



Obesity-related asthma in children is characterized by T-helper 1 rather than T-helper 2 immune response: A meta-analysis

Tawanda Maurice Nyambuya, MSc^{*,†}; Phiwayinkosi Vusi Dlodla, PhD^{‡,§};
Vuyolwethu Mxinwa, MSc^{*}; Bongani Brian Nkambule, PhD^{*}

^{*} School of Laboratory Medicine and Medical Sciences (SLMMS), College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

[†] Department of Health Sciences, Faculty of Health and Applied Sciences, Namibia University of Science and Technology, Windhoek, Namibia

[‡] Department of Life and Environmental Sciences, Polytechnic University of Marche, Ancona, Italy

[§] Biomedical Research and Innovation Platform, South African Medical Research Council, Tygerberg, South Africa

ARTICLE INFO

Article history:

Received for publication March 24, 2020.

Received in revised form June 2, 2020.

Accepted for publication June 5, 2020.

ABSTRACT

Background: Asthma is a chronic inflammatory condition characterized by T-helper (T_H) 2 polarization. In children, the prevalence of obesity is associated with an increased incidence of asthma. Notably, obesity is linked with T_H1-mediated inflammation and has been identified as a major risk factor for asthma.

Objective: To investigate the impact of obesity on T_H1 (tumor necrosis factor α , interferon gamma, interleukin (IL)-6, IL-8) and T_H2 (IL-4, IL-5, IL-10, IL-13) immune responses in children with asthma.

Methods: We searched the MEDLINE and gray literature electronic databases for eligible studies from inception up until April 2020. The quality of included studies and evidence was independently assessed by 2 reviewers. The random-effects model was used in this meta-analysis, and outcomes were reported as standardized mean difference (SMD) and 95% confidence interval (CI).

Results: Overall, 5 studies comprising 482 participants met the inclusion criteria. The meta-analysis revealed an increased T_H2-mediated immune response in lean people with asthma compared with controls without asthma (SMD: -1.15 [95% CI: $-1.93, 0.36$]; $I^2 = 93\%$; $p^H < .001$). However, in obese people with asthma, there was polarization toward T_H1 immune response compared with lean people with asthma (SMD: -0.43 [95% CI: $-0.79, -0.08$]; $I^2 = 88\%$, $p^H < .001$).

Conclusion: This meta-analysis reveals that there are differences in immune responses mediated by T-helper cells in lean and obese children with asthma. Moreover, and not unique to asthma, obesity polarizes the immune response toward T_H1 rather than the classical T_H2. This could be an important aspect to understand to establish effective therapeutic targets for obese children with asthma.

© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Reprints: Tawanda Maurice Nyambuya, MSc, Namibia University of Science and Technology, Department of Health Sciences, Faculty of Health and Applied Sciences, Windhoek, Namibia; E-mail: mnyambuya@nust.na.

Disclosures: The authors have no conflicts of interest to report.

Funding: BBN is funded by the National Research Foundation (NRF) of South Africa (Grant Number: 107519). BBN is also a fellow in the University of KwaZulu-Natal (UKZN) Developing Research Innovation, Localisation and Leadership in South Africa (DRILL). DRILL is an NIH D43 grant (D43TW010131) awarded to UKZN in 2015 to support a research training and induction programme for early-career academics. PVD was partially supported as a Post-Doctoral Fellow by funding from Research Capacity Division of the South African Medical Research Council (SAMRC) through its division of Research Capacity Development under the Inta-Mural Postdoctoral Fellowship Programme from funding received from the South African Treasury. The content hereof is the sole responsibility of the authors and do not necessarily present the official views of SAMRC or the funders.

<https://doi.org/10.1016/j.anai.2020.06.020>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Chronic respiratory diseases (CRDs) are ranked among the top 5 noncommunicable diseases that are currently posing the greatest health care burden and contributing significantly to increased mortality globally.¹ Among these CRDs is asthma, a chronic inflammatory disorder that is characterized by airway obstruction mediated by various inflammatory immune cells, including inflammatory leukocytes.^{2,3} Recently, it was estimated that asthma affects 339 million people worldwide, with a mortality rate of more than 356,000 deaths annually.⁴ This burden may be attributed to increased prevalence of childhood obesity, a major risk factor for asthma,⁵ and comorbidities such as type 2 diabetes mellitus and cardiovascular diseases.⁶ Of note, systemic inflammation has been identified as a common characteristic feature among these comorbidities^{7,8} and has led to renewed interest in understanding the pathoimmunologic aspects of asthma.

Immunoglobulin E (IgE)–mediated asthma is categorized as a type 1 hypersensitivity response that is broadly classified as either eosinophilic or noneosinophilic⁹ with exacerbated T-helper 2 (T_H2) immune responses mediated by its cytokines interleukin (IL)–4, IL–5, and IL–13.¹⁰ Hence, T_H2 polarization is regarded as a hallmark of asthma pathogenesis. Interestingly, although T_H2-mediated responses in people with asthma have been characterized,^{10–12} the clinical relevance of these findings remain controversial. This is partly due to the variable immunological responses in asthma therapy and the lack of clear mechanisms and factors that are independent of T_H2–mediated responses, as described elsewhere,^{13,14} particularly, in cases of comorbidity with other disorders such as obesity.¹⁵ Notably, obesity has been associated with disease severity and reduced efficacy of asthma treatment, which is further affected by age-dependent factors in children.^{16,17} However, the pathophysiological mechanisms of obesity-related asthma remain poorly understood. Here, we hypothesize that these detrimental phenomena are partially a consequence of altered T-helper cell responses induced by obesity. This is in conjunction with an exacerbated proinflammatory response in obesity being driven by T_H1 cells, which are characterized by increased release of its cytokines, that is, interferon gamma (IFN- γ), tumor necrosis factor (TNF)- α , and IL-6, as reported elsewhere.^{18,19} Likewise, these findings have been confirmed in obesity-related asthma,^{20–22} albeit others still suggested the T_H2 polarization hallmark.²³

Although previous systematic reviews and meta-analysis have investigated the broad associations between obesity and asthma,^{24–26} none have assessed the impact of obesity on immune responses mediated by T_H1 and T_H2 in asthma. Therefore, in this study, we aimed to investigate and establish whether obesity alters T_H1 (TNF- α , IFN- γ , IL-6, IL-8) and T_H2 (IL-4, IL-5, IL-10, IL-13) immune responses in asthma. The selected cytokines are known to mediate respiratory inflammation²⁷ and affect asthma control in obesity-asthma conundrum.²⁸

Methods

This meta-analysis was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and performed to address the following questions:

Question 1: Is the immune system of lean children with asthma polarized toward a proinflammatory T_H1 or anti-inflammatory T_H2 response?

Question 2: Does obesity alter these T-helper cell responses in obese children with asthma when compared with their lean counterparts?

Search Strategy

A comprehensive search was conducted from the inception of MEDLINE electronic database and ProQuest gray literature up until April 2020. The search was conducted by 2 independent reviewers (TMN and BBN), whereas a third reviewer (PVD) was consulted for arbitration in cases of disagreements. The search strategy comprised Medical Subject Heading and text words, such as obesity, asthma, T_H1 and T_H2 cells, and their respective synonyms. In addition to gray literature search, scanning reference lists of retrieved studies was also applied to identify relevant studies. No language restrictions were applied in the search strategy, and the Mendeley reference manager software (Elsevier, Amsterdam, Netherlands) was used to manage the reference list and remove study duplicates.

Study Selection

Studies were independently screened and selected by 2 reviewers (TMN and B.B.N.) using a predefined inclusion and exclusion criteria. Briefly, this meta-analysis only included studies that reported on both T_H1 and T_H2 immune responses in children with

asthma (aged ≤ 18 years). Moreover, the studies were only included if participants were categorized as either obese or lean. Reviews, books, editorials, letters, and studies that included adult participants (> 18 years) were excluded. In addition, studies that did not compare obese and lean people with asthma or lean people with asthma vs lean healthy controls were excluded from this study.

