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Juan Carlos Celedón *Editor*

Achieving Respiratory Health Equality

A United States Perspective

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Editor
Juan Carlos Celedón, MD, DrPH
Division of Pediatric Pulmonary Medicine,
Allergy, and Immunology
Children's Hospital of Pittsburgh of UPMC
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

ISSN 2197-7372 ISSN 2197-7380 (electronic)
Respiratory Medicine
ISBN 978-3-319-43445-2 ISBN 978-3-319-43447-6 (eBook)
DOI 10.1007/978-3-319-43447-6

Library of Congress Control Number: 2016954431

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Achieving health equality is one of the most important challenges we currently face and will continue to confront over the coming decades. Advancements in technology, transportation, communication, science, and medicine have undoubtedly revolutionized the way we live over the past century, yet risk factors for disease continue to differ amongst demographic groups, and disparities in healthcare access and delivery persist (and even have expanded) over the same period. By decreasing overall productivity and shortening life expectancy, health disparities prevent upward social mobility of disproportionately affected populations, thus denying these groups a realistic opportunity to overcome their social disadvantages. Notably, the very same advancements in technology and communication have provided unique insights into the extent of the problem and have shed light on the significant burden that health disparities place on society. This book summarizes the current state of knowledge and understanding on health disparities in the USA with a focus on respiratory health, an area of much needed attention. Its pages are replete with important facts that are otherwise difficult to obtain, but more importantly, also provide insightful recommendations on approaches aimed at making health equality a reality. Considering the importance of this issue and the colossal challenge it presents, this book is long overdue and certainly fills a very important void.

Generally speaking, health disparities are defined as variations in the incidence, prevalence, mortality, and burden of disease among distinct population segments that differ in gender, socioeconomic status, education, race or ethnicity, disability, living circumstances, or sexual orientation. Although health disparities have been the focus of significant recent attention, this is hardly a new phenomenon. In *An American Health Dilemma*, Byrd and Clayton pointed to examples of such disparities in early recorded history and suggested that the enslavement of distinct ancient populations and subsequent events led to what they termed the "slave health deficit." Richard Allen Williams later discussed how slavery gave rise to a racially discriminatory system of healthcare delivery and how social and legal scholars and medical practitioners contributed to such disparities. Both of these works emphasize the deep entrenchment of this problem in our history and communal psyche, further reinforcing our resolve towards achieving health equality.

Health disparities essentially occur in every realm of medicine. However, respiratory health disparities remain some of the most impactful, currently affecting millions of people worldwide. It is not surprising that underrepresented minorities, migrant populations, and socio-economically disadvantaged groups, among others, are disproportionately afflicted by these respiratory disorders. What remains disturbing, however, is that these populations continue to be subjected to unequal access to the care they need, despite a wide range of improvements in healthcare delivery systems.

In the following pages, a distinguished group of experts describe some of the major difficulties inherent to addressing health disparities in respiratory disorders ranging from bronchopulmonary dysplasia and cystic fibrosis to obstructive airways disorders and sickle cell disease. In addition, the authors critically discuss how social and economic conditions, air pollution, acculturation, and occupation contribute to generate and perpetuate health disparities. Furthermore, they address challenges faced by specific groups including the Lesbian, Gay, Bisexual, and Transgender community. The readers will also find thorough descriptions of the challenges confronted by researchers when studying health disparities. For example, definitions of race and ethnicity, typically and traditionally based on skin color and cultural factors, are being challenged in the context of new emergent genetic information. The authors also emphasize the importance of incorporating the newly acquired knowledge into the curricula of graduate medical education in order to prepare future generations of physicians and other healthcare providers on how to best recognize and address health equality challenges. Finally, the overarching optimistic argument is made that taking advantage of scientific discoveries such as those related to personalized/precision medicine may in fact promote health equality, but only if and when implemented in a thoughtful manner.

The US Secretary's Advisory Committee for Healthy People 2020 concluded that health disparities are systematic and plausibly avoidable health differences adversely affecting socially disadvantaged groups. This statement emphasizes an important point—the fact that health disparities are avoidable and that health equality is an attainable goal. This book not only describes the problems in this context, and delineates many of the steps required for the enormous task ahead, but also unveils innovative ideas and approaches that could be translated into public health interventions, while stimulating much needed research and awareness efforts. Whichever way we look at it, achieving health equality is all about achieving social justice. No matter how difficult and challenging the task may be, we must all rally behind it, as the very fabric and future of our society depends on it.

Louisville, KY, USA — Jesse Roman
Chicago, IL, USA — David Gozal

Contents

Contributors

John R. Balmes, MD Department of Medicine, University of California at San Francisco, San Francisco, CA, USA

Department of Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA, USA

Zuckerberg San Francisco General Hospital, San Francisco, CA, USA

Catalina Bazacliu, MD Department of Pediatrics, Division of Neonatology, University of Florida Shands Hospital, Gainesville, FL, USA

Esteban G. Burchard, MD, MPH Department of Medicine, University of California at San Francisco, San Francisco, CA, USA

Department of Bioengineering and Therapeutic Sciences, University of California at San Francisco, San Francisco, CA, USA

Glorisa J. Canino, PhD Behavioral Sciences Research Center, University of Puerto Rico, San Juan, PR, USA

Department of Pediatrics, University of Puerto Rico Medical Sciences Campus, San Juan, PR, USA

Juan Carlos Celedón, MD, DrPH Division of Pediatric Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Emily Clausen, MD Department of Medicine, Duke University, Durham, NC, USA

Colin R. Cooke, MD, MSc, MS Division of Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Center for Healthcare Outcomes & Policy, Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA

Michael R. DeBaun, MD, MPH Department of Medicine and Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

Alejandro Díaz, MD Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Ivor S. Douglas, MD, FRCP (UK) Division of Pulmonary Sciences & Critical Care Medicine, University of Colorado, Denver and Denver Health Medical Center, Denver, CO, USA

Erick Forno, MD, MPH Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA, USA

Jeffrey Glassberg, MD Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Fernando Holguin, MD, MPH Departments of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Daphne Koinis-Mitchell, PhD Departments of Psychiatry and Human Behavior and Pediatrics, Alpert Medical School, Brown University, Providence, RI, USA

Sarah M. Lyon, MD, MSCE Division of Pulmonary, Allergy & Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Division of Pulmonary and Critical Care Medicine, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA

Elizabeth L. McQuaid, PhD, ABPP Department of Psychiatry and Human Behavior and Pediatrics, Alpert Medical School, Brown University, Providence, RI, USA

Alison Morris, MD, MS Department of Medicine, University of Pittsburgh, 628 NW Montefiore University Hospital, Pittsburgh, PA, USA

Gabriela R. Oates, MD Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

Victor E. Ortega, MD, PhD Center for Genomics and Personalized Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC, USA

Kristin Riekert, PhD Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, MD, United States

Rita M. Ryan, MD Department of Pediatrics, Medical University of South Carolina Children's Hospital, Charleston, SC, USA

Jonathan Samet, MD, MS Department of Preventative Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Michael S. Schecter, MD, MPH Division of Pulmonary Medicine, Department of Pediatrics, Virginia Commonwealth University, Children's Hospital of Richmond at VCU, Richmond, VA, USA

Marc B. Schenker, MD, MPH Department of Public Health Sciences and Internal Medicine, University of California at Davis, Davis, CA, USA

Ann M. Schraufnagel, MD, MPH Department of Medicine, University of Washington, Health Sciences Building, Seattle, WA, USA

Dean E. Schraufnagel, MD Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

Neeta Thakur, MD, MPH Department of Medicine, University of California at San Francisco, San Francisco, CA, USA

Karriem S. Watson, DHSc, MS, MPH UI Health Cancer Center at University of Illinois at Chicago (UIC), Chicago, IL, USA

Marquitta J. White, PhD, MS Department of Medicine, University of California at San Francisco, San Francisco, CA, USA

Robert A. Winn, PhD UI Health Office of Vice Chancellor Health Affairs, University of Illinois at Chicago (UIC), Chicago, IL, USA

UI Health Cancer Center at University of Illinois at Chicago (UIC), Chicago, IL, USA

Juan P. Wisnivesky, MD, DrPH Divisions of General Internal Medicine and Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Chapter 1
Overview

Juan P. Wisnivesky, Kristin Riekert, and Juan Carlos Celedón

Since 1960, a reduction in cardiovascular mortality and improved overall health has led to an approximate 9-year increment in average life expectancy for the population of the United States (US). However, this gain was not experienced by all Americans, as substantial gaps in life span remain across demographic groups defined by socioeconomic status (SES), race, and ethnicity [1]. Marked differences in social determinants of health, environmental and behavioral risk factors, and healthcare access across demographic groups are largely responsible for disparities in health outcomes and, ultimately, life expectancy [2]. Variable exposure to major environmental risk factors (e.g., cigarette smoking) across demographic groups leads to health disparities for most diseases commonly encountered in the practice of pulmonary, critical care, and sleep medicine (heretofore referred to as "respiratory health disparities," for ease of exposition).

J.P. Wisnivesky, MD, DrPH
Divisions of General Internal Medicine and Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: juan.wisnivesky@mountsinai.org

K. Riekert, PhD (✉)
Division of Pulmonary and Critical Care, Johns Hopkins University, 5501 Hopkins Bayview Circle, JHAAC 3B37, Baltimore, Maryland 21224, United States
e-mail: kriekert@jhmi.edu

J.C. Celedón, MD, DrPH (✉)
Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, 4401 Penn Avenue, Pittsburgh, PA 15224, USA
e-mail: juan.celedon@chp.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*, Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_1

Eliminating health disparities is not only ethical but also financially advantageous. Approximately one-third of direct medical expenses for African Americans, Asians, and Hispanics in the USA represent excess costs due to health disparities, and eliminating healthcare disparities could decrease medical expenditures by at least 229 billion dollars [3]. Thus, improving healthcare in underserved and minority populations may contribute to controlling the growth of healthcare costs in the USA.

Definition and Extent of the Problem

The American Thoracic Society (ATS) recently defined respiratory health disparities as significant differences in respiratory health that are closely linked to racial ancestry, social, economic, and/or environmental differences. As such, health disparities adversely affect groups of people who have experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; occupation; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion [4].

Respiratory health disparities exist across all age groups in the USA [5, 6]. Minority groups represent an important and growing segment of the US population, which is projected to comprise 29 % Hispanics, 13 % non-Hispanic Blacks, and 9 % Asians by 2050 [7]. Poverty—common among minorities—is associated with risk factors for respiratory morbidity in children and adults, including exposure to secondhand smoke and air pollution, poor housing quality, inadequate nutrition, and decreased healthcare access. Indeed, the poorest social groups are up to 14 times more likely to be affected by respiratory diseases than the wealthiest [5]. Similar patterns have been described among racial and ethnic minorities in the USA, many of which are disproportionately affected by respiratory diseases, as outlined below.

Health disparities have been described for most common respiratory diseases, which affect a substantial number of minorities and economically disadvantaged individuals [5, 8]. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the USA, affecting over 12 million adults [9]. COPD is almost twice more common and more severe for adults living near or below the poverty level, and women are 37 % more likely to have COPD than men [10]. Asthma is the most common chronic childhood disease in the USA. The estimated prevalence of childhood asthma is higher in African Americans (11 %) and Puerto Ricans (16 %) than in non-Hispanic Whites (8 %) [11]. Moreover, asthma is more common in subjects whose income is less than 100 % of the poverty level than in others (estimates of prevalence = 11 % vs. 7 %) [11, 12]. Compared with non-Hispanic Whites with asthma, Puerto Ricans and African Americans with asthma have more symptoms, school absences, healthcare utilizations, and disease-related deaths [8, 13, 14].

In the USA, lung cancer is a common malignancy and the most frequent cause of cancer-related deaths [15]. In this country, the burden of lung cancer is substantially greater in African Americans than in non-Hispanic Whites, perhaps due to both smoking habits and increased susceptibility to the carcinogenic effects of tobacco

[16]. Similarly, higher mortality rates from lung cancer have been reported for Hispanics and American Indians [17, 18]. Obesity can cause respiratory impairment and is the strongest risk factor for obstructive sleep apnea. Obesity affects over 90 million Americans, with inner-city residents and ethnic minorities much more commonly affected than the affluent and non-Hispanic Whites [19]. Compared with non-Hispanic Whites, non-Hispanic Blacks and Hispanics have greater risks of obstructive sleep apnea and sleep-disordered breathing, respectively [20]. Human immunodeficiency virus (HIV) infection is a risk factor for pulmonary infections, COPD, and lung cancer [21, 22]. In the USA, HIV disproportionally affects racial and ethnic minorities (with the exception of Asian-Pacific Islanders) and men who have sex with men, thus contributing to respiratory health disparities [23].

In spite of a decreased number of cases reported in the USA over the last decade [24], tuberculosis continues to disproportionally affect racial and ethnic minorities, and foreign-born persons. Compared to the tuberculosis rates in non-Hispanic Whites, such rates are approximately sevenfold higher in Hispanics, eightfold higher in non-Hispanic Blacks, and 25-fold higher in Asians/Pacific Islanders [24]. Moreover, tuberculosis is more common in unemployed persons than in employed individuals [24, 25]. Low SES is associated with increased respiratory morbidity in patients with cystic fibrosis and sickle cell disease, and sickle cell disease mostly affects African Americans [26, 27].

A number of respiratory diseases affect women differently and with greater severity than men. In the USA, the prevalence and mortality from COPD have risen more rapidly in women than in men over the past few years, with 53 % of COPD deaths currently occurring among women [9]. Similarly, lung cancer has increased in prevalence among women, now surpassing breast and colon cancers as the main cause of cancer-related mortality in females [28]. Moreover, pulmonary diseases attributable to biomass burning and tuberculosis predominantly affect women in low-income countries [29, 30].

Some respiratory diseases disproportionately affect vulnerable subpopulations of women, such as sexual minority women (SMW). Strikingly, smoking rates in SMW are at least twice as high as those in their heterosexual peers [31]. National data also show that SMW are significantly more likely to be diagnosed with asthma [32]. While the reasons underlying these recent findings are probably multifactorial, two contributing factors are limited access to healthcare due to lack of health insurance and financial barriers [33], and limited number of culturally competent providers. Whereas a full review and discussion of gender disparities in respiratory health is beyond the scope of this book, health disparities in SMW are discussed in Chap. 7.

Factors Contributing to Respiratory Health Disparities

Few diseases affecting the respiratory system (e.g., cystic fibrosis and sickle cell disease) occur solely on the basis of (non-modifiable) genetic susceptibility. Most respiratory diseases are caused by (potentially modifiable) behavioral and environmental risk factors (e.g., cigarette smoking), with the dose of exposure needed to

Table 1.1 Key risk factors for respiratory health disparities in the United States

Risk factor	Impact on pulmonary or sleep diseases
Cigarette smoking	Multiple illnesses, including asthma, chronic obstructive pulmonary disease (COPD), lung cancer, pneumonia, and idiopathic pulmonary fibrosis
Indoor and outdoor pollutants	Morbidity and mortality from asthma and COPD
Occupational hazards	Multiple illnesses, including occupational asthma, coal miner's pneumoconiosis, hypersensitivity pneumonitis, and lung cancer
Intravenous drug use	Human immune deficiency virus (HIV) infection and pulmonary hypertension
Obesity	Obstructive sleep apnea and asthma

cause a given disease (e.g., lung cancer, COPD) varying according to individual (e.g., genetic) susceptibility [34]. Behavior and environment differ across demographic groups, thus, largely determining respiratory health disparities. Once disease occurs, lack of healthcare access and other barriers to high-quality healthcare (e.g., low health literacy) further contribute to disparities in disease severity and health outcomes.

Major environmental and behavioral risk factors for respiratory health disparities include tobacco use, air pollution, occupational hazards, intravenous drug use, and obesity (Table 1.1). Tobacco use is the main cause of preventable deaths in the USA, and the main risk factor for respiratory diseases such as COPD and lung cancer [35]. Cigarette smoking and exposure to second-hand smoke (SHS) vary widely by SES and race/ethnicity. In 2012, current smoking was thrice as common in adults who did not graduate from high school as in those with college degree (32 % vs. 10 %) [35]. Moreover, current smoking is more common in adults living below the poverty level (29 %) than in those with a higher income (16 %). The prevalence of current smoking also varies by race/ethnicity, as follows: 39 % in American Indians, 24 % in non-Hispanic Whites, 23 % in non-Hispanic Blacks, and 15 % in Hispanics (albeit with marked differences across Hispanic subgroups, see Chap. 10) [35]. Residing in multiunit housing (which is correlated with poverty) increases exposure to SHS, even among those not living with a smoker [36]. Other vulnerable populations with high rates of tobacco use include the mentally ill, substance abusers, and members of the lesbian/bisexual/gay/transgender (LGBT) community [37]. Although inequalities in tobacco use are a major cause of respiratory health disparities and thus a key target for intervention, there are few programs for smoking prevention or cessation tailored to minorities and the poor [38]. Similarly, while building-wide smoke-free policies are effective, they are rarely mandated at the local or state level [36]. Complementary approaches, combining culturally appropriate prevention and cessation programs with increased taxation of tobacco products, may have the greatest impact on reducing disparities in cigarette smoking [39].

Outdoor air pollution also contributes to morbidity and mortality from respiratory and cardiovascular diseases. In 2010, about 4 % of the US population lived within 150 m of a major highway, thus being highly exposed to traffic-related air

pollution (TRAP) [40]. Residential proximity to a major highway is more common among racial and ethnic minorities, foreign-born persons, and persons who speak a language other than English at home [40, 41]. Similarly, exposure to indoor pollutants such as allergens and SHS is more frequent in underprivileged and minority populations, partly due to poor housing conditions and crowding [42, 43].

Occupational hazards are primarily caused by long-term or intense exposure to irritants and/or toxic agents (mineral and/or organic dust, smoke, fumes, gases, etc.) in the workplace. Such hazards can cause occupational pulmonary diseases (e.g., occupational asthma, asbestosis, coal miner's pneumoconiosis) or worsen respiratory diseases (e.g., asthma, COPD, and interstitial lung diseases) [44]. Racial and ethnic minorities and the poor are often employed in low-wage occupations where they are overexposed to occupational respiratory hazards. Minorities are overrepresented in industries such as agriculture, mining (coal, silica), textiles, demolition, manufacturing (asbestos), and service maintenance (cleaning supplies)—all of which have been associated with lung disease [45, 46]. Similarly, Native Americans have been disproportionally employed in uranium mines, a strong risk factor for lung cancer due to exposure to radon by-products [47].

Intravenous drug use, a risk factor for HIV infection and pulmonary hypertension, is more common in racial or ethnic minorities than in non-Hispanic Whites in the USA. Among intravenous drug users, racial or ethnic minorities are more likely to develop HIV infection than non-Hispanic Whites [48]. Obesity (a body mass index [BMI] >95th percentile in children or >30 kg/m [2] in adults) is a major public health problem in the USA. Obesity disproportionately affects African Americans, Hispanics, and the poor [49]. Obesity is the strongest risk factor for obstructive sleep apnea (OSA) [50], as well as a risk factor for asthma and asthma morbidity in children and adults [51]. To date, however, few or no clinical trials of weight loss management or bariatric surgery to treat respiratory diseases such as asthma have included minorities.

Once a respiratory illness occurs, genetic variants may differentially affect disease severity or response to treatment across racial or ethnic groups. For example, variants in the beta(2)-adrenergic receptor gene (*ADRB2*) have been linked to differences in disease severity and bronchodilator response between Puerto Ricans and Mexicans with asthma, underscoring the need for research on genetics and pharmacogenetics in racial/ethnic minorities [52].

A multitude of factors coalesce to generate disparities in the prevention, diagnosis, and treatment of diseases encountered in pulmonary, critical care, and sleep medicine [53]. At the system level, lack of health insurance is a major barrier to healthcare. Similarly, organizational and geographic barriers to care have been linked to diagnostic delays and worse respiratory outcomes among racial and ethnic minorities [54, 55]. Low-income and minority children continue to receive poorer quality healthcare, which can worsen disparities for respiratory diseases such as asthma [56].

Although there is limited empirical evidence of frequent unconscious bias or stereotyping by healthcare providers, barriers to patient-provider communication (due to limited number of providers who are proficient in other languages and lack of cultural match between minority patients and their physicians) may contribute to

respiratory health disparities [57, 58]. For example, low-income and uninsured or publicly insured individuals report less patient-centered care [56]. Similarly, ineffective communication may result in misclassification of disease severity [59] perhaps because of racial or ethnic differences in symptom descriptors (e.g., dyspnea or wheeze in asthma) [60].

Multiple patient-level factors may also underlie disparities in morbidity from respiratory diseases. Cultural beliefs, such as fatalism or certain illness representations (beliefs about etiology, consequences, and controllability of diseases), are strong drivers of health behaviors or coping that may markedly vary across racial and ethnic groups [61]. Indeed, differences in adherence with inhaled corticosteroids between non-Hispanic Whites with asthma and non-white patients with asthma may be mediated by beliefs about efficacy or side effects from treatment. Minority patients with asthma have more negative beliefs and lower adherence with inhaled corticosteroids than Non-Hispanic Whites with asthma [62, 63]. Low health literacy, which is more common in certain minority groups and the poor, is associated with worse outcomes in asthma and COPD [64, 65]. Mistrust of healthcare providers is common among African Americans and may interfere with seeking care or adopting care modalities such as palliative care, which can lead to improved quality of life and decreased caregiver burden [66, 67].

Conclusions

Unequal exposure to major environmental and behavioral risk factors for respiratory diseases across demographic groups defined by race/ethnicity and SES leads to most disparities in respiratory health. Such disparities are common and can be worsened by inadequate healthcare for minorities and the poor.

Respiratory health equality, defined as the highest possible level of respiratory health for all people, can only be achieved through the elimination of existing health disparities [4]. Since respiratory health disparities are multifactorial, their elimination will require a comprehensive approach to address all contributing factors, as discussed in Chap. 15.

Acknowledgment *Funding*: Dr. Celedón's contribution was funded by grants HL079966, HL117191, and HL119952 from the U.S. National Institutes of Health, and by The Heinz Endowments.

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Chapter 2
Race and Ethnicity

Neeta Thakur, Marquitta J. White, and Esteban G. Burchard

Overview

Respiratory health disparities are major sources of morbidity and mortality among disadvantaged populations in the United States (US). As US demographics shift away from a white majority, existing disparities related to race and ethnicity (see Chaps. 1 and 15) will become more apparent and widespread. Across most respiratory diseases, African Americans suffer greater morbidity and mortality than non-Hispanic whites [1–5]. Although Latino populations are classified as a single ethnic group, there is considerable variability in the prevalence of and mortality from respiratory diseases across subgroups. In the USA, Puerto Ricans have one of the highest burdens from asthma, while Mexican Americans have relatively low prevalence of and morbidity from asthma [3, 6, 7]. Reducing disparities related to race and ethnicity is one of the goals for the *Healthy People 2020* initiative [8]. Approaching the differences in respiratory health related to race and ethnicity requires a transparent understanding of the scope of the problem that will be described further in this chapter. The etiology and perpetuation of these disparities will be discussed with a life course perspective [9], which harnesses tools from sociology, epidemiology, population genetics, and molecular biology. An integrated

N. Thakur, MD, MPH • M.J. White, PhD, MS
Department of Medicine, University of California at San Francisco,
1550 4th Street, Bldg 19B, Room 582, Box 2911, San Francisco, CA 94143, USA
e-mail: neeta.thakur@ucsf.edu; Marquitta.white@ucsf.edu

E.G. Burchard, MD, MPH (✉)
Department of Medicine, University of California at San Francisco,
1550 4th Street, Bldg 19B, Room 582, Box 2911, San Francisco, CA 94143, USA

Department of Bioengineering and Therapeutic Sciences, University of California at San Francisco, 1550 4th Street, 5th Floor, Room 584B,
San Francisco, CA 94158, USA
e-mail: esteban.burchard@ucsf.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_2

approach will provide structure to the study of respiratory health disparities related to race and ethnicity and may unveil new directives to address, and with time, possibly eliminate these disparities.

Shifting Demographics in the United States

Racial and ethnic minorities—who currently make up nearly 40 % of the US population—are projected to become the majority by 2043, with a more pronounced shift in the pediatric population (Fig. 2.1) [10]. This phenomenon has been ignited by the influx of more than 40 million immigrants of predominantly Latino and Asian descent over the last five decades [11, 12].

In New Mexico and California, Latinos are already the ethnic majority [13, 14], while in Hawaii, Asian/Pacific Islanders are the current ethnic majority [15]. These states offer insights on approaches to reduce racial and ethnic disparities in respiratory health. Childhood asthma disproportionately affects African American and Latino communities in Central and Northern California [16]. In response to high rates of asthma-related hospitalizations, a comprehensive statewide program was created [17] to better improve surveillance of disease and develop integrated approaches to reduce the burden from asthma in low-resource communities. In Hawaii, Native Hawaiians have more than double the mortality rate from cardiovascular disease as Caucasian residents [18]. A possible cause of this disparity is the use of clopidogrel, a drug that is commonly used to treat and prevent myocardial infarction and stroke [18] but is significantly less effective in carriers of a genotype that is more frequent in East Asians (23–45 %) [19] and Pacific Islanders (40–77 %) [20, 21] than in Caucasians (10–20 %). In March 2014, the District Attorney of Hawaii filed a lawsuit against GlaxoSmithKline, the makers of clopidogrel, claiming false, unfair and deceptive marketing of a product known to be less effective in the majority of their residents [18]. Across the Nation, local and state governments have led efforts to ban tobacco smoke, which have led to improvements in respiratory disease [22–25]. Thus, efforts at the local and state level are necessary, and often occur more swiftly and effectively than those at the federal level.

Race and Ethnicity, Are the Categories Obsolete?

In 1997, the Office of Management and Budget set the standards on how to collect and record data on race and ethnicity [26]. These set categories (Table 2.1) are used for categorizing data for federal statistics, including the U.S. Census Bureau, program administrative reporting, and civil rights compliance reporting. The National Institutes of Health also depends on these categories for study enrollment reporting, and in turn, many investigators have used these categories to shape research

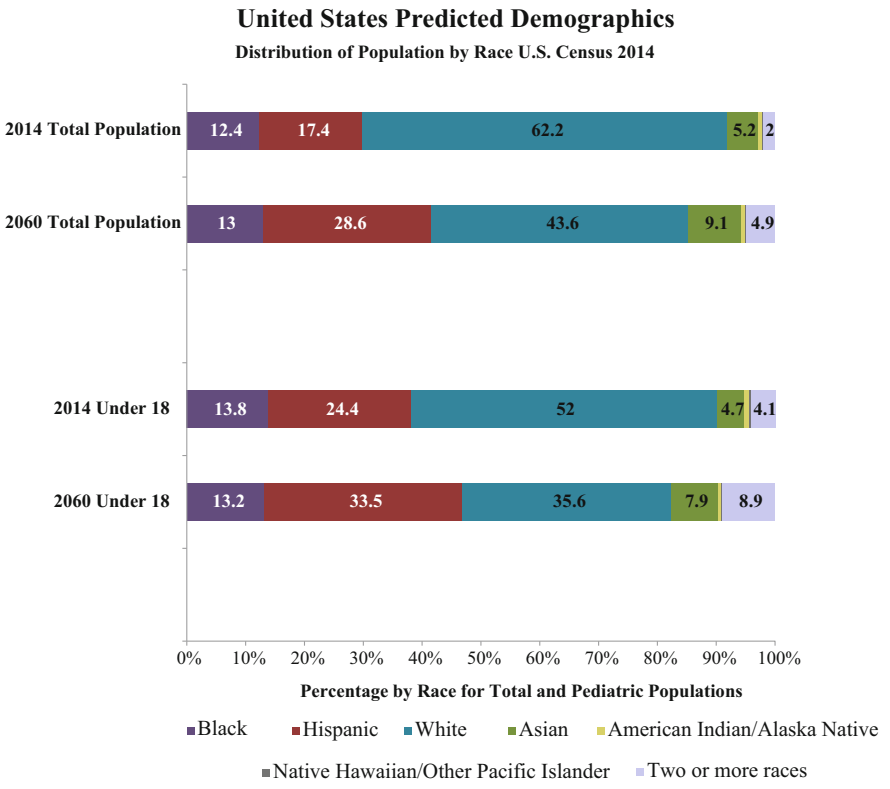

Fig. 2.1 Current and predicted distribution of US population by race/ethnic group and age group. Data from U.S. Census Bureau: 2014 National Projections. Population estimates for American Indian/Alaska Native: Total 0.7 (2014) 0.6 (2060); Under 18 0.9 (2014) 0.6 (2060). Population estimates for Native Hawaiian/Other Pacific Islander: Total 0.2 (2014) 0.2 (2060); Under 18 0.2 (2014) 0.2 (2060). *Reference*: Colby, Sandra L. and Jennifer M. Ortman, *Projections of the Size and Composition of the U.S. Population: 2014 to 2060*, Current Population Reports, P25-1143, U.S. Census Bureau, Washington, DC, 2014

conducted in different racial and ethnic groups. These defined categories of race and ethnicity have become poor proxies of multiple environmental and socioeconomic exposures, and have been inelegantly used as surrogates for determining genetic risk of disease. Detractors of the terms race and ethnicity argue that by describing disparities within the confines of these categories, efforts are shifted away from the real causes of disease [27]. However, while the current categories of race and ethnicity are limiting and not truly representative of the diversity or blending of cultures in the USA, most metrics, including health, financial, and educational, are collected using these set categories and, in turn, are used to influence policy decisions that may impact the overall respiratory health of Americans. Thus, it remains important to examine respiratory health disparities within these confines.

Table 2.1 Minimum race and ethnicity categories in the USA by the Office Management and Budget

Question 1. Ethnicity (asked before the race question)
• Hispanic or Latino
• Not Hispanic or Latino
Question 2. Race[a]
• White
• Black or African American
• American Indian or Alaska Native
• Asian
• Native Hawaiian or Other Pacific Islander

[a]More than one category may be selected

Why Race and Ethnicity Matter for Respiratory Health

Whereas race has been characterized by an individual's primary continent of origin, ethnicity is defined by a shared social, linguistic, and cultural heritage (e.g., African American, Hispanic) [28, 29]. Hispanics and African Americans have varying degrees of African, European, and Native American genetic ancestry [30], and such ancestral variability has been shown to influence lung function and airway diseases in these ethnic groups [31–34]. Hispanic is an ethnicity and not a race: Hispanics should be classified into subgroups by country or region of origin, and such subgroups often differ with regard to risk factors and disease burden (see above). For example, smoking patterns differ across various Hispanic subgroups in the USA [35]. Thus, combining subgroups or ignoring racial ancestry can lead to biased results of respiratory research studies in Hispanics and other racially admixed populations.

Race, while used to define groups of individuals from geographically distinct areas and who share physical attributes and lineage (e.g., white, black), has no genetic basis: 85 % of genetic variation occurs within individuals of the same race, while less than 15 % of variation occurs between races [36, 37]. All humans have the same set of genes and these genes may alter over time under unique evolutionary pressure. This leads to the expression of certain traits over others, and results in allelic frequencies that differ across ancestral populations [38]. Traits commonly used to distinguish between races, such as skin color and facial construction, are not genetically tied to specific race groups but instead result from environmental and behavioral forces that lead to change over time. For example, skin color is the result of the amount of sun exposure over generations—with darker skin being more common amongst those with ancestors who lived in regions near the equator. Despite similarly dark skin, the genetic variants underlying skin pigmentation differ between South Indians and Cape Verdeans [39–41]. In fact, South Asians and Western Europeans share a gene for light skin pigmentation [40] that is more reflective of colonization and migration patterns than of true racial differences. In fact, categories of race and ethnicity are more reflective of the shared experience of certain

groups in the USA. This includes their shared exposure to risk factors for respiratory disease, including air pollution and tobacco smoke, poverty, and inadequate access to medical services (see Chaps. 1 and 15).

In the USA, race has been used to segregate and deny freedoms or services to minority groups, thus allowing members of the majority to keep their leaders in control. Over centuries, these practices became institutionalized within the US political, educational, and health systems [42–45]. These practices have led communities of color to often live in urban deprived areas that lack adequate infrastructure, as evidenced by overcrowded homes and dilapidated housing units, and reduced access to reliable transportation, public education, and safe open spaces. For example, Latino and African American children often live in neighborhoods with high levels of air pollution and incur high levels of exposure to pesticides and toxic industrial chemicals [46, 47]. These same communities are not afforded optimal educational opportunities due to historical segregation of schools, a concentration of lower-performing schools in poor urban areas, and lack of financial resources to pursue higher education [48–50]. This has contributed to a concentration of racial/ethnic minorities in low wage jobs.

These forms of discrimination also impact healthcare delivery, financing, and research. The link of employment to health insurance has led to individuals with low wage jobs to have no insurance or be underinsured [51]. While the introduction of the Affordable Care Act [52] has reduced this inequity, racial and ethnic minorities are still underinsured compared with their white counterparts and more like to seek care in low performing hospitals and clinics [53–55]. The inherent bias in the educational system has led to a lack of diversity in the medical professions and a shortage of healthcare providers in minority communities, as individuals who identify as an underrepresented minority are more likely to serve their own communities (see Chap. 15) [56, 57].

The exclusion of racial and ethnic minorities also extends to biomedical research [58, 59]. For example, many studies have examined potentially detrimental exposures in white farm workers, while very few have assessed the effects of particulate matter and pesticide exposure on the respiratory health of migrant farm workers, many of who are undocumented, marginalized, and highly exposed to occupational hazards and pesticides [60, 61]. Healthcare providers and scientists are informed from and base their current practices on research extrapolated from a largely homogenous population, whom are usually white and male. Current practice is to apply findings from one group to another, which may lead to dangerous outcomes, given differences in genetic variation, socioeconomic factors, and environmental exposures across groups.

Race and ethnicity are powerful social constructs that influence day-to-day interactions, afford certain groups privileges over others, and impact how external threats or stress are distributed, perceived, and internalized. Moreover, self-identified race or ethnicity influences an individual's behavior and place of residence. Thus, race and ethnicity must be considered in the evaluation of respiratory health disparities.

What Is the Role of Genetic Ancestry in Examining Respiratory Health Disparities?

Racial differences in respiratory health cannot be solely explained by social and environmental inequalities [34, 62, 63]. Rather, the high burden of disease observed among minorities may result from the biological embodiment of specific socioeconomic, environmental, and discriminatory experiences that have occurred over generations [64–68]. However, not all individuals in minority groups develop adverse health outcomes in response to poverty and other stressors. To identify individuals or communities at risk, measures of susceptibility [69] and resilience, both behavioral and genetic [65, 70, 71], to environmental stressors may be used to predict who is most at risk from poor health outcomes based. Understanding the interaction between social and environmental upbringing with an individual's genetic and epigenetic profile [72] can broaden the understanding of disease pathology and expand potential therapeutic options for everyone.

As outlined in the previous section, race and ethnicity are sociopolitical constructs devoid of any true genetic basis. Conversely, genetic ancestry is a quantifiable variable that describes the geographical origin of different segments of an individual's genome [73]. Following the completion of the Human Genome Project in 2003 [74], genetic association studies have been applied, in increasing frequency, to identify variants that contribute to differences in disease prevalence and/or severity between human populations. Race and genetic ancestry are two related, but innately different, terms that are often used synonymously when discussing population differences and designators in biomedical research. Using race and genetic ancestry interchangeably is a dangerous practice that can lead to misconceptions and misunderstanding in the lay public, and misinterpretations for researchers [75, 76].

Genetic ancestry can be measured at the global level, which describes the total proportions of an individual's genome that derive from one or more source populations, or at the local level, where the genetic ancestry of chromosomal segments within an individual are assessed [73]. Genetic ancestry is unique to each individual, and varies both within and between racial ethnic groups. For example, individuals who self-identify as African American display a range of African, European, and Native American ancestral proportions depending on their US region of origin [28, 77, 78]. African American individuals from states that were slave-holding versus "free" show higher proportions of African ancestry than their counterparts from "free" states during the U.S. Civil War period [78].

There are also large differences in the proportions of African, European, and Native American ancestry within the Latino/Hispanic population in the USA [79, 80]. As in African Americans, ancestral proportions span the entire range of possibilities among individuals who self-identify as Latino/Hispanic, but ancestral proportions also show subgroup specific trends. For example, Mexican Americans and Puerto Ricans both display admixture from the same three aforementioned ancestral populations, but the average distribution of these ancestral estimates is quite different; Puerto Ricans have, on average, a larger proportion of African

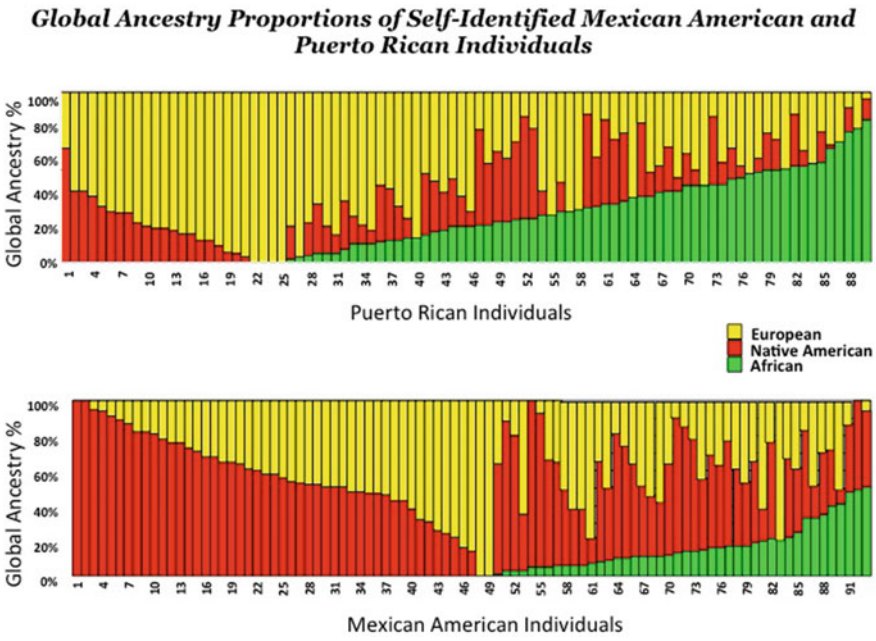

Fig. 2.2 Individual ancestry estimates for healthy Puerto Ricans and Mexican Americans, clustered by admixture levels. *Reference*: Gonzalez Burchard E, Borrell LN, Choudhry S, Naqvi M, Tsai HJ, Rodriguez-Santana JR, et al. Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. American journal of public health. 2005;95(12):2161–8. Epub 2005/11/01

Ancestry versus Native American ancestry, whereas Mexican Americans have higher proportions of both European and Native American ancestry versus African ancestry (see Fig. 2.2) [73, 81].

Recent studies have shown that both self-identified race or ethnicity and genetic ancestry are independently associated with differences in response to medication and disease prevalence and/or severity [5, 34, 69, 82–85]. For example, African ancestry is inversely correlated with lung function among African Americans [86]. Alternatively, Native American ancestry is positively associated with lung function but inversely associated with asthma risk in Latino/Hispanic children adolescents [34]. Mean global ancestry has been shown to correlate with self-identified race [87], but this correlation is not perfect and may leave a portion of the substructure within populations unidentified [88]. To avoid potential confounding leading to incorrect inference in genetic association studies, it is important to consider both self-identified race/ethnicity and genetic ancestry when constructing statistical models to assess the relationship between genotype and phenotype. The inclusion of race as a covariate in genetic association studies, or as stratification criterion, will address, in part, any inherent differences/similarities between participants due to environmental factors and other socio-cultural/political characteristics likely to be shared among individuals who self-identify within the same racial/ethnic group [34, 87].

Including genetic ancestry as a covariate in the analysis accounts for genetic differences between subjects due to shared patterns of allelic expression among members of an ancestral group, independent of phenotype status [87, 89].

An additional use of genetic ancestry information in the context of health disparities research is admixture mapping. Given significant differences in disease prevalence and allelic frequencies among racial or ethnic groups, admixture mapping is comparatively more powerful than standard association tests to detect susceptibility loci for complex diseases in racially admixed populations [90, 91]. Incorporating genetic ancestry information into disease association analyses has the potential to inform care not only in admixed population but also in source "ancestral" populations. For example, learning why black patients with kidney failure have better survival than their counterpart whites may reveal insights helpful to whites [92]. Moreover, the influence of genetically determined ancestry on health can be leveraged to provide insights into pathogenic mechanisms and new treatment approaches [93].

Taking a Life Course Perspective for Examining Respiratory Health Disparities

Understanding the complex interplay among biological, behavioral, social, and environmental determinants of respiratory disease in disadvantaged populations is crucial for improving the overall health of the population. A framework that incorporates concepts from multiple disciplines and examines determinants of health across the life span allows for a more holistic understanding of the root causes of disparities in respiratory health related to race and ethnicity (see also Chaps. 1 and 15). Racial and ethnic disparities in respiratory health are evident across all age groups: African American and Puerto Rican children [6] have higher prevalence of asthma compared with all other race/ethnic groups, and among adults, African Americans with lung cancer have a higher likelihood of death [1, 82]. The persistence of disparities across the life span suggests that the exposures and potential risks for respiratory disease should be examined as a cumulative experience that occurs over the course of one's life. This includes considering exposures that may only occur during the in utero period, to those that may have an additive effect over time [9, 94]. This approach leaves room for the consideration of multilevel influences and allows for the examination of how individuals interact within their community and with their environment and how these said exposures, and the associated psychosocial stress, may affect biological processes and have an additive effect over time (Fig. 2.3).

