

REVIEW

An Overview of Health Disparities in Asthma

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Asthma is a heterogeneous disease characterized by inflammation in the respiratory airways which manifests clinically with wheezing, cough, and episodic periods of chest tightness; if left untreated it can lead to permanent obstruction or death. In the US, asthma affects all ages and genders, and individuals from racial and ethnic minority groups are disproportionately burdened by this disease. The financial cost of asthma exceeds \$81 billion every year and despite all the resources invested, asthma is responsible for over 3,500 deaths annually in the nation. In this overview, we highlight important factors associated with health disparities in asthma. While they are complex and overlap, we group these factors in five domains: biological, behavioral, socio-cultural, built environment, and health systems. We review the biological domain in detail, which traditionally has been best studied. We also acknowledge that implicit and explicit racism is an important contributor to asthma disparities and responsible for many of the socio-environmental factors that worsen outcomes in this disease.

INTRODUCTION

Asthma is one of most prevalent respiratory diseases in the United States and it is estimated that over 25 million Americans suffer this condition including 6 million children [1]. Asthma is a heterogeneous respiratory disease characterized by airway inflammation. It presents with variable symptoms of wheeze, shortness of breath, chest tightness, and/or cough in addition to airflow limitation [2]. This constellation of symptoms and airflow limitation can vary in frequency and intensity and is often triggered by exercise, viral respiratory infections, exposure to environmental allergens and chemicals, or changes in weather among other factors [2]. The estimated financial burden of asthma exceeded \$81 billion in 2013 [3]. This figure

likely underestimates the current costs of asthma care, as the number of prescriptions for novel and expensive medications targeting biological pathways is increasing [4].

In the US, the burden of asthma is disproportionately borne by racial and ethnic minority groups and the economically disadvantaged (Figure 1) [1]. The prevalence of asthma among Puerto Rican and non-Hispanic Black children (21.2% and 14.5%, respectively) is higher than among non-Hispanic White and Mexican American children (8.2% and 7.5%, respectively). While recent studies make the distinction between Hispanic Whites and Non-Hispanic Whites, most of the studies presented do not make those distinctions, however when possible we note this issue. Similarly, the prevalence of asthma is higher among individuals of low socioeconomic status

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Abbreviations: GWAS, Genome Wide Association Studies; ICS, Inhaled Corticosteroids; IgE, Immunoglobulin E; FeNO, Fraction of Exhaled Nitric Oxide; IL, Interleukin; LABA, Long Acting Beta Agonist; SNAP, Supplemental Nutritional Assistance Program.

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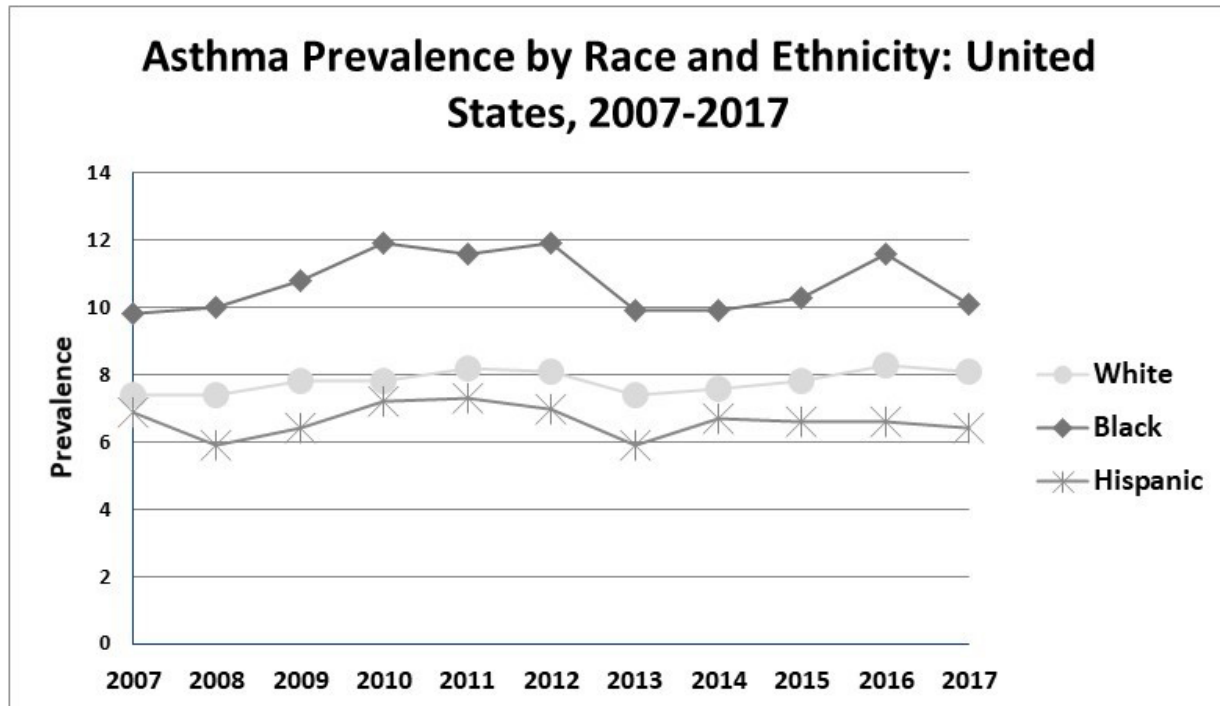


