



Published in final edited form as:

*Pediatr Pulmonol.* 2019 November ; 54(Suppl 3): S74–S83. doi:10.1002/ppul.24434.

## The Demographics of Adverse Outcomes in Cystic Fibrosis

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### Summary:

Understanding variability in cystic fibrosis (CF) health outcomes requires an understanding of factors that goes far beyond CFTR function caused by different gene mutations. Social and environmental factors that influence health have a significant influence on the trajectory of health in CF and in other chronic diseases. In this article, we review demographic factors associated with poorer health outcomes in CF, known and postulated biological mechanisms of these outcomes, and interventions that health care teams can implement that may reduce outcome disparities.

### Introduction

There have been tremendous advancements in new therapeutics for cystic fibrosis (CF), including antibiotics, mucolytics, CFTR modulators, over the past decades. This has resulted in improved mortality and morbidity for patients with CF. However, despite these advancements, many patients still suffer significantly from CF and there remains great variability in pulmonary disease progression and severity, even in patients with identical CFTR mutations. There is therefore significant discordance in the CFTR genotype-phenotype relationship. Disease progression and survival are influenced by mode of diagnosis, including meconium ileus and diagnosis by newborn screening, genes other than CFTR, health care provided and health care system factors, and adherence. However, among these and other predictive factors, numerous studies from diverse countries and healthcare settings have shown that that demographic factors, including socioeconomic and ethnic and racial minority status, have a profound influence on health and survival.

In this article, we present demographic factors associated with CF disease variability and poor health outcomes. We review known and postulated biological mechanisms of how these demographic factors influence and interact with the key drivers of health and disease in CF. We conclude with a discussion of the interventions we hypothesize to moderate the effect of

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No conflicts of interest for MEM, WAW, SAM

demographic risk factors, and that can be implemented by CF care teams to better care for at-risk populations.

## Epidemiology

### Socioeconomic Status

Low socioeconomic status (SES) has a profound negative effect on health in CF. SES is variously described based on insurance status (public versus private in the US), geographic income measures (median income by zip code in the US), education achieved by a mother (for her child) or by an individual, or composite measures that may include individual income and/or assets. All of these measures are imprecise, but all show significant effects on health. We use definitions interchangeably in this review. People with CF and low SES have increased mortality<sup>1-3</sup>, worse pulmonary function<sup>2,4-6</sup>, more frequent pulmonary exacerbations<sup>2</sup>, and are more likely to have *Pseudomonas aeruginosa* pulmonary infections<sup>4</sup>. Despite having more severe disease, patients with low SES are less likely to be accepted for lung transplantation<sup>7</sup>. Worse nutritional status is seen in patients with lower SES, including lower BMI and shorter height<sup>2,4,5,8</sup>. The pervasive effects of SES on health seems to occur early in life, without improving or widening over time<sup>4</sup>.

Low SES negatively affects outcomes in CF in many countries and healthcare systems<sup>4,9,10</sup>. In the US, patients with Medicaid, a marker of low SES, had a 64% increased risk of hospitalization for CF exacerbation than patients with non-Medicaid insurance<sup>11</sup>. However, in Canada there was no difference in hospitalization rates between low and high SES patients with CF<sup>12</sup>. This difference association of SES and hospitalization rates may be due to universal healthcare in Canada, which includes specialty CF centers, CF drug coverage, and funding for travel. Low SES is not associated with fewer clinic visits or less prescription of acute or chronic medication in the U.S.<sup>13,14</sup>. However, a UK study showed therapeutic variation by SES after adjusting for disease severity with the lowest SES receiving more intravenous antibiotics and nutritional treatments, but fewer prescriptions for inhaled antibiotics or DNase, despite the UK having a national healthcare system with no out of pocket costs for medication<sup>4</sup>. Medication adherence is decreased in low SES in diseases other than CF<sup>15</sup>. Medication adherence by SES has not been studied in CF, however there was decreased adherence to airway clearance therapies in patients with low SES<sup>6</sup>. The financial cost of the high medication burden may influence adherence more in low SES than high SES and should be investigated.

While low SES is a key driver of poor health outcomes in the CF population, individuals are also affected by family and neighborhood environment. Being in poverty in a poor county with few resources for families, low-quality schools, and limited pathways for economic gains has more of a negative impact on health trajectory for children with health conditions or disabilities than being in poverty in a wealthy county<sup>16</sup>. Community support and personal liquid assets or savings have a benefit on the impact of poverty on a child's health, especially with unexpected medical costs, but can be difficult to measure<sup>16</sup>. Incorporating healthcare costs, including the extent to which health insurance assists with affording those costs, is difficult but increasingly relevant in understanding SES and CF.

Patients with CF and their families are at risk for a decline in SES. Families with CF are at greater risk of poverty due to both increased expenditures, including costs from medical care, travel to appointments, and food expenditures to meet the caloric needs in CF. Decreased income is also common as caregivers frequently decrease their hours working to provide care. Annual medical costs for CF are high and escalate as disease severity worsens<sup>17</sup>. Housing insecurity is also a risk, as the majority of families with special needs have been late in housing payments, and 1 in 5 were faced with foreclosure<sup>18</sup>.

