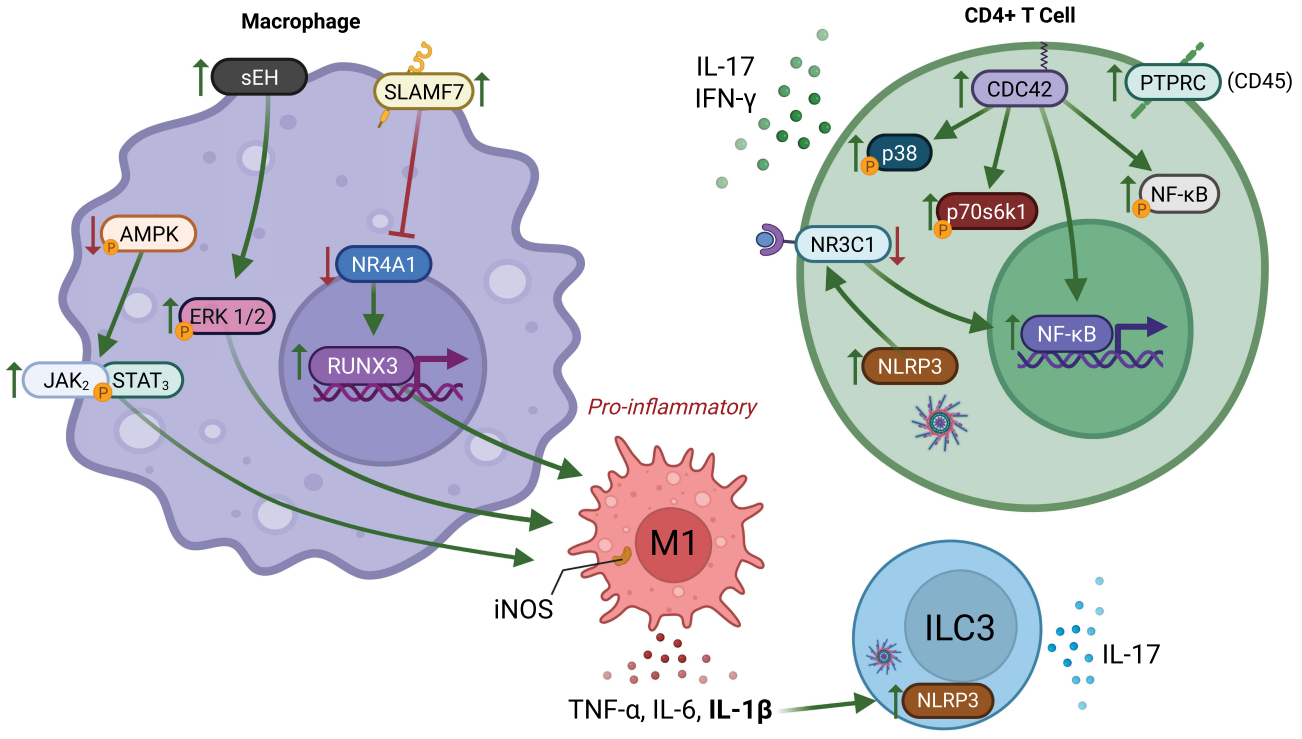

Figure 2 Summary of cellular pathways known to be associated with obesity-related asthma. Figure created with BioRender.com.

AMPK,[34] Erk1/2 pathway that is attenuated by soluble epoxide hydrolase,[35] and SLAMF7 which modulates the NR4A1-RUNX3 axis by suppressing NR4A1 and upregulating RUNX3 (Figure 2).[36] From the functional perspective, one of the earliest studies was conducted on adults with obesity-related asthma, and it demonstrated less functional airway macrophages and low efferocytosis,[37,38] a function that is traditionally associated with M2 macrophages.[39] Since

https://doi.org/10.2147/JIR.S546304

efferocytosis correlates with expression of glucocorticoid receptor α and dexamethasone-induced mitogen-activated protein kinase phosphatase 1 (MKP-1), these findings also reveal mechanisms that explain decreased glucocorticoid responsiveness in obese individuals with asthma.[38] Together, the higher proportion of M1 macrophages with diminished function of M2 macrophages in the airway, likely in response to saturated fatty acids, suggest that alteration of the airway macrophage landscape mimics changes observed in AT in response to obesity-induced inflammation. Whether the same circulating substance(s) induce these changes in multiple organs or whether these are local changes is poorly elucidated. There is also no data that directly links M1 macrophages with asthma disease burden. The mechanistic information is from adult studies highlighting the need to assess their relevance in pediatric obesity-related asthma.