For example, tobacco smoke is an important risk factor for almost all respiratory diseases. In utero tobacco exposure independently increases the incidence of wheeze and asthma among young children [95]. Postnatal exposure to tobacco smoke is associated with an increased risk of lower respiratory infections in infants [96], and continued secondhand smoke exposure during childhood is associated with asthma

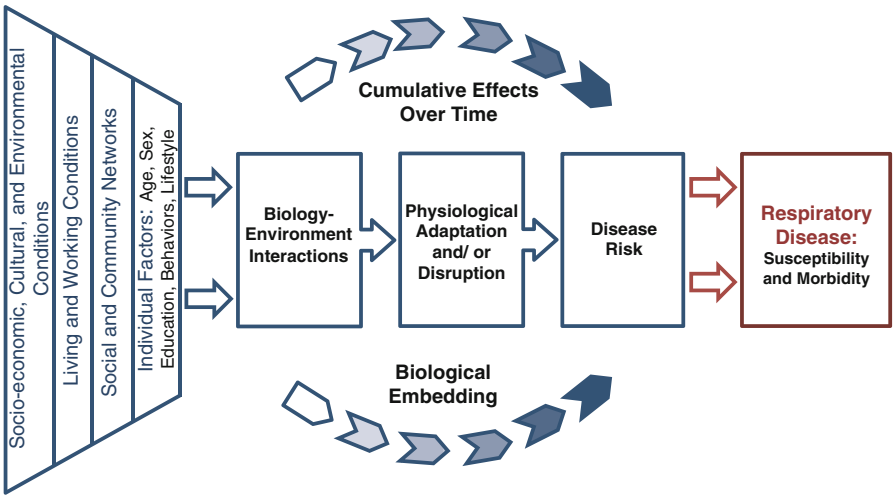

Fig. 2.3 Taking a life course perspective: a health model of respiratory disease. Adapted from Halfon et al. Life Course Health Development Model and from the biodevelopmental framework. *Reference*: Halfon N, Hochstein M. Life course health development: an integrated framework for developing health, policy, and research. *The Milbank quarterly.* 2002;80(3):433–479, iii. Center on the Developing Child. How early experiences get into the body: a biodevelopmental framework. 2014; http://developingchild.harvard.edu/index.php/resources/multimedia/interactive_features/biodevelopmental-framework/. Accessed October 2, 2014, 2014

incidence [95] and worse asthma control [97]. In adults, it is well known that cumulative exposure to tobacco smoke increases the risk for chronic obstructive pulmonary disease (COPD) and lung cancer [98–100]; however, the effects of tobacco appears to be more profound in African Americans when compared with whites. Despite lighter smoking habits, African Americans with COPD experience greater pulmonary function decline compared with whites [69]; similar results have been observed in individuals without COPD [101]. A life course perspective allows for the consideration of the exposure over several key time points (points of susceptibility) and also allows for evaluation of the cumulative effect and how this effect may be different across racial/ethnic groups. This perspective also allows for examination of how the individual or group is exposed to the risk factor, in this case—tobacco, and how the multiple levels in which the individual is nested may interact to facilitate, or impede, the exposure to a known toxin or stress. For example, greater African ancestry [101], reduced tobacco metabolism [102], and increased breath holding with menthol cigarettes [103] have all been postulated as possible reasons for the decline in pulmonary function in the presence of tobacco smoke that is observed in African Americans when compared with whites. In addition to observing the direct effects of tobacco smoke, there is the need to examine which tobacco products are used and how these products are accessed or promoted to different racial/ethnic groups. Targeted advertisement of tobacco products to minority communities, including the peddling of menthol cigarettes, which use is significantly

higher among African Americans compared with all racial/ethnic groups [104, 105]. Menthol causes a sense of coolness and local anesthesia, promotes breath holding, and reduces the metabolism of nicotine [103, 106]. Data has suggested that smokers of menthol cigarettes have more difficulty in quitting despite smoking fewer cigarettes per day and this finding is most pronounced in African Americans [104, 105]. When examining the effects of tobacco exposure, it is important to note that racial and ethnic minorities have higher exposure to secondhand smoke compared with whites [107]. This exposure occurs both in and outside the home, where there is less control: multiunit and public housing often do not regulate tobacco use inside individual units despite the high risk of exposure in close living quarters [108]. Due to financial limitations, individuals or families living in such units lack the choice to move.

A life course framework allows us to consider multiple risk factors (genetic, biologic, behavioral, and environmental) and their interactions on disease pathogenesis at multiple levels. This holistic approach also leaves room for the idea that not all individuals respond the same to known risk factors for disease, and may open new avenues for the development of targeted interventions.

Conclusions

Reducing disparities in respiratory health based on race and ethnicity requires awareness and understanding of (1) the disparities themselves, (2) the groups most vulnerable to disparities, and (3) the factors that contribute to disparities and which are the most amenable to intervention. Thus, research and innovation are crucial to understanding, treating, and controlling respiratory diseases, generally, and for addressing health disparities, specifically.

Coordination and integration of research efforts in basic sciences, computational sciences, clinical medicine, behavioral science, and public health will yield a better understanding of the root causes of disparities, which will ultimately facilitate the development of new approaches to eliminate respiratory health disparities.

Acknowledgements This chapter provides an overview of the respiratory health disparities related to race and ethnicity. We are grateful for a number of students who helped prepare several of the tables and figures included in this section. We would like to extend much gratitude to Oona Risse-Adams, a driven high school student who brought a unique energy to our group; Page Goddard, an undergraduate student who brought spunk to our group; and, lastly, Jennifer Adams, another undergraduate student who reminded us to continuously reflect on day-to-day experiences.

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Chapter 3
The Influence of Social and Economic Conditions on Respiratory Health

Dean E. Schraufnagel and Ann M. Schraufnagel

Separating "Social" and "Economic" from "Socioeconomic"

The term "socioeconomic" appears to have come into usage in the early 1940s to categorize a class of people within a social and economic class [1]. The term assumes that the two are tightly linked or that one's social class is determined by one's income or economic class. This is a convenient concept for those with wealth to jettison to a high social class, but social status and economic status are not so interlocked. The mayor or chief of a poor village has high social status but may have low economic status. Conversely, a boor who has recently become wealthy may have gained high economic status, but may retain low social behavior. In fact, much of the world with low economic status does not have low social status and putting "socio-" and "economic" together in a term can be denigrating to persons of low economic status but high social status.

It is worth considering the two factors separately when assessing their health consequences. Low economic status may force individuals to work or live in hazardous environments, such as one with high air pollution, or with unsafe materials (e.g., asbestos or radiation). Low social status, on the other hand, may be associated with poor health habits or lack of knowledge or understanding of the benefits and means of good health. Health literacy, cultural beliefs, and social situations may affect health in these individuals. An example might be individuals who grow up lacking cultural and community awareness of the hazards of tobacco use. Persons of

D.E. Schraufnagel, MD (✉)
Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago, 840 S. Wood Street, Chicago, IL 60612, USA
e-mail: schrauf@uic.edu

A.M. Schraufnagel, MD, MPH
Department of Medicine, University of Washington, RR-512, Health Sciences Building, Box 356420, 1959 NE Pacific Street, Seattle, WA 98195-6420, USA
e-mail: annschra@uw.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_3

lower social status are more likely to use unhealthy substances, such as tobacco and other drugs. They are less likely to practice healthy behaviors, such as having annual influenza vaccinations or being attentive to a healthy diet.

The association of poverty and disease raises problems beyond what can be fixed with money. Tuberculosis is an example of a disease that is widely called a disease of the poor [2], although it is difficult to understand how the tubercle bacilli can distinguish the economic status of the individuals they infect. Noting the association with poverty should only lead to trying to understand more specifically related problems, such as crowding, medication costs, or smoking rather than poverty or social class. The strong association of tuberculosis and poverty in the public mind causes stigmatization and can aggravate control efforts. Fixation on tuberculosis as a disease of the poor portrays its victims as social outcasts [3, 4].

In spite of the important distinction between social and economic factors, the two entities are often intertwined. Wealth often raises social status, and poverty often limits upward social mobility. Many factors affecting health, such as breathing unhealthy air and lack of quality health care, are root causes of respiratory diseases that are common to both poor social and economic stature.

Historical Association Between Economics, Health, and Disparities

In the early nineteenth century, earnings were low and life expectancy was only about 40 years for most people in most countries in times of peace. Later in that century, the industrial revolution raised the economic status of certain people in some countries. By the end of nineteenth century, the industrial revolution had created great wealth for a few. At the same time, the discovery of bacteria as the cause of diseases brought far-reaching changes in public health. Clean water supplies benefited everyone. By the end of the nineteenth century, the scientific revolution created better health for many. Vaccines, surgery, and effective pharmaceuticals became available. Despite these public health gains, the industrial revolution brought new health problems and wealth disparity.

The early twentieth century saw enormous expansion of both economic and health status but the gains were uneven. In the twenty-first century, all countries have encountered health and quality of life improvements, but disparities between and within countries have grown.

Respiratory Disease's Unique Status

Health disparities are more acute in respiratory disease than in disease of any other organ [5, 6] (see Chap. 1). Compared with individuals in the highest social group in Britain, those in the lowest social group are up to 14 times more likely to have respiratory disease [7]. Common causes of respiratory disease, such as occupational exposure, indoor and outdoor air pollution, tobacco smoking, and airborne infections, are

affected by social and economic factors. The poor and marginalized of society often lack access to health care, which may affect obtaining influenza vaccinations for health maintenance and antibiotics for respiratory infections. An unhealthy diet and obesity are strongly associated with obstructive sleep apnea. Environmental exposures and occupational hazards affect the lungs more than other organs and occur disproportionately in ethnic minorities and those with lower economic status [8, 9].

Poverty as a Health Factor

Most respiratory diseases disproportionally affect the poor. Disparities occur both within a country and between countries. Within a country, illness between rich and poor includes variation in prevalence, morbidity, and mortality. The extent of the disparity differs by disease and country. For example, in the United States, the prevalence of childhood asthma is 11.2 % in families living below the poverty level compared with 8.7 % for families earning 200 % above the poverty level [10]. Cystic fibrosis, a hereditary disease, is not likely to choose the poor over the rich. However, children with cystic fibrosis whose health costs are covered by Medicaid [government-funded insurance for poorer children in the United States (US)] have worse outcomes than those with other insurance (wealthier children). Children with Medicaid have a forced vital capacity that is 9.1 % lower than those not on Medicaid. They are also more than twice as likely to be below the fifth percentile in height and weight, and to have increased risk of respiratory exacerbations. Children on Medicaid have an adjusted mortality risk 3.65 times greater than those not on Medicaid [11]. Poorer cystic fibrosis patients are also less likely to receive lung transplantation [12].

Disparities between countries can be extreme and are multifactorial. For example, households in low-income countries may burn solid fuels, such as wood and dung, for indoor cooking and heating. The smoke from these fuels is associated with four million deaths per year globally, predominantly from chronic lung disease, cardiovascular disease, pneumonia, and lung cancer [13, 14]. The morbidity and mortality disproportionately affects women and children living in poverty in low- and middle-income countries [14], whereas the poorest people in high-income countries usually have access to clean cooking and heating options, such as stoves with chimneys, electric heating, and natural gas. This may help explain why more than 90 % of deaths from chronic obstructive pulmonary disease (COPD) occur in low- and middle-income countries [15] and why most of the 235 million people with asthma live in the developing world [16].

The annual economic costs of COPD and asthma in the USA are estimated to be more than $50 billion [17] and $56 billion [18], respectively (see Chap. 10). However, in the global picture, monetary statistics are misleading. What a person from a developed country might earn in a day, a person from a developing country might earn in a month, and the loss of a day's wage for a person in a low-income setting might be a greater burden than the loss of a month's salary for an individual in a high-income setting. Furthermore, economic figures tell nothing about the physical and emotional toll of being sick or unsure about one's next breath.

The risk factors for people in high- and low-income countries are evolving. Lung cancer is the most fatal of all cancers causing 1.59 million deaths in the world each year [19]. In the USA, it kills more than the next four types of cancers combined. Lung cancer is linked to tobacco smoking and has historically been more prevalent in high-income countries. Lung cancer disparities between economically advantaged and disadvantaged nations lay in detection, reporting, and treatment.

In recent years, however, the worldwide pattern of tobacco smoking has changed. Broad action against tobacco in high-income countries led to bans on public smoking and advertising, high taxes on cigarettes, and regulation of tobacco product labeling. These efforts have decreased smoking rates in these countries. Because the prevalence of lung cancer trails that of smoking by two to three decades, a decrease in lung cancer in high-income countries occurred only in the last part of the twentieth century [20]. In the face of this changing dynamic, tobacco companies have turned to other areas of the world; low- and middle-income countries often have less stringent tobacco control and are fertile grounds for tobacco sales. Smoking has risen to alarming levels in many of these countries [21], and lung cancer rates are correspondingly rising.

Decreased Access to Health Care as an Economic Factor

Both social and economic factors impede people's ability to obtain adequate health care, although these challenges may be predominantly economic for people living in countries without universal health care systems. In the USA, children in racial or ethnic minority groups and those of lower socioeconomic status have an increased prevalence of sleep disorders, but a lower likelihood of undergoing adenotonsillectomy, the most common treatment for pediatric sleep disorders [22]. One reason for this may be that fewer surgeons perform the procedure on poor children, as government medical assistance provides less reimbursement and requires more administration [23]. These findings contrast with those in other countries, where poorer children generally have a higher rate of adenotonsillectomy [22].

Poverty may also restrict access to higher levels of care. Federally Qualified Health Centers serve as safety nets for more than 19.5 million economically disadvantaged people in the USA [24]. However, diagnostic testing and management of certain diseases, such as obstructive sleep apnea, usually require sleep medicine specialists, which are undersupplied in these settings. Lack of specialty medical services for sleep may contribute to disparities in sleep apnea diagnosis and treatment [24]. Mediation analyses have estimated that impaired sleep may explain 10–25 % of the variance in health outcomes associated with low socioeconomic status in the United States [25].

Economic societal barriers may prevent equal access to health care. Historically, health care was less accessible to homosexual women in the USA because of health insurance and financial barriers [26, 27], which in part resulted from inequities in employer-sponsored health insurance for same-sex couples [28, 29] (see Chap. 7). The recent Supreme Court legalization of same-sex marriage nationwide may decrease this access disparity.

Social and Societal Factors as Health Risks

Tobacco Use

Tobacco use is an underlying risk factor for many lung diseases. Many social factors, including history of mental illness [30], substance abuse, unemployment, sexual orientation, low income, low social status, and not completing high school are correlated with smoking [31, 32]. In addition to the simple prevalence of smoking, the progression to heavy smoking, lack of smoking cessation, and lung cancer mortality have all been linked to social disadvantage in population-based studies. The disparities appear to be greater for women [33].

The increased use of tobacco in minority populations has many aspects. Sexual minority women—women who identify as lesbian or bisexual, or who have sex with women but do not identify as lesbian or bisexual—are at least twice as likely to smoke as their heterosexual peers [34, 35]. As a part of a stigmatized minority, these women experience stress [36] and may be more likely to have a maladaptive coping behavior, such as smoking. Furthermore, the tobacco industry actively targets sexual minorities [37] as well as other minorities in its advertising campaigns [38] (see Chaps. 2 and 7).

Finally, the cost of smoking is a major factor in tobacco use, especially among youth [39]. Native Americans, who have among the highest rates of smoking in the United States, pay among the lowest taxes for tobacco products on Native American lands.

Race and Ethnicity as Factors in Respiratory Health

Race and ethnicity are among the greatest predictors of health disparities [40] (see Chap. 2). Members of these minority groups have more exposure to toxic air [41], less prenatal and early life health care [42], less access to health care [43], less health knowledge, and less positive health-related behavior [44]. Although outdoor air pollution affects the health of all people, racial and ethnic minority groups generally live in neighborhoods with worse air quality and experience its adverse effects more than others [45–47]. Unfortunately, disparities are increasing. The differences in deaths from chronic obstructive lung disease from 1990 to 1998 and from chronic lower respiratory disease from 1999 to 2006 increased between racial and ethnic groups in the United States [48].

Members of minority groups, including racial, ethnic, religious, and sexual minorities, are marginalized in many parts of the world. This marginalization often denotes a lower status in society and leads to geographic segregation of similar groups of people. Marginalization and isolation often lead to poor health outcomes. A striking example of how a neighborhood affects health can be seen with sleep apnea in city dwellers. Members of racial and ethnic minority groups are more likely than whites to live in disadvantaged neighborhoods [49], and obstructive sleep apnea is associated with neighborhood disadvantage and low socioeconomic status [50].

Residents living in these neighborhoods are more likely to be exposed to factors that may contribute to sleep deficiency, including inopportune exposure to light, noise, allergens, and irritants including environmental tobacco and air pollution [51, 52].

Living in disadvantaged neighborhoods and occupational and psychosocial stressors have been linked to sleep disturbances; socioeconomic status has been related to stress [24]. Despite the higher prevalence of sleep disturbances in groups with low socioeconomic status, these disorders are less likely to be diagnosed and treated in these groups [24].

Finally, social norms within specific racial and ethnic groups may promote certain health behaviors. Evidence suggests blacks have lower adherence to sleep-disorder treatments, such as continuous positive airway pressure (CPAP) treatment, than do whites [53]. This could reflect a difference in socioeconomic resources, social support, and the perceived benefits or risks of treatment that may underlie racial differences in adherence [54].

Immigration and Acculturation Effects on Respiratory Health

Immigration and acculturation into a new society may affect respiratory health (see Chap. 5). In considering sleep disordered breathing, for example, Mexican Americans are 44 % more likely to report short duration of sleep than Mexican immigrants [24]. Another study found that acculturation, as measured by language preference and socialization in the USA before age 18 years, predicts self-reported sleep disturbances [55]. These studies provide initial evidence that acculturation is a factor that predisposes Mexican Americans to higher levels of sleep deficiency than whites. An important corollary of this is that even if some Mexican Americans are more economically stable in the USA than in Mexico, as an ethnic minority, they may suffer greater social stress and sleep disturbance.

Social Aspects of Access to Health Care

As stated, the challenges in accessing health care are both economic and societal. Minorities may be less likely to seek out care owing to their fear of being treated differently. One survey found that a third of sexual minority individuals reported not seeking health services because of their sexual orientation [56].

Disparities also may affect the diagnosis and treatment of patients. US physicians presented with a clinical vignette suggestive of COPD are more likely to make that diagnosis if the patient is male than if she is female [57], even though the prevalence of COPD among women in the USA is now greater than that of men [56]. When presented with spirometry accompanying the vignette, the gender differences in diagnosis disappear [58]. However, women with spirometry-confirmed COPD are 30 % less likely to be diagnosed clinically than men. Compared with men,

women are also less likely to have had spirometry [59], but more likely to report diagnostic delay in COPD, difficulty reaching their physician, and insufficient time spent with their physician [60].

Combination and Complexity of Social and Economic Disparities

Much research on health disparities combines social and economic factors into one socioeconomic status variable. This research is important to consider, first because it makes up the majority of disparities research, and second, because it illustrates the complex combination of social and economic factors that can contribute to differences in health outcomes.

Complexity Example: COPD

When comparing people with COPD from the lowest with the highest socioeconomic groups, the health disparities are striking (see Chap. 10). Those in the lowest socioeconomic strata have a higher prevalence [61], are at least twice as likely to have poor outcomes, are hospitalized up to 4.3 times more often, and have a mortality up to 10.8 times greater [61]. Disparities in the incidence, prevalence, hospitalizations, and mortality in COPD are larger than seen in other chronic diseases, including diabetes, heart disease, stroke, and cancer. The social and economic influences in COPD are farraginous. Smoking, occupational and prenatal exposures, air pollution, housing conditions, environmental exposures in childhood, childhood respiratory infections, history of tuberculosis, and burning of biomass fuels in the home can all play a role [61].

There are also gender disparities in COPD risk and outcomes, owing to a combination of environmental and genetic factors. Nearly 80% of never-smokers who develop COPD are women, indicating a higher exposure or susceptibility to nontobacco-related factors [62]. Globally, as more women smoke and work in jobs traditionally held men, the risk factors related to tobacco and occupation are changing [56]. With these changes, the prevalence of COPD is shifting. In 2009, more than half of deaths from COPD in the United States were in women [56].

Complexity Example: Pneumonia

Pneumonia is a main cause of death in children under 5 years of age in developing countries. Infection with human immunodeficiency virus (HIV), low birth weight, malnutrition, and lack of breastfeeding contribute to the risk of bad outcomes with

pneumonia and are associated with lower economic status [63]. Lack of health care and understanding how to maintain health are root causes of pneumonia complications that can be a target to prevent mortality. Hospital readmissions for pneumonia have been correlated with low education, low income, and unemployment, and mortality has been associated with low income [64]. Improving health care includes making available effective vaccines and essential medicines.

The complex interactions between causative factors and disease are reflected by the associations between smoking and susceptibility to tuberculosis and pneumonia in HIV-infected patients [65]. Bronchiectasis, resulting from inadequately treated pneumonia or tuberculosis, can lead to a life of recurrent respiratory infections. The rate of bronchiectasis in indigenous children from a remote Australian community was 147/10,000 [66]. Except persons with cystic fibrosis, bronchiectasis is rare in developed countries.

Complexity Example: Tuberculosis

Tuberculosis is another disease in which the social and economic risk factors are complicated and blend. Although poverty tracks strongly with tuberculosis [67], its association is mediated through crowding and other living conditions, lack of health care, smoking, and occupational risks. The association of tuberculosis and poverty is much lower in foreign-born individuals than in those born in the United States. Whereas living in zip codes associated with lower earnings is associated with five-fold increased risk of tuberculosis among persons born in the United States, living in zip codes associated with lower earnings is only associated with 1.3 times increased risk of tuberculosis among foreign-born persons in the USA [68].

For infectious diseases spread by respirable agents, concentrated living conditions have added importance to other common risk factors, such as health care availability and environmental exposures. The association between tuberculosis and pneumoconiosis is related not only to the close quarters of mining, smoking, lung damage, and coinfection with HIV, but also to specific effects of silica particles on alveolar macrophages and other pathophysiologic processes.

Complexity Example: Obstructive Sleep Apnea

Both health and health care disparities contribute to the increased burden of sleep disorders in children. Children of low-income families have higher rates of sleep disorders [69] and obesity. These children are also more likely to be exposed to secondhand smoke [70], which may cause adenoidal or nasal mucosal inflammation and sinusitis, leading to snoring and sleep disturbance. The sleep of caregivers influences the sleep of children, and sleep behaviors also reflect the influences of interrelated social, cultural, and environmental factors operating within households [24]. There are also associations between impaired sleep and negative emotions and lifelong discrimination [71].

Conclusion: Problems Are Magnified by the Interactions of Poverty and Social and Behavioral Conditions with Tobacco, the Environment, and Occupation

Many environmental and occupational situations affect the respiratory system and lead to direct damage or compound the problems in respiratory disease. Social and economic factors play a major role in exposures, disease prevalence, disease severity, disease outcomes, and comorbid conditions.

A combination of factors potentiates and magnifies the risks for respiratory health (see Chaps. 1 and 15). Tobacco use is cross-linked with many respiratory risk factors and is more common in socially marginalized groups. Children of pregnant smokers are at risk of developing lung disease. Maternal smoking leads to placental insufficiency and low birth weight, and is associated with reduced lung function and respiratory infections throughout life. Lung function at birth affects lung function in later life.

Tobacco is a leading cause of preventable illness and death because it causes lung cancer, COPD, and many other conditions. When multiple or complicated diseases occur in disadvantaged individuals, the consequences may be amplified because the resources to correct or cope with them are less. The problems are further worsened if the public health infrastructure does not intervene effectively on their behalf.

Asthmatics from low socioeconomic groups are more likely to smoke than are those from higher groups. These asthmatics also believe that they cannot intervene to control their asthma symptoms in contrast to those from higher status groups [7]. These feelings can add to poor health outcomes. Behavior can become a multilevel correlate leading to a vicious downward cycle of respiratory health fueled by social and economic forces.

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Chapter 4
Air Pollution and Climate Change

John R. Balmes

Introduction

While health disparities due to race/ethnicity and socioeconomic status (SES) exist for multiple respiratory diseases, this chapter will focus on the impact of air pollution and climate change on asthma and chronic obstructive pulmonary disease (COPD). The primary reason for this focus is that the evidence for both adverse effects of air pollution and health disparities is strongest for these two diseases.

Asthma is a relatively common disease in the USA, especially among children (see Chap. 10) [1]. In the USA, the prevalence and morbidity from asthma are higher in African Americans than in non-Hispanic whites [2, 3]. When ethnicity is considered, Puerto Rican children have the highest prevalence of asthma and Mexican-American children the lowest [3]. When asthma prevalence is categorized by poverty level, there is a clear negative association, i.e., the lower the family income, the higher the asthma prevalence [3].

COPD is also common among older adults, ranking as the third leading cause of deaths per year in the USA [4]. There is evidence for health disparities in COPD, particularly for SES (see Chap. 10) [5].

J.R. Balmes, MD (✉)
Department of Medicine, University of California at San Francisco, San Francisco, CA, USA

Department of Environmental Health Sciences, School of Public Health,
University of California, Berkeley, CA, USA

Zuckerberg San Francisco General Hospital, 1001 Potrero Street,
San Francisco, CA 94110, USA
e-mail: john.balmes@ucsf.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_4

Air Pollution Impacts on Asthma and COPD

Outdoor air pollution is a trigger for asthma exacerbations in both children and adults, resulting in increased healthcare utilization. Whereas older studies mostly investigated exposure to individual pollutants and asthma outcomes, recent evidence points to traffic-related air pollution (a mixture of gases and particles) as perhaps having the greatest adverse effects on people with asthma [6, 7]. Common traffic-related air pollutants include nitrogen dioxide (NO_2) and fine particulate matter $\leq$2.5 μm in diameter ($PM_{2.5}$). Ozone (O_3), formed when nitrogen oxides and volatile organic compounds emitted during morning rush hours react with sunlight later in the day, is also a pollutant related to motor vehicle use. Ozone, $PM_{2.5}$, and NO_2 have been associated with increased emergency department (ED) visits and hospitalizations for asthma [8, 9]. Ozone and $PM_{2.5}$ have direct effects on the airway epithelium at ambient levels, but the mechanism underlying the association between NO_2 and asthma is less clear. Because ambient levels correlate relatively well with traffic emissions, NO_2 may be acting more as a marker of exposure than as a direct cause.

Evidence is also emerging that outdoor air pollution can cause asthma, especially in children [10, 11]. Studies of adult-onset asthma have identified an increased risk associated with ozone exposure, although this effect was restricted to men [12]. Studies of asthma incidence in children have also identified an association with ozone, although the risk might be confined to heavily exposed, physically active children [10]. Several recent prospective studies of children without asthma at recruitment support the notion that traffic-related air pollution is also responsible for incident asthma [13–15], and at least one study has also shown this in a cohort of adults [16].

The evidence for outdoor air pollution as a trigger of COPD exacerbations is reasonably strong, as documented in several review papers [17, 18]. Similar to asthma, there has been considerable interest in the question of whether outdoor air pollution contributes to the etiology of COPD. A recent systematic review and quantitative synthesis concluded that the epidemiologic evidence of an effect of air pollution on incidence and prevalence of COPD remains suggestive but not conclusive [19]. Chronic exposure to air pollution affects growth and decline of lung function, but these effects are not clearly linked to COPD [20, 21].

Additional data on the risk of developing COPD from air pollution come from the European Study on Chronic Air Pollution Effects (ESCAPE) [22]. This study involved a meta-analysis of four studies in different countries with a large combined sample size. Although there was no significant association between long-term exposure to either oxides of nitrogen or particulate matter and spirometry-defined COPD, traffic intensity was associated with COPD incidence in females and never smokers.

Disparities in Exposure to Air Pollution

Minorities and the poor tend to have greater exposures to both U.S. Environmental Protection Agency (EPA) “criteria” pollutants (O_3, NO_2, $PM_{2.5}$, SO_2, CO, and Pb) and hazardous air pollutants (toxic emissions from point sources that cause cancer or adverse reproductive effects). These demographic groups tend to live in

neighborhoods through which major roadways pass, and which are also often adjacent to rail yards, ports, and distribution centers. The US consumer economy now relies on imports of goods from Asia, and surface goods movement from container ships to port cranes, to intermodal facilities for trains and trucks, to distribution centers, to "big box" stores involve exposure to diesel exhaust. Who lives along this transportation corridor?—minorities and the economically disadvantaged [23].

Public schools are also built near freeways with high diesel truck traffic because land adjacent to such roadways is usually cheap. In addition, diesel school buses are more likely to be used to transport children to public schools. Minority children represent a high proportion of public school attendance [24].

Focusing on $PM_{2.5}$ and O_3, a recent study found that (within areas covered by EPA monitoring stations) non-Hispanic blacks were consistently overrepresented in communities with the poorest air quality [25]. This was especially true for the 20 % of communities with the worst air quality. In addition, those communities with the worst air quality in terms of daily $PM_{2.5}$ had a higher percentage of residents who were Hispanic or poor than the 20 % of communities with the best air quality. An income gradient was not present for O_3, which is likely explained by the fact that it is a more regional pollutant that does not respect community borders. In the Multi-Ethnic Study of Atherosclerosis cohort, residence in majority white neighborhoods was associated with lower air pollution exposures ($PM_{2.5}$ and NO_x), while residence in majority Hispanic neighborhoods was associated with higher air pollution exposures [26]. In terms of adverse health effects, a systematic review and meta-analysis by Bell and colleagues identified strong evidence for associations between exposure to O_3 and unemployment or lower occupational status, and weaker evidence for associations with race/ethnicity, education, poverty, or lack of central air conditioning [27].

Exposure to traffic-related air pollution is greatest for people living in close proximity to roadways, e.g., within 150 m [28]. A 2010 study by the Centers for Disease Control and Prevention (CDC) documented disparities for race/ethnicity, nativity, and language spoken at home; the populations with the highest estimated percentage living within 150 m of a major highway included members of racial and ethnic minorities, foreign-born persons, and persons who speak a language other than English at home [29]. The estimated proportions of the population living within 150 m of a major highway were as follows: 2.6 % for American Indians/Alaska Natives, 3.1 % for non-Hispanic whites, 5.0 % for Hispanics, and 5.4 % for Asians/Pacific Islanders. The estimated proportions of the population living near a major highway were 5.1 % for foreign-born persons, 5.1 % for persons who speak Spanish at home, and 4.9 % for persons who speak another non-English language at home. For poverty status, the estimated proportions of the population living near a major highway were 4.2 % for those in the poor category, 3.7 % for those in the near-poor category, and 3.5 % for those in the non-poor category. Disparities by educational attainment were less pronounced. The estimated proportion of the population living near a major highway varied from 3.4 % for high school graduates to 4.1 % for those with less than a high school diploma.

Su and colleagues have developed a method to quantify disparities in air quality within a region such as Los Angeles [30]. They plot cumulative share of exposure to a pollutant against the cumulative share of the population ranked by race/ethnicity or SES to derive an "inequality curve." Figure 4.1 shows that non-white and low

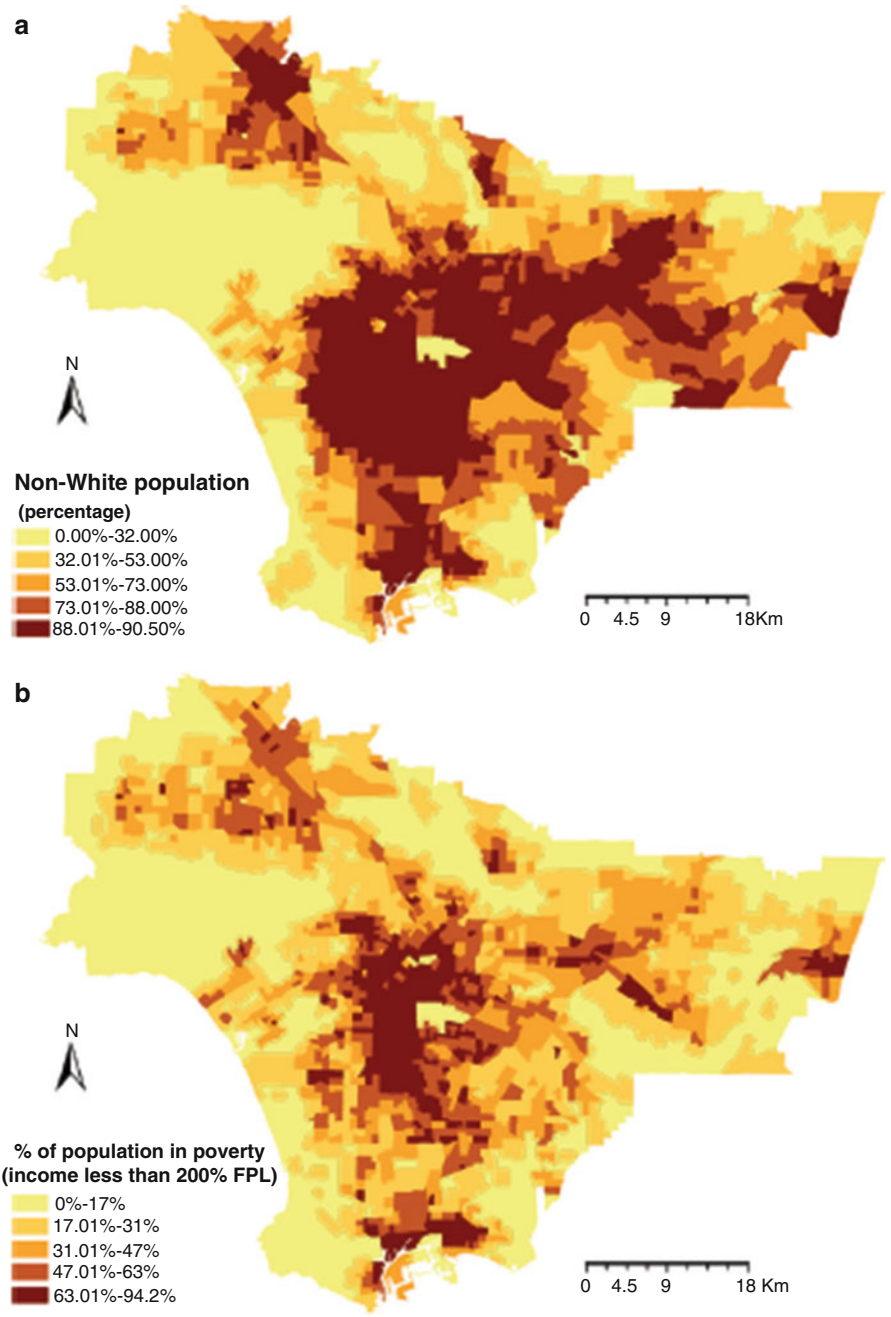

Fig. 4.1 Census tract level nonwhite population composition (**a**), percent of population at less than 200 % of the federal poverty level (**b**), and the cumulative environmental hazard using a multiplicative approach ($NO_2 \times$ diesel particulate matter). From Su et al. [30]

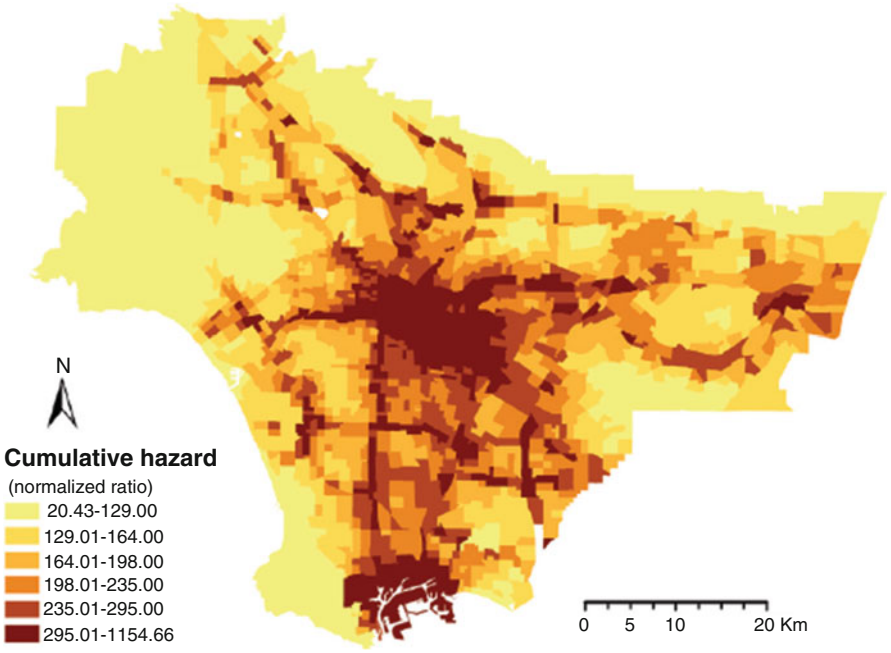

Fig. 4.1 (continued)

SES individuals are more likely to live along major roadways with the greatest exposures to NO_2 and diesel particulate.

In addition to exposures to criteria pollutants and traffic emissions, there are disparities in exposures to hazardous air pollutants from point sources such as power plants, refineries, and industrial facilities [31]. Consistent patterns of disproportionate exposure to hazardous air pollutants among minority and poor communities have been documented [32, 33]. Although most of the 187 agents listed as hazardous air pollutants by the U.S. EPA list were so classified on the basis of carcinogenicity and reproductive toxicity, many volatile organic compounds on the list can also adversely affect asthma [34].

Who Is at Greatest Risk of Adverse Health Effects from Air Pollution?

For many years, the term "susceptible" was used to describe people who are more responsive to an environmental hazard such as air pollution. More recently, the term "vulnerable" has been used to describe situations where the susceptibility arises from psychosocial or economic differences, rather than biologic differences among people exposed to the hazard. This distinction no longer seems that useful. Research into how socioeconomic factors and stress affect health has identified biological pathways

and led to the concept of allostatic load [35]. For example, stress is associated with differential baseline cortisol levels and differential response of the hypothalamic–pituitary–adrenal system. Thus, individuals who experience various levels of chronic stress may be differentially affected by environmental hazards.

Cumulative risk has been defined by the EPA as "the combined risks from aggregate exposures to multiple agents or stressors" [36]. The "agents or stressors" may not only be chemicals but also biological or physical agents or other factors that, directly or indirectly, affect health. This definition does not necessarily mean that risks should be added, but rather that consideration of how the risks from the various agents or stressors interact should occur.

To better understand the cumulative risks faced by minorities and the poor in the context of air pollution, a discussion of both intrinsic and extrinsic factors that lead to increased risk of adverse health effects follows.

Intrinsic Factors (Biological Susceptibility)

Barker hypothesized in 1998 that fetal undernutrition caused in utero programming that increased risk of diseases later in life [37]. This hypothesis has been extended to fetal exposures to other stressors, including air pollution. In utero exposure to air pollutants has been shown to be associated with increased risk of childhood asthma in multiple studies [38, 39]. Exposure to air pollutants during pregnancy is also associated with low birth weight, which may in turn increase the risk of airflow obstruction later in life [40, 41].

Epigenetic mechanisms have been proposed as the potential pathway by which environmental exposures lead to in utero programming and subsequent risk of asthma [42]. Genetic polymorphisms of antioxidant enzymes (e.g., glutathione S-transferases, arginase 1, and toll-like receptors) have also been associated with increased risk of developing asthma in relation to exposure to ozone or traffic-related air pollution [43–45].

Mothers of low SES are more likely to have unhealthy diets and to smoke or live with smokers [46, 47]. Active maternal smoking and exposure to secondhand tobacco smoke during pregnancy have both been shown to increase risk of asthma in the offspring [48]. Combined exposure to air pollution and tobacco smoke is thus likely to further increase risk.

Preexisting health conditions, like diabetes and obesity, can increase individual susceptibility to pollutants [49, 50], and individuals of low SES are more likely to have these conditions [51, 52].

Extrinsic Factors (Social Vulnerability)

An important question is whether living in a poor community is bad for health above and beyond individual-level effects of low SES. Communities with predominantly minority residents of low SES have more health-damaging factors and less

health-promoting amenities. These communities tend to have more fast food and liquor stores and fewer supermarkets [53], making it harder to maintain a healthy diet. There also tends to be more violence and less green space and recreational programs, making it harder to exercise [54]. In general, access to preventive healthcare is also more problematic in these communities [55], although the promise of the Affordable Care Act is to address this disparity.

High unemployment rates characterize communities of minority and economically disadvantaged residents, and unemployment is a strong predictor of ill health [56]. Unemployment rates for African Americans are typically double those of non-Hispanic whites, and African American men working full time earn approximately 75 % of the average earnings of comparable white men [57]. Residents of such communities who are fortunate enough to have a job are often exposed to vapors, gases, dusts, and fumes that may be respiratory irritants or toxins [58]. High unemployment among African Americans and Hispanics translates into a racial/ethnic wealth gap compared to whites. Between 2007 and 2010, Hispanic families saw their wealth cut by 40 % and black families by 31 %. In contrast, the Great Recession caused only an 11 % loss of wealth for white families [59]. African American families on average have 1/6 the wealth of white families, and as a consequence, their home ownership is much lower [60].

It is hypothesized that minorities and the poor experience more adverse health effects from air pollution because of the cumulative risk aggregated from greater exposure to pollutants, intrinsic factors that increase biological susceptibility, and extrinsic factors that increase vulnerability [61]. Evidence to support this hypothesis is emerging.

Air Pollution and Stress Interaction

Several studies show an association between adverse childhood experiences and asthma onset [62]. Findings from two studies suggest that chronic stress and maternal distress in pregnancy operate synergistically with traffic-related air pollution to increase asthma risk. Shankardass and colleagues found that high maternal stress and high exposure to traffic-related air pollution interacted to increase risk of childhood asthma (see Fig. 4.2) [63]. Similarly, Clougherty and colleagues found that neighborhood violence was not independently associated with childhood asthma, but that neighborhood violence increased the effect of traffic-related air pollution on asthma [64].

Adverse childhood experiences leading to chronic stress may lead to immune dysregulation and pro-inflammatory responses that increase risk of developing asthma when children are exposed to air pollution. Underlying mechanisms may involve biological embedding of stress, allostatic load, or early-life programming.

Differences in risk from the combination of both increased exposure and extrinsic social stressors such as low SES, occupation, crime and violence, lack of community resources, crowding, healthcare access, education, poverty, and segregation may impact adults as well as children. Low SES and race/ethnicity have been linked to perceived stress and biomarkers of chronic stress in adults [65, 66].