### Race and Ethnicity

The US population is becoming more racially and ethnically diverse, and children are more diverse than the general population. While CF is most prevalent in non-Hispanic whites, an increasing proportion of patients are minorities, mirroring general population demographics<sup>19</sup>. Race and ethnicity are social constructs, but have important health implications. The terms “African American” and “Black” are both used in the literature, as are “Hispanic”, “Latino/a” or the gender-neutral “Latinx”. For consistency we have utilized the terms “Black” and “Hispanic”. The term “minority” is used for race and ethnicity other than non-Hispanic white. The studies discussed primarily utilize self-reported race and ethnicity.

Despite great advancements in CF care and outcomes, minorities with CF suffer worse health outcomes, even after adjustment for SES. Hispanic patients have a higher rate of mortality than do non-Hispanic white patients<sup>20,21</sup>. Black patients have more severe pulmonary imaging findings and more respiratory symptoms at diagnosis than white patients<sup>22</sup>. Hispanic and Black patients with CF have worse pulmonary function than non-Hispanic white patients<sup>23,24</sup>. In the Hispanic population, the gap in pulmonary function is present at 6 years of age, but remains stable, indicating more severe lung disease early in life<sup>23</sup>. The ethnic disparity in CF morbidity and mortality is not uniform across the United States, but varies significantly by region<sup>25</sup>.

Worse outcomes in Hispanic patients occur in spite of higher body mass index (BMI), higher likelihood of pancreatic sufficiency, and presence of milder CFTR mutations<sup>23,26</sup>, all otherwise associated with better CF health outcomes. This paradox is particularly striking given that in the general population, US persons of Hispanic ethnicity have a longer life expectancy than non-Hispanic whites. The increased morbidity and mortality in Hispanic patients must be driven by something other than nutritional status or CFTR genetics. There are many unmeasured and unstudied factors that could contribute to the observed disparities that specifically affect Hispanics, such as language spoken, health literacy, medication adherence, and acculturation level.

Advances in CF have included early diagnosis, new medications, and other therapies; however, these advances may not always benefit minority patients. Minorities are less likely to be detected on prenatal and newborn screening tests due to different frequencies of CFTR mutations and use of DNA panels representing common mutations found in non-Hispanic white patients<sup>27</sup>. This can lead to delayed diagnosis in minorities. Minorities are under-represented in pharmaceutical clinical trials of non-modulator therapies in proportion to their representation in the CF population<sup>28</sup>. Some commonly used CF medications, including

dornase alfa, were not studied in any minorities. Extrapolating results to minorities can be dangerous; many medications have significant racial and ethnic differences in therapeutic responses, drug metabolism, and adverse effects<sup>29</sup>.

Minorities with CF are likely to experience racism that may contribute to negative health outcomes in the general population. A recent meta-analysis reviewing 333 studies in the general population on reported racism and health outcomes demonstrated significant associations between racism and mental and general health outcomes<sup>30</sup>. Age, sex, birthplace and education level did not reduce these health effects. Ethnicity moderated the effect of racism on negative mental and physical health, with a stronger association between racism and negative mental health in Asian and Hispanic participants compared to Black participants. Furthermore, the association between racism and physical health was stronger for Hispanic participants than for Black participants.

There is evidence for differences in health care delivery to racial and ethnic minorities that may occur due to implicit associations. Implicit association describes thoughts and feelings that exist outside of conscious awareness and are therefore difficult to consciously acknowledge and control. A 2015 systematic review of implicit racial/ethnic biases among health care professionals found low to moderate levels of implicit racial/ethnic bias were found among health care professionals<sup>31</sup>. Implicit bias was significantly related to patient-provider interactions, treatment decisions, treatment adherence, and patient health outcomes<sup>31</sup>. Implicit biases were more often significantly related to patient-provider interactions and health outcomes than treatment processes<sup>31</sup>. A systematic review in 2018 of implicit bias in health care providers found evidence of pro-White or light-skin and anti-Black, Hispanic, American Indian or dark-skin bias among health care providers<sup>32</sup>. In the 14 studies that examined implicit bias and healthcare outcomes using clinical situations, 8 found no association between implicit bias and patient care while 6 studies found an association between higher implicit bias and disparities in treatment recommendations, expectations of therapeutic bonds, pain management, and empathy<sup>32</sup>. The extent of implicit bias in CF has not been investigated but should be studied in each CF care center. Implicit biases of CF care providers may impact the care provided.