Pediatric studies have investigated monocytes, which are precursors to airway macrophages, and their dysregulation has been reported in children with obesity-related asthma. Among the two types of circulating monocytes, classical and patrolling, the latter express higher levels of CD16, a marker of monocyte activation;[40] obese adolescents with asthma had fewer classical monocytes and more patrolling monocytes in peripheral blood as compared to healthy-weight controls.[41]

Other Cells Associated with Innate Immune Responses

There is also substantive pediatric asthma research on other cells associated with innate immune responses, including innate lymphoid cells (ILCs), natural killer (NK) cells and dendritic cells. For instance, dendritic cells are critical regulators of pediatric allergic asthma by inducing and sustaining T cell mediated allergic responses,[42] while NK cells augment allergic T cell responses in the setting of viral infections, such as with respiratory syncytial virus.[43] ILCs, which are classified as ILC1, ILC2, and ILC3, based on cytokine responses as defined in T cells, but are distinct from T cells by absence of antigen-specific receptors and cell lineage markers and their activation by damage-induced signals,[44–47] are the only cells that have been investigated in the context of pediatric obesity-related asthma. Higher proportion of ILC3 cells were reported in peripheral circulation in children with obesity-related asthma, even though the proportion of ILC3 cells or expression of ILC3-specific genes did not correlate with clinical outcomes such as asthma severity.[48]

Mechanisms Linking ILCs with Obesity-Related Asthma

Of the two mechanistic studies on ILCs in obesity-related asthma, both of which are in HFD-induced obese murine models, the first one reported on the role of IL-17A-producing ILC3 cells in innate AHR (Figure 1).[49] These effects were mediated by IL-1β, which recruited M1 macrophages in pulmonary and adipose tissue (AT) and induced ILC3 expansion, and also independently induced AHR by activating IL17A production by ILC3 cells by activating the NLRP3 inflammasome; these observations were validated by the abolishment of AHR by blocking IL-1β (Figure 2).[49] The second study was distinct in identifying a role of ILC2s in inducing AHR in response to house dust mite (HDM) exposure, wherein there were higher proportions of ILC2 and ILC3 cells and Th17/Th2 specific cytokines, including IL-17, IL-4, IL-13, CCL11, and CCL17 in lung tissue.[50] These studies are highly relevant since they highlight the distinct role of ILCs in innate AHR and AHR in response to allergen exposure. Since leptin can induce Th2 and ILC2 proliferation and survival,[51] and is associated with allergic asthma in obese children,[52] it may be one mechanism linking ILCs with innate as well as allergen-induced AHR in obesity-related asthma (Figure 1).

Obesity Induced Dysregulation of Adaptive Immunity and Its Association with Obesity-Related Asthma

T Cells

We focus our report on CD4+ or T helper cells (Th cells) since they have been better investigated than CD8+ T cells in the context of pediatric obesity-related asthma. Based on their cytokine profiles, Th cells are classified as Th1, Th2, Th9, Th17, Th22, and T regulatory cells although there is improved recognition of heterogeneity and the presence of hybrid cells such as Th1/Th17 and Th2/Th17 cells.[53] In the context of asthma, traditionally Th cell responses have been simplistically classified as Th1 responses associated with non-atopic asthma and Th2 responses associated with atopic asthma (Figure 1).[54,55] Recent studies have found a role of Th17 cells in both atopic and non-atopic pediatric asthma.[56] In

the context of obesity, M1 macrophage-mediated inflammation in AT recruits naïve Th cells that differentiate into Th1 cells that then enter systemic circulation leading to a higher number of circulating Th1 cells in obese individuals.[57]

Given that obesity is a risk factor for pediatric asthma and is associated with more Th1 cells in peripheral blood, systemic Th1 polarization and an elevated Th1/Th2 ratio was one of the seminal findings in children with obesity-related asthma that distinguished them from children with healty-weight asthma.[41,58] Th1 polarization correlated with leptin and IL-6, a cytokine increased in obese AT inflammation,[58] and inversely correlated with classical monocytes and directly correlated with patrolling monocytes in children with obesity-related asthma but not among those with healthy-weight asthma.[41] Similar patterns have been observed in adults suggesting persistence of these patterns into adulthood.[59] While there are no pediatric studies on CD8+ T cells, body mass index inversely correlated with reduced expression of cytotoxic $CD8^+$ T-cell network in sputum cells from adults with severe asthma, identifying a need to examine CD8+ T cells in pediatric obesity-related asthma as well.[60]