Data Extraction

Two independent investigators (TMN and VM) carried out the data extraction process using a predefined data extraction sheet. In cases of disagreements, BBN was consulted for arbitration. The primary aim of the study was to assess T_H1 and T_H2 function in obese children with asthma. The extracted data items from each study included the names of the authors, year of publication, study design, age of participants, effect measures of T_H1 and T_H2 function (cytokines), and the main findings.

Outcomes

The outcomes of this meta-analysis were T_H1 and T_H2 immune responses that were reported as standardized mean difference (SMD).

Quality Assessment

The quality of evidence was assessed using the Grading of Recommendations Assessment Development and Evaluation²⁹ approach by 2 independent reviewers, TMN and VM. In cases of disagreements, a third reviewer, PVD, was consulted for arbitration. Furthermore, the quality of included studies was assessed using the modified Newcastle-Ottawa Scale adapted for cross-sectional studies.³⁰ The tool uses the star system to appraise studies based on the following 3 domains: selection of study groups, comparability of the groups, and outcome ascertainment. A score of 0 to 4 is rated as unsatisfactory, 5 to 6 as satisfactory, 7 to 8 as good, and 9 to 10 as very good.

Statistical Analysis

All statistical analyses were performed using REVMAN version 5.3 software (Cochrane Collaboration, Oxford, United Kingdom). In addition, heterogeneity was quantitatively assessed using Higgin's I^2 index.³¹ In cases of substantial heterogeneity ($I^2 > 50\%$) in the pooled effects estimate, the random-effects model was used. The fixed-effects model was used in cases of low heterogeneity ($I^2 < 50\%$).³² Statistical significance of heterogeneity was reported as p^H . SMD and 95% confidence interval (CI) that account for the differences in the reported effect measures were used to measure the effect size of an outcome. Moreover, Cohen's method was used to interpret the calculated effect estimate, whereby an SMD of 0.2, 0.5, and 0.8 was equated to small, medium, and large, respectively.³³ A P value less than .05 was considered statistically significant. A sensitivity analysis was conducted to evaluate the influence of each study on the overall effect size using the leave-one-out method. The interrater reliability was evaluated for both the included studies and risk of bias by means of Cohen's kappa. A kappa value of less than 0.00 was taken as poor strength of agreement, 0.00 to 0.20 as slight agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as substantial agreement, and 0.81 to 1.00 as perfect agreement.³⁴

Results

Study Selection and Data Synthesis

Overall, 369 studies were identified and independently screened for eligibility by 2 reviewers. A total of 352 studies were

excluded from the screening stage because 65 were reviews and 287 were not relevant to the topic of interest. The full texts of the remaining 17 studies were then assessed for eligibility, and a total of 5 studies were excluded owing to their study design. In the excluded studies, individuals with asthma were not grouped as either lean or obese. In addition, 6 studies were excluded due to the reported T-helper cells subtypes other than T_H1 and T_H2. One study was also excluded owing to limited data values of effect measures reported,²¹ and only 5 studies^{20,22,23,35,36} met the inclusion criteria as shown in Figure 1 (overall agreement 99.73%, kappa = 0.89). The interrater agreement in the study selection process was perfect. The meta-analysis was split into 2 major comparisons, one which compared T_H1 and T_H2 functions in lean people with asthma vs controls, whereas the other focused on lean vs obese people with asthma.

Characteristics of Included Studies

All included studies were published in peer-reviewed journals between 2012 and 2016, and the detailed study-level characteristic features are described in Table 1. Briefly, all studies were cross-sectional studies involving a total of 482 participants with an age range of 7–18 years from United States and Mexico. Of these, 109 were controls and 373 had asthma, of which 190 were lean and 185 were obese. The reported cases of asthma were based on the

physician's diagnosis and medical electronic records. Obesity was defined as having a body mass index (BMI) greater than the 95th percentile for age and sex, whereas lean was defined as having a BMI less than the 85th percentile.³⁷ For the participants of this study whose average age was approximately 9 years, obesity was defined as BMI greater than 21.1 kg/m² and lean as BMI less than 18.6 kg/m². However, for 15-year-old participants, obesity was defined as BMI greater than 26.8 kg/m² and lean as BMI less than 23.4 kg/m².

Quality Assessment

All included studies were of good quality and had a median score range of 7 (6–7) out of a possible score of 10 (eTable 1). Four of the studies were rated as good^{20,22,35,36} and the remainder as satisfactory.²³ Briefly, included studies had a selection median of 3 (3–4) of possible 5 stars (overall agreement 100%, kappa = 1), comparability median of 2 (0–2) of possible 2 stars (overall agreement 70%, kappa = 0.6), and outcome ascertainment median of 2 (2–3) of 3 possible stars (overall agreement 100%, kappa = 1).

Publication Bias

Potential publication bias was explored using visual inspection of funnel plots. However, owing to lower number of studies than recommended, we could not effectively assess publication bias

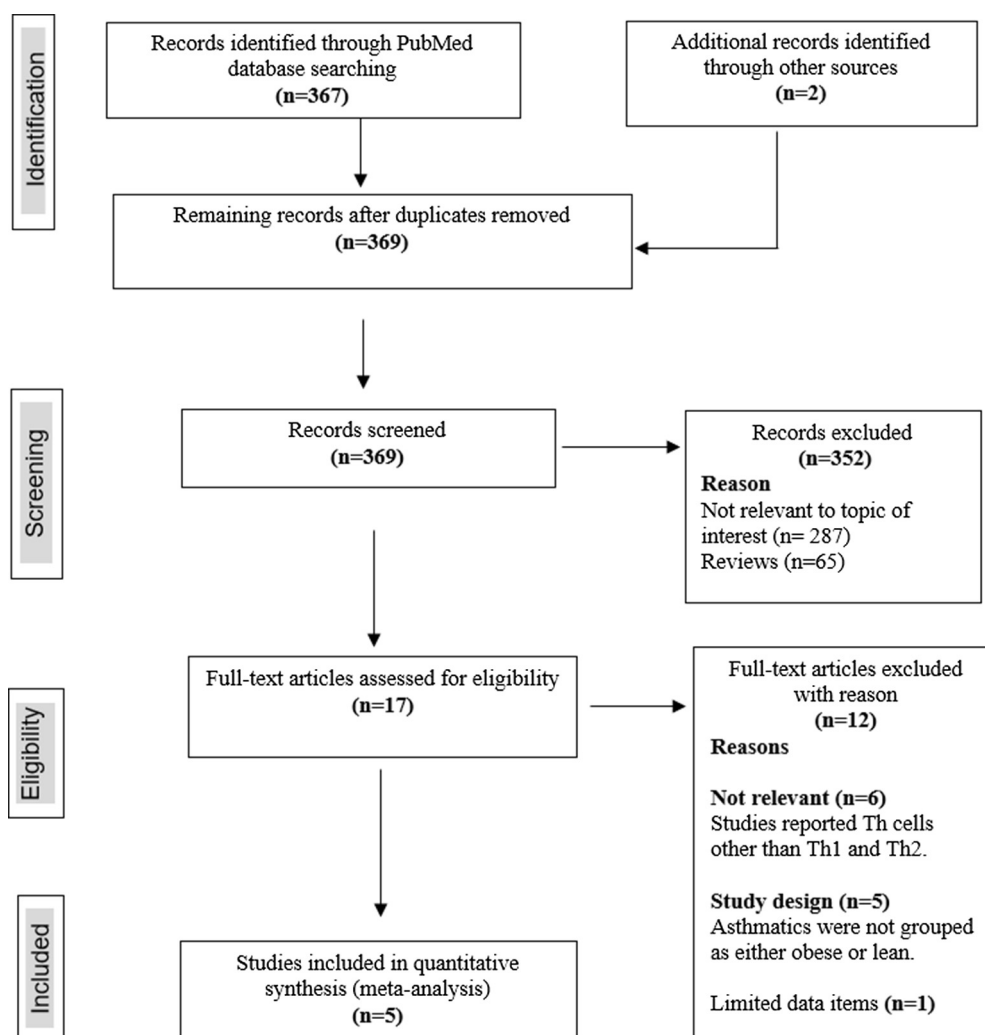


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating the study selection process.

