Health Disparities in Asthma

Minority groups represent an important and growing segment of the population of the United States, which is projected to comprise 47% non-Hispanic whites, 29% Hispanics, 13% non-Hispanic blacks, and 9% Asians by 2050 (1).

Although asthma affects all ethnic groups, the burden from this disease is disproportionately shared by certain minority groups and the economically disadvantaged. The prevalence of childhood asthma among Puerto Ricans (19.2%) or non-Hispanic blacks (12.7%) is higher than among non-Hispanic whites (8%) or Mexican Americans (6.4%) (2). Ethnic disparities in asthma morbidity and mortality are even more pronounced (3). Asthma mortality rates in children and adults are nearly eightfold and threefold higher, respectively, in non-Hispanic blacks than in non-Hispanic whites.

Ethnic and socioeconomic health disparities in asthma are the result of multiple factors operating at the individual and community levels (Figure 1). Poverty is both strongly correlated with ethnicity and a risk factor for asthma morbidity in the United States (4). Ethnicity is linked with racial ancestry and may affect asthma independently of poverty (e.g., through genetic variation); conversely, poverty can affect asthma independently of ethnicity (e.g., through access to healthcare). Very often, however, they have synergistic detrimental effects on asthma, influencing not only quality of care but also exposure to environmental and lifestyle (EL) risk factors.

Known or potential EL risk factors for disparities in asthma or asthma morbidity include cigarette smoking and environmental tobacco smoke (ETS), prematurity or low birth weight, allergen exposure, indoor and outdoor air pollution, diet, obesity, vitamin D insufficiency, viral respiratory infections (e.g., due to crowding), psychosocial stress, and poor adherence with prescribed treatment. We briefly discuss some of these factors below.

In the United States, cigarette smoking, ETS, and exposure to other indoor and outdoor pollutants vary widely by socioeconomic status (SES) and ethnicity. Current smoking in adults ranges from ~7% in subjects with a graduate degree to ~46% in those with a GED diploma (5), and from ~30% in Puerto Ricans to ~22% in Mexican Americans (6). Residents of economically deprived or inner-city communities are often exposed to allergens (e.g., cockroach) (7) and outdoor pollutants (e.g.., diesel exhaust particles) associated with asthma morbidity (8).

Vitamin D insufficiency (a serum 25[OH]D <30 ng/ml) and asthma share common risk factors, including inner-city residence and African American ethnicity. Results from experimental and observational studies suggest that reduced maternal intake of vitamin D during pregnancy increases the risk of childhood asthma or wheezing, and that vitamin D insufficiency increases asthma morbidity in children and adults (9).

Inner-city residents and minority groups are often exposed to increased violence, and are thus more likely to experience psychosocial stress, which has been shown to increase asthma morbidity in adults and their children (10, 11). Depression and anxiety are more common in lower SES groups, and can lead to altered perception and report of symptoms. In turn, psychosocial stress could lead to decreased adherence with prescribed controller medications, independently or coupled with other factors (family or community structure and support, cultural beliefs, inadequate communication from or with healthcare providers, and reduced health literacy).

Results from recent studies suggest that racial ancestry influences ethnic disparities in asthma. African Americans and Puerto Ricans share both a significant proportion of African ancestry and a high burden from lung diseases such as asthma and chronic obstructive pulmonary disease (12). Whereas African ancestry has been associated with reduced FEV_1 and FVC in African American adults without asthma (13) and Puerto Rican children (with and without asthma) (14), Native American ancestry has been associated with higher FEV_1 and reduced risk of chronic obstructive pulmonary disease in adults from New Mexico (15). These findings are intriguing and suggest that genetic or early-life EL factors correlated with racial ancestry partly explain asthma disparities. For example, discrepancies in asthma morbidity between Puerto Ricans and Mexican Americans (the "Hispanic paradox") may be partly due to differences in African versus Native American ancestry. Results from recent genome-wide association studies suggest that certain asthma-susceptibility variants will be relevant to all ethnic groups, whereas others may have ethnic-specific effects (16).

What can we do about asthma disparities? The most important step would be to implement and enforce policies increasing access to healthcare for children and adults with asthma, regardless of their ethnicity or SES. However, increasing healthcare access is unlikely to suffice; additional steps must be taken to improve understanding of disease processes and therapeutic goals in patients with low literacy (17), ensure appropriate assessment of disease severity by physicians and patients (18), and increase prescription of and adherence with controller medications. For instance, parents of black and Hispanic children have lower expectations about asthma control and worse adherence with controller medications (partly due to concerns about medication dependency or side effects) than parents of non-Hispanic white children (19). In addition to trying to improve healthcare for all, new and ongoing policies should aim at the community level, such as improving asthma education and housing conditions, and reducing detrimental EL exposures (cigarette smoking, ETS, air pollution, allergens, inactivity, and unhealthy dietary patterns).