## Sex

Mortality is higher in girls and women with CF compared to boys and men, a finding not easily explained by differences in pulmonary function, infections, or nutrition<sup>33-35</sup>. Female sex is associated with more pulmonary exacerbations and with earlier age at first exacerbation<sup>36</sup>. Female sex is also associated with more variable pulmonary function<sup>37</sup>. Not surprisingly, pulmonary function decline in females with low physical activity is steeper than males, while females that are physically active have less decline<sup>38</sup>. *Pseudomonas aeruginosa*, Staph aureus (MSSA, MRSA), *H. influenzae*, *A. xylosoxidans*, *B. cepacia*, *Aspergillus* species, and nontuberculous mycobacteria are acquired at an earlier age in female patients, which may contribute to higher morbidity and mortality<sup>39-41</sup>. Female sex is associated with increased risk of CF-related diabetes (CFRD), diagnosis due to symptoms at a later age, and have increased mortality compared to males<sup>42-44</sup>.

Despite having worse outcomes, females are diagnosed at a later age than males, especially when presenting with respiratory symptoms<sup>45</sup>. Historically, this may be due to unconscious gender bias in referring girls for sweat chloride testing. Widespread newborn screening could decrease this bias. However, diagnostic delay persisted in Wisconsin even after newborn screening began<sup>45</sup>.

Adherence to therapies is lower in girls and women with CF, who are more likely to skip medications or chest physiotherapy, decrease caloric intake to obtain thinner body stature, and suppress cough<sup>46</sup>. Female patients may be thinner due to body image issues and exacerbated by praise for an asthenic appearance. In one study, female patients who were underweight were more likely than male patients to consider their weight to be normal<sup>47</sup>.

CF seems to have more of an impact in the lives of girls and women compared to boys and men. Multiple studies have found that female CF patients have lower health-related quality of life compared to males, even with adjustment for disease severity<sup>48,49</sup>. Female patients also have more emotional impact from their CF than their male counterparts, with higher rates of emotional strain, worry about the future, lower self-esteem, and greater discouragement<sup>46</sup>.

## Biology

### Diet and Nutrition

Nutritional status is highly correlated with pulmonary function and survival in CF. Poor nutritional status is associated with more severe pulmonary disease that increases caloric demands leading to worse nutritional status. Furthermore, many CF co-morbidities, including CFRD, pancreatic insufficiency, osteoporosis, intestinal resection for meconium ileus, distal intestinal obstruction syndrome, pancreatitis, short stature, and eating disorders, require special nutritional attention. The CF population is at increased risk of disordered eating which can further impact nutritional status<sup>50</sup>.

Food insecurity, the limited or uncertain access to food, impacts 15 million US households<sup>51</sup> (Figure 1). Households with a child with any special needs are 24% more likely to have food insecurity compared to a family without special needs<sup>52</sup>. Children with special needs who are poor are 50% more likely to have food insecurity<sup>52</sup>. This is especially concerning in CF, as the high-calorie, high-fat, and high-protein diet required is costly. Within the energy dense CF diet, it is important to have nutrient dense foods, which are more expensive, rather than nutrient poor foods which are typically high in sugar and saturated fat<sup>53</sup>. Food insecurity is more prevalent in families with CF despite these families having a high median income, with approximately one quarter of families reporting food insecurity<sup>54</sup>. Families that are Black, Hispanic, immigrants, or located outside of a metropolitan area are at higher risk for food insecurity<sup>55</sup>. In many states, the percentage of families enrolled in federal food assistance programs is less than the percentage reporting food insecurity<sup>54</sup>. Furthermore, these assistance programs, may not provide enough benefits to cover the increased nutritional needs of CF.

## Environmental Exposures

In the general population, early life exposure to air pollution and pesticides is associated with abnormal pulmonary function and respiratory tract disease. In CF, air pollution exposure is associated with pulmonary exacerbation and with *Pseudomonas aeruginosa* acquisition<sup>56,57</sup>. Minority children are more likely to be exposed to air pollution than non-Hispanic white children, especially if they live in a low-income neighborhood<sup>58</sup>. There is a heterogeneous response to air pollution with Hispanic children more likely to require hospitalization for asthma from fine particulate matter exposure than non-Hispanic white children<sup>59</sup>. In California, areas with highest exposure of pesticides had the highest percentage of Hispanic residents<sup>60</sup>. Hispanic children living in California are disproportionately exposed to pesticides as their homes are more likely to be situated closer to the fields where pesticides are used<sup>60</sup>. These environmental exposures may place disproportionate health risks on Hispanic children who are already vulnerable based on socioeconomic and other disparities.

Environmental tobacco smoke exposure is associated with adverse outcomes in CF, as it is in people with other pulmonary diseases and those without lung disease<sup>5,61,62</sup>. While cigarette smoking is lower in CF population than the general population, secondhand tobacco exposure in CF patients is similar to the general population<sup>19,63</sup>. In addition to inflammatory effects in the respiratory tract, tobacco exposure inhibits CFTR function<sup>64</sup>. Heavy tobacco smoke exposure is associated with lower pulmonary function<sup>61,62</sup>, increased hospitalizations<sup>61</sup>, lower weight<sup>43</sup> in CF. Children with low SES are disproportionately exposed to tobacco smoke<sup>5,62</sup>.