Table 1Characteristics of Included Studies on T_H1/2 Cell Function in Obesity-Related Asthma in Children (n = 5)

Study	Country	Study design	Study size	Asthma diagnosis	BMI (kg/m ²)	Age (y)	T _H cell effect measures	Main findings
Rastogi et al ²⁰	United States	Cross-sectional	90 participants (30 lean people with asthma; 30 obese people with asthma and 30 controls)	Physician diagnosis based on the NAEPP guidelines	Obese people with asthma (28.4) Lean people with asthma (17.3)	9.23 ± 1.3	Serum T _H 1 cytokines IL-6, TNF- α , and IFN- γ and Serum T _H 2 cytokines (IL-4, IL-5, and IL-13).	Pediatric obesity-associated asthma is marked by T _H 1 and not T _H 2 polarization. In addition, poor pulmonary function is associated with increased T _H 1 cytokines in obese people with asthma.
Youssef et al ³⁶	Egypt	Cross-sectional	70 participants (25 lean people with asthma; 25 obese people with asthma and 20 controls)	Physician diagnosis based on GINA guidelines	Obese people with asthma (25.1) Lean people with asthma (18.6)	8.61 ± 2.8	Serum T _H 1 cytokine (IFN- γ) and T _H 2 cytokine (IL-4).	Obesity-associated asthma in children is characterized by T _H 1 and not T _H 2 polarization. Moreover, elevated levels of IFN- γ in obese people with asthma were associated with poor pulmonary function and disease severity.
Sanchez-Zauco et al ²³	Mexico	Cross-sectional	65 estimated participants (23 lean people with asthma; 19 obese people with asthma and 23 controls)	Physician diagnosis	Obese people with asthma (23.9) Lean people with asthma (17.6)	9.17	Serum T _H 1 cytokines (IL-2, IFN- γ , and TNF- α) and Serum T _H 2 cytokines (IL-4 and IL-10).	Obese people with asthma have decreased T _H 1-mediated immune response when compared with lean people with asthma and controls. In addition, T _H 2 cytokines are increased in lean people with asthma when compared with obese people with asthma and controls.
Rastogi et al ²²	United States	Cross-sectional	114 participants (39 lean people with asthma; 39 obese people with asthma and 36 controls)	Physician diagnosis and medical records	Obese people with asthma (33.2) Lean people with asthma (22.2)	15.9 ± 1.7	Serum T _H 1 cytokines (IL-2, IL-6, TNF- α and IFN- γ) and Serum T _H 2 cytokines (IL-4, IL-10, and IL-13).	T _H 1/2 cytokine ratio is higher in obese people with asthma when compared with lean people with asthma. Moreover, the high T _H 1/2 ratio directly correlated with metabolic abnormalities and poor pulmonary function.
Lautenbacher et al ³⁵	United States	Cross-sectional	143 participants (71 lean people with asthma and 72 obese people with asthma)	Physician diagnosis and medical records	Not reported	(7–18)	Serum T _H 1 cytokines (IFN- γ , TNF, IL-6, and IL-8) and Serum T _H 2 cytokines (IL-4, IL-5 and IL-13).	T _H 1 cytokines are increased in obese people with asthma vs lean people with asthma. In addition, increased T _H 1 function is associated with poor pulmonary function. T _H 2 cytokines are comparable across all 3 groups except for IL-13, which is high among lean people with asthma.

Abbreviations: BMI, body mass index; GINA, Global Initiative for Asthma; IL, interleukin; IFN, interferon; NAEPP, National Asthma Education and Prevention Program; T_H, T-helper; TNF, tumor necrosis factor.

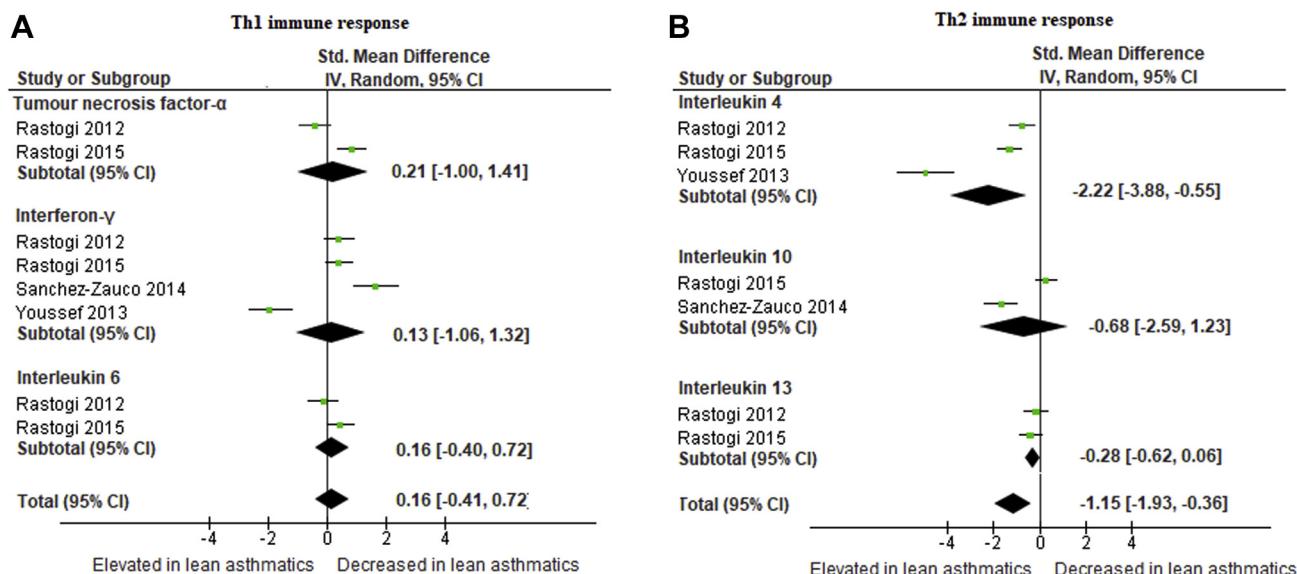


Figure 2. A comparison of standardized mean difference of T_H1 - and T_H2 -mediated responses between lean people with asthma and healthy controls. 95% CI, 95% confidence interval; T_H1 , T-helper 1; T_H2 , T-helper 2.

(eFig 1). Therefore, there may be potential publication bias among the included studies.

