2020

Obesity and Obstructive Airways Disease: Clinical Correlates and Therapeutic Considerations

John Magagna

Cali Loblundo

Raymond B. Penn

Deepak A. Deshpande

Ajay P. Nayak

Obesity and Obstructive Airways Disease: Clinical Correlates and Therapeutic Considerations

John Magagna, Cali Loblundo, Raymond B. Penn, Deepak A. Deshpande, Ajay P. Nayak

Center for Translational Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Jane & Leonard Korman Respiratory Institute, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA 19107

Correspondence:

Ajay P. Nayak, PhD, Center for Translational Medicine, Thomas Jefferson University Philadelphia, PA, USA 19107, Email: Ajay.Nayak@jefferson.edu

Deepak A. Deshpande, PhD, Center for Translational Medicine, Thomas Jefferson University Philadelphia, PA, USA 19107, Email: Deepak.Deshpande@jefferson.edu

Raymond B. Penn, PhD, Center for Translational Medicine, Thomas Jefferson University Philadelphia, PA, USA 19107, Email: Raymond.Penn@jefferson.edu

ABSTRACT:

Obese patients are more likely to suffer from severe asthma symptoms and less likely to be able to control them. In obese patients, there is evidence that shows decreased efficacy of inhaled corticosteroids and beta-2 adrenergic agonists, the core treatment options for achieving and maintaining asthma control. This may be due to mechanical reasons like decreased ventilation and medication delivery, but there are many more pathologies of obesity that interact with pathways of both asthma pathology and asthma control. This review explores the epidemiological significance of obesity, many physiological changes in patients with obesity, the physiological interactions of asthma and obesity in patients with both issues, and the therapeutic impacts of these interactions with asthma to find appropriate areas where new research is needed. More research to understand the mechanism of decreased inhaled corticosteroid and beta-2 adrenergic agonist efficacy is necessary to improve treatment efficacy and decrease morbidity and mortality in this population of patients with asthma.

The epidemiological significance of obesity

Obesity is a complex metabolic disorder that is defined as having a BMI >30 in adults or >95th percentile in children when accounting for age and sex.[cdc] Although BMI has been a convenient measure for stratifying risk groups within obesity, some refinements have been suggested. While, BMI is calculated by taking a person's weight relative to their height (kg/m^2), it fails to differentiate fat from muscle or account for anatomical fat distribution. Increases in subcutaneous fat, below the skin and in the extremities is less associated with negative health impacts than increases in visceral fat, located between abdominal organs.[Harvard] Using waist to hip ratios, abdominal circumference, and BMI will better approximate an individual's potential negative health impacts due to body fat.[Harvard]

In United States, obesity prevalence (in adults) has gradually increased from 33.7% (in 2007-08) to 39.6% (in 2015-16)[Hales] The 2017-2018 National Health and Nutrition Examination Survey (NHANES) estimated adult obesity prevalence in the US to be 42.4% with no significant difference by sex or age group.[cdc] Obesity-linked morbidity and mortality increase with its prevalence, however, not every demographic section is affected equally by the disorder. In 2017-2018 NHANES survey, Non-Hispanic black adults had the highest obesity prevalence at 49.6%.[CDC] Hispanic adults and non-Hispanic white adults prevalence are estimated at 44.8% and 42.2% respectively, while non-Hispanic Asians showed a much lower prevalence of 17.4%.[CDC] Possible explanations for this disparity include the social and economic reasons such as limited healthy nutrition options, accommodations for physical exercise, and healthcare accessiblity.[Petersen] Obesity in children is also growing more common with increasing morbidity. Prevalence in patients aged 2-19 has increased from 13.9% in data collected from 1999 and 2000 to 18.5% for data from 2015 and 2016 representing a 33% increase over 16 years.[Sanyaolu]

Obesity is a complex metabolic disorder with the capacity to affect all physiological systems and is commonly identified as a major contributor to cardiovascular diseases.[Pi-Sunyer] Obesity is also a major risk factor and modifier for other diseases. Complications of obesity include

diabetes, hypertension, heart disease, stroke, sleep apnea, fatty liver disease, gallstones, osteoarthritis, mental illness and some cancers.[CDC] Further, obesity can negatively impact mental health and quality of life through decreased mobility leading to a higher risk of social isolation and depression.[mayoclinic] Obesity in children also negatively impacts cardiovascular and mental health leading to similar increases in morbidity and mortality.[Sanyaolu] Thus, it is essential to understand the severity of obesity to enable mitigation of health risks it poses.