E-cigarette use has greatly increased due to the false assumption they are safe. E-cigarettes are now the most commonly used form of tobacco in teenagers<sup>65</sup>. Patients or families using e-cigarettes are more likely to progress to using cigarettes. Some of the e-cigarette vapor contains high levels of nickel, chromium, and cadmium which are carcinogens that can negatively affect pulmonary function<sup>66</sup>.

## Adverse childhood experiences

While the prevalence of adverse childhood experiences (ACEs), traumatic events occurring before age 18 years old, in CF is unknown, ACEs are likely to contribute to worse outcomes in people with CF. ACEs span a wide range of experiences that typically encompass abuse, neglect, and household factors. Most ACEs studies capture these categories: emotional, physical, or sexual abuse; exposure to violence, neglect, or discrimination; parental mental illness, substance abuse, divorce or death, resulting in toxic stress. The first study of ACEs evinced a dose dependent relationship between the number of maltreatments in childhood and poor social and health outcomes in adults<sup>67</sup>.

Toxic stress in childhood leads to dysfunction of the neuroendocrine-immune network. Diminished cortisol can allow persistent inflammation, while excess cortisol can suppress immune response<sup>68</sup>. Dysregulation of the immune and endocrine systems, particularly during periods of development, leaves children vulnerable for a wide array of health problems<sup>69</sup>. ACEs are associated with numerous adult health issues including depression,

alcoholism, cancer, and heart disease, and also increase the number of health problems per individual<sup>67,70</sup>.

As seen in Figure 2, 46% of children have at least one ACE. ACEs have been linked to learning and behavior problems, obesity, eating disorders, depressed mood, posttraumatic stress disorder symptoms, and suicides in youth<sup>71–75</sup>. ACEs are more prevalent in children of lower socioeconomic status, more complex health needs, and racial and ethnic minorities (Figure 2). The impact of ACEs on childhood chronic disease is less well understood. However, recent studies have found a correlation between the number of ACEs and the development of pediatric asthma and the number of unmet care needs in children with autism spectrum disorder<sup>76,77</sup>. ACEs have not been investigated in CF, but may play an important role in disease variability.

### The epigenetics of poverty

The biologic mechanisms related to poverty are starting to be elucidated. A recent report evaluated levels of DNA methylation at CpG sites across the genome and evaluated the association with SES in a cohort of young adults in the Philippines<sup>78</sup>. In comparison with high SES, low SES was associated with increased methylation at 1,777 sites, and decreased methylation at 769 sites, after adjustment for multiple comparison, represented in Figure 3. Over-representation of biological pathways and genes related to immune function and inflammation were noted in the study. Higher levels of inflammation or altered immune function may explain the observed lower pulmonary function, increased pulmonary exacerbations, and higher rates of *Pseudomonas aeruginosa* infections in CF with lower SES and should be investigated.

### Interventions

Alongside the many therapeutic advances being made in CF to reduce morbidity and mortality, the discussed demographic disparities also need to be addressed to ensure that health outcomes continue to improve equitably for all patients with CF. While systematic societal efforts are necessary to reduce or eliminate poverty and its myriad effects on human health, we propose interventions that can be implemented by healthcare providers and/or within healthcare systems (Figure 4). These interventions have not been studied systematically in CF, and some have limited evidence for interventions in other populations. Nevertheless, the impact of demographic factors is so substantial that considering specific actions is necessary.

### Ways to Reduce Health Care System Bias

**Addressing Implicit Bias**—The Implicit Association Test (IAT) measures implicit bias via tests of automatic associations between concepts. There are few studies examining the effects of IAT for health care providers or programs to reduce implicit bias<sup>32</sup>. Nevertheless, widespread IAT as a self-assessment tool can raise awareness to the unconscious biases that may affect communication and patient care. Project Implicit ([www.implicit.harvard.edu](http://www.implicit.harvard.edu)) provides free access to a variety of these tests and has a number of services for organizations interested in reducing the negative impact of implicit bias.

## Language, Culture, And Healthcare Team Diversity

Appropriate medical interpretation is essential for provision of even adequate health care to patients and their families who do not speak the language of the health care professionals caring for them. Cultural competency training is proposed to improve patient outcomes. A 2018 systematic review of 16 studies of health care professionals demonstrated that diverse programs had positive effects on practitioner knowledge and attitudes, but few studies evaluated interventions<sup>79</sup>. Increasing diversity among the health care professions is an important strategy to reduce the effects of bias and is the focus of efforts by the United States Department of Health and Human Services<sup>80</sup>.

## Food Insecurity Screening

Since food insecurity is prevalent in CF, the Cystic Fibrosis Foundation has formed a task force to address this important issue at CF centers. CF centers should identify and assist patients with food insecurity. Algorithms for routine screening can be added into the registration/intake process of visits and appointments. Screening can be done verbally or written in the patient's preferred language. There is a simple 2-question true or false screen for food insecurity "The Hunger Vital Sign" that has been developed by the American Academy of Pediatrics: "I worried about not having enough to eat. I tried to not eat a lot so our food would last"<sup>81</sup>. Electronic health records (EHR) have been used successfully to screen patients and share referral information about government and community programs for food resources, such as Supplemental Nutrition Assistance Program (SNAP), Summer Food Assistance Programs (SFAP), and local food banks. The Hunger Vital Sign is already built into Epic's Foundation System. Positive screens can be tracked with the ICD-10-CM Diagnosis Code Z59.4 (lack of adequate food and safe drinking water). Particular sensitivity and attention should be given prior to referring immigrant patients to federal nutrition programs, especially when families have mixed citizenship status.