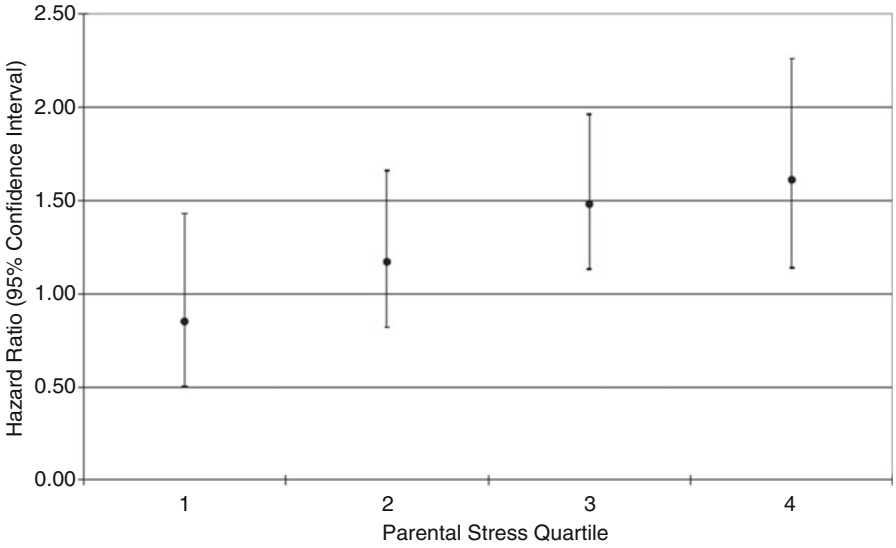

Fig. 4.2 Effect of traffic-related pollution on incident asthma across parental stress quartiles. From Shankardass et al. [63]

Approaches to Assess Cumulative Risk

Proponents of environmental justice argue that investigators and regulatory agencies should evaluate the cumulative impacts of environmental and social stressors in research studies and regulatory policies. The pollutant and source-specific assessments of potential health risks of air pollution do not reflect the multiple environmental and social stressors faced by vulnerable communities, which can interact to harm health. In a 2009 report, the National Academies of Science called for a new approach towards assessment of cumulative risk [67], and both the U.S. EPA and the California EPA (CalEPA) have been working to develop tools to implement this recommendation.

The U.S. EPA has been developing a GIS-based cumulative impacts screening tool, known as the Environmental Justice Strategic Enforcement Assessment Tool (EJSEAT), to identify areas with disproportionately high and adverse environmental health burdens nationwide [68]. The EJSEAT uses 18 indicators of cumulative impacts in four categories (demographic, environmental, compliance, and health). Although the agency has been working on the EJSEAT since 2003, it is still considered to be a draft tool in development and intended only for internal EPA use. The EJSEAT has certain limitations due to the requirement for national consistency. A major limitation is a lack of fine-scale geographic resolution because the tool scales the indicator values within each state (rather than within metropolitan region or air basin) and then applies to each census tract a composite score.

In 2014, CalEPA publically released another GIS screening tool, CalEnviroScreen, to help identify California communities that are disproportionately burdened by multiple sources of pollution [69]. The tool operates at a finer scale than EJSEAT and includes pollution burden information about water contamination, clean-up sites, solid and hazardous waste sites, pesticide use, and toxic releases in addition to O_3, $PM_{2.5}$, and diesel particulate levels. CalEnviroScreen also incorporates population characteristics including age, asthma, low birth weight, educational attainment, linguistic isolation, poverty, and unemployment. CalEPA is using the tool to designate California communities as disadvantaged pursuant to California Senate bill 535 so that 25 % of the revenue from California's cap-and-trade program to reduce carbon emissions can be allocated to benefit these communities (see Fig. 4.3) [69].

The CalEnviroScreen tool was based on pioneering work by Sadd and colleagues, who developed what they called an Environmental Justice Screening Method (EJSM) [70]. The authors included 23 indicator metrics in three categories: (1) hazard proximity and land use; (2) air pollution exposure and estimated health risk; and (3) social and health vulnerability. For hazard proximity, the EJSM uses GIS analysis to create a base map by intersecting land use data with census block polygons, and calculates hazard proximity measures based on locations within various buffer distances. These proximity metrics are then summarized at the census tract level, where they are combined with tract centroid-based estimates of pollution exposure, health risk, and SES to generate a cumulative impacts score. This score can be used to rank neighborhoods within regions, so that diverse stakeholders from community members to policymakers can identify local areas that would benefit from targeted strategies to address environmental justice. The EJSM has the advantage of including information about sensitive land use (childcare facilities, healthcare facilities, schools, and urban playgrounds) in addition to most of the indicators of pollution burden and population characteristics used by CalEnviroScreen.

Climate Change

The same framework that has been described in this chapter for understanding and addressing respiratory health disparities due to air pollution can be applied to adverse respiratory health effects of climate change. In fact, a substantial portion of the respiratory effects of climate change will be due to increased outdoor air pollution. Global warming will have a direct effect of increasing O_3 levels because of more days of excessive heat and sunlight in many areas, such as California [71]. In addition, NO_2 and $PM_{2.5}$ levels will also increase on days of excessive heat, as more power derived from combustion sources is needed to provide air conditioning. Minorities and the poor have the greatest vulnerability to excessive heat, due to lower availability of air conditioning in their homes [72]. In one recent study, residential segregation by race and ethnicity across US metropolitan areas was associated with more heat-trapping land cover [73]. The association was strongest for Hispanics, and appeared to be mediated by population density and the size of the metropolitan area.

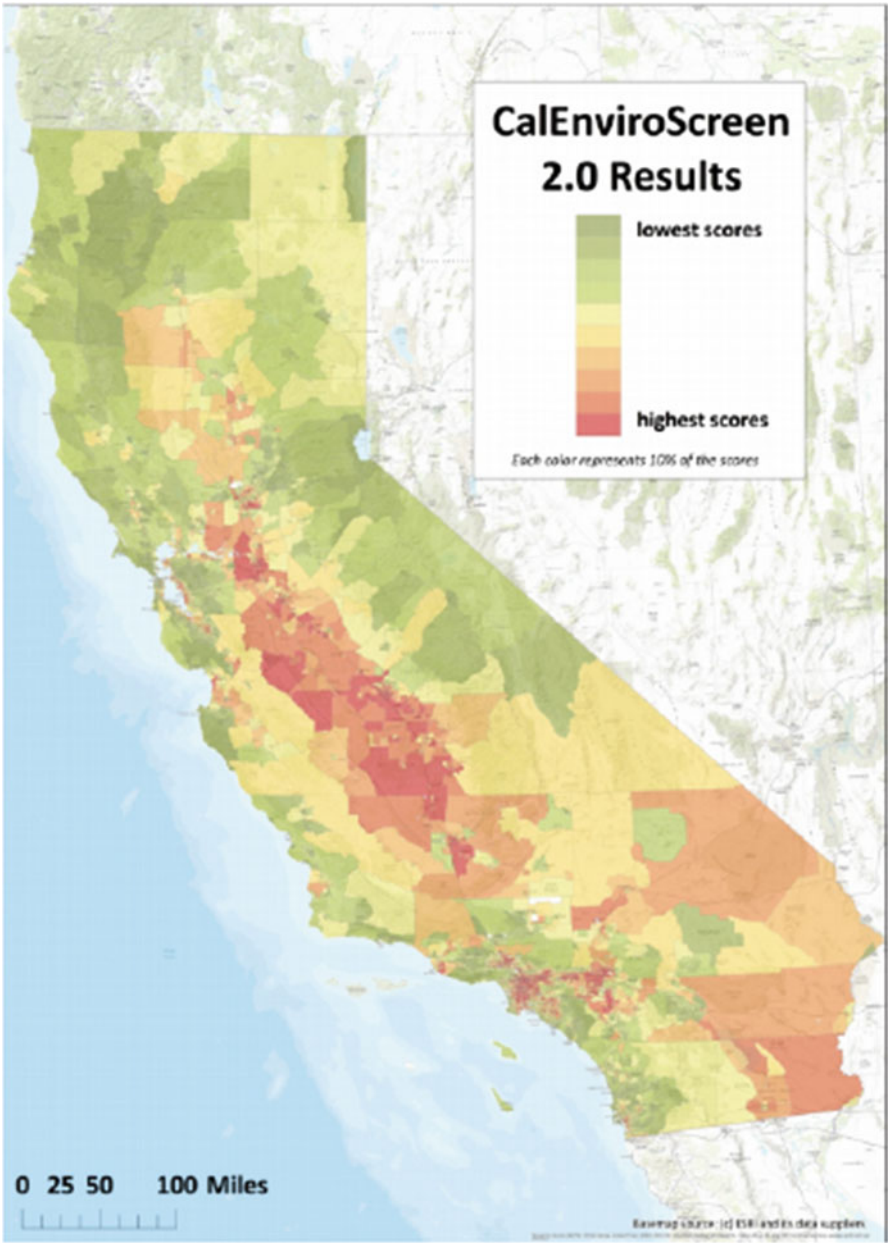

Fig. 4.3 Map of "disadvantaged" communities in California using CalEnviroScreen version 2.0. California Environmental Protection Agency [69]

Several methods have been advanced to identify populations with increased vulnerability to heat. A heat vulnerability index was developed by Reid and colleagues from ten vulnerability factors for heat-related morbidity/mortality in the USA: six demographic characteristics and two household air conditioning variables from the U.S. Census Bureau, vegetation cover from satellite images, and diabetes prevalence from a national survey [74]. Using a principal components analysis, four factors explained >75 % of the total variance in the original ten variables: (a) social/environmental vulnerability (combined education, poverty, race, and green space), (b) social isolation, (c) air conditioning prevalence, and (d) combined proportions of elderly and people with diabetes. When this heat vulnerability index was applied in an analysis of health outcome data on excessive heat days from multiple states, the results suggested that the index may be more of a marker of health vulnerability in general, rather than specific to heat stress [75].

More recently, MacDonald and colleagues developed a scalable "climate health justice assessment" model [76]. These authors demonstrated the usefulness of their model through analysis of 2008–2010 hospital discharge data at the county level in Texas. Asthma ranked first in terms of heat-related hospitalizations among the specific diseases selected for study. Non-Hispanic blacks were more burdened by the selected diseases than non-Hispanic whites. In addition to a projected >5 % increase in the incidence and treatment costs of asthma from climate change over the next 30 years, the authors also estimated increasing disparity for blacks during this period.

Inequality and Environmental Quality (Environmental Justice)

Over the last several decades, a growing body of evidence has suggested that more unequal societies have more polluted environments. One set of authors refers to this as the "equality/sustainability hypothesis" [77]. The evidence in support of this hypothesis is especially strong for air quality.

Disparities in exposures to environmental hazards in the USA are generally stronger in relation to race and ethnicity than in relation to income or class. For example, in US metropolitan areas ambient concentrations of SO_2 were found to increase with the degree of residential segregation by race [78]. In a similar study, racial segregation by race and ethnicity was associated with toxic air contaminants and risk of cancer [79]. A particularly interesting finding in another study was that greater disparities between minorities and whites in health risk from modeled concentrations of air pollutants were associated with greater risks to both populations [80]. Not surprisingly, this association was even stronger for low-income members of both groups.

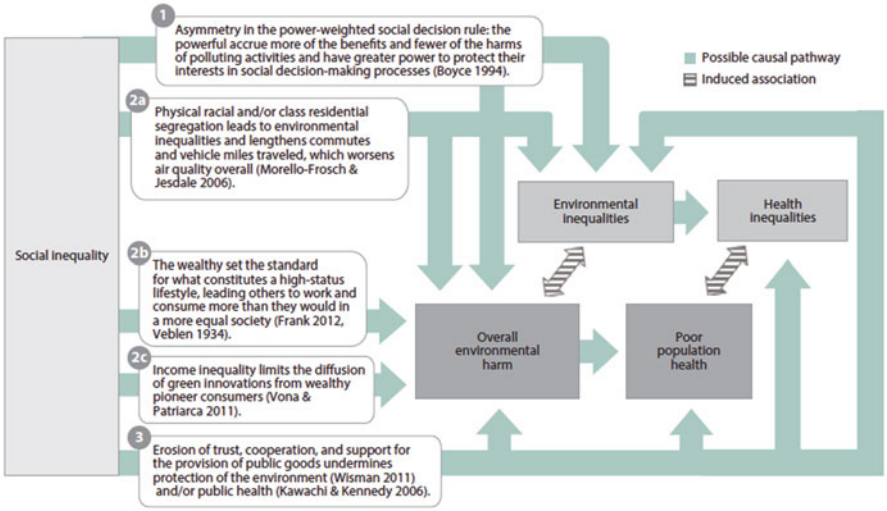

Fig. 4.4 Explanations for a contextual or spillover effect of social inequality on the environment relate to (*1*) asymmetries in political power, (*2*) the relationship between inequality and the environmental intensity of consumption, and (*3*) the erosion of social cohesion and cooperation. From Cushing et al. [77]

Why does societal inequality lead to environmental pollution? Social inequality is associated with asymmetries in political power that affect who experiences the benefits and harms of pollution. Wealthy individuals gain the economic benefits of polluting activities as both producers (e.g., shareholders of polluting industries) and consumers (as consumption increases with wealth), and they can avoid the harmful effects of pollution by moving away from polluted areas or using political power to keep polluting activities out of their neighborhoods [77]. Social inequality may also worsen environmental quality by decreasing social cohesion and the willingness to cooperate to protect common resources such as environmental quality. Trust and cooperation tend to promote collective environmental stewardship of the commonwealth, similar to how health is impacted by social capital and its relationship to income inequality [81]. A concept map for the theoretical framework of the equality/sustainability hypothesis is shown in Fig. 4.4 [77].

Research and Policy Needs

Although multiple epidemiological studies have shown evidence of modification of the effect of air pollution on asthma or COPD by race/ethnicity or low SES, more longitudinal studies from which causality can be inferred are still needed. In particular, better understanding of the impacts of extrinsic neighborhood factors (e.g., poverty, unemployment, segregation, crime, and food access) on air pollution–health effects associations is needed. Better understanding of the biologic

mechanisms underlying the air pollution–stress interactions would also be useful for future research. To this end, validated biomarkers of both stress and early effects of air pollution are necessary. Because health disparities in asthma and COPD are the consequence of multiple factors, methods to better characterize and model cumulative impacts would be extremely helpful. Spatial autocorrelation remains an issue. If pollution and inequality are spatially but not causally related, this may lead researchers to infer a spurious association when one does not actually exist.

The emerging evidence suggesting that social inequality is linked to worse environmental quality implies that development and land use policies can have disproportionate health impacts on disadvantaged groups. Indeed, research has suggested that targeting environmental regulations to improve conditions for those who are most negatively impacted by air pollution is an efficient way to improve overall outcomes at the population level. For example, Levy and colleagues found that reductions in spatial inequality of emissions of SO_2 and $PM_{2.5}$ by US power plants would result in greater total reductions in mortality than a non-targeted approach [82]. A later study that assessed potential control of mobile sources (e.g., tail-pipe emissions of public buses) in Boston also found that targeting spatial inequality would result in the greatest overall public health benefit [83].

With the new revenue for public investment generated by its cap-and-trade program, the Greenhouse Gas Reduction Fund, California is making efforts to address environmental health inequality [84]. As noted above, Senate bill 535 requires that at least 25 % of cap-and-trade revenue be invested in projects that will benefit disadvantaged communities and at least 10 % be invested in such communities. To understand the distinction between the required levels of investment, subsidizing pollution controls on heavy-duty diesel trucks is an example of the former, whereas subsidizing the purchase of energy-efficient appliances or clean vehicles by residents of poor communities is an example of the latter. The legislation gives CalEPA responsibility for identifying disadvantaged communities, and the mapping tool described previously, CalEnviroScreen, is being used for this purpose.

Another effort to address both social and environmental inequality is being undertaken by the California Air Resource Board (ARB). Plug-in hybrid and battery electric cars can make a huge difference in reducing local air quality, and can help their owners save money while staying more insulated against the volatility of fossil fuel prices. Unfortunately, most plug-in electric cars cost more than the used cars that poor families can typically afford. The ARB is initiating a pilot project in the Greater Los Angeles area and San Joaquin Valley to help low-income individuals get rid of old polluting vehicles and purchase cleaner and fuel-efficient cars [85]. The program works by providing increasingly larger cash payments for the lowest income families to move up to the very cleanest cars. Under this program, for example, it is possible for a family that meets the income guidelines to receive $12,000 toward the purchase of an electric car. More such programs are needed to address environmental justice issues and to improve air quality and public health.

In conclusion, policy approaches to air quality, which are currently focused on pollutants and their sources, should consider the cumulative impact of stressors and vulnerabilities encountered by people who live in minority or low SES communities.

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Chapter 5
Migrant Health

Fernando Holguin and Marc B. Schenker

Immigration and Nonoccupational Lung Diseases

In spite of having lower socioeconomic status and reduced healthcare access, Hispanic migrants have a lower prevalence of allergies, asthma, and COPD [1]. However, this health paradox diminishes over time, as the rates for these diseases eventually increase to levels similar to those born in the host country. This phenomenon is primarily observed among migrant populations arriving from countries that have comparatively lower prevalence rates of these chronic respiratory diseases. In a representative study, the prevalence of asthma among Mexicans who migrate to the USA is half of that among Mexicans born in the USA (~4 % vs. 8 %), suggesting that the "migrant protective effect" against asthma is lost in subsequent generations [2]. Findings from a recent cross-sectional study suggest that the "healthy immigrant advantage" lasts for up to 2.5 generations for bronchitis and allergies, and until the third generation for asthma [3]. A time-dependent increase in asthma and allergy among migrating populations is not unique to Hispanics moving to the USA, as it has been described among migrants to other industrialized nations [4–8]. Potential mechanisms include sensitization to new ubiquitous environmental allergens, increase in obesity and smoking rates, and changes in disease awareness or healthcare access. The process by which migrants adapt to norms, language, and behavior of the host country, known as acculturation, has been associated with increased risks of acquiring detrimental habits (e.g., smoking and unhealthy diet)

F. Holguin, MD, MPH
Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: holguinf@upmc.edu

M.B. Schenker, MD, MPH (✉)
Departments of Public Health Sciences and Internal Medicine, University of California at Davis, One Shields Avenue, MED-SCI 1C, Davis, CA 95616, USA
e-mail: mbschenker@ucdavis.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_5

and developing psychiatric disorders, all of which may confer greater susceptibility of developing chronic respiratory diseases [1]. For example, the prevalence of secondhand tobacco smoke (SHS) exposure is much lower among immigrant children in the USA (1.9 %) than in children born in the USA (9 %) [9]. Determining how risk and protective factors for developing lung diseases change as a result of acculturation is critical to our understanding of disease pathogenesis and development of effective interventions.

Lung Diseases in Hired Migrant Farm Workers

Demographics

There are approximately between three and five million hired farmworkers in the United States, of whom approximately half are undocumented [10]. In order to monitor and evaluate the labor status and needs of this population, the United States Department of Labor created the National Agricultural Workers Survey (NAWS), an employment-based random multi-region survey of US crop workers—including migrants—to collect demographic and employment data through face-to-face interviews every 2 years since 1989 [11]. Selective health information questions have been periodically added to the basic survey. In the NAWS 2009–2010 survey, based on 3691 interviews, 82 % of the population was of Hispanic ethnicity with over 70 % being born in Mexico. Compared to the 1999–2000 survey, the proportion of foreign-born workers that have resided in the USA for a short period of time (0–4 years) has steadily declined over this time period, from 46 to 16 %. In contrast, the proportion of those residing longer in the USA has steadily increased. These changes may reflect many factors including a decrease in overall immigration rates and a more stable current hired farmworker population that has become more acculturated. In a recent survey, only a third of hired farmworkers reported speaking no English at all (compared to approximately half in a survey conducted a decade earlier). Over the last decade, more migrant farmworker families have seen their incomes rise above the poverty line while obtaining healthcare coverage for their children, but most adults in these families lack health insurance and pay out of pocket for medical expenses. More importantly, over half of current farmworkers remain “not legally authorized” to work in the USA, which clearly limits their access to many health benefits.

Risk Factors, from Environmental to Contextual Exposures

Hired farmworkers are exposed to a wide range of respiratory hazards that occur in agricultural work, including organic and inorganic dusts, agricultural chemicals, toxic gases, and infectious agents. They may also be exposed to harmful indoor exposures due to substandard housing conditions [12, 13]. For example, temporary

housing for farmworkers may have poor ventilation, increased concentration of pesticides, infestations, and severe overcrowding, all of which are associated with respiratory morbidity. Such substandard housing conditions are more common in places with a higher proportion of children, and women and workers that lack temporary working visa permits [14]. Indoor mold has been associated with productive cough and asthma, while pesticides and tobacco use in the home have been associated with chest tightness and phlegm, respectively [15]. Contextually, hired farmworkers feel isolated because of language and acculturation barriers, as well as economic constrains from low wages and hard labor conditions. Such isolation is a risk factor for psychosocial stress and depression, which occur in 30–46 % of hired farmworkers [9, 10, 16]. The combination of environmental exposures and depression or anxiety [17] increases the risk for developing or worsening chronic respiratory diseases.

The Burden of Respiratory Diseases

Because of occupational hazards, environmental exposures, chronic diseases, and cultural barriers, hired farmworkers have a life expectancy below the national US average [18]. While the extent to which the burden of respiratory diseases determines the reduced life expectancy of hired farmworkers is unclear, such diseases are common, and often associated with substantial morbidity and increased mortality. Data from the National Center for Health Statistics and the National Health and Nutrition Examination Survey (NHANES) III show that crop farmworkers have significantly elevated mortality from several respiratory conditions, with morbidity and mortality from hypersensitivity pneumonitis being 10–50 times higher than expected. Moreover, these data show that forestry workers have significantly increased mortality from pulmonary tuberculosis, chronic airway obstruction, and pneumonia, and that agricultural workers who have ever smoked are at increased risk of asthma [19].

Occupational Lung Diseases

Exposures associated with respiratory diseases include organic and inorganic dusts, gases in animal confinement units, mold and thermophilic bacteria, nitrogen dioxide from silo gases and agrochemicals [20].

Acute respiratory diseases resulting from bioaerosol inhalation contaminated with microorganisms (e.g., aspergillus) include organic dust syndrome (usually a febrile, influenza-like syndrome, characterized by cough, dyspnea, wheezing, and leukocytosis), which typically resolves within days after the exposure and only requires supportive care [21].

Hypersensitivity pneumonitis (also known as farmer's lung) usually has an acute to subacute course, characterized by repeated exacerbations from repeated exposures in patients sensitized to an organic dust component (i.e., thermophilic

actinomyces and aspergillus). However, some cases of hypersensitivity pneumonitis are not properly diagnosed and may progress into chronic fibrotic lung disease. The diagnosis of this condition is based on characteristic clinical and radiologic features (e.g., high-resolution computed tomography), and confirmed by lung biopsy, which shows non-caseating granulomas, as well as lymphocytic and mononuclear airway and parenchymal inflammation. Cessation of the exposure to which the subject is sensitized is essential to avoid progressing into a chronic stage.

A recently recognized entity is restrictive lung disease in agricultural workers exposed to inorganic dusts, particularly in dry environments. Lung tissues from deceased migrant farmers show that mineral dust is deposited in the small airways and is associated with pneumoconiotic nodules. Unfortunately, the prevalence and natural history of this disease are unknown [22].

Airway Diseases and Respiratory Symptoms

The prevalence of self-reported physician-diagnosed asthma in migrant farmworkers has been reported to be between 2 and 6 % [11, 23], which is lower than that reported in the general adult population in the USA. However, a much larger proportion of farmworkers report asthma-like symptoms, and thus it is possible that asthma is under-diagnosed in this population. In a survey of 600 migrant farmworkers from temporary camps in Indiana, crude estimates of the prevalence of chronic cough and wheeze were 8 % and 6 %, respectively; such symptoms were more common during the farm working season (June–August) than during winter [24]. Moreover, 15 % of study participants had spirometric evidence of airflow obstruction (an $FEV_1/FVC < 0.7$). In a multivariable logistic regression analysis, being a migrant farmworker for >10 years was associated with threefold increased odds of airflow obstruction (95 % confidence interval [CI] for odds ratio = 1.4–8.3) and 3.3 times increased odds of chronic respiratory symptoms (95 % CI = 1.8–9). Interestingly, the burden of occupational exposure on lung function was similar to that reported for smoking for more than 10 years. Findings from the study in Indiana are comparable to those from a study of California farmworkers, which reported a similar prevalence of airflow obstruction but a lower prevalence of chronic respiratory symptoms [25]. In contrast, an earlier study from New Mexico found that less than 1 % of farmworkers had chronic airflow obstruction [26]. Differences in the respiratory burden of farming across studies suggest regional variation in the level of exposures, some of which may be more harmful than others. Indeed, a population-based survey of 1974 farm owners and operators in California showed large differences in the magnitude of the associations between different types of farming and respiratory symptoms. For example, persistent wheeze or asthma was more common among workers in vegetable (20 and 10 %) or livestock (11.4 and 11.8 %) farms [25] than in other types of farms. Other potential risk factors for asthma in farmworkers include time spent in the USA and degree of

acculturation. For example, a population-based survey of 467 hired farmworker households from Mendota (California) showed that both medium to high acculturation and being in the USA for over 15 years were significantly associated with increased odds of asthma among women [23]. Similar findings have been reported among Mexicans, in whom time spent in the USA is associated with increased risk of asthma [2]. This migrant paradox is likely explained by multiple factors, including changes in nutrition, obesity, recreational habits, and diagnostic bias.

Exposure to pesticides is another environmental factor associated with worsened respiratory symptoms, airflow obstruction, and increased airway responsiveness among subjects with asthma [27]. The Agricultural Health Study, which evaluated the lifetime use of 48 pesticides and the risk of adult-onset asthma in 19,000 male workers, reported that high pesticide exposure is associated with approximately two-fold increased odds of atopic or non-atopic asthma [28]. However, those results must be cautiously interpreted due to potential recall bias. Antenatal exposure to pesticides has been associated with self-reported physician-diagnosed asthma or lifetime asthma in children [29], a finding supported by those from longitudinal studies of umbilical cord levels of DDT and incident asthma. Sunyer and colleagues showed that umbilical cord level of 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (DDE), the major metabolite of the organochlorine insecticide DDT, was associated with 18 % excess risk of asthma at age 6.5 years (95 % CI for risk ratio = 1.01–1.39) [30]. Exposure to pesticides (such as organophosphate, carbamate, and paraquat) may increase the risks of chronic obstructive pulmonary disease (COPD) and reduced lung function, especially among regular sprayers and those using chlorothalonil [29].

Indoor Biomass Exposure

One-third of the world population, predominantly in developing countries, use solid fuel derived from plant materials for heating or cooking. Among migrant farmworkers in the USA, biomass exposure earlier in life could have detrimental health effects. In the absence of adequate ventilation, biomass exposure can lead to particulate matter concentrations in the milligram range, which has been associated with acute and chronic respiratory diseases. Acute biomass exposure can increase the risk of upper and lower respiratory infections, reduced lung function, and frequent and severe respiratory symptoms [31]. Chronic biomass exposure increases the risks of asthma and COPD [31]. Interventions to reduce the indoor pollution from solid fuel burning include the use of stoves that are more efficient and prevent smoke build up. In a randomized clinical trial in Mexico, adequate use of stoves was associated with significant reductions in respiratory symptoms and the rate of lung function decline [32]. Whether previous exposure to indoor biomass interacts with current environmental risk factors to worsen the respiratory health of migrant farmworkers is currently unknown but worth examining.

Tuberculosis

The incidence of tuberculosis (TB) continues to decline in the USA. According to the Centers for Disease Control and Prevention (CDC), there were 9412 incident cases of TB in 2014 (for an incidence rate of 3 cases per 100,000 persons), a decrement of 2.2 % since 2013. However, the incidence rate of TB in the USA is higher in foreign-born individuals than in those born in the USA. Compared to non-Hispanic whites, Hispanics have an eight-fold greater incidence rate of TB [33]. Although there is limited information about TB in hired farmworkers, some studies have shown a high prevalence of latent tuberculosis infection. In a 2008 study of tuberculin skin test (TST) results for 200 farmworkers at a migrant clinic in Connecticut, 57 (26 %) were positive (nearly all from Mexico) [34]. In a cross-sectional study of 469 Northern California Migrant workers (mostly Hispanic), the prevalence of a positive TST (≥10 mm) was 16.6 %, and those born outside the USA were more likely to have a positive test [35]. In a study of 600 migrant farmworkers in the U.S. Midwest, the prevalence of a positive TST ranged from 13 to 40 % across the camps surveyed, with a particularly high prevalence among workers born in Mexico (46 %) [24]. Not surprisingly, adherence with INH treatment for latent tuberculous infection is very low among migrant farmworkers, ranging from 9 to 40 % [24, 35]. This highlights existing challenges to providing long-term therapy and follow-up for latent tuberculous infection in a mobile population that is often culturally isolated.

Conclusions and Future Directions

Migrating populations are at greater risk from developing respiratory diseases, including chronic lung diseases. Moving to a new country often involves a change in environmental and occupational exposures, such as ubiquitous allergens that lead to the development of allergic sensitization, air pollution, changes in diet and behaviors, and workplace exposures. Paradoxically, although migrants often move to better their social and economic status, they also adopt many of the risks factors that lead to chronic lung diseases. Further, occupational exposures due to farming increase the risk for developing different types of occupational lung parenchymal and airway disease. The development of lung diseases in migrating populations, especially in those that come from different social and living standards, is a process likely defined by a complex interplay of losing protective factors while gaining additional risks.

Longitudinal research studies are needed to better understand the pathogenesis of respiratory diseases in migrant populations. In parallel with research efforts, health policies and regulations are needed to protect the respiratory and overall health of migrant workers.

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Chapter 6
Acculturation

Elizabeth L. McQuaid, Daphne Koinis-Mitchell, and Glorisa J. Canino

Even though acculturation may impact several respiratory diseases, this chapter will focus on acculturation and asthma. The primary reason for this focus is that there is strong evidence for an impact of acculturation on health disparities in asthma, a major public health problem in the United States (US) (Chap. 10).

In the USA, African Americans have higher asthma prevalence than non-Hispanic (NH) whites [1, 2]. Among Hispanics, there is variability in the prevalence and morbidity from asthma across subgroups. Compared with NH whites, Hispanics of Puerto Rican descent have higher prevalence and worse asthma outcomes (e.g., emergency department [ED] visits and hospitalizations), but Hispanics of Mexican descent have lower prevalence and more favorable asthma outcomes [3, 4].

Research on place of birth, immigration, and health status has enhanced our understanding of the development and progression of disease in relation to environment and cultural context. In the USA, the overall population is becoming increasingly diverse. Data from the 2010 census reveal that although the NH white racial/ethnic group remains the largest, it is experiencing the slowest growth. In the past decade, the Hispanic and Asian populations have grown more rapidly (each by ~43 %), due in

E.L. McQuaid, PhD, ABPP (✉) • D. Koinis-Mitchell, PhD
Departments of Psychiatry and Human Behavior and Pediatrics,
Alpert Medical School, Brown University, 1 Hoppin Street, Providence, RI, USA
e-mail: elizabeth_mcquaid@brown.edu; daphne_koinis-mitchell@brown.edu

G.J. Canino, PhD
Behavioral Sciences Research Center, University of Puerto Rico, San Juan, PR, USA

Department of Pediatrics, University of Puerto Rico Medical Sciences Campus,
Po Box 365067, San Juan, PR 00936-5067, USA
e-mail: glorisa.canino@upr.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_6

part to immigration patterns [5]. As of this writing, Hispanics comprise 17.1 % of the US population, and this proportion continues to increase annually [6]. Because of the substantial disparities affecting Hispanic subgroups with asthma, as well as the range of countries of origin and levels of acculturation among Hispanics, this population is a useful case example from which to investigate the influence of acculturation on asthma. The purpose of this chapter is to provide a review of studies examining acculturation as indexed by commonly used measures, such as country of origin (i.e., nativity), length of residence in host country, language preference, and identification with the host culture in relation to asthma *prevalence* and *outcomes*.

Hispanics in the United States

The designations "Latino" or "Hispanic" are ethnic labels of convenience that are applied to people living within the USA and who originate from Spain or territories previously under Spanish control (see Chap. 2). Hispanic subgroups are distributed throughout the USA. Individuals of Mexican descent live primarily in the South and the West Coast, Caribbean Hispanics are most likely to live in the Northeast, and Hispanics of South and Central American descent typically live in the South and Northeast [7]. Hispanics trace their origins to many different countries and continents. Their personal, political, linguistic, racial, and cultural histories may differ dramatically. Hispanic families who migrate to the mainland USA come from many different geographical areas, including the Caribbean (e.g., Puerto Rico, Cuba, and the Dominican Republic), Mexico, Central America, and South America. Each area has a unique relationship to the USA, and the reasons for migration from each location can vary widely. Although many individuals migrate for upward mobility and greater economic opportunity, others may migrate for political reasons, or due to trauma/unsafety in their home country [8].

Puerto Rico presents a unique case; because it is a US territory, Puerto Ricans can travel freely between the mainland USA and the island, a pattern known as "circular migration" [9]. In contrast to immigration (which is permanent), or temporary migration, circular migration allows an individual to interact repeatedly with both the home and host countries. Specifically, it typically involves migration for a specific purpose (e.g., employment), return to the country of origin, and repeated moves between both cultures and locations. Some Puerto Ricans may establish "dual home bases," in the island and in their mainland location, yet still maintain important cultural and economic ties to their place of origin [10].

Measures of Acculturation

Acculturation, the process whereby migrants change their behavior, values, and attitudes toward those of the host society, is a complex process [11]. Several constructs are thought to comprise this process, such as language preference or dominance,

acculturation stress, ethnic identity, traditional values, preference for food, and social contacts. Acculturation is often the result of direct and continuous contact with the host culture [12]. Differences in acculturation may relate to a number of factors, including but not limited to (1) the amount of time in the host culture, (2) the differences in cultural characteristics between the country of origin and the host country to which the person had immigrated, and (3) the reasons for immigration (trauma, political reasons, upward mobility, or parental upward mobility). Large scale studies, however, typically use proxies for acculturation. These include *nativity,* a term used to refer to one's country of origin (e.g., is someone of Dominican descent born in the Dominican Republic, or in the USA to Dominican parents?) A related construct is *generational status*; someone born in a foreign country is considered first generation, the offspring who are born in the host country are considered second generation [13]. *Immigration* is typically defined as the action of coming to live permanently in a host country different from one's country of origin. *Acculturative stress* (sometimes referred to as "cultural stress") is a related construct, defined as the degree to which individuals become distressed due to the pressures to adapt and conform to a culture other than their own [14].

Asthma Prevalence Among Hispanics

Within the USA, there is significant variability of asthma prevalence among Hispanic subgroups (see Chap. 10). During the early 1990s, as asthma prevalence was identified as increasing [15], Carter-Pokras and Gergen [16] analyzed data from the Hispanic Health and Nutrition Examination Survey (HHANES; 1982 through 1984 [17]) and the National Health and Nutrition Examination Survey, 1976–1980 [18]. Their analysis identified substantial heterogeneity in self-reported physician-diagnosed asthma among Hispanic children. Specifically, Puerto Ricans reported the highest prevalence of active asthma for their children (11.2 %), more than twice as prevalent as those of Cuban descent (5.2 %). Mexican Americans reported the lowest prevalence of asthma (2.7 %), lower even than that of NH whites (3.3 %). Since that time, several studies have replicated the overall finding that among Hispanic subgroups, mainland and Island Puerto Ricans have the highest asthma prevalence, and Mexican Americans have much lower prevalence, typically lower than that of NH whites [19, 20].

Nativity, Length of Residence, and Asthma Prevalence

Epidemiological studies of acculturation and asthma prevalence usually focus on simple proxies of acculturation such as nativity and length of residence in the host country. There is increasing evidence that the role of nativity in asthma may differ

depending on country of origin. In an epidemiologic study of children [2], Mexican Americans born in the USA were about as likely to have a diagnosis of asthma as NH whites (odds ratio [OR] = 1.05, 95 % confidence interval [CI] = 0.90–1.22), but those born in Mexico were less likely to be diagnosed with asthma than NH whites (OR = 0.43, 95 % CI: 0.29–0.64). These findings are consistent with the "healthy immigrant" hypothesis [21], in which more acculturated families have increased risk of disease burden over time, approaching that of the host culture. In contrast, Puerto Rican children born in the mainland USA were more likely to be diagnosed with asthma than NH whites (OR = 1.95, 95 % CI: 1.48–2.57), yet island-born children had the *greatest* likelihood of asthma diagnosis (OR = 2.50, 95 % CI: 1.51–4.13 [2]). These findings suggested that potential protective effects of low acculturation in asthma onset in immigrants suggested by some (e.g., Klinnert et al. [22]) may not apply to Puerto Ricans [2].

A more recent study evaluated nativity and current asthma, using data from NHANES (2001–2009) [23]. *Nativity* and *length of US residency* emerged as important predictors of asthma. Individuals born in the 50 US states and the District of Columbia (DC) had higher asthma prevalence than those born outside the USA and DC, whether children/adolescents (9.3 % vs. 5.1 %) or adults (7.6 % vs. 4.7 %). Consistent with previous findings [2], the pattern of results for Puerto Ricans was reversed, such that non-US-born Puerto Ricans had higher odds of asthma than those born in the USA. Length of residence (≥10 years vs. <10 years in the USA) also exerted effects among adults; specifically, non-US-born adults with greater length of US residency had higher odds of current asthma (OR = 1.55, 95 % CI 1.25, 1.93) than those who had arrived more recently [23].

Asthma Exacerbations, Impairment, and Healthcare Use

Racial or ethnic minorities have worse asthma control than NH whites (Chap. 10). Among Hispanics, rates of asthma exacerbations show a similar pattern to those noted above for asthma prevalence; specifically, Puerto Ricans have more frequent asthma exacerbations (including ED visits) than NH whites, Mexican Americans, or other Hispanic subgroups [3, 4, 19, 24].

Duration of residency in the USA may lead to lower lung function among Mexican Americans. In a study of nearly 1000 children living near the Mexican border [25], length of residency in El Paso (Texas) was associated with asthma, allergy, and reduced FEV_1/FVC (an annual declines of 0.16 %). This finding may be explained by location-specific pollutants or other environmental risk factors.

Socioeconomic status (SES) and healthcare access, which are particularly salient for immigrants (see Chap. 5), likely play an important role in disparities for asthma exacerbations or asthma control [26]. Recent immigrants often rely on urgent or emergency care instead of preventive care [27, 28], and may not know how to navigate the US healthcare system to advocate for their needs [29].

Mechanisms of Effects of Acculturation on the Onset and Course of Asthma

Asthma is a complex disease due to multiple genetic variants interacting with contextual factors, such as indoor and outdoor environmental exposures, healthcare access and use, and family and neighborhood environments [30, 31]. Thus, influence of acculturation on asthma prevalence and outcomes must be interpreted in the context of genetic and environmental effects on asthma. Over the past two decades, there has been growing evidence to indicate that genetic factors play an important role in asthma in Hispanics. Hispanics represent a diverse ethnic group, with varying proportions of African, European, and Native American ancestry; [32] racial ancestry likely plays an important role in asthma onset and course (see Chap. 2) [33].

Acculturation appears to play a unique role with respect to genetic predisposition and onset and course of asthma. In addition to genetic factors, Hispanic subgroups coming from different geographic, environmental, and cultural contexts may have been exposed to risk and protective factors for asthma [34]. Environmental and social/behavioral factors thought to influence the impact of immigration on asthma prevalence and outcomes are reviewed below.

Environmental and Socio-contextual Factors

The "hygiene hypothesis" [35] has been posed as an explanation for the increased burden of asthma associated with acculturation among US immigrants from developing regions. This framework proposes that decreased exposure to infections in early life, such as may be found in more developed regions, may alter immune responses and lead to asthma; conversely, greater early microbial exposure, such as those found in rural areas, may be protective [35]. Specifically, some Hispanic immigrants, such as those of Mexican origin, may have certain environmental protective factors that promote health (e.g., early exposure to farming environments); conversely, children of Mexican descent born in the USA may have greater exposure to risk factors for asthma (e.g., traffic-related air pollution). As a result, Hispanics emigrating from rural areas in Mexico, Central America, and South America would be less likely to develop asthma, whereas their offspring living in urban environments would have increased risk. At a population level, immigration and acculturation involve exposure not only to more allergens, but also to new types of allergens in the host country (e.g., [36]); over time the allergic status and range of allergies among immigrants and their families becomes more similar to that of the local host population [36, 37].

Some immigrants may move into communities exposed to environmental risk factors for respiratory diseases. Ozone is the most widespread air pollutant, and ozone exposure has been associated with asthma symptoms and healthcare utilization (see Chap. 4) [38]. In a nationwide study, Mexican American children were found to live in counties with over three times more "high-ozone days" annually than NH whites [39].

Social Context and Behavioral Factors

Behavioral and other socio-contextual risk factors associated with acculturation may partly explain health disparities in asthma. For example, Mexican Americans are more likely to have two-parent households [40] and lower rates of smoking than Puerto Ricans [41]. Klinnert and colleagues [22] found important differences in risk factors for asthma between low-acculturated and high-acculturated Hispanics, primarily of Mexican descent. The low-acculturated group had lower prevalence of prenatal smoke exposure and current secondhand smoke exposure, single parent status, and reported stress [22]. The authors hypothesized that this finding was parallel to the epidemiological paradox that foreign-born mothers of Mexican descent with low income are less likely to have low birth weight infants than US-born women of Mexican descent [42]. However, those findings were from a clinical sample of children at risk for asthma, and may thus not be generalizable [22]. A more recent study using a large national dataset further demonstrated that risk factors for asthma risk differ by parental nativity. In most cases, being foreign-born was associated with fewer risk factors for asthma (family history, allergies, or secondhand smoke exposure) [39].

Language and Healthcare Context

Language is often used as a proxy for acculturation but may also be a marker of increased duration of residence in the USA.

Spanish-speaking parents of Hispanic children (but not English-speaking Hispanic parents or African American parents) have been shown to have poorer experiences with care than parents of NH white children. Specifically, they were less likely to report they were ever taught what to do during an asthma attack, or advised to change their home environment [43], suggesting that they received less specific information about asthma management.

Healthcare context may also be a critical factor in evaluating the differences in asthma morbidity between Island Puerto Ricans and Puerto Ricans in the mainland USA. In one study contrasting patterns of healthcare use between Island Puerto Rican children, Hispanic children in the US mainland, and NH whites, Island Puerto Ricans had the highest rates of ED visits [28], which may be related to differences in healthcare systems. Parents of Hispanic children in the US mainland site were more likely to receive care in private physicians' offices, to identify a regular location for receiving asthma care for their child, and to have a consistent provider than parents of Island Puerto Rican children [28]. These findings suggest that differences in healthcare systems among countries or regions of origin should be considered in studies of asthma disparities in migrant populations.