Obesity and multisystem physiological disruption

Obesity can disrupt distinct physiological processes and result in hypertension, hyperglycemia, hypertriglyceridemia, decreased HDL cholesterol, and increased visceral fat.[NIDDK] Increased fat deposition near and in organs can negatively affect organ functions. Excess hepatic fat deposition leads to dysfunction and increased amounts of damaging reactive oxygen species that can harm other areas like skeletal muscle and nervous tissue.[Gonzalez] Increased perirenal fat may result in hypertension.[Hall] Increased peripancreatic fat necrosis may be the explanation for the positive association between obesity and severe acute pancreatitis.[Kim] Lung function can be affected by fat deposition in several ways.

Many studies have emphasized a link between obesity and decreased lung function.[Forno,Lawson] In obese adults all lung volumes including FEV1, FVC, TLC, and RV are decreased.[Forno] This is consistent with a restrictive lung pathology where the work of breathing is increased and ventilation is decreased. Further, both obese adults and children show a decreased FEV1/FVC ratio with the reduction in children being >2 times that of adults independent of asthma status.[Forno] This is consistent with an obstructive lung pathology.

Increase in truncal fat and associated inflammatory disposition are the two major factors that contribute to compromised lung function in obesity, This may be due to both physical restriction of movement due to fat deposition on the chest wall and inflammatory pathways decreasing airway lumen diameter. Extra adipose tissue poses a mechanical obstruction by

increasing intrathoracic pressure by compressing the chest wall downward restricting lung filling. [Lawson] Abdominal adipose tissue opposes the diaphragm contraction leading to a further increase in intrathoracic pressure.[Lawson] Further, the obstructive lung pathology found by Forno et al. in obese patients may worsen lung function even more.

Obesity as a modifier of asthma

The increasing prevalence of obesity and its specific effects on respiratory health have raised questions on the ability of obesity to influence the pathophysiology of asthma. Obesity is a major risk factor for asthma.[Peters] Almost 60% of adults with severe asthma are obese.[Schatz] A 2010 CDC survey showed that obesity rate among adults with current asthma was 38.8% while the prevalence among adults without current asthma was just 26.8%.[cdcasthma] Obese patients are also more likely to have more severe symptoms and more difficulty controlling symptoms. Obese patients with asthma are hospitalized up to 250% more for an asthma exacerbation due to uncontrollable symptoms.[Rance] Mechanisms for more severe asthma in obese patients include restriction of ventilation, decreased physical activity, increased inflammation, and activation of free fatty acid receptors.[Mohanan, Lange] Most asthmatics with severe symptoms have atopic asthma which has a known pathophysiology driven by TH2 inflammation.[Peters] Some adipokines, especially leptin, have been shown to affect airway remodeling. [Sildelva] Increased leptin has a demonstrated association with increased asthma severity and prevalence in prepubescent boys and postpubescent women, but this association is not as strong in other populations.[Assad] Leptin also has positive associations with prevalence and severity of COPD, another obstructive lung pathology.[Assad] Though the mechanism is not yet clear it seems likely leptin worsens asthma's obstructive pathology. Adiponectin has shown a more complex relationship with asthma and lung function. It has been shown to be positively associated with lung function in healthy patients while having a negative association in COPD patients.[Assad] This suggests that adiponectin can have both proinflammatory and antiinflammatory effects that may be subject to certain physiologic conditions.[Assad] These inflammatory and metabolic changes have complex and far reaching