Food insecurity is never an isolated problem. Targeting other hardships such as housing or energy costs can allow for enough funds for food<sup>82</sup>. Educating families about programs to spread their energy costs evenly over the year can be beneficial. There are lower levels of food insecurity after receiving housing assistance. There are many unreimbursed medical costs with CF, such as insurance copayments, deductibles, and vitamin costs. Medication and treatment adherence is improved with addressing food insecurity, especially with more costly therapies<sup>83</sup>. One third of families with food insecurity had to choose between paying for medical care or purchasing food<sup>84</sup>. CF care providers should educate families and advocate for insurance that covers more of the medical costs to shield families from health shocks, such as prolonged hospitalizations, which can cause a family to fall into food insecurity and poverty.

## Air Pollution and Tobacco Exposure

Avoidance of indoor and outdoor air pollution is beneficial and possible for patients with CF. Patients in high risk areas, such as areas near wildfires, should be counseled about using protective masks that filter airborne particulate matter to reduce the effect of air pollution. Proper fit and usage of masks is essential for protective effects. Masks should be kept on hand for use in cases of emergent air pollution as there are often shortages at times of need.



Monitoring air quality from the Environmental Protective Agency (EPA) or Purple Air is useful to determine current air pollution risk levels. At times of heavy air pollution, patients should be counseled to stay indoors with windows kept shut. Portable air filtration systems are affordable and can reduce the level of indoor air pollution. While avoiding living and working in high air pollution areas, such as those caused by automobile traffic, is ideal, it is often not possible. Impoverished families and minorities who are most likely to live in high air pollution areas should be targeted for counseling<sup>58</sup>.

Patients and families should be screened for tobacco use and exposure at routine visits and hospitalizations. Resources on tobacco cessation should be given to any patient or family with tobacco exposure. If smoking cessation is not possible, exposure should be reduced by implementing family “no smoking” rules indoors and in vehicles. CF providers should pay attention to screening for e-cigarette use, now the most commonly used form of tobacco in teenagers<sup>85</sup>.

### **Mitigating Adverse Childhood Experiences (ACEs)**

The American Academy of Pediatrics recognizes the toxic and compounding nature of ACEs and has announced a need for pediatricians to bolster screening and pursue childhood interventions<sup>68,69</sup>. More research is required to elucidate the most effective intercessions to ameliorate the short- and long-term impacts from childhood maltreatment<sup>86</sup>. New efforts to counsel children with trauma-informed care techniques and to educate parents demonstrates potential areas for integrated care<sup>86–88</sup>. Focusing on techniques that bolster resiliency and mindfulness have been associated with countering some of the negative impacts of ACEs, including higher rates of school engagement among children with multiple ACEs<sup>87,88</sup>. There are currently no studies that have documented the prevalence of ACEs in children with CF. Counseling and techniques that emphasize resiliency and mindfulness coupled with enhanced screening for ACEs in the CF setting may help mitigate the burden of ACEs<sup>87,88</sup>. In the US, accredited CF Centers have social workers and often psychologists, making intervention and referral highly feasible in practice.

### **Inclusion of minorities in clinical research**

Exclusion of women and minority groups has been an issue for decades in both observational and interventional research. To address this, US federal law now requires that “In conducting or supporting clinical research ... the Director of NIH shall ... ensure that (a) women are included as subjects in each project of such research; and (b) members of minority groups are included in such research 492B(a)(1)”<sup>89</sup>. It is also specifically forbidden to exclude women and minorities based on increased cost that may result from inclusion. While these legal requirements are applicable only to NIH-funded research, research sponsored by non-profit and industry sources should strive to be equally inclusive. In CF programs conducting clinical trials, making special efforts to include patients who have fewer resources or are minorities can be implemented during pre-screening activities. These inclusion efforts might include anticipating need for providing transportation (rather than reimbursing a family with a reliable means of transportation), the need for translation of study materials and consent forms, and the need to have interpreters for study visits.

## Conclusions

Epidemiologic reports demonstrate incontrovertible evidence of demographic disparities in CF health outcomes. The biologic mechanisms that are associated with low SES status are beginning to be elucidated. While there is little CF-specific literature, interventions that may reduce disparities can be implemented by health care teams at CF Centers, and studying their impact is important. While proposed interventions can be implemented by health care professionals, the authors recognize the importance of public policy, including educational, environmental, health care and other strategies to reduce disparities in the entire population.