Acculturation, Nutrition, and Physical Activity

Immigration and acculturation to the majority culture of the USA are associated with dietary changes that increase health risk. Among Hispanics, residence and duration of residence in the USA are associated with obesity [44]. In one study, Mexican Americans born in the USA were twice as likely to have a child who was either overweight or at-risk-for overweight as Mexican Americans born in Mexico [45]. Hispanic families who acculturate may adopt a diet with greater consumption of nutrient-poor and high calorie foods, and increase consumption of sugar-sweetened drinks [46]. In one study, highly acculturated Hispanic mothers were more likely to serve noncore foods to their children than Hispanic mothers who were less acculturated [47].

Obesity has been associated with asthma and asthma morbidity in the general population [48, 49], and specifically in Puerto Ricans [50]. Changes in diet associated with acculturation to the USA may thus increase asthma risk through obesity. Moreover, children who are overweight/obese may be less likely to engage in physical activity due to asthma symptoms [51], and those residing in poor neighborhoods may have less access to resources that promote physical activity and healthy nutrition.

Stress

There is a well-established literature linking stress, exposure to violence, and psychological factors (e.g., depressive symptoms, anxiety) to asthma onset and course [52, 53]. Recent theories propose the integration of certain individual factors, such as psychophysiological reactivity, to exposure to short- and long-term stressors. Stress exposure may play a role in asthma through alterations in the neuroendocrine, immunologic, and autonomic nervous systems, in the context of individual perinatal and genetic factors [54]. Current models also focus on stress and inflammation as important underlying factors influencing asthma [55, 56]. Emerging research suggests that stress may be related to epigenetic changes that are associated with asthma occurrence among Puerto Rican children [57].

As the process of immigration and acculturation can be associated with economic and psychosocial stressors, stress may be an important mediator of asthma outcomes [58]. Many immigrants may move into and eventually reside in disadvantaged neighborhoods where they are exposed to higher levels of cumulative risks of urban poverty (e.g., neighborhood violence) that can increase risk for asthma morbidity in children [59]. Some have also suggested that the stress associated with acculturation impedes effective asthma management [60]. Models that investigate the reciprocal influences among genetic vulnerability, physiological processes, psychological factors, and life circumstances surrounding immigration and acculturation may be useful for guiding future research and informing innovative intervention programs for those most at risk.

Protective, Family-Related Factors Among Those at Risk

Some research has applied strength-based, theoretical models, such as those that attempt to identify protective factors against mental health outcomes in immigrant families [61, 62]. For example, receiving social support during and after the immigration process may minimize feelings of isolation during acculturation [27]. Because the family plays an integral role in asthma management [63], strong family ties and connections may help to alleviate stress associated with managing asthma when adapting to a new geographical location.

One study sought to identify protective family characteristics relevant to the immigration experience that may decrease asthma morbidity in children [60]. Koinis Mitchell and colleagues [60] examined the protective role of family cohesion against asthma morbidity in children of caregivers residing in the mainland USA from Puerto Rican and Dominican backgrounds, building on the concept of interconnectedness inherent in "familismo" [64], an important family value in Hispanic culture. Whereas caregivers born in Puerto Rico reported the highest levels of acculturative stress, US-born caregivers (either Puerto Rican or Dominican) reported the lowest levels. Risk for asthma-related ED visits was higher for children of caregivers born in Puerto Rico than for children of US-born Hispanic caregivers. Further, Dominican-born caregivers reported higher family cohesion than their US-born counterparts. Caregivers born and raised in the Dominican Republic also reported greater contact with social networks than their US- or Puerto Rico-born counterparts. Families that have increased exposure to immediate family members or families from the same ethnic subgroup have enhanced family connectedness and social support, which may positively impact asthma outcomes.

Conclusions and Future Directions

In most Hispanic subgroups, immigration and acculturation to the USA are associated with increased risk of asthma and asthma morbidity. However, Puerto Ricans appear to have the reverse pattern, in which immigration and acculturation to the USA are associated with slightly decreased asthma burden. Among Puerto Ricans, risk factors may vary such that immigration from the island to the mainland contexts affords some protective effects (e.g., healthcare access), but this is poorly understood.

The interactions between genetic or environmental factors and the experiences of immigration and acculturation on asthma outcomes are not well understood. In addition to environmental exposures, there appears to be a complex constellation of social and behavioral factors associated with acculturation that may increase risk for asthma or poor asthma control.

Future Directions

Research on health disparities in asthma may underestimate the impact of socioeconomic and structural factors associated with acculturation [65]. Moreover, simplistic or inconsistent definitions of acculturation may fail to account for "unmeasured" factors associated with acculturation, such as education, religious beliefs, family structure, and discrimination [66]. Indeed, most large-scale studies of acculturation and asthma rely on proxies of acculturation, and do not measure many relevant processes related to acculturation. We thus provide recommendations to further research in acculturation and asthma.

1. Acculturation research in asthma should move beyond simplistic definitions of acculturation, and include a range of immigration-related factors such as child and caregiver nativity, length of stay in the USA over time, and processes related to acculturation (e.g., preferred language, comfort level with mainland norms). Expanded models of the acculturative process are needed to move beyond the traditional, three-stage model of contact, accommodation, and assimilation [66, 67], and consider the concept of biculturalism.
2. Future work in this area should carefully consider the social determinants of health that may operate in concert with acculturation, including institutional and economic barriers to healthcare access, and environmental exposures in low-income neighborhoods.
3. Longitudinal studies are necessary to investigate the complex processes related to asthma among first, second, and third generation immigrants. Such studies should ideally include individual, family, and systems level factors that may confer risk or protection. For example, genetics, indoor and outdoor environmental exposures, and social and behavioral factors (e.g., smoking and smoke exposure, family and cultural stress) should all be included as key factors. Such studies may shed light onto how to mitigate risk for asthma onset and overall asthma morbidity through enhancing protective mechanisms using public health efforts and targeted clinical interventions.
4. Qualitative approaches that examine perceptions of asthma treatment and healthcare use prior to and recently after an individual or family's arrival to the mainland may inform interventions that can be tailored to capitalize on the strengths of the healthy immigrant effect.

Further research should ultimately have important clinical implications. Educational and self-management programs for children with asthma and their parents, and adults with asthma should consider potential effects of immigration and acculturation on asthma management. Family and community-based supports to decrease stress related to acculturation, and increased social and family network support regarding the demands of asthma treatment, may help to address disparities in asthma among Hispanic children and adults.

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Chapter 7
The Lesbian, Gay, Bisexual, and Transgender Community and Respiratory Health

Emily Clausen and Alison Morris

Abbreviations

COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GOLD	Global Initiative on Obstructive Lung Disease
HIV	Human immunodeficiency virus
LGBT	Lesbian gay, bisexual, and transgender
MSM	Men seeking men

Introduction

Health disparities related to sexual orientation have been relatively unexplored despite the fact that over nine million (~3.8 %) Americans identify themselves as lesbian, gay, bisexual, or transgender (LGBT) [1]. Sexual minorities have always existed, but only in recent decades have the inequalities experienced by the LGBT community become more nationally validated, though progress is still hindered by lack of total societal acceptance.

E. Clausen, MD
Department of Medicine, Duke University,
330 Trent Drive, Durham, NC 27710, USA
e-mail: clausene@upmc.edu1

A. Morris, MD, MS (✉)
Department of Medicine, University of Pittsburgh, 628 NW Montefiore University Hospital,
3459 Fifth Avenue, Pittsburgh, PA 15213, USA
e-mail: morrisa@upmc.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_7

Table 7.1 Potential factors associated with increased risk of respiratory illnesses in LGBT populations

Barriers to care: lack of insurance, stigma, homelessness, mental health issues
Lack of physician training in LGBT health
Increased cigarette smoking
Alcohol use
Illicit drug use

Discussing respiratory health disparities due to sexual orientation is challenging for several reasons. First, few scientific investigations directly address sexual orientation and lung health. Second, this diverse demographic is commonly grouped together and referred to as the LGBT community, but each group may have unique risk factors, and sexual orientation is often a fluid concept. In particular, while LGBT is meant to include the transgender community, one could argue that they are a very distinct group. However, few studies have focused on transgender individuals. In general, obtaining accurate information about the LGBT community is limited by the relatively small number of population surveys that take sexual orientation into account, as well as the fact that an individual may not self-identify as gay, lesbian, or bisexual (even if there is a history of attraction or sexual behavior towards the same gender). Moreover, risk factors that impact respiratory health (e.g., illicit drug use) may be difficult to quantify in the LGBT community.

In spite of existing barriers, we need to improve understanding of respiratory health in sexual minorities, while also raising providers' awareness of issues unique to this population. In this chapter, we first review general factors regarding the LGBT community that may contribute to health disparities, particularly for respiratory diseases (Table 7.1). We then discuss environmental risk factors (i.e., smoking) and the burden of respiratory diseases in the LGBT community. Finally, as gay men remain at increased risk for HIV infection, we address the impact of HIV on lung health.

Barriers to Care in the LGBT Community

Healthcare Access

LGBT individuals may be less likely to have health insurance or access to care. The availability of health insurance in this population may increase with recent rulings supporting same-sex marriage. Even with health insurance, LGBT individuals may be less likely to see a doctor because of stigma or fear of disapproval.

Healthcare disparities seem to vary by sexual orientation group. In one study, lesbian women were significantly less likely to have a yearly physical examination than heterosexual women [2]. Whereas bisexual women were less likely to seek medical care because of cost than heterosexual women, gay men had healthcare access similar to that for heterosexual men. Other social factors in the LGBT population, such as homelessness and mental illness, may also lead to health disparities [3, 4].

Perhaps more so than health disparities, the LGBT community may experience more negative effects of stigma due to perceived pressure to hide sexual orientation, which is not as openly visible as gender or race.

Physician Training in Care of LGBT Individuals

Lack of knowledge of LGBT health-related issues among physicians may discourage LGBT individuals from seeking healthcare or result in inappropriate care. Without exposure and specialized instruction during training, it would be difficult for a provider to overcome these barriers. A survey of deans of medical education from North American schools showed that about a third of programs do not include designated LGBT training in their curricula, and that those that did had an estimated median of 5 h of training over 4 years [5]. Similar findings were obtained in a survey of emergency medicine residency program directors, which showed that only 0–8 h were dedicated to didactic time on LGBT health issues (with an average of 45 min spent over a year) [6]. Interestingly, that survey did note that having LGBT faculty greatly increased the likelihood of LGBT care being included in the residency curriculum [6].

As with racial/ethnic disparities (see Chaps. 14 and 15), having a physician from the same minority group may increase participation in healthcare by LGBT patients. While providing support for training of LGBT healthcare professionals who desire to serve their community would be helpful, that would likely be insufficient to decrease disparities. Thus, medical education has to be reformed to address the deficit in medical training on LGBT issues and ultimately reduce healthcare disparities due to sexual orientation.

Environmental and Behavioral Risk Factors

Tobacco Use

Over the last few years, LGBT populations have been shown to have a higher prevalence of smoking than the general population [7]. The National Adult Tobacco Survey from 2009 to 2010 found that the LGBT population overall had a higher prevalence of current smoking (38.5 %) than that of the heterosexual population (25.3 %) [8]. In another nationwide US survey, lesbian and bisexual women had increased rates of tobacco use as well as secondhand smoke exposure [9]. Other studies have reported greater smoking prevalence in lesbians and gay men than in the general population [10]. A large population-based study of US adults reported that lesbians, bisexual women and men, and gay men had increased odds of current smoking compared to heterosexual women or men [2].

The relatively high rates of smoking in LGBT adults are likely due to LGBT youth initiating smoking at higher rate and smoking more cigarettes than their

heterosexual counterparts [11]. In one study, tobacco use was significantly higher in homosexual (35 %) or bisexual (31 %) youth than in their heterosexual counterparts (22 %) [11]. Moreover, 30-day cigarette use was strikingly higher in LGBT youth than in heterosexual youth (88 % higher among homosexuals, 49 % higher among bisexuals) [11]. This disparity in tobacco use is partly due to tobacco industry marketing (see Chaps. 1 and 15).

Tobacco companies target LGBT communities both directly (in advertising) and indirectly (through support of causes that speak to LGBT-related issues). Evidence for these practices has emerged due to the Master Settlement Act (MSA) in 1998 requiring tobacco companies to make internal company documents available to the public. For example, an advertising initiative by R.J. Reynolds titled Project SCUM (Subculture Urban Marketing) described marketing strategies to increase sales in neighborhoods such as San Francisco's Castro District with the target consumer being gay males [12, 13]. Tobacco products have specifically been developed for the gay community, such as Philip Morris' Benson Special Kings cigarettes that were heavily advertised in gay men magazines [13]. Indirect attempts to capture the LGBT market include Philip Morris' program Positive Helpings Initiative, which provides food for those living with AIDS [13]. With LGBT equality becoming mainstream and homophobia becoming less acceptable, tobacco advertising has taken it as an opportunity to attract customers. Lucky Strike, for example, teamed up with the Gay and Lesbian Alliance against Defamation (GLAAD) and created the advertising slogan "Whenever someone yells, 'Dude, that's so gay,' we'll be there".

Though many laws have passed since the MSA to try to thwart tobacco companies from targeting youth, the age group that is the highest for uptake of regular smoking is still under 18 years with the second highest being age 18–24 years old [14–16]. The acronym FUBYAS (First Usual Brand Younger Adult Smokers) describes how brand loyalty is part of why tobacco companies target young adults [17]. The first type of cigarettes someone starts to smoke will likely be a brand they smoke for years to come. For youth who often feel isolated due to LGBT stigma, membership in a group may aid in attaining brand loyalty.

Tobacco advertising often utilizes sex appeal to attract consumers, showing highly attractive men or women smoking a cigarette. Other forms of media that have been criticized for encouraging smoking among youth include movies showing characters smoking. One study examined if US movies within the LGBT genre show characters smoking and if so, whether the dangers of smoking are suggested [18]. The study found that 87 % of the LGBT movies viewed had smoking present, with 49 % of the total movies showing the lead character smoking [18], but only 15 % of the movies making an association between cigarettes and poorer health [18]. Interestingly, the attitude of the LGBT community towards the targeted marketing of their group from the tobacco companies seems to have been welcoming instead of disdainful. This attitude relates to both the tobacco industry's support of LGBT causes as well as the LGBT community viewing recognition by large corporations as a valuable customer as a gain in status, despite negative health consequences. For example, a prominent publisher in gay advocacy magazines stated that tobacco companies' targeting of the LGBT "shows we're making progress" [17].

LGBT populations have an increased prevalence of stress and mental illness, which may be associated with smoking [3]. Major depressive disorder and generalized anxiety disorder are relatively common conditions among LGBT youth, who also have a high frequency of tobacco use [11]. LGBT youth also reported higher use of alcohol, marijuana, and illicit drugs, which is associated with mood disorders [11].

LGBT members have similar awareness of the negative effects of smoking as the general population and have similar desires to quit [19]. No evidence-based best practice guidelines have been established to address the disparate smoking prevalence between the LGBT community and the general population. Examples of tailored programs meant to cater to LGBT communities include "The Last Drag" and "Bitch to Quit" programs [20, 21]. Whether LGBT individuals would be more likely to choose a program tailored to LGBT individuals over a cessation program meant for the general population is unknown, but worthy of studying and potentially useful when designing successful smoking cessation programs for the LGBT community. Prevention from starting smoking would be preferable, given the difficulty of tobacco cessation. Focusing on antitobacco program efforts targeting LGBT youth is therefore essential for combating high smoking prevalence among this population in adulthood.

Alcohol and Other Substance Use

Alcohol consumption may also impact lung disease in the LGBT population. Chronic alcohol use can alter lung immunity (resulting in greater susceptibility to infection) and impair antioxidant response (which may cause acute or chronic lung damage) [22–25]. LGBT women have greater alcohol consumption than heterosexual women, but LGBT men do not show similar trends [3, 26]. A recent study found that lesbian and bisexual women were more likely to binge drink than heterosexual women [2]. Given the effects of alcohol on lung immunity and infection risk [23, 24, 27], studies of alcohol use and lung disease in sexual minorities are needed.

Marijuana use is also common, and amyl nitrite (poppers) use is common in the gay male population. These drugs do not seem to have pronounced effects on lung function [28], but evidence is scarce.

Respiratory Diseases in the LGBT Community

The burden of respiratory diseases in the LGBT population is not well defined, but the higher prevalence of smoking and other risk factors suggests that LGBT individuals may be at risk for lung disease. Along with higher rates of smoking among LGBT youth, LGBT college students experience higher rates of acute respiratory illness than heterosexual college students, even after accounting for smoking [14]. However, large studies of respiratory diseases in the LGBT population are lacking.

Obstructive Airway Diseases in the LGBT Community

Obstructive airway diseases encompass asthma and chronic obstructive pulmonary disease (COPD) (see Chap. 10). Although there are limited data, smoking causes COPD and worsens asthma, suggesting that these diseases may be more common or severe in the LGBT population. COPD has primarily been studied in this population in the setting of HIV and is discussed below. Several studies have found a higher prevalence of asthma in LGB individuals than in heterosexual individuals [3, 26]. In the 1997–2004 National Health Interview Surveys, more men and women in same-sex relationships reported a diagnosis of asthma than those in opposite-sex relationships [29]. Same-sex relationship men had a significantly increased risk of ever having asthma, while women in same-sex relationships had increased risk of current asthma [29]. Similar findings were reported in a study of data from the 2004 Behavioral Risk Factor Surveillance System [30]. A major limitation of published studies of asthma in LGBT populations is potential disease misclassification (due to reliance on a self-reported diagnosis and lack of measures of lung function or airway responsiveness).

There may also be differences in correlates of airway diseases in sexual minorities. For example, a study found that LGB individuals with asthma were more likely to be current or former smokers and to be obese than LGB individuals not diagnosed with asthma [31]. The same risk factors were associated with asthma in heterosexual study participants. In another study, both obesity and being a person of color were associated with asthma in same-sex couples [2]. In general, these risk factors appear similar in LGBT individuals and heterosexuals, but no studies have explored traditional asthma risk factors such as allergy and atopy.

Lung Cancer in the LGBT Community

Given high rates of smoking and young age of smoking initiation, smoking-related malignancies may be more common in LGBT individuals. Two studies have indirectly addressed lung cancer in sexual minorities [32, 33]. The first study examined the relation between lung cancer and geographic areas with greater density of sexual minorities [32]. Although potentially misidentifying LGBT individuals (since explicit sexual orientation data are not collected in the census), that study found that incidence and mortality from lung cancer were greater in men living in areas with a higher population density of male same-sex households than in other areas. In sexual minority women, lung cancer incidence and mortality were inversely associated with density of same-sex households. The authors postulated that this differing association by gender in sexual minorities might have resulted from a more recent increase in smoking behavior in women, which is not yet reflected in lung cancer incidence. A similar study examined the relationship between sexual minority population density and lung cancer in California, using sexual orientation data from a

health survey [33]. In that study, density of individuals representing as gay was not associated with lung cancer incidence in men, while bisexual population density was associated with decreased incidence of lung cancer. Lesbian population density was also associated with decreased incidence in women, but an increased population density of bisexual women was associated with higher incidence of lung cancer. These data demonstrate the potential inappropriateness of combining sexual orientation groups for research purposes, and highlight the need for better understanding of the relationship between sexual orientation and lung cancer.

The Impact of HIV on Pulmonary Disease

Though now more widespread in the general population, human immunodeficiency virus (HIV) still disproportionally affects the LGBT community, with rates of new disease being the highest among the MSM (male seeking male) population [34]. For example, just over half of the known US cases of individuals living with HIV were identified as MSM as of 2011. MSM also represented 63 % of new HIV infections in 2010 [35].

Pulmonary disease is a leading cause of morbidity and mortality in HIV-infected individuals. Opportunistic pneumonias and AIDS-associated neoplasms such as Kaposi's sarcoma were common prior to the advent of combination antiretroviral therapy. Although these diseases still occur, HIV is now often associated with a variety of chronic diseases such as COPD, pulmonary hypertension, and lung cancer [36–40]. Chronic respiratory complaints are frequently reported in HIV-infected individuals [41]. For example, a recent study found that 47 % of an HIV-infected cohort reported chronic cough and sputum production [42], consistent with previous findings from a study of an HIV-infected outpatient cohort [43]. In a population of primarily gay men, HIV infection was associated with dyspnea, cough, wheeze, and COPD [44]. However, HIV-infected men were not more likely to undergo pulmonary function tests than HIV-uninfected men, suggesting potential underdiagnosis of respiratory diseases in HIV-infected individuals.

A number of studies have investigated COPD in HIV-infected individuals. Although COPD is generally defined by the Global Initiative on Obstructive Lung Disease (GOLD) as a ratio of the forced expiratory volume in 1 s (FEV_1) over forced vital capacity (FVC) lower than 70 % after bronchodilator administration, COPD may encompass other lung function abnormalities such as reduced diffusing capacity for carbon monoxide (DLCO) or radiographic emphysema. A Veteran Affairs study found that HIV-infected veterans were 50–60 % more likely to have COPD (based on self-report or ICD-9 code diagnosis) than HIV-uninfected veterans [36, 37]. Multiple studies have shown that HIV-infected individuals are also more likely to have COPD based upon spirometry or imaging, even after accounting for smoking [42, 43, 45]. Interestingly, a clinically impaired DLCO is quite common, occurring in greater than 50 % of some cohorts [42, 43, 46]. HIV-infected individuals have a lower DLCO percent predicted than HIV-uninfected individuals, adjusting

for smoking and other covariates [47, 48]. A longitudinal study of injection drug users showed that HIV-specific risk factors such as higher viral loads and lower CD4 cell counts predicted accelerated decline in FEV_1 [49]. Interestingly, some studies have found a positive association between antiretroviral therapy (ART) and lung function, while others have reported an inverse relationship [41, 43]. A recent study of primarily injection drug users found increased odds for acute COPD exacerbations in HIV-infected individuals with higher CD4 cell counts and low viral levels, suggesting that an intact immune system increases respiratory symptoms during an exacerbation [50].

Conclusions

The vulnerability of the LGBT community to respiratory diseases is not well-studied. Risk factors for pulmonary disease in this population, such as smoking, may impact certain diseases such as COPD and lung cancer, but few large-scale studies have been performed. Prevention and cessation of tobacco use present unique challenges in the LGBT community, but are of the utmost importance. Pulmonary diseases such as asthma appear to be increased in certain LGBT subgroups, but these findings are questionnaire-based and understanding of risk factors is limited. Additional research and education are sorely needed to improve the respiratory health of LGBT individuals and inform physicians regarding appropriate care for this population.

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Chapter 8
Bronchopulmonary Dysplasia

Catalina Bazacliu and Rita M. Ryan

Introduction

With a higher preterm birth rate for Black infants compared with White infants [1], racial disparities in neonatal morbidity and mortality are known. A study from Michigan reported a 1.6-fold difference [2] in premature birth between Blacks and Whites; another reported higher infant mortality in Black infants than in white infants (14 vs. 5.7/1000 live births in 2000) [3]. Black race is protective for retinopathy of prematurity [4], but it is unclear whether Black race is also protective for bronchopulmonary dysplasia (BPD), partially because of the confounding factor of the higher rate of prematurity among Blacks. In this chapter, we report on the data available to examine racial predispositions to develop BPD, or chronic lung disease of prematurity.

Bronchopulmonary Dysplasia

BPD is the most common morbidity of premature birth, affecting approximately 10,000 preterm infants annually in the United States (US) alone [5]. BPD is thought to be the result of disruption of lung development, of multifactorial etiology, modulated by genetic and epigenetic factors specific to individual patients.

C. Bazacliu, MD
Department of Pediatrics, Division of Neonatology, University of Florida Shands Hospital, 1600 SW Archer Road, Gainesville, FL 32610, USA
e-mail: cbazacliu@peds.ufl.edu

R.M. Ryan, MD (✉)
Department of Pediatrics, Division of Neonatology, Medical University of South Carolina Children's Hospital, 135 Rutledge Avenue, Charleston, SC 29425, USA
e-mail: ryanr@musc.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_8

The improved survival of extremely premature neonates has led to an increased number of infants with BPD, a chronic lung disease of prematurity. The clinical, radiological, and pathological aspects of the disease have changed with improvement in prenatal care (e.g., antenatal steroids, maternal antibiotics) and postnatal care (e.g., gentle ventilation, surfactant, decreased postnatal steroid use) since its initial description by Northway in 1967. The incidence of BPD correlates strongly with gestational age (with very high rates in infants born at 22–24 weeks of gestation, which then decrease with increasing gestational age) and can vary among centers [6]. Diagnostic criteria have changed over time, and a diagnosis of BPD is not always a good predictor of respiratory outcomes in childhood [7]. Despite multiple attempts to decrease the incidence of BPD, there are only two preventive therapies (caffeine [8] and vitamin A [9]) that have proven to be effective in clinical trials.

Extensive research has been done to understand the pathogenesis of BPD. The results of the latest extensive observational prospective cohort study (NIH Prematurity and Respiratory Outcomes Program, PROP) are expected to become available in the near future [10, 11]. PROP has enrolled 835 babies <29 weeks gestation, and aims to identify clinical and biological markers predictive of respiratory morbidities during the first year of life. Despite many advances in neonatal intensive care, it appears that the rate of BPD is not decreasing. For example, in a study of 5115 infants <33 weeks gestation in California Kaiser Permanente, Smith et al. showed that while BPD rates did not change over the time period from 1994 to 2002 (overall 12 %), severe BPD did decrease significantly over time (from 9.7 to 3.7 % in the entire cohort, and from 25.7 to 8.2 % in babies <29 weeks, unrelated to race) [12].

One interesting study examined post-discharge mortality in a National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) population [13]. The authors found that African-American ethnicity was a risk factor for post-NICU discharge mortality but BPD was not. This finding was corroborated by Morris and colleagues, again in an NRN study, who showed that post-discharge mortality was 3.3 % in African-American babies vs. 1.7 % in white babies ($P = 0.007$) [14]. Akinbami and Schoendorf summarize a large portion of the literature [15], and suggest that minority children and children who live in poverty do not have a good asthma treatment "home" that is of high quality and provides continuity. This may contribute to racial/ethnic disparities in respiratory morbidity after NICU discharge.

Racial Disparities in BPD

Generally in the biomedical and social sciences literature, the definition of terms used to refer to race and ethnicity differ from article to article (see Chap. 2). The methods used to determine race and ethnicity are inconsistently reported in up to 72 % of published articles, even though two-thirds of them assigned associations among race/ethnicity, health outcome, and genotype [16]. We used the same terms as those in the primary literature source, for consistency.

Historically, White race has been considered a classic risk factor for BPD. An eight-center survey published in 1987 included 1625 infants with birth weight 700–1500 g and confirmed the association of BPD with low birth weight, White race, and male sex [17]. A large study of risk factors for chronic lung disease, including data from 361 non-surfactant treated neonates born in 1988–1989 with birth weight <1200 g, concluded that the joint effect of race and gender was significant [18]. Again, Non-Black race was a risk factor for BPD with an adjusted odds ratio (aOR) of 2.2 (95 % confidence interval [CI] = 1.0–4.7). A retrospective study of 1006 preterm neonates (born at <32 weeks gestation between 1998 and 2001) in New Jersey concluded that multiple gestation Black infants had a lower gestational age and birth weight than White and Hispanic infants, but that morbidity and mortality by gestational age categories were comparable among racial/ethnic groups. Moreover, BPD rates were not significantly different across racial or ethnic groups [19]. Similar findings for race/ethnicity were reported in a recent study of 5115 infants <33 weeks gestation, which found that race was not significantly associated with BPD cohort or severe BPD, further suggesting that race is not a risk factor for BPD [12].

A recent predictive model was developed to identify infants at highest risk of developing BPD. The model used data from infants with gestational ages of 23–30 weeks, who were enrolled in the Neonatal Research Benchmarking Trial in 2000–2004 from the 17 centers that comprised the NICHD NRN [20]. Using those data, a BPD "calculator" that estimates the probability of death and of BPD with three degrees of severity was developed, and is available online: https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start. Variables that were identified as significant predictors in a multivariable analysis were gestational age, birth weight, sex, race/ethnicity (defined as non-Hispanic White, non-Hispanic Black, or Hispanic), respiratory support, and fraction of inspired oxygen at various postnatal ages. For the same birth weight, gestational age and respiratory support increase the likelihood and severity of BPD in non-Hispanic White infants. For example, for a male infant born at 30 weeks weighing 1200 g who is 1 day old on 100 % oxygen on a high frequency ventilator, the risk for BPD is 38 % for non-Hispanic Blacks but 49 % for non-Hispanic Whites, despite a similar risk for mortality of 28 %.

A two-center (an inner-city center serving a predominantly Black population and a suburban center serving a predominantly White population) retrospective study of 306 preterm newborns (who were born at less than 30 weeks of gestation and survived to 36 weeks corrected gestational age) reported that White race (aOR = 2.5, 95 % CI = 1.1–5.8), birth weight, respiratory distress syndrome requiring surfactant, sepsis, and the presence of patent ductus arteriosus (PDA) were each significantly associated with BPD [21].

The California's Prenatal Quality Care Collaborative (CPQCC) recently published the results of a population-based cohort study that aimed to identify risk factors for BPD and hospital variation of BPD rates. The cohort included 15,779 infants with gestational age of 22–29 weeks, from which 7801 met the primary outcome of BPD or death. BPD affected approximately 45 % of VLBW infants, with rates varying among centers (from 17.7 to 73.4 %). The study identified lower gestational age, lower birth weight, low Apgar scores and male sex as risk factors, and Black

race (aOR = 0.79, 95 % CI 0.7–0.9), maternal diabetes mellitus, and lack of prenatal care as protective factors [22]. Hispanic ethnicity was not significantly associated with BPD.

Because of limited data, little is known about the risk of BPD in Asians compared to other ethnic groups. Whereas Koreans and Japanese may have a relatively low rate of BPD, the rates of BPD may be higher in Taiwan than in the USA [23, 24]. Studies that directly compare BPD rates in Asian subgroups against those in other racial/ethnic groups, receiving care at the same centers, are needed to adequately examine BDP risk in Asians.

Overall, in studies that have found a racial predisposition for BPD, White infants have 2–2.5 times increased risk of BPD, with Black race being protective. There is generally not enough information available about other racial or ethnic groups, although available data (from small samples) suggest that Hispanic infants have a similar risk of BPD to that of white infants.

Black race may be a risk factor for respiratory morbidity after NICU discharge in babies with BPD. In a study by Collaco et al. [25], subjects were infants younger than 3 years, who were diagnosed with BPD (when discharged from the NICU) and chronic lung disease of prematurity (CLDP, when seen at a specialty clinic); 71 % of the babies were not White. CLDP was defined as having respiratory symptoms, and/or receiving oxygen or other respiratory-related drugs (primarily diuretics) at the first post-NICU discharge visit. Compared with non-Hispanic Whites, non-Whites were twice as likely to have received systemic steroids and 2.5 times as likely to have received a rescue medication (primarily inhaled beta-agonists). However, race/ethnicity was not significantly associated with baseline use of inhaled steroids, secondhand smoke exposure or day care exposure. Potential but unproven explanations for the study findings include racial differences in response to bronchodilators, adherence with inhaled corticosteroids, or symptom severity (all leading to additional or more intensive treatment in non-Whites); and residual confounding by unmeasured environmental exposures.

Despite overall reductions in mortality, racial or ethnic disparities in mortality rates from BPD have increased. Because of strong correlations between race or ethnicity and socioeconomic status (SES) in the USA (see Chaps. 2 and 3), poverty, lower educational level, and poor access to health care may explain this finding. Alternatively, biological and genetic differences could be partly responsible for racial/ethnic disparities in BPD mortality. Such racial or ethnic characteristics include birth weight, physical maturity, and timing of birth.

In a study from South Carolina, mean birth weight for Black infants was 100 g lower than that for White infants, even after controlling for maternal demographic characteristics and medical complications of pregnancy [26]. Gestational age interval based on LMP might not be a valid indicator of fetal maturity across all racial groups, as Black preterm infants have on average a greater level of maturity as measured by the Ballard exam [27]. There is growing evidence to suggest that the gestation of Black African women (particularly West African) is about 6 days shorter than that of White European women [28], which could explain racial differences in level of maturity. Consistent with this theory, a prior study from South Carolina had shown that neonatal mortality was lower for Blacks with gestational

ages in the premature range than for Whites with similar gestational ages, suggesting more advanced maturation in Blacks [29]. In another study, Caucasian newborns were more than twice as likely to have a SNAP score >10 than African-American newborns (33 % vs. 14 %; $P < 0.05$). In a multivariable logistic regression analysis, African-American newborns had markedly lower odds of having a SNAP score >10 than Caucasian newborns (aOR = 0.14, 95 % CI = 0.04–0.51). This finding further suggests increased maturation in utero of Black infants, and an inherently shorter duration of gestation in Blacks [30].

A common condition in premature infants is respiratory distress syndrome (RDS) due to surfactant deficiency. Black infants have a lower rate of RDS than White infants, presumably due to earlier lung maturation [31–34]. For babies born <32 weeks gestation, 75 % of White but only 40 % of Black neonates develop RDS [35], a finding consistent with a protective effect of increased in utero maturation in Blacks.

In a recently published paper on social inequities as a result of technological changes, the authors developed a model of induced innovation that applies to medical research outcomes data, before and after introduction of surfactant therapy for RDS, to probe their hypothesis. Surfactant therapy decreased RDS morbidity and mortality in White and (to a lesser extent) Black newborns, increasing racial disparities due to a greater therapeutic effect in the majority group [36]. In another study of mortality trends in preterm neonates in South Carolina (from 1975 to 1994), gestational age-specific related mortality decreased in both Blacks and Whites, but the African-American neonatal mortality rate was 2.3 times higher than of Whites [37]. However, the gestational age defined as the limit of viability (e.g., the age at which >50 % of babies die within the first 28 days of life) was lower for Blacks (23.9 weeks) than for Whites (24.5 weeks). Since White infants are less "mature" than Blacks, any new interventions (e.g., surfactant) may benefit Whites more than Blacks.

BPD and Pulmonary Hypertension

Pulmonary hypertension complicates 17–43 % of BPD cases [25], leading to additional morbidity and mortality. A retrospective cohort study of 138 infants with restricted growth (birth weight <25th percentile for gestational age) and moderate or severe BPD showed a significant interaction between race/ethnicity and BPD on pulmonary hypertension ($P = 0.02$). In particular, the incidence of pulmonary hypertension in African-Americans with BPD (22/39 or 56 %) was higher than that in non-Hispanic Whites with BPD (7/39 or 18 %) [38]. In a study of inhaled nitric oxide study as preventive therapy for BPD in preterm infants, the estimated effect of inhaled nitric oxide appeared to differ according to race or ethnic group ($P = 0.05$ for interaction between race/ethnicity and treatment), with a greater effect of inhaled nitric oxide in African-Americans and Hispanics than in non-Hispanic Whites [39]. Findings from the studies above suggest that preventing pulmonary hypertension could reduce morbidity from BPD in African-Americans. Moreover, the nitric oxide pathway may be a target for clinical trials in Black infants.

Data from multiple studies consistently suggest that RDS is more common in White neonates, with BPD following a similar pattern but at lower amplitude. Future studies should aim to discover the mechanisms underlying racial differences in maturity for the same gestational age.

Genetic Screening Studies

As personalized medicine becomes increasingly possible, there is considerable interest in identifying genetic or epigenetic markers of BPD. Despite strong heritability [40, 41], no susceptibility gene for BPD has been confidently identified.

In a genome-wide association study (GWAS) of BPD from France [42], polymorphisms in *SPOCK2* (the gene encoding *Sp*arc/*o*steonectin, *C*wcv, and *K*azal-like domains proteoglycan [also called testican-2]) were associated with BPD in babies of African or white descent. An additional polymorphism of this gene was associated with BPD only in White subjects, a finding that may be explained by true race-specific effects or a false positive result. Of interest, *SPOCK2* is upregulated during the alveolar phase of lung development and by hyperoxia.

Vascular endothelial factor A (VEGF-A) and vascular endothelial factor receptor (VEGFR) are key in pulmonary angiogenesis, and impaired angiogenesis is critical in the etiology of BPD [43]. A Polish study found that the VEGF allele-460T was associated with a 9% higher risk of BPD (95% CI: 2–14%) in Caucasian preterm infants. However, this polymorphism was not associated with serum VEGF [44]. Findings from the Polish study were not replicated in a study of Caucasian Finns and Canadians [45], or in a study of a racially diverse population [46].

Although inflammation plays a role in BPD, a GWAS conducted in Caucasians found no significant association between genes implicated in inflammation or immune modulation (e.g., *IL6*, *IL10*, *TNF*, *NR3C1*) and BPD [47]. A candidate gene-association study in 1091 infants identified an association between SNPs in IL-18RAP (receptor ancestry protein) and IL-18R1 in African-Americans only, but this finding was not replicated in an independent cohort [48]. In a German cohort of preterm infants, IL-18 SNPs were not associated with BPD [49].

Surfactant protein B (*SPB*) polymorphisms have been associated with BPD in Han Chinese. The SP-B -18C/A polymorphism was positively associated with BPD, while the SP-B 1580 C/T polymorphism was inversely associated with BPD. As the frequency of the C (presumably unfavorable) allele of the SP-B 1580 C/T allele is higher in Asians than in Caucasians or Blacks, it has been postulated that Asian infants may be at increased risk of pulmonary diseases, but this remains highly speculative [50, 51].

A GWAS of moderate to severe BPD yielded no significant results [46]. Similarly negative results were obtained in a GWAS and gene set analysis aiming to identify SNPs and pathways associated with BPD/death, severe BPD/death or severe BPD in survivors among infants with extremely low birth weight [52]. Although non-statistically significant, pathways with a lower false discovery rate included miR-219 targets for BPD/death, and phosphorous oxygen lyase activity for severe BPD/death and severe BPD in survivors.

Summary

Improved survival of extremely preterm infants has led to increased incidence of BPD. Interventions to reduce respiratory morbidity in infants with BPD seem to have different efficacy across racial or ethnic groups, which could lead to increasing health disparities. Current evidence suggests that Black infants are at reduced risk of developing BPD or dying from preterm birth. On the other hand, Blacks with BPD may have increased respiratory morbidity after discharge from the NICU, as well as greater risk of BPD-associated pulmonary hypertension. Scarce data suggest that Hispanics have a risk of BPD similar to that of Whites, with conflicting results from a handful of studies conducted in Asians. Thus, more studies including well-defined Hispanic (e.g., Puerto Rican, Mexican American) and Asian (e.g., Han Chinese, Japanese, Korean) subgroups are needed before firm conclusions are drawn regarding their BPD risk.

To date, no susceptibility gene for BPD has been confidently identified. Large studies, including "omics" (genetics, epigenetics, transcriptomics, and proteomics) data may help identify biomarkers of risk and severity for BPD in general, and in racial or ethnic minority groups in particular. Such discovery would help develop new preventive and therapeutic approaches, ultimately reducing racial or ethnic health disparities in BPD.

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Chapter 9
Cystic Fibrosis

Gabriela R. Oates and Michael S. Schechter

Abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane regulator
CI	Confidence interval
ETS	Environmental tobacco smoke
FEV_1	Forced expiratory volume in 1 s
OR	Odds ratio
PA	*Pseudomonas aeruginosa*
SD	Standard deviation
SES	Socioeconomic status

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by defective regulation of salt and water transport across cell membranes, resulting in the production of abnormal secretions in several organ systems. Impaired mucociliary clearance in

G.R. Oates, PhD
Division of Preventive Medicine, University of Alabama at Birmingham,
1717 11th Avenue South, MT 623, Birmingham, AL 35203, USA
e-mail: goates@uab.edu

M.S. Schechter, MD, MPH (✉)
Division of Pulmonary Medicine, Department of Pediatrics, Virginia Commonwealth University, Children's Hospital of Richmond at VCU,
1112 E. Clay Street, P.O. Box 980315, Richmond, VA 23298, USA
e-mail: michael.schechter@vcuhealth.org

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_9

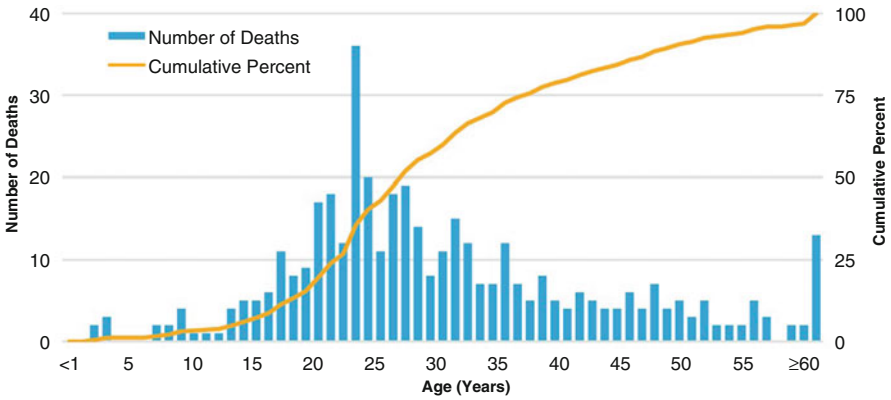

Fig. 9.1 While the median age at death of all patients followed at CF Foundation accredited programs in 2013 was 27.5 years, this figure shows that many patients still do not survive into their 20s while others attain middle age. *Source*: Cystic Fibrosis Foundation Patient Registry. 2013 Annual Data Report to the Center Directors. Bethesda, Maryland ©2014 Cystic Fibrosis Foundation

the lungs leads to chronic infection and inflammation, which eventually leads to bronchiectasis and respiratory failure, the primary cause of death [1]. Pancreatic ductal obstruction causes pancreatic exocrine insufficiency and malabsorption in 85–90 % of patients. Treatments of the pulmonary manifestations of CF focus on enhancing airway clearance, antimicrobial therapy, and immunomodulators [2]; treatment of the gastrointestinal manifestations of CF consists of pancreatic enzyme replacement and nutritional augmentation. Nutritional status and lung disease severity are closely interrelated [3].

CF is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR), which functions as a chloride channel in epithelial membranes [4]. There are >2000 known CFTR mutations, but 50 % of CF patients are homozygous for the ΔF508 mutation, and 35 % are compound heterozygotes with one ΔF508 mutation. Mutations may be classified into six classes, associated with different degrees of functional compromise in CFTR and corresponding disease severity.