ramifications. The ventilation restriction and lack of physical activity can be largely addressed with weight loss and lifestyle modifications, but the inflammation pathway changes and airway remodeling in obese asthmatics may be effective pharmacologic targets for controlling symptoms. Obesity also varies in its effects on asthmatics based on the timing of asthma development and other epidemiologic factors. Early onset obese asthmatics (less than 12 yrs at asthma diagnosis) had more airway obstruction and bronchial hyperresponsiveness. [Holguin] This suggests that age related differences also play into differences in obese asthma severity and that slowing weight gain in childhood and adolescence is important. Similar racial disparities exist in asthma and obesity. Black children are more than twice as likely to have asthma and are 4 times more likely to be hospitalized for asthma symptoms. [akinbami,minorityhealth] Mechanisms for this link may include socioeconomic and environmental reasons such as exposure to allergens or tobacco smoke.[Barnes] This is likely relevant to the increased atopic asthma prevalence in inner cities.[Kakumanu] There is also a lack of studies on asthma associated genetics that include minorities in their studies.[Barnes, White] Studies inclusive of these populations could improve the effectiveness of current management regimens and strengthen understanding of etiological differences.

Another compounding issue is that obesity has also been shown to decrease the rate of nasomucociliary clearance.[IJMRHS] In atopic asthmatics this decrease in mucous clearance would make it more difficult to clear their triggering antigens and other pathogens. Atopic asthmatics make up a significant proportion of inner-city asthmatics where obesity prevalence and associated morbidity are high.[Kakumanu] This population has a large overlap with the ethnic minority populations that are more prone to obesity and asthma intensifying the severity of asthma in these patients even further.

Impact of obesity on therapeutic management of asthma

Asthma treatment is individualized based on clinical correlates and control of symptoms is often achievable using bronchodilators and inhaled/oral corticosteroids. The simplified

American Thoracic Society table below shows the medications available and an often used step up treatment model.