Figure 1. Trend in asthma prevalence in the US among Whites, African Americans and Hispanics from 2007 to 2017. Source: Center for Disease Control and Prevention. <https://www.cdc.gov/asthma/national-surveillance-data/default.htm>

(SES) compared with those of high SES [1]. Although asthma mortality is trending down [5], asthma was responsible for the deaths of more than 3,000 Americans in 2019 [1]. Asthma mortality rates are highest for adults, women, and African Americans. African Americans have a mortality rate twice as high as White Americans (21.8 vs 9.5 death rate per million) [1]. The underlying factors contributing to these disparities are multiple and complex, but can be categorized in five domains: Biological, Behavioral, Sociocultural Environment, Built Environment, and Healthcare System (Figure 2) [6]. In this article, we provide a brief overview focusing on biological factors relevant to racial and ethnic group disparities in asthma, while also highlighting significant findings related to the behavioral, sociocultural, built environment, and healthcare system domains that are important to consider.

BIOLOGICAL DOMAIN

Genetics and Ancestry

There are several reports associating asthma and lung function with genetic ancestry, which supports the hypothesis that racial and biological factors contribute to differences observed in asthma prevalence between different racial and ethnic groups in the US [7-10]. Genome-wide association studies (GWASs) of asthma have identified many risk alleles and loci representing almost

all chromosomes in the human genome. The 6p21, 2q12, 5q22, and 9p24 loci have been consistently and frequently reported in large GWASs in asthma, but the 17q12-21 locus is recognized as the most replicated and most significant asthma locus [11,12]. This locus has been associated with early-onset asthma among European, Asian, and Latino individuals. However, the association for the 17q12-21 locus and populations from African ancestry, until recently, had been less robust secondary to a lower linkage disequilibrium for this area of the genome in the population of African ancestry [11,13,14]. Nevertheless, researchers using whole genome sequencing recently reported an association between this locus and asthma in three large cohorts of African American individuals and demonstrated that the effect is similar to populations of European descent, supporting the hypothesis that variation in this locus is associated with variation in asthma phenotype [15].

It is reported that Hispanics and Latinos in the US have a lower prevalence of asthma when compared to the general population and to White Americans (Figure 1) [1,16-18]. The finding of better health outcomes (in this case, asthma) in a population with worse socioenvironmental risk factors represents a paradox which has been labeled by epidemiologists as the “Hispanic paradox” [19]. However, within Hispanics there are significant differences in asthma prevalence, with Puerto Ricans