The life expectancy and quality of life for patients with CF have improved steadily over the past five decades, largely because of an increased appreciation for the importance of adequate nutrition and an anticipatory, aggressive approach toward chronic airway infection. Nonetheless, significant variation in CF outcomes exists (Fig. 9.1). A number of factors have been hypothesized or proven to influence disease severity and outcome. As previously suggested [5], such factors can be grouped into genetic, environmental, and healthcare-related (Fig. 9.2). *Genetic determinants* include the impact of various CFTR mutation classes, which may be additionally modified by a multitude of genetic polymorphisms. These mutations affect inflammation and host response to infection, as well as susceptibility to complications, such as diabetes mellitus [6]. A body of work over the last decade has shown *healthcare-related* variation in treatment and outcomes across CF care centers [7, 8]. Furthermore, treatment effectiveness is mediated by the self-management

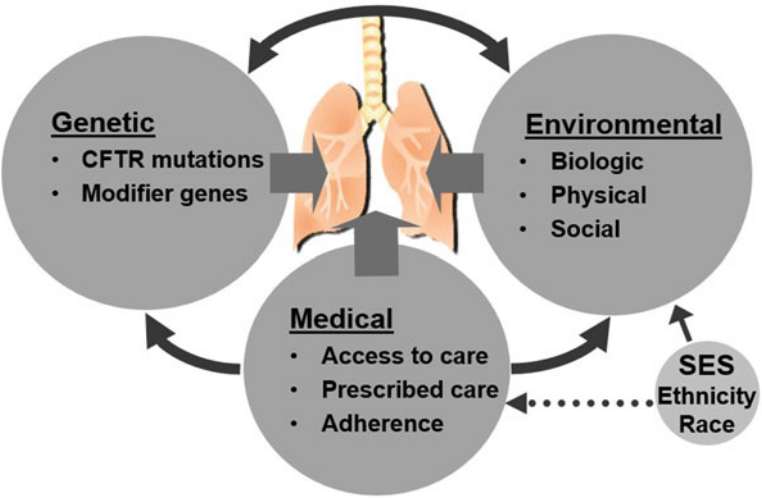

Fig. 9.2 CF disease outcomes reflect the complex interaction of genetic factors and environmental exposures (including the social milieu), as well as variations in the delivery and effectiveness of medical interventions. Socioeconomic status as well as race and ethnicity impact significantly on these interactions. Adapted from Hodson and Geddes' Cystic Fibrosis, Fourth Edition Andrew Bush, Diana Bilton, Margaret Hodson July 24, 2015 by CRC Press. ISBN 9781444180008—CAT# K17710

skills of the patient and her/his family, and adherence with treatment recommendations. *Environmental influences* include not only exposures related to the physical environment but also factors that modify the impact of these exposures, such as socioeconomic status (SES), cultural and community influences, and stress-mitigating resources. The course of disease in a person with CF depends on how these genetic, healthcare, and environmental influences interact to promote or mitigate the importance of each [9].

With its uniform etiology, a single-gene disorder such as CF offers a valuable case for understanding health disparities. Even in individuals with identical CFTR genotypes, CF disease progression and severity vary substantially [10], mostly as a result of the modifying effect of nongenetic rather than genetic determinants [11–13]. To achieve health equality in CF, it is important to understand the contribution of nongenetic factors to CF progression, and uncover pathways and mechanisms through which the social and physical environments influence disease variability in this single-gene disorder.

Nongenetic Causes of Clinical Variability in CF

Multiple pathways responsible for individuals' health status have been identified, such as differential access to material resources, stressful situations, ability to control one's surroundings or cope with disease, availability of social support, patterns

of health behavior, and healthcare utilization [14–16]. Similarly, a number of nongenetic contributors to CF severity have been reported. They cover the entire spectrum of *socioeconomic factors*, such as financial resources, educational attainment, living conditions, family environment, and social support; *physical environment*, such as exposure to secondhand tobacco smoke, air pollution, and infectious agents; *health behaviors*, such as disease self-management and adherence; and *healthcare factors*, such as access to and quality of medical care.

Socioeconomic Factors

A large body of research describes the implications of SES for health and well-being [17–19]. An individual's SES, assessed by indicators such as income, education, and occupation, is linked to a range of health problems (see Chap. 3). Typically, lower SES is associated with poorer health and higher mortality at every point across the life course. Moreover, health disparities follow a stepwise gradient pattern, with health improving incrementally as income, education, and occupational prestige increase [20–23].

One of the earliest studies that showed independent effect of SES on age at death from CF was conducted by Britton [24]. Using mortality data for England and Wales from 1959 to 1986, he found that the median age at death from CF was higher in nonmanual vs. manual occupations (odds ratio [OR] = 2.8, 95 % confidence interval [CI] = 2.2–3.5). More recently, Barr et al. [25] updated this work by performing a series of cross-sectional analyses of all deaths from CF in England and Wales between 1959 and 2008. From 1959 to 2000, SES was coded as manual vs. nonmanual occupation. From 2001 onwards, SES was split into three groups: professional and managerial, intermediate, and routine and manual occupation. Using logistic regression and adjusting for sex, the authors calculated median age at death from CF for every study year and estimated the effects of SES on the odds of death above the median age at death from CF for every decade. Individuals in the highest socioeconomic group were more likely to die above the median age of death from CF than those in the lowest socioeconomic group (OR = 2.5, 95 % CI = 2.2–2.9, for 1959–2000; OR = 1.9, 95 % CI = 1.2–3.0, for 2001–2008).

In the United States (US), Schechter et al. [26] used Medicaid as a proxy for low SES and analyzed CF Foundation Patient Registry data for 1986–1994. In that study, the adjusted risk of death was 3.65 times higher for CF patients on Medicaid than for those not on Medicaid. Similarly, O'Connor et al. [27] evaluated CF mortality at five levels of median family income by ZIP code, using U.S. Census data. They found a 44 % increased risk of death for CF patients in the lowest income group (<$20,000) compared to the highest income group (>$50,000). Equally interesting was their finding of a monotonic successive relationship between the five income categories and mortality, emphasizing that the relationship between SES and CF outcomes is an incremental rather than a dichotomous one that affects only the indigent.

The effects of SES on CF health are not evidenced by age at death alone. Key outcomes such as lung function and growth follow a similar pattern. Taylor-Robinson et al. [28] assessed the correlation between social deprivation and individual health outcomes in a longitudinal study of the CF population in the UK younger than age 40 years between 1996 and 2009. They evaluated data for weight, height, BMI, forced expiratory volume in 1 s percent predicted (FEV_1%), and risk of *Pseudomonas aeruginosa* (PA) colonization. CF patients from disadvantaged areas had worse growth and lung function than CF patients from affluent areas. Compared with the least deprived areas, CF patients from the most deprived areas weighed less (standard deviation [SD] score −0.28, 95 % CI = −0.38 to −0.18), were shorter (−0.31, −0.40 to −0.21), had a lower BMI (−0.13, −0.22 to −0.04), and were more likely to have chronic PA infection (OR 1.89, 95 % CI 1.34–2.66) and lower FEV_1% (−4.12 % points, 95 % CI −5.01 to −3.19).

The previously cited study by Schechter et al. [26] found similar disparities. The FEV_1% of Medicaid patients was 9.1 % lower (95 % CI = 6.9–11.2) than that of non-Medicaid patients. Medicaid patients were 2.2 times more likely to be below the 5th percentile for weight (95 % CI = 1.9–2.5) and 2.2 times more likely to be below the 5th percentile for height (95 % CI = 2.0–2.5) than non-Medicaid patients. The previously cited study by O'Connor et al. [27] found a relationship between their five income categories and pulmonary function and nutrition, very similar to what they had observed for mortality.

Balmer et al. [29] used a sociological approach to explore the impact of SES on preadolescents with CF and pancreatic insufficiency. They examined the relationship between financial, human, and social capital, on the one side, and growth and pulmonary status, on the other, over 24 months. Financial capital was defined as household income, human capital as educational attainment of the primary caregiver, and social capital as family structure (as number of caregivers in the household). The results showed an adverse effect of social disadvantage on health outcomes. Each social risk factor—low income, limited education, or single caregiver—was associated with suboptimal growth and pulmonary function at baseline, or a decline in growth over 24 months. The Advantage Index, a composite score of the above three dimensions of SES, was the strongest predictor of growth in this sample. In fact, the growth status of preadolescent CF children who were socially advantaged was comparable to that of a healthy population. Finally, it should be noted that socioeconomic disparities in CF health are present not only in the UK and the USA, but in other countries as well [30].

Early Onset of the SES Effect on CF

Socioeconomic disparities in CF outcomes become evident in very early childhood [26–28, 31, 32]. In fact, a significant association between SES (as defined by paternal education) and lung function has been demonstrated as early as age 12 months in infants diagnosed with CF through newborn screening [33]. These findings show that the processes linking SES with CF health operate from early postnatal life, and

possibly even in utero. Such a conclusion is supported by the concept of early-life programming [34], which stipulates that exposures and experiences during early life become "encoded" in organs and systems, and manifest later in life in the form of health or disease.

The complex ways in which biological risk interacts with social factors and influences the progression of CF disease can be understood best with longitudinal studies. Central in the life-course approach is the notion of "critical periods" in a person's biological and social development. Critical-period models emphasize the importance of timing of health risks, and demonstrate that exposures during particular biological or developmental stages can have long-lasting health impacts. Two such critical periods are pregnancy and early childhood. Maternal stress during pregnancy has been linked to preterm birth, low birth weight, and reduced cognitive ability [35–40], and early-life economic deprivation has been shown to set a child on a trajectory toward diminished health [41, 42]. Children with CF are not an exception when exposed to the health risks of poverty. On the contrary, they face the double disadvantage of low SES and a progressive chronic disease.

Mechanisms of the Link Between SES and CF Health

While further research is needed to determine the precise mechanisms of the link between CF health and SES indicators such as income, education, and occupation, several pathways have been described in the literature.

SES and Environmental Exposures

Environmental exposures, such as secondhand smoke (SHS), indoor and outdoor air quality, allergens, and infectious agents, affect CF lung health. Collaco et al. [11] estimate that they account for approximately 50 % of the clinical variation in CF. As environmental exposures are highly correlated with SES, they are one known mediator of the link between SES and CF outcomes.

Secondhand Smoke: Because of persistent differences in the prevalence of smoking according to SES [22], secondhand smoke is a primary mechanism through which SES affects CF lung health [13, 43]. Exposure to SHS is associated with poorer growth and lung function in CF [44]. A dose-dependent association between SHS exposure and overall disease severity and growth in CF was first reported by Rubin [45]. His findings have been corroborated in subsequent publications. More recently, a retrospective assessment of 800 participants in the U.S. Cystic Fibrosis Twin and Sibling Study [46] found that SHS exposure in the home was correlated with significantly lower cross-sectional (9.8 % decrease) and longitudinal (6.1 % decrease) lung function compared with individuals without such exposure. Moreover, those exposed prenatally had a lower birth weight than those who were not. A recent analysis of data from the EPIC Observational Study also found that SHS exposure

had an additive effect on SES-related disparities in lung function and anthropometric measures in children with CF [47].

Air Pollution: In general, people of low SES are more likely to live in areas with greater air pollution (see Chap. 4) [48]. Although exposure to industrial air toxins has decreased dramatically over the past couple of decades, it remains highly correlated with social class [49]. Similarly, people in poor neighborhoods have higher exposure to long-term air pollution and short-term nitrogen dioxide concentrations than people in affluent neighborhoods [50]. Exposure to air pollution compromises lung growth in children [51] and leads to increased mortality in adults [50, 52]. A recent study that followed 204 Belgian CF patients over 12 years reported a significant correlation between ambient concentrations of particulate matter, nitrogen dioxide, and ozone and prescriptions of IV antibiotics for pulmonary exacerbations [53]. Similarly, an analysis of the CF Foundation's U.S. Patient Registry investigating air pollution by residence ZIP code showed that increased exposure to ambient ozone and particulate matter is associated with an increase in the number of pulmonary exacerbations and a decrease in lung function [54]. Furthermore, a recent study that estimated exposure to fine particulate matter based on air pollution monitors within 30 miles of place of residence found exposure to be associated with an increased risk of initial *Pseudomonas aeruginosa* (PA) acquisition in a cohort of 3575 children aged 6 years or younger [55].

Infectious Agents. The acquisition of PA leads to a more rapid decline in lung function and growth status in CF patients [56–58], especially once the PA takes on mucoid characteristics [59]. A longitudinal study of 3323 patients younger than 6 years, using the CF Foundation's U.S. Patient Registry, found that children with a positive culture for PA at baseline had an 8-year risk of death that was 2.6 times higher (95 % CI = 1.6–4.1) than those who did not, and PA-positive patients had significantly lower FEV_1 and weight percentile at follow-up. The risk of PA acquisition is increased by factors such as a low maternal education [60].

SES and Nutrition

In the USA, about 8 % of CF patients ages 2–19 years, and 18 % of CF patients aged 20 and older, are below the 5th percentile for weight [61]. Nutritional status and lung function are highly correlated in CF, and while the causal relationship is bidirectional to a certain extent [62], inadequate nutrition is associated with decreased lung function and long-term survival [3, 63–66]. This effect is especially pronounced in early life. Children in the Wisconsin newborn screening cohort study whose weight z-scores at 2 years of age were equal to or above their birth weight z-scores had an FEV_1 of 99.5 at age 6 years, compared to an FEV_1 of 88.3 in children whose weight z-scores at age 2 years were below their birth weight z-score [67]. While the mechanism of this relationship remains unclear, malnutrition may impair immunologic defenses against infection [68, 69] and/or lead to respiratory muscle weakness [3].

A relationship between SES and diet quality has been shown for the general population [69]. Although such relationship in CF is underexplored, there is evidence that the nutritional status of CF patients is correlated with their SES [28, 70, 71]. Individuals with CF require a high-fat, high-protein diet and nutritional supplements that are costly and likely less affordable to lower-income families. Moreover, it has been shown that mothers with low educational attainment are less likely to understand the nutritional aspects of CF, which impacts the dietary adherence and overall nutritional status of their children with CF [72].

SES and Chronic Stress

SES is associated with differential exposure to chronic stressors [73, 74]. In fact, the disparity in stressful experiences is a primary mechanism of gender, racial, and socioeconomic health disparities [75]. While all people experience stress, those of lower SES live and work in more stressful physical and social environments. Among the factors that contribute to greater stress at lower SES levels are economic strain, job insecurity, employment with low levels of control, residential crowding, noise exposure, and social isolation [73, 76–81].

Disproportionate stress exposure affects health through elevated stress responses. Moreover, continuous and repeated stressors have a cumulative effect on the allostatic load, or the burden placed on the organism and its biological functions in responding to hardship [82, 83]. Multiple studies show that the distribution of allostatic load is patterned by SES [82, 84]. People of low SES are exposed to multiple stressors [77]. Some exposures may be simultaneous, some sequential, triggering a cascade of adverse events that harm health. Either way, people of lower SES experience an unbroken succession of stressors that stem from other stressors, a process referred to as stress proliferation [73, 76].

Macpherson et al. [32], for example, reported that children with CF who were cared for by single mothers had worse health outcomes than children with dual caregivers. Quittner et al. [85] examined the effects of SES and race/ethnicity on health-related quality of life using data from the Epidemiologic Study of Cystic Fibrosis on 4751 patients and 1826 parents who completed the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Low SES was associated with significantly lower CFQ-R scores for children, parents, and adults on the majority of domains. After controlling for disease severity and SES, African American and Hispanic patients reported worse emotional and social functioning.

Children with CF are affected by stress both directly and indirectly, through the toll that stress takes on their parents/caregivers, leading to anxiety, depression, and impaired personal and family functioning in CF families [86–88]. A significant proportion of mothers of children with CF show depressive symptoms soon after the diagnosis of their child, independent of the degree of the child's illness [89], and

many parents continue to report psychological distress years afterward [90]. Recent studies have shown that the prevalence of anxiety and depression in patients with CF and their parents is higher than in the general population [91].

Low SES is associated with a higher prevalence of depressive symptoms in the general population and in patients with CF [92]. Depression, in particular, is associated with worse health outcomes, including quality of life and lung function [88, 93, 94]. The mechanism of this relationship is likely multifactorial, but adherence and disease self-management seem to be adversely affected by depression [95]. Several studies underscore the role of family functioning [86, 87] for children and adolescents with CF. As family functioning has a major impact on child development [96], it likely exerts a powerful influence on the progression and severity of CF, affecting the child's clinical trajectory throughout life [97].

The harmful effects of stress on health can be buffered by sense of control, self-esteem, and social support [75]. A number of studies report on the importance of social support [98, 99] in CF. Moreover, Reynolds et al. [100] found that positive spiritual coping plays a key role in maintaining long-term health (lung function, nutrition, and pulmonary-related hospitalizations) in adolescents with CF.

SES and Self-Management

Goldman and Smith [101] consider a different mechanism of the link between SES and health outcomes—better self-management of disease by the more educated. They report that more educated HIV+ patients are more likely to adhere to therapy, and this adherence improves their self-reported general health. Similarly, among diabetics, the less educated are more likely to switch treatment, which worsens general health. This finding is robust across clinical trial and population-based settings.

A relationship between SES and adherence to treatment has been reported in several chronic diseases, including asthma [102] and juvenile rheumatoid arthritis [103]. Worse adherence may also be a contributor to poorer outcomes among CF children of low SES [44, 104]. Knowledge of the treatment regimen and an understanding of its rationale are a prerequisite for adherence [105, 106]. Quittner et al. [107] found that nonadherence was explained by patients' misunderstanding of the prescribed regimen, while Anthony et al. [72] reported that both caloric intake and growth outcomes in children with CF are associated with maternal nutritional knowledge specific to CF.

SES and Medical Care

To determine whether SES-related disparities in CF outcomes can be explained by differences in medical treatment, Schechter et al. [108] performed a cross-sectional analysis of data on patients age <18 years from the Epidemiologic Study of Cystic

Fibrosis. Disease severity showed a similar inverse correlation with all three SES measures. However, the number of stable clinic visits was unrelated to SES, and low SES patients tended to be prescribed more rather than fewer chronic therapies. The study concluded that while CF health outcomes are correlated with SES, the disparity is not explained by differential use of health services or prescription of therapy.

In a later study, Schechter et al. [109] used data on 9895 patients ≤18 years old from the ESCF to determine if SES influences the likelihood of antibiotic treatment of pulmonary exacerbations, and again found more rather than fewer antibiotic treatments being prescribed to low SES patients. SES-related health disparities are often attributable to unequal access to and quality of care, but research has failed to show SES differences in prescribed therapies for CF, treatment of CF pulmonary exacerbations, or CF-related hospitalization [108–110]. In the USA, CF care is provided by a network of accredited centers that are primarily housed in academic medical centers and receive support from the CF Foundation. This setup allows for the provision of protocol-driven case management by multidisciplinary teams. Thus, socioeconomic disparities in CF outcomes in the USA appear to be driven by social determinants and disease self-management rather than differential access to and use of healthcare [26, 108, 111].

Achieving Health Equality in Cystic Fibrosis

With advancements in early diagnosis and treatment, survival in CF has improved dramatically, so much so that children born in the twenty-first century are expected to have a median survival of more than 50 years [112]. However, disease progression and survival vary greatly [43, 44]. People with CF from socioeconomically disadvantaged backgrounds die younger than those in more advantaged positions [24]. Multiple mechanisms are responsible for the relationship between SES and CF health [24, 26, 28]. Our discussion identified some of the ways by which financial, human, and social resources are translated into health advantages.

As mentioned earlier, the health effect of SES is not dichotomous [113], with a stepwise gradient between wealth and health [27, 28]. Considering the ample evidence for a SES-related health gradient in CF and for specific mechanisms that mediate this relationship, the next step is to develop approaches and interventions that may not only reduce SES-related CF disparities but also optimize CF outcomes across the SES spectrum [114]. Population-level policy, system, and environmental interventions will likely be more effective and more impactful than individually focused interventions. Health differences according to income and education reflect differences in material and psychosocial advantage that are modifiable with social policies [111, 115]. To achieve equality in CF health, population-wide social policies that address the root causes of health disparities (see Chap. 15) are needed. As such, awareness of socioeconomic disparities in CF among the public and policy makers is essential for CF health equality.

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Chapter 10
Obstructive Airway Diseases

Erick Forno, Alejandro Díaz, and Juan Carlos Celedón

Asthma

Disparities in the Prevalence, Morbidity, and Mortality of Asthma

Asthma is a major public health problem in the USA, where ~7 % of adults (~16 million individuals) and ~8.3 % of children (~7 million individuals) had current asthma in 2013 (http://www.cdc.gov/asthma/asthmadata.htm).

Among subjects with asthma in the USA, 59 % of children and 48 % of adults have ≥1 disease exacerbation every year. In this country, asthma or asthma symptoms cause over 14.2 million visits to a physician's office, ~1.8 million visits to the emergency department (ED), and ~439,000 hospitalizations. The annual costs of asthma in the USA (including medical expenses, missed school and work days, and

E. Forno, MD, MPH
Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh, 4401 Penn Avenue Rangos #9130, Pittsburgh, PA 15224, USA
e-mail: Erick.Forno@chp.edu

A. Díaz
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: ADIAZ6@PARTNERS.ORG

J.C. Celedón, MD, DrPH (✉)
Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, 4401 Penn Avenue, Pittsburgh, PA 15224, USA
e-mail: juan.celedon@chp.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_10

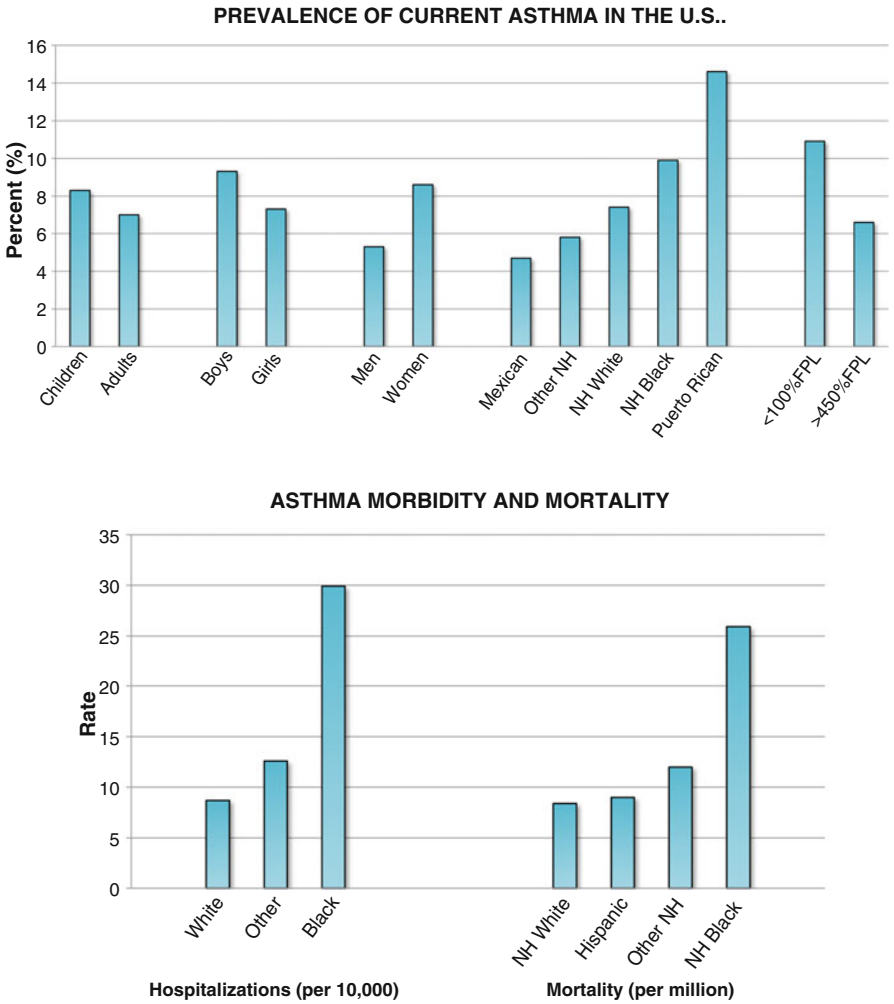

Fig. 10.1 Current prevalence, morbidity, and mortality from asthma in the USA. Data from http://www.cdc.gov/asthma/most_recent_data.htm. *NH* non-Hispanic, *FPL* federal poverty line

premature deaths) have been estimated to exceed $56 billion—or ~$3300 per person with asthma per year [1].

The prevalence, morbidity, and mortality from asthma differ among racial, ethnic, and socioeconomic groups in the USA (Figure 10.1). According to the Centers for Disease Control and Prevention (CDC) [2], estimates of the prevalence of asthma are 16.1 % in Puerto Ricans, 10 % in African Americans, 7.4 % in non-Hispanic (NH) whites, 5.2 % in Asians, and 4.7 % in Mexicans or Mexican-Americans. Similarly, the prevalence of asthma ranges from ~6.5 % in people at >450 % of the federal poverty level (FPL) to ~11 % in those living under the FPL.

While less detailed data are available, there are striking racial or ethnic differences in the age-adjusted rates of hospital discharges for asthma. In 2010, such rates were 29.9 per 10,000 in NH blacks, 12.6 per 10,000 in members of "other" races, and 8.7 per 10,000 in NH whites. Similarly, age-adjusted mortality rates from asthma are higher in NH blacks (25.9 per million) than in NH whites (8.4 per million) or Hispanics (9.0 per million) [2]. However, "aggregate rates" for morbidity or mortality in Hispanics cannot be adequately interpreted because of profound differences in asthma burden among Hispanic subgroups (e.g., Puerto Ricans and Mexican-Americans).

Risk Factors for Health Disparities in Asthma

Socioeconomic Status

Socioeconomic status (SES) plays a critical role in health disparities in asthma. SES is a complex construct, and indicators of its various dimensions at the individual and community levels include household income, educational level, residential area, home ownership, professional status, and perception of poverty.

In 2007, the USA ranked 101st among 141 countries in income inequality [3], a correlate of asthma prevalence in international surveys [4]. Indeed, asthma is more common among the economically disadvantaged in the USA. In a study linking data from the National Health Interview Survey (NHIS) with data from the US Census [5], asthma prevalence was higher in inner-city areas (12.9%) than in other areas (10.5%). Moreover, NH black race, Puerto Rican ethnicity, and lower household income were each associated with asthma. Among Puerto Ricans and non-Hispanics, household or neighborhood poverty was also associated with asthma [5]. Parental perception of their financial situation [6] or neighborhood safety [7, 8] may also increase asthma risk, but further research is needed.

Stress and Violence

Exposure to violence and psychosocial stress disproportionately affect racial or ethnic minorities. Maternal stress during pregnancy [9], early postnatal exposure to stress [10], and exposure to gun violence [11] have all been linked to asthma or asthma morbidity in children. Moreover, physical or sexual abuse during childhood or adolescence has been associated with asthma in Puerto Rican children [12] and African American women [13], and community violence has been associated with severe asthma exacerbations among adults in inner-city neighborhoods [14].

The mechanisms of stress-related asthma are incompletely understood [15], but recent studies have shown that genetic or epigenetic variation in *ADCYAP1R1* (a gene implicated in post-traumatic stress disorder (PTSD) and anxiety) is associated with childhood asthma in Puerto Ricans [16], as well as reduced response to

bronchodilators in Puerto Rican and non-Puerto Rican children with asthma [17]. Multiple stressors are present in economically deprived areas, and thus the detrimental effects of poverty on asthma may be partly explained by psychosocial stress. On the other hand, other risk factors (e.g., obesity, smoking, air pollution) may modify or mediate detrimental effects of stress on asthma [18, 19].

Tobacco, Pollutants, and Allergens

Environmental tobacco smoke (ETS) and current smoking are risk factors for asthma or asthma morbidity in children and adults. Among adults, current smoking ranges from 7 % in persons with a graduate degree to over 46 % in those with a General Education Development (GED) diploma [20]. In spite of reduced ETS exposure in all races/ethnicities over the last 15 years, such exposure is still more common in NH blacks (~47 %) than in NH whites (~22 %) or Mexican-Americans (~24 %) [21]. In addition to race, low parental income and low parental education are associated with ETS exposure in childhood [22].

Pollutants and allergens increase morbidity in patients with asthma. Exposure to indoor particulate matter with diameters under 2.5 μm ($PM_{2.5}$) or between 2.5 and 10 μm ($PM_{2.5–10}$) is greater in inner-city dwellings than in nonurban settings [23]. Such an exposure is associated with asthma, asthma symptoms, and use of rescue medications for asthma in children [24, 25]. NO_2, produced during gas and other combustion reactions, is also associated with asthma morbidity [26, 27]. Dust mite, mold, and pest allergens are often found at high levels in inner-city households, particularly old multi-family buildings with shared walls and pipelines. In inner-city areas in the USA, up to 85 % of children's bedrooms have detectable cockroach allergen, a risk factor for cockroach allergy and asthma morbidity at school age [28]. Exposure to pollutants or allergens can also occur at the school or workplace, further increasing asthma morbidity.

Of interest, recent evidence suggests that high exposure to certain allergens (e.g., mouse) in early life protects against recurrent wheeze in young children [29], but further research is needed to elucidate whether an altered "household microbiome" in early life plays a role in asthma pathogenesis and, ultimately, asthma disparities.

Diet, Nutrition, and Obesity

Poor dietary habits and obesity are also linked to race, ethnicity, and low SES. Whereas frequent consumption of sweets [30] or fast food [31] has been associated with increased risk of asthma, a "Mediterranean diet" [32] or a diet high in vegetables and fruits [30] has been linked to reduced risk of asthma. Obesity, which is more common in racial/ethnic minorities and the poor, is associated with asthma and reduced response to controller medications for asthma [33, 34].

Vitamin D insufficiency (a serum 25(OH)D <30 ng/mL) is common in groups at high risk for asthma, including NH blacks, Puerto Ricans, obese subjects, and inner-city residents [35]. Vitamin D insufficiency has been associated with severe

asthma exacerbations in school-aged children [36–38], and the role (if any) of vitamin D supplementation in preventing asthma attacks in children is now being evaluated in a clinical trial (NCT02687815). Whether other vitamins or nutrients (e.g., vitamins A or E, omega-3 or omega 6 polyunsaturated fatty acids, zinc, folate, or selenium) affect asthma risk is unclear, and it has thus been suggested that future clinical trials focus on "whole diet" interventions [39].

Genetics

Genetic and epigenetic mechanisms may contribute to asthma disparities. Over the last decade, genome-wide association studies (GWAS) have identified susceptibility genes for asthma, mostly by studying Caucasian or Asian populations. Of the 48 GWAS of asthma or related traits included in a repository of the US NIH, 19 (~40 %) were performed in NH whites/Caucasians, 17 (~35 %) included at least one non-white replication sample, and 12 (25 %) were performed primarily in non-Whites (mostly Asian).

Inclusion of racial or ethnic minorities in genetic studies matters, as some genetic variants that confer susceptibility to asthma may be more relevant to particular racial or ethnic groups (e.g., "ethnic-specific") [40]. For example, only two of ten genes associated with asthma in a meta-analysis of GWAS of asthma in Caucasians [41] (*IL33* and *GSDMB*) were replicated in a meta-analysis of ethnically diverse North American populations [42].

In addition to individual genetic variants, global racial ancestry (estimated using ancestry informative markers) has been associated with asthma and lung function in racially admixed populations, such as Hispanics and African Americans. Whereas African ancestry has been positively associated with asthma but inversely associated with lung function, Native American ancestry has been inversely associated with asthma but positively associated with lung function [43–46].

Few studies have focused on gene-by-environment interactions or epigenetics in racial/ethnic minorities (e.g., [16, 17, 47, 48]), a key need in the field of health disparities in asthma.

Disparities in Diagnosis and Management

Barriers to asthma care include lack of health insurance, low health literacy, poor adherence to controller medications, and cultural beliefs. Underdiagnosis of asthma is common among the poor and minority populations, who may lack a consistent source of care, and have inadequate knowledge about asthma or how to navigate the health system [49].

Children and adults with persistent asthma should use controller medications such as inhaled corticosteroids (ICS) [50]. However, ICS are often not prescribed for minorities, in whom nonadherence with ICS is also common [51–55]. Web-based reminders [56] and media-based peer support messages [57] have been used

in an attempt to improve adherence with ICS in underserved populations, without much success. Future interventions may be more likely to succeed if they simultaneously address psychosocial stress and other barriers to care [58–60].

More broadly, disparities in asthma diagnosis and management are related to overall medical care. Racial or ethnic minorities and the poor are more likely to use the ED as their usual source of care [61], thus missing the education and emphasis on prevention and long-term control provided by a primary care physician. Moreover, NH black and Hispanic children are less likely to have an asthma action plan after a hospital discharge [51], and parents with limited English proficiency are less likely to follow the written plan [62]. Thus, a potential intervention may be educating ED physicians and hospitalists on asthma management guidelines beyond acute disease exacerbations, particularly if decision support tools, audit and feedback, and pharmacy support are provided [63].

Low literacy and numeracy negatively impact the ability of patients and caregivers to maintain asthma control [64–66]. Parental beliefs and attitudes towards medical care are also critical. Caregiver perception of asthma severity or the patient's need for medications varies by ethnicity and is associated with acute care visits [67]. Finally, noncultural competency by healthcare provider may affect asthma care in racial or ethnic minorities, but further research is needed [68].

Chronic Obstructive Pulmonary Disease (COPD)

Prevalence, Morbidity, and Mortality

COPD affects approximately 28.9 million people in the USA [69]. However, the burden from COPD is unequally distributed across racial or ethnic groups.

If COPD is defined according to results from spirometry, its prevalence among US adults aged 40–79 years was 14 % between 2007 and 2010 [70]. However, the racial/ethnic-specific prevalence of COPD ranged from 15 % in NH whites to 14.1 % in NH blacks to 5.4 % in Mexican-Americans (Fig. 10.2) [70]. The recently observed similarities in the prevalence of COPD between NH blacks and NH whites likely reflect the increased rate of current cigarette smoking in NH blacks over the last two decades [71].

As with asthma, there is variability in the burden of COPD among Hispanic subgroups. Between 2007 and 2009, the estimated prevalence of self-reported COPD was highest in Puerto Ricans (6.9 %) and lowest (2.6 %) in Mexican-Americans, with intermediate estimates for NH whites (5.7 %) and NH blacks (4.4 %) [72]. Mexican-Americans, comprising approximately two thirds of US Hispanics, have been shown to have a lower prevalence and risk of COPD than NH whites [69, 70, 73], even after accounting for smoking, education, occupation, and nativity. Similar to findings for Mexican-Americans, Hispanics from New Mexico have been shown to have better lung function, and lower risk of COPD or lung function decline, than NH whites [74, 75]. In contrast to results in Mexican-Americans or New Mexico

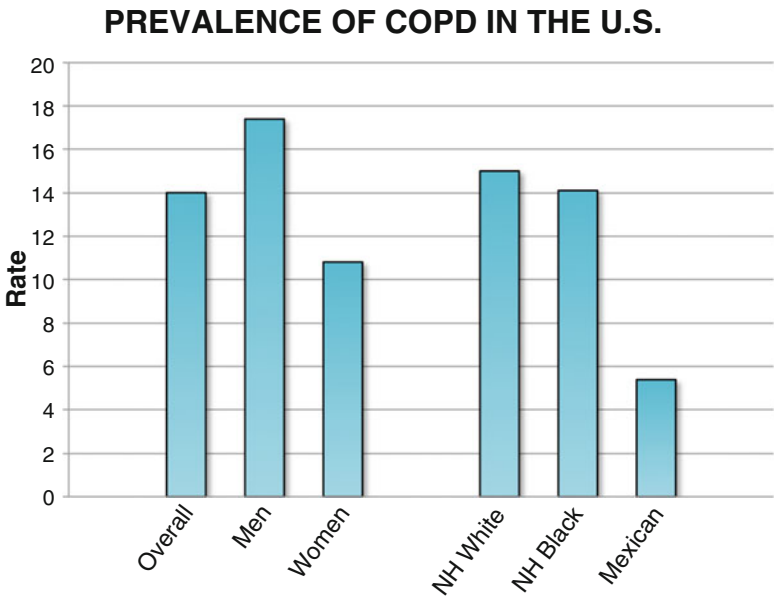

Fig. 10.2 Current prevalence of COPD in the USA. Data from Tilert et al. [70]. Source: National Health and Nutrition Examination Survey (NHANES 2007–2010). COPD was defined as FEV_1/FVC < 0.70. Estimates based on pre- and post-bronchodilator included those who completed the pre-bronchodilator test and were not selected for the post-bronchodilator test (no disease), plus those persons who completed the post-bronchodilator test, plus those persons excluded from pre-BR spirometry who had a medical diagnosis of emphysema or chronic bronchitis and used daytime supplemental oxygen therapy

Hispanics, Puerto Ricans have a relatively high prevalence of self-reported COPD [72]. Marked differences in the prevalence of COPD across Hispanic subgroups (e.g., highest in Puerto Ricans and lowest in Mexican-Americans) were confirmed in a recent population-based study (the Hispanic Community Health Study/Study of Latinos), which defined COPD according to findings from spirometry. However, such ethnic-specific differences became nonstatistically significant after the multivariable analysis was adjusted for asthma with onset before age 45 years, suggesting misclassification of asthma as COPD or a relatively high frequency of asthma-COPD overlap syndrome in Hispanics [76].

The observed disparities in COPD risk or prevalence across Hispanics subgroups may be partly explained by underlying differences in global genetic ancestry: Puerto Ricans have (on average) a greater proportion of African ancestry but a lower proportion of Native American ancestry than Mexican-Americans or New Mexico Hispanics. Whereas Native American ancestry has associated with higher lung function and reduced risk of COPD risk among New Mexican Hispanics [45] and Costa Ricans [77], African ancestry (which is prominent in Puerto Ricans) has been associated with reduced FEV_1 and faster decline in lung function [78] among NH blacks.

The prevalence of severe early-onset COPD (i.e., a COPD diagnosis before age 55 years, accompanied by a forced expiratory volume in 1 s [FEV_1] <50% predicted) is higher in NH blacks than in NH whites [79], a finding that may be explained by differences in nicotine metabolism, anthropometry, and racial ancestry. NH blacks appear to have both higher nicotine intake from cigarette smoking and slower renal clearance of cotinine than NH whites [80]. Compared to NH whites, NH blacks have lower normative lung function, which could be explained by a lower trunk: leg ratio [81], and a high proportion of African ancestry. In NH blacks, African ancestry has been linked to reduced FEV_1 and reduced forced vital capacity (FVC) [43], as well as to increased risk of FEV_1 decline among cigarette smokers [78].

Patients affected with COPD can have a reduced health-related quality of life (HRQL), and there are racial/ethnic disparities in perceived HRQL. In a study of subjects who had experienced a COPD exacerbation, NH blacks reported worse HRQL than NH whites, and Mexican-Americans reported worse health status than NH whites despite a similar degree of airflow obstruction [82, 83]. While these disparities are multifactorial, educational level and access to health care are important factors [83].

COPD is now the third leading cause of death in the USA [84, 85]. In this country, COPD-specific mortality doubled from 1970 (21.4 deaths per 100,000 people) to 2002 (43.4 deaths per 100,000 people) [86], followed by relatively stable rates until 2006 [87, 88]. In 2013, NH blacks had a lower mortality rate from COPD (22.7 per 100,000 people) than NH whites (54.8 per 100,000 people) [88]. Among Hispanics, the death rates (per 100,000 people) from COPD were highest in Cubans (28.0) and Puerto Ricans (26.9), and lowest (18.3) in Mexican-Americans [89]. Although NH blacks and Mexican-Americans have lower COPD death rates than those of other ethnic groups, long-term follow-up of subjects with COPD has not demonstrated a lower mortality risk in these ethnic groups than in NH whites [73, 90]. This finding suggests that, once airflow limitation develops, all racial or ethnic groups are subject to the effects of various conditions, resulting in a similar long-term risk of death.

Racial or Ethnic Disparities in Risk Factors for COPD

Smoking

Tobacco use remains the main risk factor for COPD. In 2014, cigarette smoking among adults was slightly more common in NH whites (18.2%) than in NH blacks (17.5%) [91]. Compared with NH whites, NH blacks are more likely to smoke menthol cigarettes, as well as to have light (1–5 cigarettes/day) and intermittent (nondaily) cigarette consumption [92]. Regular use of mentholated cigarettes

(vs. non-menthols) may lead to reduced success in smoking cessation among NH blacks [93], who have also been shown to be more susceptible to cigarette smoking than NH whites in some—but not all—studies. In particular, NH blacks have been shown to develop COPD at a younger age and with less cumulative smoking than NH whites [94–98].

In the USA, cigarette smoking was less common in Hispanics (11.2 %) than in NH whites (18.2 %) in 2014 [91], but there was a marked variability in tobacco use among Hispanic subgroups by area of origin, nativity (US born vs. non-US born), age of immigration, and gender. Among US Hispanics, the prevalence of current smoking is highest in Puerto Ricans (21.6 %) and Cubans (18.2 %), and lowest in Central/South Americans (9.2 %) and Mexican-Americans (13.0 %) [89]. Among Hispanics, those who were born in the USA (17.7 %) or are male (17.7 %) are more likely to be current smokers than those born in a foreign country (10.3 %) or females (8.9 %) [89]. Moreover, Hispanics immigrating to the USA before age 16 years are more likely to be current smokers than those immigrating to the USA after age 16 years (21.8 % vs. 18.4 %) [76].

Consumption of electronic cigarettes (e-cigarettes) has been rapidly increasing despite little information about their safety [99]. In particular, use of these products may be a gateway to initiation of conventional tobacco use, while also lowering the odds of smoking cessation [100, 101]. Although a recent study showed that use of e-cigarettes is lower in NH blacks than in NH whites, exposure to marketing ads was associated with increased e-cigarette use in NH blacks, raising concerns about trends for e-cigarette use in this minority population [102].

Secondhand Smoke

Exposure to secondhand smoke (SHS) has been linked to COPD among nonsmokers [103]. Similar to active smoking, there are racial/ethnic disparities in SHS exposure in the USA. During 2011–2012, exposure to SHS among adults aged 40–59 years was more common in NH blacks (32.3 %) or Mexican-Americans (24.9 %) than in NH whites (16.3 %) [21]. Little is known, however, about SHS exposure and lung function or COPD in racial/ethnic minorities.

Occupational Exposure

Workplace exposure to dusts and chemicals can increase the risk of airflow obstruction or COPD, and such exposure is more common in minority populations than in NH whites. In one study, the fraction of airflow obstruction attributable to workplace exposures was higher in Hispanics (49.6 %) than in NH blacks (23.4 %) or NH whites (22.2 %) [104]. Given limited information to date, more studies are needed on occupation and COPD among racial or ethnic minorities.