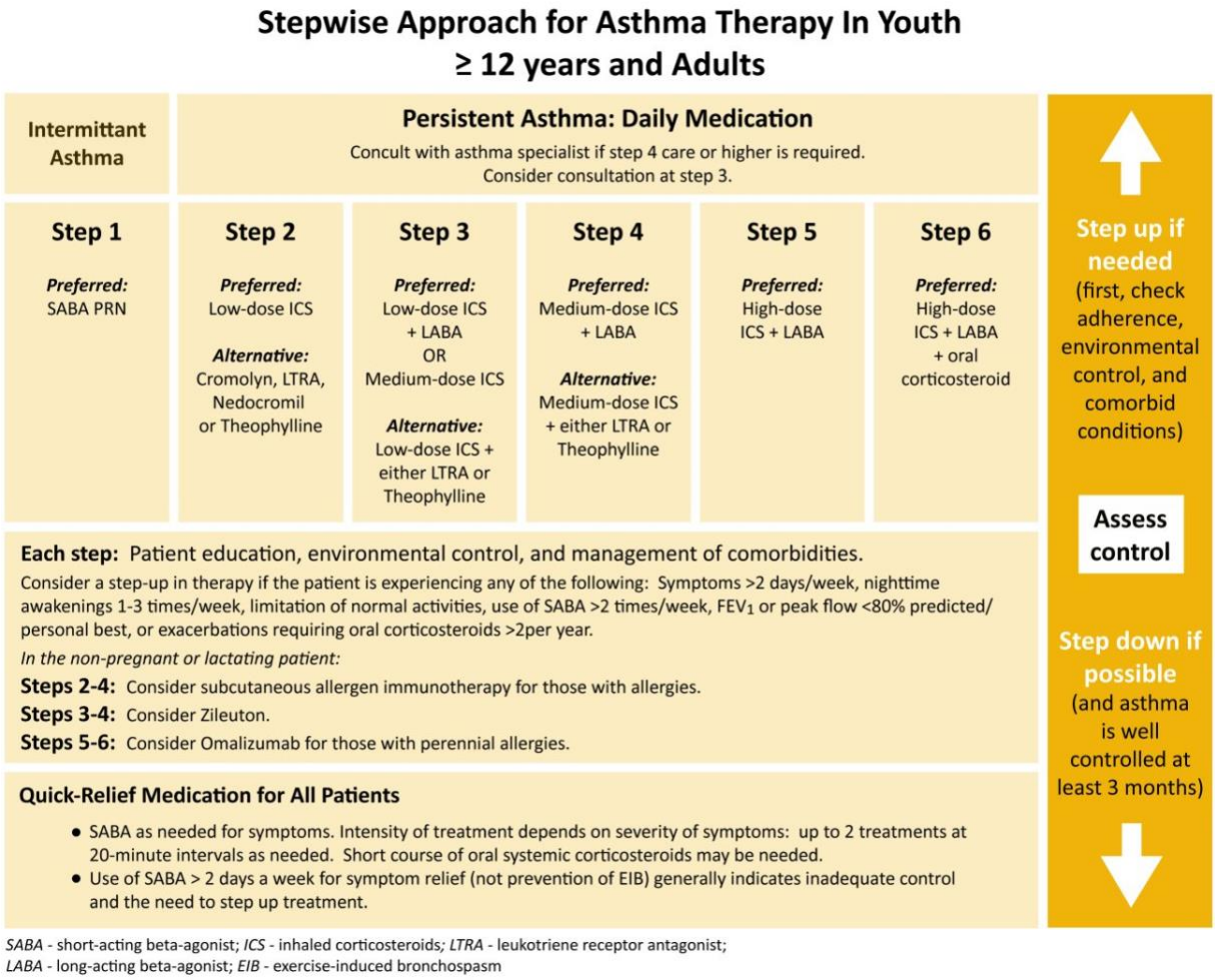

Table 1: American Thoracic Society Recommendations

Inhaled corticosteroids are the preferred treatment for any asthma that includes persistent symptoms.[Liang] Montelukast can be used if steroids are not the best patient choice due to cost, adverse effects, or issues with inhaled medication.[ATS] Beta-2 adrenergic receptor agonists (β2 agonists) are the treatment of choice for managing acute symptoms in patients with asthma.[Svedmyr] The advent of monoclonal antibody therapies (or biologics) has gained significant traction in the recent years. Omalizumab is a monoclonal antibody that binds to IgE preventing it from

associating with basophils and mast cells preventing their response to allergens.[Beck] Thus it is primarily used to treat symptoms associated with atopic IgE mediated asthma. Among the factors that could influence effectiveness of the primary asthma controller, Inhaled Corticosteroids (ICS), and the primary treatment, β2 agonists, may be the adipokines and chronic inflammation status associated with obesity. The obstructive and restrictive lung pathologies also decrease the likelihood that these inhaled medications reach their target lung tissue by decreasing lung filling and decreasing the lumen diameter these inhaled medications can flow through.

There are no specific pharmaceutical recommendations to treat asthma symptoms in obese asthmatics. The NIH guidelines mentions obesity as a possible comorbidity and that weight reduction may improve asthma control and many studies support this claim.[Juel] However, multiple studies have demonstrated that obese asthmatics receive suboptimal control of their symptoms. This could be due to the difficulty in achieving and maintaining weight control as well as the differences in responsiveness to first line medications. A study of asthma control in obese Black and Hispanic children and adolescents in the US showed decreased responsiveness to β2 agonists based on reports of increased wheezing, exacerbations of nighttime asthma symptoms, and increased use of other pharmacologic interventions like montelukast .[Mcgarry] Further studies showed therapeutic responsiveness to ICS in obese asthmatic children is diminished and that nonobese children were hospitalized 44% less frequently for asthma exacerbations.[Forno] This lack of symptom control was also demonstrated in adults with persistent asthma. Obese adult patients with asthma are more likely to be prescribed greater amounts of β2 agonists but are still 1.40 times more likely to have an emergency department visit or hospitalization.[Schatz2] This underscores an excessive reliance by physicians and their obese patients on β2 agonists, but an inability for obese asthmatics to control severe symptoms with this class of drugs.