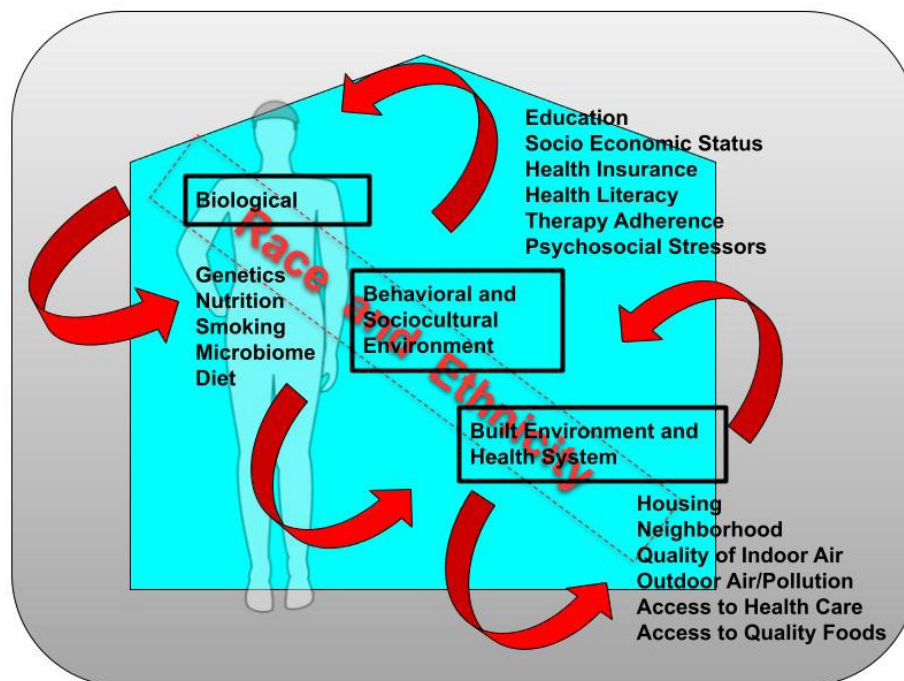


Figure 2. Factors that contribute to persistent health disparities in asthma.

having a much higher prevalence than those from other regions such as Mexicans (16.1% vs 5.4%) [1,20,21]. Some research studies suggest that this disparity in asthma prevalence among Hispanics could be explained by differences in the degree of African ancestry among different Hispanic groups and even within a single ethnic group such as Mexicans [22]. Supporting this theory, there is at least one study showing that even after adjusting for confounders such as socio-economic status and other environmental factors, Black Mexicans have higher odds of asthma (Odds Ratio (OR) 1.56 (95% Confidence Interval (CI) 1.14–2.15)) suggesting that African ancestry accounts for some of the disparity reported even within the same ethnic group [23,24].

Collectively, these reports support ancestry and genetic makeup as factors contributing to the observed disparity in the prevalence of asthma in the US. Nevertheless, asthma is a polygenic and multifactorial disease as supported by data reported in twin siblings' studies. These studies have shown that a twin sibling of an asthmatic monozygotic twin (identical twin) not always goes into developing asthma, although their risk is indeed higher than other siblings including heterozygous (non-identical) twins (OR 20.69 (95% CI 15.08-28.38) vs 4.24 respectively (95% CI 2.97-6.06)) [25]. Therefore, the impact of ancestry in this disease is difficult to quantify and confounded by multiple other factors such as environmental exposures and many other social determinants of health that can be difficult to study and to account for

epidemiologically.

Asthmatic Phenotypes

Francis Rackemann initially identified two distinct asthmatic almost 100 years ago [26]. He described a group of atopic younger asthmatics in whom the disease was mainly driven by allergens and environmental triggers and labeled this extrinsic asthma. This contrasted with intrinsic asthma, which he described in older patients who did not have atopy. Since then, significant progress has been made in our understanding of the heterogeneity of this disease and in the multiple biological inflammatory pathways involved. Large cohort studies indicate at least four clusters of asthmatics based on clinical and biological traits: (1) early-onset mild allergic asthma, (2) early-onset allergic moderate-to-severe remodeled asthma, (3) late-onset non-allergic eosinophilic asthma, and (4) late-onset non-eosinophilic non-allergic asthma [27]. These phenotypic differences may also be based on race/ethnicity, as suggested by recent studies revealing that airway inflammation in asthma may differ between African Americans and Whites, with the former group having a higher proportion of eosinophils in the airways when treated by inhaled corticosteroids (ICS) and/or neutrophils when measured in sputum [28,29]. Furthermore, racial differences in predictors of severe asthma have been found including serum immunoglobulin E (IgE) levels and family history of severe asthma. Both of these are

predictors of severe disease in African Americans (IgE level OR of 2.12 ($p=0.014$) and two or more members in the family with a history of asthma OR 2.79 ($p=0.026$)), but are not predictors of severe disease in Whites.[30] Additionally, African ancestry and comorbidities such as chronic sinusitis (OR 2.8 (95% CI 1.51-5.07)), allergic rhinitis (OR 2.2 (95% CI 1.03-4.68)), and gastro-esophageal reflux (OR 2.2 (95% CI 1.17-4.13)) are associated with asthma exacerbations in African American individuals [31].