$T_H1/2$ Immune Responses in Lean People With Asthma

Overall pooled estimates revealed a T_H1 -weighted imbalance in lean people with asthma compared with the controls without asthma (SMD: 0.16 [95% CI: -0.41, 0.72]; $I^2 = 89\%$; $p^H < .001$) (Fig 2A). Owing to substantial levels of statistical heterogeneity in the reported effect estimate, we performed a subgroup analysis to

explore sources of heterogeneity based on the reported effect measures of T_H1 response. The test for subgroup differences revealed no significant subgroup effect ($P = 1.00$) (eTable 2), suggesting that the observed differences in T_H1 immune response are not modified by varying effect measures reported. However, the pooled estimates support a T_H2 weighted response in lean children with asthma compared with controls (SMD: -1.15 [95% CI: -1.93, -0.36]; $I^2 = 93\%$; $p^H < .001$) (Fig 2B). Nonetheless, due to high statistical heterogeneity among the included studies and differences in the reported effect measures of the T_H2 responses, we

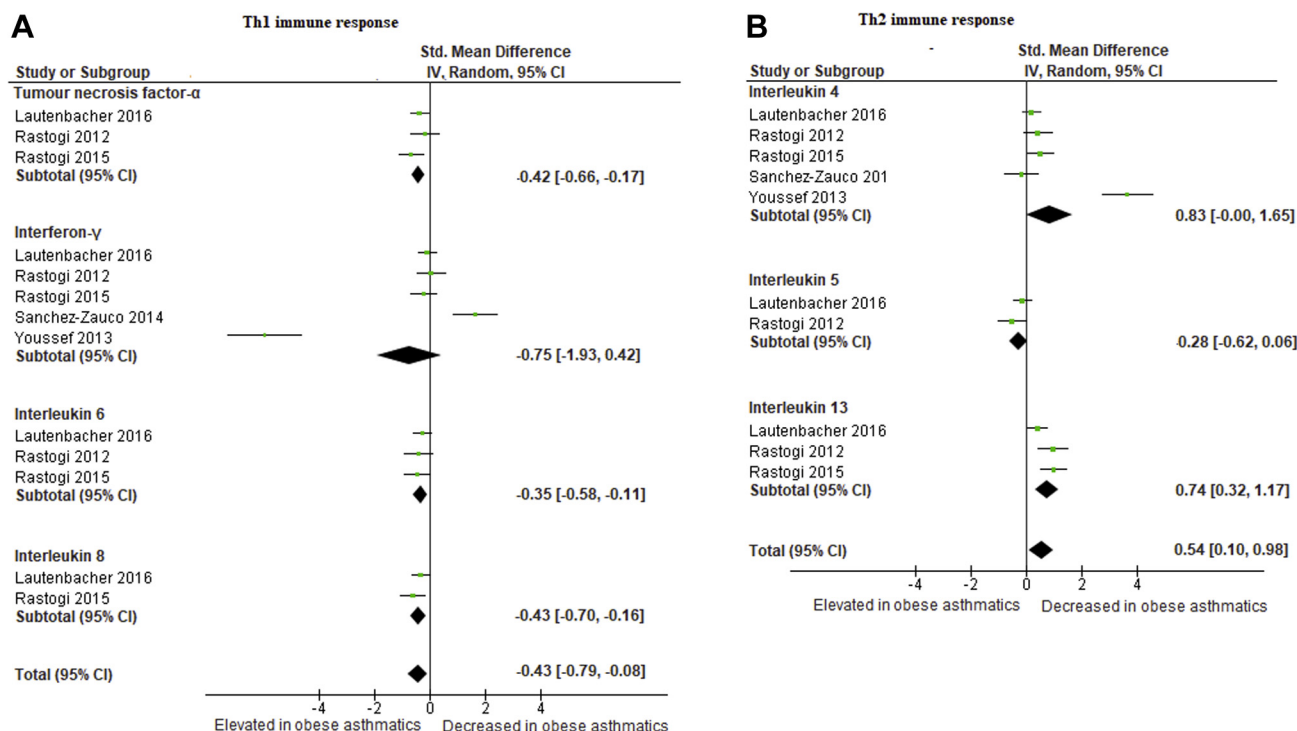


Figure 3. A comparison of standardized mean difference of T_H1 - and T_H2 -mediated responses between lean and obese people with asthma. 95% CI, 95% confidence interval; T_H1 , T-helper 1; T_H2 , T-helper 2.

performed a subgroup analysis based on the reported effect measures of T_H2 function.

Subgroup analysis of T_H2 immune response

The test for subgroup differences revealed a statistically significant subgroup effect ($P = .08$) (eTable 2). Thus, the different cytokines assessed as effect measures modified the overall effect of T_H2 immune response in lean people with asthma in comparison with controls. However, there were substantial levels of unexplained heterogeneity between included studies ($I^2 = 60.6\%$). Interestingly, there was a large effect size in IL-4 levels between lean people with asthma and controls (SMD: -2.22 [95% CI: $-3.88, -0.55$]; $I^2 = 95\%$; $p^H < .001$). Moreover, IL-13 levels were higher in lean people with asthma compared to controls (SMD: -0.28 [95% CI: $-0.62, 0.06$]; $I^2 = 0\%$; $p^H = .50$), and there was a medium effect size in IL-10 levels (SMD: -0.68 [95% CI: $-2.59, 1.23$]; $I^2 = 95\%$; $p^H < .001$).

Obesity-Related Asthma Is Characterized by T_H1 and Not T_H2 Polarization

Interestingly, unlike in the lean counterparts, immune responses in obese individuals with asthma are T_H1 weighted. The pooled estimates revealed that T_H1 cytokine levels are increased in obese people with asthma compared to lean people with asthma (SMD: -0.43 [95% CI: $-0.79, -0.08$], $I^2 = 88\%$; $p^H < .001$) (Fig 3A). However, pooled estimates of T_H2 immune-mediated responses were decreased in obese individuals with asthma compared to lean people with asthma (SMD: 0.54 [95% CI: $0.10, 0.98$]; $I^2 = 89\%$; $p^H < .001$) (Fig 3B). Nonetheless, due to substantial statistical heterogeneity, we performed a subgroup analysis based on the reported effect measures.

Subgroup analysis of T_H2 -Mediated immune response

The test for subgroup differences revealed a statistically significant subgroup effect ($P < .001$) with substantial levels of unexplained heterogeneity ($I^2 = 87.7\%$) (eTable 3). Pooled estimates of IL-4 and IL-13 levels were lower in obese people with asthma compared with lean people with asthma (SMD: 0.83 [95% CI: $0.00, 1.65$]; $I^2 = 92\%$; $p^H = .44$) and (SMD: 0.74 [95% CI: $0.32, 1.17$]; $I^2 = 64\%$; $p^H = .06$), respectively. In contrast, IL-5 levels were higher in obese people with asthma vs lean counterparts (SMD: -0.28 [95% CI: $-0.62, 0.06$]; $I^2 = 27\%$; $p^H = .24$).

Sensitivity Analysis

To investigate the levels of high unexplained sources of heterogeneity and to ascertain whether our findings were influenced by any single study, we performed a sensitivity analysis based on the guidelines followed to diagnose asthma (eTable 4). Heterogeneity among the included studies remained high in both reported outcomes involving lean and obese people with asthma. We repeated the meta-analysis by leaving out the study by Youssef et al.³⁶ due to its peculiarly large effect size in the reported outcomes. The findings remained robust except for the magnitude of T_H2 immune response, which changed from a medium (0.54 [0.10, 0.98]) to a small (0.29 [$-0.02, 0.59$]) effect size (eTable 4).

Discussion

The primary aim of this meta-analysis was to determine whether obesity alters T_H1 and T_H2 immune responses in children with asthma. As expected, the pooled effect estimates revealed increased T_H2 -mediated immune responses in lean people with asthma. However, in obesity-related asthma, there is polarization toward T_H1 immune response, which is associated with poor pulmonary function.^{20,22,35} Therefore, the overall findings from this meta-analysis suggest that obesity, although not unique to asthma,

aggravates T_H1 -mediated immune responses in obesity-related asthma.

T-helper cells are involved in the initiation and mediation of airway inflammation in asthma,^{11,12} by exacerbating cytokine release and action. Notably, cytokines play a pivotal role in generating a cytokine milieu that promotes the differentiation of naive T-helper cells into T_H2 cells.² As a consequence, T_H2 effector responses are aggravated coupled with increased secretion of cytokines such as IL-4, IL-5, and IL-13. Our findings revealed that both IL-4 and IL-13 levels were increased in lean people with asthma compared with both controls and obese people with asthma. Interestingly, IL-4 and IL-13 are central in mediating T_H2 immune responses and also share a common receptor that orchestrates B-cell activation and IgE antibody secretion.^{38,39} Moreover, IL-13 is involved in airway inflammation and obstruction by activating proinflammatory macrophages and increasing mucus production.⁴⁰ Overall, these findings are supporting evidence of T_H2 -mediated immune response in lean children with asthma.