In summary, obese patients are associated with poorer asthma control and have demonstrated lack of response to first line rescue treatments and daily controllers. This is a clarion

call for the development of strategies and therapeutic considerations that targets asthma management specifically in obese patients. Weight loss is an effective way to improve health outcomes in obese asthamtics and 5-10% of loss in body weight in adult obese asthmatics achieved through exercise and diet control effectively improves asthma control.[Scott] This study also showed that reduced circulation of saturated fat had a direct correlation with decreased neutrophils in airways, and increased exercise associated with decreased airway eosinophilia.[Scott] Although, weight loss and exercise are essential behavioral approaches in managing asthma in obese patients, effective control can be difficult to achieve and sustain weight loss especially when asthma symptoms make exercise more difficult. Weight loss is also a long-term solution however, it does not address the decreased responsiveness to asthma medications. Addressing pharmacodynamic differences in these patients could improve medication efficacy and decrease morbidity. It is possible that in obese asthmatics the β2 receptor may be more difficult to activate either due to receptor accessibility or substantial constraints in the signaling machinery at the receptor locus. Understanding why β2 agonists and ICS are less effective at controlling symptoms may allow for further pharmacologic refinements. The information from these studies will allow for clinical studies to improve asthma management and decrease morbidity and mortality in obese patients.

Conclusions

Obesity is associated with an increased prevalence and severity of asthma that coincides with racial disparities present in both conditions. The main rescue and controller medications have been shown to be less effective in obese asthmatics. Figure 1 below shows where the pathologies

of obesity may dampen or disrupt the treatment pathways available for asthma. More research is needed to understand the mechanisms for the decreased efficacy of ICS and β2 agonists in obese asthmatic patients. This may allow for improved control of asthma in patients at an increased risk of poor health outcomes.

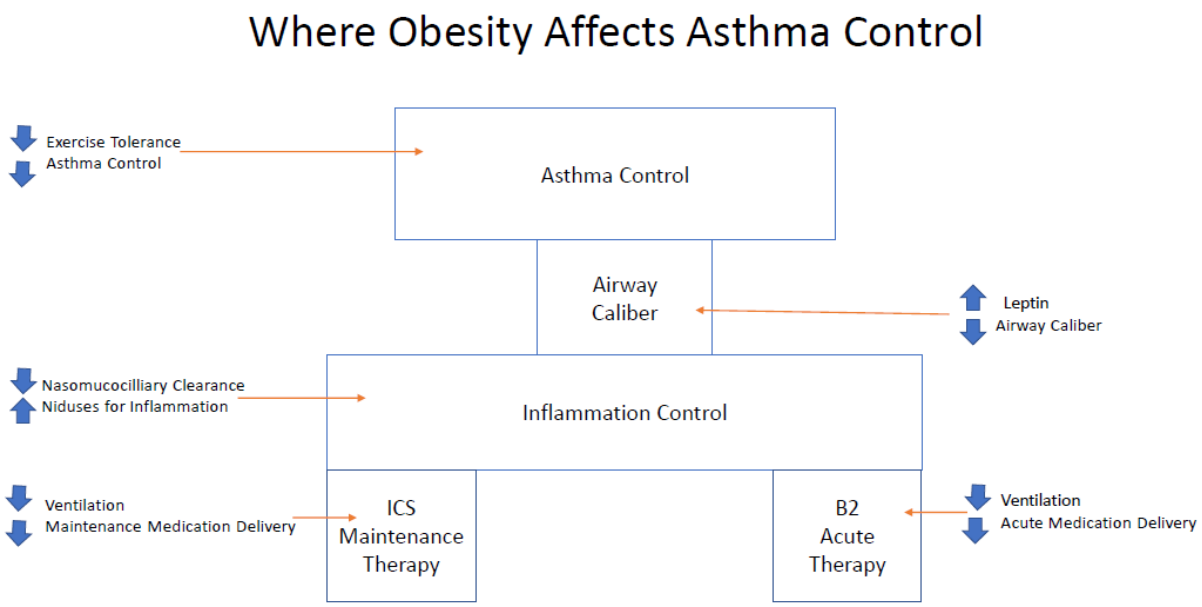

Figure 1: Obesity related pathologic changes interfere with asthma control at many levels making control with standard therapies inadequate. The blue arrows show the direction in which obesity affects specific parameters.