Observational and interventional research studies should try to identify and expand our understanding of risk factors for asthma disparities. Dissecting the genetic and EL factors underlying recently reported associations between racial ancestry and lung function or asthma is important and could help identify subpopulations at highest risk, reveal gene-by-gene and gene-by-environment interactions, and ultimately help develop new means to disease prevention, diagnosis, and treatment. In this context, it is important to include well-characterized minority populations in studies of genetics and epigenetics. Such studies should categorize subjects into appropriate subgroups (e.g., Puerto Rican, Filipino) instead of broad clusters (such as Hispanic or Asian) and objectively assess ancestry (e.g., by using genetic markers). Similarly, future studies should aim to refine characterization of SES and EL exposures at the individual and community levels, while also establishing long-term relationships with the communities under study.

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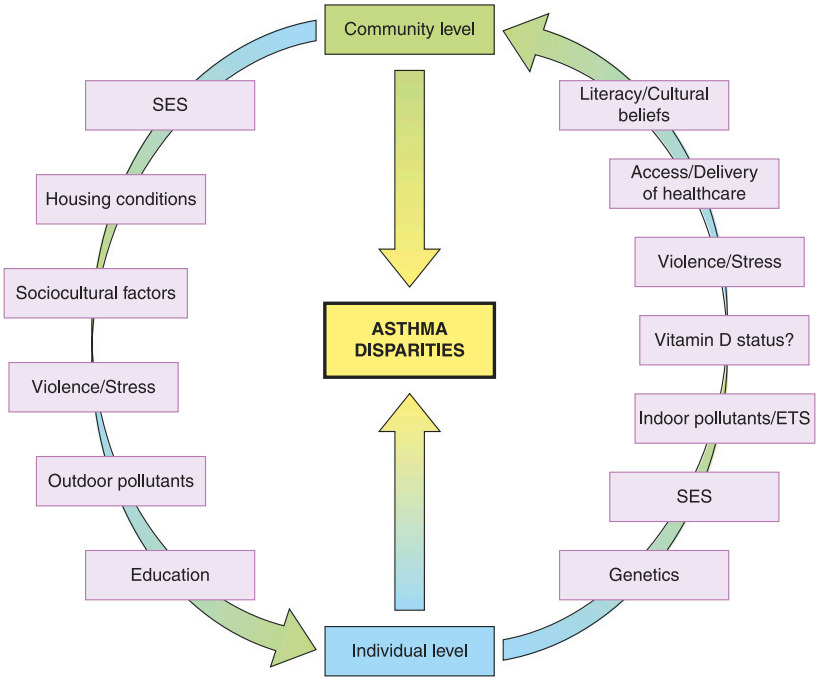

Figure 1. Known or potential determinants of asthma disparities. ETS = environmental tobacco smoke; SES = socioeconomic status.

Current financial realities dictate that cost-effective interventions to reduce asthma disparities should have the highest priority. Given available evidence, minorities and inner-city residents (who are at highest risk for vitamin D insufficiency) should be included in future clinical trials of vitamin D supplementation and asthma. Because of the multifactorial nature of such disparities, certain single-factor interventions (e.g., reduction of a single allergen) are likely to have a minor impact while generating major expenses. Multifaceted individual-, family-, or community-based interventions aimed at multiple risk factors (e.g., reducing ETS, increasing exercise and asthma education, and improving dietary practices) should be rigorously examined, as they may be more successful and cost-effective (20). Interventions aimed at physicians or healthcare organizations treating minority or economically disadvantaged groups (e.g. increasing cultural competency, changing prescription patterns, and improving communication) may have significant impact on asthma disparities (21, 22), but only limited data are available and thus further research is needed.

This is both an exciting and a challenging time for those interested in reducing unacceptable disparities in asthma. Concerned healthcare professionals and their professional societies must vigorously advocate for universal access to high-quality care for patients with asthma, as this would have a major impact on reducing existing disparities in disease morbidity. In parallel with these efforts, pragmatic and multifaceted measures to improve asthma care should be coupled with research studies targeting not only identification of risk factors but also the development of cost-effective interventions at the individual and community levels.

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More Muscle in Asthma, but Where Did It Come from?