In our previous work, we reported that in the context of T-helper cells, obesity-induced inflammation is mediated by increased T_H1 and T_H17 responses coupled with decreased T_H2 and regulatory T cells.⁴¹ These findings prompt us to postulate that obesity-related asthma may be a different entity of this disease because obesity is a low-grade inflammatory state characterized by increased adiposity and activation of various inflammatory pathways.^{42,43} As such, increased activation and release of proinflammatory cytokines and adipokines promotes systemic inflammation, which has been linked to hypersensitivity reactions.^{44,45} The meta-analysis revealed that obese individuals with asthma have increased T_H1 -mediated immune response.

Furthermore, obesity worsens the severity of asthma in children, in part by increasing IL-5 and eosinophil-mediated inflammation as previously reported.⁴⁶ IL-5 signaling can promote IL-4–induced B-cell activation and class switch to IgE-synthesizing plasma cells, resulting in marked increase in serum IgE levels and activation of eosinophils.^{47,48} In fact, elevated levels of IgE promote the activation of eosinophils through increased IgE receptor signaling^{48,49} on their cell surface subsequent to eosinophilia, thus highlighting the direct association between IL-5 and IgE levels in asthma⁵⁰ and their association with poor pulmonary function. Interestingly, in this study, the levels of IL-5 were higher in obese people with asthma than in lean counterparts. Therefore, we postulate that therapies targeting IL-5 activity may be less effective if the therapeutic doses used in obese people with asthma are similar to those prescribed for lean people with asthma. Collectively, these findings suggest that, although obesity-related asthma is characterized by T_H1 polarization, the levels of IL-5 are still increased. Therefore, therapies that inhibit IL-5 activity, such as mepolizumab combined with corticosteroids, which reduce T-cell activation while promoting the differentiation of regulatory T cells,⁵¹ maybe of therapeutic benefit and improve the response to treatment in obese people with asthma. Nevertheless, beyond the T_H1/T_H2 paradigm, other mechanisms involving additional T-cell subsets, such as CD8, T_H9 , T_H17 , T_H22 , and follicular T-helper cell subsets have to be studied in detail for their role in asthma pathogenesis in obese children, as reviewed elsewhere.^{51,52}

In addition, exacerbated inflammation in obese people with asthma has also been attributed to increased levels of leptin and TNF- α which were directly associated with enhanced activation of eosinophils in these patients.⁵³ Likewise, low levels of vitamin D concomitant to increased risk of respiratory infections in obese children with asthma have also been described.¹⁵ This may in part be attributed to impaired immunomodulatory effects of vitamin D on $T_H1/2$ and T_H17 immune responses.^{54,55} In addition to these factors, asthma outcomes are significantly influenced by socioeconomic distal factors. For instance, poor communities are most likely to have unhealthy residential environments,⁵⁶ which

together with genetics and wheezing episodes at preschool age⁵⁷ predisposes these children to develop asthma. Moreover, these societies are associated with high levels of stress, violence, and poor access to medical care, which increases morbidities.⁵⁶ Obesity-related asthma, however, is more driven by increased sedentary lifestyle and unhealthy eating that are most prevalent in developed countries.⁵⁸ Congruent to this, 60% of the included studies were from those with high income,^{20,22,35} and the remaining studies were from low- to middle-income countries.^{23,36}

The limitations of the current review include lack of standardization of asthma diagnosis, which was based on physician diagnosis and electronic records. This was a challenge because the approaches used potentially varied significantly, making it difficult to assess the validity of studies and to compare their findings. Moreover, people with asthma were generally grouped and not categorized based on their immunologic phenotypes (eosinophilic or noneosinophilic). This was a major limitation because different asthma subtypes present with unique immunologic features. Together with differences in disease duration among the participants, the heterogeneous nature of asthma and reported T_H2 effect measures, which were pooled cytokines with antagonistic effect, may potentially be the source of unexplained heterogeneity among the included studies, particularly in the analysis between lean and obese people with asthma. Finally, critical population features, such as social and economic demographics, which heavily influence the interaction between obesity and asthma in children were not reported in the included studies. Ethnicity was reported in 3 of the included studies,^{20,22,35} which involved an approximately equal number of Hispanics and African American children. The remaining 2 studies^{23,36} did not report on this aspect, and this limits the generalizability of our findings. However, our study highlights the evidence gap that needs to be explored to better understand the disease pathology in white people because they may not be represented in these patient cohorts.

Despite these limitations, our study has significant strengths. First, and to the best of our knowledge, this is the first meta-analysis to explore the effect of obesity on T_H1 and T_H2 immune responses in children with asthma. This is of special interest to understand the T_H1/T_H2 paradigm in modulating an adaptive immune response, especially in relation to the development of metabolic complications, as recently reviewed.⁵⁹ Second, the study selection and quality assessment processes employed in this study were robust and comprehensive as indicated by high levels of interrater reliability. Moreover, the reported effect sizes were consistent and the sensitivity analysis demonstrated the robustness of the presented findings. Finally, the findings of this study provide insights into future asthma therapies to consider the impact of obesity on the immune response, which we have shown to be completely different when compared with the lean counterparts, despite sharing the same condition.

In conclusion, the evidence synthesized in this meta-analysis reveals that there are differences in immune responses mediated by T-helper cells in lean and obese children with asthma. In addition, although not unique to asthma, obesity polarizes the immune response toward T_H1 rather than the classical T_H2 . Therefore, asthma therapies that particularly target immune responses should consider the underlying obese state of these patients for an effective treatment outcome.

Supplementary Data

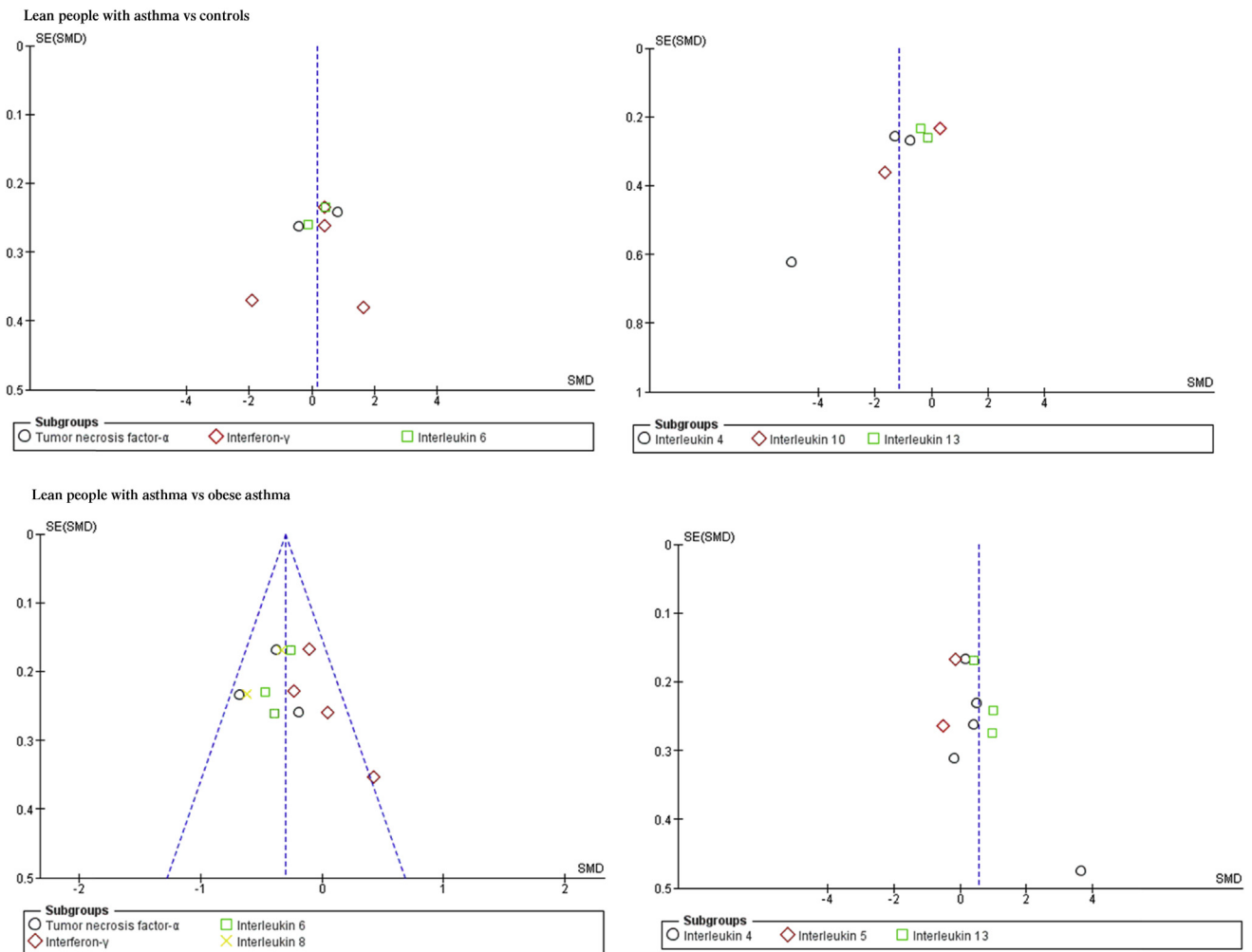
Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janai.2020.06.020>.