References

1. Defining Adult Overweight and Obesity. Centers for Disease Control and Prevention. 2020. https://www.cdc.gov/obesity/adult/defining.html

2. Hales, C., Fryar, C., Carroll, M., Freedman, D. and Ogden, C., 2018. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*, 319(16), p.1723.Hales, C., Fryar, C., Carroll, M., Freedman, D. and Ogden, C., 2018. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*, 319(16), p.1723.
3. Obesity. Mayo Clinic. 2020. https://www.mayoclinic.org/diseases-conditions/obesity/symptoms-causes/syc-20375742
4. Petersen, R., Pan, L. and Blanck, H., 2019. Racial and Ethnic Disparities in Adult Obesity in the United States: CDC's Tracking to Inform State and Local Action. *Preventing Chronic Disease*, 16.
5. Abdominal obesity and your health. Harvard Health Publishing. 2005. https://www.health.harvard.edu/staying-healthy/abdominal-obesity-and-your-health
6. Petersen R, Pan L, Blanck HM. Racial and Ethnic Disparities in Adult Obesity in the United States: CDC's Tracking to Inform State and Local Action. *Prev Chronic Dis*. 2019;16:E46. Published 2019 Apr 11.
7. Sanyaolu A, Okorie C, Qi X, Locke J, Rehman S. Childhood and Adolescent Obesity in the United States: A Public Health Concern. *Glob Pediatr Health*. 2019;6:2333794X19891305. Published 2019 Dec 1. doi:10.1177/2333794X19891305
8. Pi-Sunyer X. The medical risks of obesity. *Postgrad Med*. 2009;121(6):21-33. doi:10.3810/pgm.2009.11.2074
9. Nauli AM, Matin S. Why Do Men Accumulate Abdominal Visceral Fat?. *Front Physiol*. 2019;10:1486.
10. Health Risks of Overweight & Obesity. National Institute of Diabetes and Digestion and Kidney Disease. 2018. https://www.niddk.nih.gov/health-information/weight-management/adult-overweight-obesity/health-risks

11. Gonzalez A, Huerta-Salgado C, Orozco-Aguilar J, Aguirre F, Tacchi F, Simon F, Cabello-Verrugio C. Role of Oxidative Stress in Hepatic and Extrahepatic Dysfunctions during Nonalcoholic Fatty Liver Disease (NAFLD). Oxid Med Cell Longev. 2020 Oct 19;2020:1617805. doi: 10.1155/2020/1617805. PMID: 33149804; PMCID: PMC7603619.
12. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. *Nat Rev Nephrol*. 2019;15(6):367-385. doi:10.1038/s41581-019-0145-4
13. Kim HG, Han J. [Obesity and pancreatic diseases]. Korean J Gastroenterol. 2012 Jan;59(1):35-9. Korean. doi: 10.4166/kjg.2012.59.1.35. PMID: 22289952.
14. Lawson, R. and Pruitt, B., 2011. ISSUES IN OBESITY, PART 2. *Nursing*, 41(11), pp.42-48.
15. Peters, U., Dixon, A. and Forno, E., 2018. Obesity and asthma. *Journal of Allergy and Clinical Immunology*, 141(4), pp.1169-1179.
16. Forno, E., Han, Y., Mullen, J. and Celedón, J., 2018. Overweight, Obesity, and Lung Function in Children and Adults—A Meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice*, 6(2), pp.570-581.e10.
17. Asthmatic bronchiole and normal bronchiole. Medlineplus. 2018. https://medlineplus.gov/ency/imagepages/19375.htm
18. Tamilselvan, K., Latha, R., Nirmala, N., Susiganeshkumar, E. and Thananjayam, A., 2015. Does body mass index influence nasal mucociliary clearance?. *International Journal of Medical Research & Health Sciences*, 4(1), p.178.
19. Kakumanu S, Jaffee K, Visness CM, et al. The influence of atopy and asthma on immune responses in inner-city adults. *Immun Inflamm Dis*. 2016;4(1):80-90.
20. Asthma and Obesity. Centers for Disease Control and Prevention. 2013. https://www.cdc.gov/asthma/asthma_stats/asthma_obesity.htm