## Acknowledgments

**Financial disclosures:** MEM is supported by the NHLBI (1K23HL133437-01A1) and Cystic Fibrosis Foundation Therapeutics (MCGARR16A0). SAM is supported by the Northwestern University Clinical and Translational Sciences Institute through the National Center for Advancing Translational Sciences (UL1TR001422).

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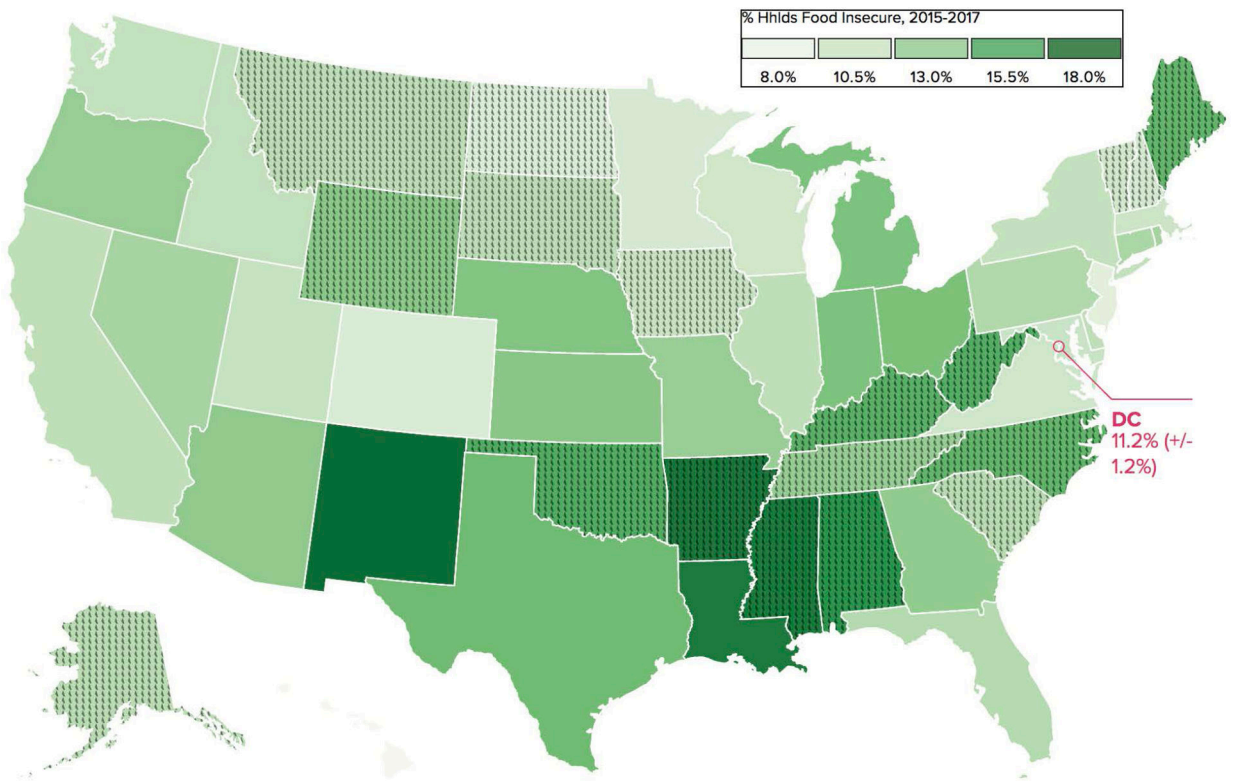
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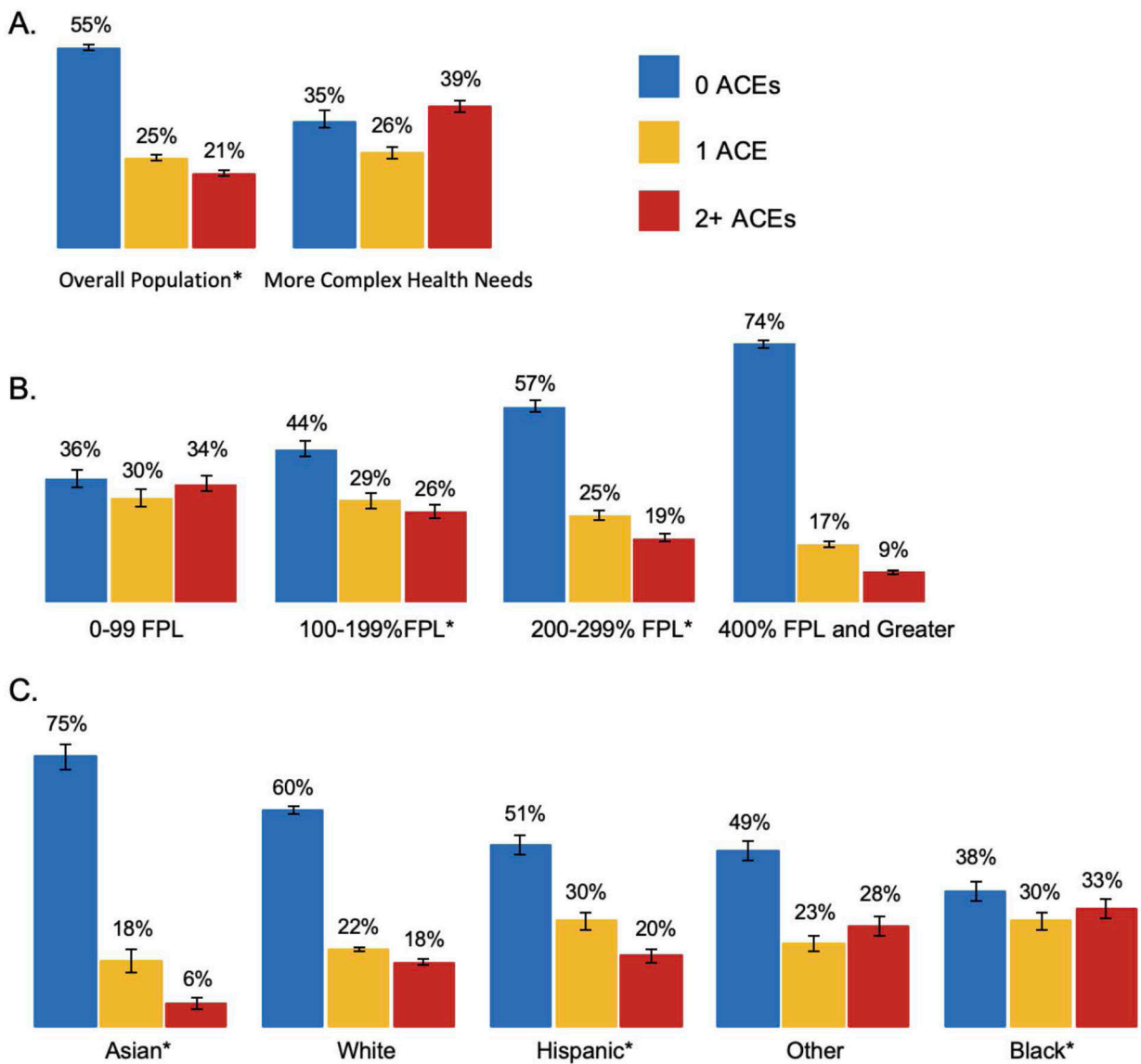
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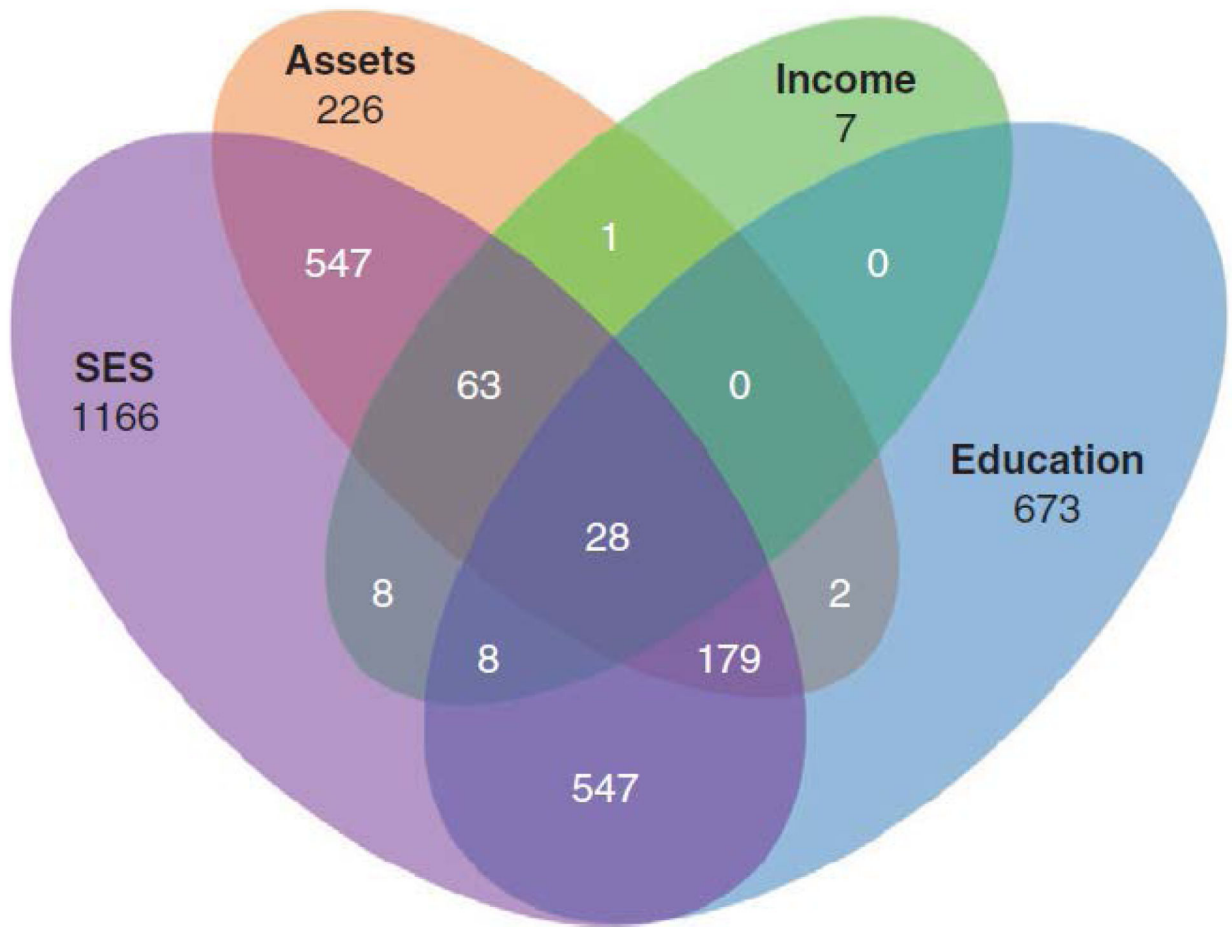