Mechanisms Linking T Cells with Obesity-Related Asthma

Investigating the mechanism underlying Th1 polarization, a transcriptomic analysis of blood Th cells from children with obesity-related asthma revealed a novel role of the CDC42 pathway, a RhoGTPase, in Th1 polarization. CDC42 upregulation was associated with p38 Mitogen-Activated Protein Kinase (MAPK) and Ribosomal Protein S6 Kinase Beta-1 (p70s6k1) activation, inducing NFκB phosphorylation, that contributes to IFNγ and IL-17 production (Figure 2).[61] Since CDC42 plays a role in Th cell adhesion and chemotaxis,[62] CDC42 upregulation with asthma pathobiology, Th cells with CDC42 upregulation from children with obesity-related asthma adhered more to obese airway smooth muscle (ASM) cells and upregulated pathways associated with ASM contractility and proliferation.[63] Together, these studies identified Th1 polarization as a distinguishing immune mechanism for childhood obesity-related asthma, and identified a novel role of CDC42 in systemic Th1 polarization and linked it with the obese asthma phenotype. These observations have informed single cell analyses of CD4+ T cells. While one study found that cells with CDC42 upregulation from children with obesity-related asthma had evidence of NLRP3 inflammasome upregulation and enhanced Th1 responses which was associated with downregulation of glucocorticoid receptor gene NR3C1,[61] another study found upregulation of CD45 in Th1 cells that was associated with enrichment of Rho-GTPases[64] (Figure 2). These studies together suggest that pediatric obesity-related asthma is not associated with alteration or dysregulation of a single Th cell subtype but rather involvement of multiple T cell clusters that are differentially activated in obesity-related asthma as compared to healthy-weight asthma, and obese and healthy weight controls. These cells together contribute to an inflammatory profile that is enriched for a steroid resistant Th1/Th17 phenotype, identifying a mechanism to explain the steroid resistance observed in pediatric obesity-related asthma.[65] Although the downstream mechanisms by which Th1/Th17 cells contribute to asthma are poorly elucidated, their prototypical cytokines, IFNγ and IL-17, are present in BAL from children with severe asthma,[66] frequently in the setting of neutrophilic asthma, suggesting that neutrophils may be end effector granulocyte cells for pediatric obesity-related asthma.[67]

Granulocytes: Neutrophils and Eosinophils

Among granulocytes, eosinophils, and to a lesser extent, neutrophils are the two cell types that have been associated with asthma.[68] Given the established role of atopy in childhood asthma and to some extent in adult asthma, eosinophils have been better investigated in their recruitment to the airway in response to Th2 cells and cytokines where they perpetuate allergic inflammation by releasing substances, such as major basic protein.[69]

Unlike pediatric healthy-weight asthma that tends to be atopic, pediatric obesity-related asthma is associated with either absence of airway inflammation, known as pauci-granulocytic asthma, or is associated with neutrophil recruitment in response to IL-17, that is verified by decrease in airway neutrophilia in response to IL-17 receptor blockade.[70] Several cytokines associated with M1 macrophage activation, including IL-1β, IL-6, and TNF-α induce neutrophilic inflammation. M1 macrophages also release CXCL2, a neutrophil chemoattractant, by activating the JNK/STAT3/AKT signaling pathways.[32] In light of these links between M1 macrophages and neutrophils, M1 macrophage polarization was associated with airway neutrophilia in recent murine obese asthma studies, with increased Th1/Th17 cytokines in BAL fluid,[32,71] reduced levels of anti-inflammatory cytokine IL-10,[72] excessive airway neutrophil extracellular traps

(NETs), inflammasome activation,[73] and increased ILC3/IL-17 cells in the lungs (Figure 1).[73] Although these pathways directly link M1 macrophages with neutrophils, the mechanisms that link Th1/ Th17 cells with airway neutrophilia are not known.

In keeping with observations in murine models, obese children, particularly girls, have evidence of non-eosinophilic asthma, as compared to healthy-weight children with asthma and obese controls without asthma,[74] with neutrophilia in blood but not in the airway.[74,75] These observations differed from adults who had higher proportion of neutrophils in both blood and sputum[76–78] – given these differences, we speculate that persistence of obesity-related asthma from childhood to adulthood may induce airway neutrophilia, a hypothesis that needs future investigation. Moreover, the overlap between murine and human studies on the association between neutrophils and obesity-related asthma also highlights the importance of investigating their role in disease pathobiology.