Genetics

Although cigarette smoking is the main risk factor for COPD, less than one-third of heavy smokers develop the disease. Severe alpha-1 antitrypsin deficiency is a known genetic risk factor for COPD, which is more common in NH whites. Hispanic carriers of a genetic mutation at one of the alpha-mannosidase genes (*MAN2B1*, which degrades alpha-1 antitrypsin) were found to have high levels of alpha-1 antitrypsin. Thus, this genetic variant may protect the lung against high levels of elastase [105]. More recently, two potential susceptibility loci for COPD (in or near the genes *KLHL7*/*NUPL2* and *DLG2*) were identified in a GWAS of Hispanic populations [106]. In parallel with studies of COPD genetics, new data is emerging on the genetics of nicotine dependence in racial or ethnic minorities. For example, a variant in the nicotinic receptor subunit gene cluster on chromosome 15 was more strongly associated with nicotine dependence in NH blacks than in NH whites [107, 108].

Disparities in Diagnosis and Management

Few studies have addressed racial or ethnic disparities in the diagnosis or management of COPD. A large study demonstrated that NH blacks with COPD are younger and more likely to be current smokers (though with fewer pack-years of smoking) than NH whites with COPD [109]. Compared with NH whites, NH blacks are also less likely to report chronic bronchitis [110] but more likely to report a history of asthma [111]. Moreover, NH blacks have been shown to have a lower burden of emphysema (assessed using computed tomography of the chest) than NH whites [96, 112].

Patients with COPD often have comorbidities, which may differentially affect disease management according to race or ethnicity. For example, osteoarthritis has been shown to have a greater adverse impact on health status, exercise capacity, and dyspnea in NH blacks than in NH whites [109].

Smoking cessation and vaccination against influenza improve survival in patients with COPD, but these interventions are not equally available or utilized across racial or ethnic groups. For example, minorities are less likely to use nicotine replacement therapy than NH whites [113, 114]. Among Medicaid and Veterans Affairs Healthcare System beneficiaries with COPD, NH blacks and Hispanics are less likely to be vaccinated against influenza than NH whites [115–117].

Oxygen therapy improves survival in patients with advanced COPD and hypoxemia, and approximately 1.1 million Medicare patients receive oxygen therapy for COPD each year [118]. Among Medicare patients with COPD, NH blacks are less likely to use oxygen therapy, either on a short- (e.g., after a disease exacerbation) or long-term basis [118].

Disparities in COPD management may be due to individual or system-level issues, including type of health insurance, household income, having a regular doctor, and area of residence [116]. Other contributing factors may include social

support, cultural beliefs (such as viewing smoking as a weakness rather than an illness), general avoidance or mistrust of drugs, misconceptions about smoking cessation or oxygen therapy, and the cultural competency of healthcare providers.

Summary and Future Directions

Health disparities in asthma and COPD are common and due to multiple factors, including low SES, environmental exposures, and barriers to medical care. Future observational studies and clinical trials of asthma and COPD must include sufficient numbers of minorities, to be able to draw valid conclusions for individual racial/ethnic groups and conduct adequate comparisons across groups. Moreover, heterogeneous ethnic groups such as Hispanics should be well characterized with regard to country of origin, place of birth, area of residence, and degree of acculturation. In light of the complex nature of health disparities in airway diseases, future observational studies should be complemented by interventional studies addressing multiple risk factors (e.g., clinical trials with a factorial design).

The Affordable Care Act increased healthcare access for most but not all racial or ethnic groups (e.g., Hispanic immigrants often lack health insurance). Beyond health insurance, there is a need for culturally sensitive health policies to address barriers to medical care for asthma and COPD in minorities, including but not limited to low health literacy, nonadherence with treatment, language barriers, patient beliefs, and cultural competency of healthcare providers.

Acknowledgments *Funding*: Dr. Celedón's contribution was funded by grants HL079966, HL117191, HL073373, and HL119952 from the US National Institutes of Health, and by The Heinz Endowments. Dr. Forno's contribution was funded by grant HL125666 from the US NIH.

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Chapter 11
Sickle Cell Disease

Jeffrey Glassberg and Michael R. DeBaun

Introduction

Sickle cell disease (SCD) is an autosomal recessive disease that predominantly affects individuals who are genetically descended from Malaria-endemic areas, most notably Africa. It is estimated that more than two million individuals are affected worldwide, with approximately 100,000 residing in the United States (US), most of whom are non-Hispanic Blacks. In modern medicine, the disease, first recognized in 1910, causes chronic organ damage, pain, and premature death. For nearly 50 years SCD has been recognized by some as "the most neglected major health problem" in the US [1]. Today, the greatest healthcare disparities in SCD relate to funding for scientific research, access to high-quality care, treatment of acute pain, and management of respiratory disease.

Pathophysiology

SCD is caused by mutations on the beta globin gene. There are hundreds of known beta globin mutations, but the most common is hemoglobin S, caused by substitution of glutamine for valine at codon 6. Each individual has one beta globin gene from each parent. If both genes carry the hemoglobin S mutation, this is called

J. Glassberg, MD
Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: jeffrey.glassberg@mountsinai.org

M.R. DeBaun, MD, MPH (✉)
Department of Medicine and Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA
e-mail: m.debaun@Vanderbilt.Edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_11

hemoglobin SS or sickle cell anemia, the most severe form of SCD. Subjects in whom only one beta globin gene carries the S mutation and the other carries a different mutation are also considered to have SCD, but typically have milder courses. Beta thalassemia (in which a promoter mutation causes less or zero hemoglobin to be made) in combination with the S mutation is also a form of SCD. Individuals with one S mutation and one normal beta globin gene have sickle cell trait.

In individuals with SCD, hemoglobin (the molecule in red blood cells that carries oxygen to tissues) aggregates into rigid, rod-shaped polymers when deoxygenated. These polymers push on the red blood cell membrane from the inside, deforming it (to the characteristic sickle shape) and causing recurrent membrane damage. After re-oxygenation, younger red blood cells are capable of returning to their original biconcave shape. This process of recurrent membrane damage activates a number of inflammatory and prothrombotic cascades within the blood, promotes hemolysis, and shortens the average lifespan of red blood cells to approximately 10 days. The result is increased cell adhesion, endothelial dysfunction, and vascular injury, which leads to the clinical manifestations of SCD: small and large vessel occlusion, anemia, and chronic repetitive injury to every organ in the body.

Prominent sequelae of SCD include stroke, pulmonary hypertension, splenic sequestration/infarction, chronic renal disease, and acute chest syndrome (a phenomenon of rapid respiratory decline that initially starts with pulmonary infiltrates), but the most common manifestation and most frequent cause of emergency department (ED) visits for SCD are the painful episode. In addition to chronic daily pain, individuals with SCD experience acute paroxysmal attacks of severe corporeal pain (most frequently in the lower back and legs—areas with higher concentration of bone marrow). Such attacks, described as like "having one's bones broken," often require high doses of opioid analgesia and inpatient admission. The average length of inpatient stay for acute pain in the US is 7 days, where individuals with SCD average 1–4 acute care visits for pain per year (although a smaller percentage of ultra-utilizers is known to utilize the ED much more frequently) [2].

Health Disparities in SCD

Research and Knowledge Translation

Since its discovery in 1910 by the hematologist James Herrick, SCD has remained one of the best-understood diseases in terms of our knowledge of the pathophysiological processes that lead to manifestations of the disease, yet our track record of using this knowledge to develop life-improving or life-sustaining therapies has lagged far behind other conditions [3]. Much of this troubling trend is attributed to disparities in research funding, a potential obstacle to health equality (see Chap. 15).

In his seminal 1970 article published in the *Journal of the American Medical Association*, Roland Scott compared grant support from the US National Institutes of Health (NIH) for SCD to other, less-common hereditary diseases that affect

Table 11.1 Disparity in research funding for sickle cell disease versus cystic fibrosis [4]

Funding 2011	Sickle cell disease	Cystic fibrosis
NIH funding	$65,094,922	$78,861,688
Foundation funding	$1,185,023	$176,209,849
Per person funding	$744	$8502

primarily whites in the US. In particular, muscular dystrophy occurs ten times less frequently than SCD, and cystic fibrosis (CF, see Chap. 9) occurs 2.5 times less frequently than SCD. However, there was more funding from the US NIH for grants focused on muscular dystrophy ($n=66$) or CF ($n=65$) than that for grants focused on SCD ($n=22$) in 1968. This funding disparity only worsened over the next 40 years. In a similar study from 2013, Strousee and colleagues systematically explored funding and research disparities between CF and SCD. Disparities in NIH funding approached those reported in the 1960s: for every dollar spent on SCD, 3.5 dollars were spent on CF. Disparities in research funding extend to nonfederal agencies. For example, CF received 370 times (in 2010) to 440 times (in 2011) more private research funding than SCD. Overall, funding per person affected by CF was 11-fold higher than that for SCD (Table 11.1) [4].

The stark difference in private foundation funding between SCD and CF is largely attributed to the fact that CF advocacy organizations are far more adept and organized at raising money and advancing their agenda than SCD advocacy organizations. Whereas the Sickle Cell Disease Association of America annual revenue was $498,577 in 2013, the annual revenue of the CF Foundation in 2013 was $152 million [5]. This translated into an 850-fold difference in revenue per person affected by these diseases. Smith et al. note that the CF Foundation has an impressive track record of "legislative advocacy and regular presentations to Congress about NIH funding, and to the Institute of Medicine regarding research efforts" [5]. In addition to directly funding research, the authors of this paper go on to describe four essential functions that philanthropic organizations play: (1) legislative advocacy, (2) serving as a patient resource to empower individuals to advocate for better care, (3) reduce the stigma of disease by disseminating positive images, (4) support the delivery of high-quality health care to affected patients. The CF Foundation, with its financial and organizational resources, has set the standard for how private foundations should function in these four domains.

Disparities in research funding translate directly to therapeutic innovation. In 2010 and 2011, there were nearly twice as many Medline indexed publications for CF as for SCD. Similarly, between 2005 and 2010, five new drugs were approved for CF but none for SCD. Since its discovery in 1910, only one drug, hydroxyurea, has gained approval from the US Food and Drug Administration (FDA) to treat SCD. Funding disparities create a self-reinforcing cycle, where less research funding leads to less research, which then leads to less preliminary data to apply for research funding.

Availability of High-Quality Health Care

Between 1973 and 1994, improved SCD care drove an increment in life expectancy, from 14 years to 42 years [6, 7]. Several factors contributed to this improvement, including broad implementation of newborn screening programs, penicillin prophylaxis to prevent sepsis deaths [8], and comprehensive multidisciplinary care. At expert centers, systematic use of hydroxyurea starting in early childhood will likely drive further increases in life expectancy for SCD. Such gains in life expectancy at tertiary care medical centers underscore the importance of multidisciplinary comprehensive care for patients with SCD. Unfortunately, only a small percentage of individuals with SCD have access to this level of care.

Several studies have documented that the majority of individuals with SCD (especially adults) do not receive care from a hematologist [9]. The situation is more severe for low-income individuals. In a cohort from Texas, only 10 % of low-income children had at least one visit to a hematologist per year [10]. Lack of access to comprehensive longitudinal follow-up is associated with higher rates of acute care utilization and readmission for SCD [11, 12]. All elements of comprehensive care have the potential to reduce SCD morbidity. In one study, lack of preventive dental care was associated with higher rates of painful episodes [13].

Some of the increased SCD morbidity associated with low socioeconomic status (SES) is attributed to the fact that these individuals have fewer personal, cognitive, economic, and community resources to draw from; however, one study suggests that disparities in access to health care are the primary driver of increased morbidity. In a multicenter derivation and validation cohort study, Glassberg et al. explored risk factors associated with 30-day ED revisits for sickle cell pain. The derivation cohort included 1456 ED visits by 193 unique individuals over 4 years (between 2007 and 2011). During this time, the comprehensive SCD clinic only accepted Medicaid insurance, and thus privately insured individuals did not have access to comprehensive care. This study served as a natural experiment, where individuals with higher SES (and private insurance) had limited access to comprehensive care. Indeed, the results demonstrated that subjects who lacked health insurance or had private health insurance had higher rates of ED utilization and 30-day ED revisits than those who had Medicaid insurance.

The problem of inadequate access to comprehensive care is a major contributor to increased SCD morbidity, as highlighted by comparisons with access to and quality of care for CF. The CF Foundation has an accreditation and monitoring system where high-quality centers can receive certification as a CF center, providing they meet certain milestones and continue to deliver high-quality care. As an incentive, CF centers receive funding from the foundation and in return they must contribute data to a registry which facilitates future research and discovery.

Disparities in Pain Care

SCD pain episodes frequently require visits to the ED and intravenous opioid analgesia. Mothers living with SCD frequently describe acute sickle cell pain as "worse than labor," while other patients describe the pain as "having your bones broken." In spite of the severity of acute SCD pain, patient experiences in the ED are reported in the literature as highly negative [14, 15]. In particular, patients feel stigmatized as "drug seeking" because of their illness [16–20]. Most concerning is that there is a disparity between the analgesic care given for SCD and that given for other painful conditions in the ED. In a retrospective cohort study, patients with renal colic received their first analgesic, on average, 38 % faster (50 min vs. 80 min) than patients with acute SCD pain. This disparity occurred despite the fact that patients with SCD had higher pain scores and higher triage acuity levels upon arrival to the ED [21].

Disparities in Respiratory Care

One final area of vulnerability for individuals with SCD is respiratory care. Asthma disproportionately affects inner-city African Americans (the sociodemographic group most commonly affected by SCD in the US) but emerging data suggest that pulmonary inflammation and airway hyper-responsiveness may also be an intrinsic manifestation of SCD. In mouse models of SCD, there is increased lung inflammation and airway responsiveness to allergic sensitization, similar to experimental asthma [22]. Moreover, humans with SCD have higher rates of airway hyperresponsiveness than sociodemographically matched control subjects [23–27]. The synergy between SCD and asthma results in increased morbidity and mortality among patients with SCD [28–32] (see Figs. 11.1 and 11.2). Moreover, substantial overlap between symptoms from anemia and asthma symptoms (e.g. dyspnea) leads to underdiagnosis of asthma in the SCD population.

Conclusions and Future Directions

As discussed above, SCD is one of the most important and under-recognized public health problems in the US and worldwide. Several steps, including increased research funding from private foundations and government agencies, standardization and accreditation for the delivery of care, and other measures to reduce healthcare disparities (e.g., improved management of pain and co-existing asthma), should have substantial benefits for subjects with SCD, including prolonging and improving life while reducing healthcare costs.

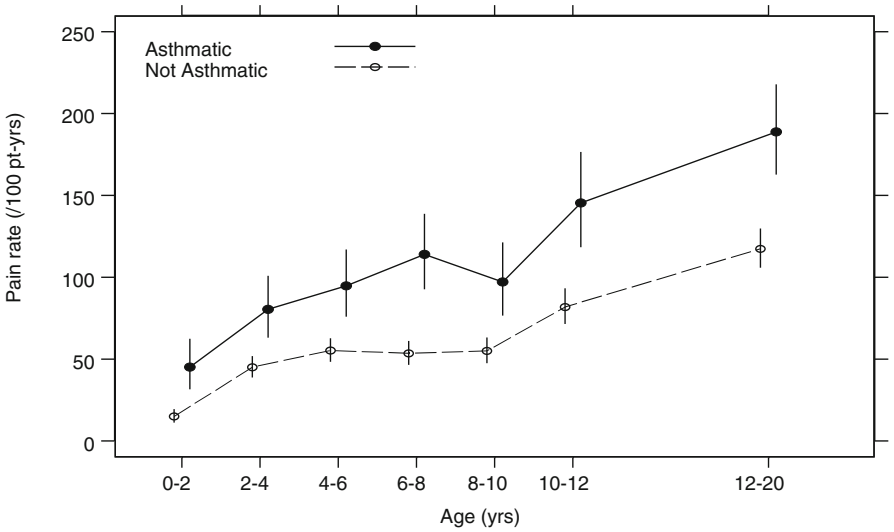

Fig. 11.1 Age-specific incidence of acute chest syndrome (ACS) and pain events classified by clinical asthma status in the infant sickle cell anemia (SCA) cohort. Overall incidence rate of painful events is higher in children with SCA and asthma (1.39 events per patient year) when compared with children with SCA and without asthma (0.47 events per patient year, $P < .001$). Line segments are point-wise exact 95 % confidence intervals

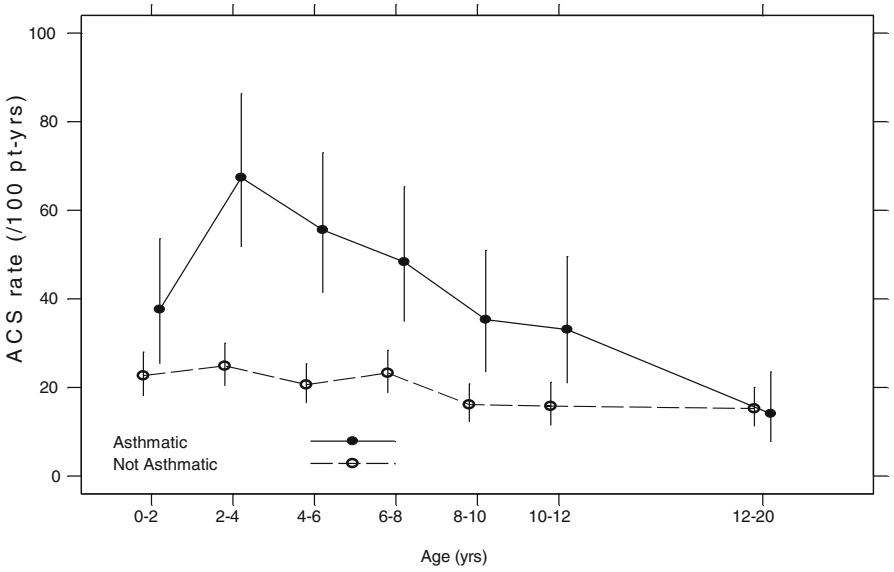

Fig. 11.2 Age-specific incidence of acute chest syndrome (ACS) and pain events classified by clinical asthma status in the infant sickle cell anemia (SCA) cohort. Overall incidence rate of ACS events is higher in children with SCA and asthma (0.39 events per patient year) when compared with children with SCA and without asthma (0.20 events per patient year; $P < .001$) [28] (legend and figure from reference 28)

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Chapter 12
Graduate Medical Education

Robert A. Winn and Karriem S. Watson

Introduction

As reviewed in Chap. 1, there are marked disparities in respiratory health across racial and ethnic groups in the United States (US). Although physicians and trainees from underrepresented racial and ethnic minority (URM) groups are more likely to provide care to underserved minority communities and the poor, there continues to be limited racial or ethnic diversity in the US physician workforce [1]. Such diversity is a key component of the roadmap to achieving respiratory health equality in the US (see Chap. 15).

An area that has gained increased attention as part of a comprehensive approach to address disparities in the healthcare workforce in pulmonary, critical care, and sleep medicine is graduate medical education (GME). GME plays an important role in ensuring a diverse workforce that can care for, and conduct research in, minority and underserved populations.

R.A. Winn, MD (✉)
UI Health Office of Vice Chancellor Health Affairs, University of Illinois at Chicago (UIC), Chicago, IL, USA

UI Health Cancer Center at University of Illinois at Chicago (UIC), Chicago, IL, USA
e-mail: rwinn@uic.edu

K.S. Watson, DHSc, MS, MPH
UI Health Cancer Center at University of Illinois at Chicago (UIC), Chicago, IL, USA
e-mail: kswatson@uic.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_12

Disparities in GME: An Overview

The American Medical Association (AMA) regards the graduate education that physicians receive after completion of their medical degree as a key step in progressing and advancing through the educational cycle [2]. The additional skills, expertise, and experience obtained during GME prepare physicians to address the complex environments in which illness develops and persists. In addition to further development of medical competencies, GME can also prepare and expose physicians to the complex environments that impact the development of health disparities, including cultural competencies and cultural sensitivity.

In 2012, a study in the *Journal of the American Medical Association* (JAMA) showed that there have been significant gains in gender equality in GME, with women now accounting for the majority of GME trainees in seven specialties [3]. While this progress in gender equality in the physician workforce is laudable, there is persistent and concerning underrepresentation of URMs among US physicians, with an even further widening gap seen between the proportions of non-Hispanic white and African American physicians. A 2012 JAMA report showed that there were no specialties where the percentage of African American or Hispanic trainees was representative of the general US population [3]. Of the 115,111 trainees in GME in 2012, only 13.8 % were African American or Hispanic [3], well below the proportion of African Americans and Hispanics in the US population in 2010 [4].

One historical area where disparities in GME are depicted is in the number of GME trainees who enter into subspecialty fellowships. The downward trend in diversity in medical specialties is creating further underrepresentation of URMs in areas such as pulmonary and critical care medicine or oncology, where racial and ethnic minorities suffer disproportionate rates of morbidity and mortality. For example, in Medical Oncology training programs, gender gaps have decreased but racial or ethnic gaps have not [5].

Even though the Patient Protection and Affordable Care Act (ACA) resulted in an increased number of URMs with insurance coverage (see Chap. 14), there has not been a proportional increment in the number of trainees equipped to address the complex health issues affecting this underserved population. A 2013 study reported that physicians from racial and ethnic minority groups care for 54 % of the minority patient population and 70 % of non-English speaking patients, yet they make up less than 15 % of the physician workforce [1]. Moreover, few GME programs address barriers to healthcare beyond non-insurance (e.g., low health literacy, inadequate language skills, or cultural beliefs), which are common among minorities and may be better understood and addressed by URM physicians [6].

The burgeoning issue of underrepresentation of URMs in GME poses both an ethical and a financial dilemma. The ethical dilemma is rooted in social injustice, where there is a paucity of members from the very communities that carry the largest burden of disease having access to upstream educational and training opportunities that will propel them into medical careers. The financial dilemma is rooted in increased healthcare costs due to poor health outcomes, which are partly due to

medical mistrust in populations that have healthcare providers who do not reflect the communities they serve [6]. One study demonstrated that a large proportion of nonadherence with treatment among URMs is due to the medical waste that ensues when providers lack cultural understanding and competencies that allow them to address complex diseases in minority patients [6]. The social and ethical injustice is marked by a healthcare workforce that neither reflects the population who is most burdened by disease nor is likely to have the cultural competency required to navigate the complex issues that give rise to health disparities, including those encountered in Pulmonary, Sleep, and Critical Care Medicine (see Chaps. 1 and 15) [7].

"Upstream" Causes of Disparities in GME

Existing disparities in GME reflect the downstream effect of a fractured educational system. Few pipeline programs effectively address the growing underrepresentation of URM students who pursue careers in Science (including biomedical fields), Technology, Engineering, and Math (STEM). The impact of STEM majors on the physician workforce has garnered national attention and has a downstream impact of GME, including that on pulmonary and critical care medicine. The influx of URM students into biomedical careers is directly reflective of upstream educational programs (at the high school and college undergraduate levels) that recruit URMs, and then peak their interest in STEM careers and help them navigate complex programs in undergraduate and graduate schools.

The report "Rising Above the Gathering Storm" highlights the key role of lagging K-12 educational systems in the fractured pipeline that prevents URMs from pursuing careers in science and medicine [8]. An inadequate K-12 STEM pipeline results in a decreased number of URM students who matriculate into and complete STEM majors and a medical or science degree. The NIH responded to rising concerns about this fractured pipeline by examining the impact of its educational and training programs on diversity among physicians and scientists pursuing biomedical research [8]. Whereas programs that narrowly focus on undergraduate students have had limited success, those that foster a holistic approach that navigate students from K-12 through undergraduate education and then to graduate and professional training programs may be most effective in increasing the pool of URMs in science and medicine [8].

Undergraduate URM students face a number of challenges when trying to advance to medical school. For example, the standardized tests required to pursue an undergraduate medical education (e.g., ACT, SAT, and MCAT) serve as early barriers for URMs gaining admission into medical school [9]. Other barriers to the success of URMs in undergraduate medical education include basic science courses and the US Medical Licensing Exam (USMLE) [9]. The small proportion of URMs among medical students leads to relatively few URMs applying to and being accepted into GME programs, ultimately impacting workforce diversity in pulmonary and critical care medicine [10].

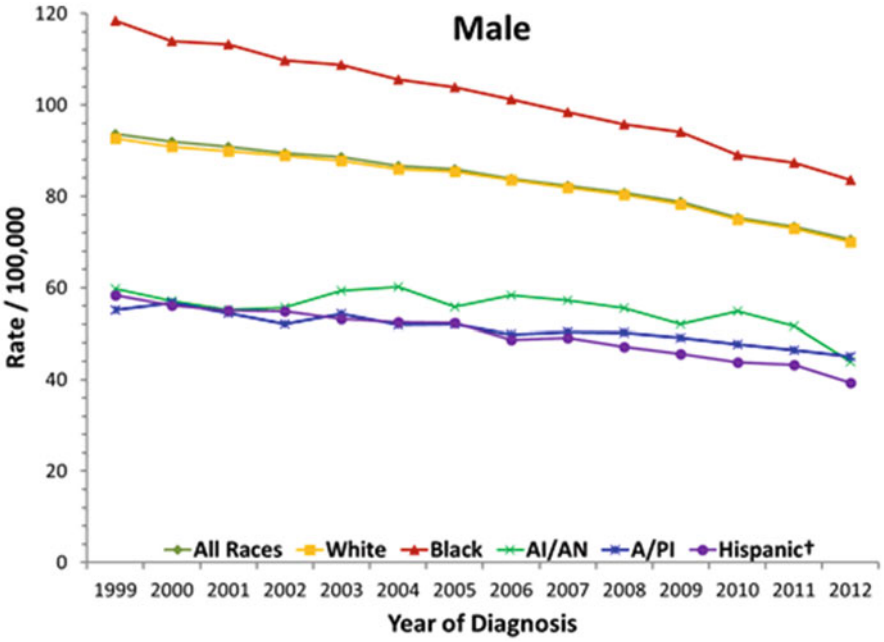

Fig. 12.1 Incidence rates of lung cancer (per 100,000 people) among men in the United States, by race or ethnicity, from 1999 to 2012

While multiple groups within URMs are underrepresented in science and medical careers, a notable trend is the marked paucity of African American males in undergraduate medical education programs. To address this gap, the Association of American Medical Colleges (AAMC) recently released a document that supports the matriculation of African American males into medical education programs [11], as that should help address health disparities, including those in respiratory health. For example, African American men have the highest rate of lung cancer incidence by race, ethnicity, and sex (see Fig. 12.1) [18]. In fact, African American men have a greater than twofold increased lung cancer incidence compared to African American women (see Fig. 12.2), yet African American women outnumber African American men in completing undergraduate medical education programs two-to-one. This further demonstrates the need for equality within medical school (and subsequently, GME programs), to ensure a healthcare workforce that is representative of those most afflicted with respiratory diseases [12]. However, some have proposed elimination of training programs that aim to increase the pipeline of URMs in the healthcare workforce (e.g., the Health Careers Opportunity Program). Such action is not justifiable, as it may help perpetuate lack of diversity in undergraduate medical education and GME programs [12].

Although a 2013 survey demonstrated that URM medical students applying to residency programs value training environments that support the holistic growth of URM physician trainees [3], there is little data to quantify the satisfaction of URMs

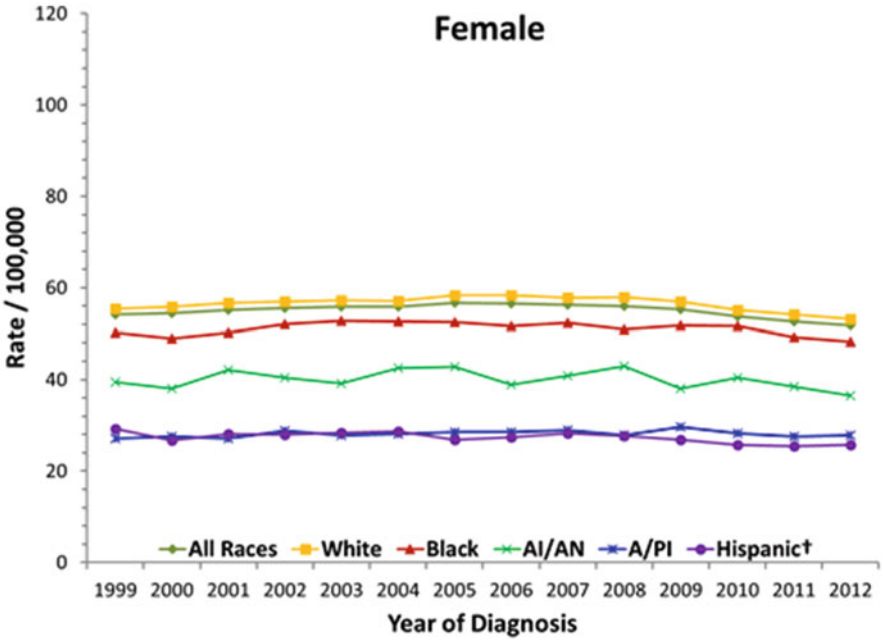

Fig. 12.2 Incidence rates of lung cancer (per 100,000 people) among women in the United States, by race or ethnicity, from 1999 to 2012

in residency and fellowship training programs. Such data would help applicants to better gage the training climate for racial and ethnic diversity [3].

The current landscape of both undergraduate medical training and GME lays little foundation to support the growth of the medical workforce in working with diverse populations. The 4-month internal medicine clerkship in undergraduate medical education plays a vital role in increasing the students' competencies in patient care, yet trainees get very little exposure to patient diversity in most academic medical center environments, thus missing key opportunities to acquire skills in addressing the complex care needs of minority patients [13]. Lack of exposure to both the multifaceted needs of diverse patients and colleagues from diverse backgrounds compounds the trainees' abilities to acquire skills that will fully equip them to address the multiple social determinants that impact respiratory health outcomes.

Following completion of medical training, there is also a fractured pipeline leading to racial and ethnic disparities in medical school faculty. For example, the percentage of URMs in this country increased by ~27 % from 2000 to 2010, but the proportion of minority faculty in US medical schools only increased from ~7 to 8 % [14]. In 2014, the number of non-Hispanic whites among faculty in medical education programs was 83 % higher than that of URMs [15]. This leads to relatively few minority mentors for URM medical students interested in clinical care, teaching, or research. Moreover, lack of URMs in academic leadership positions can negatively affect advocacy for diversity, while also depriving minority students and trainees from successful role models with a similar ethnic and cultural background.

Workforce Disparities in Respiratory Health

During the early and mid-1990s, there was a growing push in GME for increased training of primary care providers. Subspecialty training programs, such as those in pulmonary and CCM, experienced a downward shift in the number of applicants and interested trainees [16].

One of the challenges that future URM trainees in GME programs face is the lack of helpful criteria to help them select among the over 100 GME fellowship and training programs in pulmonary and/or critical care medicine. Although a nurturing environment with transparent support of diversity influences an URM trainee's decision to select a particular GME program [6], there are few tools that help students rank programs with a track record of supporting trainees from diverse backgrounds or a commitment to serve URM patients. Among GME fellowship programs, pulmonologists who treat the largest amount of respiratory health disparities are likely to be trained in a handful of fellowship programs. A 2016 report from the Electronic Residency Application Services (ERAS) showed that there were 19 programs in pulmonary disease (with 14 actively participating), 144 programs in pulmonary and critical care medicine (with 140 actively participating), and 33 programs in critical care (with 24 actively participating) [16]. The respiratory healthcare workforce that is likely to treat URM patients typically come from three fellowship training programs in GME in Pulmonary and/or Critical Care Medicine, including combined pulmonary and critical care programs, pulmonary training programs, or critical care programs [16].

URMs are markedly underrepresented in training programs in pulmonary and critical care medicine. Among pulmonary fellows, 8 % are Hispanic and 4 % are African American [10]. Consistent with this finding, there was marked underrepresentation of URMs among pulmonologists and intensivists in a membership survey from the American Thoracic Society (ATS) [10]. Moreover, the Society of Critical Care Medicine reports that by 2020, the growing needs of patients in critical care settings will create a 35 % shortage in the critical care workforce [8]. This overall shortage will worsen the existing lack of racial and ethnic diversity in fellowship programs in Critical Care Medicine (most of which are offered as a combined fellowship with Pulmonary Medicine) [17].

Workforce Diversity and Respiratory Health Disparities

Respiratory health disparities have been linked to lack of racial and ethnic diversity in the physician workforce, which is ultimately due to underrepresentation of URMs in GME programs. For example, the burden of asthma among URMs would likely lessen with increased diversity of the physician workforce [2].

The Accreditation Council on Graduate Medical Education (ACGME) and the Institute of Medicine (IOM) have identified GME as an important strategy for

lessening health disparities by diversifying the physician workforce [3], as GME programs can foster and produce a diverse workforce that is responsive to the healthcare needs of URM populations [3]. Consistent with this position, the ATS and the European Respiratory Society (ERS) issued a policy statement that supports racial and ethnic diversity in the healthcare workforce as a means to address respiratory health disparities [10].

Lack of diversity in the physician workforce for pulmonary and critical care medicine also affects research on respiratory health disparities, an engine for innovation in prevention and treatment of pulmonary and critical care diseases in minorities and the poor. From 1993 to 2013, less than 5 % of publications on respiratory diseases funded by the US National Institutes of Health (NIH) reported inclusion of minorities, despite a 1993 legislative mandate to include minorities in NIH-funded studies [18]. This disparity limits the generalizability of findings to URMs, while also impairing potential discovery of risk factors for respiratory disease that are unique or more relevant to URMs. A factor contributing to the exclusion of URMs from respiratory research is the paucity of federally funded minority physician-scientists in pulmonary and critical care medicine [18], as they are more likely to engage in clinical and translational research in minority and underserved populations. Moreover, physician-scientists from URM groups are more likely to conduct research on respiratory health disparities that examines multiple interactions among heredity, environment, behavior, and access to and quality of healthcare [18].

Conclusions and Future Directions

A necessary step to improve diversity in pulmonary and critical care medicine is to increase the number of URMs who enter and complete college, medical school, and residency training programs, as such individuals compose the pipeline of applicants to fellowship training programs. This requires educational and training programs that stimulate, encourage, and support URMs to pursue careers in science and medicine, through an integrated approach in a continuum of learning, starting with elementary school and progressing to high school, college, medical school, and residency training. There is general consensus on the wisdom of a multipronged approach to address this issue, involving nongovernmental and governmental funding agencies, academic institutions, professional organizations such as the ACGME, professional societies, community organizations, and society at large [6, 7, 19–21].

To increase diversity, GME and undergraduate medical education should also foster a “learner-centric” approach, reflect the changing technological and digital environment, and acknowledge the many layers within a learning environment that addresses the competencies of trainees [22]. A study from the University of Michigan demonstrated that students from URM groups are less likely to demonstrate medical competencies when a monolithic form of assessment is used (e.g., standardized tests) [9]. Moving towards a more “learner-centric” approach may also provide a more suitable learning environment that can model care environments that

address the various needs of patients. Thus, such approach may help reduce disparities in the pipeline that supplies GME trainees, while also addressing overarching themes that lead to poor respiratory health outcomes.

Institutional leadership is critical to achieving workforce diversity [6]. If academic leadership (e.g., the Division Chief and Department Chair) makes diversity a priority, such diversity is improved. Key components of any institutional initiative to improve academic diversity include monitoring progress in a transparent manner [6, 18] and inclusion of qualified mid-career and senior URM faculty in promotion and mentoring committees, and leadership positions [18, 20]. For example, leadership in cardiovascular medicine at The Ohio State University (OSU) made greater diversity within their fellowship training program a priority. To increase the number of URM trainees, the fellowship program employed intentional recruitment that was followed by consistent mentoring of URMs who matriculated into the program [23]. Such efforts have led to consistent representation of URMs in the cardiovascular medicine training program at OSU.

Following completion of GME, the Harold Amos Medical Faculty Diversity Program (AMFDP) offers an example of a successful approach to increasing workforce diversity among faculty in academic medicine [19]. Of the 256 alumni of the AMFDP in 2013, over 80 % were in academia, with 18 in Pulmonary Medicine [19]. Graduates from the AMFDP include 65 professors, 4 deans of medical schools, and 10 members of the National Academy of Medicine [19]. The AMFDP's success is likely due to a committed group of advisors, three levels of mentorship (within and outside the AMFDP), and a strong career development program [19].

Multifaceted and comprehensive approaches are needed to ensure adequate representation of URMs in GME programs. A diverse workforce in pediatric and adult training programs in pulmonary and critical care medicine is an essential step to achieve respiratory health equity in the US.

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Chapter 13
Personalized Medicine

Victor E. Ortega

Introduction

Personalized medicine or precision medicine aims to use a subject's characteristics to design an individualized treatment plan. Personalized medicine is based on the premise that biomarkers (e.g., genetic variants) can be used to predict disease risk or response to medications, in order to prevent or treat a disease in a given individual.

Genetic and "omics" studies of respiratory diseases, both published and ongoing, will lead the way to predictive profiles for precision medicine. This chapter will focus on asthma and chronic obstructive pulmonary disease (COPD), not only because of their public health importance (see Chap. 10) but also because of the strength of the evidence to support personalized medicine to prevent and treat these common airway diseases.

The frequency and severity of asthma and COPD differ among racial and ethnic groups in the USA (see Chaps. 2 and 10). In this chapter, we discuss the basis for the variable population structure and genetic diversity of modern human genomes from different racial and ethnic groups. We will summarize how such diversity has impacted genetic studies, and how studies in diverse populations have led to the identification of susceptibility loci for respiratory diseases and response to treatment. Finally, we highlight how future genetics and "omics" research in diverse populations should lead to identification of biomarkers for personalized medicine, which would help eliminate existing respiratory health disparities.

V.E. Ortega, MD, PhD (✉)
Center for Genomics and Personalized Medicine, Wake Forest School of Medicine,
Medical Center Boulevard, Winston-Salem, NC 27157, USA
e-mail: vortega@wakehealth.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_13

Genetic Studies in Ethnically Diverse Populations

According the US Census Bureau, the non-Hispanic White population will peak in 2012, and then slowly decrease in size from 2024 to 2060. In contrast, Hispanic and Asian populations will grow over the next four decades, making non-whites surpass non-Hispanic whites as the majority of the US population by 2060 [1].

The diverse genomes of modern racial or ethnic groups in the USA (see Chap. 2) largely resulted from racial admixture during the European colonization of the Americas over the past 500 years. Thus, African Americans and Hispanics (e.g., Puerto Ricans and Mexican Americans) have varying proportions of European, Native American, and African ancestries. On average, African Americans and Puerto Ricans have a greater proportion of African ancestry but a lower proportion of Native American ancestry than Mexican Americans. However, ancestral proportions can vary between members of an ethnic group [2, 3].

Because of human origins in Africa, subjects of sub-Saharan African descent have had a greater number of recombination events over many generations, resulting in greater genetic diversity and fewer co-inherited polymorphisms within genomic regions (i.e., shorter regions of linkage disequilibrium [LD], Fig. 13.1). In contrast, Europeans had loss of genetic diversity during a "bottleneck" as the first modern humans migrated to Europe from sub-Saharan Africa ~40,000 years ago, resulting in high correlation or co-inheritance of polymorphisms within genomic regions (i.e., greater LD, Fig. 13.1) [4]. Because European ancestry leads to lower genetic diversity but greater LD than African ancestry, fewer markers need to be genotyped to "tag" genetic variants in populations of mostly European descent (i.e., European Americans or non-Hispanic whites) than in those of mostly African descent (i.e., African Americans). For the same reasons, rare variants (allele frequency <0.05) are more frequently found in African Americans than in European Americans [4, 5].

High-throughput genotyping allows for the analysis of millions of single nucleotide polymorphisms (SNPs), which have been used in genetic association studies of airway diseases. Such studies have targeted biologically plausible candidate genes or the whole genome (genome-wide association studies or GWAS), most often—but not exclusively—in populations of European descent. More recently, next-generation DNA sequencing has expanded the catalogue of human genetic diversity, facilitating studies of ethnically diverse populations. We will next highlight salient findings from genetic studies of asthma and COPD.

Genetic Studies of Asthma

Early family-based genome-wide linkage studies failed to identify susceptibility genes for asthma or related phenotypes, yet demonstrated that asthma is caused by multiple genes [6–17]. More than 100 genes have been examined for association with asthma, based on biologic plausibility ("functional candidate genes") or location in

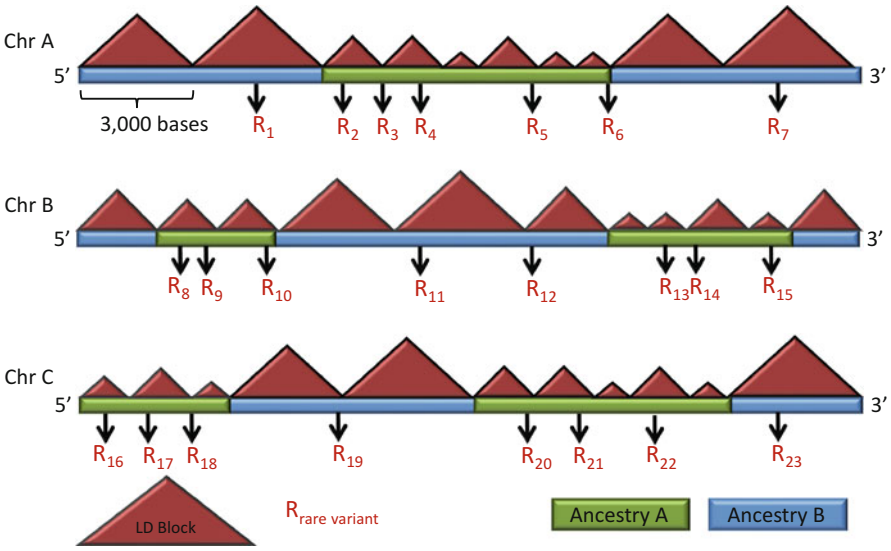

Fig. 13.1 Consequences of ancestral admixture on genetic diversity. The recent admixture of an ancient ancestry (such as African ancestry or ancestry A, highlighted in *green*) with a more recent ancestry (such as European ancestry or ancestry B, highlighted in *blue*) affects genetic diversity in chromosomal (Chr.) regions throughout the genome. The more ancient ancestry (A) has had a greater number of recombination events over more generations, resulting in greater genetic diversity with fewer co-inherited genetic variants in genomic regions, highlighted with the *red triangles* signifying shorter regions of linkage disequilibrium (LD). In comparison, ancestry B resulted from a recent loss of genetic diversity or "bottleneck," leading to gene variants that are highly co-inherited or correlated over longer genomic regions through LD (highlighted with *larger red triangles*). The more ancient ancestry A has also had more time for rare variants to occur (*red* "R") and has a higher frequency of rare variants compared to ancestry B

genomic regions linked to asthma or related phenotypes in family-based studies ("positional candidate genes") [18, 19]. Such studies were largely based on genotyping common SNPs (i.e., allelic frequency ≥0.05) in the genes of interest, which were then tested for association with asthma. Using this candidate-gene approach, the most highly replicated genes for asthma in subjects of European descent were in biologic pathways related to lung development (*ADAM33*), Th2 inflammation (*IL4, IL13, IL4R*), innate immunity (*HLA-DRB1, HLA-DQB1, CD14*), and cellular inflammation (*TNF, FCER1B, DPP10*) [18–28]. Consistent with findings for many candidate genes, *ADAM33* was associated with asthma or related phenotypes in African Americans and New Mexico Hispanics [29], but not in Puerto Ricans or Mexicans [30]. The inconsistent findings for most candidate-gene association studies of asthma could often be due to false positive results from chance or population stratification (confounding by population substructure). Alternatively, nonreplication across ethnic groups may have been due to limited statistical power because of small sample size or ethnic-specific genetic effects (due to differing allelic frequencies (Table 13.1 [31–34]) or gene-by-environment interactions) [29, 35].