**Figure 1:**  
Household Food Insecurity Rates By State, 2015–2017  
Citation: Food Research & Action Center

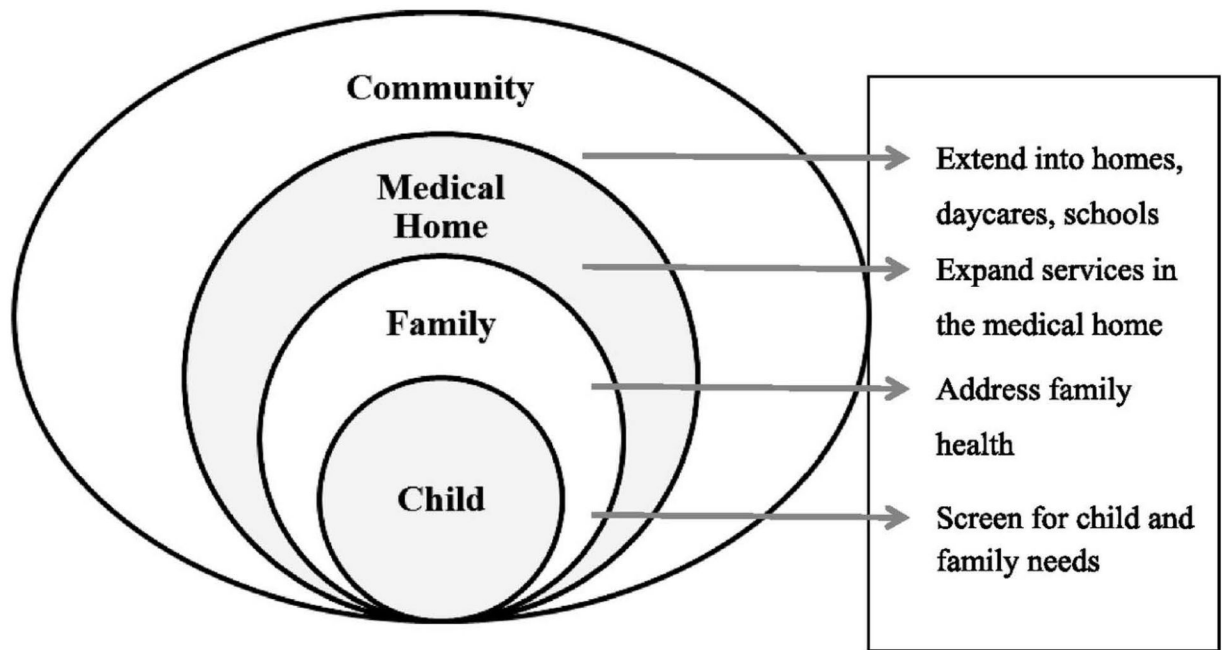




**Figure 2.** 2016–2017 National Prevalence of Adverse Childhood Experiences  
**A.** Prevalence of ACEs in the US is the overall population and in children with more complex health care needs. **B.** ACE stratified by household income. FPL represents the Federal Poverty Line. **C.** ACEs by race/ethnicity. Error Bars represents 95% confidence intervals. \*Percentages do not sum to 100 due to rounding. From the National Survey of Children’s Health. Used with permission. Child and Adolescent Health Measurement Initiative. 2016–2017 National Survey of Children’s Health (NSCH) data query. Data Resource Center for Child and Adolescent Health supported by Cooperative Agreement U59MC27866 from the U.S. Department of Health and Human Services, Health Resources and Services Administration’s Material and Child Health Bureau (HRSA MCHB). Retrieved [05/16/19] from [www.childhealthdata.org](http://www.childhealthdata.org). CAHMI: [www.cahmi.org](http://www.cahmi.org).



**Figure 3:** Venn diagram showing areas of DNA methylation significantly associated with SES and its components (household assets, education, household income), based on the contrast between low/low and high/high groups within each SES component.



**Figure 4.**  
Four approaches to address health disparities in clinical practice.