In addition, mixed granulocytic responses have also been found in murine models of obesity-related asthma, where combined eosinophilic and neutrophilic airway inflammation induced AHR.[19,79,80] We speculate that the type of antigenic stimulus influences the association of mixed granulocytic inflammation with AHR. For instance, when obese mice were exposed to diesel exhaust particles, which is associated with non-atopic neutrophilic asthma, they were resistant to eosinophilic inflammation,[81,82] while exposure to ovalbumin and HDM that are known triggers for eosinophilic responses was associated with eosinophilia in BAL samples and peribronchial space with increase in airway resistance.[37,80,83–85] These murine models of obesity and atopic or non-atopic asthma support the complexity of the effects of obesity on the immune profile in children with asthma with and without atopy and define a need for investigations among humans with and without atopy.

Serum and Plasma Biomarker Studies

In light of the importance of systemic immune responses in obesity-related asthma, several studies discussed above also reported on circulating immune markers that are products of macrophages, T cells and granulocytes. We highlight three recent pediatric studies that have identified novel biomarkers that may aid in further distinguishing the phenotypes of pediatric obesity-related asthma and be key areas of interest for future mechanistic studies. Plasma profiling has revealed elevated CCL8, IL-33, IL-17C, CLECL12A, and FGF-23 in children with obesity-related asthma as compared to those with healthy-weight asthma and obesity alone.[86] There are several sources for these cytokines; while macrophages can produce CCL8, IL-33, CLECL12A, and FGF-23, dendritic cells can produce IL-33. In addition, airway epithelial cells also secrete IL-33, IL-17C, and FGF-23. Serum analysis in another study reported increased leptin, and cytokines IL-6 and TNF-α, typically produced by macrophages and Th1 cells, coupled with reduced IL-10, produced by Th2 and T regulatory cells, and vitamin D in obese as compared to healthy-weight children with asthma.[87] However, TNF-α was not significantly increased and Vitamin D levels were not significantly decreased when compared to obesity alone. IL-4 levels were also comparable across groups. A limitation of this study is that it lacked a healthy control group and did not elucidate for presence of atopy. The third study exploring serum markers found that co-existence of obesity and asthma had a significant effect on leptin levels, as well as IL-5, IL-10, IL-17A, IL-33, TNF-α levels, produced by macrophages and Th cells,[88] but the effects were not synergistic as compared to those of obesity and asthma alone. For example, IL-10 was decreased in groups of asthma alone or obesity alone, contradicting the prior study, but there was no further significant decrease among those with obesity-related asthma. These observations highlight the limitation of the earlier report by Jiang et al,[87] where they did not evaluate the individual effects of obesity and asthma alone. These studies add to prior literature by identifying a deficiency in anti-inflammatory processes which may themselves contribute to the pro-inflammatory state discussed extensively in the sections above, and highlight the importance of simultaneous investigation of the balance between pro- and anti-inflammatory responses and their comparison to the patterns among the independent contributions of obesity and asthma, while also considering atopy in obesity-related asthma.

Obesity as a Disease Modifier for Atopic Asthma

In addition to being a risk factor for non-atopic asthma, obesity is a disease modifier and is associated with higher disease severity among those with atopic asthma.[52,89] Although this area of investigation is relatively new, we speculate that leptin plays a role. While leptin has been linked with T2 inflammation, it may also exert its influence via eosinophil

activation and chemotaxis,[90] without increasing the proportion of airway eosinophils (Figure 1).[74] For instance, obesity in pediatric asthma was associated with eosinophil activation[90] and submucosal eosinophilia was found in obese adults with severe asthma,[91] suggesting their role in the airway pathobiology of obesity-related asthma. As additional support for the role of eosinophils in obesity-related asthma, a clinical trial comparing the effect of weight loss by dietary restriction to that due to exercise reported that exercise-induced weight loss decreased airway eosinophils,[92] while dietary restriction-induced weight loss decreased airway neutrophils.