Proper phenotypic characterization is important to personalize therapies with maximum benefit while minimizing risks and toxicity. However, some of the tools used to clinically characterize airway inflammation have not been appropriately tested among racial and ethnic minority populations. Most studies from which “normal” parameters have been derived have been conducted in mainly Non-Latino White cohorts. An example of this lack of appropriate normal ranges was recently identified as fractional exhaled nitric oxide (FeNO) [32]. Elevated FeNO serves as a surrogate of the inflammatory effects of the cytokines IL-4 and IL-13 in the airways, with higher levels suggesting the presence of airway eosinophilic inflammation and steroid responsiveness (T2 high asthma) [33]. However, the current acceptable values could misclassify a significant proportion of individuals from racial and ethnic minority populations [32,34]. This demonstrates the need for further research among minority populations to allow personalized care and improve outcomes in asthma.

Nevertheless, potential differences in pulmonary function tests need to be explored carefully and in large diverse populations, while understanding that race and ethnicity are constructs mainly determined by social and environmental factors. Even as of today, controversy exists regarding how to properly interpret some of the pulmonary function tests including spirometry since racial corrections are automatically applied based on data that is based on “potential differences on body build” and may lack biological foundation [35,36]. Therefore, clinicians, researchers, and the public in general ought to be cautious, as most of these reported differences in pulmonary function based on race or ethnicity are based on ill-conceived research and even eugenics that have transcended time rather than true biological differences [37].

Personalized Therapies

The heterogeneity of asthma as a disease combined with the lack of a single objective diagnostic test has led clinicians to overuse this diagnosis for a variety of respiratory complaints. This hampers progress towards better understanding the disease and the development of more advanced therapies [38]. For most patients presenting for healthcare with a persistent cough and wheeze, a prescrip-

tion of beta-agonist and steroids is quickly generated and explains why misdiagnosis of respiratory disease could be as high as 1 in 3 of all patients who have been given the diagnosis of asthma by medical providers [39,40]. Studying how this affects the differences in asthma prevalence among populations that have been traditionally underserved is an important priority. Similarly, there is an urgent need to better understand the therapeutic response to asthma therapies among racial and ethnic minorities and to increase their participation in clinical trials [41]. It has been shown that African American patients may respond differently to corticosteroids when compared with White patients [42-44]. Additionally, significant racial differences have been found in response to beta agonists, with use of the long acting beta agonist (LABA) salmeterol associated with higher risk of death or life-threatening events among African Americans who have a risk ratio (RR) of asthma-related deaths or life-threatening experience of 4.92 (95% CI 1.68-14.45) [45]. At least one trial has shown that Hispanics and non-Hispanic White children have better responses to stepping up therapy with LABA than higher doses of ICS, while African American children were less likely to respond to adding leukotriene receptor antagonists to their regimen [46]. More recently, another trial showed that African American children had better response to increasing the dose of ICS, while African American adults with asthma had better asthma control when adding LABA [47]. A potential explanation for differences in response to medications among African Americans and other minority populations could be related to genetic variants in the receptors for these pharmaceutical agents, which are distributed differentially according to racial background [48,49].

More recently the therapeutic approach to the asthmatic patient has been broadened by better phenotypic characterization and the recognition of particular inflammatory pathways that can be targeted through novel medications produced in living organisms. These medications are commonly known as biologicals. Currently, there are five biologicals approved by the Federal Drug Administration for use in asthma, particularly for asthma characterized by a T2 high phenotypic profile. Thus, omalizumab (Anti-IgE) is approved for moderate-to-severe allergic asthma; dupilumab (Anti IL-4/IL-13) is approved for moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma; and mepolizumab (Anti-IL5), reslizumab (Anti-IL5), and benralizumab (Anti-IL-5 Receptor alpha) are approved for severe eosinophilic asthma [50]. These medications have been shown to significantly affect important outcomes in asthma care, including healthcare utilization, number of asthma exacerbations, the use of systemic corticosteroids, and quality of life among others [50]. However, this class of medications may be utilized

differently according to racial group and socio-economic status, with those who have access to specialty care and higher income more likely to be prescribed these type of medications and get better control of their disease [51]. Further studies monitoring the utilization of these novel and effective therapies should be encouraged and barriers to their use with racially diverse and low-income populations should be identified and addressed. Moreover, efforts to recruit and include populations of minority origin should be made in order to properly determine the effectiveness of such novel therapies among them. Unfortunately, many of these clinical trials do not report the distribution of race and ethnicity among their participants, limiting the generalizability of their findings and/or the ability to conduct subgroup post-hoc analysis in these populations.