Table 13.1 Allele frequencies of asthma risk loci in different racial and ethnic groups

Asthma risk loci		Associated							
Gene names	Gene ID	SNP	CEU	YRI	ASW	MEX	CHB	JPT	References
Interleukin-6 receptor	*IL6R*	rs4129267	0.35	0.07	0.15	0.52	0.39	0.36	[39]
Pyrin and HIN domain family member 1	*PYHIN1*	rs1102000	0.00	0.35	NA	NA	0	0	[42]
Interleukin-1 receptor	*IL1RL1*	rs1420101	0.35	0.32	0.43	0.27	0.39	0.46	[37, 44]
Interleukin-18 receptor	*IL18R1*	rs3771166	0.41	0.72	0.65	0.28	0.13	0.18	[37]
Dipeptidyl peptidase-10	*DPP10*	rs1435879	0.10	0.03	0.04	0.19	0.31	0.30	[42]
GRB2-associated binding protein 1	*GAB1*	rs1397527	0.45	0.84	0.74	NA	0.31	0.30	[31]
Ubiquitin specific peptidase 38	*USP38*	rs7686660	0.21	0.47	0.44	0.52	0.74	0.72	[31]
cAMP-specific phosphodiesterase 4D	*PDE4D*	rs1588265	0.36	0.16	0.22	0.22	0.70	0.73	[43]
WD repeat domain 36	*WDR36*	rs2416257	0.14	0.14	0.10	0.06	0.07	0.04	[45]
Thymic stromal lymphopoietin	*TSLP*	rs1837253	0.28	0.34	0.29	0.30	0.62	0.66	[31, 37, 42, 44]
RAD50 homolog	*RAD50*	rs2244012	0.20	0.73	0.51	0.18	0.19	0.19	[28]
Interleukin-13	*IL13*	rs1295686	0.22	0.73	0.59	0.48	0.34	0.30	[28, 50]
α-1B-adrenergic receptor	*ADRA1B*	rs10515807	0.16	0.03	NA	NA	0.32	0.34	[48]
TNFAIP3 interacting protein 1	*TNIP1*	rs1422673	0.19	0.43	0.37	0.47	0.56	0.51	[50]
Psoriasis susceptibility 1 candidate 1	*PSORS1C1*	rs3094663	0.27	0.24	0.36	0.28	0.31	0.35	[44]
Human leukocyte antigen complex DQB1	*HLA-DQB1*	rs9273349	0.42	0.48	0.47	0.23	0.39	0.44	[28, 37, 44]
Human leukocyte antigen complex DRA	*HLA-DRA*	rs2395185	0.43	0.19	0.20	0.35	0.37	0.39	[50]
Interleukin-33	*IL33*	rs1342326	0.17	0.35	0.32	0.15	0.00	0.00	[37, 42, 44]
GATA Binding Protein 3	*GATA3*	rs10508372	0.04	0.22	0.21	0.35	0.59	0.56	[31]
Ikaros Family Zinc Finger 4	*IKZF4*	rs1701704	0.32	0.07	0.15	0.21	0.23	0.22	[31]
SMAD Family Member 3	*SMAD3*	rs744910	0.45	0.68	0.67	0.54	0.58	0.56	[37]
RAR-Related Orphan Receptor A	*RORA*	rs11071559	0.15	0.56	0.43	0.11	0.14	0.23	[37]
ORM1-Like 3	*ORMDL3*	rs7216389	0.49	0.88	0.70	0.60	0.66	0.72	[36–38, 40–43]
Gasdermin-like B	*GSDMB*	rs2305480	0.47	0.05	0.25	0.40	0.33	0.28	[37, 41, 44, 50]

Asthma risk loci		Associated							
Gene names	Gene ID	SNP	CEU	YRI	ASW	MEX	CHB	JPT	References
Ikaros family Zinc finger 3	*IKZF3*	rs907092	0.49	0.07	0.28	0.39	0.33	0.34	[44]
Prion-related protein	*PRNP*	rs6052761	0.10	0.35	0.39	0.17	0	0.03	[48]
Interleukin-2 receptor, β subunit	*IL2RB*	rs2284033	0.42	0.39	0.45	0.32	0.65	0.58	[37]

Asthma risk loci were among the first identified and denoted by reference sequence number (rs) [28, 31, 36–45, 48, 50]
Minor or less common, variant allele frequencies are based on data from the International HapMap Project Genome Browser release 28, phases 1–3 [32]
Abbreviations from each group are as follows: *CEU* Utah residents with ancestry from northern and western Europe, *YRI* individuals from Yoruba in Ibadan, Nigeria, *ASW* African Americans from the southwest United States, *MEX* Mexican Americans from Los Angeles, CA, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan [33]
Adapted from Ortega VE et al. *Curr Opin Allergy Clin Immunol* 2014;14(5):381–9 [34]

The first GWAS of asthma susceptibility (conducted in Europeans) identified a novel locus on chromosome 17q21 (containing *ORMDL3* and *GSDMB*), which has been well replicated across multiple racial or ethnic groups [36–44]. *ORMDL3* encodes a transmembrane protein anchored to the endoplasmic reticulum, but its role (or that of *GSDMB*) in asthma is unclear. Subsequent GWAS have identified additional asthma-susceptibility loci, notably including genes (*IL33*, *IL1RL1*, and *TSLP*) conferring susceptibility to asthma in ethnically diverse North American populations (non-Hispanic whites, African Americans, Afro-Caribbeans, Puerto Ricans, and Mexicans) [28, 37, 42, 45]. Many of these genes are involved in pathways related to epithelial integrity and adaptive immune responses, suggesting that they promote T_H2-mediated airway inflammation through altered production of cytokines (i.e., *TSLP* and *IL33*) and/or damage of the airway epithelium.

The first GWAS conducted primarily in subjects of African descent identified the genes for the α-1B-adrenergic receptor (*ADRA1B*) and prion-related protein (*PRNP*) as novel asthma-susceptibility loci, while also replicating findings for *DPP10* from an earlier study of Europeans [11, 18, 46–48]. A multiethnic GWAS in North America (see above) also identified a gene (*PYHIN1)* that appears to only confer susceptibility to asthma in subjects of African descent [42].

Severe asthma (characterized by baseline airflow obstruction, uncontrolled symptoms, or frequent exacerbations despite adequate treatment) occurs more frequently among African Americans and Puerto Ricans [49]. Emerging evidence suggests that genes that influence asthma severity differ from those that determine asthma susceptibility [50, 51]. Identifying such loci should thus help to discover mechanisms underlying interethnic differences in asthma severity [52–55].

Lung function is an indicator of asthma severity. SNPs in the gene encoding the hedgehog-interacting protein (*HHIP*) are associated with reduced lung function in African American and non-Hispanic whites with asthma in the Severe Asthma Research Program (SARP) [56]. Moreover, variants in *HHIP* and genes previously associated with lung function in the general population (*FAM13A* and *PTCH1*) had additive effects on lung function and asthma severity in non-Hispanic whites and African Americans with asthma (Fig. 13.2a, b) [3, 56, 57].

SNPs from whole-genome genotyping can be used to estimate whole-genome or global genetic ancestry [58]. As reviewed in Chap. 2, global African genetic ancestry has been associated with an increased risk of asthma, lower FEV_1, and lower FVC in African Americans and Puerto Ricans [3, 57, 59–61]. Conversely, global Native American ancestry has been associated with reduced risk of asthma but higher FEV_1 and FVC in Latinos [60]. Of interest, global African ancestry has also been shown to be associated with severe asthma exacerbations in African American males, further suggesting a role for genetic or environmental risk factors correlated with African ancestry on asthma severity [62].

Admixture mapping (AM) is a whole-genome scanning approach that can be used to identify susceptibility loci for complex diseases in racially admixed populations. AM tests for association between local ancestry at each SNP locus and phenotype, under the assumption of significant differences in both disease prevalence and allelic variation between ancestral groups for a population of interest

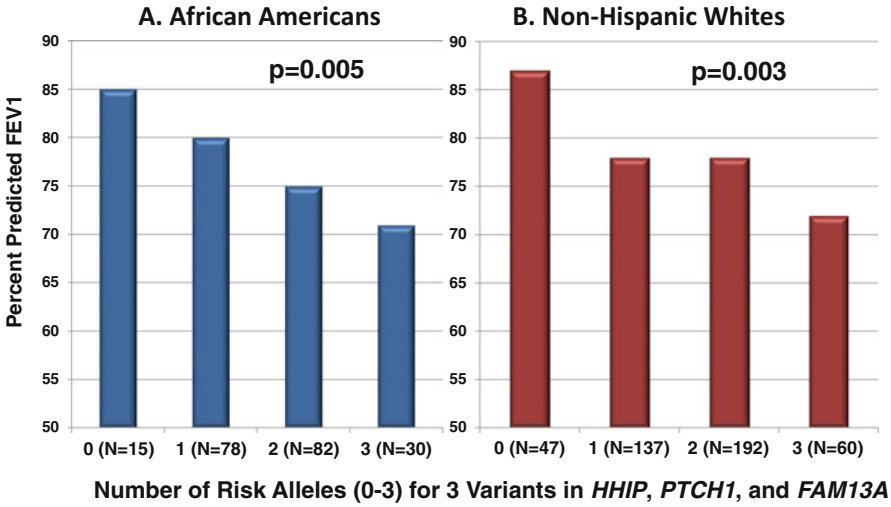

Fig. 13.2 (**a**, **b**): Additive genetic effects of major lung function loci from the general population. An additive effect of risk variants from GWAS of lung function measures in the general population on lung function was shown in 1441 asthma subjects from three asthma cohorts. An increase in the number of risk alleles for SNPs in *HHIP*, *PTCH1*, and *FAM13A* resulted in a significant stepwise decrease in FEV1, FVC, and FEV1/FVC in both non-Hispanic Whites and African Americans. Data for FEV1 is shown for (**a**) African Americans and (**b**) non-Hispanic Whites. Adapted from Li X et al. *J Allergy Clin Immunol* 2011;127(6):1457–65 [56]

(see Chap. 2) [63, 64]. An AM study identified an AM peak for asthma in African Americans on chromosome 6q14, which contained an SNP surrounded by a European ancestral background. This finding was replicated in Puerto Ricans, and an interaction between a susceptibility locus and local genetic ancestry was shown in both African Americans and Puerto Ricans [65]. In another study, six AM peaks containing known asthma risk loci and a novel locus in the *LYN* gene were identified in Puerto Ricans and Mexicans [66, 67]. More recently, AM was combined with allelic association testing to identify a potential asthma-susceptibility locus (*PSORS1C1*) in Latinos [44]. Like genome-wide linkage studies, AM has limited resolution, thus requiring subsequent fine-mapping studies, replication in external cohorts, and functional studies to confidently identify disease-susceptibility variants.

Failure to replicate findings from studies of non-Hispanic whites in minority populations (or vice versa) may be explained by differing allelic frequencies among ancestral populations (Table 13.1), insufficient genomic coverage in populations of African descent, small sample size, or true ethnic-specific effects. Current evidence suggests that most asthma-susceptibility loci identified to date are "cosmopolitan" (affecting all racial/ethnic groups), but that a few such loci may be "ethnic-specific" (affecting one or a few ethnic groups). Pending additional work, however, no ethnic-specific asthma-susceptibility variant has been confidently identified to date.

Genetic Studies of COPD

COPD is a multifactorial disease, caused by the interaction between genetic variants and environmental risk factors such as tobacco smoke [68–72]. Candidate-gene association studies, largely conducted in non-Hispanic whites, have identified a small number of potential COPD-susceptibility loci in inflammatory (*TGFB1*), protease-anti-protease (*ADAM33*, *MMP12*), and oxidant-antioxidant (*GSTM1*, *GSTP1*) gene pathways, some of which (e.g., *MMP12*) have been confirmed in subsequent genome-wide scans [72–78].

Airflow obstruction and lung function decline are key intermediate phenotypes of COPD. GWASs in non-Hispanic whites have identified susceptibility genes for lung function (*GSTO2* and *IL6R*) [79] and airflow obstruction (seven loci, including *HHIP*) [80–82]. Subsequent studies confirmed a role of *HHIP* in COPD susceptibility and showed an association with airflow obstruction in asthma [56, 83–86]. Evidence from murine models suggests that *HHIP* variants alter lung development and baseline respiratory reserve, ultimately increasing the risk of lung function decline and COPD [87–89]. Subsequent meta-analyses of GWASs have identified additional susceptibility loci for lung function in genes which regulate inflammation (*HTR4, THS4D*), lung development (*ADAM19*, *GPR126*), the antioxidant pathway (*GSTCD*), and tissue remodeling (*ADAM19*, *HTR4, THSD4, AGER*, *TNS1*). Of interest, alleles in these genes have differing frequencies across racial or ethnic groups (Table 13.2 [90]) [81, 82, 91, 92]. Cumulative risk scores combining risk SNPs from lung function genes (including *HHIP*, *TNS1*, *GSTCD*, *HTR4*, *AGER*, and *THSD4*) have been shown to be associated with a stepwise decrement in FEV1 and FEV1/FVC, both in non-Hispanic whites and African Americans with asthma, and in non-Hispanic whites from a general population cohort (Fig. 13.2a, b) [56, 85].

Although global African ancestry has been shown to be inversely associated with FEV_1 and FVC in African Americans and Latinos (see Chap. 2), there has been no GWAS of lung function in these populations. An admixture-based genetic study of Mestizo individuals and Native Mexicans demonstrated a strong correlation between Native American ancestry and geographic location within Mexico, resulting in ancestral clusters and ancestry-specific principal components. An analysis of ancestry-specific principal components in Mexicans and Mexican Americans then demonstrated that increased regional variation in Native American ancestry was positively associated with lung function [93]. Native American ancestry was also shown to be positively associated with lung function in a Costa Rican cohort of adolescents and adults with and without COPD [94], as well as in a study of Hispanic adults from New Mexico [95]. In the latter study, Native American ancestry was also inversely associated with lung function decline and COPD [95].

To date, GWASs of COPD have been conducted mostly in subjects of European descent. The first such GWAS identified susceptibility SNPs for COPD chromosome 15q25, a genomic region encompassing genes encoding the α-nicotinic acetylcholine receptors (*CHRNA3/5*) and a gene in the antioxidant pathway (*IREB2*) [86, 96–98].

Table 13.2 Allele frequencies of loci from major lung function genes from general population GWAS by biologic pathway

Lung function genes by pathway	Gene ID	SNP	Phenotype	CEU	YRI	ASW	MEX	CHB	JPT	References
Inflammatory pathway										
Interleukin-6 receptor	*IL6R*	rs4129267	FEF25-75 %	0.35	0.07	0.15	0.52	0.39	0.36	[79]
Transforming growth factor-β2	*TGFB2*	rs993925	FEV1, FEV1/FVC	0.42	0.3	NA	NA	0.42	0.48	[92]
Histone deacetylase-4	*HDAC4*	rs12477314	FEV1, FEV1/FVC	0.13	0	NA	NA	0.28	0.26	[92]
Thrombospondin Type 1 domain containing-4	*THSD4*	rs12899618	FEV1/FVC	0.11	0.09	0.1	0.05	0.11	0.04	[81, 82]
Tensin-1	*TNS1*	rs2571445	FEV1	0.39	0.14	0.24	0.35	0.42	0.45	[81, 82]
5-hydroxytryptamine receptor-4	*HTR4*	rs6889822	FEV1, FEV1/FVC	0.36	0.15	0.2	0.56	0.67	0.6	[81, 82]
Proteolytic pathway										
A Disintegrin and metalloprotease-19	*ADAM19*	rs2277027	FEV1, FEV1/FVC	0.32	0.64	0.62	0.43	0.14	0.16	[81]
Matrix metallopeptidase-15	*MMP15*	rs12447804	FEV1, FEV1/FVC	0.23	0.01	0.11	0.45	0.41	0.34	[92]
Advanced glycosylation end product receptor	*AGER*	rs2070600	FEV1/FVC	0.06	0.01	0.02	NA	0.24	0.13	[81, 82]
Oxidative stress and antioxidant pathway										
Glutathione S-transferase omega-1 subunit	*GSTO2*	rs156697	FEV1, FVC	0.38	0.83	0.69	0.22	0.27	0.29	[79]
Family with sequence similarity 13, member A	*FAM13A*	rs2869967	FEV1/FVC	0.41	0.71	0.65	0.45	0.49	0.59	[81]
C-terminal domain-containing glutathione S-transferase	*GSTCD*	rs17331332	FEV1, FVC	0.06	0	0.01	0.06	0	0.01	[81, 91]
Cell division cycle 123 homolog	*CDC123*	rs7068966	FEV1, FEV1/FVC	0.46	0.13	0.3	0.57	0.29	0.5	[92]
WW domain-containing oxidoreductase	*WWOX*	rs1079572	FVC	0.42	0.43	NA	NA	0.46	0.37	[91]
Lung development pathway										
Hedgehog-interacting protein	*HHIP*	rs13147758	FEV1, FEV1/FVC	0.38	0.02	0.1	0.33	0.31	0.32	[81, 82]
Patched 1 receptor for hedgehog proteins	*PTCH1*	rs16909898	FVC, FEV1/FVC	0.13	0.12	0.11	0.03	0.07	0.1	[81, 91]

(continued)

Table 13.2 (continued)

Lung function genes by pathway	Gene ID	SNP	Phenotype	CEU	YRI	ASW	MEX	CHB	JPT	References
G Protein-coupled receptor 126	*GPR126*	rs3817928	FEV1, FEV1/FVC	0.2	0.21	0.15	0.1	0.08	0.1	[81]
Retinoic acid receptor β	*RARB*	rs1529672	FEV1, FEV1/FVC	0.14	0.27	0.14	0.26	0.42	0.32	[92]
Craniofacial development protein 1	*CFDP1*	rs2865531	FEV1, FEV1/FVC	0.47	0.69	NA	NA	0.44	0.48	[92]
Bone morphogenetic protein-6	*BMP6*	rs6923462	FVC	0.13	0.31	0.24	0.11	0	0	[91]
EGF-containing Fibulin-like extracellular matrix protein-1	*EFEMP1*	rs1430193	FVC	0.42	0.79	NA	NA	0.91	0.86	[91]
PR domain-containing-11	*PRDM11*	rs2863171	FVC	0.16	0.38	0.34	0.09	0	0	[91]
Hydroxysteroid (17-beta) dehydrogenase-12	*HSD17B12*	rs4237643	FVC	0.25	0.39	NA	NA	0.13	0.13	[91]

These gene loci have been identified through GWAS of lung function measures in the general population
Allele frequencies are provided for each ethnic group and ancestral population based on the International HapMap Project Genome Browser release 28, phases 1–3 [32]
ASW African Americans from the southwest United States, *CEU* Utah residents with ancestry from northern and western Europe, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan, *MEX* Mexican Americans from Los Angeles, CA, *YRI* Individuals from Yoruba in Ibadan, Nigeria [33]
Adapted from Ortega VE et al. *Curr Allergy Asthma Rep* 2015;15(4):516 [90]

A second GWAS identified susceptibility SNPs for COPD in *FAM13A,* a gene previously associated with lung function [81, 99]. A subsequent (and larger) GWAS identified a COPD-susceptibility locus containing *CYP2A6*, a key enzyme for nicotine metabolism in the nicotine dependence pathway [100]. The first GWAS to include both non-Hispanic whites and African Americans confirmed risk loci for COPD in *CHRNA3*, *FAM13A*, and *HHIP,* while also identifying a novel locus in *RIN3* (distantly adjacent to *SERPINA1,* which encodes α-1 antitrypsin, the strongest known genetic risk factor for COPD) [101]. A subsequent genome-wide admixture mapping in African Americans identified a novel locus for airflow obstruction (*FAM19A2*) [102]. The first GWAS of COPD in Hispanics (a meta-analysis of three cohorts in Costa Rica, the US Multi-ethnic Study of Atherosclerosis, and New Mexico) identified potential novel COPD-susceptibility loci (adjacent to *KLHL7/NUPL2*, and *DLG2*) and confirmed *FAM13A* as a locus for COPD in Hispanics [103].

Consistent with results in asthma, ancestry influences lung function and COPD in racially admixed populations. Moreover, most COPD-susceptibility loci appear to be "cosmopolitan," but a few may be truly ethnic-specific. Thus, inclusion of large cohorts of minorities in COPD studies may yield novel insights into the role of ancestry and genetics in ethnic differences in the prevalence and severity of COPD.

Pharmacogenetic Studies of Respiratory Diseases

Pharmacologic responses have been shown to have both interindividual variability and significant heritability [104, 105]. Pharmacogenetic studies, which analyze gene-by-drug interactions on clinical outcomes, have been highly successful in identifying targeted therapies in cystic fibrosis. Most pharmacogenetic studies in pulmonary medicine have been conducted in subjects with asthma [106, 107] and have included mostly non-Hispanic whites. However, pharmacogenetic studies of response to inhaled β_2-adrenergic receptor agonists (inhaled β_2-agonists) have included racial and ethnic minorities with asthma.

Inhaled β_2-agonists include short-acting β_2-agonists (SABA, used most often as rescue therapy) and long-acting β_2-agonists (LABA, often used in combination with an inhaled corticosteroid (ICS) for chronic treatment). Findings from surveillance studies and meta-analyses suggest that LABA increase the risk of life-threatening asthma exacerbations and asthma-related deaths when administered as a monotherapy without ICS therapy [108–110]. The largest and most cited of these surveillance studies included 26,355 subjects (4685 African American), who were randomized to salmeterol or placebo with "usual therapy." An interval analysis of that trial (SMART) demonstrated increased risk of asthma or respiratory-related life-threatening exacerbations and death among African Americans randomized to salmeterol [109]. Although limited by lack of a requirement for ICS in all study subjects, such findings formed the basis for a LABA safety controversy, leading to two advisory panel meetings by the US Food and Drug Administration (FDA),

public health advisories, and a boxed warning for all inhalers containing LABA [111]. This controversy, further fueled by findings contradicting those from SMART [112–115], is now being evaluated in an international FDA-mandated LABA safety study of over 40,000 asthmatics [111, 116].

Results from recent clinical trials suggest that African Americans with asthma have a reduced response to LABA-containing combination therapies compared to non-Hispanic Whites and Hispanics [117, 118]. In a study of adults with asthma, African Americans were less likely to respond to LABA than non-Hispanic Whites [117]. Similarly, Puerto Ricans with asthma have been shown to have a lower response to SABA than Mexicans, a finding that could be explained by ethnic-specific differences in genetic variants or response to psychosocial stress [119, 120].

Pharmacogenetic studies of response to inhaled β_2-agonists have focused on the gene encoding the β_2-adrenergic receptor (*ADRB2*), the pharmacologic target for β_2-agonists. Although the most extensively studied *ADRB2* variant is a coding SNP which substitutes a glycine for an arginine in amino acid position 16 ($Gly^{16}Arg$), up to 49 SNPs have been identified through DNA sequencing in multiethnic populations, including rare variants [121, 122]. In vitro studies have shown that beta agonist stimulation results in enhanced downregulation of the β_2-adrenergic receptor with the Gly^{16} allele compared to Arg^{16} [123, 124]. In vitro studies of the rare *ADRB2* variant, $Thr^{164}Ile$, show that this variant causes a marked decrease in receptor ligand binding and coupling to G_s protein in response to different SABAs and LABAs, and impaired salmeterol binding to its receptor "exosite" [125, 126].

Early association studies of *ADRB2* in non-Hispanic whites consistently demonstrated that Arg^{16} homozygotes show greater response to SABA than Gly^{16} homozygotes, a finding confirmed in some ethnic groups (i.e., Puerto Ricans) but not in others (i.e., Mexican Americans) [127, 128]. An SNP in a pathway-related gene (*GSNOR*, encoding S-nitroso-glutathione reductase) has been shown to alter the genetic effect of $Gly^{16}Arg$ on response to SABA in Puerto Ricans but not in Mexican Americans, and thus this gene-gene interaction requires further replication [129].

Two pharmacogenetic studies using data from previous clinical trials (which randomized non-Hispanic whites with asthma to long-term treatment with SABA) demonstrated that *ADRB2* Arg^{16} homozygotes were more likely to have a decline in lung function during SABA treatment than *ADRB2* Gly^{16} homozygotes [130, 131]. The genetic effects of the $Gly^{16}Arg$ locus were confirmed in a genotype-stratified, cross-over pharmacogenetic study, the Beta Agonist Response by Genotype (BARGE) trial. In that trial, 37 Arg^{16} homozygotes and 41 Gly^{16} homozygotes were randomized to regular albuterol or placebo for 16 weeks, with ipratropium provided as a rescue inhaler to minimize β_2-agonist use. Whereas Gly^{16} homozygotes had improved lung function and symptom control during regular albuterol therapy, Arg^{16} homozygotes had no change in lung function and a loss of symptom control during regular albuterol therapy [132].

In the BARGE trial, the proportion of Arg^{16} homozygotes was higher in African Americans (22 %) than in non-Hispanic whites (17 %) (see *ADRB2* in Fig. 13.3) [132]. This is likely because Gly^{16} is the ancestral allele of $Gly^{16}Arg$, and chromosomes from ancient African ancestors have had more generations to distribute the

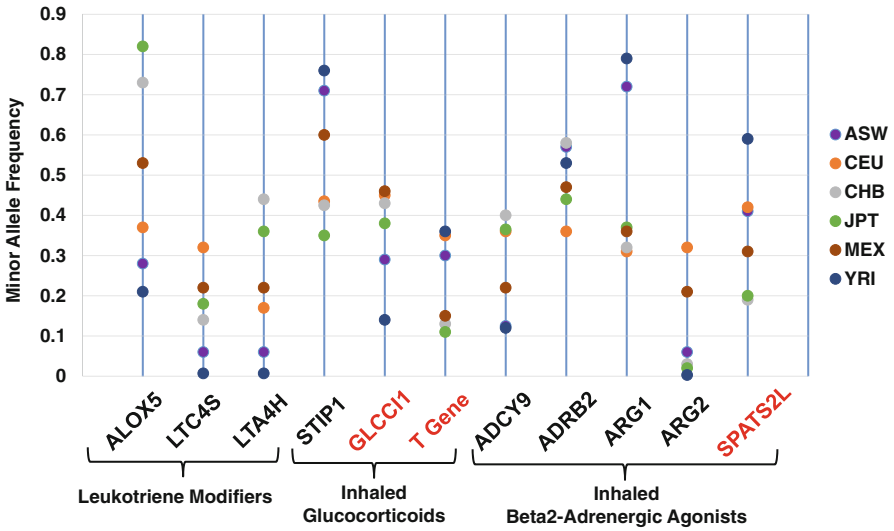

Fig. 13.3 Allele frequencies of different pharmacogenetic loci by race or ethnic group. These pharmacogenetic loci have been identified through candidate-gene studies and GWAS in asthma clinical trials [141, 143–153]. Loci with SNPs identified through GWAS are highlighted in *red*. Allele frequencies are provided for each ethnic group and ancestral population based on the International HapMap Project Genome Browser release 28, phases 1–3 [32]. *ASW* African Americans from the southwest United States, *CEU* Utah residents with ancestry from northern and western Europe, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan, *MEX* Mexican Americans from Los Angeles, CA, *YRI* Individuals from Yoruba in Ibadan, Nigeria [33]

more recent Arg^{16} variant than chromosomes from a European ancestor [133]. The frequency of the Arg^{16} allele is thus higher in African Americans and Puerto Ricans than in non-Hispanic Whites [122], potentially explaining ethnic differences in response to β_2-agonists. However, findings from genotype-stratified clinical trials have largely failed to show an effect of the Arg^{16} allele on response to LABA, with or without concurrent therapy with ICS [134–138]. $Gly^{16}Arg$ (which has a frequency between 40 % and 60 % in different ethnic groups [*ADRB2,* Fig. 13.3]) should not be used to stratify patients for LABA treatment. Rare genetic variants with strong effects could explain the severe adverse effects found in <1 % of the LABA-treated subjects in SMART, but this is highly speculative [109].

Sequencing of *ADRB2* in different ethnic groups has identified $Thr^{164}Ile$, a rare *ADRB2* variant primarily found in non-Hispanic Whites, and a rare 25 base-pair insertion variant at nucleotide position −376 relative to the start codon in the *ADRB2* promoter (−376 In-Del) in African Americans and Puerto Ricans [121, 122, 139]. In a recent study, these rare variants were both associated with asthma-related hospitalizations, asthma-related urgent outpatient visits, and regular use of systemic corticosteroids among non-Hispanic whites and African Americans with asthma treated with LABA (Fig. 13.4a, b) [122]. In another study, an analysis combining results from AM and a GWAS showed an association between rare variants in two solute carrier genes (*SLC24A4* and *SLC22A15*) and response to SABA in Puerto Ricans and Mexican

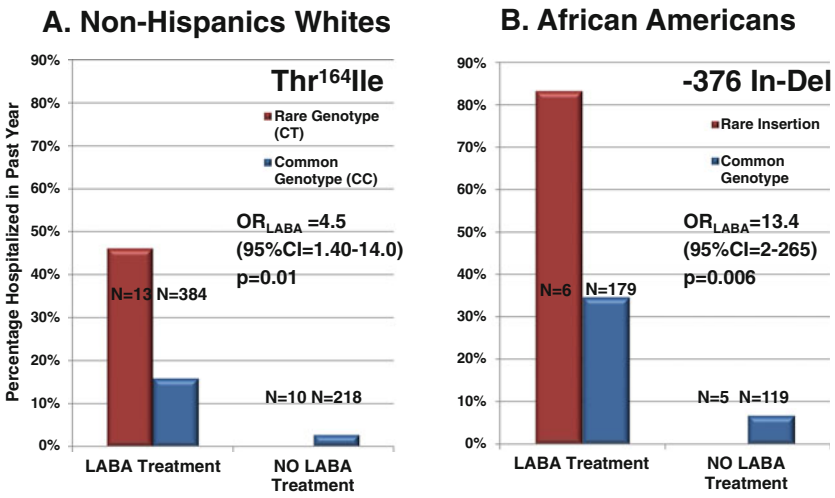

Fig. 13.4 (**a**, **b**): Rare *ADRB2* variants and asthma-related hospitalization with long-acting beta agonist treatment. Two rare ADRB2 variants, Thr^{164}Ile and a 25 base-pair promoter insertion-deletion (−376 In-Del), are shown with odds ratio (OR) for hospitalization in those treated with a long-acting beta agonist (LABA). Reproduced from Ortega VE et al. *Lancet Respir Med* 2014;2(3):204–13 [122]

American with asthma [140]. In that study, rare variants in two genes previously associated with response to SABA in non-Hispanic whites, *ADCY9* and *CRHR2*, were shown to be associated with response to SABA in Latinos [140–142].

Large candidate-gene and GWAS of the pharmacogenetics of asthma have been mostly conducted in non-Hispanic whites. Such studies identified loci for therapeutic responsiveness to SABA, ICS, and leukotriene modifiers, each of which shows varying allele frequencies among different racial and ethnic groups (Fig. 13.3) [141, 143–153]. More recently, large-scale whole-genome sequencing studies have found rare ethnic-specific variants in populations of African descent [5], suggesting that rare variants (such as those in *ADRB2* and solute carrier genes) could be biomarkers for personalized treatment approaches in racial or ethnic minorities (e.g., avoiding inhaled LABA in nonresponders or in subjects likely to experience severe adverse effects).

Future Directions

Whereas most susceptibility alleles for respiratory diseases (or response to treatment for such diseases) are "cosmopolitan," a small but non-negligible proportion of such susceptibility alleles are likely to be ethnic-specific (particularly rare variants). Moreover, differences in environmental and behavioral exposures across racial or ethnic groups are likely to affect gene expression through gene-by-environment interactions or epigenetic mechanisms that remain largely unexplored as potential contributors to respiratory health disparities.

A potential short-term implication of the studies summarized above (including studies of African ancestry and lung function summarized in Chap. 2) is that global ancestry (determined by genetic markers) could replace self-reported race or ethnicity when developing predicted (or reference) values for lung function. For instance, traditional race-based calculations of reference values for lung function can misclassify disease severity in up to 5 % of African Americans with asthma, as African Americans have different proportions of African ancestry [3].

In the medium to long term, predicted values of lung function could be personalized on the basis of whole-genome profiling, as all rare and common susceptibility genes for lung function (and other determinants, see below) become known as a result of large-scale studies of multiethnic populations. Similarly, such studies should lead to the identification of both common and rare (e.g., ethnic-specific) variants associated with response to, or severe adverse effects from specific therapies for pulmonary, critical care, and sleep disorders. In fact, ongoing whole-exome and whole-genome sequencing projects such as the NHLBI GO Exome Sequencing Program, the 1000 Human Genomes Project, and the Consortium on Asthma in African Ancestry Populations (CAAPA) have identified, and will continue to identify, common and rare genetic variation for future genetic studies in racial and ethnic minorities [5, 154].

The path to personalized medicine for all members of society requires enrollment of sufficiently large numbers of subjects from racial or ethnic minorities in studies of gene-by-environment interactions and "omics" (genetics, epigenetics, transcriptomics, proteomics, and metabolomics) of respiratory diseases, as such integrated approaches are more likely to yield novel insights into disease pathogenesis or pharmacogenetics than traditional genetic studies. Such inclusive and diverse studies should lead to personalized medicine for all people, a key step toward eliminating respiratory health disparities and achieving respiratory health equality in the USA.

Acknowledgements NIH NHLBI Grants K08 HL118128, R01 NR013700, U10 HL109164, U01 HL 65899, and U10 HL098103.

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Chapter 14
Health Policy: Toward Achieving Respiratory Health Equality

Sarah M. Lyon, Ivor S. Douglas, and Colin R. Cooke

Introduction

Access to affordable and high-quality healthcare varies widely in the United States (US). Pervasive disparities in access exist across multiple domains, including geographic locations, gender, racial and ethnic groups, and socioeconomic status (SES). Variability in health insurance coverage is a key factor that interacts with these domains and plays an important role in disparities in both healthcare access and health outcomes among patients with respiratory disease or critical illness. For example, relative to the insured, individuals who lack health insurance have a greater incidence of lung cancer, are often diagnosed at a later stage of disease, and experience worse survival [1]. Similarly, among those with asthma (see Chap. 10), lack of health insurance has been associated with markers of poor outpatient care, such as lack of inhaled corticosteroid use and decreased likelihood of admission to the hospital from the emergency

S.M. Lyon, MD, MSCE (✉)
Division of Pulmonary, Allergy & Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Division of Pulmonary and Critical Care Medicine, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA
e-mail: Sarah.Lyon@uphs.upenn.edu

I.S. Douglas, MD, FRCP (UK)
Division of Pulmonary Sciences & Critical Care Medicine, University of Colorado, Denver and Denver Health Medical Center, Denver, CO, USA
e-mail: Ivor.Douglas@dhha.org

C.R. Cooke, MD, MSc, MS
Division of Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Center for Healthcare Outcomes & Policy, Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA
e-mail: cookecr@med.umich.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_14

department (ED) [2]. Uninsured critically ill patients are less likely to receive potentially life-saving critical care procedures [3, 4], receive less post-acute care after a critical illness [5], and have greater mortality than those with insurance [6–8].

Racial or ethnic minorities are more likely to be uninsured. US census data from 2012 to 2013 shows that non-Hispanic (NH) blacks and Hispanics were one and a half times and twice as likely to be uninsured, respectively, than NH whites. NH blacks and Hispanics were also more likely to be without a usual source of care, with 43 % of Hispanics versus 21 % of whites reporting no usual source of care. Minorities were also more likely to go without care because of cost, with 24 % of NH blacks and 29 % of Hispanics versus 15 % of whites reporting going without healthcare because of associated cost. Such racial and ethnic disparities in access persisted after accounting for health status and income [9]. Given that noninsurance is common among minorities, health insurance expansion may significantly mitigate racial/ethnic disparities in healthcare.

The Patient Protection and Affordable Care Act

To address health disparities from lack of insurance, President Obama signed the Patient Protection and Affordable Care Act into law in March of 2010, the most comprehensive healthcare reform since the creation of Medicare and Medicaid in 1965. The Affordable Care Act (ACA) protects patient by eliminating insurance discrimination for those with pre-existing conditions, and establishes minimal standards for health insurance policies under the Essential Health Benefits. The ACA also expands access to health insurance through several mechanisms: children up to age 26 can be covered under their parents' policies, and the ACA mandates insurance exchanges to provide insurance to individuals without access to employer coverage. The ACA also created an employer mandate, which requires businesses with over 50 full-time employees to provide health insurance to ≥95 % of their employees and dependents, or pay a fine. In addition, the ACA created an individual mandate that requires most US citizens and legal residents to have health insurance or face a tax penalty. The ACA also increased access to health insurance for those with low or moderate income, through increasing Medicaid income eligibility to individuals with an income up to 138 % of the federal poverty level (FPL), as well as by creating insurance premium subsidies for those with incomes between 138 and 400 % of the FPL (as tax credits). While several of these policies expand the private insurance market, the largest proportion of uninsured Americans is expected to gain health insurance under the ACA through Medicaid expansion.

Medicaid Expansion

Created by the Social Security Amendments of 1965, Medicaid and the Children's Health Insurance Program (CHIP) were designed as the nation's healthcare safety net. Prior to the ACA, Medicaid and CHIP provided insurance coverage to nearly

18 % of nonelderly Americans [10], including many low-income individuals, such as children, their parents, pregnant women, and those with disabilities. While federal law required states to provide coverage for school-aged children up to 100 % of the poverty level, this was only mandated for those with incomes below an individual state's 1996 welfare eligibility levels. Ultimately, two-thirds of states limited parental eligibility to less than 100 % of the current poverty level [11], with states such as Alabama limiting the parental eligibility to as low as 23 % the federal poverty level in 2013 [10]. Individuals without children have typically been ineligible for Medicaid coverage regardless of income, with only nine states providing non-Medicaid, state-funded benefits to childless adults in 2009 [12]. Medicaid plays an important role in providing access to healthcare for minorities, with approximately 21 % of Medicaid beneficiaries—over 11 million Americans—being African-American [13].

The ACA was designed to expand Medicaid eligibility, particularly for adults. In its initial design, the ACA required states to provide Medicaid for both parents and those without dependent children with incomes at or below 138 % the FPL—$33,465 for a family of four in 2015—or lose federal Medicaid subsidies. To offset the financial burden of covering more individuals, the ACA stipulates that the federal government would cover the full cost of Medicaid expansion for each state, with a stepwise decrease in federal government cost-sharing down to 90 % in 2020. Anticipating that hospitals will be responsible for less uncompensated care as patients gain coverage, the ACA will also reduce the Disproportionate Share Hospital payments, federal payments that help hospitals offset the cost of care for low-income individuals. Slated to begin in 2014, but delayed until Fiscal Year 2017 by subsequent legislation, these reductions will start at 1.2 billion dollars per year, increasing yearly to 4 billion dollars in 2020. The annual reduction each state will receive will vary and has yet to be determined [14].

Supreme Court Challenge: *National Federation of Independent Business v Sebelius*

Under new eligibility requirements, the Congressional Budget Office estimated that 17 million nonelderly adults would have gained coverage under Medicaid expansion [15]. However, in June 2012 the ACA underwent judicial challenge in the Supreme Court in *National Federation of Independent Business v Sebelius*. While the Supreme Court ruling in this case upheld the challenge to the individual mandate that requires all individuals to purchase health insurance or face a tax penalty, the Court also ruled that the states could not be compelled to participate in the proposed Medicaid expansion, giving states the option to expand Medicaid under the ACA or keep their pre-existing level of Medicaid benefits without loss of federal funding. As of October 2015, the number of states expanding Medicaid continues to increase and is at 32 (Fig. 14.1) [16, 17]. While the Congressional Budget Office anticipates that most states will eventually participate in Medicaid expansion despite initially declining, the revised enrollment estimates project 4 million fewer new enrollees by 2023, or ~25 % fewer than initially anticipated under mandated Medicaid expansion [15].