Functional Implications of Immune Dysregulation in Obesity-Related Asthma

While we have discussed each cell type for ease of understanding, in keeping with the complexity and redundancy in biological processes, there is ample evidence supporting the presence of a mixed cellular phenotype in obesity-related asthma ranging from paucigranulocytic to what is being described by new nomenclature including Type IVb, that is driven by Th2/ILC2 with a role of IL-4, 5, 9, and 13, Type IVc which is Th17/ILC3 driven, with a role of IL-17 and neutrophils, and Type V, that has a mixed phenotype of Th1/Th2/Th17 and Type VI, that is associated with inflammation in response to metabolic dysregulation.[10,93]

In addition to distinguishing obesity-related asthma from healthy-weight asthma, systemic T cell and neutrophilic inflammation among obese individuals with asthma has functional relevance. Biomarkers of Th1 polarization, IFNγ and interferon-gamma induced protein (IP-10), and activation of RhoGTPase pathways, have been associated with airflow obstruction, as defined by lower FEV_1/FVC ratio and lower lung volumes including expiratory reserve volume and residual volume in children with obesity-related asthma,[6,41,58,94] lung function deficits that were traditionally reported in adults with obesity-related asthma.[95] Although there are no reports that link M1 macrophage inflammation with pulmonary function deficits, expression of the CCR2 receptor on monocytes, that decreases as cells differentiate from classical to patrolling monocytes,[96] correlated with lung volumes, suggesting that monocyte activation links with lung volume deficits in children with obesity-related asthma.[41] In keeping with these observations, circulating sCD163 levels, a marker for macrophage activation, was higher in girls and correlated with lower lung function and asthma quality of life.[29] As further evidence of the importance of non-allergic immune responses in asthma disease burden among obese children, a recent study found no association between different systemic measures of atopic responses and asthma disease burden.[97]

Less is known about airway immune patterns and their association with disease burden among children with obesity-related asthma with most studies limited to reporting on the association of fractional exhaled nitric oxide (FeNO), a measure of allergic airway inflammation. While one study found no association of FeNO with asthma burden in obese children,[98] another study reported an association of adiposity measures with low FeNO but high FeNO among obese children was associated with worse asthma morbidity.[99] These disparate results from cross-sectional studies verify existence of multiple phenotypes of obesity-related asthma, which thus far have largely been investigated as one disease entity. Initial forays into distinguishing the distinct subtypes of disease is based on the chronology of asthma and obesity onset - when obesity precedes asthma, it is a risk factor primarily for non-atopic asthma,[100] but when it is a consequence of asthma, it functions as a disease modifier for atopic asthma, and is associated with higher disease burden in some,[9] and not in other studies.[97] These observations re-iterate the need for continued research in the field of obesity-related asthma to establish its sub-phenotypes and endotypes to enable better disease classification and targeted investigation to enable precision medicine, an aspect addressed in a recent study that reported on the utility of 91 circulating proteins in defining asthma phenotypes.[101]

Immunometabolism and Obesity-Related Asthma

Systemic inflammation in obesity is intricately linked with systemic metabolic dysregulation, particularly insulin resistance and dyslipidemia, such that they have been combined in the term "metaflammation".[102] Both insulin resistance and dyslipidemia have been epidemiologically linked with obesity-related asthma,[4,5,41,103] and therapeutic interventions with glucose lowering and lipid lowering medications lower asthma burden with improvement in lung function

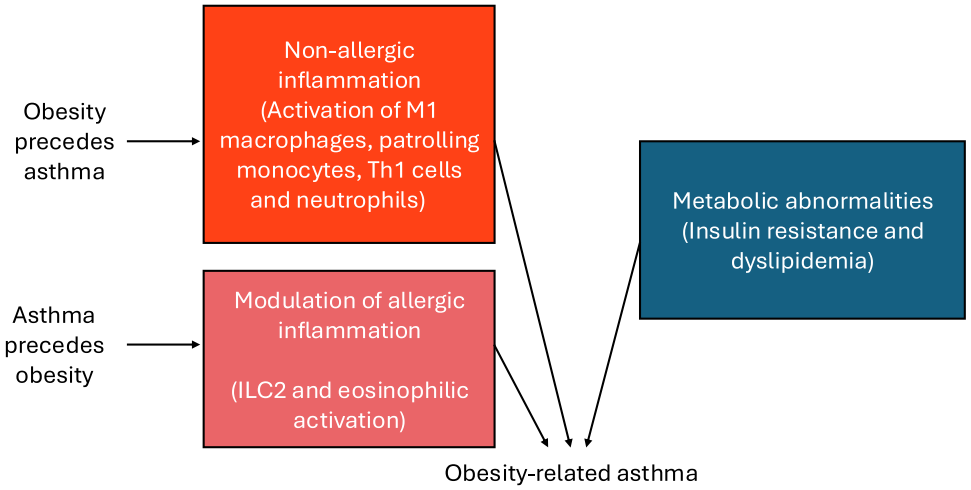

Figure 3 Summary of the association of systemic inflammation and metabolic abnormalities in pediatric obesity-related asthma.