The Microbiome

Until recently, it was believed that the human lungs were sterile [52]; however, the existence of a healthy lung microbiome is now generally accepted and disturbance of this microbiome has been associated with different respiratory diseases [53]. The human microbiome is affected by multiple factors that range from genetic composition to geographic location. Several studies have shown that exposure to a rich microbial environment early in life can protect against asthma development [54]. For example, in the US, the Amish community, which is genetically and culturally similar to the Hutterite community, has a much lower prevalence of asthma when compared to the latter, suggesting that environmental factors and the interaction between the genetic composition and the environment, perhaps through the microbiome, are responsible for differences in the risk of asthma [55]. Furthermore, some authors suggest that differences in the microbiome may be responsible for ethnic and racial disparities in asthma. Differences in the microbiome have been reported in different ethnic groups in the US [56]; however, it remains unclear if the differences in the microbiome are drivers of disease, and whether socioenvironmental factors attached to ethnicity are causing microbiome differences [57]. In addition to affecting the risk of asthma, the microbiome also affects therapy response, with at least one study showing that patients with corticosteroid-resistant asthma had higher levels of Proteobacteria and Fusobacteria in bronchoalveolar lavage samples compared to those who were corticosteroid responsive [58].

BEHAVIORAL AND SOCIOCULTURAL DOMAINS

Therapy Adherence

Asthma management involves recognition of symp-

oms, appropriate medication use, including adherence to daily controller medication as well as administration of quick relief medications when indicated [2]. The evidence available shows that racial and ethnic minority patients with asthma have lower rates of medication adherence when compared with Non-Latino Whites, contributing to ongoing health disparities in asthma [59,60]. The reasons for lower levels of medication adherence are varied and have been conceptualized as relating to individual patient factors such as medication beliefs, preference for complementary and alternative medicines, and depressive symptoms; patient-provider interaction factors such as language barriers and racial concordance; and healthcare system factors such as insurance coverage and pharmacy availability [60-63].

Psychosocial Stressors

For racial and ethnic minority groups, experiences of racism and discrimination contribute to psychosocial stress and negative health outcomes [64,65]. In asthma, perceived discrimination is associated with greater odds of worse asthma control and with higher odds of asthma among African Americans [66]. For African American caregivers, the perception of discrimination is associated with higher levels of asthma functional limitation and more frequent asthma-related emergency department use in their children. [67,68]. Parents and caregivers of children with asthma report higher levels of psychosocial stress and lower expectation of asthma control for their children [69,70]. Furthermore, psychosocial stress can affect the therapeutic response to bronchodilators and glucocorticoids [71,72]. Taken together, these reports support addressing and eliminating the sources of psychosocial stressors such as systemic racism and discrimination as a just and worthwhile strategy to improve asthma as well as general health for racial and ethnic minority populations.

BUILT ENVIRONMENT AND HEALTHCARE SYSTEM DOMAINS

Nutrition and Diet

Diets that are rich in fruits and vegetable may protect against asthma and reduce asthma severity [73-75]. Diet composition can modulate systemic inflammation, oxidative stress, and the microbiome, all factors that have significant effects on asthma [76]. Unfortunately, in the US, over 12% of households are at significant risk of limited or uncertain access to adequate food, a problem that is highly prevalent among racial and ethnic minority groups [77]. Furthermore, racial and ethnic minority populations are more likely to live in urban areas in which access to affordable and good quality fresh food is limited and this has been linked to higher asthma risk [78]. Micronu-

trients such as vitamin D are essential for good health. Vitamin D deficiency has been associated with asthma and atopy (OR 2.31; $P < 0.001$ and OR 1.59; $P < 0.001$, respectively) [79], and African Americans are more likely to have lower levels of vitamin D [80-82]. This body of literature supports public health policies aligned with the elimination of “food deserts” or urban areas where the lack of supermarkets or grocery stores limits the access to affordable high quality fresh foods with implications for asthma and overall health. Governmental efforts such as the supplemental nutritional assistance program also known as “SNAP” have shown significant benefits in reducing the number of emergency room visits due to asthma [83] and could contribute to eliminating the “eat or breathe” challenge that many low income families face [84] and overall healthcare [85]. However, negative public perception of government safety net programs, such as SNAP, is a significant threat to their continued survival.