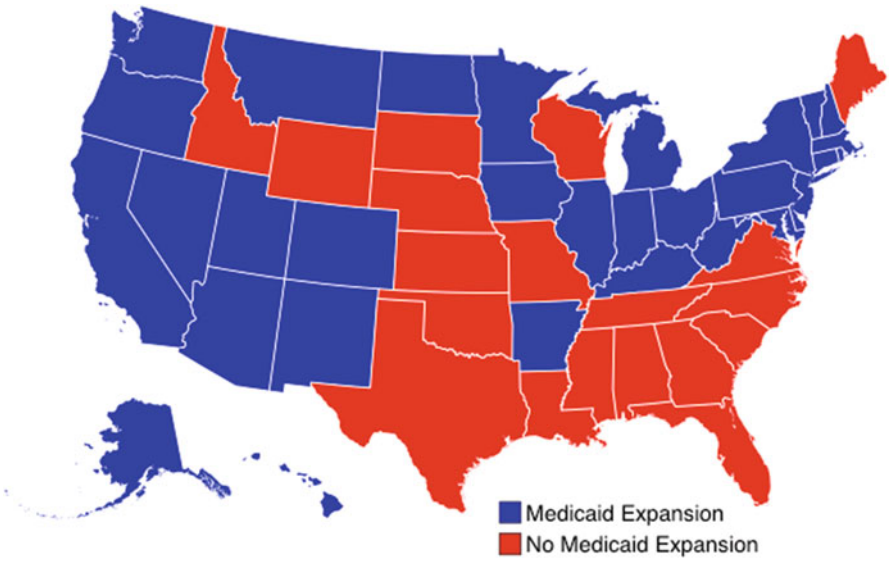

Fig. 14.1 Medicaid expansion October 2015

Nonparticipation in Medicaid Expansion Increases Disparities

In states that fail to expand access to Medicaid, millions of low-income parents and childless adults may remain without health insurance. Paradoxically, many states choosing not to expand Medicaid coverage have the most to gain, as they have a greater proportion of residents without health insurance (Table 14.1). Many uninsured individuals in these states are low-income, have no access to employee-based coverage, and will remain ineligible for their state's current Medicaid coverage after reform. Furthermore, their incomes will be too low (i.e., less than 100 % of the FPL) to qualify for health insurance premium credits, which would otherwise offset the expense of purchasing insurance coverage through state insurance exchanges. These individuals are left in a "coverage gap" where they are ineligible for both subsidies to purchase private insurance (because their income is too low) and Medicaid (because their income is too high). Although subsidies are not required to purchase insurance through the exchange, the cost of purchasing coverage without premium credits will likely remain prohibitive for those in this coverage gap, as the average US premium for a single adult making $20,000 per year (171 % of the FPL) without subsidies is $216 a month for a silver plan [18].

Failure to expand Medicaid has important implications for minorities. Uninsured NH blacks with incomes that would qualify for Medicaid under expansion are more likely to live in states that continue to forgo Medicaid expansion [19]. Two of the six states with large Hispanic populations (Florida and Texas), and all six of the states with the largest percentage of African-American residents are among those that continue to decline Medicaid expansion (Table 14.2). The Kaiser Family Foundation estimates that failure to expand Medicaid has left 3.6 million Hispanics and 2.9 million NH black adults ineligible for subsidized health plans [19].

Table 14.1 2015 Medicaid expansion among states with highest and lowest rates of nonelderly uninsured

State	% Nonelderly uninsured 2011–2012 [1]	Expanding Medicaid in 2015	% Below 100 % poverty level [46]	Life expectancy at birth (State's rank)
United States	17.9		15.0	
Texas	26.8	No	17.4	32
Nevada	26.5	Yes	15.5	38
Florida	24.7	No	14.9	23
New Mexico	24.3	Yes	22.2	34
Louisiana	22.4	No	21.1	50
Connecticut	9.5	Yes	10.1	5
Vermont	9.3	Yes	11.6	8
Hawaii	9.1	Yes	12.1	1
District of Columbia	9.1	Yes	19.9	45
Massachusetts	4.4	Yes	10.6	6

Table 14.2 2015 Medicaid expansion among states with highest percentage of African-American and Hispanic residents

State	% African-American US census 2013	% Hispanic US census 2013	Expanding Medicaid in 2015
Mississippi	37.4		No
Louisiana	32.4		No
Georgia	31.4		No
South Carolina	27.9		No
Alabama	26.6		No
North Carolina	22.0		No
New Mexico	47.3		Yes
California	38.4		Yes
Texas	38.4		No
Arizona	30.0		Yes
Nevada	27.5		Yes
Florida	23.6		No

Failure to expand Medicaid access in these states may also have consequences for insured patients who access care through the safety net. Those who fall into the coverage gap will likely continue to face barriers to nonemergent care, with associated worse health outcomes and potentially serious financial hardships when they do seek care. Failure to expand Medicaid will likely have adverse effects on the health of indigent women: more than half of states who elected not to expand Medicaid have higher than average rates of women without health insurance [20]. Safety net health service providers and hospitals in these states—systems that typically serve minorities and the poor—are also likely to suffer from limitations in resources and reduced Disproportionate Share Hospital payments, as they continue to shoulder the burden of uncompensated care costs. For example, safety-net hospitals tend to have slower gains in the quality of care provided to patients with

pneumonia and tend to be poorer performers relative to non-safety-net hospitals [21, 22]. Importantly, these deficiencies in care quality spill over to impact all of those served by safety-net health systems, not just those who lack insurance. Without the infusion of resources from newly covered Medicaid patients, these disparities in quality will likely persist.

Does Insurance Expansion Improve Health Equality?

Several recent studies highlight the potential benefits—and challenges—of Medicaid expansion on healthcare access, health outcomes, and financial peace of mind for the poor. Yet, Medicaid is an imperfect program that may not reach the full potential of private plans.

One can gain insight into the expected impact of Medicaid expansion from prior observational and quasi-experimental analyses of health insurance expansion in the US. Massachusetts initiated health insurance reform in 2006, in a program that includes many provisions incorporated in the ACA, including having most new insurance beneficiaries obtain insurance through Medicaid expansion. In Massachusetts, health insurance reform was associated with increased primary care utilization [23], decreased ED visits for low-severity conditions [24] and nonurgent conditions [25], decreased hospitalizations for preventable conditions [23, 26], and fewer critically ill patients without health insurance. However, intensive care unit (ICU) utilization (as measured by ICU admissions per capita or ICU admissions per hospitalization) was unchanged, and there were no changes in mortality or use of post-acute care facilities among patients admitted to the ICU [27]. Massachusetts health insurance reform was also associated with an increase in outpatient surgical referrals among lower income racial/ethnic minorities in the post-reform period [28]. In addition, after Massachusetts implemented health insurance reform, Hispanic adults with a primary care provider rose significantly but still remained lower than for NH whites [9].

Several states expanded Medicaid benefits before the advent of the ACA. Arizona, Maine, and New York significantly expanded Medicaid access to poor parents and childless adults between 2000 and 2005. Compared to neighboring states that did not undertake expansion, these states had an increase in Medicaid coverage and a concomitant decrease in the numbers of uninsured. States that expanded Medicaid also experienced a reduction in overall mortality compared to those that did not expand. Furthermore, the decrement in All-Cause Mortality was most significant in non-whites and in counties with the highest levels of poverty, suggesting that Medicaid expansion may significantly improve health outcomes for minorities and the poor. Finally, Medicaid expansion was associated with increased rates of self-reported health status of “excellent” or “very good” [29].

Perhaps the most definitive study of the impact of gaining Medicaid insurance was the Oregon Health Insurance Experiment. In 2008, Oregon offered Medicaid coverage to ~30,000 uninsured poor adults from a waiting list of almost 90,000

people. Individuals selected for Medicaid coverage were chosen via lottery, effectively randomizing those on the wait list to either coverage or no coverage, setting up the largest randomized controlled trial of insurance expansion in history. Medicaid coverage was responsible for increments in preventive healthcare (e.g., mammograms, cholesterol screening, and pap smears), improvements in self-reported general health and quality of life, and reduced incidence of depression. Although gaining Medicaid did result in greater use of medications for those with diabetes, it did not improve hemoglobin A1C levels. Other preventive health outcomes, such as blood pressure and cholesterol levels, were also unchanged, but residents of Oregon had lower rates of hypertension and hypercholesterolemia than the national average. The impact of gaining insurance on the care for patients with asthma or chronic obstructive pulmonary disease (COPD, see Chap. 10) has not yet been reported. Access to, and use of primary care, prescription drugs, and preventive services were improved among Medicaid beneficiaries. Medicaid also dramatically reduced Medical debt and the need to borrow money to pay for medical bills [30]. In the year following health insurance acquisition, hospital admissions increased by 30% in 1 year for those who gained insurance [31]. Similarly, those who acquired Medicaid insurance had a 40% relative increase in ED visits compared to controls [32]. While this suggests that acquiring health insurance provides financial stability and decreases financial barriers to healthcare for low-income individuals, it did not provide subgroup analyses of the impact of insurance acquisition for minority populations within the study.

Overall, findings from studies of prior state-level expansions suggest that individuals who gain Medicaid coverage have greater access to healthcare and preventive care, and discrete improvements in health outcomes while experiencing reduced financial strain. Despite increased access to health services in Massachusetts, health insurance expansion did not significantly increase intensive care use, suggesting that in the short term, there may be similarly no increase in critical care utilization after national healthcare expansion. It is reasonable to anticipate that the ACA's Medicaid expansion provision will begin to address some of the insurance-related disparities in healthcare in the US.

Insurance Expansion: Important But Not Sufficient

Medicaid expansion under the ACA represents an important step toward mitigating disparities related to health insurance. However, availability of insurance does not guarantee high-quality healthcare. Even when insurance is available, patients must enroll and overcome deficiencies in access to covered services, clinicians and institutions, and deficiencies in access to high-quality primary care and specialty services [33]. In this regard, Medicaid is often underfunded compared to private insurance, potentially impairing its ability to eliminate insurance-related disparities.

Even with Insurance, Black and Hispanic Patients Experience Disparities in Healthcare Access

Data prior to the ACA shows that health insurance can significantly reduce, but not eliminate, disparities in access to care, with NH black and Hispanic patients with insurance reporting smaller, but still significant, differences in access to a regular provider [9]. Access to high-quality care is also not likely to be solved with insurance expansion. Studies in disparities in outcomes for patients with in-hospital cardiac arrest show that a significant proportion of disparities in outcomes for NH blacks can be due to care in poorer performing hospitals, where all patients do worse [34].

There is also variation in quality in the types of hospitals that provide care to large percentages of Medicaid patients. Previous research has shown that hospitals that treat higher percentages of Medicaid patients are less likely to meet quality indicators for critical illnesses [21]. As Disproportionate Share Hospital payments are reduced, disparities in quality of care at hospitals caring for most Medicaid patients are likely to increase.

There is also regional variability in quality of care. A 2009 study showed significant regional variation in survival to hospital discharge for patients who had an out-of-hospital cardiac arrest. Whereas the survival to hospital discharge rate in Seattle was 39.9 %, those in Portland and Dallas were 22.5 % and 9.5 %, respectively [35]. While the cause of this disparity requires investigation, it is likely multifactorial and could include regional variation in access to preventive care, high-quality prehospital emergency services care, and inpatient hospital quality.

Deficiencies in Essential Health Benefits Package

The ACA includes an essential health benefits package, which establishes a comprehensive set of the minimum necessary services that a Medicaid expansion plan must provide (Table 14.3). The ACA mandates coverage in ten essential health benefits categories. Coverage is thus assured for most services commonly performed and billed by pulmonary and critical care providers. However, states ultimately have discretion to determine how many services within each of the ten categories their Medicaid plans will cover, which may lead to state-to-state variability in benefits. Furthermore, newly eligible groups may not receive benefits as comprehensive as traditional Medicaid, provided they cover at least one service within each of the ten categories [36].

Variability among individual states' interpretation and implementation of the essential health benefits when expanding Medicaid may impact patients with pulmonary disease, critical illness, or sleep disorders. The essential health benefits requirement for prescription drug coverage does not guarantee access to the range of *necessary* medications that could best meet a patient's needs, but instead stipulates that patients must have access to a specific *number* of medications. Lung transplant recipients, for example, typically require at least three immunosuppressant medications, which are in the same class and category. Under the current essential

Table 14.3 Services required for an insurance plan to be considered compliant with the essential health benefits package

The essential health benefits package	
Ambulatory patient services (e.g., initial and subsequent visits, procedures, pulmonary function studies)	Prescription drugs
Emergency services	Rehabilitative and habilitative services and devices (e.g., physical therapy)
Hospitalization (e.g., inpatient initial and subsequent visit, consultation, procedures, critical care, transplantation)	Laboratory services
Maternity and newborn care	Preventive and wellness services and chronic disease treatment (e.g., vaccination)
Mental health and substance use services, including behavioral health treatment	Pediatric services including oral and vision care

health benefits, health plans are only required to cover two drugs per class, potentially limiting access to these life-saving medications [37]. The current prescription drug rule could also impact providers' ability to treat drug-resistant tuberculosis. Combination therapies (e.g., fluticasone/salmeterol inhaler) are also not recognized under the current proposal, which may affect the health of patients with cystic fibrosis, bronchiectasis, asthma, and pulmonary hypertension [37, 38]. Tobacco cessation aides, which are more effective in combination [39], will also potentially be limited to one medication per class or category, limiting therapeutic options for this vulnerable population [37, 38].

Beyond the limitations of the prescription drug benefit, the essential health benefits also fail to adequately address other services essential to the care of patients with pulmonary, critical care, and sleep disorders. In particular, the essential health benefits does not describe whether patients will have access to durable medical equipment such as ventilators, nebulizers, and continuous positive pressure machines, leaving open the possibility that patients will have to pay for these life-saving devices out of pocket [37]. Lastly, diagnostic testing, evaluation and treatment of sleep disorders, and patient-physician counseling regarding end-of-life and palliative care are not included in minimum benefit standards under the current essential health benefits proposal, such as that provided to current Medicaid or Medicare beneficiaries [37].

Cost-Sharing: A Barrier to Access to Necessary Services

In addition to the significant variability in state's Medicaid benefit benchmark, the ACA allows states to set cost-sharing limits for certain services. By requiring individuals to share in the costs of accessing the healthcare system, cost-sharing is an effective means through which insurance plans can reduce unnecessary healthcare utilization. Several studies have shown that for the poorest and sickest patients,

cost-sharing plans worsen outcomes relative to free plans, because cost-sharing reduces the likelihood that individuals will seek necessary care. Among the poor, patients with cost-sharing plans are also less likely to fill prescriptions for essential medications, and as a result experience increases in emergency department visits, and a greater likelihood of adverse health events [40].

States can set their own cost-sharing limits for nonemergency use of the ED for individuals with incomes greater than 150 % of the FPL. In many areas of the country, EDs are the only healthcare facilities continuously available for the treatment of urgent respiratory illness such as asthma [41]. Cost-sharing in this context may be a significant deterrent to seeking timely care and could lead to worse outcomes. Patients who gain Medicaid insurance will also be required to share in the costs of preventive services, whereas individuals that are newly insured under a private-market insurance plan can receive preventive services and immunizations recommended by the US Preventative Task Force without cost-sharing [38, 41]. Cost-sharing is also proposed for tobacco cessation counseling and medications for all nonpregnant Medicaid recipients. Together, these cost-sharing policies have the potential to adversely impact the health of Medicaid beneficiaries [38].

Medicaid and Access to Specialty Care

Medicaid patients with pulmonary or sleep disorders may experience disparities that result from providers and groups choosing not to accept Medicaid insurance in their practices [42]. Medicaid typically reimburses physicians at a lower rate than Medicare or private insurance; yet Medicaid patients often present with equally complicated medical illness in the context of social situations that complicate medical treatment. Recognizing this financial disincentive for providers to accept new Medicaid patients, the ACA requires states to pay physicians Medicaid fees that are at least equal to Medicare's for inpatient and outpatient eval uation and management services, including E/M codes (99201 through 99449). This group of E&M codes includes many of the services commonly performed and billed by pulmonary and critical care providers. However, there is no similar parity in physician fees for other subspecialty services, including but not limited to procedures or interpretation of pulmonary function tests and sleep studies. As such, some of the financial disincentives for pulmonary, sleep, and critical care providers to deliver care for Medicaid patients will persist. Even when providers do accept Medicaid insurance, access and outcomes disparities will remain. At least one study showed that children with Medicaid faced significant delays in accessing specialty care, even when specialists accepted Medicaid, compared to those with private insurance [43]. For patients with cystic fibrosis, Medicaid insurance was associated with a 1.56 odds of *not* being listed for lung transplant, independent of other socioeconomic factors [44]. Similarly, while outcomes for those with Medicaid are generally better than for the uninsured, Medicaid beneficiaries continue to experience delays in diagnoses (lung cancer [1]) and increased mortality (cancer [1], critical care [27]) when compared to those with private health insurance.

Faced with decreasing reimbursements, specialty service providers will need to adopt innovative and creative approaches to sustain economic viability and ensure high-quality care. Potential options to support Medicaid expansion while mitigating expenses include distributing Medicaid patients proportionately across providers in the area, expanding the role for mid-level providers, and group-clinic management for patients with chronic diseases.

Medicaid's Reach Will Not Be Universal Under the ACA

Even if Medicaid expansion were implemented in all states, important segments of the population would remain marginalized under the current program. Undocumented immigrants, and lawfully present immigrants who have been in the US for fewer than 5 years, remain ineligible for Medicaid. Undocumented migrants make up approximately 25 % of the uninsured population (see Chap. 5). Access to coverage for women's health established by the ACA, particularly contraceptives, is mired in complex legal challenges [20]. Such disparities in access to and delivery of healthcare represent complex policy issues that require a more comprehensive legislative response. As Medicaid expands, and states become more responsible for bearing the costs of expansion, alternative safety-net resources for those in coverage gaps may be further limited.

In a positive step toward universal coverage, the Supreme Court's landmark case on marriage equality, *Obergefell v. Hodge*, held that the Fourteenth Amendment requires a State to license a marriage between two people of the same sex and to recognize a marriage between two people of the same sex when their marriage was lawfully licensed and performed out-of-State [45]. This important victory in the gay rights movement opens access to both state and federal benefits, and protections for same-sex couples that marry (see Chap. 7). In healthcare, this includes equal status as parents, recognition for spousal surrogate decision-making or healthcare proxy, and access to spousal employer-sponsored health insurance. A study showed that implementation of New York's Marriage Equality act was associated with increases in employer-sponsored health insurance for both men and women, and a reduction in Medicaid coverage [46], suggesting that same-sex marriage equality may increase private health insurance for US patients.

Supreme Court Challenge: *King v. Burwell*

In 2015, the ACA survived what may be the last significant judicial challenge to the law: *King v. Burwell*. Through the ACA, low- and moderate-income individuals and families with incomes of 138–400 % of the FPL are eligible for insurance premium subsidies when purchasing policies on the health insurance marketplace exchanges. In *King v. Burwell*, the plaintiffs challenged whether people who purchased health insurance in states that chose to use the federal insurance marketplace healthcare.gov, rather than set up a state-run marketplace, were eligible to receive insurance

premium subsidies under the ACA. At the time of the ruling, 34 states use the federal exchange for their marketplace, and as a result nearly 7.5 million people could have lost their health insurance if the court had ruled in favor of the plaintiffs [1, 2]. However in *King v. Burwell* the Court ruled 6–3 in supporting the legality of subsidies regardless of type of marketplace states use, thereby ensuring not only continued health insurance coverage for our patients in states using the federal marketplace exchange, but also that the ACA is likely here to stay [47, 48].

Impact of the ACA on Health Equality

Results from the 2014 National Health Interview Survey were recently released, and show that among Hispanics younger than 65 years, the rate of uninsured subjects decreased from 30.3 % in 2013 to 25.2 % in 2014. Among African Americans, the rate of uninsured dropped from 18.9 % in 2013 to 13.5 % in 2014. Nearly 1.7 million African Americans have gained insurance through the ACA, and roughly 8 million African Americans with pre-existing medical conditions have gained coverage [49]. While these represent significant gains in coverage, they are still well behind the rates of coverage for NH whites, whose rate of noninsurance is 9.8 % [50].

Healthcare Access Disparities: Room for Improvement

Although those who have gained health insurance are satisfied with their coverage, continued efforts to improve the ACA are needed. Issues such as the "family glitch," where affordability of plans for low- and moderate-income families is based on the cost for individual-only coverage, without considering the often substantially higher cost of family plans [51], need to be addressed. Increasingly, private health insurance plans are also relying on out-of-pocket spending, with high deductibles, copayments, and co-insurance putting those with health insurance and moderate incomes at risk of forgoing care because of cost [52]. From a provider perspective, reduced reimbursement for Medicaid patients will likely continue to be a hurdle to access to care, particularly subspecialty care. Although the ACA provided a 2-year increase in reimbursements for Medicaid patients to primary care physicians (likely improving access) [53], most states returned to pre-ACA reimbursement levels in 2015 [54].

Even though we have largely addressed the impact of health insurance expansion on healthcare disparities through the ACA, key health policy efforts are needed to address disparities in Medicare outcomes for minority patients. African-American Medicare beneficiaries have higher poverty rates than older white Americans, with 65 % of African-American Medicare recipients versus 41 % of white Medicare recipients living below the poverty line [55]. From a health outcomes perspective, 43 % of African-American Medicare recipients report living in poor health versus

26 % of whites. As an important first step in addressing these disparities, the Centers for Medicare and Medicaid Services (CMS) announced an "Equity Plan" in September 2015 to improve quality of care for minority recipients [56].

Conclusions

As of the first quarter of 2015, the average rate of noninsurance has dropped from about 17.1 to 10.1 % [57]. African Americans and Hispanics have benefited significantly, with approximate 5.4 % and 5.1 % decreases in rates of noninsurance as a result of the ACA [49]. Those who have gained insurance report a decrease in health-related financial concerns [58] and high satisfaction with their coverage [59]. Despite these gains, public opinion of the ACA remains divided along party lines. In a recent poll, 62 % of Americans agree with the recent *King v. Burwell* decision, but only 29 % of Republicans supported the decision. Overall, only 43 % of Americans have a favorable opinion of the ACA, and 40 % polled report an unfavorable opinion [60].

Medicaid expansion under the ACA is an important step forward in addressing gaps in safety net coverage in the US for low-income individuals, thus providing an important remedy for health disparities in the US. Evidence from prior insurance expansions, as well as early reports from the ACA insurance expansion, suggests that increasing access to health insurance will improve self-reported health, increase utilization of preventive and primary care services, and decrease financial strain due to medical illness. Importantly, increasing access to health insurance may help mitigate disparities in healthcare access for African-American and Hispanic patients. While Medicaid expansion continues to gain traction in the states, lack of Medicaid expansion remains perhaps the most important barrier to improving rates of health insurance for US minorities. Without national adoption of Medicaid expansion, and wide variation in income eligibility thresholds across states electing to expand, coverage gaps will exist for millions of Americans, potentially exacerbating health disparities for minorities and the poor in these areas.

Although expanding health insurance should improve access to healthcare for minority patients with respiratory diseases, sleep disorders, and critical illness, health insurance acquisition alone is unlikely to eliminate all disparities in access to high-quality care. Among contributors to health, access to healthcare is essential but plays only a partial role. Until society definitively addresses disparities in social and economic domains that are key to health, such as behaviors, education, income, and environment, health disparities will persist (see Chap. 15). Nonetheless, medical practitioners, researchers, and their professional societies should constructively support health insurance expansion under the ACA, advocating for improving existing policies to expand patient access to pulmonary, critical care, and sleep medicine services, and reducing barriers for providers, with the goal of facilitating access to outpatient and acute care services for all of our patients and improving health outcomes at both the individual and societal level.

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Chapter 15
A Roadmap for Achieving Respiratory Health Equality

Juan Carlos Celedón and Jonathan Samet

Introduction

Because exposure to major risk factors for respiratory diseases differs across the diverse population of the United States, respiratory health disparities are widely documented, and challenge prevention and the practice of pulmonary, critical care, and sleep medicine (see Chap. 1). The Health Equality Sub-Committee of the American Thoracic Society (ATS) recently defined respiratory health disparities as significant differences in respiratory health that are closely linked to racial ancestry, social, economic, and/or environmental differences [1].

Achieving respiratory health equality, the highest level of respiratory health for all people, requires eliminating respiratory health disparities [1]. Thus, identifying and mitigating preventable causes of health disparities is essential to attaining respiratory health equality.

J.C. Celedón, MD, DrPH (✉)
Division of Pediatric Pulmonary Medicine, Allergy and Immunology,
Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine,
4401 Penn Avenue, Pittsburgh, PA 15224, USA
e-mail: juan.celedon@chp.edu

J. Samet, MD, MS
Department of Preventive Medicine, Keck School of Medicine of the University
of Southern California, 2001 North Soto Street Suite 330A, Los Angeles,
CA 90089-9239, USA
e-mail: jsamet@med.usc.edu

J.C. Celedón (ed.), *Achieving Respiratory Health Equality*,
Respiratory Medicine, DOI 10.1007/978-3-319-43447-6_15

A Causal Framework

An extensive body of literature demonstrates substantial disparities in socioeconomic determinants of health (e.g., education), environmental risk factors (e.g., cigarette smoking), healthcare access, and health outcomes across demographic groups in the USA [2]. Here we draw on that broad literature, extending the general concepts to the more circumscribed domain of respiratory health. Figure 15.1 illustrates the determinants of onset and severity of respiratory diseases. Overall, environmental exposures drive the burden of respiratory diseases, and thus patterns of exposures to key environmental risk factors largely account for respiratory health disparities. In this context, "upstream" factors that are tied to demographic factors drive patterns of exposure. In this framework, the higher level of exposures received by some groups increases risk of disease onset and may also adversely affect the natural history of the disease. Moreover, the same correlates of being within a particular subgroup that lead to increased exposure may also result in less than optimal access to and quality of healthcare for those developing disease.

"Upstream" factors are major societal determinants of an individual's exposure to environmental risk factors. For example, economically disadvantaged individuals have limited housing options, and those living below the poverty level are more likely to live within 150 m of a major road and thus be highly exposed to traffic-related air pollution [2]. The targeted marketing campaigns of the tobacco industry towards particular minority groups are a further example. The tobacco industry directed highly focused marketing of menthol cigarettes at African-Americans,

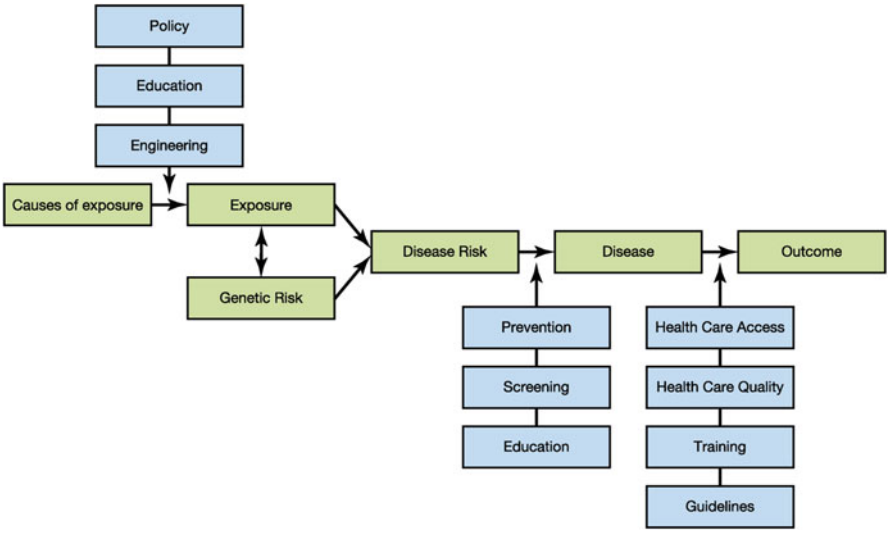

Fig. 15.1 Causal framework for respiratory diseases. Group differences at any stage in this pathway can lead to respiratory health disparities. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Cite: Celedón JC, Roman J, Schraufnagel DE, Thomas A, Samet J. Ann Am Thorac Soc. 2014 May;11(4):473–9

achieving well-documented success such that the majority of African-American cigarette smokers purchase menthol cigarettes [1, 3, 4].

Some genetically determined disorders that affect respiratory health are more prevalent in certain racial/ethnic groups. Genetic variants may directly cause an illness involving the respiratory system (e.g., sickle cell disease). Alternatively, genetic mutations may confer susceptibility to an environmental exposure (e.g., cigarette smoking in people with severe alpha 1-antitrypsin deficiency [AAT]). However, monogenic diseases are rare, none are sufficiently common and so tightly linked to a particular group as to make the genome a major contributor to health disparities, and an individual's genetic make-up cannot be modified. Thus, most respiratory health disparities are caused by differential patterns of environmental exposures (e.g., tobacco use) and behavioral (e.g., a sedentary lifestyle) risk factors in certain demographic groups (see Table 1.1).

Prevention may eliminate or at least reduce the occurrence of diseases due to infectious or environmental (e.g., through antismoking campaigns) risk factors. For example, over the twentieth century in the United States, tuberculosis moved from being the leading cause of death to an uncommon disease, particularly among those born in this country. Otherwise, sufficient levels of exposure will lead to pre- or subclinical respiratory disease in susceptible individuals. In that case, early detection may still allow for effective treatment (e.g., for phase I non-small cell lung cancer) [5] or enhance avoidance of detrimental exposures (e.g., smoking in children with severe AAT deficiency [6]).

Unfortunately, low education and low income can be barriers to obtaining preventive services and limit access to high-quality screening programs. Moreover, low socioeconomic status (SES) is associated with tobacco smoking, employment in hazardous occupations, and higher exposure to air pollution, but also with lower likelihood of adopting healthy behaviors [2].

Because lack of access to (or poor quality of) healthcare negatively affects disease outcomes, universal health insurance coverage could markedly reduce respiratory health disparities, particularly if preventive and screening services were covered [7–10]. However, health insurance does not address other challenges to achieving optimal health outcomes, including low health literacy, cultural beliefs that may be barriers, lack of transportation to healthcare facilities, language barriers that limit communication with providers, lack of cultural competency in healthcare providers, and a lack of clinical guidelines targeted towards underserved populations.

In 2013, ~34 % of US residents (123 million people) self-identified as underrepresented minorities (URMs): Hispanics (17 %), non-Hispanic Blacks or African-Americans (13.2 %), American Indians or Alaskan Natives (1.2 %), Native Hawaiians or Pacific Islanders (0.2 %), and two or more races (2.4 %) [11]. URM physicians, who are more likely to know and address cultural differences, often care for minorities and the poor. In a recent study of 7070 adult patients, nonwhite physicians cared for 53.5 % of minorities and 70.4 % of non-English speakers, yet there is a profound shortage of minority physicians [12]. Although the percentage of URMs in the US population increased by ~27 % between 2000 and 2010 (from ~76.7 million to ~97.2 million people) [13], the percentage of URMs among faculty in US

medical schools increased by only 1.2 % (from 6.8 to 8 %) during the same decade [14]. Moreover, URMs comprised only 8.9 % of the entire physician workforce in the USA in 2013 [15].

A Roadmap to Respiratory Health Equality

A 2011 report showed that 93 % of the health disparities targeted by the Healthy People 2010 program had either not improved or worsened over the period from 2000 to 2010 [16]. This persistent failure to reduce disparities is unacceptable and costly in many ways, reducing quality of life and productivity, and leading to increased healthcare costs. According to one estimate, eliminating racial/ethnic disparities in health could have reduced total medical costs by over $1.2 trillion dollars over the period from 2003 to 2006 [17]. Respiratory health disparities are particularly amenable to intervention, given that a number of powerfully contributing causal factors have been identified: tobacco smoking, occupational agents, and indoor and outdoor air pollution. Thus, there is a powerful rationale for taking steps to address these causal factors and their upstream or "root" causes. The main benefits can be predicted with confidence—less lung cancer, chronic obstructive pulmonary disease (COPD) and asthma, childhood lower respiratory infections, tuberculosis, and sleep-disordered breathing. The disease burden could thus be substantially reduced, with attendant cost savings at the local, state, and federal levels.

As outlined by the ATS, eliminating respiratory health disparities is a challenging but plausible goal, which can be achieved through multidisciplinary, society-wide actions, including advocacy to influence governmental policies and regulations directed at environmental agents. Strategies to influence the diverse upstream factors will need to be broadly based, as demonstrated by the approaches taken to end the tobacco epidemic: regulation, taxation, education, cessation, and litigation. Powerful advocacy will be needed to sway governmental entities. Initiatives also need to address environmental and behavioral risk factors; to make preventive and therapeutic healthcare services accessible to all, while also increasing workforce diversity; to support state-of-the-art research that informs health policy; and to improve prevention and management of respiratory diseases for all demographic groups in our society (Fig. 15.2).

Attaining "*environmental justice*"*:* Because modifiable environmental and behavioral exposures cause most respiratory health disparities, their elimination is imperative in the pursuit of health equality. This was recognized in President Clinton's Executive Order on Environmental Justice, signed on February 11, 1994. The landmark Order required that all federal agencies "make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations"[18]. Attainment of "environmental justice" thus requires public health policies and regulatory measures, as well as effective education of individuals afflicted with respiratory diseases and the general public.

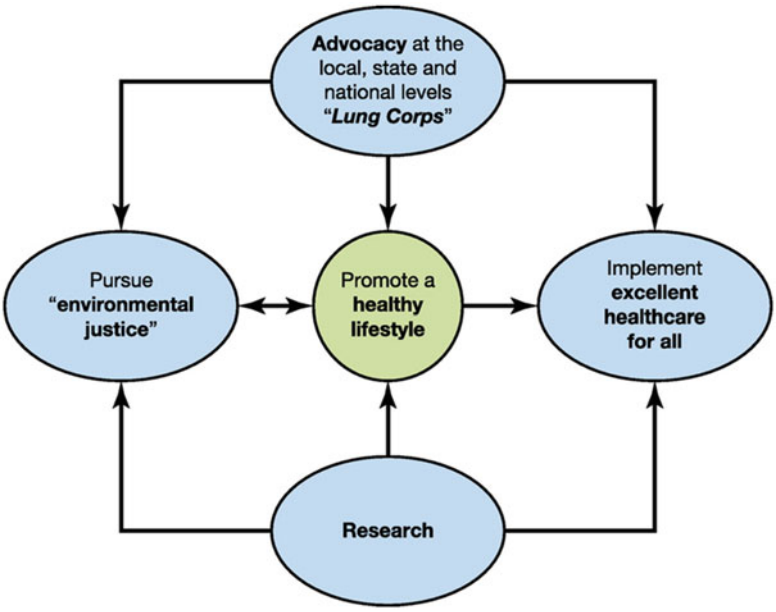

Fig. 15.2 Overview of an approach to achieving respiratory health equality by eliminating health disparities (adapted from Celedón JC et al. Ann Am Thorac Soc 2014;11(4):473–9). Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Cite: Celedón JC, Roman J, Schraufnagel DE, Thomas A, Samet J. Ann Am Thorac Soc. 2014 May;11(4):473–9

Among environmental and behavioral risk factors for disparities in respiratory health (see Chap. 1), four deserve emphasis due to their strong impact on respiratory health in minorities: tobacco use, air pollution, occupational hazards, and obesity.

Tobacco use: Over the last half century, tobacco control measures led to a 60 % reduction in the prevalence of current smoking among adults in the USA (from 42 % in 1965 to 16.8 % in 2014) [3, 19]. Yet tobacco use persists as the largest preventable cause of premature death in the USA, with well-documented adverse causal effects on the respiratory health of minorities. Moreover, the tobacco and vaping industries are constantly manufacturing and marketing new products to promote and maintain nicotine addiction (e.g., menthol-flavored cigarettes, flavored electronic cigarettes), and hookah use is rising. Thus, vigorous and comprehensive tobacco control measures, including media campaigns, smoke-free policies, tobacco excise taxes, smoking cessation programs, and restricted sales of tobacco products, are needed to accomplish a smoke-free society [3]. Along these lines, the Food and Drug Administration (FDA) now regulates almost all tobacco products, including forbidding sales of tobacco products to minors or through vending machines, registering manufacturers and ingredients, and premarket review of products claiming a "modified risk or harm." However, more could be done to address issues relevant to

minorities, including prohibiting the sale of menthol-flavored tobacco products or internet sales of tobacco products. A ban on menthol-flavored products and flavored e-cigarettes may help prevent tobacco use in minorities. On the other hand, professional societies and community organizations must be vigilant about detrimental relaxation of tobacco control, such as a proposal to exempt premium cigars from FDA's proposed deeming regulations to take authority over a number of products beyond cigarettes.

Air pollution: Professional and governmental organizations (notably, the Environmental Protection Agency [EPA]) have strongly advocated for "clean air," achieving implementation of stringent federal standards for the major or "criteria" pollutants, such as ozone and particulate matter. The ATS has had a strong role in achieving cleaner air through the research of its members, their involvement in key EPA committees, particularly the Clean Air Scientific Advisory Committee (CASAC), and ATS testimony and organizational positions. The improvements in air quality since the enactment of the Clean Air Act have had major and well-documented benefits for respiratory health [20]. Such gains benefit everybody's respiratory health, including underserved and minority populations. As new findings emerge, there is an ongoing need to protect the progress made and to advocate for the best possible evidence-based standards for "clean air."

Traffic-related air pollution (TRAP) disproportionately affects minorities and the poor because of residential patterns [2]. TRAP can be reduced by policies that promote reduced use of motor vehicles and enhance use of other means of transportation, while fostering use of low-emission vehicles [21, 22]. Improving indoor environments could also reduce healthcare costs, resulting in health improvement in minorities [23].

Occupational hazards: Minorities and those with low education are more likely to be employed in occupations that expose them to a hazardous environment [24]. Since such occupations cause or worsen multiple respiratory diseases (including but not limited to occupational asthma, silicosis, asbestosis, and berylliosis), occupational exposures are an important determinant of respiratory health disparities. The Occupational and Safety Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), in conjunction with and informed by professional societies and labor organizations, aim to ensure safe and healthy working conditions for all, by enforcing standards and providing workplace safety training. Occupational hazards can be addressed by replacing use of a toxic agent, reducing exposure through engineering or protective equipment, or removing affected individuals from a particular occupation within the workplace.

Obesity is common among US minorities [25]. Obesity contributes to respiratory health disparities, as it is associated with asthma and obstructive sleep apnea in minorities. Thus, professional societies in respiratory medicine ought to collaborate with governmental organizations and other medical societies (e.g., in pediatrics, endocrinology, and cardiology), to advocate for educational campaigns and policies to prevent obesity in childhood (e.g., through healthier school meals and increased physical activity).

Ensuring Universal Healthcare and Increasing Workforce Diversity

Universal healthcare: The Affordable Care Act (ACA) of 2010 has decreased the proportion of Americans without health insurance. Although too early to assess the ACA's long-term impact, within-state assessments suggest that having insurance increases use of preventive services and improves outcomes, particularly in minorities and the poor [8–10]. However, 20 states (some with sizable minority populations) have yet to enact the Medicaid expansion provision of the ACA [26], and thus healthcare providers and professional organizations must advocate for such expansion.

While not a complete solution to achieving needed coverage, the ACA has funded initiatives not usually covered by traditional health insurance, including community health centers, preventive services (e.g., screening for tobacco use and lung cancer), training of minority healthcare providers, and collecting relevant demographic data (e.g., race, ethnicity, and language proficiency) across federal health programs. Of note, however, some minority groups (e.g., migrant workers) are ineligible for the ACA due to non-citizenship status [27], and alternative sources of funding are needed to care for these vulnerable populations.

Achieving high-quality healthcare in underserved populations entails not only broadening health insurance coverage but also addressing other barriers to care, including low health literacy, limited language skills, cultural beliefs, lack of transportation, missing clinical guidelines, and lack of cultural competency in healthcare providers. Although addressing low health literacy, cultural beliefs, and adherence with therapy is needed to improve disparities in healthcare [1, 24, 28], robust evidence to support interventions to address health literacy or adherence in minorities, or to improve the cultural competency of their providers, is lacking.

Increasing workforce diversity: Development of a diverse workforce in pulmonary, critical care, and sleep medicine requires concerted efforts, by professional and governmental organizations, to create a pipeline of minorities committed to a career in medicine or biomedical research at several stages (high school, college, and medical school). Such a pipeline would create a pool of healthcare providers and investigators who can then be attracted to careers in respiratory health during their medical residency or doctoral studies.

The US National Institutes of Health (NIH) has allocated substantial funds to promote and enhance the career development of URMs, starting as early as high school and extending to mid-career stages for physicians or scientists (e.g., the NIH Building Infrastructure Leading to Diversity (BUILD) Initiative). However, such efforts need to be accompanied by vigorous approaches to recruit, promote, and retain minority faculty in US medical schools, including mentoring programs and placing more value on minority-led research in racial or ethnic minorities, two areas currently neglected at some institutions [24].

Research: A comprehensive agenda for research on respiratory health disparities is needed, as some diseases that predominantly affect minorities have no known cure. Moreover, ethnic-specific effects of allelic variants or environmental exposures,

as well as ethnic-specific responses or side effects from certain medications (e.g., albuterol), can be missed if minorities are not included in observational or interventional studies of respiratory diseases.

Two major barriers to research studies of health disparities are lack of funding and noninclusion of minorities in many studies [11]. First, some diseases that affect mostly minority groups (e.g., sickle cell disease) have historically received much less funding than diseases affecting nonminorities (e.g., cystic fibrosis) [29]. Although federal funding for such diseases has recently increased, there is still a considerable gap in funding by private nonprofit foundations. Second, a recent report showed that less than 5 % of NIH-funded publications reported inclusion of minorities [11]. Solving the two problems outlined above is key to achieving health equality. This can be done by implementation of short- to long-term approaches by governmental, professional, and private organizations. Such approaches include incentives to conduct minority research, ensuring fair review of grant applications focusing on minorities, fostering the career development of minority scientists, and emphasizing the value on research in minorities.

A broad research agenda on respiratory health disparities should address personalized medicine (e.g., pharmacogenetics) [30], key environmental and behavioral risk factors (e.g., tobacco use, air pollution, occupation, obesity, low health literacy, and nonadherence with treatment), migrant health, development and updating of clinical guidelines, fostering and supporting community-based participatory research, and effective strategies to nurture the careers of investigators focused on disparities.

Advocacy: Professional and community organizations must advocate for "environmental justice," universal healthcare, research, and sound public health policies. The ATS has recently proposed the creation and encouragement of a "lung corps" of advocates for respiratory health, including patients, community members, healthcare providers, and public health practitioners [31].

Summary

Achieving respiratory health equality requires elimination of environmental risk factors, ensuring access to high-quality healthcare for all, and conducting cutting-edge research on minority populations. Such an ambitious agenda can only be fulfilled with the participation of key stakeholders, including the general public, patients afflicted with respiratory illnesses, governmental agencies (at the local, state, and federal levels), private foundations, and professional societies. While facing this formidable challenge, we would do well by remembering the words of President Franklin D. Roosevelt: "There are many ways to move forward, but only one way of standing still." Thus, we must all work towards respiratory health equality, fueled by the firm conviction of those who pursue a worthy goal.

Acknowledgments *Funding:* Dr. Celedón's contribution was funded by grants HL079966, HL117191, and HL119952 from the US National Institutes of Health, and by The Heinz Endowments.

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