(Figure 3).[104–107] However, the pathobiology underlying the therapeutic effectiveness is minimally investigated. Over the past decade, there has also been increased awareness of the relevance of cellular metabolism in healthy and pathological functioning of immune cells where bioenergetics within the cell can directly impact immune cell fate and functions. For instance, T cell activation in physiologic and pathologic states is influenced by extracellular and intracellular lipids, including sphingolipids, and is intricately linked to change in glucose metabolism from oxidative phosphorylation to glycolysis (Figure 3).[108,109] The interaction between systemic and cellular-level metabolic dysregulation have been investigated in obesity-induced neurological, cardiovascular and hepatic diseases[13–16] but remains to be investigated in obesity-related asthma.

Early Exploration of Therapeutics for Immune Dysregulation of Obesity-Related Asthma

In the discussion above, we have summarized the distinct patterns of immune dysregulation in obesity-related asthma as compared to healthy-weight asthma, obesity alone and among healthy-controls. These can be categorized into non-atopic obesity-related asthma when asthma is a consequence of obesity and atopic or mixed pattern of disease when obesity is a complication of asthma. As these mechanisms are being elucidated, there are advances in investigating diverse molecules as potential mitigators of disease-specific pathobiology. For instance, in a murine model of obesity-related asthma with airway neutrophilia and higher concentration of airway NETs, Involucrasin B, a plant-derived dihydroflavonoid, inhibited the TLR4-NFκB-NLRP3 pathway to prevent inflammasome activation.[73] Given attenuation of asthma burden in response to glucose lowering and lipid lowering drugs,[104–107] preclinical studies have identified some underlying mechanisms. For instance, metformin decreases NLRP3 mediated inflammation by upregulating AMPK,[110] GLP-1R agonists inhibit NLRP3 and neutrophilic airway inflammation by inhibiting cytokines IL-33 and Thymic Stromal Lymphopoietin (TSLP),[111] while lipid lowering medications like statins inhibit cytokines and also modulate airway epithelial cell mucus production (Figure 3).[112] While these preclinical findings show promise in murine models, we are far from translating them for human use. We therefore propose that targeted research is needed to elucidate mechanisms, preferably in ex-vivo human disease models to facilitate their use for precision medicine for obesity-related asthma. As novel pathways such as RhoGTPase pathways are linked with obesity-related asthma, they also afford the opportunity to identify novel biomarkers of pediatric obese asthma, which will serve as targets for therapeutic development to prevent onset of asthma among obese children and to modulate the disease to prevent airway remodeling and its related loss of lung function among those with prevalent disease.

Conclusion

In conclusion, this review discussed the varied immune patterns observed in obesity-related asthma, highlighting the roles of both innate and adaptive immune dysregulation. While asthma secondary to obesity is non-allergic, as evidenced by Th1/Th17 immune patterns in non-allergic asthma, obesity is a disease modifier for allergic asthma, as evidenced by persistence and worsening of eosinophilic inflammation among children with asthma that become obese. We also highlight several areas of future investigation. One is the exploration of the mechanistic links between macrophage, Th cell, and granulocyte activation in obesity-related asthma and distinguish it from obesity alone. In addition, an understanding of the interaction of immune cells with airway cells, including the airway epithelial cells and ASM is also needed. Investigations are also needed to define the mechanisms by which glucose lowering and lipid lowering medications decrease obesity-related asthma. Given the key role of nutrition in obesity, and its role in immunometabolism, studies are needed to understand the beneficial effects of dietary interventions. Each of these areas of investigation will inform preventative strategies as well as therapeutic approaches facilitating the potential of precision immunometabolic medicine in management of pediatric obesity-related asthma.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Sarai Duran – Conceptualization, Writing – original draft, Writing -review and editing. Anna Reichenbach - Conceptualization, Writing – original draft, Writing -review and editing. Deepa Rastogi – Conceptualization, Writing - review and editing. All authors have given final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This article was partially supported by funding from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

Disclosure

The authors have no conflict of interest.

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