Air Pollution, Neighborhood Safety, and Housing

The over-representation of racial and ethnic minorities in urban areas characterized by substandard housing, greater exposure to pollutants, and crime is the consequence of longstanding policies. These policies stemmed from the Home Owners’ Loan Corporation that classified areas with higher concentration of African American households and other racial minorities as “least stable” or at higher financial risk outlining them in red, a practice that gave rise to the infamous term “redlining” [86]. This practice of redlining unfortunately was widespread across the country, contributing to worsening racial segregation and systematically decreasing the potential for wealth growth for racial and ethnic minority groups with many downstream effects in overall health for these populations [87-90]. For asthma in particular, it has been reported that emergency visits are 2.4 times higher for residents of areas that were more likely to be redlined (median 63.5 (IQR 34.3)) than areas that were less likely to be redlined (median 26.5 (IQR 18.4)). Even after adjusting for poverty rate, diesel exhaust particle emissions, and particulate matter (PM₂₅) pollution levels, the risk ratio for residents of redlined areas of having an asthma related emergency room visit was almost 40% higher than for those from areas less likely to be redlined (RR 1.39 (95% CI 1.21-1.57)) [86].

Air pollution is a significant contributor to asthma incidence and morbidity across the world and it is estimated that 4 million cases of new pediatric asthma could be attributable to a single pollutant: Nitrogen Dioxide (NO₂), which is a gas commonly associated with traffic pollution [91]. Significant differences in regional air quality are reported within cities, with neighborhoods predominantly populated by minorities being affected disproportionately by air pollutants when compared to

White neighborhoods, and even though progress has been made, these disparities persisted over the last 3 decades [92,93].

Furthermore, neighborhoods are also associated with differences in the prevalence of multiple diseases, including cardiovascular disease, obesity, and asthma, among others [94-97]. The effect of the neighborhood in health has been related in some studies to exposure to violence and overall safety perception [98]. Thus, Perceptions of poor neighborhood safety have been associated with worse asthma control (OR 2.2 (95% CI 1.2-3.9)), increased symptoms, use of rescue medications (OR 4.7 (95% CI 1.7-13.0)), and activity limitation (OR 3.2 (95% CI 1.3-4.0)) [67,98,99]. Poor housing is strongly associated with asthma (OR 1.45 (95%CI 1.28-1.66)) and with a higher number of asthma related emergency room visits (OR 1.59 (95%CI 1.21-2.10)) [100], and housing quality, affordability, and stability have been associated with better overall health outcomes [101,102].

This body of literature supports the concept that in order to improve asthma care and to tackle the disparities existing in this condition we consider interventions that transcend the clinical settings but that must address housing and environmental policies that have adversely affected the health of minorities in the US and the have been ingrained in society.

HEALTHCARE SYSTEM

There is a documented history of mistreatment of racial and ethnic minority patients in healthcare, including substandard clinical care and discriminatory practices when accessing care [103]. Consequently, racial and ethnic minority patients endorse high levels of healthcare system mistrust, which is associated with lower satisfaction with the care received and undermines a healthy patient-provider relationship [104-106]. African American caregivers of children with asthma reported higher levels of dissatisfaction with the patient-provider relationship, which is associated with lower odds of contacting the healthcare provider prior to a preventable emergency room visit [107]. Medical providers who serve racial and ethnic minority patients may be less adherent to asthma guideline recommendations and may underestimate their asthma severity, which is compounded by limited access to specialized care and medication affordability [59,108,109]. Implicit bias by providers significantly contributes to differences in asthma morbidity seen in minority populations [110]. Furthermore, for children with asthma, differences in caregiver perceptions of discrimination leads to higher emergency room utilization for asthma and overall worse functional status [67,68]. On the other hand, racially and ethnically diverse urban caregivers who feel more confident and empowered to

manage problems within their family reported a lower rate of emergency room utilization for their children's asthma [111-113]. Therefore, supporting a diverse health-care workforce, enhancing training to support culturally responsive healthcare services, and facilitating access to high quality and affordable healthcare should be prioritized as potential solutions to health disparities in asthma care. This along with culturally responsive education and empowerment of racial and ethnic minority patients to effectively manage their asthma may have a beneficial effect for asthma outcomes.

SUMMARY

Asthma is a highly complex and heterogeneous disease that is further complicated by social and behavioral determinants of health. In the US, racial and ethnic minorities are disproportionately burdened, with higher prevalence rates and worse outcomes. Continued efforts to identify the contribution of factors within the biological, behavioral, sociocultural, built environment, and healthcare domains is critical to allow systematic efforts to decrease asthma disparities. These efforts should be broad and far-reaching, ranging from identifying and developing targets in biological pathways to combating the entrenched effects of structural racism on health in order to diminish the burden of this disease. Beyond examining structural racism's impact at the individual level (eg, interpersonal interactions), further study is needed to better understand its effect on healthcare policies and service delivery given its invisible yet ubiquitous nature [114].

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