References

- World Health Organization. Noncommunicable diseases country profiles 2018. Available at: <https://apps.who.int/iris/handle/10665/274512>. Accessed February 01, 2020.
- Borish L. The immunology of asthma: asthma phenotypes and their implications for personalized treatment. *Ann Allergy Asthma Immunol*. 2016;117(2):108–114.
- National Institute of Health. *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3*. 2017. Available at: <http://www.globalasthma-report.org/>. Accessed February 01, 2020.
- World Health Organization. The Global Asthma Report 2018. Available at: <http://globalasthma-report.org/Global%20Asthma%20Report%202018.pdf>. Accessed February 01, 2020.
- Khaltaev N, Axelrod S. Chronic respiratory diseases global mortality trends, treatment guidelines, life style modifications, and air pollution: preliminary analysis. *J Thorac Dis*. 2019;11(6):2643–2655.
- Kankaanranta H, Kauppi P, Tuomisto LE, Ilmarinen P. Emerging comorbidities in adult asthma: risks, clinical associations, and mechanisms. *Mediators Inflamm*. 2016;2016:3690628.
- Elizondo-Montemayor L, Gonzalez-Gil AM, Tamez-Rivera O, et al. Association between Irisin, hs-CRP, and metabolic status in children and adolescents with type 2 diabetes mellitus. *Mediators Inflamm*. 2019;2019:6737318.
- Cvejaska-Cholakovska V, Kocova M, Velikj-Stefanovska V, Vlashki E. The association between asthma and obesity in children - inflammatory and mechanical factors. *Open Access Maced J Med Sci*. 2019;7(8):1314–1319.
- Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Respir Crit Care Med*. 2018;197(1):22–37.
- Lambrech BN, Hammad H, Fahy JV. The cytokines of asthma. *Immunity*. 2019;50(4):975–991.
- Azzawi M, Bradley B, Jeffery PK, et al. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. *Am Rev Respir Dis*. 1990;142(6 Pt 1):1407–1413.
- Robinson DS, Hamid Q, Ying S, et al. Predominant $TH2$ -like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med*. 1992;326(5):298–304.
- Bagnasco D, Caminati M, Ferrando M, et al. Anti-IL-5 and IL-5RA: efficacy and safety of new therapeutic strategies in severe uncontrolled asthma. *Biomed Res Int*. 2018;2018:5698212.
- Bhatnagar P, Guleria R, Kukreti R. Variable therapeutic response in asthma: a genetic perspective. *Per Med*. 2006;3(1):61–78.
- Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol*. 2018;141(4):1169–1179.
- Holguin F, Bleeker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol*. 2011;127(6):1486–1493.e2.
- Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med*. 2007;101(11):2240–2247.
- Pacifico L, Di Renzo L, Anania C, et al. Increased T-helper interferon-gamma-secreting cells in obese children. *Eur J Endocrinol*. 2006;154(5):691–697.
- Jensen ME, Collins CE, Gibson PG, Wood LG. The obesity phenotype in children with asthma. *Paediatr Respir Rev*. 2011;12(3):152–159.
- Rastogi D, Canfield SM, Andrade A, et al. Obesity-associated asthma in children: a distinct entity. *Chest*. 2012;141(4):895–905.
- Magrone T, Simone M, Altamura M, Munno I. Characterization of the immune inflammatory profile in obese asthmatic children. *Endocr Metab Immune Disord Drug Targets*. 2014;14(3):187–195.
- Rastogi D, Fraser S, Oh J, et al. Inflammation, metabolic dysregulation, and pulmonary function among obese urban adolescents with asthma. *Am J Respir Crit Care Med*. 2015;191(2):149–160.
- Sánchez-Zaucos N, Del Río-Navarro B, Gallardo-Casas C, et al. High expression of Toll-like receptors 2 and 9 and $Th1/Th2$ cytokines profile in obese asthmatic children. *Allergy Asthma Proc*. 2014;35(3):34–41.
- Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis. *Eur Respir J*. 2016;48(4):1063–1073.
- Liu P-C, Kieckhefer GM, Gau B-S. A systematic review of the association between obesity and asthma in children. *J Adv Nurs*. 2013;69(7):1446–1465.
- Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respir Med*. 2013;107(9):1287–1300.
- Moldoveanu B, Otmishi P, Jani P, et al. Inflammatory mechanisms in the lung. *J Inflamm Res*. 2009;2:1–11.
- Bellantini JA, Settipane RA. Unraveling the conundrum of asthma phenotypes and endotypes. *Allergy Asthma Proc*. 2018;39(1):1–2.
- Balslem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401–406.
- Newcastle-Ottawa scale adapted for cross-sectional studies. Available at: <https://wellcomeopenresearch.s3.amazonaws.com/supplementary/13880/ea30a2fb-a15a-44a9-b35e-5f0914db80b3.docx>. Accessed May 9, 2020.
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
- Schroll JB, Moustgaard R, Gøtzsche PC. Dealing with substantial heterogeneity in Cochrane reviews. Cross-sectional study. *BMC Med Res Methodol*. 2011;11:22.
- Sullivan G, Feinn R. Using effect size—or why the P value is not enough. *J Grad Med Educ*. 2012;4(3):279–282.

34. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–174.
35. Lautenbacher LA, Jariwala SP, Markowitz ME, Rastogi D. Vitamin D and pulmonary function in obese asthmatic children. *Pediatr Pulmonol*. 2016;51(12):1276–1283.
36. Youssef DM, Elbehidy RM, Shokry DM, Elbehidy EM. The influence of leptin on Th1/Th2 balance in obese children with asthma. *J Bras Pneumol*. 2013;39(5):562–568.
37. Kuczmarski RJ, Ogden CL, Guo S, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11*. 2002;246:1–190.
38. Chomarat P, Banchereau J. Interleukin-4 and interleukin-13: their similarities and discrepancies. *Int Rev Immunol*. 1998;17(1–4):1–52.
39. Bao K, Reinhardt R. The differential expression of IL-4 and IL-13 and its impact on type-2 Immunity. *Cytokine*. 2015;75(1):25–37.
40. Gour N, Wills-Karp M. IL-4 and IL-13 signaling in allergic airway disease. *Cytokine*. 2015;75(1):68–78.
41. Nyambuya TM, Dlodla PV, Mxinwa V, Nkambule BB. Obesity-induced inflammation and insulin resistance: a mini-review on T-cells. *Metab Open*. 2019;3:100015.
42. Deiluiis J, Shah Z, Shah N, et al. Visceral adipose inflammation in obesity is associated with critical alterations in Tregulatory cell numbers. *PLoS One*. 2011;6(1), e16376.
43. Priceman SJ, Kujawski M, Shen S, et al. Regulation of adipose tissue T cell subsets by Stat3 is crucial for diet-induced obesity and insulin resistance. *Proc Natl Acad Sci USA*. 2013;110(32):13079–13084.
44. Pence BD, Lowder TW, Keylock KT, et al. Relationship between systemic inflammation and delayed-type hypersensitivity response to Candida antigen in older adults. *PLoS One*. 2012;7(5):e36403.
45. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008;454(7203):445–454.
46. Kouro T, Takatsu K. IL-5- and eosinophil-mediated inflammation: from discovery to therapy. *Int Immunol*. 2009;21(12):1303–1309.
47. Purkerson JM, Isakson PC. Interleukin 5 (IL-5) provides a signal that is required in addition to IL-4 for isotype switching to immunoglobulin (Ig) G1 and IgE. *J Exp Med*. 1992;175(4):973–982.
48. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? *Respir Res*. 2018;19(1):113.
49. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S73–S80.
50. Crestani E, Lohman IC, Guerra S, Wright AL, Halonen M. Association of IL-5 cytokine production and in vivo IgE levels in infants and parents. *J Allergy Clin Immunol*. 2007;120(4):820–826.
51. Robinson DS. The role of the T cell in asthma. *J Allergy Clin Immunol*. 2010;126(6):1081–1091. quiz 1092–1093.
52. Vock C, Hauber H, Wegmann M. The other T helper cells in asthma pathogenesis. *J Allergy (Cairo)*. 2010;2010:519298.
53. Grotta MB, Squebola-Cola DM, Toro AADC, et al. Obesity increases eosinophil activity in asthmatic children and adolescents. *BMC Pulm Med*. 2013;13:39.
54. Zhang H, Shih DQ, Zhang X. Mechanisms underlying effects of 1, 25-dihydroxyvitamin D3 on the th17 cells. *Eur J Microbiol Immunol (Bp)*. 2013;3(4):237–240.
55. Sloka S, Silva C, Wang J, Yong VW. Predominance of Th2 polarization by vitamin D through a STAT6-dependent mechanism. *J Neuroinflammation*. 2011;8:56.
56. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics*. 2009;123 Suppl 3(Suppl 3):S174–S184.
57. Moustaki M, Loukou I, Tsabouri S, Douros K. The role of sensitization to allergen in asthma prediction and prevention. *Front Pediatr*. 2017;5:166.
58. Lang JE. Obesity, nutrition, and asthma in children. *Pediatr Allergy Immunol Pulmonol*. 2012;25(2):64–75.
59. Mahlangu T, Dlodla PV, Nyambuya TM, et al. A systematic review on the functional role of Th1/Th2 cytokines in type 2 diabetes and related metabolic complications. *Cytokine*. 2020;126:154892.

Supplementary Data



eFigure 1. Funnel plots reporting publication bias. SMD, standardized mean difference.

eTable 1

Quality Assessment of Included Studies Using the Modified Newcastle–Ottawa Scale for Cross-Sectional Studies (n = 5)

Study and year	Selection					Comparability		Outcome			Total quality score	Rating
	Representativeness of the sample	Selected group of users	Sample size	Diagnose	Average	Confounders	Score	Assessment of methods	Statistical test	Average		
Rastogi, 2012	0	0	0	***	3	**	2	*	*	2	7	Good
Lautenbacher, 2016	0	0	0	***	3	**	2	*	*	2	7	Good
Rastogi, 2015	0	0	0	***	3	**	2	*	*	2	7	Good
Youssef, 2013	0	*	0	***	4	0	0	**	*	3	7	Good
Sanchez-Zauco, 2014	0	*	0	***	4	0	0	*	*	2	6	Satisfactory

* represents the number of scores awarded per domain.

eTable 2Forest Plot Text Data for T_H1/T_H2 Immune Responses in Lean Individuals With Asthma

Outcome	Effect measure	Study	Control			Lean individuals with asthma			Weight	Random effects		I ² , p ^H
			Mean	SD	Total	Mean	SD	Total		SMD [95% CI]		
T _H 1 immune response	Tumor necrosis factor- α	Rastogi, 2012	1.01	0.33	30	1.21	0.59	30	12.7%	-0.41 [-0.92, 0.10]		
		Rastogi, 2015	0.65	0.43	36	0.29	0.44	39	12.9%	0.82 [0.35, 1.29]		
		Subtotal			66			69	25.6%	0.21 [-1.00, 1.41]		92%, <.001
	Interferon gamma	Rastogi, 2012	1.1	0.66	30	0.72	1.15	30	12.7%	0.40 [-0.11, 0.91]		
		Rastogi, 2015	0.64	1.01	36	0.27	0.81	39	13.0%	0.40 [-0.06, 0.86]		
		Sanchez-Zauco, 2014	25.7	7.8	23	13.0	7.4	16	11.4%	1.63 [0.89, 2.37]		
		Youssef, 2013	20.0	9.5	20	40.8	11.3	25	11.5%	-1.94 [-2.66, -1.22]		
		Subtotal			109			110	48.6%	0.13 [-1.06, 1.32]		94%, <.001
	Interleukin 6	Rastogi, 2012	0.88	1.1	30	1.03	1.11	30	12.7%	-0.13 [-0.64, 0.37]		
		Rastogi, 2015	0.03	0.59	36	-0.19	0.39	39	13.0%	0.44 [-0.02, 0.90]		
		Subtotal			66			69	25.7%	0.16 [-0.40, 0.72]		63%, .10
		Total			241			248	100%	0.16 [-0.41, 0.72]		89%, <.001 (P = 1.00), 0%
		Test for subgroup differences										
T _H 2 immune response	Interleukin 4	Rastogi, 2012	-0.27	0.82	30	0.48	1.11	30	14.8%	-0.76 [-1.28, -0.23]		
		Rastogi, 2015	1.1	0.5	36	1.76	0.5	39	14.9%	-1.31 [-1.81, -0.81]		
		Youssef, 2013	10.0	2.2	20	89.0	20.9	25	11.4%	-4.95 [-6.17, -3.73]		
		Subtotal			86			94	41.1%	-2.22 [-3.88, -0.55]		95%, <.001
	Interleukin 10	Rastogi, 2015	0.21	0.71	36	0.04	0.49	39	15.0%	0.28 [-0.18, 0.73]		
		Sanchez-Zauco, 2014	0.3	0.3	20	14.9	11.7	23	14.0%	-1.67 [-2.38, -0.97]		
		Subtotal			56			62	29.1%	-0.68 [-2.59, 1.23]		95%, <.001
	Interleukin 13	Rastogi, 2012	0.79	1.08	30	0.96	1.12	30	14.8%	-0.15 [-0.66, 0.35]		
		Rastogi, 2015	0.34	0.88	36	0.6	0.35	39	15.0%	-0.39 [-0.85, 0.07]		
		Subtotal			66			69	29.9%	-0.28 [-0.62, 0.06]		0%, .50
		Total			208			225	100.0%	-1.15 [-1.93, -0.36]		93%, <.001 (P = .08), I ² = 60.6%
		Test for subgroup differences										

Abbreviations: CI, confidence interval; T_H1, T-helper 1; T_H2, T-helper 2; SMD, standardized mean difference.