The airway wall of individuals with asthma displays prominent structural changes including the following: areas of epithelial loss, the presence of intraepithelial eosinophils, goblet cell metaplasia, subepithelial reticular basement membrane thickening, increased vascularity, and inflammatory cell infiltration of the subepithelial connective tissue. Thickened layers of airway smooth muscle (ASM) lie closer to the epithelium (1, 2). ASM hyperplasia is more prominent in severe asthma. Hypertrophy of ASM in proximal airways has been reported in biopsy (1) and in *post mortem* studies (3), but is not always observed (4). These structural changes continue to intrigue those active in asthma research, because they are linked to airway hyperresponsiveness, fixed airway obstruction, and loss of bronchodilator response to deep inspiration. However, the nature and extent of these functional impacts on asthma severity is still debated, as evidence is limited to inferences from correlative studies.

The article by James and colleagues in this issue of the *Journal* (pp. 1058–1064) comprises the largest systematic structural investigation of *post mortem* airways in asthma (5). The consolidation of data from multiple centers required careful analysis of potential systematic differences, as fixation, sampling, and specimen availability differed between some of the collaborating centers. The investigators used a stereological approach to focus on the volume occupied by ASM and the composition of this volume: the numerical density of ASM, the size of ASM, and the volume of extracellular matrix (ECM) within the ASM layer. Tissue was stained with Masson's trichrome on thin 0.5-μm sections to estimate areas occupied by ECM or ASM cells, and hematoxylin was used for thick 30-μm sections analyzed using an optical disector to estimate the numerical density of ASM cells. Although the presence of a thickened ASM layer in individuals with asthma is uncontroversial, the reasons for it are still contested, with hyperplasia, hypertrophy, and ECM expansion all thought to contribute. James and coworkers report that ASM hypertrophy in nonfatal and fatal asthma is evident in more proximal airways, whereas hyperplasia is detected in all airways of fatal asthma, but is limited to proximal airways of nonfatal asthma. The hypertrophic response is modest by comparison with the increase in ASM number. The volume of ECM in fatal asthma is greater than either the nonfatal asthma or the control groups, but the fractional area occupied by ECM *declined* significantly in fatal asthma. This decline is interesting in light of recent studies showing that ECM can be remodeled by ASM to markedly reduced volumes and much tighter fibril packing by processes that are not inhibited by β_2-adrenoceptor agonists agents or glucocorticoids (6, 7). Whether the ECM density (i.e., dehydrated weight/volume) is increased in fatal asthma remains to be established. Collectively, the findings of James and colleagues suggest that hyperplasia, rather than either hypertrophy or ECM expansion, is the dominant reason for the increase in ASM volume.

The principal conclusion of James and coworkers is that there is little effect of asthma duration on the extent of smooth muscle layer thickening (5). Analysis of asthma severity did not reveal further significant associations beyond those identified by comparison of fatal and nonfatal cases. The apparent lack of effect of asthma duration on the extent of airway remodeling is consistent with a number of studies suggesting that remodeling is an early event in the natural history of asthma. ASM hyperplasia has been reported in biopsies of children with asthma of short duration (8), as has reticular basement membrane thickening (9). When is the formative period for the ASM hyperplasia, and remodeling more generally? How dynamic are these processes throughout the course of asthma in different patient populations? Is severe pediatric asthma characterized, not only by different drivers of inflammation (10), but also distinct processes of remodeling? Indeed, the findings of James and colleagues are not inconsistent with the notion of "premodeling": that the defect in smooth muscle may precede diagnosable asthma, and perhaps even precede the onset of airway inflammation (9). There is circumstantial evidence that ASM hyperplasia constitutes a response to inflammation. Airway smooth muscle in culture is stimulated to proliferate by a diverse set of inflammatory mediators present in asthma. Moreover, induction of inflammation in mice, rats, guinea pigs, and nonhuman primates is sufficient to induce airway smooth muscle hyperplasia and many of the other features of airway wall remodeling (11). Based on these findings, we would expect to observe evidence of dynamic remodeling in inflamed airways. Work in animal models of inflammation-induced airway remodeling demonstrates an increase in the fraction of ASM within the airway showing markers of cell cycle progression (i.e., proliferation). However, several studies have reported that ASM cells of individuals with severe asthma do not show increased frequency of expression of cell cycle progression markers, such as cyclin D1 and proliferating cell nuclear antigen (PCNA) in *post mortem* specimens (12), or in biopsies, measuring either cyclin D1 (2) or Ki67 (13). A more recent biopsy study reports increases in Ki67 and proliferating cell nuclear antigen frequency in severe asthma (14). Although there is clearly a need for further studies

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