21. Schatz, M., Hsu, J., Zeiger, R., Chen, W., Dorenbaum, A., Chipps, B. and Haselkorn, T., 2014. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *Journal of Allergy and Clinical Immunology*, 133(6), pp.1549-1556.
22. Mohanan, S., Tapp, H., McWilliams, A. and Dulin, M., 2014. Obesity and asthma: Pathophysiology and implications for diagnosis and management in primary care. *Experimental Biology and Medicine*, 239(11), pp.1531-1540.
23. Lange, L., Norris, J., Langefeld, C., Nicklas, B., Wagenknecht, L., Saad, M. and Bowden, D., 2005. Association of adipose tissue deposition and beta-2 adrenergic receptor variants: the IRAS family study. *International Journal of Obesity*, 29(5), pp.449-457.
24. Sideleva, O., Suratt, B., Black, K., Tharp, W., Pratley, R., Forgione, P., Dienz, O., Irvin, C. and Dixon, A., 2012. Obesity and Asthma. *American Journal of Respiratory and Critical Care Medicine*, 186(7), pp.598-605.
25. Ali Assad, N. and Sood, A., 2012. Leptin, adiponectin and pulmonary diseases. *Biochimie*, 94(10), pp.2180-2189.
26. Liang TZ, Chao JH. Inhaled Corticosteroids. [Updated 2020 May 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470556/
27. Svedmyr N, Löfdahl CG. The use of beta 2-adrenoceptor agonists in the treatment of bronchial asthma. Pharmacol Toxicol. 1996 Jan;78(1):3-11. doi: 10.1111/j.1600-0773.1996.tb00172.x. PMID: 8685084.
28. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fce psilon RI expression and function. J Allergy Clin Immunol. 2004 Sep;114(3):527-30. doi: 10.1016/j.jaci.2004.06.032. PMID: 15356552.
29. Juel CT, Ali Z, Nilas L, Ulrik CS. Asthma and obesity: does weight loss improve asthma control? a systematic review. *J Asthma Allergy*. 2012;5:21-26. doi:10.2147/JAA.S32232

30. McGarry ME, Castellanos E, Thakur N, et al. Obesity and bronchodilator response in black and Hispanic children and adolescents with asthma. *Chest*. 2015;147(6):1591-1598.
31. Schatz,M. Et al. Prospective Study on the Relationship of Obesity to Asthma Impairment and Risk.The Journal of Allergy and Clinical Immunology: In Practice. 2015; 3(4): 560-565.
32. Rance, Karen et al. Obesity and Asthma: A Dangerous Link in Children. The Journal for Nurse Practitioners, 7(4), pp. 287 - 292.
33. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. *J Allergy Clin Immunol*. 2014;134(3):547-553.e5.
34. Asthma and African Americans. U.S. Department of Health and Human Services: Office of Minority Health. 2018. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=15
35. Barnes KC, Grant AV, Hansel NN, Gao P, Dunston GM. African Americans with asthma: genetic insights. *Proc Am Thorac Soc*. 2007;4(1):58-68.
36. White, M., Risse-Adams, O., Goddard, P., Contreras, M., Adams, J., Hu, D., Eng, C., Oh, S., Davis, A., Meade, K., Brigino-Buenaventura, E., LeNoir, M., Bibbins-Domingo, K., Pino-Yanes, M. and Burchard, E., 2016. Novel genetic risk factors for asthma in African American children: Precision Medicine and the SAGE II Study. *Immunogenetics*, 68(6-7), pp.391-400.
37. Holguin F, Bleecker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol*. 2011;127(6):1486-93.e2.
38. Scott, H., Gibson, P., Garg, M., Pretto, J., Morgan, P., Callister, R. and Wood, L., 2012. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clinical & Experimental Allergy*, 43(1), pp.36-49.

39. Forno E, Lescher R, Strunk R, et al. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol*. 2011;127(3):741-749.