Bold values are the pooled effect size of the cytokine reported.

eTable 3Forest Plot Text Data for T_H1/T_H2 Immune Responses in Obese Individuals With Asthma

Outcome	Effect measure	Study	Lean individuals with asthma			Obese individuals with asthma			Weight	Random effects		I ² , p ^H		
			Mean	SD	Total	Mean	SD	Total		SMD [95% CI]				
T _H 1 immune response	Tumor necrosis factor-α	Lautenbacher, 2016	0.68	0.69	71	0.92	0.57	72	8.5%	−0.38 [−0.71, −0.05]		5%, .35		
		Rastogi, 2012	1.21	0.59	30	1.31	0.43	30	7.8%	−0.19 [−0.70, 0.32]				
		Rastogi, 2015	0.29	0.44	39	0.6	0.46	39	8.0%	−0.68 [−1.14, −0.22]				
		Subtotal			140			141	24.3%	−0.42 [−0.66, −0.17]				
	Interferon-γ	Lautenbacher, 2016	0.46	0.99	71	0.56	0.87	72	8.6%	−0.11 [−0.43, 0.22]		96%, <.001		
		Rastogi, 2012	0.72	1.15	30	0.68	0.85	30	7.8%	0.04 [−0.47, 0.55]				
		Rastogi, 2015	0.27	0.81	39	0.47	0.89	39	8.1%	−0.23 [−0.68, 0.21]				
		Sanchez-Zauco, 2014	13.0	7.4	16	4.2	1.3	17	6.3%	1.64 [0.84, 2.44]				
		Youssef, 2013	40.8	11.3	25	203.0	36.0	25	4.0%	−5.98 [−7.33, −4.64]				
	Interleukin 6	Subtotal			181			183	34.7%	−0.75 [−1.93, 0.42]		0%, .75		
		Lautenbacher, 2016	0.32	0.98	71	0.58	0.98	72	8.6%	−0.26 [−0.59, 0.07]				
		Rastogi, 2012	1.03	1.11	30	1.41	0.74	30	7.8%	−0.40 [−0.91, 0.11]				
		Rastogi, 2015	−0.19	0.39	39	0.05	0.6	39	8.0%	−0.47 [−0.92, −0.02]				
	Interleukin 8	Subtotal			140			141	24.4%	−0.35 [−0.58, −0.11]		2%, <.001		
		Lautenbacher, 2016	0.78	1.08	71	1.12	0.95	72	8.5%	−0.33 [−0.66, −0.00]				
		Rastogi, 2015	0.18	0.74	39	0.59	0.55	39	8.0%	−0.62 [−1.08, −0.17]				
		Subtotal			110			111	16.6%	−0.43 [−0.70, −0.16]				
	Test for subgroup differences	Total			571			576	100.0%	−0.43 [−0.79, −0.08]		88%, <.001		
		P = .89, I ² = 0%												
		T _H 2 immune response	Interleukin 4	Lautenbacher, 2016	0.51	0.77	71	0.38	0.77	72	10.9%	0.17 [−0.16, 0.50]		92%, <.001
				Rastogi, 2012	0.48	1.11	30	0.06	0.87	30	10.0%	0.42 [−0.10, 0.93]		
Rastogi, 2015				1.76	0.5	39	1.42	0.8	39	10.3%	0.50 [0.05, 0.96]			
Sanchez-Zauco, 2014				107.7	23.4	23	112.4	30.3	19	9.5%	−0.17 [−0.78, 0.44]			
Youssef, 2013				89.0	20.9	25	30.0	8.2	25	7.6%	3.66 [2.73, 4.59]			
Interleukin 5		Subtotal			188			185	48.3%	0.83 [−0.00, 1.65]		27%, .24		
		Lautenbacher, 2016	−0.4	0.68	71	−0.29	0.72	72	10.9%	−0.16 [−0.48, 0.17]				
		Rastogi, 2012	−0.11	1.05	30	0.4	0.87	30	10.0%	−0.52 [−1.04, −0.01]				
	Subtotal			101			102	20.8%	−0.28 [−0.62, 0.06]					
Interleukin 13	Lautenbacher, 2016	0.37	0.96	71	0.03	0.75	72	10.8%	0.39 [0.06, 0.72]		64%, .06			
	Rastogi, 2012	0.96	1.12	30	−0.03	0.89	30	9.9%	0.97 [0.43, 1.50]					
	Rastogi, 2015	0.6	0.35	39	0.1	0.62	39	10.2%	0.98 [0.51, 1.45]					
	Subtotal			140			141	30.9%	0.74 [0.32, 1.17]					
Test for subgroup differences	Total			429			428	100.0%	0.54 [0.10, 0.98]		89%, <.001			
	P < .001, I ² = 87.7%													

Abbreviations: CI, confidence interval; T_H1, T-helper 1; T_H2, T-helper 2; SMD, standardized mean difference.**eTable 4**Sensitivity Analysis of T_H1 and T_H2 Immune Responses in Obese Individuals With Asthma Based on the Guidelines Followed in Diagnosing Asthma

Outcomes	Asthma diagnosis guidelines followed	Number of studies	Omitted studies	SMD [95% CI]	I ² (%), p ^H value	Overall effect: Z (P value)
T _H 1 immune response	All	5 ^{20,22,23,35,36}	None	−0.43 [−0.79, −0.08]	88% (p ^H <.001)	2.37 (.02)
	NAEPP	1 ²⁰	4 ^{22,23,35,36}	−0.18 [−0.48, 0.11]	Not applicable	1.21 (.22)
	GINA	1 ³⁶	4 ^{20,22,23,35}	−5.98 [−7.33, −4.64]	Not applicable	8.74 (<.001)
	Unspecified	3 ^{22,23,35}	2 ^{20,36}	−0.25 [−0.51, 0.01]	73% (p ^H <.001)	1.88 (.06)
			After removal of Youssef et al, 2013 ³⁶	−0.24 [−0.45, −0.03]	65% (p ^H = .01)	2.26 (.02)
T _H 2 immune response	All	5 ^{20,22,23,35,36}	None	0.54 [0.10, 0.98]	89% (p ^H <.001)	2.42 (.02)
	NAEPP	1 ²⁰	4 ^{22,23,35,36}	0.28 [−0.56, 1.13]	Not applicable	0.66 (.51)
	GINA	1 ³⁶	4 ^{20,22,23,35}	3.66 [2.73, 4.59]	Not applicable	7.71 (<.001)
	Unspecified	3 ^{22,23,35}	2 ^{20,36}	0.29 [−0.03, 0.61]	74% (p ^H = .002)	1.75 (.08)
			After removal of Youssef et al ³⁶	0.29 [−0.02, 0.59]	77% (p ^H <.001)	1.85 (.06)

Abbreviations: CI, confidence interval; T_H1, T-helper 1; T_H2, T-helper 2; SMD, standardized mean difference.

eReferences

20. Rastogi D, Canfield SM, Andrade A, et al. Obesity-associated asthma in children: a distinct entity. *Chest*. 2012;141(4):895–905.
22. Rastogi D, Fraser S, Oh J, et al. Inflammation, metabolic dysregulation, and pulmonary function among obese urban adolescents with asthma. *Am J Respir Crit Care Med*. 2015;191(2):149–160.
23. Sánchez-Zauco N, Del Rio-Navarro B, Gallardo-Casas C, et al. High expression of Toll-like receptors 2 and 9 and Th1/Th2 cytokines profile in obese asthmatic children. *Allergy Asthma Proc*. 2014;35(3):34–41.
35. Lautenbacher LA, Jariwala SP, Markowitz ME, Rastogi D. Vitamin D and pulmonary function in obese asthmatic children. *Pediatr Pulmonol*. 2016;51(12):1276–1283.
36. Youssef DM, Elbehidy RM, Shokry DM, Elbehidy EM. The influence of leptin on Th1/Th2 balance in obese children with asthma. *J Bras Pneumol*. 2013;39(5):562–568.